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QUASI-STATIC NETWORK MODELS FOR ALZHEIMER'S DISEASE

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Abstract

In the field of neurodegenerative diseases, biological *in vivo* research suffers from experimental limitations and *in silico* models often provide useful complementary results. In this Thesis we consider Network Transport Models (*NTM*s), mathematical models on graphs with transport phenomena on the edges, to describe the role of the toxic Beta Amyloid (Aβ) and Tau proteins in Alzheimer's disease (*AD*). The Thesis is part of a much broader project to develop a flexible simulation platform to test therapies and model hypotheses and to predict the evolution of the pathology in individual patients. Our goal is to formulate a mathematical background for such a platform, a rigorous but flexible analytical framework for the development and validation of advanced and computationally efficient models for neurodegenerative diseases.

At least two very different timescales occur in *AD*, a fast one for the microscopic dynamics of proteins and a slow one for the global evolution of the pathology. Therefore it is natural to use quasi-static models, approximations where the fast timescale becomes instantaneous with respect to the slow one. This leads to a substantial reduction of mathematical and computational complexity, but, even formally, it also poses a first and highly nontrivial mathematical challenge to identify, in quasi-static *NTM*s, the correct mass balances between nodes and edges.

A second mathematical challenge is the design of models that give more insight in the fundamental question why different timescales occur in *AD*. In this context we will identify potential *bottlenecks*, biological mechanisms which slow down the global evolution of the pathology.

The Thesis consists of four chapters. In Chapter 1 we describe and analyse a first quasi-static *NTM* for intracellular Tau. We use a basic and intuitive approximation of the correct mass balance of Tau between nodes and edges. The presence of the Axonal Initial Segment and the synaptic cleft along the edges is chosen as the main bottleneck, which strongly reduces the microscopic diffusive properties of Tau on the edges. In Chapter 2 we introduce and analyse a quasi-static model for extracellular Aβ. This time, the bottleneck is the presence of efficient clearance mechanisms that reduce the spread of Aβ in the brain. In Chapter 3 we combine the two models, where the Tau dynamics is influenced by the presence of toxic Aβ. Here the intuitive approach of Chapter 1 cannot be applied and we are forced to give a formal derivation of the correct mass balance of Tau between nodes and edges. Although mathematically the formal derivation is satisfactory, the prize to pay is high: the resulting model is extremely complex, both from an analytical and computational point of view. In Chapter 4 we adapt the model to avoid these drawbacks and specify the physical mechanism of *release and uptake* which is at the base of the bottleneck for Tau along the cell membrane. This requires the introduction of extracellular Tau in the nodes of the graph.

In addition to mathematical well-posedness results, we provide numerical simulations to highlight relevant properties of solutions and compare the different models in terms of computational performance. The discretisation of the brain domain, the quasi-static approach and ultimately the simplifications in the Release-Uptake Tau model described in Chapter 4 certainly contribute to a reduction of the computational costs. However, further efforts will be needed to improve computational efficiency, which is crucial for large-scale simulations, parameter testing and, in particular, inference and comparison with clinical data. For example, machine learning tools could speed up the time-consuming implementation of Tau transport along edges. This topic is far beyond the scope of the Thesis, but some first attempts in this direction are most promising.

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Introduction

Among several forms of dementia, Alzheimer's disease (*AD*) is the most common. The estimate of the number of affected people over the age of 65 years in 2015 is approximately $29,8$ million [29]. More recent estimates report that the total number of people affected by Alzheimer's disease is 416 million, including cases of prodromal and preclinical *AD* [39]. The pathology is characterised by progressive neurodegeneration; the early symptoms are related to a decline in mental abilities associated with memory and reasoning along the Mild Cognitive Impairment (*MCI*) phase. This mild stage could progress to dementia, where the cognitive abilities of the subject are severely affected.

Alzheimer's disease is characterised by the formation of toxic aggregates of Beta Amyloid ($A\beta$) and Tau proteins. Their action is associated with neuronal impairment and synapses loss. These proteins inhabit different environments of aggregation: Beta Amyloid diffuses in the extracellular areas, while Tau protein is mainly contained inside neuronal cells. The role of Aβ in the development of Alzheimer's disease has been highly debated. The "amyloid cascade hypothesis" has been first introduced in the early $90'$s [42], [43] and postulates the pivotal role of Beta Amyloid as a causing factor of *AD*. It refers to the imbalance between the production and clearance of A$\beta - 42$ and other peptides as an early trigger factor for *AD* [81]. The theory has widely influenced the development of potential therapies that focus on the reduction of Aβ aggregation and production. However, several clinical trials in this direction have failed [52]. The therapeutic approach towards the remotion of Aβ is controversial due to the nature of this protein. Despite the Aβ toxic role being proved and stated, Aβ monomers are also involved in protective mechanisms such as regulation of synaptic function, modulation of synaptic activity and antimicrobial effect [80]. These features clearly need to be addressed in therapeutic interventions. Indeed some studies suggest that inhibition of production can lead to neuronal cell death [71].

The failure of clinical trials based on the "amyloid cascade hypothesis" has led to the exploration of new theories on the pathogenesis of AD involving both Aβ and Tau proteins. Increasing attention towards Tau protein can be justified by observing that the spread of Tau is a crucial feature of a variety of Tau-associated neurodegenerative diseases that manifest different symptoms and involve different regions of the brain depending on the specific Tau isoform [40]. Tau protein is physiologically synthesized along the axonal site of neurons, where it promotes microtubule assembly and stability [100]. Along the axon, Tau protein may be subjected to hyperphosphorylation [7], thus adopting a pathological conformation. Once misfolded, Tau protein aggregates along the axon leading to the formation of neurofibrillary tangles (*NFTs*) by further sequestering functional Tau, thus impeding its physiological stability function [7]. Soluble misfolded Tau aggregates also migrate to the somatodentritic compartment [7], [17], [102], hence amplifying their toxic effect towards neighbouring cells.

Although the chemical mechanisms behind the formation and aggregation of toxic aggregates are well known, the interaction between the two proteins remains unclear. The challenges concerning this topic also relate to the difficulties in conducting *in vivo* experiments in patients and the cost of collecting PET and MRI scans. Together with a lack of data and scarce understanding of the underlying interactive dynamics between the two proteins, the presence of multiple time and length scales enhances the level of complexity of the pathology [45]. Effectively, the occurring spatial scales are: protein level $\sim 10^{-9}m$, neuron level $\sim 10^{-6}m$, organ level $\sim 10^{-1}m$. Meanwhile, the time scales are: transit of the cerebrospinal fluid $\sim 1s - 10^4 s$, protein aggregation $\sim 10^4 s - 10^6 s$, neurodegeneration $\sim 10^8 s$ [45]. Moreover, both Beta Amyloid and Tau proteins diffuse along different time scales. For instance, the biomarker magnitude for $A\beta$ increases faster than that associated to Tau-mediated neuronal injury, followed by alterations in brain structure, memory loss and clinical dysfunctions [56]. In this scenario, the complexity of the brain topology also plays a role. As observed in [38], the problem of establishing the number of total neurons in the human brain is still open. For instance the estimates provided in [45] suggest an approximation of 86 billion neurons. As we shall see later, this level of intricacy naturally finds its reflection in the definition of suitable theoretical models.

In this context, mathematical modelling can contribute to the understanding of the evolution of Alzheimer's disease. First, elaborating a reliable mathematical model requires the identification of the most relevant processes involved in the phenomenon, which is a massive challenge given the high level of complexity cited above. This approach necessarily implies the reduction of a complex problem to its essential core by eliminating redundancies. Then, a prerequisite for the validity of the mathematical structure is its ability to correctly describe such fundamental biological mechanisms. The advantages of mathematical modelling are multiple, the most prominent being its predictive capability concerning future developments. Regarding the specific application to Alzheimer's disease and neurodegeneration, as cited earlier, the occurrence of the first symptoms and the consequent diagnosis usually occur in late life stages. For this reason the identification of biomarkers that could lead to an earlier diagnosis and the adaptation of the model parameters to the specific patient condition in the early stages could be crucial to make predictions about the progression of the disease.

Theoretical models can also be employed to test new theories through numerical simulations, verify them by analysing their outcomes and eventually adopt or reject them. This feature is potentially promising in the field of neuroscience, where measurements and experimentation *in vivo* are particularly difficult to execute and *in vitro* experiments often portray a scenario that is much more elementary than the reality of living tissues in the brain. In this context, the flexibility property of the model is essential; the mathematical structure should be versatile enough to be easily adapted to new dynamics, especially when dealing with such complex biological settings as in the case of *AD*.

Mathematical models are the natural tool to bridge the gap between microscopic biological knowledge and macroscopic observed patterns. By capturing the microscopic features of a phenomenon, the theory generalises biophysical processes by exploring how changes in the parameters of the model affect the global system behaviour. From an applied perspective, the property of controlling macroscopic outcomes through microscopic parameters can be exploited to test the efficacy of therapeutic interventions, which often target microscopic mechanisms.

When dealing with the definition of a suitable mathematical model for Alzheimer's disease, the first issue to address is the selection of the spatial domain due to the extreme intricacy of the brain topology and physiology.

Two main approaches can be distinguished for identifying a spatial domain that accurately captures the topology of the human brain. The first one consists in the geometrical definition of a continuous medium, meanwhile the second one adopts a discrete approximation of the brain network by means of graph theory. Among the numerous contributions to the continuous analysis, we refer to [2], [10], [32], [33], [34], [97]. The classical approach relies on the construction of perforated domains and the selection of linear diffusion at microscopical scales as spatial operator [2], [10], or the introduction of anisotropic diffusion by means of spatial dependent diffusion tensors [33], [97]. Concerning the latter, the authors model protein spread along the extracellular space by means of linear isotropic diffusion, whereas diffusion along neuronal pathways takes place along the preferred axonal fiber direction, thus adopting anisotropic propagation. Lastly, we observe that all the contributions mentioned above share the use of *local* spatial operators for the description of misfolded proteins spread along the brain network. As we shall discuss later, the occurrence of Release-Uptake processes, which describe the spreading of Tau to neighbouring neurons, may indicate an inclination of Tau diffusion towards nonlocal propagation. It is worth mentioning that some attention has been devoted to this topic, as we can see in [3], [51], [64].

The continuous approach is naturally characterized by remarkable computing efforts when dealing with the quantitative analysis of solutions to PDE systems on intricate $3D$ spatial domains. In addition, the complexity increases when modeling the dynamics of the brain fluids (interstitial cerebrospinal fluid, arterial and venous blood) together with toxic protein propagation. We refer to [5], [6], [26], [36] as possible numerical approaches to domain discretization by means of discontinuous Galerkin methods and Machine Learning tools.

The graph approach relies on the construction of a discrete domain that encapsulates the geometry of the brain network. Starting from structural and diffusion MRI scans, the graph is obtained by means of whole brain tractography [74]. The nodes of the graph correspond to gray matter regions and the edges of the network portray the fiber tracts connections between nodes. The weight of each edge corresponds to the strength of the respective connection and is proportional to the number of fiber tracts [74]. As in [13], [74] we refer to the resulting network as the *connectivity* graph. This modeling choice is particularly suitable for the description of Microtubule-associated Tau spread since it physiologically propagates along the axonal connections. As stated previously, Aβ is mainly present in the extracellular space. This fundamental difference requires the definition of a different spatial domain to include the diffusion of Aβ, since the action of the spatial operator on the network strictly depends on the underlying node-edge structure. To this end, we refer to [62] as an example of construction of an appropriate network, namely the *proximity* graph. The graph is obtained by selecting the same set of vertices of the *connectivity* graph and a different set of edges. The weight of an edge between two nodes consists in the reciprocal of the Cartesian distance between the centre of mass of each gray matter region. Therefore edges between the same nodes may be equipped with different weights in the *connectivity* and *proximity* graph. Two regions may also be adjacent in the *connectivity* graph and not connected in the *proximity* graph, for example if the respective distance is greater than a fixed threshold as in [13].

After defining an accurate underlying structure, we can define the spatial operator acting on the nodes of the graph, namely the Graph Laplacian.

The dynamics described by the Graph Laplacian operator resembles the standard Laplace operator since its action *formally* corresponds to the second-order central finite difference formula for the approximation of the second order derivative at each node. The *Network-Diffusion Model* was first introduced in [74] and extensive work has been devoted to this class of models later on to expand it by including diffusion and reactions between multiple species [12], [13], [32], [73], [89], [98]. Despite the simplicity of a discrete approach, Graph diffusion models predict fundamental patterns of evolution such as the Braak staging of AD [97], [98]. These models possess important computational and analytical benefits. For example, spatial discretization implies the passage from PDEs on the continuous domain to ODEs on the nodes and the Graph Laplacian operator exhibits several properties related to the well-posedness for such dynamical systems [19]. However, the effective dynamical property of the operator strongly reflects the topological characteristics of the underlying graph.

For example, in [8] the authors discuss the case of an infinite directed graph with a Graph Laplacian acting as a first order operator on the nodes. This counterexample is crucial to understand the relation between the edge structure of the network and the action of the spatial operator: although the definition of the Graph Laplacian formally corresponds to the discretisation of the second order derivative at each node, the occurrence of edges incident to the node is necessary to yield non-zero terms in the computed derivative. This implies a possible loss in the order of the resulting operator and suggests a criticality in the interpretation of the Graph Laplacian as a diffusive operator. As observed in [69], the issue pertains to the more general problem of model selection which, in turn, consists of the choice for mathematical parameters and spatial operators, specifically the Graph Laplacian weights. Models adopting different Graph Laplacian weights have been shown to produce distant outcomes in comparison with clinical data [15], [73]. For example, in [1],[74] the weight of an edge in the *connectivity* graph is defined as the number of fiber tracts between the respective gray matter regions. In [32], the edge-weight of the *connectivity* network for Tau spread is the number of fibers divided by the mean fiber length. In [89], the weight is selected as the number of fibers divided by the square mean fiber length. One of the goals of this Thesis is to overcome, at least in the case of the *connectivity* graph, the arbitrariness related to the selection of the Graph Laplacian operator by explicitly modelling the mass transport between nodes.

The models presented in this Thesis deal with processes of dynamical spread and interactions of toxic proteins on graphs. Specifically we describe the evolution of Tau and Beta Amyloid aggregates. The importance of selecting a suitable spatial operator on the graph is particularly relevant when modeling the spread of Microtubule-associated Tau protein, due to its intracellular nature. The species of Tau that we consider in the first model are misfolded soluble and insoluble clusters. To gain a more precise description of the diffusion and advection dynamics between nodes, we model these processes along the edges of the graph. The starting point consists in the description of the dynamics observed along the two-neurons connection as suggested in [92], where the axonal connection is identified with a one-dimensional interval. At network level, we interpret the single edge of the graph as a bundle of connected neurons with independent tau dynamics. Under these modelling assumptions, by describing the mass transfer mechanism between edges and nodes, we then obtain a spatial operator acting on the nodes that collects the incoming fluxes at each node and correctly depicts the diffusion and advection dynamics on the global network.

One of the novelty of the resulting model, namely the *Network-Transport Model* (*NTM*), with respect to previous work is the introduction of an advection process between nodes. In this direction, a recent rigorous framework on the definition of advective operators on the nodes of distance-weighted directed graphs has been proposed in [9] in the fields of Network Science and Graph Theory.

Concerning the explicit definition of the advection operator, based on [92], we introduce a dependence of the transport velocity on the concentration of soluble and insoluble toxic Tau. The justification for this choice relies on some evidence regarding the reciprocal influence of toxic Tau on axonal transport [7], [17], [102]. Axons host signal propagation, hence they are oriented along the direction of spread of the potentials, which is referred to as the *anterograde* direction. *In vitro* experiments show that Microtubule-associated Tau controls motor protein–driven transport along microtubules by obstructing kinesin-1, an anterograde intracellular motor-protein, at physiological levels [22], [30]. In the disease stage, aberrant Tau has been shown to reduce the inhibition of kinesin-1 [27], [78], [83], whereas neurofibrillary tangles (NFT) are associated with a reduction of kinesin-1 [82]. The ultimate dominance of anterograde or retrograde (i.e. opposite to anterograde) directed motor proteins determines the direction of axonal transport [22], [78], [94], therefore the advection velocity along the two-neurons connection is defined as a function of soluble and insoluble toxic Tau. The immediate consequence of this type of selection is the requirement of a directed graph to model advection occurring along the opposite direction of the axonal signal propagation, provided that the anterograde direction corresponds to the orientation of the respective edge.

The second relevant novelty of the *NTM* is the quasi-static approach. As mentioned before, Alzheimer's disease is characterized by the occurrence of extremely different time scales. We distinguish two different approaches to handle them at the level of mathematical modelling. The first one is empirical: the coefficients are selected of order one in the fast time scale, such as for example diffusion and aggregation (coefficients which would become huge in the slow timescale), in such a way that the numerical outcome fits biomedical data. One could say that the rescaled coefficients express *effective* diffusion, aggregation etc. This approach has been shown to work quite well [10], [13], [21], [75] but does not add additional insight to the question

Why is the evolution of the disease extremely slow?

In this Thesis we opt for a second approach: we formulate possible *microscopic* modelling hypotheses which lead to two very different *macroscopic* timescales. The key idea is the concept of *bottlenecks*. For example, the diffusion and aggregation of Aβ in the extracellular space are fast, but the presence of an efficient clearance mechanism may considerably slow down the fast spread of Aβ over the brain. Similarly, a possible bottleneck for fast Tau spreading is a trans-synaptic mechanism which describes a very slow transmission of Tau from one neuron to neighbouring neurons. Such bottleneck naturally involves Tau transport along edges of the *connectivity* graph and therefore the *NTM* is an appropriate mathematical environment to describe it. This time the coefficients describing the bottlenecks will be chosen in such a way that the numerical outcome fits biomedical data.

An important computational drawback of the *NTM* is the description of Tau transport along edges through a partial differential equation (PDE), which poses a considerable numerical challenge in terms of solvability and computational costs. To reduce this drawback at least partially, we follow an idea which was introduced in [92] on a single edge, and generalized in [91] to full networks: the transport equation on a single edge concerns the fast timescale, whence solutions will tend very fast to a stable (quasi-static) equilibrium configuration. This leads to a limiting procedure which renders the fast timescale instantaneous in the slow timescale. Mathematically this means that the PDE on the edge is transformed in an ordinary differential equation (ODE), which is easier to deal with computationally. *Quasi-static modelling* is a standard tool in problems with different timescales, but it is usually quite hard to make the underlying limiting procedure rigorous. In our specific case, it is immediate to guess the limiting ODEs on the edges by keeping the formulation of the quasi-static limit merely formal. However in general it is much harder to describe how, in the quasi-static limit, Tau transport on the edges influences the evolution of Tau in the nodes. The reason is hidden behind the non-triviality of the quasi-static limit of the incoming Tau fluxes along the edge-node interface. The key is a detailed study of local mass balances in the nodes in the quasi-static limit, which in general leads to *feedback* phenomena in the equations for Tau in the nodes. As we shall see below, the mathematical challenge of determining the correct mass balance at node level consists in the correct formulation of the node equations, along which the concentrations correspond to the Dirichlet boundary conditions for the edge profiles.

With regard to Beta Amyloid, the species we are interested in are monomers, soluble oligomers and insoluble plaques at node level. The spatial spread of toxic Beta Amyloid is described by the Graph Laplacian associated with the *proximity* graph acting on monomers and oligomers. It is worth noticing that by definition the *proximity* graph is undirected. As in the *NTM*, we identify fast processes such as diffusion, aggregation and fragmentation and assume a quasi-static regime by approximating the ODEs solutions with a respective steady state. Previous models (e.g. [32], [89]) have dealt with similar systems by considering homogeneous dynamics between the nodes, i.e. by analysing graph-harmonic steady states. If the graph is connected, then this steady state is spatially homogeneous and is determined as a zero of the reaction term of the equation. To account for regional variability, we propose a proof of the existence of a steady state for the Beta Amyloid system without assuming homogeneous dynamics. The time evolution of such steady states is then defined by the production rate of the monomers, which is assumed to depend on a measure of the health state of neurons at each node. The system is coupled with a continuity equation for the above mentioned measure by assuming that the concentration of soluble oligomers at each node impacts the overall level of neuronal impairment of the respective region.

The Aβ model and the *NTM* are then coupled with the assumption that soluble Aβ enhances Tau aggregation and diffusion in a one-way fashion. As discussed in [104], Aβ interferes with Tau oligomerisation and aggregation. Mediated by Aβ-activated *CDK-5* and *GSK-3β* kinases, hyperphosphorylated Tau is released by microtubules and its tendency to bind with Tau monomers induces Tau oligomers formation [104]. Oligomeric Tau is the most disruptive in terms of induced neuronal damage as it is transmitted along neuronal cells and engages in a *seeding* activity by promoting Tau misfolding. Therefore the interference of Aβ on Tau aggregation is a crucial factor to explore. Mathematically this implies however that the coefficients in the equations for Tau on the edges depend on Aβ, and so on time. Since edge fluxes depend on these coefficients, the feedback issue again shows up to formulate the correct mass exchange of Tau between nodes and edges.

As we shall see later, this coupled model for Tau and Aβ exhibits several problems, both from the analytical and computational point of view. The structure of the node equations is enriched with respect to the model of Chapter 1 by a non-local *feedback* mechanism unravelling the dependence of the mass flux at the node on Tau concentration at the neighbouring nodes. The drawback of a detailed *feedback* formulation is also reflected in the numerical implementation of the model, which results in extremely high computational costs. To avoid these drawbacks, we propose a different version of the *NTM* through the introduction of soluble and insoluble *extracellular* Tau protein.

The interaction between intracellular and extracellular Tau is modelled by the mechanism of Release and Uptake, which takes place along the two-neurons connection and enables soluble Tau to spread very slowly (here we recognise the bottleneck for Tau spreading) along the extracellular domain. The resulting model is coupled with the Aβ system by introducing a bidirectional interaction. Since the direct influence of misfolded Tau on Aβ toxicity remains unclear, we propose a passive interplay between soluble Aβ and misfolded Tau by postulating that both proteins contribute to neuronal impairment through the aforementioned probability measure, as in [13]. Recent evidence also suggests a further shared contribution to the enhancement of neuroinflammation [67], [104]. The role of extracellular Tau as a critical mediator of disease progression has been sustained by increasing transneuronal propagation of misfolded species [96] and the interaction with glial cells, initiating neuroinflammatory responses that may contribute to neuronal dysfunction [70]. Although the *Release-Uptake NTM* does not include glial-mediated effects and inflammation, the introduction of the extracellular compartment defines a suitable theoretical background for future studies in this direction.

Summarising, the main purpose of this Thesis is to provide a theoretical background for modelling Tau and Beta Amyloid proteins in the human brain by introducing the novelty of the quasi-static approach in the field of mathematical modelling for neurodegenerative diseases. By detailing the mathematical structure of the models, we build the foundations for the practical application of such systems. For example, we refer to the process of statistical inference of the model parameters to fit the available medical data. In this context, although we do not effectively employ such a statistical analysis, we mention the computational properties and outline possible algorithmic strategies to simulate the models we develop.

The manuscript is organised as follows.

In Chapter 1, we introduce the PDE-*Network-Transport Model* for toxic Tau on the *proximity* graph. We develop a first quasi-static approximation to the PDE-*NTM* under some hypothesis on the behaviour of the *feedback* phenomenon. The purpose of this Chapter is to describe the global structure of the quasi-static model and introduce the problem of balancing the local mass exchange at node level. To this end, we provide a first possible approximation of the *feedback* term and propose a general method for proving the well-posedness for the system.

In Chapter 2, we present a model for Beta Amyloid protein on the *proximity* graph. The main result of this Chapter is the proof of existence of the quasi-static solution under no hypothesis of spatial homogeneity.

In Chapter 3, we propose a formal description of the multiscale PDE-*NTM* problem for Tau to gain a precise definition of the mass exchange between edges and nodes of the *connectivity* graph. This approach enables us to improve the results of Chapter 1 and consider the case of time-varying coefficients in the edge advection-diffusion equations. By recapitulating the correct, but highly complex, node mass balance in the case of time-dependent parameters we couple the Tau and Beta Amyloid systems by assuming that Beta Amyloid oligomers enhance soluble Tau aggregation and diffusion. Chapter 3 provides a well-posedness argument for the resulting coupled system.

We conclude the Thesis with Chapter 4, where we present a new version of the *NTM* by introducing the Release and Uptake (*RU*) process for soluble misfolded Tau. The novelty of this model is the inclusion of extracellular Tau species along the nodes of the *connectivity* graph. This localisation enables us to mathematically define Release and Uptake of soluble Tau through boundary conditions of Neumann-Robin type along the edges. The formal tools developed in Chapter 3 are adopted to show that in the *RU-NTM* case, under the hypothesis of slow Release-Uptake, the effective flux at each node is solely determined by the incoming fluxes along the edges incident to the node, therefore the model significantly simplifies the *NTM* in Chapter 3 as it does not exhibit any *feedback* phenomena. In addition, the setting is biologically more feasible than the original *NTM* since it eventually allows the introduction of the complex theme of neuroinflammation and microglia activation, which involves both extracellular Tau and Beta Amyloid.

In Chapter 4, we couple the *RU-NTM* with the Beta Amyloid model in Chapter 2 in a bidirectional way and provide a well-posedness proof for the global system.

The material of Chapter 1 was recently published in [11] and several other publications are in preparation. The modelling and simulations of the *Release-Uptake NTM* (without Aβ) will be contained in a preprint which is about to be finished. The mathematical contents of Chapters 2 and 3 will be combined in a future publication, with particular emphasis on the formal derivation of the correct mass balance of Tau between the edges and nodes of the *connectivity* graph. Also the mathematical well-posedness of the Release-Uptake model (with Aβ) will be treated in a future publication.

Beyond the material discussed in the Thesis, a publication is in preparation on the application of machine learning models to approximate the computationally expensive calculation of the edge fluxes for the *NTM* discussed in Chapter 1, an issue which is important for effective parameter fitting with experimental data. In addition a preprint ([69]) on network advection-reaction-diffusion models has recently appeared, where the original *NTM* is formulated in a general framework to account for multiple species and reaction-advection processes, together with some relevant case studies which require minimal computational efforts for the calculation of the edge fluxes.

Chapter 1

A Network Transport Model of Tau progression

In this chapter we analyse a quasi-static model on a directed graph to describe the spread and aggregation of intracellular toxic Tau proteins in the Alzheimer's brain. This Network Transport Model *(NTM)* was recently proposed in [91] and extends an earlier model on single edges, introduced in [92], to the entire *connectivity* graph. We review the model, including the approximation of the correct mass balance of Tau between nodes and edges, and show that the *NTM* is mathematically well-posed.

The results presented in this Chapter were recently discussed in [11].

1.1 Introduction and biological setting

The network of neuron cells is modelled by a graph $G_c = (V, E)$, where the edges in E represent white matter tracts and the nodes in V gray matter regions. More precisely, G_c is a weighted, directed and connected graph with a finite number h of nodes $P_i \in V$ and edges $e_{ij} \in E$. We denote by $e_{ij} \in E$ the edge directed from $P_i \in V$ to $P_j \in V$. We often refer to the existence of an edge between nodes P_i and P_j $-$ either directed from P_i to P_j or vice versa $-$ with the notation $P_i \sim P_j$, or alternatively $i \sim j$.

It follows from the biological interpretation of G_c that the graph has no loops, in other words if $e_{ij} \in E$ then $i \neq j$. The network is endowed with a weight function c which satisfies

$$c(P_i, P_j) = \begin{cases} c_{ij} > 0 & \text{if } e_{ij} \in E \\ 0 & \text{otherwise.} \end{cases} \tag{1.1}$$

The connectivity weights c_{ij} express the strength of the connection between the i-th and j-th brain compartment. In a directed graph the weight function is not required to be symmetric, so the weights c_{ij} and c_{ji} may be different. Both the gray matter regions and the connectivity weights can be chosen according to available experimental data (so-called "connectivity atlasses") in human or mouse brains.

In vitro and *in vivo* evidence suggests that Tau predominantly migrates trans-synaptically, while white matter tracts between regions serve as the conduits for the transmission of Tau from affected to unaffected regions [24], [53], [60], [95]. The main trend in the reference literature is to describe trans-synaptic Tau spread through "graph diffusion models": given an initial distribution of regional pathology in the brain, the diffusion process is governed by the concentration gradients and connectivity weights between all region pairs and it is modelled by means of the Graph Laplacian matrix. The so-called Network Diffusion Model was introduced in [74], and several examples of subsequent connectome-based spread models can be found in [13], [32], [50], [79], [97], [98]. Graph diffusion models have been shown to be robust in predicting important patterns of disease propagation as the canonical Braak staging of *AD* [97], [98] and the pathology progression in human subjects [75], [76], [79], but they lack of adequate sophistication to fully capture the more complex mechanisms of Tau spreading. Indeed, in addition to pure diffusion, Tau propagation is also governed by active transport via molecular motors attached to microtubules in either *anterograde* (i.e., with axon polarity) or *retrograde* (i.e., against axon polarity) directions [7], [27], [77], [83], [102], resulting in distinct directional patterns of Tau deposition. The first attempt to model axonal-Tau transport within a two-neuron system was developed in [92], where it was shown that the emergence of net retrograde directionality in pathological Tau transmission can be explained via its interaction with transport kinetics.

Here we present the Network Transport Model (*NTM*) as a natural extension of the single-edge model in [92] to a macroscopic model on the entire network. With respect to existing models for neurodegenerative disease, *NTM* aims at accommodating two main empirical evidences: directional tau transport [27], [59], [77], [83] and the occurrence of tau pathology into brain-wide circuits at a much slower time scale than its kinetic and transmission processes. Thus, the main innovations of the *NTM* consist in its quasi-static character to handle different time scales and in modelling active transport processes on the brain network in addition to passive diffusion, in contrast with the usual simplification in the reference literature to model tau spreading as a passive graph diffusion between nodes. This topic needs to be addressed from two different perspectives. The first issue concerns diffusive spatial operators acting on the nodes of a graph. The formal action of the aforementioned Graph Laplacian matrix L resembles the second order central finite difference scheme for the approximation of the second order derivative at each node. For example, consider the undirected finite *path graph* defined as

$$G_c = (V, E), \quad V = \{1, 2, \dots, N\}, \quad N \in \mathbb{N}, \quad E = \{\{n, n+1\} : n \in \{1, \dots, N-1\}\}$$

with constant weights $c(m, n) = c$ for all $\{m, n\} \in E$ and a function $u : V \longrightarrow \mathbb{R}$. A straightforward calculation yields

$$Lu(i) = \sum_{j \sim i} c_{ij}(u(j) - u(i)) = c\left(u(i-1) - 2u(i) + u(i+1)\right), \quad i \in \{2, \dots, N-1\}$$

which corresponds to (up to a constant) the central finite difference formula approximating the second order derivative of u at node i on a homogeneous spatial grid. This property suggests a diffusion-like behaviour of L on G_c. It is clear though that this kind of property is strictly related to the topology of the underlying graph. For example, as discussed in [8], if we consider the following infinite directed network

$$G_c = (V, E), \quad V = \mathbb{Z}, \quad E = \{(n, n+1) : n \in \mathbb{Z}\} \tag{1.2}$$

with constant weights $c(m, n) = c$ for all $(m, n) \in E$, the corresponding out-degree Graph Laplacian acts in the following advective manner

$$Lu(i) = c\left(u(i) - u(i-1)\right). \tag{1.3}$$

Although the directed infinite *path graph* is an extremely pathological setting, this observation suggests the need to investigate the topology of the network and the actual diffusivity of the resulting dynamics. The second controversy regarding the use of the Graph Laplacian is the issue of defining its weights. As discussed in [73], given the length of the connections between nodes, the choice of the spatial operator exhibits a degree of freedom in the definition of the diffusion weights. This kind of arbitrariness poses a crucial modelling problem because different selections have been shown to produce different outputs with respect to clinical data [15]. In view of these limitations, we propose an alternative approach by modelling the diffusion and advection mechanisms occurring along the edges of the graph. Then, by extracting the fluxes of soluble Tau on the node-edge boundary, we obtain a precise and physical description of the mass flow between nodes as a function of the edge parameters.

The novelty of the model presented in [92] is the introduction of an advection term with transport velocity depending on the concentration of soluble and insoluble toxic Tau. The justification for this choice relies on some evidence regarding the reciprocal influence of Tau on axonal transport. Once misfolded, axonal Tau protein aggregates along the axon and migrates towards the somatodentritic compartment [7], [17], [102]. At this stage, recent foundings suggest that Microtubule-associated Tau protein might be involved in the establishment and maintenance of neuronal polarity [100]. Specifically, this leads to the hypotheses that axonal transport plays a role in the development of neurological diseases. Communication between neural cells and presynaptic areas is established through the transport of essential molecules such as vesicles, ion channels and signaling molecules [84]. These structures are associated with vital functions such as synaptic plasticity and neurotransmission. On the other hand, accumulating evidence suggests that some of the molecules affecting axonal transport processes also participate in the progression of neuronal diseases. This association may indicate a role of axonal transport failure in neurodegeneration. Effectively, in vitro experiments show that Microtubule-associated Tau controls motor protein–driven transport along microtubules by obstructing kinesin-1, an anterograde intracellular motor-protein, at physiological levels [22], [30]. In the disease stage, aberrant Tau has been shown to reduce the inhibition of kinesin-1 [27] [78] [83], whereas neurofibrillary tangles (NFT) are associated with a reduction of kinesin-1 [82]. The ultimate dominance of either retrograde or anterograde directed motor proteins determines the direction of axonal transport [22], [78], [94], therefore the advection velocity along the two-neurons connection is defined as a function of soluble and insoluble toxic Tau. In particular, the full *NTM* contains a transport-reaction PDE on the edges which represents the dynamics of soluble and insoluble Tau within white matter tracts. The Tau dynamics in the gray matter regions is modelled by a system of ordinary differential equations at the nodes of the graph. The resulting spatio-temporal evolution relies both on the underlying graph topology and the physical rates of diffusion and advection happening on the microscopical scale of the edges. As previously stated, the *NTM* characterizes macroscopic tauopathy dynamics in terms of the microscopic properties of soluble and insoluble Tau species and their active transport along axons.

We then introduce the quasi-static approximation of the full *NTM*, where the fast timescale is treated as instantaneous in the slow timescale. This implies that the evolutionary PDE on the edges becomes a steady state equation, i.e. a 1D elliptic equation. The presence of an elliptic equation on the edge is a mathematical novelty, and the most delicate point in the quasi-static model is the correct description of the mass balance of Tau between edges and vertices.

This chapter is devoted to provide a first approximation of the local mass balance at node levels. The key Ansatz of this work is the assumption that a change in Tau concentration at node i induces a perturbation of the edge mass that is localised near the node and does not affect the neighbouring vertices. This local character is then implicitly inherited by the definition of the spatial operator acting on the nodes. The purpose of this Chapter is to introduce the theoretical quasi-static framework to describe the local mass balance problem and provide a systematic analytical well-posedness argument. In Chapter 3 we improve the approximation for the mass balance and adopt this analytical method to prove well-posedness for the complete system.

Proofs are elementary, but address a few non-trivial issues. The Ansatz of quasi-stationarity simplifies the full *NTM* (also computationally, which was important to obtain the results in [91]) and essentially eliminates the equations for insoluble Tau. However, as we shall see below, the elimination of insoluble

Tau generically creates a singularity in the nonlinear equation for soluble Tau and this complicates the analysis of the resulting (possibly singular) stationary transport-diffusion equation on the edges. Secondly, quasi-stationarity on the edges implies that initial conditions should be only prescribed for soluble Tau at the vertices. Unfortunately, initial sub-criticality of soluble Tau at the vertices does not guarantee global well-posedness of the problem, so we must restrict the admissible initial conditions. We shall show that the correct initial conditions can be completely explained in terms of *finite* total mass of Tau at time $t = 0$. The quasi-static *NTM* for Tau is only a first step towards a realistic quantitative model for *AD* which, among other things, should provide a more precise mathematical description of the *feedback* mechanism governing the local mass balance, i.e. recover an accurate network spatial operator, and should take into account the role of toxic Aβ protein in *AD*.

1.2 The model

Let G_c be the *structural connectivity graph* described in the Introduction, a weighted, directed, strongly connected graph with a finite number h of nodes P_i. The edges e_{ij} ($i \neq j$) are directed from vertex P_i to P_j, and the connectivity weights c_{ij} express the strength of the connection between the brain compartments P_i and P_j (see (1.1)). If $c_{ij} > 0$, the edge e_{ij} represents a bundle of connected neurons with independent Tau dynamics and the weight c_{ij} is proportional to the number of axons belonging to the bundle, which is related to the diameter of its cross section [74], [91], [97]. Therefore the mass flow of soluble Tau at each vertex-edge boundary is determined by the single-axon flux multiplied by c_{ij}.

Below we formulate both the full *NTM* on G_c and its quasi-static approximation. Let $t > 0$ indicate the *slow timescale*, typical for the progression of the disease, and let $M_i(t)$ and $N_i(t)$ denote the densities (mass per unit volume) of insoluble and soluble pathological Tau, respectively, at node P_i. Finally, if $c_{ij} > 0$ we denote by $m_{ij}(x, t)$ and $n_{ij}(x, t)$ the densities per unit volume of insoluble and soluble pathological Tau, respectively, at the edge e_{ij}. Whenever there is no ambiguity in the formulas, we shall omit the condition $c_{ij} > 0$, meaning that $e_{ij} \in E \iff c_{ij} > 0$.

1.2.1 The full Network Transport Model

We summarize the microscopic model for the axonal transport dynamics of pathological Tau on the edges, developed by Torok *et al.* [92], where, in addition to passive diffusion, an active transport mechanism has been introduced to describe directionally biased spreading of pathological Tau. To model the single-axon dynamics on e_{ij} we describe the position within a two-neuron system by a 1D variable $x \in [0, L]$, where L is the length of the neuron bundle. For simplicity we assume that L does not depend on i and j: mathematically this is justified by the fact that our results and proofs are independent of this assumption; in addition, as was explained in [91], biologically the simplification is reasonable if one considers mice brains. Identifying the vertices P_i and P_j by $x = 0$ and $x = L$, respectively, we distinguish five segments, which represent biological compartments with distinct Tau dynamics:

- **Presyn. SD**: presynaptic somatodendritic compartment, $(0, x_1)$,
- **AIS**: axon initial segment, (x_1, x_2),
- **Axon**: axonal component, (x_2, x_3),
- **SC**: synaptic cleft, (x_3, x_4),
- **Postsyn. SD**: postsynaptic somatodendritic compartment, (x_4, L).

The governing equations of the single axon dynamics of pathological Tau are: for all $t > 0$

$$\begin{cases} \phi(m_{ij})_t = -\Gamma(m_{ij}, n_{ij}) & \text{in } (0,L) \setminus (x_3, x_4) \\ m_{ij} = 0 & \text{in } (x_3, x_4) \\ \phi(n_{ij})_t = (a(x)(n_{ij})_x - Q(x, m_{ij}, n_{ij}))_x + \Gamma(m_{ij}, n_{ij}) & \text{in } (0,L), \end{cases} \tag{1.4}$$

where $\phi > 0$ is a small constant which represents the proportion between the slow and fast timescale,

$$Q(x,m,n) = \begin{cases} (1-f)v(m,n)n & \text{if } x \in (x_2, x_3) \\ 0 & \text{otherwise,} \end{cases} \qquad a(x) = \begin{cases} D & \text{if } x \in (0, x_1) \cup (x_4, L) \\ D\lambda_1 & \text{if } x \in (x_1, x_2) \\ fD & \text{if } x \in (x_2, x_3) \\ D\lambda_2 & \text{if } x \in (x_3, x_4) \end{cases} \tag{1.5}$$

and

$$\Gamma(m,n) = \beta m - \gamma_1 n^2 - \gamma_2 nm. \tag{1.6}$$

Here, $\pm\Gamma$ are relatively simple reaction terms taking into account aggregation and fragmentation processes. The terms $a(x)(n_{ij})_x$ and $v(m,n)n$ are diffusive and advective fluxes of n_{ij}, with coefficients expressed in the fast timescale. Since insoluble aggregates do not move, the diffusive and active transport flux of m is defined to be 0. The parameter $f \in [0,1]$ is the average fraction of soluble pathological Tau that is undergoing diffusion as opposed to active transport at any given time [27], [57], and $\lambda_1, \lambda_2 \in (0,1)$ are the reductions of diffusivity in the AIS and the SC, respectively. We consider two model cases for the velocity $v(m,n)$,

$$v(m,n) = v_a e^{\delta n - \varepsilon m} - v_r \tag{1.7}$$

and

$$v(m,n) = v_a(1 + \delta n)(1 - \varepsilon m) - v_r, \tag{1.8}$$

where the constants $v_a, v_r > 0$ are the baseline anterograde and retrograde velocities of Tau, respectively; the parameters $\delta, \epsilon > 0$ modulate the interactions between pathological Tau and the molecular motors of the axon.

The equations (1.4) on the edges are completed by requiring continuity of the density of soluble Tau at the edge-node boundaries:

$$n_{ij}(0,t) = N_i(t), \qquad n_{ij}(L,t) = N_j(t). \tag{1.9}$$

To take into account the mass balance of soluble Tau at a vertex P_i, we define the fluxes of soluble Tau at the neuron-edge boundary P_i for all neurons belonging to e_{ij} and e_{ji}:

$$J^{\phi}_{ij}(i,t) = -D(n_{ij})_x(0,t), \qquad J^{\phi}_{ji}(i,t) = -D(n_{ji})_x(L,t). \tag{1.10}$$

We define the total mass of Tau on e_{ij} at time t as

$$c_{ij} \int_0^L (m_{ij}(x,t) + n_{ij}(x,t)) \, dx. \tag{1.11}$$

This leads to the following equations for $M_i(t)$ and $N_i(t)$ at P_i:

$$\begin{cases} \phi\, M_i' = -\Gamma(M_i, N_i) \\ \phi\, N_i' = \frac{1}{V_i} \underbrace{\sum_{j \neq i} \left(-c_{ij} J^{\phi}_{ij}(i,t) + c_{ji} J^{\phi}_{ji}(i,t) \right)}_{\text{incoming mass flow at compartment } P_i} + \Gamma(M_i, N_i). \end{cases} \tag{1.12}$$

Here N_i' and M_i' denote derivatives with respect to t, the reaction term Γ is defined by (1.6), and V_i is the volume of the brain compartment P_i. For convenience of the reader, we summarize the parameters of the *NTM* in table 1.1.

Different choices of the reaction term would have been possible. Here, we distinguish between soluble and insoluble Tau since they are very different Tau species and are involved in distinct biological processes. It would have been possible to make a finer distinction of tau polimers by their size leading to more complex reaction terms than Γ, such as Smoluchowski type terms. However, we have chosen the simplest reaction term allowing us to model interconversion between soluble and insoluble Tau, since we prefer to focus on the two major novelties of the model, i.e., the quasi-static approach introduced below to handle the quite different timescales and the transport mechanism on the edges.

In conclusion, the full *NTM* is described by equations (1.4), (1.9) and (1.12), completed by biologically plausible initial conditions for $M_i(0)$, $N_i(0)$, $m_{ij}(x, 0)$ and $n_{ij}(x, 0)$.

Symbol	**Description**	**Remark**
$D*$	Theoretical diffusivity of n	Estimated to be 12 μm^2/s
$f*$	Diffusing fraction of n	Estimated to be 0.92
v_a*	Native ant. transport velocity of n	Estimated to be 0.7 μm/s
v_r*	Native ret. transport velocity of n	Estimated to be 0.7 μm/s
β	Fragmentation rate of m, M	Unimolecular process by which $m \to n$, $M \to N$
γ_1	Aggregation rate: $n + n$, $N + N$	Bimolecular process by which $n \to m$, $N \to M$
γ_2	Aggregation rate: $n + m$, $N + N$	Bimolecular process by which $n \to m$, $N \to M$
δ	Ant. vel. enhancement factor	Effect modulated by n
ϵ	Ret. vel. enhancement factor	Effect modulated by m
λ_1	Diffusivity barrier, AIS	Reduces the rate of diffusion within AIS
λ_2	Diffusivity barrier, SC	Reduces the rate of diffusion within the SC
$c_{ij^{**}}$	Connectivity weight	Strength of the connections between i and j brain's parcels
$V_{i^{**}}$	Volume	Volume of the ith brain's parcel

Table 1.1: Glossary of symbols for the *NTM*, adapted from [92]. The values marked with an asterisk were estimated from previous experimentally derived values [57]. The parameters marked with double asterisk describe the structure of the brain and can be retrieved from available experimental data (i.e, the "connectivity atlasses"). For simplicity, the parameters not marked with a double asterisk are modelled as global, regionally invariant constants. Ant. = anterograde, ret. = retrograde, conc. = concentration, vel. = velocity., AIS = axon initial segment, SC = synaptic cleft.

1.2.2 The quasi-static Network Transport Model

Since ϕ is a small number, it is natural to approximate the full *NTM* by considering processes in the fast time scale as instantaneous in the slow time scale. So the approximating problem will be formulated in the slow time scale. In particular, fluxes on edges will be expressed in the slow time case and, from now on, the diffusion coefficient D (in (1.5)) and the velocities v_a and v_r (in (1.7) e (1.8)) are always assumed to be given in the slow time scale (in other words, the coefficients in the fast scale are divided by ϕ).

In this approximation, problem (1.4)-(1.9) formally becomes

$$\text{for all } t \geq 0: \qquad \begin{cases} m_{ij} = g(n_{ij}) & \text{in } (0,L) \setminus (x_3, x_4) \\ m_{ij} = 0 & \text{in } (x_3, x_4) \\ \left(a(x)(n_{ij})_x + h(x, n_{ij})\right)_x = 0 & \text{in } (0,L) \\ n_{ij}(0,t) = N_i(t), \quad n_{ij}(L,t) = N_j(t). \end{cases} \tag{1.13}$$

Here $Q(x,m,n)$ and $a(x)$ are defined as in (1.5) and

$$h(x,n) = -Q(x, g(n), n), \tag{1.14}$$

where $g(n)$ is determined by $\Gamma(g(n), n) = 0$:

$$g(n) = \frac{\gamma_1 n^2}{\beta - \gamma_2 n} \;\Leftrightarrow\; \Gamma(g(n), n) = 0. \tag{1.15}$$

In problem (1.13) $t \geq 0$ plays the role of a parameter. In view of the elliptic equation for n_{ij} in (1.13),

$$J_{ij}(t) := -\left(a(x)(n_{ij})_x + h(x, n_{ij})\right) \tag{1.16}$$

is constant along the edge and only depends on time.

More precisely, in the slow time scale t of the network dynamics, m_{ij} and n_{ij} are quasi-static distributions on the edge, which are supposed to be reached instantaneously. Similarly, we approximate the equations (1.12) in the nodes. The first equation, for $M_i(t)$, is approximated by $\Gamma(M_i, N_i) = 0$: $M_i = g(N_i)$. Therefore also in the second equation of (1.12), for $N_i(t)$, the reaction Γ disappears in the approximation. To recover the approximated equation for N_i we need to examine the global mass balance of the system. The full *NTM* does not allow mass loss or production, hence as we shall see in Section 1.4 the system is closed and the total mass $\mathcal{M}(t)$ satisfies

$$\mathcal{M}(t) := \underbrace{\sum_i V_i(M_i(t) + N_i(t))}_{\text{Total Node Mass}} + \underbrace{\sum_i \sum_{j \neq i} \int_0^L c_{ij}(n_{ij}(x,t) + m_{ij}(x,t))\, dx}_{\text{Total Edge Mass}}, \tag{1.17}$$

$$\mathcal{M}'(t) = 0 \text{ for all } t \geq 0. \tag{1.18}$$

This key relationship implies that to ensure an effective mass exchange between the set of nodes and edges, i.e. that the total edge mass is not constant in time, the mass balances between the brain compartments P_i and P_j and the edges e_{ij} and e_{ji} should contain two contributions: (i) the constant mass fluxes entering P_i and P_j (see (1.16)) and (ii) a *feedback* mechanism due the change of the Dirichlet conditions $N_i(t)$ and $N_j(t)$ for n_{ij} and n_{ji} (see (1.9)), which causes a change of the total mass on the edges e_{ij} and e_{ji} that must be compensated by a change of the total mass at P_i and P_j. The resulting mass balance at node P_i takes the following form:

$$\underbrace{V_i(N_i'(t) + M_i'(t))}_{\text{Mass increase at } P_i} = \underbrace{\sum_j \left(c_{ji} J_{ji}(t) - c_{ij} J_{ij}(t)\right)}_{\text{Incoming Mass Flow at } P_i} \; - \underbrace{\mathcal{F}_i(\boldsymbol{N}, \boldsymbol{N}', \boldsymbol{n}, \partial_t \boldsymbol{n})}_{\text{Feedback Mechanism}} \tag{1.19}$$

where

$$\boldsymbol{N} : \mathbb{R}^+ \mapsto \mathbb{R}^h$$

is the vector of Tau concentration on the nodes and

$$\boldsymbol{n} : [0, L] \times \mathbb{R}^+ \mapsto \mathbb{R}^{|E|}$$

is the vector of Tau concentration on the edges. In this setting, the main modelling issue is to determine the expression of the *feedback* mechanism $\mathcal{F}_i$ at node P_i. By (1.18), the function $\mathcal{F}$ satisfies the following condition

$$\sum_{i=1}^{h} \mathcal{F}_i = \frac{d}{dt} \sum_{i=1}^{h} \sum_{j \neq i} \int_0^L c_{ij}(n_{ij}(x,t) + m_{ij}(x,t))\, dx \tag{1.20}$$

which describes the global effect of the *feedback* mechanism on the entire set of edges. As we shall see below (see (1.28) and (1.29), the rates of change of the total Tau mass on both e_{ij} and e_{ji} are well-defined and depend linearly on $N_i'(t)$ e $N_i'(t)$. Unfortunately this information is not enough to determine which part of these rates of mass change must be compensated by the mass balances at P_i and which part by the mass balances at P_j, which leaves an undetermined degree of freedom for the definition of $\mathcal{F}_i$ in (1.19), i.e. for the evolution of the total Tau mass at P_i and P_j. We shall come back to this fundamental question in Chapter 3, where we consider the full multi-scale PDE problem. In the present Chapter we make, as a first step, the Ansatz that the *feedback* mechanism in P_i is local, in the sense that it depends only on the variation $N_i'(t)$ and not on $N_j'(t)$. This assumption translates into

$$\mathcal{F}_i(\boldsymbol{N}, \boldsymbol{N}', \boldsymbol{n}, \partial_t \boldsymbol{n}) = \mathcal{F}_i(N_i, N_j, N_i', n_{ij}, n_{ji}) \quad \text{for } j \sim i. \tag{1.21}$$

Using the linearity in $N_i'(t)$, this leads to the following evolution equation for Tau at the compartment P_i:

$$\underbrace{V_i(N_i'(t) + M_i'(t))}_{\text{Mass increase at } P_i} = \underbrace{\sum_j (c_{ji} J_{ji}(t) - c_{ij} J_{ij}(t))}_{\text{Incoming Mass Flow at } P_i} - \underbrace{\sum_j (C_{ij}^i(t) + C_{ji}^i(t)) N_i'(t)}_{\text{Feedback Mechanism}}. \tag{1.22}$$

Section 1.2.3 is devoted to a formal justification of this Ansatz. In addition, we observe that in the setting of the PDE *NTM* the total mass balance and the structure of equations (1.4) yield the node system (1.12), hence the *feedback* mechanism is implicitly encapsulated in the incoming flux of soluble Tau on the edges.

1.2.3 The Ansatz

Setting $q_{ij} = (n_{ij})_t$, the rate of change of the total mass on e_{ij} (see also (1.11)) is given by

$$c_{ij} \int_0^L (n_{ij} + m_{ij})_t(x,t)\, dx \tag{1.23}$$

$$= c_{ij} \left(\int_0^L q_{ij}(x,t)\, dx + \int_{(0,x_3)\cup(x_4,L)} \frac{\gamma_1 n_{ij}(2\beta - \gamma_2 n_{ij})}{(\beta - \gamma_2 n_{ij})^2} q_{ij}(x,t)\, dx \right). \tag{1.24}$$

Recalling that $n_{ij}(t)$ satisfies (1.13), we obtain that $q_{ij}(t)$ satisfies the linear problem

$$\begin{cases} \left(a(x)(q_{ij})_x + \frac{\partial h(x, n_{ij})}{\partial n} q_{ij} \right)_x = 0 & \text{in } (0, L) \\ q_{ij}(0,t) = N_i'(t), \quad q_{ij}(L,t) = N_j'(t). \end{cases} \tag{1.25}$$

The linearity of the equation makes it possible to decompose q_{ij} in the following form:

$$q_{ij}(x,t) = N_i'(t)q_{ij}^i(x,t) + N_j'(t)q_{ij}^j(x,t), \tag{1.26}$$

where, for all fixed t, the functions $q_{ij}^i(x,t)$ and $q_{ij}^j(x,t)$ satisfy, respectively,

$$\begin{cases} \left(a(x)(q_{ij}^i)_x + \frac{\partial h(x,n_{ij})}{\partial n} q_{ij}^i\right)_x = 0 & \text{in } (0,L) \\ q_{ij}^i(0,t) = 1, \quad q_{ij}^i(L,t) = 0, \end{cases} \qquad \begin{cases} \left(a(x)(q_{ij}^j)_x + \frac{\partial h(x,n_{ij})}{\partial n} q_{ij}^j\right)_x = 0 & \text{in } (0,L) \\ q_{ij}^j(0,t) = 0, \quad q_{ij}^j(L,t) = 1. \end{cases} \tag{1.27}$$

Hence (1.23) becomes

$$\begin{aligned} c_{ij}&\int_0^L (n_{ij} + m_{ij})_t(x,t)\,dx \\ &= c_{ij}N_i'(t)\left(\int_0^L q_{ij}^i(x,t)\,dx + \int_{(0,x_3)\cup(x_4,L)} \frac{\gamma_1 n_{ij}(2\beta - \gamma_2 n_{ij})}{(\beta - \gamma_2 n_{ij})^2} q_{ij}^i(x,t)\,dx\right) \\ &\quad + c_{ij}N_j'(t)\left(\int_0^L q_{ij}^j(x,t)\,dx + \int_{(0,x_3)\cup(x_4,L)} \frac{\gamma_1 n_{ij}(2\beta - \gamma_2 n_{ij})}{(\beta - \gamma_2 n_{ij})^2} q_{ij}^j(x,t)\,dx\right). \end{aligned} \tag{1.28}$$

Similarly, the rate of mass change on e_{ji} is given by

$$\begin{aligned} c_{ji}&\int_0^L (n_{ji} + m_{ji})_t(x,t)\,dx \\ &= c_{ji}N_j'(t)\left(\int_0^L q_{ji}^j(x,t)\,dx + \int_{(0,x_3)\cup(x_4,L)} \frac{\gamma_1 n_{ji}(2\beta - \gamma_2 n_{ji})}{(\beta - \gamma_2 n_{ji})^2} q_{ji}^j(x,t)\,dx\right) \\ &\quad + c_{ji}N_i'(t)\left(\int_0^L q_{ji}^i(x,t)\,dx + \int_{(0,x_3)\cup(x_4,L)} \frac{\gamma_1 n_{ji}(2\beta - \gamma_2 n_{ji})}{(\beta - \gamma_2 n_{ji})^2} q_{ji}^i(x,t)\,dx\right). \end{aligned} \tag{1.29}$$

The linear structure of problem (1.25) leads to the Ansatz that the local mass balance at vertex P_i only concerns the contributions coming from the terms q_{ij}^i and q_{ji}^i, and not those from q_{ij}^j and q_{ji}^j. Therefore we interpret (1.26) as separated into two terms:

$$q_{ij}(x,t) = \underbrace{N_i'(t)q_{ij}^i(x,t)}_{\text{Mass variation contribute at node } i} + \underbrace{N_j'(t)q_{ij}^j(x,t)}_{\text{Mass variation contribute at node } j} \tag{1.30}$$

which suggests to define, in (1.22),

$$C_{ij}^i(t) = c_{ij}\left(\int_0^L q_{ij}^i(x,t)\,dx + \int_{(0,x_3)\cup(x_4,L)} \frac{\gamma_1 n_{ij}(2\beta - \gamma_2 n_{ij})}{(\beta - \gamma_2 n_{ij})^2} q_{ij}^i(x,t)\,dx\right) \tag{1.31}$$

$$C_{ji}^i(t) = c_{ji}\left(\int_0^L q_{ji}^i(x,t)\,dx + \int_{(0,x_3)\cup(x_4,L)} \frac{\gamma_1 n_{ji}(2\beta - \gamma_2 n_{ji})}{(\beta - \gamma_2 n_{ji})^2} q_{ji}^i(x,t)\,dx\right). \tag{1.32}$$

Summarizing, the quasi-static *NTM* consists of the edge equations (1.13), the node system

$$\begin{cases} M_i = g(N_i) \\ \left(V_i\left(1 + \frac{\gamma_1 N_i(2\beta - \gamma_2 N_i)}{(\beta - \gamma_2 N_i)^2}\right) + \sum_j \left(C_{ij}^i + C_{ji}^i\right)\right) N_i' = \sum_j \left(c_{ji}J_{ji} - c_{ij}J_{ij}\right) \end{cases} \qquad \text{for } t \geq 0,$$

and a given initial condition for N_i at each node P_i:

$$N_i(0) = N_{0i}, \quad \text{where} \begin{cases} 0 \le N_{0i} < \frac{\beta}{\gamma_2} & \text{if } \gamma_2 > 0 \\ N_{0i} \ge 0 & \text{if } \gamma_2 = 0. \end{cases}$$

The initial condition needs some additional explanation. If $\gamma_2 > 0$, the constraint that $N_{0i} < \frac{\beta}{\gamma_2}$ follows naturally from the singularity of the function g in (1.15). Given $N_i(0) = N_{0i}$, we obtain that $M_i(0) = g(N_{0i})$. In addition we would like to use (1.13) at $t = 0$ to define the pair of nonnegative initial functions $(m_{ij}(x,0), n_{ij}(x,0))$ on the edge e_{ij}. If $\gamma_2 = 0$, the pair $(m_{ij}(x,0), n_{ij}(x,0))$ turns out to be uniquely defined, but if $\gamma_2 > 0$, we need an additional smallness condition on N_{0i} to ensure that (1.13) at $t = 0$ has a unique steady state which satisfies

$$0 \le n_{ij}(x,0) < \tfrac{\beta}{\gamma_2}, \quad 0 \le m_{ij}(x,0) < \infty.$$

More precisely, if $\gamma_2 > 0$ and N_{0i} and N_{0j} are "too close" to β/γ_2 at two connected vertices P_i and P_j, then such a subcritical steady state does not exist (see Remark 1.4.1). We shall see that the latter phenomenon is physically equivalent to the occurrence of infinite total initial mass on the edge.

So we may formulate the additional condition on N_{0i} as follows: if $\gamma_2 > 0$ we require that the values N_{0i} are such that initially, at $t = 0$, each edge problem (1.13) with $c_{ij} > 0$ has a solution with finite initial mass. Such condition is difficult to characterize analytically, on the other hand it is very natural and can be easily checked computationally. The main result in Section 1.3 essentially states that the additional smallness condition on N_{0i} implies well-posedness of the quasi-static problem: once the total mass at vertices and edges is initially finite, there exist uniquely defined functions $N_i(t)$, $M_i(t)$, $n_{ij}(x,t)$ and $m_{ij}(x,t)$ ($t \ge 0$, $0 \le x \le L$) which solve the quasi-static *NTM* and satisfy $0 \le N_i(t)$, $n_{ij}(x,t) < \beta/\gamma_2$.

1.3 The main result

We recall the quasi-static *NTM* which we consider. For notations we refer to the previous sections. The equations for the concentrations of insoluble and soluble Tau at the nodes of the graph, M_i and N_i, are

$$\begin{cases} M_i = g(N_i) \\ \left(V_i \left(1 + \frac{\gamma_1 N_i (2\beta - \gamma_2 N_i)}{(\beta - \gamma_2 N_i)^2} \right) + \sum_j \left(C^i_{ij} + C^i_{ji} \right) \right) N_i' = \sum_j \left(c_{ji} J_{ji} - c_{ij} J_{ij} \right), \end{cases} \quad \text{for } t \ge 0, \tag{1.33}$$

with a given initial condition for N_i at each node P_i:

$$N_i(0) = N_{0i}, \quad \text{where} \begin{cases} 0 \le N_{0i} < \frac{\beta}{\gamma_2} & \text{if } \gamma_2 > 0 \\ N_{0i} \ge 0 & \text{if } \gamma_2 = 0. \end{cases} \tag{1.34}$$

The RHS of $(1.33)_2$ expresses the incoming mass flow at node i, and J_{ij}, a function of t only, is determined by a system for insoluble and soluble Tau, m_{ij} and n_{ij}, on the edge e_{ij} ($j \ne i$): $J_{ij}(t) = -\left(a(x)(n_{ij})_x + h(x, n_{ij}) \right)_x$, where

$$\text{for all } t \ge 0: \quad \begin{cases} m_{ij} = g(n_{ij}) & \text{in } (0,L) \setminus (x_3, x_4) \\ m_{ij} = 0 & \text{in } (x_3, x_4) \\ \left(a(x)(n_{ij})_x + h(x, n_{ij}) \right)_x = 0 & \text{in } (0,L) \\ n_{ij}(0,t) = N_i(t), \quad n_{ij}(L,t) = N_j(t). \end{cases} \tag{1.35}$$

The LHS of $(1.33)_2$ expresses the rate of change of total Tau-mass at node i by assuming the local Ansatz introduced in Sections 1.2.2 and 1.2.3. Here the terms with C^i_{ij} and C^i_{ji} describe a *feedback* mechanism due to the rate of change of N_i at node i (since N_i is a boundary condition for n_{ij}, a change in N_i causes an instantaneous modification of the total Tau-mass on the edges connected with node i). The analytical expression of $C^i_{ij}(t)$ and $C^i_{ji}(t)$ are integrals in terms of $\frac{\partial}{\partial t}n_{ij}$, specified in (1.31) and (1.32).

So the mathematical problem is to face the nontrivial coupling of the system of ODEs, (1.33), for the concentrations at the nodes, to a quasi-static elliptic reaction-diffusion-transport problem, (1.35), for the concentrations on the incoming edges.

Before stating the main result we define what we mean by a solution of the quasi-static *NTM*. Again we refer to the previous sections for notations.

Definition 1.3.1. *Let $1 \le i, j \le h$. Let, for all i,*

$$N_{i0} \in [0, \tfrac{\beta}{\gamma_2}),\;\; N_i \in C^1\left([0,\infty); [0, \tfrac{\beta}{\gamma_2})\right),\;\; M_i \in C^1\left([0,\infty); [0,\infty)\right)$$

and, for all $i \neq j$ such that $c_{ij} > 0$,

$$n_{ij} \in C\left([0,L]\times[0,\infty); [0,\infty)\right),\;\; m_{ij} \in L^\infty\left([0,L]\times[0,\infty); [0,\infty)\right),\;\; J_{ij} \in C\left([0,\infty); \mathbb{R}\right)$$

and

$$n_{ij}(t) < \tfrac{\beta}{\gamma_2} \quad \textit{a.e. in } (0,L) \quad \textit{if } \gamma_2 > 0.$$

Then $(M_i, N_i, m_{ij}, n_{ij})$ is said to be a solution of the quasi-static NTM if equations (1.33) *and* (1.34) *are satisfied, and*

$$\textit{for all } t \ge 0: \quad \begin{cases} m_{ij}(t) = g(n_{ij}(t)) & \textit{a.e. in } (0,L)\setminus(x_3,x_4) \\ m_{ij}(t) = 0 & \textit{in } (x_3,x_4) \\ J_{ij}(t) = -\left(a(x)(n_{ij}(t))_x + h(x, n_{ij}(t))\right) & \textit{in } \mathcal{D}'(0,L) \\ n_{ij}(0,t) = N_i(t) \\ n_{ij}(L,t) = N_j(t). \end{cases} \tag{1.36}$$

If in addition the initial total mass of Tau is positive and bounded, i.e. if

$$0 < \mathcal{M}_0 = \sum_i \left(V_i(M_i(0) + N_{0i}) + \sum_{j\neq i} \int_0^L c_{ij}(m_{ij}(x,0) + n_{ij}(x,0))dx \right) < \infty, \tag{1.37}$$

we call $(M_i, N_i, m_{ij}, n_{ij})$ a finite mass solution of the quasi-static NTM.

As we shall see in Section 1.4.1, (1.37) is always satisfied if $\gamma_2 = 0$. If $\gamma_2 > 0$, it follows from $(1.36)_{1,2}$ that $\mathcal{M}_0 < \infty$ if and only if $g(n_{ij}(0)) \in L^1((0,x_3)\cup(x_4,L))$ for all $i \neq j$ ($c_{ij} > 0$). Below we shall see that this is equivalent to requiring that $n_{ij}(0) < \frac{\beta}{\gamma_2}$ in $(0,L)$ (Lemma 1.4.6); in addition the total Tau mass is conserved in time (Lemma 1.4.3).

Theorem 1.3.1. *Let $N_{i0} \in [0, \frac{\beta}{\gamma_2})$ for all $1 \le i \le h$.*

(i) *Let $\gamma_2 = 0$. Then the quasi-static NTM possesses a unique solution.*

(ii) *Let $\gamma_2 > 0$. If, for all $i \neq j$ such that $c_{ij} > 0$, there exists $n_{ij}(0) \in C\left([0,L]; [0, \frac{\beta}{\gamma_2}]\right)$ which satisfies*

$$\begin{cases} n_{ij}(0) < \frac{\beta}{\gamma_2} & \textit{a.e. in } (0,L) \\ a(x)(n_{ij}(x,0))_x + h(x, n_{ij}(x,0)) = \text{ constant} & \textit{in } \mathcal{D}'(0,L) \\ n_{ij}(0,t) = N_{i0},\;\; n_{ij}(L,t) = N_{j0}. \end{cases}$$

If $g(n_{ij}(0)) \in L^1(0,L)$ for all $i \neq j$ such that $c_{ij} > 0$, the quasi-static NTM possesses a unique solution.

1.4 Conservation of mass

Since the hypothesis of Theorem 1.3.1(i) does not contain information about the total initial mass of Tau if $\gamma_2 = 0$, we first address this question.

1.4.1 Finite initial mass if $\gamma_2 = 0$; mass conservation if $\gamma_2 \geq 0$

Lemma 1.4.1. *Let $\gamma_2 = 0$ and $N_{i0} \in [0, \infty)$ for $1 \leq i \leq h$. If $c_{ij} > 0$, there exists a unique $J \in \mathbb{R}$ such that*

$$\begin{cases} a(x)n'(x) = -h(x, n(x)) - J & \textit{in } (0, L) \\ n(0) = N_i, \ n(L) = N_j. \end{cases} \tag{1.38}$$

has a solution $n = n_{ij}(0)$. In addition $n_{ij}(0)$ is nonnegative and continuous in $[0, L]$.

Proof. We consider $J \in \mathbb{R}$ as a shooting parameter and consider the problem

$$\begin{cases} a(x)n'(x) = -h(x, n(x)) - J & \text{in } (0, L) \\ n(0) = N_i. \end{cases} \tag{1.39}$$

Observe that $n(x)$ is pointwise decreasing with respect to the parameter J, which implies that there exists at most one value J such that $n(x)$ is well-defined in $[0, L]$ and $n(L) = N_j$. We recall that, by (1.15), $g(n) = \frac{\gamma_1}{\beta} n^2$ if $\gamma_2 = 0$ and, by (1.14),

$$-h(x, n) = Q(x, g(n), n) = \begin{cases} (1 - f)v(\frac{\gamma_1}{\beta} n^2, n)n & \text{in } (x_2, x_3) \\ 0 & \text{otherwise.} \end{cases}$$

If $v(m, n)$ is given by (1.7), then

$$-h(x, n) = (1 - f)(v_a e^{\delta n - \frac{\varepsilon \gamma_1}{\beta} n^2} - v_r)n \quad \text{in } (x_2, x_3),$$

so $-h \approx -(1 - f)v_r n$ in (x_2, x_3) as $n \to \pm\infty$. This linear growth implies that n is well-defined in $[0, L]$ for all $J \in \mathbb{R}$. Let $A \in \mathbb{R}$ be the value of n at x_3 if $J = 0$. By the monotonicity with respect to J, $n(x_3) < A$ if $J > 0$ and $n(x_3) > A$ if $J < 0$. Since $Dn' = -J$ in (x_3, L) this implies that $n(L) < A - (J/D)(L - x_3) \leq N_j$ if $J > 0$ is large enough and $n(L) > A - (J/D)(L - x_3) \geq N_j$ if $-J > 0$ is large enough. Hence there exists $J_0 \in \mathbb{R}$ such that $n(L) = N_j$ if $J = J_0$.

If instead $v(m, n)$ is given by (1.8), then

$$h(x, n) = -(1 - f)\left(v_a(1 + \delta n)(1 - \tfrac{\varepsilon\gamma_1}{\beta} n^2) - v_r\right)n \quad \text{in } (x_2, x_3),$$

so $-h \approx -\frac{(1-f)\delta\varepsilon\gamma_1 v_a}{\beta} n^4 \to -\infty$ in (x_2, x_3) as $n \to \pm\infty$. Hence, given $J \in \mathbb{R}$, the solution n can be continued as long as it is bounded from below. We set

$$\begin{aligned} \mathcal{P}^+ &= \{J \in \mathbb{R} : \ n \text{ exists in } [0, L] \text{ and } n(L) > N_j\}, \\ \mathcal{P}^- &= \{J \in \mathbb{R} : \ \text{either } n \text{ exists in } [0, L] \text{ and } n(L) < N_j, \text{ or } n \text{ does not exist in } [0, L]\}. \end{aligned}$$

By the monotonicity of the solution with respect to J, we have that

$$J^+ < J^- \quad \text{for all } J^+ \in \mathcal{P}^+ \text{ and } J^- \in \mathcal{P}^-.$$

The sets $\mathcal{P}^\pm$ are clearly open. To prove that there exists $J_0 \in \mathbb{R}$ such that $n(L) = N_j$ if $J = J_0$, it is enough to show that both $\mathcal{P}^+$ and $\mathcal{P}^-$ are non-empty. Arguing as above, it follows that $J \in \mathcal{P}^-$ if J is large enough and $J \in \mathcal{P}^+$ if $-J$ is large enough. $\square$

It follows from Lemma 1.4.1 that the total initial mass of Tau is always finite if $\gamma_2 = 0$.

Corollary 1.4.2. *Let $\gamma_2 = 0$ and let $\mathcal{M}_0$ be the total initial mass, defined by* (1.37)*. Then $\mathcal{M}_0 < \infty$. In particular every solution of the quasi-static NTM is a finite mass solution.*

If $\gamma_2 \geq 0$, the total mass of Tau on the edges and at the vertices is conserved, as suggested by the construction of the quasi-static model.

Lemma 1.4.3. *Let $\gamma_2 \geq 0$, let $N_{0i} \in [0, \beta/\gamma_2)$ for all $1 \leq i \leq h$ and let $(M_i, N_i, m_{ij}, n_{ij})$ be a finite mass solution of the quasi-static NTM in the sense of Definition 1.3.1. Then*

$$\mathcal{M}(t) := \sum_i \left(V_i(M_i(t) + N_i(t)) + \sum_{j \neq i} \int_0^L c_{ij}(n_{ij}(x,t) + m_{ij}(x,t))dx \right) = \mathcal{M}_0 \quad \textit{for all } t > 0,$$

where $0 < \mathcal{M}_0 < \infty$ is the total initial mass defined by (1.37)*.*

The proof is based on the equations for N_i, M_i, n_{ij} and m_{ij}, which imply that $\mathcal{M}'(t) = 0$.

1.4.2 Subcritical behavior if $\gamma_2 > 0$

In the remainder of this section we study the steady state problem (1.13) on the edge if $\gamma_2 > 0$. We fix $i \neq j$ such that $c_{ij} > 0$. Since $t \geq 0$ plays merely the role of a parameter, we also fix t. We suppress i, j, t where possible. In addition it turns out to be convenient, in view of the proof of Theorem 1.3.1, to relax the nonnegativity of n_{ij}, N_i and N_j:

$$\begin{cases} -\varepsilon_1 \leq n_{ij} < \frac{\beta}{\gamma_2} & \text{a.e. in } (0, L) \\ -\varepsilon_2 \leq N_i, N_j < \beta/\gamma_2 \\ (a(x)(n_{ij})_x + h(x, n_{ij}))_x = 0 & \text{in } \mathcal{D}'(0, L), \\ n_{ij}(0) = N_i, \ n_{ij}(L) = N_j, \end{cases} \tag{1.40}$$

where $\varepsilon_1 \geq \varepsilon_2 > 0$ are small numbers.

Below we shall need the following technical result. We omit its straightforward proof.

Lemma 1.4.4. *Let $g(n)$ and $h(x, n)$ be defined by* (1.15) *and* (1.14)*, and let $\varepsilon_1 > 0$. Then $g' > 0$ in $(0, \frac{\beta}{\gamma_2})$, $g(n) \to \infty$ as $n \to \frac{\beta}{\gamma_2}$, and*

$$h, \ \tfrac{\partial h}{\partial n}, \ \tfrac{\partial^2 h}{\partial^2 n} \in L^\infty((0, L) \times (-\varepsilon_1, \tfrac{\beta}{\gamma_2})) \qquad \textit{if } v(m, n) = v_a e^{\delta n - \varepsilon m} - v_r.$$

If instead $v(m, n) = v_a(1 + \delta n)(1 - \varepsilon m) - v_r$, then there exists $C > 0$ such that

$$h, \ \tfrac{\partial h}{\partial n} \geq -C \textit{ in } (0, L) \times (-\varepsilon_1, \tfrac{\beta}{\gamma_2}), \qquad h, \ \tfrac{\partial h}{\partial n}, \ \tfrac{\partial^2 h}{\partial^2 n} \in L^\infty_{\mathrm{loc}}([0, L] \times [-\varepsilon_1, \tfrac{\beta}{\gamma_2})).$$

The following result shows that the condition of finite total mass at time $t \geq 0$ implies that, if $\gamma_2 > 0$, the solution n_{ij} of (1.40) is subcritical.

Lemma 1.4.5. *Let $\gamma_2 > 0$ and let $t \geq 0$ be fixed. Let $\varepsilon_1 \geq \varepsilon_2 > 0$, $\gamma_2 > 0$, $N_i \in [-\varepsilon_2, \beta/\gamma_2)$ for all $1 \leq i \leq h$, and let $n_{ij} \in C([0, L])$ satisfy* (1.40) *for all $i \neq j$ such that $c_{ij} > 0$. If*

$$\mathcal{M} = \sum_i \left(V_i(N_i + g(N_i)) + \sum_{j \neq i} c_{ij} \left(\int_0^L n_{ij} \, dx + \int_{(0,L) \setminus (x_3, x_4)} g(n_{ij}) \, dx \right) \right), \tag{1.41}$$

then

$$\begin{aligned}\mathcal{M} < \infty \ &\Leftrightarrow \ g(n_{ij}) \in L^1((0,x_3)\cup(x_4,L)) \ \forall\, i,j \text{ such that } c_{ij} > 0 \\ &\Leftrightarrow \ n_{ij} < \tfrac{\beta}{\gamma_2} \text{ in } [0,L] \ \forall\, i,j \text{ such that } c_{ij} > 0.\end{aligned} \tag{1.42}$$

Setting $t = 0$, we obtain the following characterization of initial data with finite mass:

Corollary 1.4.6. *Let $\gamma_2 > 0$ and $N_{0i} \in [0, \beta/\gamma_2)$ for all $1 \le i \le h$. Let $n_{ij}(0) \in C([0,L])$ satisfy, for all $i \neq j$ such that $c_{ij} > 0$,*

$$\begin{cases} 0 \le n_{ij}(0) < \frac{\beta}{\gamma_2} & \text{a.e. in } (0,L) \\ \left(a(x)(n_{ij}(0))_x + h(x, n_{ij}(0))\right)_x = 0 & \text{in } \mathcal{D}'(0,L) \\ n_{ij}(0,0) = N_{i0}, \ n_{ij}(L,0) = N_{j0}. \end{cases} \tag{1.43}$$

Let $\mathcal{M}_0$ be defined by (1.41) *at $t = 0$. Then*

$$\mathcal{M}_0 < \infty \ \Leftrightarrow \ g(n_{ij}(0)) \in L^1((0,x_3)\cup(x_4,L)) \ \Leftrightarrow \ n_{ij}(0) < \tfrac{\beta}{\gamma_2} \text{ in } [0,L].$$

Proof of Lemma 1.4.5. By $(1.13)_{1,2}$, the first equivalence in (1.42) is immediate, so it remains to prove the second one. Since $(\Leftarrow)$ is obvious, we only prove the implication $(\Rightarrow)$.

Let $g(n_{ij}) \in L^1((0,x_3)\cup(x_4,L))$. We fix $i \neq j$ and set $n = n_{ij}$. Since $h(x,n) = 0$ if $x \notin [x_2, x_3]$, n_x is constant in $(0,x_2)$. Since $n(0) = N_i < \frac{\beta}{\gamma_2}$ and $n(x_2) \le \frac{\beta}{\gamma_2}$, this implies that $n < \frac{\beta}{\gamma_2}$ in $[0,x_2)$. We claim that also $n(x_2) < \frac{\beta}{\gamma_2}$: if not, the linear growth of n and the behaviour of $g(n)$ as $n \to \frac{\beta}{\gamma_2}$ imply that $g(n)$ is not integrable in $(0,x_2)$. So $n < \frac{\beta}{\gamma_2}$ in $[0,x_2]$.

If $n(\xi) = \frac{\beta}{\gamma_2}$ for some $\xi \in (x_2,x_3]$, it follows from Lemma 1.4.4 that

$$\lim_{x\to\xi^-} h((n(x)) \begin{cases} = \infty & \text{if } v(m,n) = v_a(1+\delta n)(1-\varepsilon m) - v_r \\ \in \mathbb{R} & \text{if } v(m,n) = v_a e^{\delta n - \varepsilon m} - v_r. \end{cases}$$

In the first case $n_x(x) \to -\infty$ as $x \to \xi^-$, which is obviously impossible. In the second case we argue as before and find that $g(n)$ is not integrable in (x_2,x_3). So $n < \frac{\beta}{\gamma_2}$ in $[0,x_3]$.

Finally, since n_x is constant in (x_3,L) and $n(x_3), n(L) < \frac{\beta}{\gamma_2}$, we conclude that $n < \frac{\beta}{\gamma_2}$ in $(x_3,L]$. So $n < \frac{\beta}{\gamma_2}$ in $[0,L]$. This completes the proof of Lemma 1.4.5.

The condition of finite total mass turns out to be "stable" in the following sense.

Lemma 1.4.7. *Let $t \ge 0$ be fixed. Let $\varepsilon_1 \ge \varepsilon_2 > 0$, $\gamma_2 > 0$, $N_i \in [-\varepsilon_2, \beta/\gamma_2)$ for all $1 \le i \le h$, let $n_{ij} \in C([0,L])$ satisfy* (1.40) *for all $i \neq j$ such that $c_{ij} > 0$, and let $\mathcal{M}$, defined by* (1.41)*, be finite. Then there exists $\varepsilon_3 > 0$ which does not depend on i, j such that for all $\tilde{N}_i < \beta/\gamma_2$ satisfying*

$$|\tilde{N}_i - N_i| \le \varepsilon_3,$$

there exists a unique $\tilde{n}_{ij} \in C([0,L])$ which satisfies, for all $i \neq j$ such that $c_{ij} > 0$,

$$\begin{cases} -2\varepsilon_1 \le \tilde{n}_{ij} < \frac{\beta}{\gamma_2} & \text{in } (0,L) \\ \left(a(x)(\tilde{n}_{ij})_x + h(x,\tilde{n}_{ij})\right)_x = 0 & \text{in } \mathcal{D}'(0,L), \\ \tilde{n}_{ij}(0) = \tilde{N}_i, \ \tilde{n}_{ij}(L) = \tilde{N}_j. \end{cases} \tag{1.44}$$

Proof. We fix i, j. Let $J \in \mathbb{R}$ be a shooting parameter and consider the problem

$$\begin{cases} n' = -\frac{1}{a(x)}\left(J + h(x,n)\right) & \text{for } x \in [0,L] \\ n(0) = \tilde{N}_i. \end{cases} \tag{1.45}$$

Observe that, as long as $n < \beta/\gamma_2$, n is pointwise decreasing with respect to J. By (1.42), we know that if $\tilde{N}_i = N_i$ and $J = J_{ij}$, we obtain the solution $n = n_{ij}$ which satisfies $n(L) = N_j$. Using this as a starting point and using the monotonicity of n with respect to J, one easily obtains that, for some $J = \tilde{J}_{ij}$, there exists a solution $n = \tilde{n}_{ij} > -2\varepsilon_1$ of problem (1.45) which satisfies $\tilde{n}_{ij}(L) = \tilde{N}_j$, provided that $|\tilde{N}_i - N_i|, |\tilde{N}_j - N_j| \leq \varepsilon_{ij}$ for some sufficiently small $\varepsilon_{ij} > 0$. Since the number of i, j is finite, we define $\varepsilon_3 > 0$ as the minimum of ε_{ij}.

The uniqueness of the pair $(\tilde{n}_{ij}, \tilde{J}_{ij})$ follows from (1.47), which will be proved below. □

Remark 1.4.1. *If $\gamma_2 > 0$, the initial condition of finite mass is not only natural, but also necessary to have subcritical behaviour. Indeed, it follows from an elementary shooting argument, similar to those used in the proofs of Lemma's 1.4.1 and 1.4.7, that if N_i and N_j are both less than but close enough to β/γ_2, then the solution n_{ij} on the edge is not necessarily subcritical. In other words, the condition that $N_i \in [0, \frac{\beta}{\gamma_2})$ for all i does not guarantee that $m_{ij} < \infty$.*

Remark 1.4.2. *We have formulated and proved Lemma 1.4.7 if $\gamma_2 > 0$. Actually the case $\gamma_2 = 0$ is easier to handle, and Lemma 1.4.7 continues to hold if $\gamma_2 = 0$ (with $\beta/\gamma_2 = \infty$).*

1.5 A fixed point argument

In this section we provide a local solution of the quasi-static *NTM*. Its nonnegativity and continuation to a global solution will be considered in Sections 1.6 and 1.7, respectively.

We begin with collecting some technical results which will be needed in the proof.

1.5.1 Some preliminary results

The following result follows from a straightforward calculation.

Lemma 1.5.1. *Let $t \geq 0$, $i \neq j$ and $c_{ij} > 0$. Let $N_i(t), N_j(t) \in [-\varepsilon_2, \beta/\gamma_2)$ and $J_{ij}(t)$ be given numbers. Let $x \mapsto n_{ij}(x,t)$ be a Lipschitz continuous solution of*

$$\begin{cases} a(x)(n_{ij})_x(x,t) + h(x, n_{ij}) = -J_{ij}(t) & \textit{for a.e. } x \in [0,L] \\ -\varepsilon_1 < n_{ij}(x,t) < \frac{\beta}{\gamma_2} \quad \forall x \in [0,L] \\ n_{ij}(0,t) = N_i(t), \; n_{ij}(L,t) = N_j(t), \end{cases} \tag{1.46}$$

and let q_{ij}^i and q_{ij}^j be defined by (1.27)*. Then*

$$q_{ij}^i(x,t) = e^{-\int_0^x \frac{h_n(s, n_{ij}(s,t))}{a(s)} ds} \left(\frac{e^{\int_0^L \frac{h_n(s,n_{ij}(s,t))}{a(s)} ds} \int_0^x \frac{e^{\int_0^y \frac{h_n(s,n_{ij}(s,t))}{a(s)} ds}}{a(y)} dy}{\int_0^L \frac{e^{\int_0^y \frac{h_n(s,n_{ij}(s,t))}{a(s)} ds}}{a(y)} dy} \right) \geq 0\,,$$

where h_n stands for $\frac{\partial h}{\partial n}$. Similarly, if $c_{ji} > 0$, we have that

$$q^i_{ji}(x,t) = e^{-\int_0^x \frac{h_n(s,n_{ji}(s,t))}{a(s)}ds} \left(1 - \frac{\int_0^x \frac{e^{\int_0^y \frac{h_n(s,n_{ji}(s,t))}{a(s)}ds}}{a(y)} dy}{\int_0^L \frac{e^{\int_0^y \frac{h_n(s,n_{ji}(s,t))}{a(s)}ds}}{a(y)} dy} \right) \geq 0\,.$$

The explicit expressions for q^i_{ij} and q^i_{ji} in Lemma 1.5.1 considerably reduce the computational time for numerical solutions of the quasi-static *NTM.*

The proof of local existence is based on the construction of a contraction, and in this sense the following two results are natural.

Lemma 1.5.2. *Let $t \geq 0$ and $c_{ij} > 0$. Let $n_{ij}(t), \tilde{n}_{ij}(t) \in C([0,L])$ be such that*

$$-\varepsilon_1 < n_{ij}(t), \tilde{n}_{ij}(t) < \beta/\gamma_2 \quad \text{in } [0,L].$$

If $n_{ij}(x,t)$ and $\tilde{n}_{ij}(x,t)$ satisfy (1.13)$_{3,4}$ *with given boundary conditions $(N_i(t), N_j(t))$, respectively $(\tilde{N}_i(t), \tilde{N}_j(t))$ contained in $[-\varepsilon_2, \frac{\beta}{\gamma_2})$. Let $J_{ij}(t)$, respectively $\tilde{J}_{ij}(t)$, satisfy* (1.16)*. Then there exists a constant C such that*

$$|n_{ij}(x,t) - \tilde{n}_{ij}(x,t)|,\ |J_{ij}(t) - \tilde{J}_{ij}(t)| \leq C\left(|N_i(t) - \tilde{N}_i(t)| + |N_j(t) - \tilde{N}_j(t)|\right). \tag{1.47}$$

Proof. Let $K = \max\{n_{ij}(x,t), \tilde{n}_{ij}(x,t); x \in [0,L]\}$. We set $w = n_{ij} - \tilde{n}_{ij}$. By the mean value theorem, w satisfies

$$\begin{cases} (a(x)w' + b(x)w)' = 0 & \text{in } (0,L) \\ w(0) = N_i(t) - \tilde{N}_i(t) \\ w(L) = N_j(t) - \tilde{N}_j(t), \end{cases}$$

where $b = 0$ in $(0,x_2) \cup (x_3, L)$ and, if $x_2 < x < x_3$, $b(x) = \frac{\partial h}{\partial n}(x, \nu(x,t))$ for some function $\nu(x,t) \in [-\varepsilon_1, K] \subset [-\varepsilon_1, \beta/\gamma_2)$. By Lemma 1.4.4, $b \in L^\infty(0,L)$. Since

$$\left(ae^{-\int b/a}\left(e^{\int b/a}w\right)'\right)' = (aw' + bw)' = 0 \quad \text{in } (0,L),$$

$\left|e^{\int b/a}w\right|$ attains its maximum at $x = 0$ or $x = L$. Since $e^{\pm\int b/a}$ are bounded functions, this implies the estimate for $|n_{ij} - \tilde{n}_{ij}|$ in (1.47).

Finally, by (1.16),

$$(J_{ij} - \tilde{J}_{ij}) \int_0^L \tfrac{1}{a} e^{\int b/a}\, dx = -\int_0^L \tfrac{1}{a} e^{\int b/a}(aw_x + bw)\, dx = -\int_0^L \left(e^{\int b/a}w\right)' dx = -\, e^{\int b/a}w\Big|_0^L$$

and the estimate for $|J_{ij} - \tilde{J}_{ij}|$ in (1.47) follows from that for $|n_{ij} - \tilde{n}_{ij}|$. □

Lemma 1.5.3. *Let $t \geq 0$ and $c_{ij} > 0$ and let $n_{ij}(t), \tilde{n}_{ij}(t) \in C([0,L])$ be as in Lemma 1.5.2. Let $q_{ij} = (n_{ij})_t$ and $\tilde{q}_{ij} = (\tilde{n}_{ij})_t$, and let $q^i_{ij}(t)$ and $q^j_{ij}(t)$, respectively $\tilde{q}^i_{ij}(t)$ and $\tilde{q}^j_{ij}(t)$, be defined by* (1.27)*. Then there exists a constant C such that*

$$|q^i_{ij}(x,t) - \tilde{q}^i_{ij}(x,t)|,\ |q^i_{ji}(t) - \tilde{q}^i_{ji}(t)| \leq C\left(|N_i(t) - \tilde{N}_i(t)| + |N_j(t) - \tilde{N}_j(t)|\right). \tag{1.48}$$

Proof. A possible proof follows the lines of that of Lemma 1.5.2, using Lemma's 1.4.4 and 1.5.2 to handle the difference of the coefficients $\frac{\partial h}{\partial n}(x, n_{ij})$ and $\frac{\partial h}{\partial n}(x, \tilde{n}_{ij})$ in (1.27).

An alternative and straightforward proof is based on the explicit formula's provided by Lemma 1.5.1. □

1.5.2 Local existence

In this section we set up the fixed point argument.

In Definition 1.3.1 we have defined finite mass solutions of the quasi-static *NTM* as *nonnegative* functions which satisfy certain equations for *all* $t \geq 0$. In the following result we prove the existence of not necessarily nonnegative finite mass solutions in some interval $[0, T]$.

Theorem 1.5.4. *Let $\gamma_2 \geq 0$ and let the hypotheses of Theorem 1.3.1 be satisfied. Then there exists $T > 0$ such that the quasi-static NTM possesses a unique solution which is defined for $t \in [0, T]$ and is not necessarily nonnegative.*

Proof. Let $N_{i0} \in [0, \beta/\gamma_2)$ for $i = 1, \ldots, h$, let $\sigma > 0$ and $T > 0$. We set

$$X_{\sigma,T} = \{(N_1, N_2, \ldots, N_h);\ N_i \in C([0,T]),\ N_{i0} - \sigma \leq N_i(t) \leq N_{i0} + \sigma < \tfrac{\beta}{\gamma_2} \text{ for all } i, t\}.$$

In particular we have that, for all $t \in [0, T]$ and i,

$$N_i(t) \leq C_{\sigma,T} := \max_{1 \leq k \leq h} N_{k0} + \sigma < \tfrac{\beta}{\gamma_2} \quad \text{if } (N_1, N_2, \ldots, N_h) \in X_{\sigma,T}. \tag{1.49}$$

Observe that if $t > 0$ then $N_i(t)$ may be negative if $(N_1, \ldots, N_h) \in X_{\sigma,T}$.

So let $(N_1, \ldots, N_h) \in X_{\sigma,T}$ and $i \neq j$, $c_{ij} > 0$. By Lemma 1.4.1 (if $\gamma_2 = 0$) and the hypothesis of Theorem 1.3.1(ii) and Corollary 1.4.6 (if $\gamma_2 > 0$), there exists $n_{ij}(0) \in C([0, L]; [0, \beta/\gamma_2))$ which satisfies the edge problem (1.43) at $t = 0$. By Lemma 1.4.7 and Remark 1.4.2 we can choose $\sigma > 0$ so small that there exists $n_{ij} \in C([0, L] \times [0, T])$ such that

$$\max_{[0,L]\times[0,T]} n_{ij} < \tfrac{\beta}{\gamma_2} \tag{1.50}$$

and, for all $t \in [0, T]$,

$$\begin{cases} (a(x)(n_{ij}(x,t))_x + h(x, n_{ij}(x,t)))_x = 0 & \text{in } (0, L) \\ n_{ij}(0,t) = N_i(t), \quad n_{ij}(L,t) = N_j(t). \end{cases} \tag{1.51}$$

Having in mind the equation for N_i in (1.33), we define the following operator Φ on $X_{\sigma,T}$:

$$\begin{aligned} &\Phi(N_1, \ldots, N_h) = (\tilde{N}_1, \ldots, \tilde{N}_h), \\ &\tilde{N}_i(t) = N_i(0) + \int_0^t \frac{\sum_{j\neq i} (c_{ji} J_{ji}(s) - c_{ij} J_{ij}(s))}{V_i\left(1 + \frac{\gamma_1 N_i(s)(2\beta - \gamma_2 N_i(s))}{(\beta - \gamma_2 N_i(s))^2}\right) + \sum_{j\neq i}(C^i_{ij}(s) + C^i_{ji}(s))} ds \quad (t \in [0, T]), \end{aligned}$$

where $J_{ij}(t)$, $C^i_{ij}(t)$ and $C^i_{ji}(t)$ are defined by (1.16), (1.31) and (1.32). Observe that the factor

$$r(N) := 1 + \frac{\gamma_1 N(2\beta - \gamma_2 N)}{(\beta - \gamma_2 N)^2} \geq c > 0 \quad \text{if } N \in [0, \tfrac{\beta}{\gamma_2})$$

for some $c > 0$, whence $r(N) \geq \frac{1}{2}c$ for $N \in [-\sigma, \frac{\beta}{\gamma_2})$ if we choose $\sigma > 0$ small enough.

Similarly we obtain that $C^i_{ij}(t) \geq 0$ and $C^i_{ji}(t) \geq 0$ if $N_i(t), N_j(t) \in [-\sigma, C_{\sigma,T}]$ (where $C_{\sigma,T} < \frac{\beta}{\gamma_2}$ is defined by (1.49)) if we choose $\sigma > 0$ small enough. For example, $C^i_{ij}(t) \geq 0$ if and only if

$$\int_{(0,x_3)\cup(x_4,L)} \frac{\gamma_1 n_{ij}(2\beta - \gamma_2 n_{ij})}{(\beta - \gamma_2 n_{ij})^2} q^i_{ij}(x,t)\, dx \geq -\int_0^L q^i_{ij}(x,t)\, dx. \tag{1.52}$$

By (1.47) with $\tilde{N}_i, \tilde{N}_i, \tilde{n}_{ij} \equiv 0$, we have that $n_{ij} \geq -C\sigma$ if $N_i, N_j > -\sigma$, whence we can choose $\sigma > 0$ so small that (1.52) is satisfied if $N_i(t), N_j(t) \in [-\sigma, C_{\sigma,T}]$.

Having chosen $\sigma > 0$, we choose $\tilde{T} > 0$ so small that $\tilde{N}_i$ is continuous on $[0, \tilde{T}]$ and $(\tilde{N}_1, \ldots, \tilde{N}_h) \in X_{\sigma,\tilde{T}}$. Hence $\Phi(X_{\sigma,T}) \subseteq X_{\sigma,T}$ for all $0 < T < \tilde{T}$.

A straightforward calculation based on Lemma's 1.5.2 and 1.5.3 shows that we can choose $\tilde{T} > 0$ so small that Φ is a contraction on $X_{\sigma,\tilde{T}}$. Hence we have obtained a local (for $0 \leq t \leq \tilde{T}$) smooth solution of the quasi-static *NTM*, with values between $-\sigma$ and $\frac{\beta}{\gamma_2}$. □

In the next section we shall prove that the solution is nonnegative for $0 \leq t \leq \tilde{T}$.

1.6 Positivity properties

In this section we prove some a priori estimates of independent interest, which ensure nonnegativity of finite mass solutions of the quasi-static *NTM*.

We consider the problem for n_{ij} on the edge e_{ij} at a fixed time $t \geq 0$, where $i \neq j$, $c_{ij} > 0$; $N_i(t)$ and $N_j(t)$ are given real numbers belonging to $[0, \frac{\beta}{\gamma_2})$.

Lemma 1.6.1. *Let $t \geq 0$ be fixed, let $\gamma_2 \geq 0$, $i \neq j$ and $c_{ij} > 0$. Let $N_i(t), N_j(t) \in [0, \beta/\gamma_2)$ and $J_{ij} = J_{ij}(t)$ be given numbers and let $n_{ij} = n_{ij}(t) \in C([0, L])$ satisfy* (1.16)*: $a(x)(n_{ij})_x + h(x, n_{ij}) = -J_{ij}$ in $\mathcal{D}'(0, L)$. Let*

$$n_{ij}(x, t) < \beta/\gamma_2 \quad \textit{for all } 0 \leq x \leq L.$$

(i) *If $J_{ij} = 0$, then either $n_{ij}(x, t) = 0$ for all $x \in [0, L]$ or $n_{ij}(x, t) > 0$ for $x \in [0, L]$; in particular, either $N_i(t) = N_j(t) = 0$ or $N_i(t) > 0$ and $N_j(t) > 0$.*

(ii) *If $J_{ij} > 0$, then $n_{ij}(x, t) > 0$ for $0 \leq x < L$; in particular $N_j(t) > 0$.*

(iii) *If $J_{ij} < 0$, then $n_{ij}(x, t) > 0$ for $0 < x \leq L$; in particular $N_i(t) > 0$.*

In particular

$$n_{ij}(x, t) \geq 0 \quad \textit{for all } x \in [0, L],\ t \geq 0. \tag{1.53}$$

Proof. (i) If $J_{ij} = 0$ then $n_{ij} \equiv 0$ is a solution of (1.16) (since $h(x, 0) = 0$). Since $N_i(t)$ and $N_j(t)$ are nonnegative, the uniqueness properties of solutions of (1.16) imply that either $n_{ij}(x, t) = 0$ for all $x \in [0, L]$ or $n_{ij}(x, t) > 0$ for all $x \in [0, L]$.

(ii) Let $J_{ij} > 0$. Arguing by contradiction we suppose that $n_{ij} = 0$ at some $y_0 \in [0, L)$. Since $h(x, 0) = 0$, $a(n_{ij})_x = -J_{ij} < 0$ at $x = y_0$, whence $n_{ij} < 0$ in $(y_0, L]$. Since $n_{ij} = N_j(t) \geq 0$ at $x = L$, we have found a contradiction.

The proof of (iii) is similar. □

Corollary 1.6.2. *Let $t \geq 0$ be fixed, let $\gamma_2 \geq 0$ and $i \neq j$, $c_{ij} \neq 0$. Let $0 \leq N_j(t) < \beta/\gamma_2$, $J_{ij} = J_{ij}(t) \in \mathbb{R}$, $J_{ji} = J_{ji}(t) \in \mathbb{R}$ and*

$$N_i(t) = 0.$$

Let $n_{ij}(t) \in C([0, L])$ satisfy $a(x)(n_{ij})_x + h(x, n_{ij}) = -J_{ij}$ in $\mathcal{D}'(0, L)$ and let $n_{ij} < \frac{\beta}{\gamma_2}$ in $[0, L]$. Then

(i) *$J_{ji}(t) \geq 0$ if $c_{ji} > 0$ and $J_{ij}(t) \leq 0$ if $c_{ij} > 0$;*

(ii) *if $N_j(t) > 0$, then $J_{ji}(t) > 0$ if $c_{ji} > 0$ and $J_{ij} < 0$ if $c_{ij} > 0$.*

In particular, if $N_i(t) = 0$ the term $\sum_j (c_{ji}J_{ji}(t) - c_{ij}J_{ij}(t))$ in the equation for N_i in (1.33) *is nonnegative for all i; it is strictly positive if there exists $j \neq i$ such that $N_j(t) > 0$ and $c_{ij} > 0$ or $c_{ji} > 0$.*

The previous results imply a "strong maximum principle" for N_i in the network.

Lemma 1.6.3. *Let $\gamma_2 \geq 0$, $N_{0i} \in [0, \beta/\gamma_2)$ for all $1 \leq i \leq h$ and let $(M_i, N_i, m_{ij}, n_{ij})$ be a solution of the quasi-static NTM in the sense of Definition 1.3.1. Let $n_{ij}(x,t) < \frac{\beta}{\gamma_2}$ for all $x \in [0, L]$, $t \geq 0$ and $i \neq j$ such that $c_{ij} > 0$. Then either $N_i(t) = 0$ for all $t \geq 0$ and $1 \leq i \leq h$, or $N_i(t) > 0$ for all $t > 0$ and $1 \leq i \leq h$.*

Proof. We must prove that if $N_{0k} > 0$ for some $1 \leq k \leq h$, then $N_i(t) > 0$ for all $t > 0$ and $1 \leq i \leq h$.

If $N_{0k} > 0$, there exists $t_0 > 0$ such that $N_k(t) > 0$ for all $t \in (0, t_0]$. Hence, by Corollary 1.6.2 and the equation for N_i in (1.33), for all $t \in (0, t_0]$

$$N_i(t) > 0 \quad \text{for all } 1 \leq i \leq h \text{ such that } c_{ik} > 0 \text{ or } c_{ki} > 0.$$

Here we have used that, by Lemma 1.5.1, the factors C^i_{ji} and C^i_{ji} in the equation for N_i are nonnegative.

Since the network is finite and connected, a finite number of iterations of this reasoning shows that there exists $t_1 \in (0, t_0]$ such that $N_i > 0$ in $(0, t_1]$ for all $1 \leq i \leq h$.

Finally, setting

$$T = \sup\{t : \ N_i > 0 \text{ in } (0, t) \text{ for all } 1 \leq i \leq h\},$$

it remains to show that $T = \infty$. Arguing by contradiction we assume that $T < \infty$. Then $N_m(T) = 0$ for some $1 \leq m \leq h$. Hence $N'_m(T) = 0$ and, by Corollary 1.6.2, $N_i(T) = 0$ for all i such that $c_{im} > 0$ or $c_{mi} > 0$. Since the network is finite and connected, a finite number of iterations imply that $N_i(T) = 0$ for all $1 \leq i \leq h$. Hence the total mass of Tau at $t = T$ vanishes, which, by the mass conservation in Lemma 1.4.3, yields a contradiction since $N_{0k} > 0$. □

1.7 Proof of Theorem 1.3.1

We summarize the local existence result of finite mass solutions of the quasi-static *NTM*. Let $\gamma_2 \geq 0$ and $0 \leq N_{i0} < \beta/\gamma_2$ for $1 \leq i \leq h$. By Theorem 1.5.4, the quasi static *NTM* has a local solution, defined in an interval $[0, T]$. If $\gamma_2 = 0$, its total mass is conserved and finite (by Corollary 1.4.2 and Lemma 1.4.3) and $N_i(t) \geq 0$ for all $t \in [0, T]$ and $1 \leq i \leq h$ (by Lemma 1.6.3). If $\gamma_2 > 0$, its total mass is finite at $t = 0$ (by hypothesis) and remains finite in $(0, T]$ (by Lemma 1.4.3); in addition, N_i and n_{ij} are subcritical in $[0, T]$ (by Lemma 1.4.5) and $N_i(t) \geq 0$ for all $t \in [0, T]$ and $1 \leq i \leq h$ (by Lemma 1.6.3).

Now we must extend the local solution to $[0, \infty)$. Observe that, as long as it exists, it continues to satisfy all properties discussed above (conservation and finiteness of total mass, nonnegativity, subcriticality). Therefore, if the solution exists in an interval $[0, T^*)$ with $T^* < \infty$, it is well defined, nonnegative and subcritical at $t = T^*$, whence, by the local existence result proved above, can be continued in a right neighbourhood of T^*. Hence it can be extended to $[0, \infty)$, and since it satisfies all required properties we have proved Theorem 1.3.1.

1.8 Numerical algorithms

In this section we introduce a discretisation of the *NTM* adopted in [91]. The MATLAB codes are available at https://github.com/Raj-Lab-UCSF/Tau_Transport.git. The algorithm is as follows.

Algorithm 1: An algorithm for the *NTM*

Input : $(N_i(0))_{i=1}^h$
Output: $(N_i(t))_{i=1}^h$
for $k = 1, \dots, k_{end}$ **do**
  for $(i, j) \in E$ **do**
    $(n_{ij}(t^k), J_{ij}(t^k)) \leftarrow$ *FluxCalculator*$(N_i(t^k))$;
  end
  for $(i, j) \in E$ **do**
    $(q_{ij}^i(t^k), q_{ij}^j(t^k) \leftarrow$ *MassBalance*$(n_{ij}(t^k), J_{ij}(t^k))$;
    Calculate $C_{ij}^i(t^k)$, $C_{ij}^j(t^k)$;
  end
  Update $N_i(t^{k+1})$;
end

To account for the distinct spatial spread along the edge (i, j), an inhomogeneous spatial grid is introduced in the interval $[0, L]$. The five edge compartments are defined as the intervals

$$(x_k, x_{k+1}) \quad \text{for } k = 0, \dots, 4.$$

Each compartment is discretised through an inhomogeneous grid

$$x_k < x_{k_1} < x_{k_2} < \dots < x_{k_N} = x_{k+1}.$$

We observe that equation (1.13) can be integrated to get

$$a(x)(n(x))_x(x) + h(x, n) = -J \tag{1.54}$$

(where we have dropped the edge subscripts and the time dependence) with boundary conditions

$$n(0) = N_i, \quad n(L) = N_j.$$

The strategy adopted to solve the edge problem consists in a shooting argument. Equation (1.54) is solved as a first order ODE by calculating n as a function of J, $\tilde{n}(J, x)$, on the compartment $(0, x_1)$ with boundary condition $\tilde{n}(J, 0) = N_i$. By requiring continuity of $\tilde{n}(J, \cdot)$ at the compartment interfaces x_k, the solution $\tilde{n}(J, \cdot)$ is continued by solving the first order ODE until the last compartment. Ultimately, the edge profile n and its flux are obtained by solving the problem

$$\text{find } J \in \mathbb{R} \text{ s.t.} \quad \tilde{n}(J, L) - N_j = 0.$$

This procedure is encapsulated by the *FluxCalculator* function. The shooting argument on each edge and time step is solved using MATLAB's functions `fsolve` and `ODE45`. In principle problem (1.25) should be integrated as per the edge profile n_{ij}. However, its linear structure allows for less expensive numerical computations. Indeed it is sufficient to compute the explicit expressions in Lemma 1.5.1 and then calculate the quantities (1.31), (1.32). In [91], the integration method adopted is the trapezoidal, which exhibits a negligible computational cost compared to the other operations. The overall computational cost for solving the quasi-static *NTM* for general advection terms adopting an Implicit Euler scheme to solve the edge ODEs and an Explicit Euler scheme to solve the node ODEs system is of order

$$\mathcal{O}(\underbrace{k_{Newton} \cdot k_{ODE} N_X |E| N_T}_{\text{Edge problem}} + \underbrace{|V|\,|E| N_T}_{\text{Node problem}}) \tag{1.55}$$

where we have set

- $|E|$: number of edges of the graph,
- $|V|$: number of nodes of the graph,
- N_X: number of points of the spatial edge grid,
- N_T: number of points of the temporal node grid,
- k_{ODE}: number of iteration of Newton's method to solve the implicit system,
- k_{Newton}: number of iteration of Newton's method to solve the shooting problem.

Notice that the order of the node problem cost corresponds to the cost required to solve the standard Network-Diffusion model, where the incoming fluxes at each node are given by the Graph Laplacian, hence the additional operations concern the computation of the Edge solutions. Observe that k_{ODE} increases as the spatial derivative of the edge soluble Tau concentration becomes highly nonlinear. The overall computational burden is naturally amplified in rich and complex networks such as the brain connectome, as shown by the dependence on $|E|$ and $|V|$. A remarkable property of the computational *NTM* is that the structure of the edge problem is compatible with parallelisation. Indeed at fixed time t the profile is a function of Tau concentration at the respective two nodes defining the edge, therefore distinct edges lead to independent solutions. Notice that this also holds for edges of the form e_{ij} and e_{ji} since the edge problem (1.13) is not symmetric in P_i, P_j.

1.9 Limitations and future developments

In the present Chapter we have proved existence and uniqueness of a quasi-static Network Transport Model on a directed graph for intro-neural toxic Tau, one of the proteins which play an important role in Alzheimer's disease. The model was introduced and extensively discussed in [91] for Alzheimer's brains of mice; in particular several promising computational results were presented there.

Quasi-stationarity expresses the existence of two timescales, a long one which is typical for the evolution of *AD* and a much shorter one which in the Ansatz of quasi-stationarity becomes instantaneous in the long timescale. An active intro-neural transport mechanism leads to a stationary equation on the single edges of the graph, a mathematical novelty which requires a careful analysis, since the model is further complicated by the possible occurrence of a singularity in the equations (if $\gamma_2 > 0$).

A further consequence of the quasi-static approach is a profound change in the structure of the equations compared to the existing Network-Reaction-Diffusion models. Computing the total network mass balance, we found that the correct mass exchange between nodes and edges consists of two contributes: the incoming flux of the edge profiles and a *feedback* term due to the mass variation on the edge induced by the mass variation at the node. The resulting global *feedback* term can be quantified in terms of the variation of the total edge mass, but it cannot be explicitly computed by means of the sole quasi-static approximation, meaning that in principle the quasi-static approximation does not provide the correct separation of such a mass change between the two nodes. That is, the variation of Tau at a node induces a mass change on the incident edges through a globally described effect. As we shall see in Chapter 3, the issue of determining the correct mass balance at node level is not limited to the case of varying Dirichlet boundary conditions, but it also pertains to the change in time of the coefficients of the edge equations. In the present Chapter we have introduced a (seemingly reasonable) approximation of the correct mass balance, but this issue will be extensively discussed in Chapter 3.

Regarding the limitations of the present model, several topics are worth mentioning. First, when comparing the *NTM* to the standard Diffusion-Network models, we have seen that the implementation typically requires higher computational costs. The numerical criticality associated with the PDE equation on a single edge with Dirichlet boundary conditions is due to the nonlinearity in the advection term and the presence of discontinuous coefficients. Moreover, the structure of the equation implies the existence of a singularity in the long time limit. These features represent an inevitable critical point in numerical applications. The inaccuracy along the single edge is eventually amplified at network level, where the algorithm for solving the *NTM* requires integrating the PDE equation along all the edges of the graph with Dirichlet boundary conditions that satisfy, in turn, a coupled system of ODEs on the nodes. This results in extreme computational costs to reach accuracy and eventually accumulation of rounding-off errors, which make the edge-PDE model on the network computationally unfeasible. The quasi-static approach undoubtedly improves the computational costs of the original PDE *NTM* but still requires expensive computations to reach accuracy along the whole network due to the integration of the nonlinear elliptic ODEs on the edges. However, we stress that by inserting a nonlinearity along the edges the model produces several different spatial patterns according to the directionality bias induced by the parameter sets [91], in terms of net anterograde-retrograde coefficients and aggregation-fragmentation terms. The exploration of new and rich dynamics with respect to existing models is also a promising feature in terms of applicability of the model to specific Tau species and tauopathies. In fact, different Tau isoforms and sites of hyperphosphorylation [41] are associated with different spatio-temporal evolution patterns, as proved in [63], [93]. In this sense, the model could explain tauopathy as a function of the model parameters.

The issue of the extensive computational costs poses the necessity for future computational improvements of the model algorithm for the adaptation to human brains and the comparison with experimental data to optimize the choice of parameter values. Indeed, the *NTM* has quite a large number of parameters and not all of them can be learned from experimental studies (see also table 1.1). Data concerning the structure of the brain and its connectivity in humans and in mice are rich and reliable (see for example [58], [66]). However, accurate experimental estimates of kinetic parameters and transport/diffusion parameters are usually challenging to obtain. Although we were able to retrieve some of these quantities from *in vitro* studies in mice available in the literature (see table 1.1), these parameters are difficult to estimate accurately *in vivo*, and likely do not match with measurements taken *in vitro* that have been previously reported. On the other hand, data concerning the spatio-temporal distribution of Tau pathology in human and mice brains are abundant (see ADNI dataset: https://adni.loni.usc.edu and [16], [24], [47], [54], [63]). In this context, model fitting with data of Tau pathology becomes crucial to determine model parameters and to validate computational results with real data. Therefore, future developments shall consist of reducing the Edge term in (1.55) by means of further approximations to the edge solutions. This problem can possibly be overcome by approximating the fluxes through linearisation of the nonlinearity [69] or Machine Learning models.

Secondly, the role of Beta Amyloid, another protein which plays an important role in *AD* and is mainly present in the extracellular space, needs to be included in the quasi-static model. From a biomedical point of view it is important to get more insight into the interaction mechanisms between Tau and Aβ. For these types of models, both the modelling itself and the mathematical analysis become particularly challenging. For example, some of the governing parameters in the Tau-model (aggregation rates etc.) will become Aβ-dependent, a substantial complication of both the modelling of the *feedback* mechanism (see (1.22)) and the proof of well-posedness. In this more general context, the results obtained in the present Chapter are a first but crucial step towards the analysis of more general systems.

A third limitation of the mathematical framework developed in Chapter 1 is the assumption of stability of the steady states (1.13). A numerical study on this topic has been developed in [92] in the case of

Neumann boundary conditions. However, the issue of recovering the correct limit as $\phi \to 0^+$ remains to be addressed.

A fourth relevant applicative restriction of the *NTM* is the necessity of a directed graph to define the advection velocity along the edges. The connectivity graph obtained by means of tractography techniques is undirected, meaning that the edges are not oriented and no preferred direction is defined. In fact, diffusion imaging methods are not capable of detecting the directions of the fiber tracts, thus posing a limitation in this specific field of application. Axons host signal propagation through conduction of the action potential from the cell body to the presynaptic terminals, hence they are equipped with well-established directions that cannot be captured by undirected network models. In the specific case of the *NTM*, directionality is necessary to define *anterograde* and *retrograde* directions of advection along the edges, hence a directed spatial domain is a fundamental requirement for the definition of the model itself. The adoption of mouse brain connectomes is natural in this sense [68] and serves as a starting point to test the model. However the lack of a directed human connectome is a remarkable limitation. The first attempts to bridge the gap between axonal directionality and connectivity network theory can be found in [55], [87].

Chapter 2

A Network Diffusion Model of Beta Amyloid progression

In the previous Chapter we have studied a quasi-static model for toxic intracellular tau protein in the Alzheimer brain. In the present Chapter we introduce a mathematical model for the diffusion of Beta Amyloid (Aβ) protein. The foundation of the model relies on [14], where a probability measure is introduced to describe the overall toxic state of neurons in the continuous brain medium. Here, we adapt the model to the discrete spatial setting of the *proximity* graph and introduce a quasi-static approximation. The well-posedness analysis of the mathematical model will require a sufficiently strong clearance mechanism of Aβ monomers, which is compatible with the introduction of the clearance mechanism as the bottleneck to justify the use of the quasi-static approximation.

2.1 Introduction and biological setting

The network of neuron cells is represented by a graph $G_p = (V, E)$, where the nodes in V represent gray matter regions. More precisely, G_p is a weighted, undirected and connected graph with a finite number h of nodes $P_i \in V$ and edges $e_{ij} \in E$. We denote by $e_{ij} \in E$ the edge connecting $P_i \in V$ and $P_j \in V$ and $e_{ij} = e_{ji}$. We often refer to the existence of an edge between nodes P_i and P_j with the notation $P_i \sim P_j$, or alternatively $i \sim j$.

The network is endowed with a weight function ω which satisfies

$$\omega(P_i, P_j) = \begin{cases} \omega_{ij} > 0 & \text{if } e_{ij} \in E \\ 0 & \text{otherwise.} \end{cases} \tag{2.1}$$

The weight ω_{ij} of the edge e_{ij} consists in the reciprocal of the Cartesian distance between the centre of mass of the gray matter regions corresponding to P_i and P_j. This definition implies that $\omega_{ij} = \omega_{ji}$ for all $i, j \in V$, therefore the graph is undirected and the corresponding adjacency matrix $A \in \mathbb{R}^{h \times h}$, $A_{ij} = \omega_{ij}$ is symmetric.

The species we are interested in are monomers, soluble oligomers and plaques of Beta Amyloid, which are mainly found in the extracellular space and propagate through proximity [86]. The spatial operator acting on monomers and oligomers is defined from the standard Graph Laplacian on the *proximity* graph, that is the matrix

$$L \in \mathbb{R}^{h \times h}, \quad L = D - A \tag{2.2}$$

where A is the symmetric adjacency matrix of G_p and D is the degree matrix of G_p, i.e. the diagonal matrix such that $D_{ii} = \sum_{j\sim i} \omega_{ij}$. Among the numerous properties of the matrix L we highlight that, since G_p is undirected, L is symmetric and by the First Gershgorin theorem [46] its spectrum lies in the set $\{\lambda \in \mathbb{R} : \lambda \geq 0\}$. A direct calculation shows that, if G_p has no loops, $0 \in \Lambda(L)$:

$$(L\boldsymbol{e})_i = \sum_{j=1}^{h} \omega_{ij} - \sum_{j\neq i} \omega_{ij} = 0, \quad \text{where } \boldsymbol{e} = (1, \dots, 1)^T \in \mathbb{R}^h. \tag{2.3}$$

Moreover, the rank of L is strictly related to the topology of the graph [19]. Specifically, the number of connected components of the graph dictates the multiplicity of $\lambda = 0$ by the law rank$(L) = h - r$, where r is the number of connected components of G_p. In our case, $r = 1$ and the eigenspace related to $\lambda = 0$ is entirely generated by the vector $\boldsymbol{e}$. In the following, in analogy with the continuous notation, we will select the matrix $\Delta := -L$ as the spatial operator acting on the node concentrations of Beta Amyloid, as in [12], [13], [32], [73], [89], [98].

In this Chapter we adhere to the mathematical approach of [14] and show that the spatial-continuous model can be adapted on the network of the *proximity* graph. The resulting model exhibits the same existence and time-regularity properties as the original one and it accounts for a quasi-static approximation of the Beta Amyloid node system. As in Chapter 1, we identify a *bottleneck* mechanism which slows down the overall spread of Beta Amyloid along the brain network. This process consists in the physiological clearance mechanism of Aβ which involves degradation along enzymatic pathways, remotion via perivascular drainage along blood vessels, efflux through the cerebrospinal fluid into the glymphatic system and microglia-mediated displacement through the cellular uptake process [48], [99]. Remotion of Aβ is a fundamental process that obstructs the aggregation of soluble oligomers and the subsequent formation of toxic plaques, thus a relapse or impairment may induce pathology. From the mathematical point of view, the model presented in this Chapter captures the key role of clearance as a crucial factor in the existence of the solution.

The model also deals with the processes of Aβ production, aggregation and fragmentation. The production of Aβ is mediated by enzymes called $\beta-$ secretase and $\gamma-$ secretase via cleavage of the amyloid precursor protein (*APP*). Among the resulting peptides, A$\beta-40$ and A$\beta-42$ are released and can aggregate to form Aβ toxic plaques, with A$\beta - 42$ being highly prone to aggregation.

As previously stated in [14], we model the production of Aβ as a function of the health state of neurons located at the brain compartments of the *proximity* graph. We assume that the production of Aβ monomers increases when neurons are impaired below a certain threshold above which brain cells start to reduce their protective activity of monomers release. A precise definition of such dependency requires the introduction of a degree of malfunction $a \in [0, 1]$, where $a = 0$ means that neurons at the brain compartment are healthy and $a = 1$ stands for neuronal death. This relation implies a further link between monomers production and the proportion of neurons at each brain compartments with degree a. To include this factor we introduce a probability measure $f_{i,t}$ at each node such that $df_{i,t}(a)$ denotes the fraction of neurons at node P_i, time t and degree between a and $a + da$ [14]. We model the time evolution of $f_{i,t}$ via a first order transport PDE, where the transport velocity depends on $f_{i,t}$ and the concentration of soluble Aβ oligomers at node P_i. The model consists of a system of reaction-diffusion ODEs on the nodes of the *proximity* graph coupled with a system of PDEs for $f_{1,t}, \dots, f_{h,t}$ and corresponds to a discretisation in space of the model in [14].

Starting from here, we observe that diffusion, aggregation, fragmentation, production and clearance are fast processes relatively to the slow time scale of evolution of $f_{i,t}$ (and *AD*), hence we assume a quasi-static approximation of the ODE system on the nodes by treating the fast processes as instantaneous on the slow time scale. The resulting system is a set of nonlinear equations involving the concentrations of Aβ on the nodes which evolve in time by means of $f_{i,t}$ through the production term. The quasi-static model does not alter the structure of the velocity of $f_{i,t}$. As a result, the nonlinear equations on the nodes are coupled with the PDE for $f_{i,t}$ for all $i \in V$.

The assumption of equilibrium at each time t on the slow time scale induces a technical difficulty in solving the nonlinear system on the nodes. In fact, we do not assume spatially homogeneous production terms, hence the constant vector $u \in \text{span}(\boldsymbol{e})$ is not an admissible solution. As stated in [21], regional variability is an important feature of *AD* dynamics. The disease spreads according to a selective spatial progression, showing a certain vulnerability of some regions of the brain [65]. Aβ deposition typically begins in the neocortex and subsequently involves allocortical brain regions, subcortical nuclei, brain stem and finally cerebellum [88]. Recent studies have adopted PET scanning techniques to identify the distribution and extent of amyloid burden and quantify its global load [101], leading to a more complex spatial evolution than the linear sequence cited above [31], [85]. Several different spatial subtypes have emerged from the analysis of large PET datasets, highlighting differences in both seeding areas and order of involvement of some regions according to factors such as age of onset, genetic background and comorbidity [25], [61]. In our model, we recover this heterogeneity relying on linear algebra tools and exploiting the structure of the Graph Laplacian matrix.

In this Chapter, we show that the coupled Aβ-$f_{i,t}$ quasi-static problem admits a unique solution under suitable conditions on the initial datum $f_{i,0}$ and the parameters of the Aβ system. Specifically, we require that $f_{i,0}$ is a probability measure on $[0, 1]$ for all $i \in V$ and that the clearance rate of monomers is sufficiently large. We first deal with the case of a mass-conserving continuity equation for $f_{i,t}$ to illustrate the general well-posedness argument. This setting crucially simplifies the problem, since the solution $f_{i,t}$ is uniquely determined as the push-forward of a fixed time-constant measure g_i through the characteristics. We then proceed to consider the non-conservative case by introducing a drift in the transport PDE for the measure. The well-posedness argument previously introduced is extended to consider $f_{i,t}$ as the push-forward of a time-dependent measure $g_{i,t}$ through the characteristics by selecting the 1-Wasserstein distance as the metric for $g_{i,t}$.

We conclude the present Chapter by improving the properties of time-regularity proved in [14] and present some numerical results.

2.2 The model

Consider the *proximity* graph $G_p = (V, E)$ introduced in Section 2.1. Let $h = |V|$. We recall that the weight function ω_{ij} is symmetric, hence we do not assume directionality of the edges of the network. Let $t > 0$ indicate the *slow timescale*, typical for the progression of the disease, and let $u_1(t), u_2(t), u_3(t)$ denote the density of Aβ monomers, soluble oligomers and plaques, respectively. The functions $t \mapsto u_k(t)$ are vectors of densities on the set of nodes, meaning that $u_k(t) \in \mathbb{R}^h$ and $(u_k(t))_i$ coincides with the density of species k at node P_i and time t. We will often refer to the i^{th} coordinate of the vector $u_k(t)$ as $u_k(i, t)$.

2.2.1 The full Network Diffusion Model

Following [14], we introduce the parameter $a \in [0, 1]$ which describes the level of neuronal impairment at each node. Values of a close to zero denote a healthy state, while a close to one represents neuronal death. Given this biological interpretation, fixing a node P_i and a time $t > 0$, we introduce a probability measure $f_{i,t}$ on the space $[0, 1]$. Setting $a \in (0, 1)$, $df_{i,t}(a)$ denotes the fraction of neurons at node P_i and time t with degree of malfunctioning between a and $a + da$. We assume that neuronal degradation evolves at the following rate:

$$v[f_{i,t}](a,t) = C_G \int_{[0,1]} (b-a)^+ \, df_{i,t}(b) + C_s(1-a)(u_2(i,t) - \bar{U}_2)^+. \tag{2.4}$$

The first term in (2.4) accounts for the prion-like diffusion of the disease, meaning that damaged neighbouring neurons at node P_i induce malfunctioning by increasing the malfunctioning rate, whereas healthy neurons are harmless. The second term in (2.4) expresses the toxic action of soluble oligomers of Aβ on the overall health state: once a certain threshold $\bar{U}_2(i)$ is reached, toxic soluble Aβ acts by increasing the speed $v[f_{i,t}]$ and its effect is amplified if the neurons are healthy. In this setting, we do not take into account the neurotoxic action of Aβ monomers; their harmful effect is related to the possibility of aggregation and formation of oligomers and plaques. It is not clear whether to consider monomers as beneficial or threatening actors in the development of the disease. Indeed, Aβ monomers are also involved in protective mechanisms such as regulation of synaptic function, modulation of synaptic activity and antimicrobial effect [80].

The measure $f_{i,t}$ evolves in time according to the following transport PDE

$$\partial_t(f_{i,t}) + (v[f_{i,t}]f_{i,t})_a = J[f_{i,t}], \quad i \in V. \tag{2.5}$$

The term $J[f_{i,t}]$ represents the onset of the disease. As in [14], we assume that along the nodes belonging to the subgraph which corresponds to the brain hippocampus i_H, the health state b can jump to a worse state $a > b$ with probability $P(t,b,a)$. We model the signed measure $J[f_{i,t}]$ as

$$J[f_{i,t}] = \eta(t)\chi_H(t) \left\{ \left(\int_{[0,1]} P(t,b,a) \, df_{i,t}(b) \right) da - df_{i,t}(a) \right\}, \quad i \in V \tag{2.6}$$

where η is the jump frequency and χ_H is the characteristic function of the hippocampal area, i.e.

$$\chi_H(t) = \begin{cases} 1 & \text{if } i \in i_H \\ 0 & \text{otherwise.} \end{cases} \tag{2.7}$$

We now introduce the global system on G_p for u_1, u_2, u_3 and f. Let $\Delta := -L$ the standard heat operator on G_p and let t denote the slow time scale. The general ODE-PDE system we are interested in is given by

$$\begin{cases} \partial_t(f_{i,t}) + (v[f_{i,t}]f_{i,t})_a = J[f_{i,t}], & (a,t) \in [0,1] \times [0,T], \, i \in V \\ u_1' = d_1 \Delta u_1 - \sigma_1 u_1 + F[f](t) + \Gamma_1, & t \in [0,T] \\ u_2' = d_2 \Delta u_2 - \sigma_2 u_2 + \Gamma_2, & \\ u_3' = -\sigma_3 u_3 + \Gamma_3. & \end{cases} \tag{2.8}$$

The coefficients d_1 and d_2 are the diffusion rates of spread; in principle, $d_1 \neq d_2$. We assume that the insoluble plaques do not diffuse. The reaction terms Γ_k are given by

$$\begin{cases} \Gamma_1 = -u_1(a_{11}u_1 + a_{12}u_2) + k_1 u_3 \\ \Gamma_2 = a_{11}u_1^2 - a_{21}u_1u_2 + k_2u_3\Gamma_3 = -(\Gamma_1 + \Gamma_2) = u_1u_2(a_{12} + a_{21}) - (k_1 + k_2)u_3. \end{cases} \tag{2.9}$$

according to the Smoluchowski model. Here, aggregation is modelled by the coefficients a_{ij} as in [2], [14], [35]. We assume that plaques are formed by aggregation of monomers and oligomers at rates a_{12} and a_{21}.

We also include fragmentation of plaques into smaller aggregates through the factors $-k_1 u_3$ and $-k_2 u_3$. The clearance process involving Aβ is defined by the linear terms $-\sigma_k u_k$ in (2.8).

The dynamics of Aβ is governed by fast processes such as aggregation, fragmentation, diffusion, clearance and production and therefore the respective coefficients in (2.8), being expressed on the slow time scale, are large. Lastly, we couple the ODEs system for u with the PDE equations for f by introducing a production term $F[f]$. Here, $F[f_{i,t}]$ is defined at each node $i \in V$ as

$$F[f_{i,t}] = C_\mu \int_0^1 (\mu_0 + a)(1 - a)\, df_{i,t}(a), \quad i \in V,\, t > 0. \tag{2.10}$$

This formulation expresses the idea of increasing monomers release when neurons are damaged under a certain threshold as a protective mechanism. Observe that when neurons are healthy, they produce Aβ monomers at rate μ_0. On the other hand, dead neurons do not release monomers.

2.2.2 The quasi-static Network Diffusion Model

Since the microscopic processes of diffusion, aggregation, fragmentation, clearance and production take place on the fast time scale, the solution of the ODE system

$$\begin{cases} u_1' = d_1 \Delta u_1 - \sigma_1 u_1 + F[f](t) + \Gamma_1, & t \in [0, T] \\ u_2' = d_2 \Delta u_2 - \sigma_2 u_2 + \Gamma_2, \\ u_3' = -\sigma_3 u_3 + \Gamma_3. \end{cases} \tag{2.11}$$

quickly converges to a steady state associated to (2.11), which satisfies

$$\begin{cases} d_1 \Delta u_1 - \sigma_1 u_1 + F[f](t) + \Gamma_1 = 0, \\ d_2 \Delta u_2 - \sigma_2 u_2 + \Gamma_2 = 0, & i \in V, \\ -\sigma_3 u_3 + \Gamma_3 = 0, \end{cases} \tag{2.12}$$

where the coefficients are expressed in the slow time scale. In other words, the evolution of the ODE system in (2.11) is fast enough to be indistinguishable from the dynamics defined by the steady state system (2.12). We stress that in (2.12), t is a parameter that allows the solution to evolve on the slow time scale. Once the steady state is reached, the monomers' source F is updated by means of the evolution equation for f, as well as u. The implicit assumption we make is the local stability of the steady states of (2.8). We will refer to this topic in the following sections.

The system (2.12) satisfies a mass balance at node level. Summing the equations (2.12) we get

$$d_1 \Delta u_1(i,t) + d_2 \Delta u_2(i,t) + F[f_{i,t}] = \sigma_1 u_1(i,t) + \sigma_2 u_2(i,t) + \sigma_3 u_3(i,t) \tag{2.13}$$

and, summing (2.13) over all the nodes, we obtain

$$\sum_{k=1}^{3} \int_G \sigma_k u_k = \int_G F[f_{i,t}] \tag{2.14}$$

where $\int_G := \sum_{i=1}^h$. Here, we have used that

$$\begin{aligned} \sum_{i=1}^h d(\Delta u)_i &= -d \sum_{i=1}^h ((D - A)u)_i = -d \sum_{i=1}^h \left(D_{ii} u_i - \sum_{j=1}^h \omega_{ji} u_j \right) = -d \sum_{i=1}^h \left(\sum_{j=1}^h \omega_{ij} u_i - \sum_{j=1}^h \omega_{ji} u_j \right) \\ &= -d \sum_{i=1}^h \deg(i) u_i - \sum_{j=1}^h \sum_{i=1}^h \omega_{ji} u_j = -d \sum_{i=1}^h \deg(i) u_i - d \sum_{j=1}^h \deg(j) u_j = 0 \end{aligned}$$

by the symmetry of ω_{ij} and the fact that the diffusion coefficient is constant on the nodes.

Observe that, by (2.14), since the equilibrium problem (2.12) is naturally expressed on the slow time scale, the quantities $\sum_{k=1}^{3}\sigma_k$ and $\int_G F[f_{i,t}]$ exhibit the same order of magnitude on the slow time scale, i.e. they are of order $O(1/\phi)$, where ϕ is the proportion between the slow and fast time scales. This suggests a relationship between the microscopic processes and the observed proportion of time scales.

The equilibrium system (2.12) is then coupled with the PDE for f

$$\partial_t(f_{i,t}) + (v[f_{i,t}]f_{i,t})_a = J[f_{i,t}] \quad i \in V, \tag{2.15}$$

where the deterioration rate v is given by

$$v[f_{i,t}](a,t) = C_G \int_{[0,1]} (b-a)^+ \, df_{i,t}(b) + C_s(1-a)(u_2(i,t) - \bar{U}_2)^+, \tag{2.16}$$

and the signed measure J satisfies

$$J[f_{i,t}] = \eta(t)\chi_H(t)\left\{\left(\int_{[0,1]} P(t,b,a)\, df_{i,t}(b)\right) da - df_{i,t}(a)\right\}, \quad i \in V. \tag{2.17}$$

Equations (2.12) and (2.15) are coupled by the dependence of the monomers' source F on f in the expression

$$F[f_{i,t}] = C_\mu \int_0^1 (\mu_0 + a)(1-a)\, df_{i,t}(a), \quad i \in V,\, t > 0 \tag{2.18}$$

and the relation between the deterioration rate v and the concentration of soluble oligomers u_2 in (2.16).

2.3 The main result

To state the main result of this Chapter, we first introduce the definition of a solution for the quasi-static Aβ model introduced above.

We denote by $X_{[0,1]}$ the space of probability measures on $[0,1]$ endowed with the 1-Wasserstein distance and by $\mathcal{M}(0,1)$ the space of signed Radon measures on $[0,1]$. We write

$$f \in \mathcal{L}(V; C([0,T]; X_{[0,1]})) \tag{2.19}$$

if $t \mapsto f_{i,t} \in C([0,T]; X_{[0,1]})$ for all $i \in V$ and

$$t \mapsto \int \rho(a) df_{i,t}(a) \tag{2.20}$$

is measurable as a function from $[0,T]$ to $\mathcal{M}(0,1)$ for all $\rho \in C([0,1])$ and $i \in V$.

The model is given by

$$\begin{cases} \partial_t f_{i,t} + (v[f_{i,t}]f_{i,t})_a = J[f_{i,t}], \\ f_{i,0} = f_i(0) \quad i \in V, \end{cases} \tag{2.21}$$

$$\begin{cases} d_1 \Delta u_1(i,t) - \sigma_1 u_1(i,t) + F[f_{i,t}] + \Gamma_1(u(i,t)) = 0, \\ d_2 \Delta u_2(i,t) - \sigma_2 u_2(i,t) + \Gamma_2(u(i,t)) = 0, \qquad i \in V, \\ -\sigma_3 u_3(i,t) + \Gamma_3(u(i,t)) = 0, \end{cases} \tag{2.22}$$

where $f(0) \in \mathcal{L}(V; C([0,T]; X_{[0,1]}))$.

Remark 2.3.1. *Observe that the Aβ system* (2.22) *on the proximity graph does not require a prescription of the initial data since it is defined as the solution to* (2.22) *where the monomers' source is given by* (2.18) *with* $f_{i,t} = f_i(0)$.

2.3.1 Hypotheses and Notations

The hypotheses on the model parameters that we adopt in the following are:

(i) $\sigma_1,\ \sigma_2,\ \sigma_3,\ a_{11},\ a_{12},\ a_{21}\ k_1,\ k_2,\ d_1,\ d_2,\ C_\mu,\ \mu_0, C_G,\ C_s$ are positive constants. The monomers' clearance parameter σ_1 is sufficiently large, i.e. $\sigma_1 > \bar{\sigma}_1$ for some $\bar{\sigma}_1 > 0$. The aggregation and fragmentation rates are symmetric: $a_{ij} = a_{ji}$, $k_1 = k_2$;

(ii) $\eta \in C([0,T])$, $\eta > 0$. We require that P satisfies

$$P \in C([0,T] \times [0,1]^2), \quad P \geq 0, \tag{2.23}$$

$$\int_{[0,1]} P(t,b,a)\,da = 1 \quad \text{for } b \in [0,1],\ P(t,b,a) = 0 \quad \text{if } b > a \tag{2.24}$$

since impaired neurons do not recover, and that P is Lipschitz continuous:

$$\exists L > 0 :\ |P(t,b'',a'') - P(t,b',a')| \leq L(|b''-b'| + |a''-a'|), \tag{2.25}$$

for all $a', a'', b', b'' \in [0,1]$, $t \in [0,T]$.

We will denote distributional derivatives with ∂, ∇ and the standard Euclidean norm on $\mathbb{R}^{3h}$ with $|\cdot|$, when no other vector norm is under consideration. We may refer to the solution of system (2.12) as $u \in \mathbb{R}^{3h}$, where 3 is the number of species and h the number of nodes, or with $u_k \in \mathbb{R}^h$ for $k = 1,2,3$ as the vector of concentration of species k on the nodes.

Definition 2.3.1. *A* $4-$*tuple* (f, u_1, u_2, u_3) *is a solution to* (2.21), (2.22) *if*

1. $f \in \mathcal{L}(V; C([0,T]; X_{[0,1]}))$*;* $u_k \in C([0,T], \mathbb{R}^h)$, $u_k(i) \geq 0$ *for all* $k = 1,2,3$ *and* $i = 1,\dots,h$*;*
2. f *is a solution to* (2.21) *in a weak sense:*

$$\int_0^t \left(\int (\phi_s(a,s) + \phi_a(a,s) v_i(a,s)) df_{i,s}(a) + \int \phi(a,s) dJ_{i,s}(a) \right) ds \tag{2.26}$$
$$= \int \phi(\cdot,t)\, df_{i,t} - \int \phi(\cdot,0)\, df_i(0)$$

for all $\phi \in C^1([0,1] \times [0,T])$ *and* $i = 1,\dots,h$, *where* v *is defined in* (2.16)*;*

3. (u_1,u_2,u_3) *satisfies the following graph equations:*

$$\begin{cases} d_1 \Delta u_1(t) - \sigma_1 u_1(t) + F[f(t)] + \Gamma_1(t) = 0, \\ d_2 \Delta u_2(t) - \sigma_2 u_2(t) + \Gamma_2(t) = 0, \\ -\sigma_3 u_3(t) + \Gamma_3(t) = 0, \end{cases} \tag{2.27}$$

where $F[f]$ *and the reaction terms* Γ_k *are given by* (2.18) *and* (2.9).

Remark 2.3.2. *Definition 2.3.1 (3) does not contain the boundary conditions given by the "flux"* vf *at* $a = 0$ *and* $a = 1$. *First we observe that* $v(1,t) \equiv 0$ *hence the outflowing flux at* $a = 1$ *is zero. Then we recall that* $f_{i,t}$ *is a probability measure on* $[0,1]$, *therefore by the weak formulation of* (2.21) *we have that the inflowing* *and outflowing fluxes at $a = 0$ and $a = 1$ are equal in the distributional sense. For example, if f has a density ρ, we have*

$$\int_0^T \int (\phi_t + v_i \phi_a)\rho(a,t)\, da\, dt + \int_0^T \int \phi(a,t) dJ_{i,t}(a)\, dt$$
$$= \int \phi(a,T)\rho(a,T)\, da - \int \phi(a,0)\rho(a,0)\, da + \int_0^T (\phi(1,t)v_i(1,t)\rho(1,t) - \phi(0,t)v_i(0,t)\rho(0,t))\, dt$$

for all $\phi \in C^1([0,1] \times [0,T])$, $\quad i \in V$.

If $\phi(a,t) = \eta(t)$, the previous equality becomes

$$\int_0^T \int \eta'(t)\rho(a,t)\, da\, dt + \int_0^T \eta(t) \int dJ_{i,t}(a)\, dt \tag{2.28}$$
$$= \int \eta(T)\rho(a,T)\, da - \int \eta(0)\rho(a,0)\, da + \int_0^T \eta(t)(v_i(1,t)\rho(1,t) - v_i(0,t)\rho(0,t))\, dt$$
$$= \eta(T) - \eta(0) + \int_0^T \eta(t)(v_i(1,t)\rho(1,t) - v_i(0,t)\rho(0,t))\, dt.$$

By Tonelli's theorem and (2.24)*, the LHS of* (2.28) *is equal to*

$$\eta(T) - \eta(0) + \eta(t)\chi_H \int_0^1 \left(\int P(t,b,a)\, df_{i,t}(b) \right) da - \eta(t)\chi_H \int df_{i,t}(a) = \eta(T) - \eta(0), \tag{2.29}$$

and therefore

$$\int_0^T \eta(t)v_i(1,t)\rho(1,t)\, dt = \int_0^T \eta(t)v_i(0,t)\rho(0,t)\, dt, \quad \eta \in C^1([0,T]), \quad i \in V. \tag{2.30}$$

The Chapter is devoted to the proof of the following result:

Theorem 2.3.1. *Let G_p be the proximity graph defined in Sections 2.1 and 2.2. Let $T > 0$ and the hypotheses $(i) - (ii)$ be satisfied. Then the quasi-static problem* (2.21)-(2.22) *admits a unique solution on $[0,T]$ in the sense of Definition 2.3.1.*

2.4 The equilibrium solution for fixed $F[f]$

In this Section, we consider the reaction-diffusion ODE system

$$\begin{cases} u_1'(i,t) = d_1 \Delta u_1(i,t) - \sigma_1 u_1(i,t) + F[f_t] + \Gamma_1(u(i,t)), \\ u_2'(i,t) = d_2 \Delta u_2(i,t) - \sigma_2 u_2(i,t) + \Gamma_2(u(i,t)), \\ u_3'(i,t) = -\sigma_3 u_3(i,t) + \Gamma_3(u(i,t)) \end{cases} \qquad i \in V, \tag{2.31}$$

where $F[f]$ is a given function evolving in time. A necessary requirement to define the quasi-static approximation to system (2.8) is the existence of a steady state for (2.31) satisfying the nonlinear problem

$$\begin{cases} d_1 \Delta u_1 - \sigma_1 u_1 + F[f_t] + \Gamma_1(u) = 0, \\ d_2 \Delta u_2 - \sigma_2 u_2 + \Gamma_2(u) = 0, \\ -\sigma_3 u_3 + \Gamma_3(u) = 0, \end{cases} \qquad i \in V, \tag{2.32}$$

where t denotes a parameter. In the following Section we show that for sufficiently small t and sufficiently large σ_1 system (2.32) admits a solution whose spatial disposition depends on the spatial distribution of $F[f_t]$ on the nodes of the *proximity* graph.

2.4.1 Local existence

We start by introducing the new variables:

$$v_k := \sigma_1^k u_k, \quad s := 1/\sigma_1, \quad \text{for } k = 1, 2, 3. \tag{2.33}$$

We require the clearance process to slow down the global temporal dynamics of the quasi-static system, hence we are interested in large values of σ_1 i.e. small values of s. System (2.32) becomes

$$\begin{cases} sd_1\Delta v_1 - v_1 + F[f_t] + ks^3 v_3 - s^2 v_1(a_{11}v_1 + sa_{12}v_2) = 0, \\ d_2\Delta v_2 - \sigma_2 v_2 + a_{11}v_1^2 + skv_3 - sa_{12}v_2 v_1 = 0, \\ -\sigma_3 v_3 + 2v_1 v_2 a_{12} - 2kv_3 = 0. \end{cases} \tag{2.34}$$

In this Section we prove existence of a local solution $v(s,t) \in \mathbb{R}^{3h}$ to (2.34) near $(s,t) = (0,0)$.

Theorem 2.4.1. *Let G_p be the proximity graph. If $\sigma_2, \sigma_3 > 0$, $t \mapsto F[f_t]$ is continuous and $F[f_t] > 0$, then there exist $\bar{s} > 0$ and $\bar{t} > 0$ such that the system* (2.34) *admits a non-negative solution $v \in C^0([0,\bar{s}] \times [0,\bar{t}]; \mathbb{R}^{3h})$.*

Proof. The proof relies on the construction of a contractive operator for the system (2.34). First we observe that in $s = t = 0$

$$\begin{cases} -v_1 + F[f_0] = 0, \\ d_2\Delta v_2 - \sigma_2 v_2 + a_{11}v_1^2 = 0, \\ -\sigma_3 v_3 + 2v_1 v_2 a_{12} - 2kv_3 = 0. \end{cases} \tag{2.35}$$

System (2.35) exhibits a unique solution $\bar{v}$ which can be obtained by subsequently solving the equations in (2.35). We start by solving

$$\bar{v}_1 = F[f_0] > 0.$$

Consider now the matrix

$$M_2 := d_2\Delta - \sigma_2 I_h$$

where I_h is the identity matrix in $\mathbb{R}^{h\times h}$. By the First Gershgorin Theorem [46], M_2 is invertible. Moreover, M_2 is Metzler, i.e. $(M_2)_{ij} \geq 0$ if $i \neq j$, and its spectrum satisfies

$$\Lambda(M_2) \subset \{z \in \mathbb{C} : \Re(z) < 0\}$$

therefore its inverse is entry-wise non-positive [19], meaning that $(M_2)^{-1}_{ij} \leq 0$ for all $i,j = 1,\ldots,h$. We can now solve

$$\bar{v}_2 = -a_{11}M_2^{-1}(\bar{v}_1^2) > 0.$$

Finally, concerning the density of the plaques, we have

$$\bar{v}_3 = \frac{2a_{12}\bar{v}_1\bar{v}_2}{(\sigma_3 + 2k)} > 0.$$

The Jacobian matrix at $t = s = 0$, $v = \bar{v}$ is given by

$$J(0,0,\bar{v}) = \begin{pmatrix} -I_h & 2a_{11}\operatorname{diag}(\bar{v}_1) & 2a_{12}\operatorname{diag}(\bar{v}_2) \\ 0 & d_2\Delta - \sigma_2 I_h & 2a_{12}\operatorname{diag}(\bar{v}_1) \\ 0 & 0 & -(\sigma_3 + 2k)I_h \end{pmatrix}. \tag{2.36}$$

Since σ_2, $\sigma_3 > 0$, the matrix $J(0,0,\bar{v})$ is invertible, hence the Implicit Function Theorem assures the existence of a local surface $\Phi(s,t) = v(s,t)$ with $\Phi(0,0) = \bar{v}$ and $\phi(s,t,\Phi(s,t)) = 0$, where ϕ is the vector field associated to system (2.34):

$$\phi(s,t,v) = \begin{pmatrix} sd_1\Delta v_1 - v_1 + F[f_t] + ks^3 v_3 - s^2 v_1(a_{11}v_1 + sa_{12}v_2) \\ d_2\Delta v_2 - \sigma_2 v_2 + a_{11}v_1^2 + skv_3 - sa_{12}v_2 v_1 \\ -\sigma_3 v_3 + 2v_1 v_2 a_{12} - 2kv_3 \end{pmatrix} \in \mathbb{R}^{3h}. \tag{2.37}$$

Indeed the map

$$G(s,t,v) := v - J(0,0,\bar{v})^{-1}\phi(s,t,v) \tag{2.38}$$

is a contraction on the closed ball $\overline{B_R(0,0,\bar{v})}$ uniformly in s,t. Since $G_v(0,0,\bar{v}) = 0_h$, by continuity of G and G_v there exist $K \in (0,1)$ and $\bar{s}$, $\bar{t} > 0$ such that

$$\sup_{\substack{y \in \overline{B_R(0,0,\bar{v})} \\ s\in[0,\bar{s}],\ t\in[0,\bar{t}]}} ||G_v(s,t,y)|| < K. \tag{2.39}$$

It immediately follows that

$$|G(s,t,v_1) - G(s,t,v_2)| \leq \sup_{y\in\overline{B_R(0,0,\bar{v})}} ||D_v G(s,t,y)|| \cdot |v_1 - v_2| < K|v_1 - v_2| \tag{2.40}$$

for all $v_1, v_2 \in \overline{B_R(0,0,\bar{v})}$. Hence $v \mapsto G(v)$ is contractive on

$$X = \{v \in C^0([0,\bar{s}] \times [0,\bar{t}]; \mathbb{R}^{3h}) : \ |v(s,t) - \bar{v}| \leq R,\ \forall s,t \in [0,\varepsilon] \times [0,T]\}.$$

To get the invariance on X, first we observe that by continuity of ϕ and $F[f_t]$, if $v \in X$, then $G(v) \in C^0([0,\bar{s}] \times [0,\bar{t}]; \mathbb{R}^{3h})$. Moreover, if $v \in X$,

$$\begin{aligned} |G(v(s,t)) - \bar{v}| = |G(v(s,t)) - G(\bar{v}(0,0))| &\leq |G(v(s,t)) - G(v(0,0))| \\ +K|v(0,0) - \bar{v}(0,0)| &\leq |G(v(s,t)) - G(v(0,0))| + KR. \end{aligned}$$

By continuity of v, ϕ and $F[f_t]$ and the uniform bound $|v| \leq R + |\bar{v}|$ we can choose $\bar{s}$ and $\bar{t}$ small enough such that $G(v) \in X$. Since $\bar{v} > 0$, by continuity of Φ, up to reducing $\bar{s}$ and $\bar{t}$ we can conclude that $v(s,t) \geq 0$ for all $(s,t) \in [0,\bar{s}] \times [0,\bar{t}]$. □

2.4.2 Positivity properties

In this Section we establish some positivity results regarding the equilibrium solutions to system (2.34). In Theorem 2.4.1 we have shown that $v(0,0) > 0$ and $v(s,t) \geq 0$ by restricting its domain. We now show that the local solution satisfies a positivity constraint induced by the structure of the nonlinear equations (2.34), which implies a "strong maximum principle" for v.

Lemma 2.4.2. *Let $F(t,i) := F[f_{i,t}] > 0$ for all $i \in V$. Let v be a solution to* (2.34) *on a closed rectangle $\mathcal{R} \subset \mathbb{R}^+ \times \mathbb{R}^+$ such that $(0,0) \in \mathcal{R}$. Then $v(i,s,t) > 0$ for all $i \in V$, $(s,t) \in \mathcal{R}$.*

Proof. By contradiction, suppose there exist $i \in V$, $k \in \{1,2,3\}$, $(\bar{s},\bar{t}) \in R$ such that $v_k(i,\bar{s},\bar{t}) = 0$. Assume that $k = 1$. The equation for v_1 at node i and $(s,t) = (\bar{s},\bar{t})$ is

$$sd_1\Delta v_1(i,\bar{s},\bar{t}) + F[f_{i,t}] + ks^3 v_3(i,\bar{s},\bar{t}) = 0. \tag{2.41}$$

Since $F[f_{i,t}] > 0$ and $v_3(i, \bar{s}, \bar{t}) \geq 0$ we have

$$0 > sd_1 \Delta v_1(i, \bar{s}, \bar{t}) = sd_1 \sum_{j \sim i} \omega_{ij} v_1(j, \bar{s}, \bar{t}) \tag{2.42}$$

hence there exists a node $j \sim i$ such that $v_1(j, \bar{s}, \bar{t}) < 0$, which is impossible. Now assume $k = 2$ and evaluate the equation for v_2 at node i and $(s, t) = (\bar{s}, \bar{t})$:

$$d_2 \Delta v_2(i, \bar{s}, \bar{t}) + a_{11} v_1^2(i, \bar{s}, \bar{t}) + skv_3(i, \bar{s}, \bar{t}) = 0. \tag{2.43}$$

Again we know that $v_1(i, \bar{s}, \bar{t}) > 0$ and $v_3(i, \bar{s}, \bar{t}) \geq 0$, therefore

$$0 > d_2 \Delta v_2(i, \bar{s}, \bar{t}) = d_2 \sum_{j \sim i} \omega_{ij} v_2(j, \bar{s}, \bar{t}) \tag{2.44}$$

which is impossible. Recall that the explicit expression for v_3 is

$$v_3 = \frac{2a_{12} v_1 v_2}{\sigma_3 + 2k} \tag{2.45}$$

and by the argument above $v_3(i, \bar{s}, \bar{t}) > 0$, therefore $v(i, s, t) > 0$ for all $i \in V$, $(s, t) \in \mathcal{R}$. □

The positivity result can be extended to the weaker case of $F \geq 0$ to obtain $v \geq 0$.

Lemma 2.4.3. *Let $F(t, i) := F[f_{i,t}] \geq 0$ for all $i \in V$. Let v be a solution to* (2.34) *on a closed rectangle $\mathcal{R} \subset \mathbb{R}^+ \times \mathbb{R}^+$ such that* $(0, 0) \in \mathcal{R}$. *Then $v(i, s, t) \geq 0$ for all $i \in V$, $(s, t) \in \mathcal{R}$.*

Proof. Let $\delta > 0$ and consider the nonlinear system (2.34) issued by the monomers' source $F[f_{i,t}] + \delta$. The problem rephrases as

$$\text{find } v_\delta \in \mathbb{R}^{3h} \text{ s.t. } \phi_\delta(v_\delta) = 0 \tag{2.46}$$

where

$$\phi_\delta(v) = \begin{pmatrix} sd_1 \Delta v_1 - v_1 + F[f] + \delta + k_1 s^3 v_3 - s^2 v_1 (a_{11} v_1 + s a_{12} v_2) \\ d_2 \Delta v_2 - \sigma_2 v_2 + a_{11} v_1^2 + sk_2 v_3 - s a_{12} v_2 v_1 \\ -\sigma_3 v_3 + 2 v_1 v_2 a_{12} - (k_1 + k_2) v_3 \end{pmatrix} \in \mathbb{R}^{3h}, \quad v \in \mathbb{R}^{3h}. \tag{2.47}$$

Theorem 2.4.1 assures that there exists a local solution v_δ to (2.46) and Lemma 2.4.2 implies that $v_\delta > 0$ on its domain. We want to show that $v_\delta \to v$ as $\delta \to 0$ in

$$X = \{z \in C^0(\mathcal{R}; \mathbb{R}^{3h}),\ |z(s, t) - \bar{v}| \leq R \text{ for all } s, t \in \mathcal{R}\},$$

where v is a solution to the nonlinear system (2.46) with $\delta = 0$, i.e. $\phi(v) := \phi_0(v) = 0$, and $\bar{v} := v(0, 0)$. Up to reducing δ, we may assume that $v_\delta \in X$. We have

$$\begin{aligned} |v_\delta(s, t) - v(s, t)| &= |G_\delta(v_\delta(s, t)) - G(v(s, t))| \\ &\leq |G_\delta(v_\delta(s, t)) - G_\delta(v(s, t))| + |G_\delta(v(s, t)) - G(v(s, t))| \\ &\leq K |v_\delta(s, t) - v(s, t)| + |G_\delta(v(s, t)) - G(v(s, t))|, \end{aligned} \tag{2.48}$$

where, by (2.38),

$$G_\delta(v) := v - J(0, 0, v_\delta(0, 0))^{-1} \phi_\delta(v), \quad G := G_0.$$

Observe that

$$\begin{aligned}|G_\delta(v(s,t)) - G(v(s,t))| &= |v - J(0,0,v_\delta(0,0))^{-1}\phi_\delta(v(s,t)) - v + J(0,0,v(0,0))^{-1}\phi(v(s,t))| \\ &= |J(0,0,v_\delta(s,t))^{-1}\phi_\delta(v(s,t))| \end{aligned} \tag{2.49}$$

where we have used that $\phi(v(s,t)) = 0$ and J depends on δ only through v_δ. Clearly by (2.47)

$$\phi_\delta(v) = (\underbrace{\delta,\dots,\delta}_{\in\,\mathbb{R}^h}, \underbrace{0,\dots,0}_{\in\,\mathbb{R}^{2h}})^T. \tag{2.50}$$

Recall that $J(0,0,v_\delta)$ is a non singular block-upper-triangular matrix, hence the inverse is still block-upper-triangular and we can explicitly calculate the RHS of (2.49)

$$J(0,0,v_\delta(0,0))^{-1}\phi_\delta(v(s,t)) = (\delta J_{1,1}(0,0,v_\delta(0,0))^{-1}\boldsymbol{e}, \underbrace{0,\dots,0}_{\in\,\mathbb{R}^{2h}})^T$$

where $\boldsymbol{e}^T = (1,1,\dots,1) \in \mathbb{R}^h$ and $J_{1,1}(0,0,v_\delta(0,0))^{-1}$ is the inverse of the block of $J(0,0,v_\delta(0,0))$ in position $(1,1)$. By definition of $J(0,0,v)$ in (2.36) and (2.50) we can see that

$$J(0,0,v_\delta(0,0))^{-1}\phi_\delta(v(s,t)) = (-\delta\,\mathrm{Id}\,\boldsymbol{e}, \underbrace{0,\dots,0}_{\in\mathbb{R}^{2h}})^T = (\underbrace{\delta,\dots,\delta}_{\in\,\mathbb{R}^h}, \underbrace{0,\dots,0}_{\in\,\mathbb{R}^{2h}})^T. \tag{2.51}$$

Inserting this expression in (2.48) gives

$$|v_\delta(s,t) - v(s,t)| \le \frac{\delta\sqrt{h}}{1-K}, \qquad \text{for all } s,t \in \mathcal{R}, \tag{2.52}$$

which ensures uniform convergence of $v_\delta \to v$, therefore $v \ge 0$. □

2.4.3 Global existence

So far we have treated s as a parameter for the local surface Φ. Returning to the model, we have proved the existence of an equilibrium for large values of σ_1. We now investigate the extension of the result for smaller values of $\sigma_1 > 0$, namely for larger values of $s > 0$. Let us suppose that the solution $(s,t) \mapsto v(s,t)$ exists on the maximal domain $[0,s^*) \times [0,t^*)$, where $t^* \le T$. The regularity in time of v depends on the regularity of $F[f_t]$. Here, we assume that $t \mapsto F[f_t]$ is Lipschitz continuous on $[0,T]$. As we shall see later, this condition is natural and follows from the construction of the solution to the evolution equation for f. Moreover, $s \mapsto \phi(s,t,v)$ is Lipschitz continuous on compact subsets of $\mathbb{R}^+$ uniformly in t. It follows that the map $(s,t) \mapsto v(s,t)$ is Lipschitz continuous on rectangles of the form $[0,S] \times [0,T]$ for all $S > 0$. Hence, fixing $S > s^*$, it can be extended to $[0,s^*] \times [0,t^*]$ and it is positive by Lemma 2.4.2. To apply the argument in Theorem 2.4.1, we need to prove that the Jacobian matrix of the system (2.34) is invertible at $v(s^*,t^*)$. The Jacobian is given by

$$J(v) = D\Delta + P(v) \tag{2.53}$$

where $D\Delta$ is the $3h \times 3h$ block diagonal matrix

$$D\Delta = \begin{pmatrix} d_1\Delta & & \\ & d_2\Delta & \\ & & O_h \end{pmatrix} \tag{2.54}$$

and P is the reaction matrix

$$P = \begin{pmatrix} P_{11} & P_{12} & P_{13} \\ P_{21} & P_{22} & P_{23} \\ P_{31} & P_{32} & P_{33} \end{pmatrix}$$

where $P_{ij} \in \mathbb{R}^{h\times h}$ and

$$\begin{aligned} &P_{11} = -I_h - 2s^2 a_{11}\operatorname{diag}(v_1) - s^3 a_{12}\operatorname{diag}(v_2), \qquad P_{12} = 2a_{11}\operatorname{diag}(v_1) - sa_{12}\operatorname{diag}(v_2), \\ &P_{13} = 2a_{12}\operatorname{diag}(v_2), \qquad P_{21} = -s^3 a_{12}\operatorname{diag}(v_1), \qquad P_{22} = \sigma_2 I_h - sa_{12}\operatorname{diag}(v_1), \\ &P_{23} = 2a_{12}\operatorname{diag}(v_1), \qquad P_{13} = ks^3 I_h, \qquad P_{23} = ksI_h, \qquad P_{33} = (\sigma_3 + 2k)I_h. \end{aligned} \tag{2.55}$$

In general, the precise characterisation of the spectral properties of the matrix J is not a trivial problem. Moreover, the argument in Theorem 2.4.1 does not provide a constructive definition of the equilibrium solution v. Hence we need to exploit the particular structure of the system (2.34). We start by taking derivatives in the following order

$$(v_1(1), v_2(1), v_3(1), v_1(2), v_2(2), v_3(2), \dots, v_1(h), v_2(h), v_3(h)). \tag{2.56}$$

This approach enables us to localise the nonlinear reaction terms in a block diagonal matrix and write the Jacobian as:

$$\tilde{J}(s,t,v) = \operatorname{diag}(P_i)_{i\in V} + B \tag{2.57}$$

where B is the spatial operator and P_i the Jacobian of the reaction terms at node i:

$$P_i = \begin{pmatrix} -(1 + 2s^2 a_{11}v_1(i) + s^3 a_{12}v_2(i)) & 2a_{11}v_1(i) - sa_{12}v_2(i) & 2a_{12}v_2(i) \\ -s^3 a_{12}v_1(i) & -(\sigma_2 + sa_{12}v_1(i)) & 2a_{12}v_1(i) \\ s^3 k & sk & -(\sigma_3 + 2k) \end{pmatrix}. \tag{2.58}$$

Now solve the equation for v_3 in (2.34) to get

$$v_3 = \frac{2a_{12}v_1v_2}{\sigma_3 + 2k}. \tag{2.59}$$

System (2.34) becomes

$$\begin{cases} sd_1\Delta v_1 - v_1 + F[f] + s^3\frac{2k}{\sigma_3+2k}a_{12}v_1v_2 - s^2 v_1(a_{11}v_1 + sa_{12}v_2) = 0, \\ s^2 d_2\Delta v_2 - s^2\sigma_2 v_2 + a_{11}s^2 v_1^2 + s^3\frac{2k}{\sigma_3+2k}a_{12}v_1v_2 - s^3 a_{12}v_2v_1 = 0. \end{cases} \tag{2.60}$$

where we have multiplied the equation for v_2 by $s^2 > 0$. The Jacobian of the reaction terms at node i becomes

$$P_i = \begin{pmatrix} -(1 + 2s^2 a_{11}v_1(i) + \frac{\sigma_3}{\sigma_3+2k}s^3 a_{12}v_2(i)) & 2s^2 a_{11}v_1(i) - \frac{\sigma_3}{\sigma_3+2k}s^3 a_{12}v_2(i) \\ -\frac{\sigma_3}{\sigma_3+2k}s^3 a_{12}v_1(i) & -s^2(\sigma_2 + \frac{\sigma_3}{\sigma_3+2k}sa_{12}v_1(i)) \end{pmatrix} \tag{2.61}$$

and it exhibits the following row Gershgorin disks:

$$\mathcal{G}_1^r = \left\{ \left| z + 1 + 2s^2 a_{11}v_1(i) + \frac{\sigma_3}{\sigma_3 + 2k}s^3 a_{12}v_2(i) \right| \le \left| 2s^2 a_{11}v_1(i) - \frac{\sigma_3}{\sigma_3 + 2k}s^3 a_{12}v_2(i) \right| \right\},$$

$$\mathcal{G}_2^r = \left\{ \left| z + s^2\left(\sigma_2 + \frac{\sigma_3}{\sigma_3 + 2k}sa_{12}v_1(i)\right) \right| \le \frac{\sigma_3}{\sigma_3 + 2k}s^3 a_{12}v_1(i) \right\}.$$

Clearly the disks are located in the halfplane $\{\Re(z) < 0\}$, so by the First Gershgorin Theorem [46], P_i is invertible for all $i \in V$. Now the global Jacobian of system (2.60) is

$$\tilde{J}(s,t,v) = \mathrm{diag}(P_i)_{i\in V} \, + \, B,$$

B being the matrix obtained by permuting in the order (2.56) rows and columns of the block-Laplacian

$$\begin{pmatrix} d_1\Delta & 0 \\ 0 & s^2 d_2 \Delta \end{pmatrix}.$$

Therefore the row disks of $\tilde{J}$ are shifted in the direction $(-1,0)$ by $d_1 \sum_{j\sim 1} \omega_{1,j}$ or $s^2 d_2 \sum_{j\sim 2} \omega_{2,j}$, respectively, with radius augmented by the same quantity:

$$\begin{aligned} \tilde{\mathcal{G}}_1^r = \Bigg\{ &\left| z + d_1 \sum_{j\sim 1} \omega_{1,j} + 1 + 2s^2 a_{11} v_1(i) + \frac{\sigma_3}{\sigma_3 + 2k} s^3 a_{12} v_2(i) \right| \\ &\leq \left| 2s^2 a_{11} v_1(i) - \frac{\sigma_3}{\sigma_3 + 2k} s^3 a_{12} v_2(i) \right| + d_1 \sum_{j\sim 1} \omega_{1,j} \Bigg\}, \end{aligned} \tag{2.62}$$

$$\begin{aligned} \tilde{\mathcal{G}}_2^r = \Bigg\{ &\left| z + s^2 d_2 \sum_{j\sim 2} \omega_{2,j} + s^2 \left(\sigma_2 + \frac{\sigma_3}{\sigma_3 + 2k} s a_{12} v_1(i) \right) \right| \\ &\leq \frac{\sigma_3}{\sigma_3 + 2k} s^3 a_{12} v_1(i) + s^2 d_2 \sum_{j\sim 2} \omega_{2,j} \Bigg\}. \end{aligned} \tag{2.63}$$

We can conclude that $\tilde{J}$ is invertible by the First Gershgorin Theorem [46], hence the Implicit Function Theorem can be applied to the nonlinear system (2.60) at $(s,t) = (s^*, t^*)$ to extend v on $[s^*, s^{*'}] \times [t^*, t^{*'}]$ with continuity. Observe that the set of equilibria for (2.34) coincides with the set of equilibria for (2.60), hence the extension of v satisfies the equations in (2.34) and by Lemma 2.4.2 it is positive.

Finally, we have proven that $[0, s^*] \times [0, t^*]$ is not the maximal domain of existence, thus giving rise to a contradiction.

Remark 2.4.1. *We have shown that the Jacobian matrix related to the system* (2.60) *is Hurwitz, hence the steady state v is a locally stable solution to the $2h-$dimensional dynamical system*

$$\begin{cases} v_1' = s d_1 \Delta v_1 - v_1 + F[f] + s^3 \frac{2k}{\sigma_3 + 2k} a_{12} v_1 v_2 - s^2 v_1 (a_{11} v_1 + s a_{12} v_2), \\ v_2' = s^2 d_2 \Delta v_2 - s^2 \sigma_2 v_2 + a_{11} s^2 v_1^2 + s^3 \frac{2k}{\sigma_3 + 2k} a_{12} v_1 v_2 - s^3 a_{12} v_2 v_1. \end{cases} \tag{2.64}$$

Clearly, this does not imply local stability for the dynamical system defined by (2.31)-(2.34).

2.4.4 Local Stability

The quasi-static approximation of the full ODE-PDE model requires the fast convergence of the solution to the ODE system (2.31)-(2.34) towards the respective equilibrium. In the previous Section we observed that the structure of the Jacobian (2.53)-(2.55) of the ODE system does not immediately yield information about the localisation of its spectrum. In this Section, we consider the global system of ODEs on the nodes and prove that the associated equilibrium solution is locally stable under suitable conditions on the parameters of the model. Specifically, we require the clearance rate parameters to be sufficiently large.

Consider the dynamical system

$$\begin{cases} u_1' = d_1\Delta u_1 - \sigma_1 u_1 + F(t) + \Gamma_1, \\ u_2' = d_2\Delta u_2 - \sigma_2 u_2 + \Gamma_2, \\ u_3' = -\sigma_3 u_3 + \Gamma_3, \\ u(0) = u_0 \in \mathbb{R}^{3h}, \end{cases} \tag{2.65}$$

$$\begin{cases} \Gamma_1 = -u_1(a_{11}u_1 + a_{12}u_2) + ku_3, \\ \Gamma_2 = a_{11}u_1^2 - a_{12}u_1u_2 + ku_3, \\ \Gamma_3 = -2a_{12}u_1u_2 - 2ku_3, \end{cases} \tag{2.66}$$

on the slow time scale, where the coefficients of diffusion, aggregation, fragmentation, production and clearance are of order $O(1/\phi)$ provided that ϕ is the proportion between the slow and fast timescale. In Section 2.4 we have proved the existence of a non-negative steady state $\boldsymbol{u}^*$ to (2.65) under the assumption $\sigma_1 > \bar{\sigma}_1$ (or equivalently $s^* < S$). Let $\boldsymbol{u}$ be a solution to (2.65) and set $\boldsymbol{z} := \boldsymbol{u} - \boldsymbol{u}^*$. Let $P \in \mathbb{R}^{3\times 3}$ be a diagonal positive-definite matrix

$$P = \begin{pmatrix} p_1 & 0 & 0 \\ 0 & p_2 & 0 \\ 0 & 0 & p_3 \end{pmatrix}, \quad p_k > 0 \text{ for } k = 1,2,3 \tag{2.67}$$

and consider the energy

$$E(t) := \sum_{i\in V} \boldsymbol{z_i}^T P \boldsymbol{z_i}, \tag{2.68}$$

where

$$\boldsymbol{z_i} = (z_1(i,t), z_2(i,t), z_3(i,t)) \in \mathbb{R}^3, \quad i \in V.$$

To obtain local stability of $\boldsymbol{u}^*$ we show that the map E is a Lyapunov function for system (2.65).

Theorem 2.4.4. *Let $\boldsymbol{u_0} \in \mathbb{R}^{3h}$ and $\boldsymbol{u}$ be a solution to (2.65) such that $\boldsymbol{u}(0) = \boldsymbol{u_0}$. Let $\boldsymbol{u}^*$ be an equilibrium solution to (2.65). Then there exist $C = C(k, a_{ij}, C_\mu)$ and $\delta > 0$ such that if $\tilde{\sigma} := \min_{k=1,2,3} \sigma_k > C$, then $|\boldsymbol{u}(t) - \boldsymbol{u}^*| \to 0$ provided that $\boldsymbol{u_0} \in B_\delta(\boldsymbol{u}^*)$.*

Proof. By definition of E we have

$$E'(t) = 2\sum_{i\in V} \boldsymbol{z_i}^T P \boldsymbol{z_i'} = 2\sum_{i\in V} \boldsymbol{z_i}^T P\left(d\Delta \boldsymbol{z_i} - \Sigma \boldsymbol{z_i} + \Gamma(\boldsymbol{u_i}) - \Gamma(\boldsymbol{u_i^*})\right) \tag{2.69}$$

where

$$d\Delta \boldsymbol{z_i} = \begin{pmatrix} d_1\Delta z_1(i,t) \\ d_2\Delta z_2(i,t) \\ 0 \end{pmatrix} = \begin{pmatrix} d_1 \sum_{j\in V} \omega_{ij}\left(z_1(j,t) - z_1(i,t)\right) \\ d_2 \sum_{j\in V} \omega_{ij}\left(z_2(j,t) - z_2(i,t)\right) \\ 0 \end{pmatrix} \in \mathbb{R}^3,\ i \in V \tag{2.70}$$

and the reaction terms are

$$\Sigma = \begin{pmatrix} \sigma_1 & 0 & 0 \\ 0 & \sigma_2 & 0 \\ 0 & 0 & \sigma_3 \end{pmatrix} \in \mathbb{R}^{3\times 3}, \quad \Gamma(\boldsymbol{u_i}) = \begin{pmatrix} \Gamma_1(u(i,t)) \\ \Gamma_2(u(i,t)) \\ \Gamma_3(u(i,t)) \end{pmatrix} \in \mathbb{R}^3. \tag{2.71}$$

In (2.69), for all $i \in V$ we linearise Γ near $\boldsymbol{u_i^*}$ to get

$$E'(t) = 2\sum_{i\in V} \boldsymbol{z_i}^T P\left(d\Delta \boldsymbol{z_i} - \Sigma \boldsymbol{z_i} + J_\Gamma(\boldsymbol{u_i^*})\boldsymbol{z_i} + R(\boldsymbol{z_i})\right) =: T_{diff} + T_{react} + T_R. \tag{2.72}$$

To simplify the notations we will often write $J_i := J_\Gamma(\boldsymbol{u_i^*})$. Now consider the diffusive contribution in (2.72):

$$\begin{aligned} T_{diff} &= 2\sum_{i\in V} \boldsymbol{z_i}^T P d\Delta \boldsymbol{z_i} = 2\sum_{i\in V}\sum_{k=1}^{2} z_k(i,t)p_k d_k \sum_{j\in V}\omega_{ij}\left[z_k(j,t) - z_k(i,t)\right] \\ &= 2\sum_{k=1}^{2} p_k d_k \sum_{i,j\in V}\omega_{ij} z_k(i,t)\left[z_k(j,t) - z_k(i,t)\right] = 2\sum_{k=1}^{2} p_k d_k z_k^T \Delta z_k. \end{aligned} \tag{2.73}$$

By a standard result on the quadratic form associated to the symmetric Graph Laplacian we conclude that $T_{diff} \le 0$. Indeed we have

$$\begin{aligned} \sum_{i,j\in V}\omega_{ij}(z_k(j,t) - z_k(i,t))^2 &= \sum_{i,j\in V}\omega_{ij} z_k(j,t)^2 + \sum_{i,j\in V}\omega_{ij} z_k(i,t)^2 - 2\sum_{i,j\in V}\omega_{ij} z_k(i,t) z_k(j,t) \\ &= \sum_{j\in V}\deg(j) z_k(j,t)^2 + \sum_{i\in V}\deg(i) z_k(i,t)^2 - 2\sum_{i,j\in V}\omega_{ij} z_k(i,t) z_k(j,t) \\ &= 2\sum_{i\in V}\deg(i) z_k(i,t)^2 - 2\sum_{i,j\in V}\omega_{ij} z_k(i,t) z_k(j,t) = -2 z_k^T \Delta z_k. \end{aligned} \tag{2.74}$$

Inserting the expression (2.74) in (2.73) yields

$$T_{diff} = -\sum_{k=1}^{2} p_k d_k \sum_{i,j\in V}\omega_{ij}(z_k(j,t) - z_k(i,t))^2 \le 0. \tag{2.75}$$

The reaction term T_{react} is

$$T_{react} = 2\sum_{i\in V}\boldsymbol{z_i}^T P\left(J_i \boldsymbol{z_i} - \Sigma \boldsymbol{z_i}\right) = 2\sum_{i\in V}\boldsymbol{z_i}^T P J_i \boldsymbol{z_i} - 2\sum_{i\in V}\boldsymbol{z_i}^T P \Sigma \boldsymbol{z_i} =: A - B. \tag{2.76}$$

A straightforward calculation on B gives

$$2\sum_{i\in V}\boldsymbol{z_i}^T P\Sigma \boldsymbol{z_i} = 2\sum_{i\in V}\sum_{k=1}^{3} z_k(i,t)^2 p_k \sigma_k \ge 2\underbrace{\min_{k=1,2,3}\sigma_k}_{=:\tilde\sigma}\sum_{i\in V}\sum_{k=1}^{3} z_k(i,t)^2 p_k = 2\tilde\sigma\sum_{i\in V}\boldsymbol{z_i}^T P \boldsymbol{z_i}. \tag{2.77}$$

Concerning A, since we do not control the sign of the entries of J_i, we cluster the matrix PJ_i in a single matrix by means of

$$\tilde J_i := P^{1/2} J_i P^{-1/2}. \tag{2.78}$$

Defining the vector $\boldsymbol{w_i} = P^{1/2}\boldsymbol{z_i}$ we get

$$\boldsymbol{z_i}^T P \boldsymbol{z_i} = \boldsymbol{z_i^T} P^{1/2} P^{1/2} J_i P^{-1/2} P^{1/2} \boldsymbol{z_i} = \boldsymbol{w_i^T}\tilde J_i \boldsymbol{w_i} \tag{2.79}$$

and

$$||\boldsymbol{w_i}||_{\mathbb{R}^3} = ||P^{1/2}\boldsymbol{z_i}||_{\mathbb{R}^3} = \sqrt{\boldsymbol{z_i^T} P \boldsymbol{z_i}}. \tag{2.80}$$

By (2.79) and Young's inequality, we get

$$
\begin{aligned}
2|\boldsymbol{w_i^T}\tilde{J}_i\boldsymbol{w_i}| &\le 2||\boldsymbol{w_i}||_{\mathbb{R}^3}\cdot||\tilde{J}_i\boldsymbol{w_i}||_{\mathbb{R}^{3h}} \le \varepsilon||\boldsymbol{w_i}||^2_{\mathbb{R}^3}+\frac{1}{\varepsilon}||\tilde{J}_i\boldsymbol{w_i}||^2_{\mathbb{R}^3}\\
&\le \varepsilon||\boldsymbol{w_i}||^2_{\mathbb{R}^3}+\frac{1}{\varepsilon}\underbrace{||\tilde{J}_i||^2_{op}}_{=:\kappa^2_{i,p}}\cdot||\boldsymbol{w_i}||^2_{\mathbb{R}^3},\quad \forall\varepsilon>0.
\end{aligned}
\tag{2.81}
$$

The RHS of (2.81) attains its minimum at $\varepsilon=\kappa_{i,p}$, hence by (2.80) we get

$$
2|\boldsymbol{w_i^T}\tilde{J}_i\boldsymbol{w_i}| \le 2\kappa^2_{i,p}||\boldsymbol{w_i}||^2_{\mathbb{R}^3} = 2\kappa^2_{i,p}\boldsymbol{z_i^T}P\boldsymbol{z_i} \le 2\max_{i\in V}\{\kappa^2_{i,p}\}\cdot\boldsymbol{z_i^T}P\boldsymbol{z_i}. \tag{2.82}
$$

Inserting the estimates (2.77) and (2.82) in (2.76) gives

$$
T_{react} \le 2\left(\max_{i\in V}\{\kappa^2_{i,p}\}-\tilde{\sigma}\right)\sum_{i\in V}\boldsymbol{z_i^T}P\boldsymbol{z_i}. \tag{2.83}
$$

By selecting P such that $\max_{i\in V}\{\kappa^2_{i,p}\}=\max_{i\in V}||P^{1/2}J_iP^{-1/2}||^2_{op}<\tilde{\sigma}$ we get

$$
T_{react} \le -2\alpha\sum_{i\in V}\boldsymbol{z_i^T}P\boldsymbol{z_i} = -2\alpha\, E(t),\quad \alpha>0. \tag{2.84}
$$

For example let $P=I_h$. Since $||A||_2=\max_\ell\sigma_\ell(A)$ and $||A||_F=\left(\sum_\ell\sigma^2_\ell(A)\right)^{1/2}$ for all $A\in\mathbb{R}^{h\times h}$, where $\sigma_1(A),\dots,\sigma_h(A)$ are the singular values of A (for details on matrix norms, see [46]), it follows that

$$
||P^{1/2}J_iP^{-1/2}||^2_{op} = ||J_i||^2_{op} = ||J_i||^2_2 \le ||J_i||^2_F = \sum_{\ell,m}(J_i)^2_{\ell m}. \tag{2.85}
$$

Recalling that

$$
J_i = \begin{pmatrix} -2a_{11}u_1^*(i)-a_{12}u_2^*(i) & 2a_{11}u_1^*(i)-a_{12}u_2^*(i) & 2a_{12}u_2^*(i)\\ -a_{12}u_1^*(i) & -a_{12}u_1^*(i) & 2a_{12}u_1^*(i)\\ k & k & -2k \end{pmatrix} \tag{2.86}
$$

we obtain the uniform (in $i\in V$) estimate

$$
||J_i||^2_2 \le ||J_i||^2_F \le 8a^2_{11}u_1^*(i)^2+12a^2_{12}u_2^*(i)^2+6k^2 \underbrace{\le}_{(2.14)} \frac{C(F)}{\tilde{\sigma}^2}+6k^2 \tag{2.87}
$$

where

$$
F \le C_\mu =: C(F).
$$

Clearly $\frac{C(F)}{\tilde{\sigma}^2}+6k^2<\tilde{\sigma}^2$ if $\tilde{\sigma}$ is large enough.

We conclude by estimating the remainder term T_R, where $R(\boldsymbol{z_i})=O(||\boldsymbol{z_i}||^2)$ as $\boldsymbol{z_i}\to\boldsymbol{0}$. Hence there exist $\delta,C>0$ such that $||\boldsymbol{u_i}-\boldsymbol{u_i^*}||<\delta$ implies

$$
\begin{aligned}
|T_R| &\le 2\sum_{i\in V}|\boldsymbol{z_i^T}PR(\boldsymbol{z})| \le 2\sum_{i\in V}||\boldsymbol{z_i}||_{\mathbb{R}^3}\cdot||PR(\boldsymbol{z_i})||_{\mathbb{R}^3} \le 2\sum_{i\in V}||\boldsymbol{z_i}||_{\mathbb{R}^3}\cdot||P||_{op}\cdot||R(\boldsymbol{z_i})||_{\mathbb{R}^3}\\
&\le 2C\sum_{i\in V}||\boldsymbol{z_i}||^3_{\mathbb{R}^3}\cdot||P||_{op}.
\end{aligned}
$$

Now observe that for all $i \in V$

$$||\boldsymbol{z_i}||^2_{\mathbb{R}^3} \cdot ||P||_{op} = ||\boldsymbol{z_i}||^2_{\mathbb{R}^3} \cdot ||P||_2 = \left(\sum_{k=1}^{3} z_k(i,t)^2\right) \max_k p_k = \left(\sum_{k=1}^{3} \frac{p_k}{p_k} z_k(i,t)^2\right) \max_k p_k \leq \underbrace{\frac{\max_k p_k}{\min_k p_k}}_{=:C_P} \boldsymbol{z_i^T} P \boldsymbol{z_i}.$$

The remainder term rewrites as

$$|T_R| \leq 2C'_P \sum_{i\in V} ||\boldsymbol{z_i}||_{\mathbb{R}^3} \cdot \boldsymbol{z_i^T} P \boldsymbol{z_i} \leq 2\delta\, C'_P \sum_{i \in V} \boldsymbol{z_i^T} P \boldsymbol{z_i} = 2\delta\, C'_P E(t). \tag{2.88}$$

Selecting δ such that $2\delta C'_P \leq \alpha$ we finally obtain

$$E'(t) \leq -\alpha E(t) \Rightarrow E(t) \leq E(0)\exp(-\alpha t), \quad \alpha > 0. \tag{2.89}$$

Recalling the definition of E we get

$$E(t) = \sum_{i\in V} \boldsymbol{z_i}^T P \boldsymbol{z_i} = \sum_{i \in V}\sum_{k=1}^{3} z_k(i,t)^2 p_k \geq \sum_{i\in V}\sum_{k=1}^{3} z_k(i,t)^2 \min_k p_k = \min_k p_k ||z(t)||^2_{\mathbb{R}^{3h}} \tag{2.90}$$

hence, (2.89) implies local stability. □

2.5 Existence: the case $J[f] \equiv 0$

The following sections are devoted to the proof of Theorem 2.3.1. We first deal with the conservative case $J[f] \equiv 0$, which notably simplifies the proof. In fact, under the assumption of vanishing drifts in the transport equation for f, the measure f is solely determined by the characteristics associated with (2.15) and the initial datum $f(0)$.

For clarity, we briefly recall the model. The unknowns are the measure f and the Aβ concentrations u_1, u_2, u_3 satisfying the equations

$$\begin{cases} \partial_t f_{i,t} + (v[f_{i,t}]f_{i,t})_a = 0, \\ f_{i,0} = f_i(0) \quad i \in V, \end{cases} \tag{2.91}$$

$$\begin{cases} d_1 \Delta u_1 - \sigma_1 u_1 + F[f] + \Gamma_1 = 0, \\ d_2\Delta u_2 - \sigma_2 u_2 + \Gamma_2 = 0, \\ -\sigma_3 u_3 + \Gamma_3 = 0, \end{cases} \qquad \sigma_k > 0 \quad k = 1,2,3, \quad i \in V. \tag{2.92}$$

The monomers' production term is

$$F[f_{i,t}] = C_\mu \int_0^1 (\mu_0 + a)(1-a)\, df_{i,t}(a) \tag{2.93}$$

and the rate of degeneration is

$$v[f_{i,t}](a,t) = C_G \int_{[0,1]} (b-a)^+\, df_{i,t}(b) + C_s(1-a)(u_2(i,t) - \bar{U}_2)^+. \tag{2.94}$$

In this setting, Definition 2.3.1 becomes

Definition 2.5.1. *A* $4-$*tuple* (f, u_1, u_2, u_3) *is a solution to* (2.91), (2.92) *if*

1. $f \in \mathcal{L}(V; C([0,T]; X_{[0,1]}))$; $u_k \in C([0,T], \mathbb{R}^h)$, $u_k(i) \geq 0$ *for all* $k = 1, 2, 3$ *and* $i = 1, \dots, h$;

2. f *is a solution to* (2.91) *in a weak sense:*

$$\int_0^t \left(\int (\phi_s(a,s) + \phi_a(a,s) v_i(a,s)) df_{i,s}(a) \right) ds = \int \phi(\cdot, t)\, df_{i,t} - \int \phi(\cdot, 0)\, df_i(0) \tag{2.95}$$

for all $\phi \in C^1([0,1] \times [0,T])$ *and* $i = 1, \dots, h$, *where* v *is defined in* (2.94);

3. (u_1, u_2, u_3) *satisfies the following graph equations:*

$$\begin{cases} d_1 \Delta u_1(t) - \sigma_1 u_1(t) + F[f(t)] + \Gamma_1(t) = 0, \\ d_2 \Delta u_2(t) - \sigma_2 u_2(t) + \Gamma_2(t) = 0, \\ -\sigma_3 u_3(t) + \Gamma_3(t) = 0, \end{cases} \tag{2.96}$$

where $F[f]$ *and the reaction terms* Γ_k *are given by* (2.93) *and* (2.9), *respectively.*

2.5.1 The Characteristics

Let $f_{i,t} \in C^0([0,T]; X_{[0,1]})$ and $u \in C^0([0,T]; \mathbb{R}^{3h})$. Consider the characteristics problem associated with (2.95)

$$\begin{cases} \partial_t A_i(y,t) = v_i(A_i(y,t), t), \\ A_i(y,0) = y \in [0,1], \quad i \in V. \end{cases} \tag{2.97}$$

Since (u_1, u_2, u_3) belongs to a compact set B in $\mathbb{R}^{3h}$ (where $u_1 = (u_1(i))_{i=1}^h \in \mathbb{R}^h$), it is uniformly bounded by a constant $C = C(B)$ and by (2.94) we have that $a \mapsto v_i(a,t)$ is Lipschitz continuous uniformly in t for all $i \in V$. By continuity of $t \mapsto f_{i,t}$ and $t \mapsto u(t)$, $t \mapsto v_{i,t}$ is continuous on $[0,T]$, so the Picard–Lindelöf theorem ensures existence of a classical local solution to problem (2.97). Several regularity properties of A_i follow from standard ODE theory, e.g. the continuity of A_i in t and y. We also have

$$v_i(a,t) \geq 0 \quad \text{for all } a \in [0,1] \text{ and } t \geq 0 \Rightarrow t \mapsto A_i(y,t) \text{ is increasing for all } y \in [0,1].$$

The characteristics map $[0,1]$ in $[0,1]$ for all t: consider the problem

$$\begin{cases} \partial_t A_i(1,t) = v_i(A_i(1,t), t), \\ A_i(1,0) = 1, \quad i \in V. \end{cases} \tag{2.98}$$

Since $v_i(1,t) = 0$ for all $t \in [0,T]$, it follows that $A_i(1,t) \equiv 1$ is a steady-state solution of (2.98). The uniqueness of the solution to (2.97) implies $A_i(1,t) = 1$ for all $t \in [0,T]$. Now set $\phi_i(y,t) = \partial_y A_i(y,t)$. The function ϕ_i satisfies the following problem

$$\begin{cases} \partial_t \phi_i(y,t) = \partial_a v_i(A_i(y,t), t) \phi_i(y,t), \\ \phi_i(y,0) = 1, \quad i \in V \end{cases} \tag{2.99}$$

which yields

$$\partial_y A_i(y,t) = \exp\left(\int_0^t \partial_a v_i(A_i(y,s),s)\,ds\right) > 0. \tag{2.100}$$

By (2.100) we have

$$0 \le A_i(y_1,t) < A_i(y_2,t) \le A_i(1,t) = 1 \quad \text{if } 0 \le y_1 < y_2 \le 1. \tag{2.101}$$

Specifically $y \mapsto A_i(y,t)$ is injective for all $t \in [0,T]$.

Following the lines of [14], before formulating problem (2.91) in terms of the characteristics, we prove a result on the support of the measure $f_{i,t}$.

Lemma 2.5.1. *Let $f \in \mathcal{L}(V; C([0,T]; X_{[0,1]}))$ a solution to* (2.95) *and $A_i(y,t)$ a solution to* (2.97). *Then*

$$\operatorname{supp} f_{i,t} \subseteq [A_i(0,t),1] \quad \textit{for all } i \in V \textit{ and } t \in (0,T]. \tag{2.102}$$

Proof. We recall that by Section 2.5.1 the characteristics $A_i(y,t)$ exist in the classical sense as a solution to (2.97) for all $i \in V$. Let $i \in V$ and $t \in (0,T]$. Let $h \in C^1(\mathbb{R})$ a non-decreasing function such that $h \equiv 0$ on $(-\infty,0]$ and $h \equiv 1$ on $[1,+\infty)$. Let $\delta > 0$ and set

$$h_\delta(s) = h\left(\frac{s}{\delta}\right), \quad \psi_\delta(a,\tau) = h_\delta(A_i(0,\tau)-a), \quad a \in [0,1],\, \tau \in [0,T].$$

Then $\psi_\delta \in C^1([0,1]\times[0,T])$, $\operatorname{supp}\psi_\delta(\cdot,\tau) = [0, A_i(0,\tau))$ for all $\tau \in (0,T]$, $\delta > 0$ and

$$\lim_{\delta\to 0^+} \psi_\delta(a,\tau) = \mathbb{1}_{[0,A_i(0,\tau))}(a) \quad \text{for } \tau \in (0,T].$$

Testing equation (2.95) on ψ_δ gives

$$\int_0^t \left(\int (\partial_\tau\psi_\delta(a,\tau) + \partial_a\psi_\delta(a,\tau)v_i(a,\tau))df_{i,\tau}(a)\right) d\tau \tag{2.103}$$

$$= \int \psi_\delta(\cdot,t)\,df_{i,t} - \int \psi_\delta(\cdot,0)\,df_i(0) = \int \psi_\delta(\cdot,t)\,df_{i,t} \tag{2.104}$$

since $\psi_\delta(a,0) = h\left(-\frac{a}{\delta}\right) = 0$ if $a \in [0,1]$. By (2.103) it suffices to show that

$$\int_0^t \left(\int (\partial_\tau\psi_\delta(a,\tau) + \partial_a\psi_\delta(a,\tau)v_i(a,\tau))df_{i,\tau}(a)\right) d\tau \to 0 \text{ as } \delta \to 0^+. \tag{2.105}$$

We have

$$\partial_\tau\psi_\delta = h'\left(\frac{A_i(0,\tau)-a}{\delta}\right)\frac{1}{\delta}\partial_\tau A_i(0,\tau) = h'\left(\frac{A_i(0,\tau)-a}{\delta}\right)\frac{v_i(A_i(0,\tau),\tau)}{\delta},$$

$$\partial_a\psi_\delta = h'\left(\frac{A_i(0,\tau)-a}{\delta}\right)\left(-\frac{1}{\delta}\right),$$

and therefore

$$|\partial_\tau\psi_\delta + v_i\partial_a\psi_\delta| = \left|h'\left(\frac{A_i(0,\tau)-a}{\delta}\right)\frac{v_i(A_i(0,\tau),\tau)-v_i(a,\tau)}{\delta}\right| \tag{2.106}$$

$$\le L_i\left|h'\left(\frac{A_i(0,\tau)-a}{\delta}\right)\frac{A_i(0,\tau)-a}{\delta}\right| \le L_i \sup_{z\in\mathbb{R}} zh'(z) \le C_i$$

where we have used that $v_i(\cdot, \tau)$ is Lipschitz continuous uniformly in time. Moreover $z \mapsto zh'(z)$ is continuous and compactly supported, hence $\sup_{z\in\mathbb{R}} zh'(z) < \infty$ and the bound does not depend on δ. By (2.106) we have

$$\begin{aligned} &\left|\int_0^t \left(\int (\partial_\tau \psi_\delta(a,\tau) + \partial_a \psi_\delta(a,\tau) v_i(a,\tau)) df_{i,\tau}(a)\right) d\tau\right| \\ &\leq L_i \int_0^t \left(\int \left| h'\left(\frac{A_i(0,\tau)-a}{\delta}\right) \frac{A_i(0,\tau)-a}{\delta}\right| df_{i,\tau} \llcorner E_{\delta,i,\tau}\right) d\tau \\ &\leq C_i \int_0^t \int df_{i,\tau} \llcorner E_{\delta,i,\tau}\, d\tau \end{aligned} \tag{2.107}$$

where $f_{i,\tau} \llcorner E_{\delta,i,\tau}$ denotes the restriction of $f_{i,\tau}$ on the set $E_{\delta,i,\tau} = (A_i(0,\tau)-\delta, A_i(0,\tau)) \cap [0, A_i(0,\tau)) = \operatorname{supp} h'\left(\frac{A_i(0,\tau)-a}{\delta}\right) \cap [0,1]$. Since $f_{i,\tau}$ is a probability measure we have

$$\left|\int df_{i,\tau} \llcorner E_{\delta,i,\tau}\right| \leq 1 \quad \text{for } \tau \in [0,T], i \in V, \delta > 0$$

hence by the dominated convergence theorem

$$\int_0^t \int df_{i,\tau} \llcorner E_{\delta,i,\tau}\, d\tau \to 0 \text{ as } \delta \to 0^+. \tag{2.108}$$

Now (2.103), (2.107) and (2.108) give

$$\int \psi_\delta(\cdot,t)\, df_{i,t} \to 0 \text{ as } \delta \to 0^+ \tag{2.109}$$

and

$$\int \psi_\delta(\cdot,t)\, df_{i,t} = \int \psi_\delta(\cdot,t) df_{i,t} \llcorner [0, A_i(0,t)) \to \int df_{i,t} \llcorner [0, A_i(0,t)) \text{ as } \delta \to 0^+ \tag{2.110}$$

by the dominated convergence theorem. Indeed $\psi_\delta(a,\tau) \leq 1$ for all $a \in [0,1], \tau \in [0,T]$ and $\lim_{\delta\to 0^+} \psi_\delta(a,\tau) = \mathbb{1}_{[0,A_i(0,\tau))]}(a)$. Finally (2.109) and (2.110) imply

$$\int df_{i,t} \llcorner [0, A_i(0,t)) = 0 \text{ for all } t \in (0,T]. \tag{2.111}$$

□

We look for a probability measure $g_{i,t}$ such that $f_{i,t}$ is the push forward of $g_{i,t}$ through the action of A_i:

$$f_{i,t} = A_i \# g_{i,t}, \quad i \in V. \tag{2.112}$$

Then $g_{i,t}$ satisfies the problem

$$\begin{cases} \partial_t g_{i,t} = 0, \\ g_{i,0} = f_i(0), \quad i \in V. \end{cases} \tag{2.113}$$

in a weak sense, whence $g_{i,t} \equiv g_{i,0}$ is a solution.

We reformulate the original problem in terms of the characteristics. $f_{i,t}$ is the push forward of g_i through A_i where g_i and A_i satisfy for all $i \in V$

$$\begin{cases} \partial_t A_i(y,t) = C_G \int_{[0,1]} (A_i(\xi,t) - A_i(y,t))^+ \, dg_{i,t}(\xi) + C_s(1 - A_i(y,t))(u_2(i,t) - \bar{U}_2)^+, \\ \partial_t g_{i,t} = 0, \\ d_1 \Delta u_1(t) - \sigma_1 u_1(t) + C_\mu \int_{[0,1]} (\mu_0 + A_i(\xi,t))(1 - A_i(\xi,t)) \, dg_{i,t}(\xi) + \Gamma_1(t) = 0, \\ d_2 \Delta u_2(t) - \sigma_2 u_2(t) + \Gamma_2(t) = 0, \\ -\sigma_3 u_3(t) + \Gamma_3(t) = 0, \end{cases} \tag{2.114}$$

with initial boundary conditions

$$\begin{cases} g_{i,0} = f_i(0), \\ A_i(y,0) = y, \end{cases} \qquad i \in V. \tag{2.115}$$

Definition 2.5.1 translates in the following formulation.

Definition 2.5.2. *A* $5-$*tuple* (g, A, u_1, u_2, u_3) *is a solution to* (2.114), (2.115) *if*

1. $g \in \mathcal{L}(V; C([0,T]; X_{[0,1]}))$;
2. $A_i \in C([0,1] \times [0,T]; [0,1])$, $\partial_t A_i \in C([0,1] \times [0,T]; \mathbb{R})$ *for all* $i \in V$;
3. A_i *satisfies* $(2.114)_1$ *and* $A_i(y,0) = y$ *for all* $i \in V$ *and* $y \in [0,1]$;
4. $u_k \in C([0,T], \mathbb{R}^h)$, $u_k(i) \geq 0$ *for all* $k = 1,2,3$ *and* $i = 1,\dots,h$;
5. g *is a solution to* $(2.114)_2(2.115)_1$ *in a weak sense: for all* $\phi \in C^1([0,1] \times [0,T])$

$$\int_0^t \left(\int (\phi_s(y,s) dg_{i,s}(y) \right) ds = \int \phi(\cdot,t) \, dg_{i,t} - \int \phi(\cdot,0) \, df_i(0); \tag{2.116}$$

6. (u_1, u_2, u_3) *satisfies the following graph equations:*

$$\begin{cases} d_1 \Delta u_1(t) - \sigma_1 u_1(t) + F[g(t)] + \Gamma_1(t) = 0, \\ d_2 \Delta u_2(t) - \sigma_2 u_2(t) + \Gamma_2(t) = 0, \\ -\sigma_3 u_3(t) + \Gamma_3(t) = 0, \end{cases} \tag{2.117}$$

   where $F[g]$ *is defined in* $(2.114)_3$ *and the reaction terms* Γ_k *are given by* (2.9).

We now need to prove the equivalence of problems (2.91)-(2.92) and (2.114)-(2.115). We begin by proving that a solution to (2.114)-(2.115) provides a solution to (2.91)-(2.92) following the proof of Theorem 3.3 in [14].

Theorem 2.5.2. *Let* (A, g, u_1, u_2, u_3) *be a solution of* (2.114)-(2.115) *in* $[0,T]$. *Set*

$$f_{i,t} = A_i \# g_{i,t}, \quad \textit{for all } t \in [0,T], \ i \in V.$$

Then (f, u_1, u_2, u_3) *is a solution to* (2.91)-(2.92).

Proof. Several properties of $f_{i,t}$ follow from the proof of [14]. Specifically, $f_{i,t}$ is a Borel regular probability measure on $[0,1]$. Since $y \mapsto A_i(y,t)$ is continuous and injective for all $i \in V$ and $t \in [0,T]$, $\operatorname{supp} f_{i,t} = A_i(\operatorname{supp}(g_{i,t},t)) \subseteq A_i([0,1],t) = [A_i(0,t),1]$. Since $g \in C([0,T];X_{[0,1]})$ and $y \mapsto A_i(y,t)$ is open, $f_{i,t} \in C([0,T];X_{[0,1]})$. Moreover $f \in \mathcal{L}(V;C([0,T];X_{[0,1]}))$.
In Section 2.5.1 we have seen that $A_i(1,t)=1$, $A_i(0,t) \geq 0$ and $y \mapsto A_i(y,t)$ is injective, therefore the map

$$A_i(\cdot,t) : [0,1] \mapsto [A_i(0,t),1]$$

is invertible for all $i \in V$ and $t \in [0,T]$. Let $B_i(\cdot,t) = A_i(\cdot,t)^{-1}$. Then $y \mapsto B_i(y,t)$ is Lipschitz continuous uniformly in t by (2.100). By definition of B_i we have $A_i(B_i(a,t),t) = a$ for $a \in [A_i(0,t),1]$. Differentiating this identity in a and t gives

$$\begin{cases} \partial_y A_i(B_i(a,t),t)\partial_a B_i(a,t) = 1, \\ \partial_y A_i(B_i(a,t),t)\partial_t B_i(a,t) + \partial_t A_i(B_i(a,t),t) = 0, \end{cases}$$

which give the following ODE for B_i

$$\partial_t B_i(a,t) = -v_i(a,t)\partial_a B_i(a,t). \tag{2.118}$$

Let $\psi \in C^1([0,1]\times[0,T])$ and $\phi(y,t) = \psi(A_i(y,t),t)$. The boundary conditions terms of (2.116) give

$$\begin{aligned} C_\phi &= -\int \phi(y,t)\,dg_{i,t}(y) + \int \phi(y,0)\,df_{i,0}(y) \\ &= -\int \phi(B_i(A_i(y,t),t),t)\,dg_{i,t}(y) + \int \phi(a,0)\,df_{i,0}(a) \\ &= -\int \phi(B_i(a,t))\,df_{i,t}(a) + \int \phi(a,0)\,df_{i,0}(a) \\ &= -\int \psi(a,t)\,df_{i,t}(a) + \int \psi(a,0)\,df_{i,0}(a). \end{aligned}$$

Meanwhile the equation for g tested on ϕ gives

$$-\int_0^t \int \partial_s \phi(y,t)\,dg_{i,s}(y)\,ds = C_\phi. \tag{2.119}$$

The LHS of (2.119) can be written as

$$\begin{aligned} -\int_0^t \int \partial_s \phi(y,t)\,dg_{i,s}(y)\,ds &= -\int_0^t \int \partial_s \phi(B_i(A_i(y,t),t),t)\,dg_{i,s}(y)\,ds \\ &= -\int_0^t \int \partial_s \phi(B_i(a,t),t)\,df_{i,s}(a)\,ds. \end{aligned} \tag{2.120}$$

Since $\psi(a,t) = \psi(A_i(B_i(a,t),t),t) = \phi(B_i(a,t),t)$, we have

$$\partial_t \psi(a,t) = \partial_y \phi(B_i(a,t),t)\partial_t B_i(a,t) + \partial_t \phi(B_i(a,t),t), \tag{2.121}$$

therefore

$$\int_0^t \int \partial_s \psi(a,s)\, df_{i,s}(a)\, ds = \int_0^t \int \partial_y \phi(B_i(a,s),s) \partial_t B_i(a,s)\, df_{i,s}(a)\, ds \tag{2.122}$$
$$+ \int_0^t \int \partial_s \phi(B_i(a,s),s)\, df_{i,s}(a)\, ds$$

$$= \int_0^t \int \partial_y \phi(B_i(a,s),s) \underbrace{\partial_t B_i(a,s)}_{(2.118)}\, df_{i,s}(a)\, ds + \underbrace{\int_0^t \int \partial_s \phi(y,s)\, dg_{i,s}(y)\, ds}_{=-C_\phi \text{ by } (2.119)} \tag{2.123}$$

$$= -\int_0^t \int \partial_y \phi(B_i(a,s),s) v_i(a,t) \partial_a B_i(a,s)\, df_{i,s}(a)\, ds - C_\phi \tag{2.124}$$

$$= -\int_0^t \int \partial_a \psi(a,t) v_i(a,t)\, df_{i,s}(a)\, ds - C_\phi. \tag{2.125}$$

So $f_{i,t}$ satisfies (2.95). To obtain the equivalence for the u system it is sufficient to observe that

$$F[f_{i,t}] = C_\mu \int (\mu_0 + a)(1-a)\, df_{i,t}(a) = C_\mu \int (\mu_0 + A_i(y,t))(1 - A_i(y,t))\, dg_{i,t}(y) = F[g_{i,t}]. \tag{2.126}$$

$\square$

Theorem 2.5.3. *Let (f, u_1, u_2, u_3) be a solution to* (2.91)-(2.92) *and A a solution to* (2.97)*. Then there exists a measure $g_{i,t}$ such that*

$$f_{i,t} = A_i \# g_{i,t}, \qquad \textit{for all } t \in [0,T],\ i \in V$$

and (g, A, u_1, u_2, u_3) is a solution to (2.114)-(2.115).

Proof. The existence of g follows from Theorem 3.4 of [14] by setting $x = i \in V$. The calculations in the previous theorem imply that such g satisfies (2.116). $\square$

2.5.2 Local Existence

The next step is to define the contractive operator whose fixed point gives a solution to (2.114)-(2.115). Let $T > 0$ and define the metric space

$$X_T := C^0([0,T] \times [0,1]; [0,1]^h) \times C^0([0,T]; \mathbb{R}^{3h}). \tag{2.127}$$

Let $(A, u) \in X_T$ and $g_{i,t} = f_i(0)$ for $i \in V$. The first step is to consider the problem

$$\begin{cases} \partial_t \tilde{A}_i(y,t) = \tilde{v}_i(\tilde{A}_i(y,t),t), \\ \tilde{A}_i(y,0) = y \in [0,1] \end{cases} \qquad i \in V, \tag{2.128}$$

$$\tilde{v}_i(a,t) = C_G \int_{[0,1]} (A_i(y,t) - a)^+\, dg_{i,t}(y) + C_s(1-a)(u_2(i,t) - \bar{U}_2)^+ \geq 0$$

where $\tilde{v}_i$ is defined and non-negative also in the case of negative u. We show that (2.128) has a unique solution $\bar{A}_i(y,t)$ on $(0,T]$ with the same regularity properties as the characteristics of Section 2.5.1. Then, for all $i \in V$, $t \in [0,T]$, we are able to define

$$\tilde{F}[g_{i,t}] = C_\mu \int (\mu_0 + \bar{A}_i(y,t))(1 - \bar{A}_i(y,t))\, dg_{i,t}(y) \geq 0, \tag{2.129}$$

which is Lipschitz continuous on $[0,T]$, thus Section 2.4 guarantees existence of a non-negative solution $\bar{u} \in C^0([0,T];\mathbb{R}^{3h})$ to

$$\begin{cases} d_1\Delta\tilde{u}_1 - \sigma_1\tilde{u}_1 + \tilde{F}[g] + \Gamma_1 = 0, \\ d_2\Delta\tilde{u}_2 - \sigma_2\tilde{u}_2 + \Gamma_2 = 0, & i \in V \\ -\sigma_3\tilde{u}_3 + \Gamma_3 = 0, \end{cases} \tag{2.130}$$

provided that $\sigma_1 = 1/s$ is large enough. The operator is then defined as

$$\mathcal{H}(A,u) = (\bar{A},\bar{u}). \tag{2.131}$$

We proceed by showing that $\mathcal{H}$ in (2.131) is well defined.

Lemma 2.5.4. *Let $g_{i,t} = f_i(0)$ for all $t \in [0,T]$, $i \in V$ and $(A,u) \in X_T$. For all $i \in V$ set*

$$\tilde{v}_i(a,t) = C_G \int_{[0,1]} (A_i(y,t)-a)^+ \, dg_{i,t}(y) + C_s(1-a)(u_2(i,t)-\bar{U}_2)^+. \tag{2.132}$$

Then the problem

$$\begin{cases} \partial_t\tilde{A}_i(y,t) = \tilde{v}_i(\tilde{A}_i(y,t),t), \\ \tilde{A}_i(y,0) = y \in [0,1] \end{cases} \tag{2.133}$$

has a unique solution on $(0,T]$ denoted by $\bar{A}_i(y,t)$ for all $i \in V$. The function $y \mapsto \bar{A}_i(y,t)$ is continuous and strictly increasing on $[0,1]$ for all $t \in [0,T]$. Moreover $\bar{A}_i([0,1],t) = [\bar{A}_i(0,t),1]$ and $\bar{A} \in C^0([0,T]\times[0,1];[0,1]^h)$.

Proof. By uniform continuity of A on $[0,1]\times[0,T]$ and u on $[0,T]$ we have that the map $(a,t) \mapsto \tilde{v}_i(a,t)$ is continuous and Lipschitz continuous in a uniformly in t. This implies existence of a unique local solution to problem (2.133) which is continuous in t and y. Since $\tilde{v}_i(a,t) \geq 0$ for $a \in [0,1]$, the map $t \mapsto \bar{A}_i(y,t)$ is increasing for all $y \in [0,1]$, therefore $\bar{A}_i(0,t) \geq 0$ for all $i \in V$. Observe that $\tilde{v}_i(1,t) = 0$ for all $t \in [0,T]$, so $\bar{A}_i(1,t) = 1$ for all $t \in [0,T]$ and $i \in V$ as in Section 2.5.1.

Repeating the argument in Section 2.5.1 we also have

$$\partial_y\bar{A}_i(y,t) = \exp\left(\int_0^t \partial_a\tilde{v}_i(\bar{A}_i(y,s),s)\,ds\right) > 0 \quad \text{for } i \in V,\ y \in [0,1],\ t \in [0,T] \tag{2.134}$$

hence $\partial_y\bar{A}_i(y,t)$ is bounded uniformly in t. Specifically, $y \mapsto \bar{A}_i(y,t)$ is Lipschitz continuous uniformly in t for all $i \in V$. □

Set $g_{i,0} = f_i(0)$ for all $i \in V$. The monomers' source

$$\tilde{F}[g_{i,0}](t) = C_\mu \int_{[0,1]} (\mu_0 + \bar{A}_i(\xi,t))(1-\bar{A}_i(\xi,t))\,dg_{i,0}(\xi), \quad i \in V \tag{2.135}$$

defines the elliptic equilibrium problem on the *proximity* graph

$$\begin{cases} d_1\Delta u_1 - \sigma_1 u_1 + \tilde{F}[g(0)](t) + \Gamma_1 = 0, \\ d_2\Delta u_2 - \sigma_2 u_2 + \Gamma_2 = 0, \\ -\sigma_3 u_3 + \Gamma_3 = 0. \end{cases} \tag{2.136}$$

Now $\tilde{v}_i$ is bounded uniformly in time by the mass balance

$$\sum_{k=1}^{3} \int_G \sigma_k u_k = \int_G F[f_{i,t}] \tag{2.137}$$

and the bound $|\tilde{F}[g]| \leq C$. It follows that $t \mapsto \bar{A}_i(y,t)$ is Lipschitz continuous uniformly in y. As a result, the map $t \mapsto \tilde{F}[g(0)](t)$ is Lipschitz continuous on $[0,T]$. By Section 2.4 and hypothesis (i), the system (2.136) has a non-negative solution $\bar{u} \in C^0([0,T];\mathbb{R}^{3h})$. In particular, we may define $u_0 := u(0) \in \mathbb{R}^{3h}$.

Subsequently, fix $\rho, T > 0$ and denote with $X_{\rho,T} \subset X_T$ the ball of radius ρ centred at (y, u_0), which corresponds to the initial data of problem (2.114)-(2.115). We then show that $\mathcal{H}$ is a contraction on $X_{\rho,T}$ if T is small enough.

Theorem 2.5.5 (Local Existence)**.** *Let $\rho > 0$ and $\mathcal{H}$ defined by* (2.131)*. If $\tau > 0$ is sufficiently small then $\mathcal{H}(X_{\rho,\tau}) \subset X_{\rho,\tau}$ and $\mathcal{H}$ is a contraction on $X_{\rho,\tau}$.*

Proof. We begin to show that $\mathcal{H}(A,u) \in X_{\rho,\tau}$ for all $(A,u) \in X_{\rho,\tau}$ if τ is small enough. We do so by proving

$$\max_{y\in[0,1]} |\bar{A}_i(y,t) - y| \to 0, \quad ||\bar{u}(t) - u_0||_{\mathbb{R}^{3h}} \to 0 \quad \text{as } t \to 0^+. \tag{2.138}$$

By (2.128) we have

$$\begin{aligned} |\bar{A}_i(y,t) - y| &= |\bar{A}_i(y,t) - \bar{A}_i(y,0)| \\ &= C_G \int_0^t \int (A_i(\xi,s) - \bar{A}_i(y,s))^+ \, dg_i(\xi)\, ds \\ &\quad + C_S \int_0^t (1 - \bar{A}_i(y,s))(u_2(i,s) - \bar{U}_2)^+ \, ds \\ &\leq C_G \int_0^t \int (A_i(\xi,s) - \bar{A}_i(y,s))^+ \, dg_i(\xi)\, ds \; + C_\rho t \end{aligned} \tag{2.139}$$

where we have used that $u_2(i,\cdot)$ is bounded in $X_{\rho,\tau}$ uniformly in τ. Applying Gronwall's Lemma on (2.139) yields

$$|\bar{A}_i(y,t) - y| \leq C_\rho t e^{C_G t} \to 0 \text{ as } t \to 0^+ \quad \text{for all } i \in V,\ y \in [0,1]. \tag{2.140}$$

Now observe that by the mass balance

$$\sum_{k=1}^{3} \int_G \sigma_k u_k = \int_G F[f_{i,t}] \tag{2.141}$$

and the non-negativity of $\bar{u}$ we have the following estimate

$$\underbrace{\left(\min_{k=1,2,3} \sigma_k\right)}_{=:\tilde{\sigma}} \bar{u}_m(j,t) \leq \sum_{k=1}^{3} \int_G \sigma_k \bar{u}_k(i,t) = \int_G F[g_{i,t}] \tag{2.142}$$

for all $m \in \{1, 2, 3\}$, $j \in V$, $t \in [0, \tau]$. This implies

$$|\bar{u}_k(i,t) - (u_0)_k(i)| = |\bar{u}_k(i,t) - \bar{u}_k(i,0)| \leq \frac{1}{\tilde{\sigma}} \sum_{j=1}^{h} |F[g_{j,t}] - F[g_{j,0}]| \tag{2.143}$$

$$\leq \frac{C_\mu}{\tilde{\sigma}} \sum_{j=1}^{h} \int \left|(\mu_0 + \bar{A}_j(\xi,t))(1 - \bar{A}_j(\xi,t)) - (\mu_0 + \xi)(1-\xi)\right| \, dg_{j,0}(\xi)$$

$$\leq \frac{C_\mu(\mu_0 + 2)}{\tilde{\sigma}} \sum_{j=1}^{h} \int \left|\bar{A}_j(\xi,t) - \xi\right| \, dg_{i,0}(\xi) \underbrace{\leq}_{(2.140)} \tilde{C}_\rho \sum_{j=1}^{h} t e^{C_G(j)t} \to 0$$

for all $k = 1, 2, 3$, $i \in V$. As a result, $\mathcal{H}$ is invariant on $X_{\rho,\tau}$ is τ is small enough.

Let $(A^1, u^1), (A^2, u^2) \in X_{\rho,\tau}$. Concerning the characteristics, let $i \in V$ and consider the quantity

$$
\begin{aligned}
|\bar{A}_i^1(y,t) - \bar{A}_i^2(y,t)| &= |\bar{A}_i^1(y,t) - \bar{A}_i^1(y,0) + \bar{A}_i^2(y,0) - \bar{A}_i^2(y,t)| \\
= \Bigg| C_G \int_0^t \int (A_i^1(\xi,s) - \bar{A}_i^1(y,s))^+ \, dg_{i,s}(\xi) \, ds &+ C_S \int_0^t (1 - \bar{A}_i^1(y,s))(u_2^1(i,s) - \bar{U}_2)^+ \, ds \\
- C_G \int_0^t \int (A_i^2(\xi,s) - \bar{A}_i^2(y,s))^+ \, dg_{i,s}(\xi) \, ds &- C_S \int_0^t (1 - \bar{A}_i^2(y,s))(u_2^2(i,s) - \bar{U}_2)^+ \, ds \Bigg| \\
\leq C_G \int_0^t \int \left|(A_i^1(\xi,s) - \bar{A}_i^1(y,s))^+ - (A_i^2(\xi,s) - \bar{A}_i^2(y,s))^+\right| \, dg_{i,s}(\xi) \, ds \\
+ C_S \int_0^t \left|(1 - A_i^1(y,t))(u_2^1(i,s) - \bar{U}_2)^+ - (1 - A_i^2(y,t))(u_2^2(i,s) - \bar{U}_2)^+\right| \, ds \\
= C_G \int_0^t \Bigg\{ \int | \, (A_i^1(\xi,s) - \bar{A}_i^1(y,s))^+ - (A_i^1(\xi,s) - \bar{A}_i^2(y,s))^+ \\
+ (A_i^1(\xi,s) - \bar{A}_i^2(y,s))^+ - (A_i^2(\xi,s) - \bar{A}_i^2(y,s))^+ \big| \, dg_{i,s}(\xi) \Bigg\} \, ds \\
+ C_S \int_0^t \Bigg\{ \big|(1 - \bar{A}_i^1(y,s)) \left[(u_2^1(i,s) - \bar{U}_2)^+ - (u_2^2(i,s) - \bar{U}_2)^+\right] \\
+ (u_2^2(i,s) - \bar{U}_2)^+ (\bar{A}_i^2(y,s) - \bar{A}_i^1(y,s))\big| \Bigg\} \, ds \\
\leq \tilde{C}_{\rho,1} \int_0^t \left|\bar{A}_i^1(y,s) - \bar{A}_i^2(y,s)\right| \, ds + \tilde{C}_{\rho,2} t \, d((A^1, u^1), (A^2, u^2)).
\end{aligned}
$$

Gronwall's Lemma implies

$$|\bar{A}_i^1(y,t) - \bar{A}_i^2(y,t)| \leq \tilde{C}_{\rho,2} t d((A^1, u^1), (A^2, u^2)) e^{\tilde{C}_{\rho,1} t} \quad \forall i \in V, \ y \in [0,1]. \tag{2.144}$$

Consider now the functions $\bar{u}^1, \bar{u}^2$. By (2.142) we have

$$
\begin{aligned}
&|\bar{u}_k^1(i,t) - \bar{u}_k^2(i,t)| \qquad (2.145)\\
&\leq \frac{C_\mu}{\tilde{\sigma}} \sum_{i=1}^{h} \int \left|(\mu_0 + \bar{A}_i^1(\xi,t))(1 - \bar{A}_i^1(\xi,t)) - (\mu_0 + \bar{A}_i^2(\xi,t))(1 - \bar{A}_i^2(\xi,t))\right| dg_{i,t}(\xi)\\
&\leq \frac{C_\mu(\mu_0+2)}{\tilde{\sigma}} \sum_{i=1}^{h} \int \left|\bar{A}_i^2(\xi,t) - \bar{A}_i^1(\xi,t)\right| dg_{i,t}(\xi)\\
&\underbrace{\leq}_{(2.144)} \tilde{C}_\rho t d((A^1,u^1),(A^2,u^2)) \sum_{i=1}^{h} e^{\tilde{C}_{\rho,1}(i)t} \leq \tilde{C}_{\rho,3} t d((A^1,u^1),(A^2,u^2)).
\end{aligned}
$$

It follows from (2.144) and (2.145) that $\mathcal{H}$ is a contraction on $X_{\rho,\tau}$ if τ is small enough. □

2.5.3 Global Existence

Let $[0,t^*)$ be the maximal interval of existence of (A,u) and suppose by contradiction that $t^* < T$. Observe that

$$
F[g_{i,t}] = C_\mu \int (\mu_0 + A_i(y,t))(1 - A_i(y,t))\, dg_{i,t}(y) \leq C \quad \text{for all } i \in V,\ t \in [0,t^*). \tag{2.146}
$$

By (2.142) and (2.146) it follows that

$$
|u_k(i,t)| \leq \tilde{C} \text{ for } t \in [0,t^*),\ i \in V,\ k = 1,2,3. \tag{2.147}
$$

Now by (2.147) we have that $v_i(A_i(y,t),t)$ is bounded uniformly in t, hence $t \mapsto A_i(y,t)$ is Lipschitz continuous and it can be extended to $[0,t^*]$. By Lipschitz continuity of $t \mapsto A_i(y,t)$ and boundedness of $v_i(A_i(y,t),t)$ it follows that $F[g_{i,t}]$ is Lipschitz continuous. Proceeding as in (2.142) we conclude that u is Lipschitz continuous, hence it can be extended to $[0,t^*]$. Iterating the contraction argument of Theorem 2.5.5 at $(A(t^*),u(t^*))$, the solution can be extended to $[t^*,t_1^*]$, thereby violating the maximality of $[0,t^*)$.

2.6 Existence: the case $J[f] \not\equiv 0$

In this section, we extend the proof of the existence for the Aβ system to the non-conservative case. We first recall the equations of the model. The probability measure f satisfies

$$
\begin{cases}
\partial_t f_{i,t} + (v[f_{i,t}]f_{i,t})_a = J[f_{i,t}],\\
f_{i,0} = f_i(0)
\end{cases} \qquad i \in V, \tag{2.148}
$$

where $J[f_{i,t}]$ is a signed measure that accounts for upward jumps in the degree of neuronal malfunction.

$$
J[f_{i,t}] = \eta(t)\chi_H(t) \left\{ \left(\int_{[0,1]} P(t,b,a)\, df_{i,t}(b) \right) da - df_{i,t}(a) \right\}. \tag{2.149}
$$

Here $P(t,b,a)$ is the probability of jumping from degree b to degree a, where $b \leq a$ (meaning a transition towards a more toxic state) and $\eta > 0$ is the jump frequency. χ_H is the "characteristic function" of the set

$i_H \times I_T$, where i_H is the set of nodes corresponding to the hippocampus region of the brain and $I_T \subset [0,T]$ is a measurable set. In other words

$$J[f_{i,t}] = \begin{cases} \eta(t) \left[\left(\int_{[0,1]} P(t,b,a)\, df_{i,t}(b) \right) da - df_{i,t}(a) \right] & \text{if } i \in i_H \text{ and } t \in I_T, \\ 0 \quad \text{otherwise.} \end{cases}$$

The elliptic Aβ system is

$$\begin{cases} d_1 \Delta u_1 - \sigma_1 u_1 + F[f] + \Gamma_1 = 0, \\ d_2 \Delta u_2 - \sigma_2 u_2 + \Gamma_2 = 0, & i \in V, \\ -\sigma_3 u_3 + \Gamma_3 = 0, \end{cases} \tag{2.150}$$

where the monomers' source is

$$F[f_{i,t}] = C_\mu \int_0^1 (\mu_0 + a)(1-a)\, df_{i,t}(a) \tag{2.151}$$

and the rate of degeneration is

$$v[f_{i,t}](a,t) = C_G \int_{[0,1]} (b-a)^+\, df_{i,t}(b) + C_s(1-a)(u_2(i,t) - \bar{U}_2)^+. \tag{2.152}$$

We adopt the same strategy employed in Section 2.5 to prove the existence. The introduction of a drift term $J[f]$ induces deep changes in the structure of the problem. In fact, the measure g is no longer constant in time. Accordingly, it enters the problem as an unknown in addition to the characteristics and the Aβ concentrations. Hence X_T is enlarged to include the space of time-continuous Borel probability measures endowed with the $1-$Wasserstein distance.

For the sake of completeness, we recall the definition of the solution to (2.148)-(2.150).

Definition 2.6.1. *A $4-$tuple (f, u_1, u_2, u_3) is a solution to* (2.148), (2.150) *if*

1. *$f \in \mathcal{L}(V; C([0,T]; X_{[0,1]}))$ and $u_k \in C([0,T], \mathbb{R}^h)$, $u_k(i) \geq 0$ for all $k = 1,2,3$ and $i = 1,\dots,h$;*

2. *f is a solution to* (2.91) *in a weak sense:*

$$\int_0^t \left(\int (\phi_s(a,s) + \phi_a(a,s) v_i(a,s)) df_{i,s}(a) + \int \phi(a,s) dJ_{i,s}(a) \right) ds = \int \phi(\cdot,t)\, df_{i,t} - \int \phi(\cdot,0)\, df_i(0) \tag{2.153}$$

   for all $\phi \in C^1([0,1] \times [0,T])$ and $i = 1,\dots,h$, where v is defined in (2.152)*;*

3. *(u_1, u_2, u_3) satisfies the following graph equations:*

$$\begin{cases} d_1 \Delta u_1(t) - \sigma_1 u_1(t) + F[f(t)] + \Gamma_1(t) = 0, \\ d_2 \Delta u_2(t) - \sigma_2 u_2(t) + \Gamma_2(t) = 0, \\ -\sigma_3 u_3(t) + \Gamma_3(t) = 0, \end{cases} \tag{2.154}$$

   where $F[f]$ and the reaction terms Γ_k are given by (2.151) *and* (2.9).

2.6.1 The Characteristics

Remark 2.6.1. *The characteristics problem*

$$\begin{cases} \partial_t A_i(y,t) = v_i(A_i(y,t),t), \\ A_i(y,0) = y \in [0,1], \end{cases} \qquad i \in V, \tag{2.155}$$

exhibits the same properties as in Section 2.5.1.

We now show that a similar result on the support of f and J holds as in Lemma 2.5.1. The proof is an adaptation of the proof of Lemma 2.5.1.

Lemma 2.6.1. *Let $f \in \mathcal{L}(V; C([0,T]; X_{[0,1]}))$ be a solution to* (2.148) *and $A_i(y,t)$ a solution to* (2.155)*. Then for all $i \in V$ and $t \in (0,T]$*

$$\text{supp}\, f_{i,t},\ \text{supp}\, J[f_{i,t}] \subseteq [A_i(0,t),1]. \tag{2.156}$$

Proof. Let $h \in C^1(\mathbb{R})$ a non-decreasing function such that $h \equiv 0$ on $(-\infty,0]$ and $h \equiv 1$ on $[1,+\infty)$. Let $\delta > 0$ and set

$$h_\delta(s) = h\left(\frac{s}{\delta}\right), \quad \psi_\delta(a,\tau) = h_\delta(A_i(0,\tau)-a), \quad a \in [0,1],\ \tau \in [0,T].$$

Then $\psi_\delta \in C^1([0,1]\times[0,T])$, $\text{supp}\,\psi_\delta(\cdot,\tau) = [0,A_i(0,\tau))$ for all $\tau \in (0,T]$, $\delta > 0$ and

$$\lim_{\delta\to 0^+} \psi_\delta(a,\tau) = \mathbb{1}_{[0,A_i(0,\tau))}(a) \quad \text{for } \tau \in (0,T].$$

Testing equation (2.153) on ψ_δ gives

$$\begin{aligned} &\int_0^t \left(\int (\partial_\tau \psi_\delta(a,\tau) + \partial_a \psi_\delta(a,\tau) v_i(a,\tau)) df_{i,\tau}(a) \right) d\tau \\ &= \int \psi_\delta(\cdot,t)\, df_{i,t} - \int \psi_\delta(\cdot,0)\, df_i(0) - \int_0^t \int \psi_\delta(\cdot,s)\, dJ_{i,s}\, ds \\ &= \int \psi_\delta(\cdot,t)\, df_{i,t} - \int_0^t \int \psi_\delta(\cdot,s)\, dJ_{i,s}\, ds \end{aligned} \tag{2.157}$$

since $\psi_\delta(a,0) = h\left(-\frac{a}{\delta}\right) = 0$ if $a \in [0,1]$. Repeating verbatim the calculations in Lemma 2.5.1 yields

$$\int \psi_\delta(\cdot,t)\, df_{i,t} - \int_0^t \int \psi_\delta(\cdot,s)\, dJ_{i,s}\, ds \to 0 \text{ as } \delta \to 0^+. \tag{2.158}$$

Moreover,

$$\int \psi_\delta(\cdot,t)\, df_{i,t} = \int \psi_\delta(\cdot,t) df_{i,t} \llcorner [0,A_i(0,t)) \to \int df_{i,t} \llcorner [0,A_i(0,t)) \text{ as } \delta \to 0^+ \tag{2.159}$$

by the dominated convergence theorem. Indeed, $\psi_\delta(a,\tau) \le 1$ for all $a \in [0,1]$, $\tau \in [0,T]$ and $\lim_{\delta\to 0^+} \psi_\delta(a,\tau) = \mathbb{1}_{[0,A_i(0,\tau))]}(a)$. In addition,

$$\left| \psi_\delta(a,s) \int P(s,b,a)\, df_{i,s}(b) \right| \le C,$$

$$\left|\int \psi_\delta dJ_{i,s}\right| \leq \eta\chi_H \left|\int \psi_\delta(a,s)\left(\int P(s,b,a)\,df_{i,s}(b)\right)\,da\right| + \eta\chi_H\left|\int \psi_\delta(a,s)\,df_{i,s}(a)\right| \leq C\eta + \eta \leq \tilde{C},$$

therefore by (2.159) and the dominated convergence theorem

$$\begin{aligned}\lim_{\delta\to 0^+} \eta\chi_H \int \psi_\delta(a,s)\left(\int P(s,b,a)\,df_{i,s}(b)\right)\,da \\ = \eta\chi_H \int \mathbb{1}_{[0,A_i(0,s))]}(a)\left(\int P(s,b,a)\,df_{i,s}(b)\right)\,da \\ = \eta\chi_H \int_0^{A_i(0,s)}\left(\int P(s,b,a)\,df_{i,s}(b)\right)\,da,\end{aligned}$$

$$\begin{aligned}\lim_{\delta\to 0^+}\int \psi_\delta\,dJ_{i,s} = \eta\chi_H \int_0^{A_i(0,s)}\left(\int P(s,b,a)\,df_{i,s}(b)\right)\,da \\ -\eta\chi_H\int df_{i,s}\llcorner[0,A_i(0,s)) = \int dJ_{i,s}\llcorner[0,A_i(0,s)),\end{aligned}$$

$$\lim_{\delta\to 0^+}\int_0^t\int \psi_\delta\,dJ_{i,s}\,ds = \int_0^t\int dJ_{i,s}\llcorner[0,A_i(0,s))\,ds. \tag{2.160}$$

Now (2.158), (2.159) and (2.160) imply

$$\int df_{i,t}\llcorner[0,A_i(0,t)) = \int_0^t\int dJ_{i,s}\llcorner[0,A_i(0,s))\,ds. \tag{2.161}$$

It follows from Tonelli's theorem and (2.23) that

$$\begin{aligned}\int dJ_{i,s}\llcorner[0,A_i(0,s)) &= \eta\chi_H\int_0^{A_i(0,s)}\left(\int P(s,b,a)\,df_{i,s}(b)\right)\,da - \eta\chi_H\int_0^{A_i(0,s)} df_{i,s} \\ &= \eta\chi_H\int\left(\int_b^{A_i(0,s)} P(s,b,a)\,da\right)\,df_{i,s}(b)\llcorner[0,A_i(0,t)) - \eta\chi_H\int_0^{A_i(0,s)} df_{i,s} \\ &\leq \eta\chi_H\int\left(\int_0^1 P(s,b,a)\,da\right)\,df_{i,s}(b)\llcorner[0,A_i(0,s)) - \eta\chi_H\int_0^{A_i(0,s)} df_{i,s} \\ &\underbrace{=}_{(2.24)}\eta\chi_H\left(\int df_{i,s}\llcorner[0,A_i(0,s)) - \int df_{i,s}\llcorner[0,A_i(0,s))\right) = 0.\end{aligned}$$

By (2.161) and the fact that $\int df_{i,s}\llcorner[0,A_i(0,s))\geq 0$ it follows that

$$\int df_{i,s}\llcorner[0,A_i(0,s)) = 0 \quad \text{for all } i\in V, t\in[0,T] \tag{2.162}$$

therefore supp $f_{i,t}\subseteq[A_i(0,t),1]$. Moreover, by definition of $J[f]$ and (2.162),

$$\int dJ_{i,t}\llcorner[0,A_i(0,t)) = \eta\chi_H\int\left(\int_b^{A_i(0,t)} P(t,b,a)\,da\right)\,df_{i,t}(b)\llcorner[0,A_i(0,t))\geq 0$$

hence we conclude that

$$\int dJ_{i,t} \llcorner [0, A_i(0,t)) = 0 \Rightarrow \text{ supp } J_{i,t} \subseteq [A_i(0,t), 1] \quad \text{for all } i \in V, t \in [0,T].$$

$\square$

We aim at searching for a probability measure $g_{i,t}$ such that $f_{i,t}$ is the push forward of $g_{i,t}$ through the action of A_i:

$$f_{i,t} = A_i \# g_{i,t}, \quad i \in V \tag{2.163}$$

where g and A satisfy

$$\begin{cases} \partial_t A_i(y,t) = C_G \int_{[0,1]} (A_i(\xi,t) - A_i(y,t))^+ \, dg_{i,t}(\xi) + C_s(1 - A_i(y,t))(u_2(i,t) - \bar{U}_2)^+, \\ \partial_t g_{i,t} = \eta(t)\chi_H \left[\partial_y A_i(y,t) \int P(t, A_i(\xi,t), A_i(y,t)) \, dg_{i,t}(\xi) \, dy - g_{i,t}(\xi)\right], \quad i \in V \\ d_1 \Delta u_1(t) - \sigma_1 u_1(t) + C_\mu \int_{[0,1]} (\mu_0 + A_i(\xi,t))(1 - A_i(\xi,t)) \, dg_{i,t}(\xi) + \Gamma_1(t) = 0, \\ d_2 \Delta u_2(t) - \sigma_2 u_2(t) + \Gamma_2(t) = 0, \\ -\sigma_3 u_3(t) + \Gamma_3(t) = 0, \end{cases} \tag{2.164}$$

with initial boundary conditions

$$\begin{cases} g_{i,0} = f_i(0), \\ A_i(y,0) = y, \end{cases} \qquad i \in V. \tag{2.165}$$

Definition 2.6.2. *A $5-$tuple (g, A, u_1, u_2, u_3) is a solution to* (2.164), (2.165) *if*

1. *$g \in \mathcal{L}(V; C([0,T]; X_{[0,1]}))$;*
2. *$A_i \in C([0,1] \times [0,T]; [0,1])$, $\partial_t A_i \in C([0,1] \times [0,T]; \mathbb{R})$ for all $i \in V$;*
3. *A_i satisfies* $(2.164)_1$ *and $A_i(y,0) = y$ for all $i \in V$ and $y \in [0,1]$;*
4. *$u_k \in C([0,T], \mathbb{R}^h)$, $u_k(i) \geq 0$ for all $k = 1,2,3$ and $i = 1, \dots, h$;*
5. *g is a solution to* $(2.164)_2$ *in a weak sense: for all $\phi \in C^1([0,1] \times [0,T])$*

$$\begin{aligned} &\int \phi(\cdot,t) \, dg_{i,t} - \int \phi(\cdot,0) \, df_i(0) - \int_0^t \left(\int (\phi_s(y,s) dg_{i,s}(y) \right) ds \\ &= \int_0^t \eta \chi_H \left[\int \phi(y,s) \partial_y A_i(y,s) \left(\int P(s, A_i(\xi,s), A_i(y,s)) \, dg_{i,s}(\xi) \right) dy \right. \\ &\qquad \left. - \int \phi(\xi,s) \, dg_{i,s}(\xi) \right] ds; \end{aligned} \tag{2.166}$$

6. *(u_1, u_2, u_3) satisfies the following graph equations:*

$$\begin{cases} d_1 \Delta u_1(t) - \sigma_1 u_1(t) + F[g(t)] + \Gamma_1(t) = 0, \\ d_2 \Delta u_2(t) - \sigma_2 u_2(t) + \Gamma_2(t) = 0, \\ -\sigma_3 u_3(t) + \Gamma_3(t) = 0, \end{cases} \tag{2.167}$$

where $F[g]$ is defined in $(2.164)_3$ *and the reaction terms Γ_k are given by* (2.9).

We now need to prove that the problems (2.148)-(2.150) and (2.164)-(2.165) are equivalent. Again, we follow the proof of Theorem 2.5.2.

Theorem 2.6.2. *Let* (A, g, u_1, u_2, u_3) *be a solution of* (2.164)-(2.165) *in* $[0, T]$. *Set*

$$f_{i,t} = A_i \# g_{i,t}, \qquad \text{for all } t \in [0, T],\ i \in V.$$

Then (f, u_1, u_2, u_3) *is a solution to* (2.148)-(2.150).

Proof. As in Theorem 2.5.2, $f_{i,t}$ is a Borel regular probability measure on $[0, 1]$. Since $y \mapsto A_i(y, t)$ is continuous and injective for all $i \in V$ and $t \in [0, T]$,

$$\operatorname{supp} f_{i,t} = A_i(\operatorname{supp}(g_{i,t}, t)) \subseteq A_i([0, 1], t) = [A_i(0, t), 1].$$

By (2.24), if $a < A_i(0, t)$, then $\int P(t, b, a)\, df_{i,t}(b) = 0$, therefore $\operatorname{supp} J_{i,t} \subseteq [A_i(0, t), 1]$. Since $g \in C([0, T]; X_{[0,1]})$ and $y \mapsto A_i(y, t)$ is open, $f_{i,t} \in C([0, T]; X_{[0,1]})$. Moreover $f \in \mathcal{L}(V; C([0, T]; X_{[0,1]}))$. In Section 2.5.1 we have seen that $A_i(1, t) = 1$, $A_i(0, t) \geq 0$ and $y \mapsto A_i(y, t)$ is injective, therefore the map

$$A_i(\cdot, t) : [0, 1] \mapsto [A_i(0, t), 1]$$

is invertible for all $i \in V$ and $t \in [0, T]$. Let $B_i(\cdot, t) = A_i(\cdot, t)^{-1}$. Then $y \mapsto B_i(y, t)$ is Lipschitz continuous uniformly in t by (2.100). By definition of B_i we have $A_i(B_i(a, t), t) = a$ for $a \in [A_i(0, t), 1]$. Differentiating this identity in a and t gives

$$\begin{cases} \partial_y A_i(B_i(a, t), t)\partial_a B_i(a, t) = 1, \\ \partial_y A_i(B_i(a, t), t)\partial_t B_i(a, t) + \partial_t A_i(B_i(a, t), t) = 0, \end{cases}$$

which defines the following ODE for B_i

$$\partial_t B_i(a, t) = -v_i(a, t)\partial_a B_i(a, t). \tag{2.168}$$

Let $\psi \in C^1([0, 1] \times [0, T])$ and $\phi(y, t) = \psi(A_i(y, t), t)$. The boundary conditions terms of (2.166) give

$$\begin{aligned} C_\phi &= -\int \phi(y, t)\, dg_{i,t}(y) + \int \phi(y, 0)\, df_{i,0}(y) = -\int \phi(B_i(A_i(y, t), t), t)\, dg_{i,t}(y) + \int \phi(a, 0)\, df_{i,0}(a) \\ &= -\int \phi(B_i(a, t))\, df_{i,t}(a) + \int \phi(a, 0)\, df_{i,0}(a) = -\int \psi(a, t)\, df_{i,t}(a) + \int \psi(a, 0)\, df_{i,0}(a). \end{aligned}$$

Meanwhile the equation for g tested on ϕ gives

$$\begin{aligned} &-\int_0^t \int \partial_s \phi(y, t)\, dg_{i,s}(y)\, ds \\ &= \int_0^t \eta\chi_H \left[\int \phi(y, s)\partial_y A_i(y, s) \left(\int P(s, A_i(\xi, s), A_i(y, s))\, dg_{i,s}(\xi)\right) dy \right. \\ &\qquad \left. - \int \phi(y, s)\, dg_{i,s}(y)\right] ds + C_\phi \\ &= \int_0^t \eta\chi_H \left[\int \phi(y, s)\partial_y A_i(y, s) \left(\int P(s, b, A_i(y, s))\, df_{i,s}(b)\right) dy - I(s)\right] ds + C_\phi \\ &\underbrace{=}_{a = A_i(y,t)} \int_0^t \eta\chi_H \left[\int_{A_i(0,s)}^{A_i(1,s)} \phi(B_i(a, s), s) \left(\int P(s, b, a)\, df_{i,s}(b)\right) da - I(s)\right] ds + C_\phi \\ &= \int_0^t \eta\chi_H \left[\int_{A_i(0,s)}^{1} \phi(B_i(a, s), s) \left(\int P(s, b, a)\, df_{i,s}(b)\right) da - I(s)\right] ds + C_\phi, \end{aligned} \tag{2.169}$$

where we have written $I(s) = \int \phi(B_i(A_i(y,s),s),s)\,dg_{i,s}(y)$.

The LHS of (2.169) can be written as

$$-\int_0^t \int \partial_s \phi(y,t)\,dg_{i,s}(y)\,ds = -\int_0^t \int \partial_s \phi(B_i(A_i(y,t),t),t)\,dg_{i,s}(y)\,ds \\ = -\int_0^t \int \partial_s \phi(B_i(a,t),t)\,df_{i,s}(a)\,ds. \tag{2.170}$$

Since $\psi(a,t) = \psi(A_i(B_i(a,t),t),t) = \phi(B_i(a,t),t)$, we have

$$\partial_t \psi(a,t) = \partial_y \phi(B_i(a,t),t)\partial_t B_i(a,t) + \partial_t \phi(B_i(a,t),t), \tag{2.171}$$

therefore

$$\begin{aligned}
&\int_0^t \int \partial_s \psi(a,s)\,df_{i,s}(a)\,ds \\
&= \int_0^t \int \partial_y \phi(B_i(a,s),s)\partial_t B_i(a,s)\,df_{i,s}(a)\,ds + \int_0^t \int \partial_s \phi(B_i(a,s),s)\,df_{i,s}(a)\,ds \\
&= \int_0^t \int \partial_y \phi(B_i(a,s),s)\,\underbrace{\partial_t B_i(a,s)}_{(2.168)}\,df_{i,s}(a)\,ds + \underbrace{\int_0^t \int \partial_s \phi(y,s)\,dg_{i,s}(y)\,ds}_{(2.169)} \\
&= -\int_0^t \int \partial_y \phi(B_i(a,s),s)v_i(a,t)\partial_a B_i(a,s)\,df_{i,s}(a)\,ds - C_\phi \\
&\quad - \int_0^t \eta\chi_H \left[\int_{A_i(0,s)}^1 \phi(B_i(a,s),s)\left(\int P(s,b,a)\,df_{i,s}(b)\right)da - \int \phi(B_i(A_i(y,s),s),s)\,dg_{i,s}(y)\right]ds \\
&= -\int_0^t \int \partial_a \psi(a,t)v_i(a,t)\,df_{i,s}(a)\,ds - C_\phi \\
&\quad - \int_0^t \eta\chi_H \left[\int_{A_i(0,s)}^1 \phi(B_i(a,s),s)\left(\int P(s,b,a)\,df_{i,s}(b)\right)da - \int \phi(B_i(A_i(y,s),s),s)\,dg_{i,s}(y)\right]ds \\
&= -\int_0^t \int \partial_a \psi(a,t)v_i(a,t)\,df_{i,s}(a)\,ds - C_\phi \\
&\quad - \int_0^t \eta\chi_H \left[\int_{A_i(0,s)}^1 \psi(a,s)\left(\int P(s,b,a)\,df_{i,s}(b)\right)da - \int \phi(B_i(a,s),s)\,df_{i,s}(a)\right]ds \\
&= -\int_0^t \int \partial_a \psi(a,t)v_i(a,t)\,df_{i,s}(a)\,ds - C_\phi - \int_0^t \eta\chi_H \left[\int_{A_i(0,s)}^1 \psi(a,s)\left(\int P(s,b,a)\,df_{i,s}(b)\right)da\right. \\
&\quad \left. - \int \psi(a,s)\,df_{i,s}(a)\right]ds \\
&\underbrace{=}_{(2.24),\ \operatorname{supp} f_{i,s}\subseteq[A_i(0,s),1]} -\int_0^t \int \partial_a \psi(a,t)v_i(a,t)\,df_{i,s}(a)\,ds - C_\phi - \int_0^t \int \psi(\cdot,s)\,dJ_{i,s}\,ds
\end{aligned}$$

which ensures that $f_{i,t}$ is a weak solution of (2.148). To obtain the equivalence for the u system it is sufficient to observe that

$$F[f_{i,t}] = C_\mu \int (\mu_0 + a)(1-a)\,df_{i,t}(a) = C_\mu \int (\mu_0 + A_i(y,t))(1 - A_i(y,t))\,dg_{i,t}(y) = F[g_{i,t}].$$

□

The converse follows as in Theorem 2.5.3.

Theorem 2.6.3. *Let* (f, u_1, u_2, u_3) *be a solution to* (2.148)-(2.150) *and* A *a solution to* (2.155). *Then there exists a measure* $g_{i,t}$ *such that*

$$f_{i,t} = A_i \# g_{i,t}, \quad \text{for all } t \in [0,T],\ i \in V$$

and (g, A, u_1, u_2, u_3) *is a solution to* (2.164)-(2.165).

Proof. The existence of g follows from Theorem 3.4 of [14] by setting $x = i \in V$. The calculations in the previous theorem imply that such g satisfies (2.166). □

2.6.2 Local Existence

The construction of the contractive operator is the same as in Section 2.5, but we need to include the space for g. Let $T > 0$ and consider

$$X_T := C^0([0,T] \times [0,1]; [0,1]^h) \times \mathcal{L}(V; C([0,T]; X_{[0,1]})) \times C^0([0,T]; \mathbb{R}^{3h}). \tag{2.172}$$

where $\mathcal{L}(V; C([0,T]; X_{[0,1]})) = \{f \in C([0,T]; X^h_{[0,1]}) : f_i \text{ is weakly* measurable}\}$ is endowed with the $1-$Wasserstein distance.

Let $(A, g, u) \in X_T$. First, consider the problem given by

$$\begin{cases} \partial_t \tilde{A}_i(y,t) = \tilde{v}_i(\tilde{A}_i(y,t), t), \\ \tilde{A}_i(y,0) = y \in [0,1] \end{cases} \qquad i \in V, \tag{2.173}$$

$$\tilde{v}_i(a,t) = C_G \int_{[0,1]} (A_i(y,t) - a)^+ \, dg_{i,t}(y) + C_s(1-a)(u_2(i,t) - \bar{U}_2)^+ \geq 0$$

and prove that it admits a solution $\bar{A}$. Then we define

$$d(F[g])_{i,t} = \eta \chi_H \left[\partial_y \bar{A}_i(y,t) \int P(t, \bar{A}_i(\xi,t), \bar{A}_i(y,t)) \, dg_{i,t}(\xi) \, dy - dg_{i,t}(y) \right] \tag{2.174}$$

and show that the problem

$$\begin{cases} \partial_t g_{i,t} = d(F[g])_{i,t}, \\ g_{i,0} = f_i(0) \end{cases} \tag{2.175}$$

has a solution $\bar{g}$ in the weak sense. Once we have defined $(\bar{A}, \bar{g})$, we can introduce the monomers' source

$$\tilde{F}[\bar{g}_{i,t}] = C_\mu \int (\mu_0 + \bar{A}_i(y,t))(1 - \bar{A}_i(y,t)) \, d\bar{g}_{i,t}(y) \geq 0 \tag{2.176}$$

and, by Section 2.4, the elliptic problem

$$\begin{cases} d_1 \Delta \tilde{u}_1 - \sigma_1 \tilde{u}_1 + \tilde{F}[\bar{g}] + \Gamma_1 = 0, \\ d_2 \Delta \tilde{u}_2 - \sigma_2 \tilde{u}_2 + \Gamma_2 = 0, \\ -\sigma_3 \tilde{u}_3 + \Gamma_3 = 0, \end{cases} \qquad \sigma_k > 0 \quad k = 1,2,3, \quad \sum_{k=1}^{3} \Gamma_k(i) = 0 \quad i \in V, \tag{2.177}$$

has a unique non-negative solution $\bar{u}$. The operator is defined as

$$\mathcal{H}(A, g, u) = (\bar{A}, \bar{g}, \bar{u}). \tag{2.178}$$

We start with (2.173), which satisfies the same properties as in Lemma 2.5.4.

Lemma 2.6.4. *Let $(A, g, u) \in X_T$. For all $i \in V$ set*

$$\tilde{v}_i(a,t) = C_G \int_{[0,1]} (A_i(y,t) - a)^+ \, dg_{i,t}(y) + C_s(1-a)(u_2(i,t) - \bar{U}_2)^+. \tag{2.179}$$

Then the problem

$$\begin{cases} \partial_t \tilde{A}_i(y,t) = \tilde{v}_i(\tilde{A}_i(y,t),t), \\ \tilde{A}_i(y,0) = y \in [0,1] \end{cases} \tag{2.180}$$

has a unique solution on $(0,T]$ denoted by $\bar{A}_i(y,t)$ for all $i \in V$. The function $y \mapsto \bar{A}_i(y,t)$ is continuous and strictly increasing on $[0,1]$ for all $t \in [0,T]$.
Moreover $\bar{A}_i([0,1],t) = [\bar{A}_i(0,t),1]$ and $\bar{A} \in C^0([0,T] \times [0,1]; [0,1]^h)$.

Proof. We need to prove that the map $(a,t) \mapsto \tilde{v}_i(a,t)$ is continuous and Lipschitz continuous in a uniformly in t. This implies existence of a unique local solution to problem (2.180) which is continuous in t and y. Then since $\tilde{v}_i(a,t) \geq 0$ for $a \in [0,1]$, $t \mapsto \bar{A}_i(y,t)$ is increasing for all $y \in [0,1]$, which implies $\bar{A}_i(0,t) \geq 0$ for all $i \in V$. Observe that $\tilde{v}_i(1,t) = 0$ for all $t \in [0,T]$, so $\bar{A}_i(1,t) = 1$ for all $t \in [0,T]$ and $i \in V$ as in Section 2.5.1.

Repeating the argument in Section 2.5.1 we also have

$$\partial_y \bar{A}_i(y,t) = \exp\left(\int_0^t \partial_a \tilde{v}_i(\bar{A}_i(y,s),s)\, ds \right) > 0 \quad \text{for } i \in V,\ y \in [0,1],\ t \in [0,T] \tag{2.181}$$

hence $\partial_y \bar{A}_i(y,t)$ is bounded uniformly in t. Specifically $\bar{A}_i(y,t)$ is Lipschitz continuous in y uniformly in t for all $i \in V$.

We now prove Lipschitz continuity of $\tilde{v}$ in a uniformly in t and continuity in t. We immediately observe that the second term in (2.179) satisfies these conditions since u is bounded by a constant depending solely on T. For the first term in (2.179), let $a_1, a_2 \in [0,1]$ and $t_1, t_2 \in [0,T]$. We have

$$\begin{aligned} &\left| \int_{[0,1]} (A_i(y,t_2) - a_2)^+ \, dg_{i,t_2}(y) - \int_{[0,1]} (A_i(y,t_1) - a_1)^+ \, dg_{i,t_1}(y) \right| \\ &\leq \left| \int_{[0,1]} (A_i(y,t_2) - a_2)^+ \, dg_{i,t_2}(y) - \int_{[0,1]} (A_i(y,t_1) - a_1)^+ \, dg_{i,t_2}(y) \right| \\ &+ \left| \int_{[0,1]} (A_i(y,t_1) - a_1)^+ \, dg_{i,t_2}(y) - \int_{[0,1]} (A_i(y,t_1) - a_1)^+ \, dg_{i,t_1}(y) \right| = I_1 + I_2. \end{aligned} \tag{2.182}$$

Regarding I_1 we have

$$I_1 \leq \int_{[0,1]} \left| (A_i(y,t_2) - a_2)^+ - (A_i(y,t_1) - a_1)^+ \right| \, dg_{i,t_2}(y) \tag{2.183}$$

where $(y,a,t) \mapsto (A_i(y,t) - a)^+$ is continuous on $[0,1]^2 \times [0,T]$, hence it is uniformly continuous and $I_1 \to 0$ as $(t_2,a_2) \to (t_1,a_1)$. As for I_2, $y \mapsto A_i(y,t)$ is continuous on $[0,1]$ and $t \mapsto g_{i,t}$ is continuous as a function from $[0,T]$ to $X_{[0,1]}$, therefore $\mathcal{W}_1(g_{i,t_2}, g_{i,t_1}) \to 0$ as $t_2 \to t_1$. Since $[0,1]$ is a compact space, it follows that $g_{i,t}$ is narrowly continuous in time [4], therefore $I_2 \to 0$ as $t_2 \to t_1$. By the uniform boundedness of $\partial_a (A_i(y,t) - a)^+$ it follows that $\tilde{v}$ is Lipschitz continuous in a uniformly in t. $\square$

Lemma 2.6.5. *Let* $(A, g, u) \in X_T$ *and* $\bar{A}$ *the solution to* (2.173)*. Let* $(F[g])_{i,t}$ *the signed measure on* $[0,1]$ *defined as*

$$d(F[g])_{i,t} = \eta(t)\chi_H(t)\left[\partial_y \bar{A}_i(y,t)\int P(t,\bar{A}_i(\xi,t),\bar{A}_i(y,t))\,dg_{i,t}(\xi)\,dy - dg_{i,t}(y)\right], \tag{2.184}$$

for $i \in V,\ t \in [0,T]$*. Then for all* $i \in V$

1. *The equation*

$$\bar{g}_{i,t} = f_i(0) + \int_0^t (F[\bar{g}_{i,s}])\,ds \tag{2.185}$$

has a unique solution in $C([0,T];X_{[0,1]})$ *for all* $i \in V$*, where the measure* $\int_0^t \mu(s)\,ds$ *is defined as* $\left(\int_0^t \mu(s)\,ds\right)(\mathrm{A}) = \int_0^t (\mu(s)(\mathrm{A}))\ ds$ *for any Borel set* $\mathrm{A} \subset [0,1]$ *and* $\mu \in C([0,T],X_{[0,1]})$*;*

2. *The measure* $\bar{g}_{i,t}$ *is a weak solution to*

$$\begin{cases} \partial_t \bar{g}_{i,t} = \eta\chi_H\left[\partial_y \bar{A}_i(y,t)\int P(t,\bar{A}_i(\xi,t),\bar{A}_i(y,t))\,d\bar{g}_{i,t}(\xi)\,dy - \bar{g}_{i,t}(y)\right], \\ \bar{g}_{i,0} = f_i(0) \end{cases} \tag{2.186}$$

in the sense of (2.166).

Proof. Let $i \in V$ and $s \in [0,T]$. We first want to show that

$$\int_{[0,1]} d(F[g])_{i,s} = 0. \tag{2.187}$$

If i does not correspond to the brain region of the hippocampus, then $\chi_H \equiv 0$, therefore (2.187) is obvious by (2.184). Suppose now $i = i_H$. By Tonelli's theorem we have

$$\begin{aligned}\int d(F[g])_{i,s} &= \eta(s)\int \partial_y \bar{A}_i(y,s)\int P(s,\bar{A}_i(\xi,s),\bar{A}_i(y,s))\,dg_{i,s}(\xi)\,dy - \int dg_{i,s}(y)\\ &= \eta(s)\int\left(\int P(s,\bar{A}_i(\xi,s),\bar{A}_i(y,s))\partial_y\bar{A}_i(y,s)\,dy\right)dg_{i,s}(\xi) - \int dg_{i,s}(y)\\ &= \eta(s)\int\left(\int_{\bar{A}_i(0,s)}^{\bar{A}_i(1,s)=1} P(s,\bar{A}_i(\xi,s),a)\,da\right)dg_{i,s}(\xi) - \int dg_{i,s}(y)\\ &= \eta(s)\int\left(\int_0^1 P(s,\bar{A}_i(\xi,s),a)\,da\right)dg_{i,s}(\xi) - \int dg_{i,s}(y) \underbrace{=}_{(2.24)} 0\end{aligned}$$

where we have used that $\int_0^{\bar{A}_i(0,s)} P(s,\bar{A}_i(\xi,s),a)\,da = 0$ since $\bar{A}_i(0,s) \leq \bar{A}_i(\xi,s)$ by Lemma 2.6.4 and $P(s,\bar{A}_i(\xi,s),a) = 0$ if $a < \bar{A}_i(\xi,s)$.

From now on, we fix a node i and often drop the node subscript. In view of (2.184), consider the "integrating factor" measure

$$q_t := \exp\left(\int_0^t \eta(s)\chi_H(s)\,ds\right) g_{i,t}, \quad t \in [0,T]. \tag{2.188}$$

Let Y be the space of measures such that $q \in Y$ if $t \mapsto e^{-\int_0^t \eta(s)\chi_H(s)\,ds} q$ is continuous from $[0,T]$ to $X_{[0,1]}$. The metric we consider on Y is

$$d_Y(q_1,q_2) = \mathcal{W}_1\left(e^{-\int_0^t \eta(s)\chi_H(s)\,ds} q_1, e^{-\int_0^t \eta(s)\chi_H(s)\,ds} q_2\right). \tag{2.189}$$

Formally, we have

$$\begin{aligned}\partial_t q_t(t) &= \exp\left(\int_0^t \eta(s)\chi_H(s)\,ds\right)[\partial_t g_{i,t} + \eta(t)\chi_H(t) g_{i,t}]\\ = \exp\left(\int_0^t \eta(s)\chi_H(s)\,ds\right) &\eta(t)\chi_H(t)\partial_y \bar{A}_i(y,t)\int P(t,\bar{A}_i(\xi,t),\bar{A}_i(y,t))\,dg_{i,t}(\xi)\,dy\\ &= \eta(t)\chi_H(t)\partial_y \bar{A}_i(y,t)\int P(t,\bar{A}_i(\xi,t),\bar{A}_i(y,t))\,dq_{i,t}(\xi)\,dy\end{aligned}$$

therefore q_t satisfies the following problem

$$\begin{cases}\partial_t q_t(y) = Lq_t(y)\\ q_t(0) = f_i(0),\end{cases} \tag{2.190}$$

$$Lq_t(y) = \eta(t)\chi_H(t)\partial_y \bar{A}_i(y,t)\int P(t,\bar{A}_i(\xi,t),\bar{A}_i(y,t))\,dq_t(\xi)\,dy.$$

We claim that the map

$$Q(q)(t) = f_i(0) + \int_0^t Lq_s\,ds \tag{2.191}$$

is a contraction on Y. We first show that

$$\int dLq_t = \eta(t)\chi_H(t)\exp\left(\int_0^t \eta(s)\chi_H(s)\,ds\right), \quad t\in[0,T]. \tag{2.192}$$

Indeed, by Tonelli's theorem we have

$$\begin{aligned}\int dLq_t &= \eta(t)\chi_H(t)\int \partial_y \bar{A}_i(y,t)\int P(t,\bar{A}_i(\xi,t),\bar{A}_i(y,t))\,dq_t(\xi)\,dy \\ &= \eta(t)\chi_H(t)\int\int P(t,\bar{A}_i(\xi,t),\bar{A}_i(y,t))\partial_y\bar{A}_i(y,t)\,dy\,dq_t(\xi)\\ &= \eta(t)\chi_H(t)\int\int_{\bar{A}_i(0,t)}^1 P(t,\bar{A}_i(\xi,t),a)\,da\,dq_t(\xi)\\ &= \eta(t)\chi_H(t)\int\int_0^1 P(t,\bar{A}_i(\xi,t),a)\,da\,dq_t(\xi)\\ &= \eta(t)\chi_H(t)\int dq_t(\xi) = \eta(t)\chi_H(t)\exp\left(\int_0^t \eta(s)\chi_H(s)\,ds\right).\end{aligned} \tag{2.193}$$

It will follow from the following calculations that Q is a contraction on Y. First we need to prove that $Q(q)\in Y$ for $q\in Y$, namely

$$\int_0^t Lq_t\,ds \in Y \quad \Leftrightarrow \quad t\mapsto \exp\left(-\int_0^t \eta(s)\chi_H(s)ds\right)\cdot\left(f_i(0)+\int_0^t Lq_t\,ds\right)\in C([0,T],X_{[0,1]}). \tag{2.194}$$

We now prove that $\exp(-\int \eta\chi_H)Q(q)$ is a probability measure on $[0,1]$:

$$\begin{aligned}
\int \exp\left(-\int_0^t \eta(s)\chi_H(s)ds\right) d\left(f_i(0)+\int_0^t Lq_t\,ds\right)(y) \qquad (2.195)\\
= \int \exp\left(-\int_0^t \eta(s)\chi_H(s)ds\right) df_i(0)(y)\\
+\int \exp\left(-\int_0^t \eta(s)\chi_H(s)ds\right) d\left(\int_0^t Lq_t\,ds\right)(y)\\
= \exp\left(-\int_0^t \eta(s)\chi_H(s)ds\right) + \exp\left(-\int_0^t \eta(s)\chi_H(s)ds\right)\int_0^t\int dLq_s\,ds\\
\underbrace{=}_{(2.192)} \exp\left(-\int_0^t \eta(s)\chi_H(s)ds\right)\\
+\exp\left(-\int_0^t \eta(s)\chi_H(s)ds\right)\int_0^t \eta(s)\chi_H(s)\exp\left(\int_0^s \eta(\tau)\chi_H(\tau)\,d\tau\right)ds\\
= \exp\left(-\int_0^t \eta(s)\chi_H(s)ds\right) + 1 - \exp\left(-\int_0^t \eta(s)\chi_H(s)ds\right) = 1.
\end{aligned}$$

Since $[0,1]$ is compact, it is sufficient to show that $\exp(-\int_0^t \eta\chi_H)Q(q)$ is narrowly continuous in time to get continuity on $[0,T]$ [4]. For this purpose, let $\phi \in C([0,1])$ and consider the function

$$\begin{aligned}
\int \phi(y)e^{-\int_0^t \eta\chi_H} d\left(f_i(0)+\int_0^t dLq_s\,ds\right)(y) = I_1+I_2 := \int \phi(y)e^{-\int_0^t \eta\chi_H}\,df_i(0)(y) \qquad (2.196)\\
+\int \phi(y)e^{-\int_0^t \eta\chi_H}\int_0^t\left[\eta\chi_H\partial_y\bar{A}_i(y,t)\int P(s,\bar{A}_i(\xi,s),\bar{A}_i(y,s))\,dq_s(\xi)\right]ds\,dy.
\end{aligned}$$

Concerning I_1, since $\left|\phi(y)e^{-\int_0^t \eta\chi_H}\right| \le C$ and $\phi(y)e^{-\int_0^t \eta\chi_H} \to \phi(y)e^{-\int_0^{\bar{t}} \eta\chi_H}$ for $t \to \bar{t}$, the dominated convergence theorem guarantees $I_1 \to \int \phi(y)e^{-\int_0^{\bar{t}} \eta\chi_H}\,df_i(0)(y)$. Using a similar argument, we can show, by means of (2.23), (2.181) and the facts that $\phi, \eta \in C([0,T])$ and $q \in Y$, that

$$\begin{aligned}
\left|\phi(y)e^{-\int_0^t \eta\chi_H}\int_0^t\left[\eta\chi_H\partial_y\bar{A}_i(y,t)\int P(s,\bar{A}_i(\xi,s),\bar{A}_i(y,s))\,dq_s\right]ds\right| \qquad (2.197)\\
\le C\int_0^t\int P(s,\bar{A}_i(\xi,s),\bar{A}_i(y,s))\,dq_s(\xi)\,ds\\
\le C\int_0^t\int dq_s(\xi)\,ds \le C\int_0^T\int dq_s\,ds \le CTe^{\int_0^T \eta(s)\chi_H(s)\,ds}.
\end{aligned}$$

We conclude that, by the dominated convergence theorem, $\exp(-\int_0^t \eta\chi_H)Q(q)$ is continuous.

We now have to show that $d_Y(Q(q_1),Q(q_2)) \le K d_Y(q_1,q_2)$ for $K<1$ on $[0,t]$ if t is sufficiently small. The metric on Y is

$$d_Y(q_1,q_2) = \sup_{t\in[0,T]}\left\{e^{-\int_0^t \eta(s)\chi_H(s)\,ds}\sup\left\{\int \phi\,d(q_1-q_2)\ :\ \phi\in \mathrm{Lip}_1([0,1],\mathbb{R})\right\}\right\} \qquad (2.198)$$

hence the distance between $Q(q_1)$ and $Q(q_2)$ in Y is

$$\sup_{t\in[0,T]}\left\{e^{-\int_0^t \eta(s)\chi_H(s)\,ds}\sup\left\{\int \phi\,d\int_0^t (Lq_1(s)-Lq_2(s))\,ds\ :\ \phi\in \mathrm{Lip}_1([0,1],\mathbb{R})\right\}\right\}.$$

Let $\phi \in \mathrm{Lip}_1([0,1];\mathbb{R})$. By Fubini's theorem and (2.192) it follows that

$$\int \phi \, d \int_0^t (Lq_1(s) - Lq_2(s)) \, ds = 0$$

for all $t \in [0,T]$ if ϕ is constant on $[0,1]$, hence we can assume that $\phi(0) = 0$. Otherwise, it suffices to shift the function by $\phi(0)$ and the contribution given by $\phi(0)$ vanishes in $\int \phi \, d \int_0^t (Lq_1(s) - Lq_2(s)) \, ds$. Since now $\phi(0) = 0$ and $\phi \in \mathrm{Lip}_1([0,1];\mathbb{R})$, $|\phi| \le 1$. By Fubini's theorem

$$\begin{aligned} &\int \phi \, d \int_0^t (Lq_1(s) - Lq_2(s)) \, ds \\ &= \int \phi(y) \int_0^t \left(\eta \chi_H \int P(s, \bar{A}_i(\xi,s), \bar{A}_i(y,s)) \partial_y \bar{A}_i(y,s) \, d(q_1 - q_2)(\xi) \right) ds \, dy \\ &= \int_0^t \eta \chi_H \left(\int \int \phi(y) P(s, \bar{A}_i(\xi,s), \bar{A}_i(y,s)) \partial_y \bar{A}_i(y,s) \, dy \, d(q_1 - q_2)(\xi) \right) ds \\ &= \int_0^t \eta \chi_H \left(\int \int_{\bar{A}_i(0,s)}^1 \phi(B_i(a,s)) P(s, \bar{A}_i(\xi,s), a) \, da \, d(q_1 - q_2)(\xi) \right) ds. \end{aligned} \tag{2.199}$$

Now by (2.25) the function

$$\xi \mapsto \int_{\bar{A}_i(0,s)}^1 \phi(B_i(a,s)) P(s, \bar{A}_i(\xi,s), a) \, da \tag{2.200}$$

is Lipschitz continuous:

$$\begin{aligned} &\left| \int_{\bar{A}_i(0,s)}^1 \phi(B_i(a,s)) \left(P(s, \bar{A}_i(\xi_2,s), a) - P(s, \bar{A}_i(\xi_1,s), a) \right) da \right| \\ &\le \int_{\bar{A}_i(0,s)}^1 \left| P(s, \bar{A}_i(\xi_2,s), a) - P(s, \bar{A}_i(\xi_1,s), a) \right| da \\ &\le \int_0^1 \left| P(s, \bar{A}_i(\xi_2,s), a) - P(s, \bar{A}_i(\xi_1,s), a) \right| da \le C|\xi_2 - \xi_1| \quad \text{for all } s \in [0,T], \end{aligned} \tag{2.201}$$

whence $\xi \mapsto \frac{1}{C} \int_{\bar{A}_i(0,s)}^1 \phi(B_i(a,s)) P(s, \bar{A}_i(\xi,s), a) \, da \in \mathrm{Lip}_1([0,1],\mathbb{R})$ for all $s \in [0,T]$. Returning to (2.199) we have

$$\begin{aligned} &\int_0^t \eta \chi_H \left(\int \int_{\bar{A}_i(0,s)}^1 \phi(B_i(a,s)) P(s, \bar{A}_i(\xi,s), a) \, da \, d(q_1 - q_2)(\xi) \right) ds \\ &\le L \int_0^t \eta \chi_H \sup \left\{ \int \psi \, d(q_1 - q_2) \, : \psi \in \mathrm{Lip}_1([0,1];\mathbb{R}) \right\} ds. \end{aligned} \tag{2.202}$$

It follows from (2.199) that

$$\sup \left\{ \int \phi \, d \int_0^t (Lq_1(s) - Lq_2(s)) \, ds \right\} \le C \int_0^t \sup \left\{ \int \psi \, d(q_1 - q_2) \, : \psi \in \mathrm{Lip}_1([0,1];\mathbb{R}) \right\} ds. \tag{2.203}$$

Multiplying by $e^{-\int_0^t \eta(s)\chi_H(s) \, ds}$ and taking the sup in time it follows that

$$d_Y(Q(q_1), Q(q_2)) \le CT d_Y(q_1, q_2) \tag{2.204}$$

therefore Q has a unique fixed point $\bar{q} \in Y$ on $[0,t]$ if t is small enough. The measure $\bar{q}$ satisfies

$$\bar{q} = f_i(0) + \int_0^t L\bar{q}\, ds \tag{2.205}$$

so $\bar{g} = e^{-\int_0^t \eta\chi_H}\bar{q}$ is a solution to (2.185). We now proceed to prove part 2 of the Lemma. Consider the map

$$L\bar{q}(y,t) = \eta(t)\chi_H(t)\partial_y \bar{A}_i(y,t) \int P(t, \bar{A}_i(\xi,t), \bar{A}_i(y,t))\, d\bar{q} \geq 0. \tag{2.206}$$

By construction we have $\bar{g} \in C([0,T]; X_{[0,1]})$, therefore it is narrowly continuous (and so is $\bar{q}$). Moreover by continuity of P and $\bar{A}_i$ we have that $L\bar{q} \in L^\infty((0,1)\times(0,T))$. Now define

$$\tilde{q} = \bar{q} - f_i(0). \tag{2.207}$$

By (2.205)

$$\tilde{q}(t) = \bar{q}(t) - f_i(0) = \int_0^t L(\tilde{q}(s) + f_i(0))\, ds. \tag{2.208}$$

Observe that $t \mapsto \tilde{q}(t)$ is absolutely continuous on $[0,T]$ for a.e. $y \in (0,1)$ since $L(\tilde{q}(s) + f_i(0))$ is bounded. Therefore we can write for all $\tau \in (0,T]$

$$\int_0^1 \psi(y,\tau)\tilde{q}_\tau(y)\, dy = \int_0^1 \int_0^\tau \partial_s \left(\psi(y,s)\tilde{q}_s(y)\right)\, ds\, dy \tag{2.209}$$

$$= \int_0^1 \int_0^\tau \left[\partial_s\psi(y,s)\tilde{q}_s(y) + \psi(y,s)L(\tilde{q}_s(y) + f_i(0))\right]\, ds\, dy \tag{2.210}$$

where $\psi \in L^\infty([0,1]\times[0,T])$ and $\partial_\tau\psi \in L^\infty([0,1]\times[0,T])$. Observe that, since $\bar{q}$ is AC with respect to the Lebesgue measure, $\tilde{q}$ is AC and the following calculations are justified. The notation q_s stands for the measure $q(s)$. Let ϕ as in the proof of part 1. We define $\psi(y,t) = e^{-\int_0^t \eta(s)\chi_H(s)\, ds}\phi(y,t)$ and test (2.209) with this function. The LHS of (2.209) gives

$$\int_0^1 \psi(y,\tau)\tilde{q}_\tau(y)\, dy = \int_0^1 \phi(y,\tau)e^{-\int_0^\tau \eta\chi_H\, ds}\, d\bar{q}_s(y) - \int_0^1 \phi(y,\tau)e^{-\int_0^\tau \eta\chi_H\, ds}\, df_{i,0}(y) \tag{2.211}$$

$$= \int_0^1 \phi(y,\tau)\, d\bar{g}_s(y) - \int_0^1 \psi(y,\tau)\, df_{i,0}(y).$$

By Fubini's theorem, (2.206) and (2.207) the RHS in (2.210) yields

$$
\begin{aligned}
&\int_0^1 \int_0^\tau [\partial_s \psi(y,s) \tilde{q}_s(y) + \psi(y,s) L(\tilde{q}_s(y) + f_{i,0}(y)]\, ds\, dy \qquad (2.212)\\
&= \int_0^1 \int_0^\tau \partial_s \psi(y,s)(\bar{q}_s(y) - f_{i,0}(y))\, ds\, dy + \int_0^1 \int_0^\tau \psi(y,s) L\bar{q}_s(y)\, ds\, dy \\
&= \int_0^1 \int_0^\tau \partial_s \phi(y,s) e^{-\int_0^s \eta\chi_H} \bar{q}_s(y)\, ds\, dy - \int_0^1 \int_0^\tau \phi(y,s)\eta\chi_H e^{-\int_0^t \eta\chi_H} \bar{q}_s(y)\, ds\, dy \\
&\quad - \int_0^1 \int_0^\tau \partial_s \psi(y,s) f_{i,0}\, ds\, dy + \int_0^1 \int_0^\tau \phi(y,s) e^{-\int_0^t \eta\chi_H} L\bar{q}_s(y)\, ds\, dy \\
&= \int_0^\tau \int_0^1 \partial_s \phi(y,s) e^{-\int_0^s \eta\chi_H} \bar{q}_s(y)\, dy\, ds - \int_0^\tau \int_0^1 \phi(y,s)\eta\chi_H e^{-\int_0^t \eta\chi_H} \bar{q}_s(y)\, dy\, ds \\
&\quad - \int_0^\tau \int_0^1 \partial_s \psi(y,s) f_{i,0}\, dy\, ds + \int_0^\tau \int_0^1 \phi(y,s) e^{-\int_0^t \eta\chi_H} L\bar{q}_s(y)\, dy\, ds \\
&= \int_0^\tau \int_0^1 \partial_s \phi(y,s)\, d\bar{g}_s(y)\, ds - \int_0^\tau \int_0^1 \phi(y,s)\eta\chi_H\, d\bar{g}_s(y)\, ds \\
&\quad - \int_0^\tau \int_0^1 \partial_s \psi(y,s)\, df_{i,0}(y)\, ds + \int_0^\tau \int_0^1 \phi(y,s) e^{-\int_0^t \eta\chi_H} L\bar{q}_s(y)\, dy\, ds \\
&= \int_0^\tau \int_0^1 \partial_s \phi(y,s)\, d\bar{g}_s(y)\, ds - \int_0^\tau \int_0^1 \phi(y,s)\eta\chi_H\, d\bar{g}_s(y)\, ds \\
&\quad - \int_0^1 (\psi(y,\tau) - \psi(y,0))\, df_{i,0}(y) + \int_0^\tau \int_0^1 \phi(y,s) e^{-\int_0^t \eta\chi_H} L\bar{q}_s(y)\, dy\, ds.
\end{aligned}
$$

It follows from (2.211) and (2.212) that

$$
\begin{aligned}
&\int_0^1 \phi(y,\tau)\, d\bar{g}_s(y) - \int_0^1 \psi(y,0)\, df_{i,0}(y) \\
&= \int_0^\tau \int_0^1 \partial_s \phi(y,s)\, d\bar{g}_s(y)\, ds - \int_0^\tau \int_0^1 \phi(y,s)\eta\chi_H\, d\bar{g}_s(y)\, ds \\
&\quad + \int_0^\tau \int_0^1 \phi(y,s)\eta(t)\chi_H(t)\partial_y \bar{A}_i(y,t) \int P(t, \bar{A}_i(\xi,t), \bar{A}_i(y,t)) e^{-\int_0^t \eta\chi_H}\, d\bar{q}(\xi)\, dy\, ds.
\end{aligned}
$$

Recalling definition (2.184) and the fact that $\psi(y,0) = \phi(y,0)$ it follows that

$$
\begin{aligned}
&\int_0^1 \phi(y,\tau)\, d\bar{g}_s(y) - \int_0^1 \phi(y,0)\, df_{i,0}(y) \qquad (2.213)\\
&= \int_0^\tau \int_0^1 \partial_s \phi(y,s)\, d\bar{g}_s(y)\, ds + \int_0^\tau \int_0^1 \phi(y,s) d(F[\bar{g}_s])(y)\, ds
\end{aligned}
$$

hence $\bar{g}$ satisfies (2.186) in the weak sense of (2.166). □

So far we have proved that, given $(A, g, u) \in X_T$, we can uniquely define the characteristics $\bar{A}$ of Lemma 2.6.4. Then, $\bar{A}$ uniquely defines the measure $\bar{g}$ in Lemma 2.6.5. Accordingly, we consider the monomers' source

$$
F[\bar{g}_{i,t}] := C_\mu \int_{[0,1]} (\mu_0 + \bar{A}_i(\xi,t))(1 - \bar{A}_i(\xi,t))\, d\bar{g}_{i,t}(\xi) \geq 0. \qquad (2.214)
$$

Remark 2.6.2. *The continuity of u_2 on $[0,T]$ implies uniform boundedness of $\tilde{v}$, hence $t \mapsto \bar{A}_i(y,t)$ is Lipschitz continuous uniformly in y and it follows that $t \mapsto F[g_{i,t}]$ is Lipschitz continuous on $[0,T]$. In fact, let $t_1, t_2 \in [0,\tau^*]$. Then*

$$
\begin{aligned}
|F[g_{i,t_2}] - F[g_{i,t_1}]| &= C_\mu \left| \int (\mu_0 + \bar{A}_i(y,t_2))(1-\bar{A}_i(y,t_2))\, dg_{i,t_2}(y) \right. \\
&\qquad \left. - \int (\mu_0 + \bar{A}_i(y,t_1))(1-\bar{A}_i(y,t_1))\, dg_{i,t_1}(y) \right| \\
&\le C_\mu \int \left|(\mu_0 + \bar{A}_i(y,t_2))(1-\bar{A}_i(y,t_2))\right| \, d(g_{i,t_2} - g_{i,t_1})(y) \\
+C_\mu \int \Big|(\mu_0 + \bar{A}_i(y,t_2))&(1-\bar{A}_i(y,t_2)) - (\mu_0 + \bar{A}_i(y,t_1))(1-\bar{A}_i(y,t_1))\Big| \, dg_{i,t_1}(y) \\
&\le C' \mathcal{W}_1(g_{i,t_1}, g_{i,t_2}) + C_\mu \int \left|(\mu_0 + \bar{A}_i(y,t_2))(\bar{A}_i(y,t_1) - \bar{A}_i(y,t_2))\right| dg_{i,t_1}(y) \\
&\qquad + C_\mu \int \left|(1-\bar{A}_i(y,t_1))(\bar{A}_i(y,t_2) - \bar{A}_i(y,t_1))\right| \, dg_{i,t_1}(y) \\
&\le C''|t_2 - t_1| + C'''(\mu_0+1)|t_2 - t_1| + C''''|t_2 - t_1| \le \tilde{C}|t_2 - t_1|
\end{aligned}
\tag{2.215}
$$

where we have also used the Lipschitz continuity of $y \mapsto \bar{A}_i(y,t)$ uniformly in t and the Kantorovich-Rubinstein duality for $\mathcal{W}_1$ [4].

By Remark 2.6.2 and Section 2.4 the elliptic graph system

$$
\begin{cases}
d_1 \Delta u_1 - \sigma_1 u_1 + F[\bar{g}] + \Gamma_1 = 0, \\
d_2 \Delta u_2 - \sigma_2 u_2 + \Gamma_2 = 0, & \qquad i \in V, \\
-\sigma_3 u_3 + \Gamma_3 = 0,
\end{cases}
\tag{2.216}
$$

exhibits a non negative solution $\bar{u} \in C([0,T];\mathbb{R}^{3h})$ which satisfies the mass balance

$$
\sum_{k=1}^{3} \int_G \sigma_k u_k(i,t) = \int_G F[\bar{g}_{i,t}]. \tag{2.217}
$$

We can now define the operator $\mathcal{H}$ on X_T as

$$
\mathcal{H}(A,g,u) = (\bar{A}, \bar{g}, \bar{u}). \tag{2.218}
$$

In the following, we will prove that $\mathcal{H}$ is invariant on $X_{\rho,\tau}$ if τ is small enough. By the Kantorovich-Rubinstein duality for $\mathcal{W}_1$, $\mathcal{H}$ is a contraction only on its image $\mathcal{H}(X_{\rho,\tau}) \subset X_{\rho,\tau}$, which in principle is not a complete space, hence we need to adapt the fixed-point argument by proving the continuity of $\mathcal{H}$ as a map from $X_{\rho,\tau}$ with the standard metric topology to the same space endowed with a weaker topology. In particular, we refer to $\mathcal{T}_d$ as the metric topology of $X_{\rho,\tau}$ and with $\mathcal{T}$ as the weaker topology on $X_{\rho,\tau}$ obtained by endowing the characteristics space $C([0,1]\times[0,\tau];\mathbb{R}^h)$ with the L^1 topology on $[0,1]\times[0,\tau]$.

Theorem 2.6.6. *Let $\rho > 0$ fixed and $\mathcal{H}$ defined by* (2.218)*. If $\tau > 0$ is sufficiently small then $\mathcal{H}(X_{\rho,\tau}) \subset X_{\rho,\tau}$, if $(A_n, g_n, u_n) \to (A,g,u)$ in $\mathcal{T}_d$ then $\mathcal{H}(A_n,g_n,u_n) \to H(A,g,u)$ in $\mathcal{T}$ and $\mathcal{H}$ is a contraction on $\mathcal{H}(X_{\rho,\tau})$.*

Proof. We first prove that $\mathcal{H}(X_{\rho,\tau}) \subset X_{\rho,\tau}$ by adapting the argument in Section 2.5. By (2.139) and (2.140) with $g_i = g_{i,t}$ it follows that

$$\max_{y\in[0,1]} |\bar{A}_i(y,t) - y| \to 0. \tag{2.219}$$

The argument (2.143) for the u component needs some attention since now $g_{i,t}$ is not constant in time. By (2.217) and the non-negativity of $\bar{u}$ we have the following estimate

$$\underbrace{\left(\min_{k=1,2,3} \sigma_k\right)}_{=:\tilde{\sigma}} \bar{u}_j(\ell,t) \le \sum_{k=1}^{3} \int_G \sigma_k \bar{u}_k(i,t) = \int_G F[g_{i,t}] \quad j \in \{1,2,3\},\ \ell \in V,\ t \in [0,T], \tag{2.220}$$

which gives

$$|\bar{u}_k(i,t) - (u_0)_k(i)| = |\bar{u}_k(i,t) - \bar{u}_k(i,0)| \le \frac{1}{\tilde{\sigma}} \sum_{j=1}^{h} |F[g_{j,t}] - F[g_{j,0}]| \tag{2.221}$$

$$\begin{aligned}
&= \frac{C_\mu}{\tilde{\sigma}} \sum_{j=1}^{h} \left| \int_{[0,1]} (\mu_0 + \bar{A}_j(\xi,t))(1 - \bar{A}_j(\xi,t))\, dg_{j,t}(\xi) - \int_{[0,1]} (\mu_0 + \xi)(1-\xi)\, df_{j,0}(\xi) \right| \\
&\le \frac{C_\mu}{\tilde{\sigma}} \sum_{j=1}^{h} \int_{[0,1]} \left|(\mu_0 + \bar{A}_j(\xi,t))(1 - \bar{A}_j(\xi,t)) - (\mu_0 - \xi)(1-\xi)\right| \, dg_{j,t}(\xi) \\
&\quad + \frac{C_\mu}{\tilde{\sigma}} \sum_{j=1}^{h} \int_{[0,1]} |(\mu_0 + \xi)(1-\xi)| \, d(g_{i,t} - f_{j,0})(\xi) \\
&\le \frac{\tilde{C}_\mu}{\tilde{\sigma}} \sum_{j=1}^{h} \int_{[0,1]} \left|\bar{A}_j(\xi,t) - \xi\right| \, dg_{j,t}(\xi) + \frac{C_\mu}{\tilde{\sigma}} \sum_{j=1}^{h} \int_{[0,1]} |(\mu_0 + \xi)(1-\xi)| \, d(g_{j,t} - f_{j,0})(\xi) \\
&\le \frac{\tilde{C}_\mu}{\tilde{\sigma}} \sum_{j=1}^{h} \max_{y\in[0,1]} |\bar{A}_j(\xi,t) - \xi| + \frac{C_\mu}{\tilde{\sigma}} \sum_{j=1}^{h} \int_{[0,1]} |(\mu_0 + \xi)(1-\xi)| \, d(g_{j,t} - f_{j,0})(\xi).
\end{aligned}$$

By (2.219) and the narrow continuity of $t \mapsto g_{i,t}$, we have that $|\bar{u}_k(i,t) - (u_0)_k(i)| \to 0$ as $t \to 0^+$ for all $i \in V$ and $k = 1,2,3$. It remains to show that

$$||\bar{g}_{i,t} - f_i(0)||_{X_{[0,1]}} \to 0 \quad \text{for all } i \in V. \tag{2.222}$$

By Lemma 2.6.5, for all $i \in V$ $\bar{g}_{i,t}$ is the unique solution to the integral equation

$$\bar{g}_{i,t} = f_i(0) + \int_0^t (F[\bar{g}_{i,t}])\, ds, \quad t \in [0,T], \tag{2.223}$$

and $g_{i,t} \in C([0,T], X_{[0,1]})$, whence $g_{i,t} \to f_i(0)$. This implies $\mathcal{H}(X_{\rho,\tau}) \subset X_{\rho,\tau}$ if τ is small enough.

We proceed by proving the $(\mathcal{T}_d, \mathcal{T})$ continuity of $\mathcal{H}$. Let $((A_n, g_n, u_n))_n$ be a sequence in $X_{\rho,\tau}$ such that $(A_n, g_n, u_n) \to (A, g, u)$ in $(X_{\rho,\tau}, \mathcal{T}_d)$ as $n \to \infty$. We have to show that $(\bar{A}_n, \bar{g}_n, \bar{u}_n) \to (\bar{A}, \bar{g}, \bar{u})$ in $(X_{\rho,\tau}, \mathcal{T})$. From now on, $\bar{A}_i^n$ denotes the characteristics at node i in the sequence $(\bar{A}_n, \bar{g}_n, \bar{u}_n)$. It follows from Lemma 2.6.4 that $\bar{A}_i^n$ and $\bar{A}_i$ are bounded uniformly in $i \in V$, $t \in [0,T]$ and $n \in \mathbb{N}$, therefore by the dominated convergence theorem, if $\bar{A}_i^n - \bar{A}_i \to 0$ a.e. in $[0,1] \times [0,T]$ for all $i \in V$, then $(\bar{A}_n, \bar{g}_n, \bar{u}_n) \to (\bar{A}, \bar{g}, \bar{u})$ in $(X_{\rho,\tau}, \mathcal{T})$.

It follows from (2.180) that

$$
\begin{aligned}
|\bar{A}_i^n(y,t) - \bar{A}_i(y,t)| &= |\bar{A}_i^n(y,t) - \bar{A}_i^n(y,0) - \bar{A}_i(y,t) + \bar{A}_i(y,0)| \qquad (2.224)\\
= \Big| C_G \int_0^t \int (A_i^n(\xi,s) - \bar{A}_i^n(y,s))^+ \, dg_{i,s}^n(\xi)\, ds &+ C_S \int_0^t (1 - \bar{A}_i^n(y,s))(u_2^n(i,s) - \bar{U}_2)^+ \, ds \\
- C_G \int_0^t \int (A_i(\xi,s) - \bar{A}_i(y,s))^+ \, dg_{i,s}(\xi)\, ds &- C_S \int_0^t (1 - \bar{A}_i(y,s))(u_2(i,s) - \bar{U}_2)^+ \, ds \Big| \\
\le C_G \int_0^t \int \left|(A_i^n(\xi,s) - \bar{A}_i^n(y,s))^+ - (A_i(\xi,s) - \bar{A}_i(y,s))^+\right| \, dg_{i,s}^n(\xi)\, ds \\
+ C_G \int_0^t \int \left|(A_i(\xi,s) - \bar{A}_i(y,s))^+\right| \, d(g_{i,s}^n - g_{i,s})(\xi)\, ds \qquad (2.225)\\
+ C_S \int_0^t \left|(1 - \bar{A}_i^n(y,s)) \left[(u_2^n(i,s) - \bar{U}_2)^+ - (u_2(i,s) - \bar{U}_2)^+\right]\right| \, ds \\
+ C_S \int_0^t \left|\bar{A}_i^n(y,s) - \bar{A}_i(y,s)\right| (u_2(i,s) - \bar{U}_2)^+ \, ds =: I_1 + I_2 + I_3 + I_4.
\end{aligned}
$$

Since $(A_n, g_n, u_n), (A, g, u) \in X_{\rho,\tau}$, we have that $\max_{[0,\tau]} ||u_n(\tau) - u(\tau)||_{\mathbb{R}^{3h}} \le \mathrm{diam}(X_{\rho,\tau}) = 2\rho$, therefore we can easily bound I_3 and I_4:

$$
|I_3| \le C_\rho \, t \, d((A_n, g_n, u_n), (A, g, u)) \qquad (2.226)
$$

$$
|I_4| \le C_\rho \int_0^t \left|\bar{A}_i^n(y,s) - \bar{A}_i(y,s)\right| \, ds. \qquad (2.227)
$$

Concerning I_1 we have

$$
\begin{aligned}
|I_1| &\le C_G \int_0^t \int \left|(A_i^n(\xi,s) - \bar{A}_i^n(y,s))^+ - (A_i^n(\xi,s) - \bar{A}_i(y,s))^+\right| \, dg_{i,s}^n(\xi)\, ds \qquad (2.228)\\
&+ C_G \int_0^t \int \left|(A_i^n(\xi,s) - \bar{A}_i(y,s))^+ - (A_i(\xi,s) - \bar{A}_i(y,s))^+\right| \, dg_{i,s}^n(\xi)\, ds \\
&\le \tilde{C}_G \int_0^t \int \left|\bar{A}_i^n(y,s) - \bar{A}_i(y,s)\right| \, dg_{i,s}^n(\xi)\, ds + \tilde{C}_G \int_0^t \int \left|A_i^n(\xi,s) - A_i(\xi,s)\right| \, dg_{i,s}^n(\xi)\, ds \\
&\le \tilde{C}_G \int_0^t \left|\bar{A}_i^n(y,s) - \bar{A}_i(y,s)\right| \, ds + \tilde{C}_G t \, d((A_n, g_n, u_n), (A, g, u)).
\end{aligned}
$$

Finally we obtain

$$
\begin{aligned}
|\bar{A}_i^n(y,t) - \bar{A}_i(y,t)| \le \tilde{C}_\rho \int_0^t \left|\bar{A}_i^n(y,s) - \bar{A}_i(y,s)\right| \, ds \qquad (2.229)\\
+ C \, t \, d((A_n, g_n, u_n), (A, g, u)) + I_2
\end{aligned}
$$

whence by Gronwall's inequality

$$
|\bar{A}_i^n(y,t) - \bar{A}_i(y,t)| \le (C \, t \, d((A_n, g_n, u_n), (A, g, u)) + I_2) \, e^{\tilde{C}_\rho t}, \qquad (2.230)
$$

where $d((A_n, g_n, u_n), (A, g, u)) \to 0$ as $n \to \infty$. Here, $I_2 \to 0$ by the dominated convergence theorem since $g_{i,s}^n \to g_{i,s}$ weakly* and

$$
\int \left|(A_i(\xi,s) - \bar{A}_i(y,s))^+\right| \, d(g_{i,s}^n - g_{i,s})(\xi) \le 4.
$$

It remains to show that $\mathcal{H}$ is a contraction on $\mathcal{H}(X_{\rho,\tau})$. Let (A^1, g^1, u^1), $(A^2, g^2, u^2) \in \mathcal{H}(X_{\rho,\tau})$. The characteristics satisfy

$$|\bar{A}_i^1(y,t) - \bar{A}_i^2(y,t)| \leq \big(C\,\tau\, d((A^1, g^1, u^1), (A^2, g^2, u^2)) \tag{2.231}$$
$$+C_G \int_0^\tau \int \left|(A_i^2(\xi,s) - \bar{A}_i^2(y,s)^+\right| d(g_{i,s}^1 - g_{i,s}^2)\, ds\bigg) e^{\tilde{C}_\rho \tau}.$$

By Lemma 2.6.4, since $(A^2, g^2, u^2) \in \mathcal{H}(X_{\rho,\tau})$, the functions $\xi \mapsto A_i^2(\xi,s)$, $\xi \mapsto \bar{A}_i^2(\xi,s)$ are Lipschitz continuous uniformly in s, therefore

$$|\bar{A}_i^1(y,t) - \bar{A}_i^2(y,t)| \leq \left(C\,\tau\, d((A^1, g^1, u^1), (A^2, g^2, u^2)) + C_G \int_0^\tau \mathcal{W}_1(g_{i,s}^1, g_{i,s}^2)\, ds\right) e^{\tilde{C}_\rho \tau} \tag{2.232}$$
$$\leq \tilde{C}\tau d((A^1, g^1, u^1), (A^2, g^2, u^2)),$$

for all $i \in V$, $t \in [0,\tau]$. Concerning the g component, from the calculations in Lemma 2.6.5 it follows that

$$\mathcal{W}_1(\bar{g}_{i,t}^1, \bar{g}_{i,t}^2) \leq C\tau \max_{t\in[0,\tau]} \mathcal{W}_1(\bar{g}_{i,t}^1, \bar{g}_{i,t}^2) \leq C\tau d((A^1, g^1, u^1), (A^2, g^2, u^2)) \text{ for all } i \in V,\ t \in [0,\tau]. \tag{2.233}$$

Lastly, we repeat the calculations in (2.143) by inserting the time dependence of $g_{i,s}$. Let $i \in V$ and $k \in \{1,2,3\}$. We have

$$|\bar{u}_k^1(i,t) - \bar{u}_k^2(i,t)| \leq \frac{1}{\tilde{\sigma}} \sum_{j=1}^h \left|F[g_{j,t}^1] - F[g_{j,t}^2]\right| \leq \frac{C_\mu}{\tilde{\sigma}} \sum_{j=1}^h \bigg|\int (\mu_0 + \bar{A}_j^1(\xi,t))(1 - \bar{A}_j^1(\xi,t))\, dg_{j,t}^1(\xi) \tag{2.234}$$
$$- \int (\mu_0 + \bar{A}_j^2(\xi,t))(1 - \bar{A}_j^2(\xi,t))\, dg_{j,t}^2(\xi)\bigg| \leq \frac{C_\mu}{\tilde{\sigma}} \sum_{j=1}^h \int \left|(\mu_0 + \bar{A}_j^1(\xi,t))(1 - \bar{A}_j^1(\xi,t))\right| d(g_{j,t}^1 - g_{j,t}^2)(\xi)$$
$$+\frac{C_\mu}{\tilde{\sigma}} \sum_{j=1}^h \int \left|(\mu_0 + \bar{A}_j^1(\xi,t))(1 - \bar{A}_j^1(\xi,t)) - (\mu_0 + \bar{A}_j^2(\xi,t))(1 - \bar{A}_j^2(\xi,t))\right| dg_{j,t}^2(\xi).$$

Again by the Lipschitz continuity of $\xi \mapsto \bar{A}_j^1(\xi,t)$ uniformly in t we have

$$|\bar{u}_k^1(i,t) - \bar{u}_k^2(i,t)| \leq \frac{\tilde{C}_\mu}{\tilde{\sigma}} \sum_{j=1}^h \mathcal{W}_1(g_{j,t}^1, g_{j,t}^2) \tag{2.235}$$
$$+\frac{C_\mu}{\tilde{\sigma}} \sum_{j=1}^h \int \left|(\mu_0 + \bar{A}_j^1(\xi,t))(\bar{A}_j^2(\xi,t) - \bar{A}_j^1(\xi,t))\right| dg_{j,t}^2(\xi)$$
$$+\frac{C_\mu}{\tilde{\sigma}} \sum_{j=1}^h \int \left|(1 - \bar{A}_j^2(\xi,t))(\bar{A}_j^1(\xi,t) - \bar{A}_j^2(\xi,t))\right| dg_{j,t}^2(\xi) \leq \frac{\tilde{C}_\mu}{\tilde{\sigma}} \sum_{j=1}^h \mathcal{W}_1(g_{j,t}^1, g_{j,t}^2)$$
$$+\frac{C_\mu}{\tilde{\sigma}} \sum_{j=1}^h (\mu_0 + 1) \max_{y\in[0,1]} |\bar{A}_j^2(y,t) - \bar{A}_j^1(y,t)| + \frac{C_\mu}{\tilde{\sigma}} \sum_{j=1}^h \max_{y\in[0,1]} \left|(\bar{A}_j^1(y,t) - \bar{A}_j^2(y,t))\right|.$$

By (2.232) and (2.233) it follows that

$$|\bar{u}_k^1(i,t) - \bar{u}_k^2(i,t)| \leq C\tau d((A^1, g^1, u^1), (A^2, g^2, u^2)) \tag{2.236}$$

for all $i \in V$, $k = 1,2,3$, $t \in [0,\tau]$. Combining (2.232), (2.233) and (2.236) we find that $\mathcal{H}$ is a contraction on $\mathcal{H}(X_{\rho,\tau})$ if τ is sufficiently small. $\square$

The local existence on $[0,\tau^*)$ follows from Proposition 4.8 in [14].

2.6.3 Global Existence

To extend the solution to the whole interval $[0, T]$, suppose that $[0, \tau^*)$ is the maximal interval. We observe that, as in Section 2.5, the monomers' source is uniformly bounded

$$F[g_{i,t}] = C_\mu \int (\mu_0 + A_i(y,t))(1 - A_i(y,t))\, dg_{i,t}(y) \leq C \quad \text{for all } i \in V, t \in [0, t^*), \tag{2.237}$$

hence by (2.217) it follows that

$$|u_k(i,t)| \leq \tilde{C} \quad \text{for } t \in [0, \tau^*),\ i \in V,\ k = 1, 2, 3. \tag{2.238}$$

By (2.238), $v_i(A_i(y,t), t)$ is bounded uniformly in t, therefore $t \mapsto A_i(y,t)$ is Lipschitz continuous. By Lemma 2.6.4, $y \mapsto A_i(y,t)$ is Lipschitz continuous uniformly in t. Moreover, by Lemma 2.6.5, $t \mapsto g_{i,t} \in X_{[0,1]}$ is Lipschitz continuous, therefore both can be extended with continuity to $[0, \tau^*]$ and the limit $\lim_{t \to \tau^*} A_i(y,t) = A_i(y, \tau^*)$ is Lipschitz continuous in y.

By Remark 2.6.2, $t \mapsto F[g_{i,t}]$ is Lispchitz continuous. Now repeating the argument leading to (2.236) we obtain that $t \mapsto u \in \mathbb{R}^{3h}$ is Lipschitz continuous, hence it can be extended to $[0, \tau^*]$. We conclude that $[0, \tau^*)$ is not maximal, contradicting the definition of τ^*.

2.7 Time regularity

In this section, we improve the regularity properties developed in [14] by proving that $u \in C^1([0, T])$. Let $\phi \in C^1([0, T])$. For the convenience of the reader, we recall that

$$\partial_t g_{i,t} = \eta \chi_H \left[\partial_y A_i(y,t) \int P(t, A_i(\xi, t), A_i(y,t))\, dg_{i,t}(\xi)\, dy - g_{i,t}(y) \right]. \tag{2.239}$$

Lemma 2.7.1. *Let $(A, g, u) \in X_{\rho,T}$ be a solution to* (2.164), (2.165). *The function $t \mapsto F[g_{i,t}]$ satisfies*

$$\partial_t F[g_{i,t}](t) = \mathcal{G}_i(t) \tag{2.240}$$

in the weak sense (2.166), *where*

$$\begin{aligned} \mathcal{G}_i(t) = C_\mu \int (1 - \mu_0 - 2A_i(y,t)) v_i(A_i(y,t), t)\, dg_{i,t}(y) \\ + C_\mu \eta(t) \chi_H(t) \int \left[(\mu_0 + A_i(y,t))(1 - A_i(y,t)) \partial_y A_i(y,t) \left(\int P(t, A_i(\xi, t), A_i(y,t))\, dg_{i,t}(\xi) \right) \right] dy \\ - C_\mu \eta(t) \chi_H(t) \int (\mu_0 + A_i(y,t))(1 - A_i(y,t))\, dg_{i,t}(y). \end{aligned}$$

Proof. Define $h_i(y,t) := (\mu_0 + A_i(y,t))(1 - A_i(y,t))$. Since $t \mapsto v_i(y,t)$ is continuous for all $y \in [0,1]$ and $t \mapsto A_i(y,t)$ is continuous, the map $t \mapsto \partial_t A_i(y,t) = v_i(A_i(y,t), t)$ is continuous for all $y \in [0,1]$.

This implies that $t \mapsto h_i(y,t) \in C^1([0,T])$ for all $y \in [0,1]$. Now let $\phi \in C^1([0,T])$. We have

$$\int_0^T \phi'(t) F[g_{i,t}]\, dt = C_\mu \int_0^T \int_{[0,1]} \phi'(t) h_i(y,t)\, dg_{i,t}(y)\, dt$$

$$= C_\mu \int_0^T \int_{[0,1]} (\phi(t) h_i(y,t))_t\; dg_{i,t}(y)\, dt - C_\mu \int_0^T \int_{[0,1]} \phi(t)\partial_t h_i(y,t)\, dg_{i,t}(y)\, dt$$

$$= C_\mu \int_{[0,1]} \phi(T) h_i(y,T)\, dg_{i,T}(y) - C_\mu \int_{[0,1]} \phi(0) h_i(y,0)\, dg_{i,0}(y)$$

$$-C_\mu \int_0^T \eta(t)\chi_H(t) \int_{[0,1]} \phi(t) h_i(y,t)\partial_y A_i(y,t) \int P(t, A_i(\xi,y), A_i(y,t))\, dg_{i,t}(\xi)\, dy\, dt$$

$$+C_\mu \int_0^T \eta(t)\chi_H(t) \int_{[0,1]} \phi(t) h_i(y,t)\, dg_{i,t}(y)\, dt - C_\mu \int_0^T \int_{[0,1]} \phi(t)\partial_t h_i(y,t)\, dg_{i,t}(y)\, dt$$

where the last equality follows from Definition $(2.6.2)_5$. By definition of h_i we have

$$\begin{aligned}\int_0^T \phi'(t) F[g_{i,t}]\, dt &= \phi(T) F[g_{i,T}] - \phi(0) F[g_{i,0}] \\ -C_\mu \int_0^T \eta(t)\chi_H(t)\phi(t) \int_{[0,1]} &\Big[(\mu_0 + A_i(y,t))(1 - A_i(y,t))\partial_y A_i(y,t) \\ &\left(\int P(t, A_i(\xi,y), A_i(y,t))\, dg_{i,t}(\xi)\right) dy\Big]\, dt \\ +C_\mu \int_0^T \eta(t)\chi_H(t)\phi(t) &\int_{[0,1]} (\mu_0 + A_i(y,t))(1 - A_i(y,t))\, dg_{i,t}(y)\, dt \\ -C_\mu \int_0^T \phi(t) &\int_{[0,1]} (1 - \mu_0 - 2A_i(y,t)) v_i(A_i(y,t),t)\, dg_{i,t}(y)\, dt \\ &= \phi(T) F[g_{i,T}] - \phi(0) F[g_{i,0}] - \int_0^T \phi(t)\mathcal{G}_i(t)\, dt.\end{aligned} \tag{2.241}$$

□

Remark 2.7.1. *Observe that $\partial_t F[g_{i,t}]$ depends on u_2 through $v_i(A_i(y,t),t)$ and $\partial_y A_i(y,t)$.*

Remark 2.7.2. *It follows from Lemma 2.7.1 that for a.e. $t \in [0,T]$*

$$\begin{aligned}|\partial_t F[g_{i,t}]| &\le C_\mu \sup_{y\in[0,1]} v_i(A_i(y,t),t) \int dg_{i,t} + C_\mu \max_{t\in[0,T]} \eta(t)(\mu_0+1) \int |\partial_y A_i(y,t)| \int dg_{i,t}(\xi)\, dy \\ &+C_\mu \max_{t\in[0,T]} \eta(t)(\mu_0+1) \int dg_{i,t} \le C_\mu C_\rho + C_\mu \max_{t\in[0,T]} \eta(t)(\mu_0+1) \sup_{y\in[0,1]} |\partial_y A_i(y,t)| + C_\mu \max_{t\in[0,T]} \eta(t)(\mu_0+1)\end{aligned} \tag{2.242}$$

where we have used that $|A_i| \le 1$ and $y \mapsto A_i(y,t)$ is bounded uniformly in t. Now recall that, by (2.181), *the map $y \mapsto \partial_y A_i(y,t)$ is bounded uniformly in t, hence we can conclude that $\partial_t F[g_{i,t}] \in L^\infty([0,T])$.*

Lemma 2.7.2. *Let $(A,g,u) \in X_{\rho,T}$ be a solution to* (2.164), (2.165). *If $t \mapsto P(t,a,b)$ is Lipschitz continuous uniformly in (a,b), then $t \mapsto \partial_t F[g_{i,t}]$ is continuous as a function from $[0,T]$ to $\mathbb{R}$.*

Proof. The explicit expression for $\partial_t F[g_{i,t}]$ is given by

$$\begin{aligned} \partial_t F[g_{i,t}] = C_\mu \int (1-\mu_0 - 2A_i(y,t)) v_i(A_i(y,t),t)\, dg_{i,t}(y) \\ + C_\mu \eta(t)\chi_H(t) \int \left[h(y,t)\partial_y A_i(y,t) \int P(t, A_i(\xi,t), A_i(y,t))\, dg_{i,t}(\xi)\right] dy \\ - C_\mu \eta(t)\chi_H(t) \int h(y,t)\, dg_{i,t}(y). \end{aligned} \tag{2.243}$$

Performing the change of variable $a = A_i(y,t)$ as in (2.199), the integral in (2.243) becomes

$$\begin{aligned} C_\mu \eta(t)\chi_H(t) \int \left[h(y,t)\partial_y A_i(y,t) \int P(t, A_i(\xi,t), A_i(y,t))\, dg_{i,t}(\xi)\right] dy \\ = C_\mu \eta(t)\chi_H(t) \int \left[h(B_i(a,t),t) \int P(t, A_i(\xi,t), a)\, dg_{i,t}(\xi)\right] da \\ = C_\mu \eta(t)\chi_H(t) \int \left[(\mu_0 + a)(1-a) \int P(t, A_i(\xi,t), a)\, dg_{i,t}(\xi)\right] da. \end{aligned} \tag{2.244}$$

We write

$$\begin{aligned} \partial_t F[g_{i,t}] = C_\mu \int (1-\mu_0 - 2A_i(y,t)) v_i(A_i(y,t),t)\, dg_{i,t}(y) \\ + C_\mu \eta(t)\chi_H(t) \int \left[(\mu_0 + a)(1-a) \int P(t, A_i(\xi,t), a)\, dg_{i,t}(\xi)\right] da \\ - C_\mu \eta(t)\chi_H(t) \int h(y,t)\, dg_{i,t}(y) =: I_1(t) + I_2(t) + I_3(t). \end{aligned}$$

We consider a sequence $t_n \to t$ in $[0,T]$. Concerning the first integral I_1, we have the following uniform estimate:

$$\begin{aligned} |(1-\mu_0-2A_i(y,t_n))v_i(A_i(y,t_n))| \le (\mu_0+3)\left[C_G \int (A_i(\xi,t_n) - A_i(y,t_n))^+\, dg_{i,t_n}(\xi) \right. \\ \left. + C_S(1-A_i(y,t_n))(u_2(t_n) - \bar{U}_2)^+ \right] \le (\mu_0+3)\left(2\int dg_{i,t_n}(\xi) + C_S C_\rho \right) = (\mu_0+3)\left(2 + C_S C_\rho\right). \end{aligned}$$

We write $I_1(t_n)$ as

$$\begin{aligned} I_1(t_n) = C_\mu \int [(1-\mu_0-2A_i(y,t_n))v_i(A_i(y,t_n),t_n) \\ -(1-\mu_0-2A_i(y,t))v_i(A_i(y,t),t)]\, dg_{i,t_n}(y) \\ + C_\mu \int (1-\mu_0-2A_i(y,t))v_i(A_i(y,t),t)\, dg_{i,t_n}(y). \end{aligned} \tag{2.245}$$

Concerning the first integral in (2.245), we recall that $t \mapsto A_i(y,t)$ is Lipschitz continuous uniformly in y. Moreover, by Lipschitz continuity of $t \mapsto F[g_{i,t}]$, it follows that u_2 is Lipschitz continuous in time (for example by (2.217)). This implies Lipschitz continuity of $t \mapsto v_i(A_i(y,t),t)$ uniformly in y and therefore

$$\begin{aligned} \left| C_\mu \int [(1-\mu_0-2A_i(y,t_n))v_i(A_i(y,t_n),t_n) \;\; -(1-\mu_0-2A_i(y,t))v_i(A_i(y,t),t)]\, dg_{i,t_n}(y) \right| \\ \le C_{\mu,\rho}|t_n - t| \int dg_{i,t_n}(y) = C_{\mu,\rho}|t_n - t| \to 0 \text{ as } t_n \to t. \end{aligned}$$

As for the second integral in (2.245), by narrow continuity of g_{i,t_n} we have

$$\lim_{n\to\infty} C_\mu \int (1-\mu_0-2A_i(y,t))v_i(A_i(y,t),t)\,dg_{i,t_n}(y) \tag{2.246}$$
$$= C_\mu \int (1-\mu_0-2A_i(y,t))v_i(A_i(y,t),t)\,dg_{i,t_n}(y).$$

Hence $I_1(t_n) \to I_1(t)$. If $i \notin i_H$, then $I_2 = I_3 \equiv 0$, so we assume that $i \in i_H$. I_2 is given by

$$I_2(t_n) = C_\mu \eta(t_n) \int \left[(\mu_0+a)(1-a) \int P(t_n, A_i(\xi,t_n),a)\,dg_{i,t_n}(\xi) \right] da. \tag{2.247}$$

We first show that

$$\int P(t_n, A_i(\xi,t_n),a)\,dg_{i,t_n}(\xi) \to \int P(t, A_i(\xi,t),a)\,dg_{i,t}(\xi) \tag{2.248}$$

as $t_n \to t$ for all $a \in [0,1]$. We have

$$\int P(t_n, A_i(\xi,t_n),a)\,dg_{i,t_n}(\xi) = \int \left(P(t_n, A_i(\xi,t_n),a) - P(t, A_i(\xi,t),a)\right)\,dg_{i,t_n}(\xi) \tag{2.249}$$
$$+ \int P(t, A_i(\xi,t),a)\,dg_{i,t_n}(\xi).$$

Arguing as above, the Lipschitz continuity of $t \mapsto P(t, A_i(\xi,t),a)$ and narrow continuity of $t \mapsto g_{i,t}$ give (2.248). Moreover

$$\left| (\mu_0+a)(1-a) \int P(t_n, A_i(\xi,t_n),a)\,dg_{i,t_n}(\xi) \right| \le (\mu_0+1) \tag{2.250}$$

whence by the dominated convergence theorem and the continuity of $t \mapsto \eta(t)$, $I_2(t_n) \to I(t)$ as $t_n \to t$.

We conclude with the term $I_3(t_n)$:

$$I_3(t_n) = -C_\mu \eta(t_n) \int h(y,t_n)\,dg_{i,t_n}(y) \tag{2.251}$$
$$= -C_\mu \eta(t_n) \int (\mu_0 + A_i(y,t_n))(1-A_i(y,t_n))\,dg_{i,t_n}(y).$$

Again, arguing as in (2.245), the Lipschitz continuity of $t \mapsto A_i(y,t)$, the continuity of $t \mapsto \eta(t)$ and the narrow continuity of $t \mapsto g_{i,t}$, imply that $I_3(t_n) \to I_3(t)$ as $t_n \to t$. □

Remark 2.7.3. *As in Lemma 2.7.2, it can be proved that $t \mapsto \partial_t F[g_{i,t}]$ is Lipschitz continuous.*

Lemma 2.7.3. *Let $(A,g,u) \in X_{\rho,T}$ be a solution to* (2.164), (2.165). *If $t \mapsto P(t,a,b)$ is Lipschitz continuous uniformly in (a,b), then $t \mapsto \partial_t u(t)$ is continuous as a function from $[0,T]$ to $\mathbb{R}^{3h}$.*

Proof. We recall that $v_k = u_k/s^k$ is a fixed point of the map

$$G(s,t,v) := v - J(0,0,\bar{v})^{-1}\phi(s,t,v) \tag{2.252}$$

where ϕ is the vector field of the system (2.150) which depends on t through $F[g_t]$ and $v(t)$. In this setting, σ_1 is fixed, so we drop the dependency on s in (2.252). Since $v(t) = G(t, v(t))$, we formally have that

$$\partial_t v = \partial_t G(t, v(t)) + \partial_v G(t, v(t)) \partial_t v(t). \tag{2.253}$$

This yields

$$\begin{aligned}(\mathrm{Id} - \partial_v G(t, v(t)))\ \partial_t v(t) &= \partial_t G(t, v(t)) = -J(0)^{-1}\partial_t \phi(t, v(t)) \\ &= -J(0)^{-1}(\partial_t F[g_{1,t}], \partial_t F[g_{2,t}], \dots, \partial_t F[g_{h,t}], \underbrace{0, \dots, 0}_{\in\mathbb{R}^{2h}})^T \\ &\underbrace{=}_{(2.36)} (\partial_t F[g_{1,t}], \partial_t F[g_{2,t}], \dots, \partial_t F[g_{h,t}], \underbrace{0, \dots, 0}_{\in\mathbb{R}^{2h}})^T\end{aligned} \tag{2.254}$$

where we have used that the unique time-dependent parameter in the vector field is $F[g_t]$. Observe that

$$\mathrm{Id} - \partial_v G(t, v(t)) = J(0)^{-1}\partial_v \phi(t, v) = J(0)^{-1}J(t) \tag{2.255}$$

is invertible in $[0, T]$. Therefore the problem

$$(\mathrm{Id} - \partial_v G(t, v(t)))\ z(t) = (\partial_t F[g_{1,t}], \partial_t F[g_{2,t}], \dots, \partial_t F[g_{h,t}], 0, \dots, 0)^T \in \mathbb{R}^{3h} \tag{2.256}$$

has a unique solution

$$z(t) = (\mathrm{Id} - \partial_v G(t, v(t)))^{-1}\,(\partial_t F[g_{1,t}], \partial_t F[g_{2,t}], \dots, \partial_t F[g_{h,t}], 0, \dots, 0)^T \tag{2.257}$$

which is continuous in time. In fact, the map $t \mapsto \partial_t F[g_{i,t}]$ is continuous for all $i \in V$. In addition, since $v \mapsto G(t, v)$ is a contraction, we can write the inverse of $\mathrm{Id} - \partial_v G(t, v(t))$ as the limit of the series

$$(\mathrm{Id} - \partial_v G(t, v(t)))^{-1} = \sum_{k=0}^{\infty} (\partial_v G(t, v(t)))^k \tag{2.258}$$

where $t \mapsto G_v(t, v(t))$ is continuous on $[0, T]$ and the series converges uniformly in t, hence the limit is continuous and we can conclude that $v'(t) = z(t)$. □

2.8 Numerical algorithms and experiments

Following the approach of [13], we numerically solve the full PDE problem (2.5)-(2.8) in the case of $J[f_t] \equiv 0$, its quasi-static approximation and the ODEs system (2.11) in the context of Section 2.2.2.

Concerning the PDE problem, we implement a first-order discretisation along the a direction to obtain a system of ODEs in the time variable. The ODE problem is then solved using the MATLAB function `ode23`. We first introduce a uniform grid $a^0 = 0 < a^1 < \cdots < a^{N_a} = 1$ and approximate the rate v according to (2.4) using the rectangle formula. Then we introduce a uniform time grid $0 = t^0 < t^1 < \dots t^{N_t} = T$ and define the time derivative of f_i according to (2.5) as $\partial_t f_i(a_\ell, t_m) = -\partial_a(f_i v_i[f_i])(a_\ell, t_m)$ where the RHS is calculated by a first-order explicit Euler scheme. The resulting ODE system is coupled with the Aβ system through the production term (2.10), which is discretised by the rectangle formula.

The quasi-static model (2.12)-(2.15) is implemented by Algorithm 2.

Both the production term and the velocity are approximated by the rectangle formula. The nonlinear system for $u_k(i, t)$ is solved with the MATLAB nonlinear solver `fsolve`. The PDE equation for f_i is discretised using an explicit Euler scheme in both the a and t directions.

The numerical implementation of the ODEs system (2.11) with constant monomers' source is based on the MATLAB ODE solver `ode23`.

Algorithm 2: An algorithm for the Aβ system

Input : $(f_i(0,0))_{i=1}^{h}$
Output: $(f_i(a^\ell,t^k), u_1(i,t^k), u_2(i,t^k), u_3(i,t^k))$ for $i = 1,\dots,h,\ k = 0,\dots,N_t,\ \ell = 0,\dots,N_a$

for $k = 0, \dots, N_t$ **do**
    for $i \in V$ **do**
        Calculate $F[t^k]$
    end
    Solve $\phi(u(t^k)) = 0$;
    for $i \in V$ **do**
        for $\ell = 0,\dots,N_a$ **do**
            Calculate $v[f_i(a^\ell,t^k), u(i,t^k)]$;
        end
    end
    for $i \in V$ **do**
        for $\ell = 0,\dots,N_a$ **do**
            Update $f_i(a^\ell,t^{k+1})$;
        end
    end
end

2.8.1 The Aβ ODE system

We solve the system (2.11) on a small network equipped with 5 nodes and 9 edges. The seeding node is selected as the node with the largest out-degree centrality measure. In Figure 2.1 and 2.2 we observe that the system evolves toward a locally stable equilibrium.

Based on the structure of the Jacobian matrix (2.53), we expect the speed of convergence to increase with the clearance rates σ. Figures 2.1 and 2.2 confirm this behaviour.

2.8.2 The quasi-static model

The full PDE problem and its quasi-static approximation are solved on the $83-$nodes Budapest Reference Connectome v3.0 [28]. We first show that the quasi-static model reproduces the spatial disposition of the production term $F[f_t]$. Figure 2.3 indicates that a non-uniform monomers' source defines a non-constant equilibrium solution on the nodes (rows 1 and 2). On the other hand, constant sources define constant solutions on the network (row 3).

To recover a suitable timescale of evolution of the quasi-static model, we identified a bottleneck mechanism in the clearance processes. As shown in Figure 2.4, the effective time evolution depends on σ_1, σ_2 and σ_3 and the global dynamics is faster in the case of smaller clearance rates.

2.9 Conclusions and future developments

In the present Chapter, we have developed a quasi-static diffusion-reaction model for Aβ on the *proximity* graph. Identifying the node dynamics as fast processes on the long timescale, the short timescale becomes instantaneous. This results in a reduction of the ODEs on the nodes in a system of nonlinear equations depending on f_t through $F[f_t]$. We have proved the existence and uniqueness of a solution. To do so, we

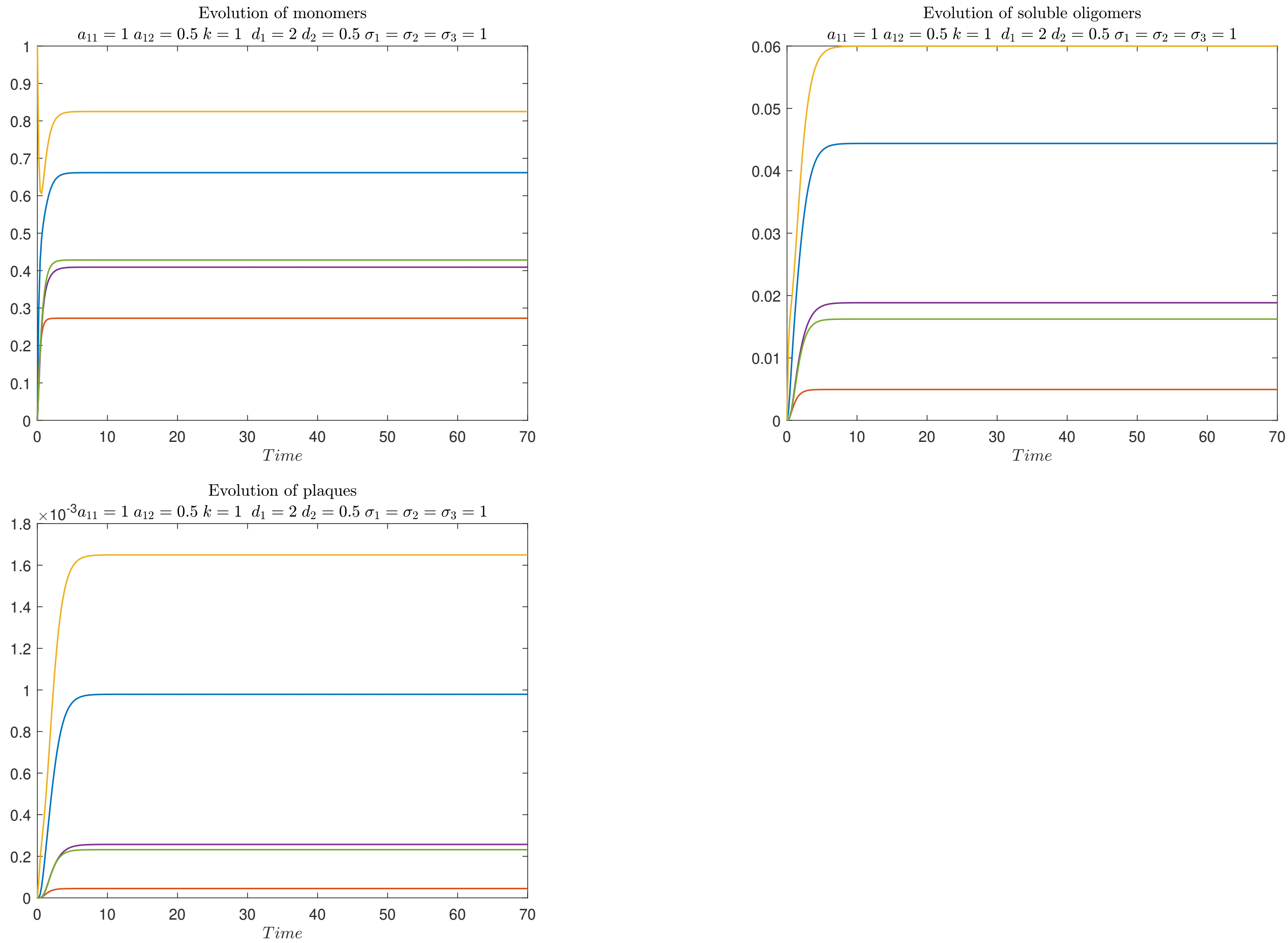

Figure 2.1: Example simulation of the ODEs system (2.11) on a five-node network. (a) Temporal evolution of the monomers concentration u_1 at each node of the graph. (b) Temporal evolution of the oligomers concentration u_2 at each node of the graph. (c) Temporal evolution of the plaques concentration u_3 at each node of the graph.

have adapted some of the techniques developed for the PDE system on a continuum in [14] to our quasi-static model on a graph. In particular we must overcome the technical difficulty in proving the existence of a steady state. In this Chapter we are able to do so by requiring the symmetry of the aggregation a_{ij} and fragmentation k_i terms and a sufficiently large monomers' clearance rate σ_1. The discreteness of the graph reduces the complexity of the proof in [14].

The argument in [14] is also extended to improve the regularity in time of $F[f_t]$ and obtain C^1-continuity of u with respect to time. This regularity property is not necessary to the proof of the main result of the Chapter, but will prove useful in the following Chapters when taking into account u_2-dependent parameters in the *NTM* for Tau. In that case, the formulation of the mass balance at node level is based on the definition of the variation of the mass of soluble and insoluble Tau on the edges, which strictly depends on the variation in time of u_2.

Further developments on the model shall consist in extending the range of parameters adopted in the existence argument of Section 2.4, for example by admitting non-symmetric aggregation and fragmentation rates. Another possible generalisation concerns the number of species of Aβ: one could consider a larger number of classes of oligomers of different sizes, as in [10], [13], [14], [34], to gain more insight into

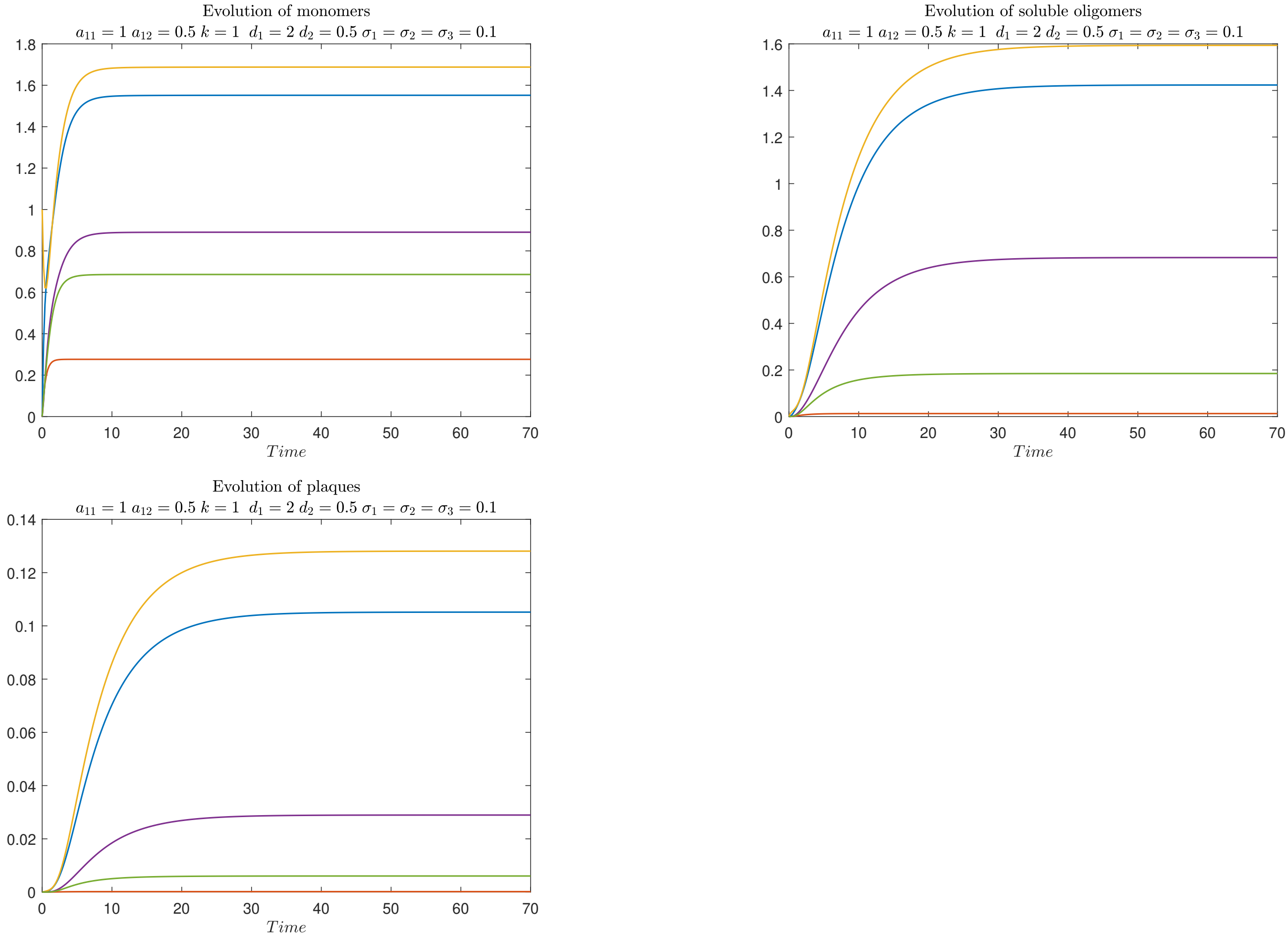

Figure 2.2: Example simulation of the ODEs system (2.11) on a five-node network. (a) Temporal evolution of the monomers concentration u_1 at each node of the graph. (b) Temporal evolution of the oligomers concentration u_2 at each node of the graph. (c) Temporal evolution of the plaques concentration u_3 at each node of the graph.

the dynamics and spread of Aβ. As in Chapter 1, we stress that the analysis developed in this Chapter is a first step towards the validation of the model. Indeed, a detailed comparison with clinical data is needed to make an empirically meaningful selection of the model parameters.

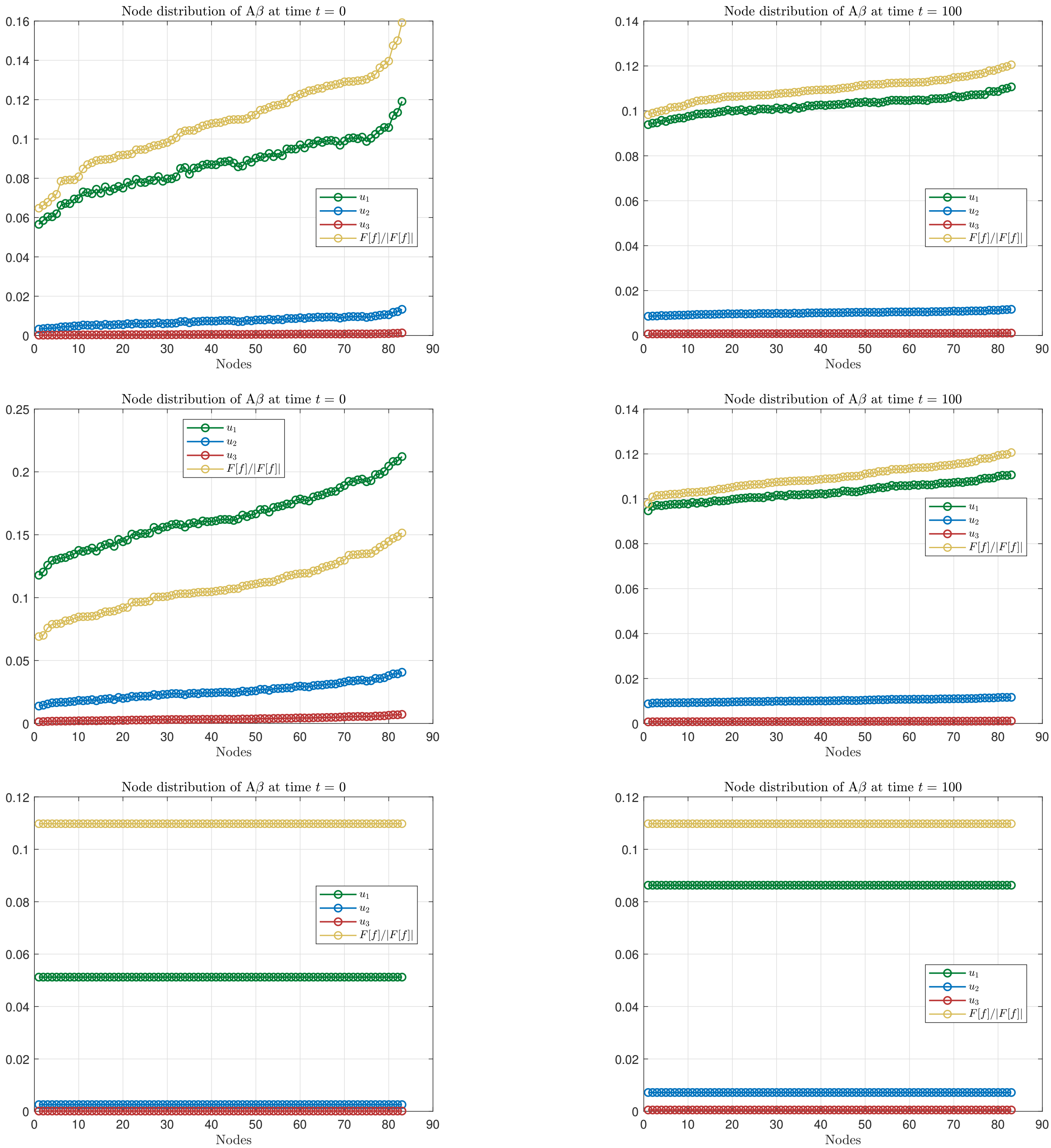

Figure 2.3: Spatial distribution of the concentrations of u_1, u_2 and u_3 on the nodes at time $t = 0$ (first column) and $t = 100$ (second column). The simulation of rows 1, 2 and 3 differ for the production term. To improve visualisation of the plots, we order the nodes so that the entries of the vector $F[f_{i,t}]$ form a monotonically increasing sequence.

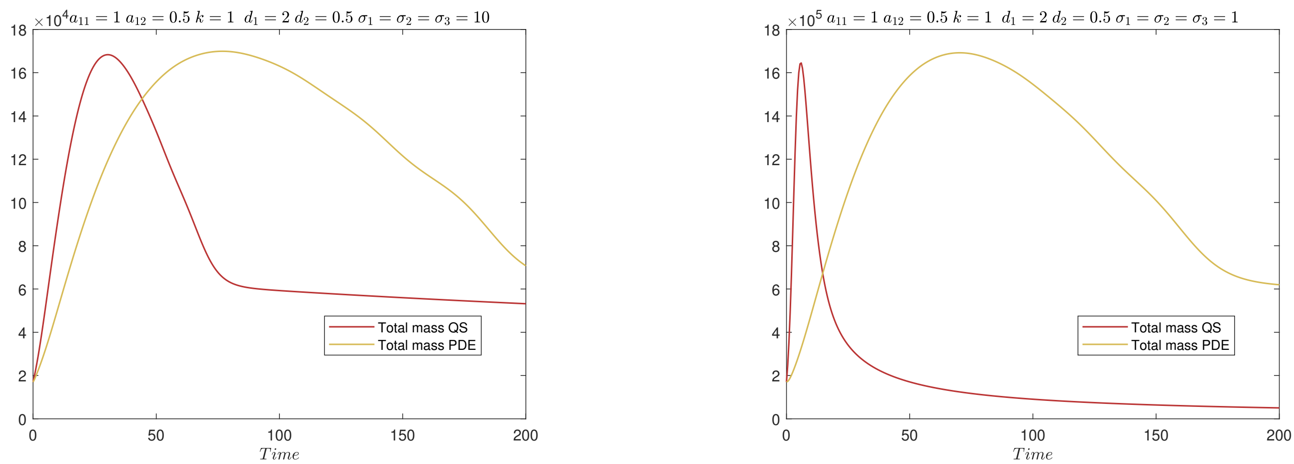

Figure 2.4: Time evolution of the total mass of the full PDE-ODE solution (yellow line) and its quasi-static approximation (red line) in the case of (a) $\sigma_1 = \sigma_2 = \sigma_3 = 10$ and (b) $\sigma_1 = \sigma_2 = \sigma_3 = 1$.

Chapter 3

A combined model for Tau and Beta Amyloid

In this chapter, we address the synergistic interplay between Tau and Beta Amyloid proteins by coupling the mathematical models of Chapters 1 and 2. The interaction between the two species is modelled assuming that Aβ enhances Tau spread by promoting Tau aggregation and diffusion along the nodes and edges of the *connectivity* graph. Introducing time-dependent parameters into the edge equations of the *NTM* poses a mathematical challenge in determining the correct mass exchange between nodes and edges. In the following,we recover the correct local mass balance and subsequently define the quasi-static *NTM*, thus allowing us to consider the interaction between Tau and Aβ. In the special case of time-independent parameters, we compare the newly obtained mass balance with its approximation used in Chapter 1.

3.1 Introduction and biological setting

The pathological relationship between Beta Amyloid and Tau proteins represents a central topic in *AD*. Although each protein can aggregate and diffuse independently, converging evidence suggests that Beta Amyloid modulates Tau's molecular behaviour, spatial propagation and structural evolution.

Aβ primarily influences Tau progression by altering its cellular environment in ways that promote Tau misfolding and aggregation. Soluble Aβ oligomers can activate signalling pathways such as GSK3β and CDK5, increasing Tau phosphorylation and destabilising its microtubule-binding activity [90] at axonal level. The disruption of axonal transport and cytoskeletal stability leads to a detachment of Tau from microtubules and a mislocalisation from the physiological axonal site to the somatodendritic regions [49], [103]. In the meantime, Aβ induced synaptic stress and calcium dysregulation may promote formation of seeding tau species, accelerating the nucleation phase of aggregation [20], [72].

Aβ also shapes the spatial dynamics of tau pathology by modulating its diffusion and intercellular propagation. Misfolded tau exhibits prion-like properties, propagating via trans-synaptic processes and misfolding of native tau. The efficiency and spatial evolution of this spread strongly depend on the presence of Aβ. In fact, regions enriched with Aβ show increased susceptibility to tau seeding and tau dissemination follows pathways defined in part by the distribution of Aβ pathology [44].

At the network level, Beta Amyloid acts as an enhancer and promoter of Tau pathology by accelerating the aggregation kinetics and amplifying the spatial domain over which it can propagate. These factors contribute to the shape of a complex framework in which Aβ actively modulates Tau pathology. In this Chapter, we model this interaction in both the macroscopic network context and the edge microscopic environment detailed by the *NTM* by considering Aβ-dependent node and edge parameters. We first consider the general case in which the aggregation, diffusion and production parameters evolve in time and show that the quasi-static setting does not provide an exact description of the mass exchange between nodes and edges. Hence, we consider the PDE-*NTM* and, by decomposing the edge solution n_{ij} as the sum of its equilibrium profile $\bar{n}_{ij}$ and the "remainder" function u_{ij}, we are able to recover the correct *feedback* mechanism at each node. The resulting quasi-static model improves the approximation of the *feedback* mechanism introduced in Chapter 1 and establishes a new dependence of the *feedback* term at node P_i on its neighbouring nodes.

In the present Chapter, we first calculate the correction terms under some assumptions on the PDE-edge model and then consider the coupled system obtained by selecting Aβ-dependent parameters in the *NTM*. In order to define the interaction between Tau and Aβ correctly, we shall overcome the problem that Tau and Aβ are defined on different graphs, the directed *connectivity* graph and the undirected *proximity* graph. We show that the resulting quasi-static Aβ-*NTM* system admits a solution on $[0, T]$ and present some numerical experiments.

3.2 The *NTM* with time varying coefficients

Let $G_c = (V, E_c)$ be the structural *connectivity* graph described in Chapter 1. In the following, L_{ij} stands for the length of the edge $e_{ij} \in E_c$.

3.3 The Model

For all $i \in V$ and $t \geq 0$, soluble and insoluble Tau concentrations, $N,\ M$ respectively, satisfy the following equations on the slow time scale at node level:

$$
\begin{cases}
N_i' = \frac{1}{\mathrm{Vol}(i)} \underbrace{\sum_{j \neq i} \left(-c_{ij} J_{ij}(0,t) + c_{ji} J_{ji}(L_{ji}, t)\right)}_{\text{incoming mass flow at compartment } P_i} + F_i + \Gamma(M_i, N_i, t), \\
M_i' = -\Gamma(M_i, N_i, t), \\
N_i(0) = N_{0i}, \\
M_i(0) = M_{0i} \quad i \in V,
\end{cases}
\tag{3.1}
$$

where soluble and insoluble Tau $n_{ij},\ m_{ij}$ satisfy

$$
\begin{cases}
J_{ij} := -a(x,t)(n_{ij})_x - h(x, n_{ij}, m_{ij}) \qquad \text{for } x \in [0, L_{ij}], \\
(n_{ij})_t + (J_{ij})_x = F_\tau + \Gamma(m_{ij}, n_{ij}, t) \qquad \text{for } x \in [0, L_{ij}] \\
(m_{ij})_t = -\Gamma(m_{ij}, n_{ij}, t) \qquad \text{for } x \in [0, L_{ij}] \\
n_{ij}(0,t) = N_i(t) \\
n_{ij}(L_{ij}, t) = N_j(t).
\end{cases}
\tag{3.2}
$$

Here, $\mathrm{Vol}(i)$ denotes the volume of the brain compartment P_i. The diffusion coefficient for soluble tau is

$$
a(x,t) = \begin{cases}
D & \text{in } (0, x_1) \\
D\lambda_1(t) & \text{in } (x_1, x_2) \\
fD & \text{in } (x_2, x_3) \\
D\lambda_2(t) & \text{in } (x_3, x_4) \\
D & \text{in } (x_4, L_{ij}),
\end{cases}
\tag{3.3}
$$

where $0 < f < 1$ is a constant and the coefficients $\lambda_1, \lambda_2 < 1$ are possibly Aβ-dependent. The transport term is

$$h(x,n,m) = \begin{cases} (1-f)(v_a(1+\delta n)(1-\varepsilon m) - v_r)n & \text{if } x \in (x_2, L_{ij}) \\ 0 & \text{otherwise} \end{cases} \tag{3.4}$$

where the coefficients v_a, v_r, δ, ε are positive. The reaction term is

$$\Gamma(M,N,t) = \beta M - N(\gamma_1(t)N + \gamma_2(t)M). \tag{3.5}$$

The coefficients are expressed on the slow time scale. In $(3.1)_1$ and $(3.2)_2$, F_i and F_τ represent a source of pathological soluble Tau. Specifically, F_τ describes the misfolding and hyperphosphorylation of microtubule-associated-Tau at the axon site [7]. In the following, we assume that the production terms on nodes and edges evolve in time. Since the production terms on the nodes and the edges are the sole mass exchange processes of the system, setting $F_i, F_\tau \equiv 0$ restores the mass conserving property of Chapter 1.

Observe that the model presented in (3.1)-(3.2) also differs from the full *NTM* introduced in Chapter 1 by means of the time-dependent parameters

$$\gamma_1,\ \gamma_2,\ \lambda_1,\ \lambda_2. \tag{3.6}$$

In this section, we assume a general time dependence of the parameters (3.6). In Section 3.5, we shall explicitly model their temporal evolution as a function of the concentration of soluble Aβ.

We allow for a spatial dependence of the edge parameters $\gamma_1,\ \gamma_2,\ \lambda_1,\ \lambda_2$. Set $\gamma_1(i,t),\ \lambda_k(i,t) \in C^1(0,T)$ for $k = 1,2$ at each node $i \in V$ and define $\gamma_k(x,t;i,j),\ \lambda_k(x,t;i,j) \in C^1([0,L_{ij}] \times [0,T])$ so that

$$\gamma_k(0,t;i,j) = \gamma_k(i,t), \quad \gamma_k(L_{ij},t;i,j) = \gamma_k(j,t),$$

$$\lambda_k(0,t;i,j) = \lambda_k(i,t), \quad \lambda_k(L_{ij},t;i,j) = \lambda_k(j,t).$$

This choice allows us to take into account the possible spatial variability of the aggregation and diffusion phenomena along the edges. In the following, we may write, for $k = 1,2$,

$$(\gamma_k)_{ij}(x,t) := \gamma_k(x,t;i,j), \quad (\lambda_k)_{ij}(x,t) := \lambda_k(x,t;i,j)$$

or

$$\gamma_k(i,j)(x,t) := \gamma_k(x,t;i,j), \quad \lambda_k(i,j)(x,t) := \lambda_k(x,t;i,j).$$

3.3.1 The quasi-static model

To establish the quasi-static equations for N_i we must state the correct mass exchange of soluble tau between node i and edges e_{ij} and e_{ji} ($j \neq i$). In general, this exchange is not only described by the boundary conditions for the fluxes at all incoming and outgoing edges at a given node, since in the quasi-static description the variation of the total mass also depends on the *feedback* mechanism, as shown in Section 1.2 of Chapter 1. That is, the variation of the mass on the nodes induces a variation of the mass along the edge that must be compensated for in the node equations. Moreover, as we will see, inserting time-dependent coefficients in the equation introduces time-dependent quantities in the variation of the edge mass. The problem reduces to establish how this "corrective" mass is distributed between the external points of the edge. We refer to both of these phenomena as the *feedback* mechanism. The following calculation shows that the quasi-static regime is not a suitable framework for defining the mass correction needed to correctly reproduce the *feedback* mechanism.

The idea of the quasi-static approximation is to consider the dynamics on the fast time scale as instantaneous on the slow time scales. In this setting, fast processes occur on the edges, hence we assume that the soluble and insoluble tau edge concentrations satisfy the equilibrium problem associated to (3.2)

$$\begin{cases} (a(x,t)(n_{ij})_x + h(x,n_{ij}))_x + F_\tau = 0 \\ m_{ij}(x) = g(x, n_{ij}(x), t) \quad \text{for } x \in [0, L_{ij}], \\ n_{ij}(0,t) = N_i(t), \\ n_{ij}(L_{ij}, t) = N_j(t), \quad e_{ij} \in E_c. \end{cases} \tag{3.7}$$

The function g satisfies $\Gamma(g(x,n_{ij},t), n_{ij}, t) = 0$. By (3.5), on the edge e_{ij},

$$g(x,n,t) = \frac{(\gamma_1)_{ij}(x,t)\, n^2}{\beta - (\gamma_2)_{ij}(x,t)\, n}$$

and we write $g(n,t) := g(x,n,t)$.

We begin with the variation of the mass of insoluble tau at node i. Since

$$M_i(t) = g(N_i(t)) = \frac{\gamma_1(i,t) N_i^2(t)}{\beta - \gamma_2(i,t) N_i(t)},$$

we obtain that the rate of change of the mass of insoluble tau at node i is given by

$$\mathrm{Vol}(i) M_i' = \frac{\gamma_1(i) N_i (2\beta - \gamma_2(i) N_i)}{(\beta - \gamma_2(i) N_i)^2} \mathrm{Vol}(i) N_i' + \frac{\mathrm{Vol}(i)(i) N_i^2}{\beta - \gamma_2(i) N_i} \left(\partial_t \gamma_1(i) + \frac{\gamma_1(i) \partial_t \gamma_2(i) N_i}{\beta - \gamma_2(i) N_i} \right).$$

The growth rate of the total mass of tau at node i is

$$\mathrm{Vol}(i)(N_i' + M_i') = \left(1 + \frac{\gamma_1(i) N_i (2\beta - \gamma_2(i) N_i)}{(\beta - \gamma_2(i) N_i)^2} \right) \mathrm{Vol}(i) N_i' + \frac{\mathrm{Vol}(i)(i) N_i^2}{\beta - \gamma_2(i) N_i} \left(\partial_t \gamma_1(i) + \frac{\gamma_1(i) \partial_t \gamma_2(i) N_i}{\beta - \gamma_2(i) N_i} \right). \tag{3.8}$$

On the other hand, the growth rate of the total mass of tau on the edge e_{ij} is given by

$$\begin{aligned} c_{ij} \int_0^{L_{ij}} (n_{ij} + m_{ij})_t(x,t)\, dx = \\ c_{ij} \left(\int_0^{L_{ij}} q_{ij}\, dx + \int_{(0,x_3)\cup(x_4,L_{ij})} \frac{\gamma_1(i,j) n_{ij} (2\beta - \gamma_2(i,j) n_{ij})}{(\beta - \gamma_2(i,j) n_{ij})^2} q_{ij}\, dx \right) \\ + c_{ij} \int_{(0,x_3)\cup(x_4,L_{ij})} \frac{n_{ij}^2}{\beta - \gamma_2(i,j) n_{ij}} \left(\partial_t \gamma_1(i,j) + \frac{\gamma_1(i,j) \partial_t \gamma_2(i,j) n_{ij}}{\beta - \gamma_2(i,j) n_{ij}} \right) dx, \end{aligned} \tag{3.9}$$

where c_{ij} is the connectivity coefficient of e_{ij} in G_c, and

$$q_{ij} := \frac{\partial n_{ij}}{\partial t}.$$

Differentiating the equation for n_{ij} in (3.7) with respect to t we obtain the equation for q_{ij}:

$$\left(a(x)(q_{ij})_x + \frac{\partial h(x, n_{ij})}{\partial n} q_{ij} + G(x, n_{ij}, u_2') \right)_x + \frac{\partial F_\tau}{\partial t} = 0 \quad \text{in } (0, L_{ij}), \tag{3.10}$$

where

$$G(x,t,n_{ij}) = b_1(x)\partial_t\lambda_1(i,j)(n_{ij})_x + b_2(x)\partial_t\lambda_2(i,j)(n_{ij})_x \\ +c(x)\frac{n_{ij}^3(1+\delta n_{ij})}{\beta-\gamma_2(i,j)n_{ij}}\left(\partial_t\gamma_1(i,j) + \frac{\gamma_1(i,j)\partial_t\gamma_2(i,j)n_{ij}}{\beta-\gamma_2(i,j)n_{ij}}\right), \tag{3.11}$$

with

$$b_1 = D\chi_{(x_1,x_2)},\ b_2 = D\chi_{(x_3,x_4)},\ c = -(1-f)v_a\varepsilon\chi_{(x_2,x_3)}.$$

Since $q_{ij}(0,t) = N_i'(t)$, $q_{ij}(L_{ij},t) = N_j'(t)$ and (3.10) is a linear equation, we see that

$$q_{ij}(x,t) = N_i'(t)q_{ij}^i(x,t) + N_j'(t)q_{ij}^j(x,t) + q_{ij}^0(x,t), \tag{3.12}$$

where $q_{ij}^i(x,t)$, $q_{ij}^j(x,t)$ and $q_{ij}^0(x,t)$ satisfy, as functions of x, respectively

$$\begin{cases} \left(a(x)(q_{ij}^i)_x + \frac{\partial h(x,n_{ij})}{\partial n}q_{ij}^i\right)_x = 0 \quad \text{in } (0,L_{ij}), \\ q_{ij}^i(0,t) = 1, \quad q_{ij}^i(L,t) = 0 \end{cases} \tag{3.13}$$

$$\begin{cases} \left(a(x)(q_{ij}^j)_x + \frac{\partial h(x,n_{ij})}{\partial n}q_{ij}^j\right)_x = 0 \quad \text{in } (0,L_{ij}), \\ q_{ij}^j(0,t) = 0, \quad q_{ij}^j(L,t) = 1 \end{cases} \tag{3.14}$$

$$\begin{cases} \left(a(x)(q_{ij}^0)_x + \frac{\partial h(x,n_{ij})}{\partial n}q_{ij}^0 + G(x,t,n_{ij})\right)_x + \frac{\partial F_\tau}{\partial t} = 0 \quad \text{in } (0,L_{ij}). \\ q_{ij}^0(0,t) = 0, \quad q_{ij}^0(L_{ij},t) = 0, \end{cases} \tag{3.15}$$

Integrating the equation for n_{ij} in (3.7) over $(0,L_{ij})$, we have that

$$\int_0^{L_{ij}} F_\tau\, dx = c_{ij}D[(n_{ij})_x(0,t) - (n_{ij})_x(L_{ij},t)]. \tag{3.16}$$

According to the notation of Chapter 1, for now, we set

$$C_{ij}^i(t) := c_{ij}\left(\int_0^{L_{ij}} q_{ij}^i(x,t)\,dx + \int_{(0,x_3)\cup(x_4,L_{ij})} \frac{\gamma_1 n_{ij}(2\beta-\gamma_2 n_{ij})}{(\beta-\gamma_2 n_{ij})^2} q_{ij}^i(x,t)\,dx\right), \tag{3.17}$$

$$C_{ji}^i(t) := c_{ji}\left(\int_0^{L_{ji}} q_{ji}^i(x,t)\,dx + \int_{(0,x_3)\cup(x_4,L_{ji})} \frac{\gamma_1 n_{ji}(2\beta-\gamma_2 n_{ji})}{(\beta-\gamma_2 n_{ji})^2} q_{ji}^i(x,t)\,dx\right). \tag{3.18}$$

In addition, we need to define two quantities, $B_{ij}^i(t)$ and $B_{ij}^j(t)$, which satisfy

$$B_{ij}^i(t) + B_{ij}^j(t) = B_{ij}(t) \\ = c_{ij}\int_{(0,x_3)\cup(x_4,L_{ij})} \frac{n_{ij}^2}{\beta-\gamma_2(i,j)n_{ij}}\left(\partial_t\gamma_1(i,j) + \frac{\gamma_1(i,j)\partial_t\gamma_2(i,j)n_{ij}}{\beta-\gamma_2(i,j)n_{ij}}\right)dx \\ + c_{ij}\int_{(0,x_3)\cup(x_4,L_{ij})} \frac{\gamma_1 n_{ij}(2\beta-\gamma_2 n_{ij})}{(\beta-\gamma_2 n_{ij})^2} q_{ij}^0(x,t)\,dx + c_{ij}\int_0^{L_{ij}} q_{ij}^0(x,t)\,dx. \tag{3.19}$$

A careful but straightforward calculation based on (3.9), (3.12), (3.16), (3.17), (3.18) and (3.19) leads to the following mass balance at node i, provided that $B^i_{ij}(t)$ and $B^j_{ij}(t)$ satisfy (3.19):

$$\mathrm{Vol}(i)(N_i'+M_i') = \underbrace{\mathrm{Vol}(i)F_\tau(i,t)}_{\tau \text{ production at } P_i} + \sum_{j\neq i}\Bigg(\underbrace{Dc_{ij}(n_{ij})_x(0,t) - Dc_{ji}(n_{ji})_x(L_{ji},t)}_{\text{incoming mass flow at } P_i} - \underbrace{(C^i_{ij}(t)+C^i_{ji}(t))N_i'(t)}_{\text{feedback by } N_i \text{ variation at } P_i} - \underbrace{(B^i_{ij}(t)+B^i_{ji}(t))}_{\tau \text{ feedback by production and edge par. variation}}\Bigg). \tag{3.20}$$

Combined with (3.8), we obtain the following equation for $N_i(t)$:

$$\left(\mathrm{Vol}(i)\left(1+\frac{\gamma_1 N_i(2\beta-\gamma_2 N_i)}{(\beta-\gamma_2 N_i)^2}\right) + \sum_{j\neq i}\left(C^i_{ij}+C^i_{ji}\right)\right)N_i' \tag{3.21}$$

$$= D\sum_{j\neq i}\left(c_{ij}(n_{ij})_x(0,t) - c_{ji}(n_{ji})_x(L_{ji},t)\right) + \mathrm{Vol}(i)F_\tau(i,t) - \sum_{j\neq i}(B^i_{ij}+B^i_{ji}) - \frac{\mathrm{Vol}(i)N_i^2}{\beta-\gamma_2(i)N_i}\left(\partial_t\gamma_1(i) + \frac{\gamma_1(i)\partial_t\gamma_2(i)N_i}{\beta-\gamma_2(i)N_i}\right). \tag{3.22}$$

It remains to define the quantities B^i_{ij} and B^j_{ij} such that (3.19) holds. In contrast with Chapter 1, where the setting allowed for a straightforward separation of the rate of change of the edge mass, here no natural split of B_{ij} between the two contributions seems possible. In fact, the action of the time-dependent parameters is global on the edge and the quasi-static approach does not suggest a decomposition of B_{ij} without further hypotheses on the edge parameters.

We have shown that the quasi-static framework is not sufficient to uniquely define the evolutive equations for N_i on the nodes in the case of generic time-dependent edge parameters. Observe that the *feedback* mechanism solely arises from the dynamics of mass exchange between edges and nodes, hence the quasi-static setting allows for time-dependent parameters on the nodes and their effect is confined to the terms depending on $\gamma_1(i,t)$, $\gamma_2(i,t)$ and $F_\tau(i,t)$ in (3.21). However, the interaction between Aβ and Tau also takes place along the edges [49], [90], [103], and the structure of the *NTM* is detailed enough to possibly incorporate these local edge phenomena. Secondly, the influence of Aβ on the diffusion and spread of Tau at network level cannot be depicted by the node parameters since the mass flow (i.e. the fluxes) of soluble Tau is defined edge-wise. This motivates further investigation of the mass balance problem by considering the full PDE-*NTM* and the resulting multiscale setting.

3.4 The multiscale PDE problem

To recover the correct separation of the term B_{ij} in the respective nodal contributions B^i_{ij} and B^j_{ij}, we consider the effective evolution of N_i in the PDE setting (3.1). For completeness, we recall the model equations:

$$\begin{cases} N_i' = \frac{1}{Vol(i)}\sum_{j\neq i}\left(-c_{ij}J_{ij}(0,t)+c_{ji}J_{ji}(L_{ji},t)\right)+F_i+\Gamma(M_i,N_i,t), \quad i\in V \\ M_i' = -\Gamma(M_i,N_i,t), \quad i\in V \\ J_{ij} := -a(x,t)(n_{ij})_x - h(x,n_{ij},m_{ij}) \qquad \text{for } x\in[0,L_{ij}],\ e_{ij}\in E_c \\ (n_{ij})_t+(J_{ij})_x = F_\tau+\Gamma(m_{ij},n_{ij},t) \qquad \text{for } x\in[0,L_{ij}],\ e_{ij}\in E_c \\ (m_{ij})_t = -\Gamma(m_{ij},n_{ij},t) \qquad \text{for } x\in[0,L_{ij}],\ e_{ij}\in E_c \\ n_{ij}(0,t)=N_i(t), \quad n_{ij}(L_{ij},t)=N_j(t), \\ N_i(0)=N_{0i}, \quad M_i(0)=M_{0i} \quad i\in V. \end{cases} \tag{3.23}$$

Here, $Vol(i)$ stands for the volume of the brain compartment P_i. On the single edge $e_{ij}\in E_c$, we introduce the variables $\overline{n}_{ij}$ and $\overline{m}_{ij}$ as the solution to the *current equilibrium* problem

$$\begin{cases} J_{ij} := -a(x,t)(n_{ij})_x - h(x,n_{ij},m_{ij}) \qquad \text{for } x\in[0,L_{ij}],\ e_{ij}\in E_c \\ (J_{ij})_x = F_\tau \qquad \text{for } x\in[0,L_{ij}] \\ \Gamma(m_{ij},n_{ij},t)=0 \\ n_{ij}(0,t)=N_i(t), \quad n_{ij}(L_{ij},t)=N_j(t), \end{cases} \tag{3.24}$$

where $(N_i(t))_{i=1}^h$ is defined as the solution of system (3.23).

Here, to simplify the calculations, we fix $\gamma_2 \equiv 0$. However, the analysis can be readily extended to the case $\gamma_2 \not\equiv 0$, yielding a similar structure. Let $\phi_0 << 1$ be the proportion between the physical slow timescale and the fast one. We set:

$$\begin{aligned} &M_i(t) = g(N_i(t),t)+\phi_0 V_i(t) \quad i\in V, \\ &n_{ij}(x,t) = \overline{n}_{ij}(t)+\phi_0 u_{ij}(x,t) \quad e_{ij}\in E_c, \\ &m_{ij}(x,t) = g(\overline{n}_{ij}(x,t),t)+\phi_0 v_{ij}(x,t) \quad e_{ij}\in E_c. \end{aligned} \tag{3.25}$$

To simplify the notation, we erase the edge subscripts when dealing with edge variables. Since

$$g(n,t)=\frac{\gamma_1 n^2}{\beta}, \qquad g_n = 2\frac{\gamma_1}{\beta}n, \qquad g_t = \frac{\partial_t\gamma_1}{\beta}n^2,$$

and

$$\Gamma(m,n,t)=\beta m-\gamma_1(t)n^2,$$

we have that

$$\Gamma(m,n,t)=\Gamma(g(\overline{n}(t),t)+\phi_0 v(s),\overline{n}(t)+\phi_0 u(s),t)=\phi_0\left(\beta v-2\gamma_1(t)\bar{n}(t)u-\gamma_1(t)\phi_0 u^2\right). \tag{3.26}$$

Consider now the operator

$$\begin{aligned} &a(x,t)n_x+h(x,n,m) \\ &\quad= \phi_0 a(x,t)u_x + a(x,t)\overline{n}_x - (1-f)\chi_{(x_2,x_3)}\left[v_a(1+\delta(\overline{n}+\phi_0 u))(1-\varepsilon(\overline{m}+\phi_0 v))-v_r\right](\overline{n}+\phi_0 u) \\ &\qquad + (1-f)\chi_{(x_2,x_3)}\phi_0[v_a\varepsilon v(1+\delta\overline{n})](\bar{n}+\phi_0 u) \\ &\qquad - (1-f)\chi_{(x_2,x_3)}\phi_0[v_a\delta u(1-\varepsilon\bar{m}-\varepsilon\phi_0 v)](\bar{n}+\phi_0 u) \\ &\quad= \phi_0 a(x,t)u_x + \underbrace{a(x,t)\overline{n}_x-(1-f)\chi_{(x_2,x_3)}[v_a(1+\delta\overline{n})(1-\varepsilon\overline{m})-v_r]\overline{n}}_{=:-\overline{J}(x,t)} \\ &\qquad + (1-f)\chi_{(x_2,x_3)}\left(\phi_0 R_1^{u,v}+\phi_0^2 R_2^{u,v}+\phi_0^3 R_3^{u,v}\right) \\ &\quad=: -\bar{J}(x,t)-J_{ij}^{u,v}(x,t), \end{aligned}$$

where

$$
\begin{aligned}
R_1^{u,v} &:= -\left(v_a(1+2\delta\overline{n})(1-\varepsilon\overline{m})-v_r\right)u+v_a(1+\delta\overline{n})\varepsilon\overline{n}v,\\
R_2^{u,v} &:= v_a\left(\varepsilon(1+2\delta\overline{n})uv-\delta(1-\varepsilon\overline{m})u^2\right),\\
R_3^{u,v} &:= v_a\delta\varepsilon u^2 v,\\
J_{ij}^{u,v}(x,t) &:= -\phi_0 a(x,t)u_x-(1-f)\chi_{(x_2,x_3)}\left(\phi_0 R_1^{u,v}+\phi_0^2 R_2^{u,v}+\phi_0^3 R_3^{u,v}\right).
\end{aligned}
$$

Finally we obtain

$$
\begin{aligned}
(a(x,t)n_x+h(x,n,m))_x &= -\bar{J}_x-(\bar{J}_{ij}^{u,v})_x\\
&= -F_\tau+\phi_0(a(x,t)u_x)_x+\phi_0(1-f)\left[\chi_{(x_2,x_3)}\left(R_1^{u,v}+\phi_0R_2^{u,v}+\phi_0^2R_3^{u,v}\right)\right]_x,
\end{aligned}
\tag{3.27}
$$

where we have used that $\bar{n}$ satisfies the *current equilibrium* problem (3.24).

According to the decomposition (3.25) and equations (3.23) - (3.26), we have

$$
\begin{aligned}
\phi_0u_t &= -\overline{n}_t+n_t=-\overline{n}_t+(an_x-h(x,n,m))_x+F_\tau+\Gamma(\overline{m}+\phi_0v,\overline{n}+\phi_0u)\\
&= -\overline{n}_t+\phi_0(au_x)_x+\phi_0(1-f)\left[\chi_{(x_2,x_3)}\left(R_1^{u,v}+\phi_0R_2^{u,v}+\phi_0^2R_3^{u,v}\right)\right]_x\\
&\quad+\phi_0(\beta v-2\gamma_1\overline{n}u-\gamma_1\phi_0u^2),
\end{aligned}
$$

$$
\phi_0v_t=-\overline{m}_t+m_t=-\frac{\partial_t\gamma_1\overline{n}}{\beta}-2\frac{\gamma_1\overline{n}\,\overline{n}_t}{\beta}-\phi_0\left(\beta v-2\gamma_1\overline{n}u-\gamma_1\phi_0u^2\right). \tag{3.28}
$$

Observe that the boundary conditions at $x=0$ and $x=L_{ji}$ for n and $\overline{n}$ coincide by definition of the *current equilibrium* problem. It follows that $(u,v)=(u_{ij},v_{ij})$ satisfies the equation

$$
\begin{cases}
\phi_0u_t=-\overline{n}_t+\phi_0(au_x)_x+\phi_0(1-f)\left[\chi_{(x_2,x_3)}\left(R_1^{u,v}+\phi_0R_2^{u,v}+\phi_0^2R_3^{u,v}\right)\right]_x\\
\qquad+\phi_0(\beta v-2\gamma_1\bar{n}u-\phi_0\gamma_1u^2),\\
\phi_0v_t=-\frac{\partial_t\gamma_1\overline{n}}{\beta}-2\frac{\gamma_1\overline{n}\,\overline{n}_t}{\beta}-\phi_0\left(\beta v-2\gamma_1\overline{n}u-\phi_0\gamma_1u^2\right),\\
u(0,t)=u(L_{ij},t)=0,\\
v(0,t)=V_i(t),\ v(L_{ij},t)=V_j(t),\quad e_{ij}\in E_c.
\end{cases}
\tag{3.29}
$$

The function $t\mapsto V_i(t)$ satisfies

$$
\phi_0V_i'=-\partial_tg(N_i)-\Gamma(g(N_i)+\phi_0V_i,N_i)
$$

where

$$
\partial_tg(N_i)=\frac{\partial_t\gamma_1(t)}{\beta}N_i+\frac{2\gamma_1N_iN_i'}{\beta},
$$

$$
\Gamma(g(N_i)+\phi_0V_i,N_i)=\beta\left(\frac{\gamma_1N_i^2}{\beta}+\phi_0V_i\right)-\gamma_1N_i^2=\beta\phi_0V_i.
$$

Hence we obtain the ODE

$$
\phi_0V_i'=-\frac{\partial_t\gamma_1(t)}{\beta}N_i-\frac{2\gamma_1N_iN_i'}{\beta}-\phi_0\beta V_i\quad i\in V. \tag{3.30}
$$

Lastly, we reformulate the node equation for N_i. Recall that

$$N_i' = \frac{1}{Vol(i)}\sum_{j\neq i}\left(-c_{ij}J_{ij}(0,t)+c_{ji}J_{ji}(L_{ji},t)\right)+\Gamma(M_i,N_i,t) \tag{3.31}$$
$$= \frac{1}{Vol(i)}\sum_{j\neq i}\left(-c_{ij}J_{ij}(0,t)+c_{ji}J_{ji}(L_{ji},t)\right)+\Gamma\left(g(N_i)+\phi_0V_i,N_i,t\right)$$
$$= \frac{1}{Vol(i)}\sum_{j\neq i}\left(-c_{ij}J_{ij}(0,t)+c_{ji}J_{ji}(L_{ji},t)\right)+\beta\phi_0V_i.$$

Concerning the net incoming flux at node P_i, on the single edge e_{ij} we have

$$\begin{aligned} Dn_x(0,t) &= D\bar{n}(0,t)+\phi_0Du_x(0,t) = -\bar{J}(0,t)+\phi_0Du_x(0,t),\\ Dn_x(L_{ij},t) &= D\bar{n}(L_{ij},t)+\phi_0Du_x(L_{ij},t) = -\bar{J}(L_{ij},t)+\phi_0Du_x(L_{ij},t).\end{aligned} \tag{3.32}$$

The resulting system is

$$\begin{cases} N_i' = \frac{1}{Vol(i)}\sum_{j\neq i}\left(-c_{ij}\bar{J}_{ij}(0,t)+c_{ji}\bar{J}_{ji}(L_{ji},t)\right)+F_i\\ +\frac{1}{Vol(i)}\sum_{j\neq i}\left(-c_{ij}(-\phi_0D(\bar{u}_{ij})_x(0,s))+c_{ji}(-\phi_0D(\bar{u}_{ji})_x(L_{ji},s)\right)+\phi_0\beta V_i, \quad i\in V\\ M_i' = -\phi_0\beta V_i, \quad i\in V\\ \phi_0u_t = -\overline{n}_t+\phi_0(au_x)_x+\phi_0(1-f)\left[\chi_{(x_2,x_3)}\left(R_1^{u,v}+\phi_0R_2^{u,v}+\phi_0^2R_3^{u,v}\right)\right]_x\\ \qquad +\phi_0(\beta v-2\gamma_1\overline{n}u-\phi_0\gamma_1u^2),\\ \phi_0v_t = -\frac{\partial_t\gamma_1\overline{n}}{\beta}-2\frac{\gamma_1\overline{n}\,\overline{n}_t}{\beta}-\phi_0\left(\beta v-2\gamma_1\overline{n}u-\phi_0\gamma_1u^2\right),\\ \phi_0V_i' = -\frac{\partial_t\gamma_1(t)}{\beta}N_i-\frac{2\gamma_1N_iN_i'}{\beta}-\phi_0\beta V_i \quad i\in V,\\ u(0,t)=u(L_{ij},t)=0,\\ v(0,t)=V_i(t),\ v(L_{ij},t)=V_j(t), \quad e_{ij}\in E_c. \end{cases} \tag{3.33}$$

Consider the order of magnitude of the single terms in (3.33): ϕ_0 is a small parameter which represents the proportion of the physical timescales. The parameters D, β, γ_1, v_a and v_r are large constants of order $O(1/\phi_0)$ on the slow time scale. The function F_τ is of order $O(1/\phi_0)$ too, therefore the quantities

$$\tilde{D}=\phi_0D,\quad \tilde{\beta}=\phi_0\beta,\quad \tilde{\gamma}_1=\phi_0\gamma_1,\quad \tilde{v}_a=\phi_0v_a,\quad \tilde{v}_r=\phi_0v_r,\quad \tilde{F}_\tau=\phi_0F_\tau \tag{3.34}$$

are all of order $O(1)$. We recall that

$$a(x,t)=\begin{cases} D & \text{in } (0,x_1)\\ D\lambda_1(t) & \text{in } (x_1,x_2)\\ fD & \text{in } (x_2,x_3)\\ D\lambda_2(t) & \text{in } (x_3,x_4)\\ D & \text{in } (x_4,L_{ij}),\end{cases}$$

hence, it is also natural to introduce the function

$$\tilde{a}=\phi_0a.$$

The problem (3.33) can be rephrased as

$$\begin{cases} N_i' = \frac{1}{Vol(i)}\sum_{j\neq i}\left(-c_{ij}\bar{J}_{ij}(0,t)+c_{ji}\bar{J}_{ji}(L_{ji},t)\right)+F_i \\ \qquad +\frac{1}{Vol(i)}\sum_{j\neq i}\Big(-c_{ij}(-\tilde{D}(\bar{u}_{ij})_x(0,t))+c_{ji}(-\tilde{D}(\bar{u}_{ji})_x(L_{ji},t)\Big)+\tilde{\beta}V_i, \quad i\in V \\ M_i' = -\tilde{\beta}V_i, \quad i\in V \\ \phi_0 u_t = -\overline{n}_t+(\tilde{a}u_x)_x+(1-f)\left[\chi_{(x_2,x_3)}\left(\tilde{R}_1^{u,v}+\phi_0\tilde{R}_2^{u,v}+\phi_0^2\tilde{R}_3^{u,v}\right)\right]_x \\ \qquad +(\tilde{\beta}v-2\gamma_1\bar{n}u-\phi_0\gamma_1u^2), \\ \phi_0 v_t = -\frac{\partial_t\gamma_1\overline{n}}{\beta}-2\frac{\gamma_1\overline{n}\,\overline{n}_t}{\beta}-\left(\tilde{\beta}v-2\gamma_1\overline{n}u-\phi_0\gamma_1u^2\right), \\ \phi_0 V_i' = -\frac{\partial_t\gamma_1(t)}{\beta}N_i-\frac{2\gamma_1N_iN_i'}{\beta}-\tilde{\beta}V_i \quad i\in V, \\ u(0,t)=u(L_{ij},t)=0, \\ v(0,t)=V_i(t),\ v(L_{ij},t)=V_j(t) \quad e_{ij}\in E_c, \end{cases} \tag{3.35}$$

where

$$\begin{aligned} \tilde{R}_1^{u,v} &:= -\left(\tilde{v}_a(1+2\delta\overline{n})(1-\varepsilon\overline{m})-\tilde{v}_r\right)u+\tilde{v}_a(1+\delta\overline{n})\varepsilon\overline{n}v, \\ R_2^{u,v} &:= \tilde{v}_a\left(\varepsilon(1+2\delta\overline{n})uv-\delta(1-\varepsilon\overline{m})u^2\right), \\ R_3^{u,v} &:= \tilde{v}_a\delta\varepsilon u^2 v. \end{aligned}$$

Since ϕ_0 is extremely small, we formally set $\phi_0=0$ in (3.35):

$$\begin{cases} -\overline{n}_t+(\tilde{a}(x,t)u_x)_x+(1-f)\left(\chi_{(x_2,x_3)}\tilde{R}_1^{u,v}\right)_x+\tilde{\beta}v-2\gamma_1\bar{n}u=0, \\ \left(\tilde{\beta}v-2\gamma_1\overline{n}u\right)=-\frac{\partial_t\gamma_1\overline{n}}{\beta}-2\frac{\gamma_1\overline{n}\,\overline{n}_t}{\beta}, \\ \tilde{\beta}V_i=-\frac{\partial_t\gamma_1(t)}{\beta}N_i-\frac{2\gamma_1N_iN_i'}{\beta} \quad i\in V, \\ u(0,t)=u(L_{ij},t)=0, \\ v(0,t)=V_i(t),\ v(L_{ij},t)=V_j(t) \quad e_{ij}\in E_c. \end{cases} \tag{3.36}$$

This formal simplification immediately leads to a quasi-static equation for N_i:

$$\begin{aligned} Vol(i)\frac{d}{dt}\Big(\underbrace{g(N_i,t)}_{\overline{M}_i}+N_i\Big)(t) &= \underbrace{\sum_{j\neq i}\left(-c_{ij}\bar{J}_{ij}(0,t)+c_{ji}\bar{J}_{ji}(L_{ji},t)\right)}_{\text{Net incoming flux at node } P_i}+Vol(i)F_i \\ &\quad -\underbrace{\sum_{j\neq i}\Big(-c_{ij}\tilde{D}(\bar{u}_{ij})_x(0,t)+c_{ji}(\tilde{D}\bar{u}_{ji})_x(L_{ji},t)\Big)}_{\text{Feedback mechanism}}. \end{aligned} \tag{3.37}$$

In the following Section we elaborate these basic ideas to quantify the feedback effect in the quasi-static model. The Ansatz that we may set $\phi_0=0$ in (3.35) to obtain a good (quasi-static) approximation of the solution of the PDE system can be intuitively justified by the facts that all other terms in (3.35) are $O(1)$ and that the equations for u, v and V_i in (3.35) suggest that these quantities converge almost instantaneously to the "quasi-steady states" (i.e. for fixed t) defined by the (3.36). To make this reasoning at least formally consistent, one should analyse the stability of these quasi-steady states.

Remark 3.4.1. *We are interested in the effective flux on the slow time scale at the endpoints of the edge e_{ij}, so we consider the quantities in* (3.32). *Observe that the flux of u at $x=0$ and $x=L_{ij}$ on the slow time scale* *satisfies*

$$-Du_x(0,t) = \frac{-\bar{J}(0,t) - Dn_x(0,t)}{\phi_0} = O(1/\phi_0^2)$$
$$-Du_x(L_{ij},t) = \frac{-\bar{J}(L_{ij},t) - Dn_x(L_{ij},t)}{\phi_0} = O(1/\phi_0^2)$$

since D is of order $O(1/\phi_0)$ on the slow time scale. This suggests a relevant contribution of the feedback mechanism due to the change in time of the parameters (3.6).

Remark 3.4.2. *The corrective feedback terms depend on ϕ_0 through the parameters* (3.34). *This dependency motivates the different notation for the scaling parameter ϕ in Chapter 1, which disappears in the quasi-static formulation of the NTM.*

3.4.1 Calculation of the correction terms

In this Section we calculate the feedback terms indicated in the equation for N_i (3.37).

We rewrite system (3.36) as

$$\begin{cases} -\overline{n}_t + (\tilde{a}(x,t)u_x)_x - (1-f)\left(\chi_{(x_2,x_3)}(\tilde{v}_a(1+2\delta\overline{n})(1-\varepsilon\overline{m}) - \tilde{v}_r)u + \tilde{v}_a(1+\delta\overline{n})\varepsilon\overline{n}v\right)_x \\ \qquad +\tilde{\beta}v - 2\gamma_1\bar{n}u = 0, \\ \left(\tilde{\beta}v - 2\gamma_1\overline{n}u\right) = -\frac{\partial_t\gamma_1\overline{n}}{\beta} - 2\frac{\gamma_1\overline{n}\,\overline{n}_t}{\beta}, \\ \tilde{\beta}V_i = -\frac{\partial_t\gamma_1(t)}{\beta}N_i - \frac{2\gamma_1 N_i N_i'}{\beta} \quad i \in V, \\ u(0,t) = u(L_{ij},t) = 0, \\ v(0,t) = V_i(t),\ v(L_{ij},t) = V_j(t) \quad e_{ij} \in E_c. \end{cases} \tag{3.38}$$

Solving v from the second equation and substituting it in the equation for u we obtain

$$\begin{aligned}(\tilde{a}(x,t)u_x)_x = \bar{n}_t + 2\frac{\gamma_1}{\beta}\bar{n}\bar{n}_t + \frac{\partial_t\gamma_1}{\tilde{\beta}}\bar{n}^2 + (1-f)\chi_{(x_2,x_3)}\left[(\tilde{v}_a(1+2\delta\bar{n})(1-\varepsilon\bar{m}) - \tilde{v}_r)u\right. \\ \left. -\tilde{v}_a\frac{\varepsilon}{\beta}(1+\delta\bar{n})\bar{n}\left(2\gamma_1\bar{n}u - 2\frac{\gamma_1}{\beta}\bar{n}\bar{n}_t - \frac{\partial_t\gamma_1}{\beta}\bar{n}^2\right)\right]_x.\end{aligned} \tag{3.39}$$

Now integrate equation (3.39) in $[0,x]$:

$$\begin{aligned}\tilde{a}(x,t)u_x - \tilde{D}u_x(0) = \int_0^x \left(\bar{n}_t(y) + 2\frac{\gamma_1}{\beta}\bar{n}(y)\bar{n}_t(y) + \frac{\partial_t\gamma_1}{\beta}\bar{n}^2(y)\right) dy \\ + (1-f)\chi_{(x_2,x_3)}\left[(\tilde{v}_a(1+2\delta\bar{n})(1-\varepsilon\bar{m}) - \tilde{v}_r)u - \tilde{v}_a\frac{\varepsilon}{\beta}(1+\delta\bar{n})\bar{n}\left(2\gamma_1\bar{n}u - 2\frac{\gamma_1}{\beta}\bar{n}\bar{n}_t - \frac{\partial_t\gamma_1}{\beta}\bar{n}^2\right)\right],\end{aligned}$$

and rewrite it as

$$u_x(x) + \frac{h_n(x,\bar{n}(x))}{\tilde{a}(x,t)}u(x) = \frac{\tilde{D}}{\tilde{a}(x,t)}u_x(0) + \ell(x,\bar{n}(x),\bar{n}_t(x)), \tag{3.40}$$

where

$$h_n(x,\bar{n}(x)) := -(1-f)\chi_{(x_2,x_3)}(x)\left(\tilde{v}_a(1+2\delta\bar{n})(1-\varepsilon\bar{m}) - \tilde{v}_r - \tilde{v}_a\frac{2\varepsilon\gamma_1}{\beta}(1+\delta\bar{n})\bar{n}^2\right),$$

$$\ell(x,t,\bar{n}(x),\bar{n}_t(x)) := \frac{1}{\tilde{a}(x,t)} \int_0^x \left(\bar{n}_t(y) + 2\frac{\gamma_1}{\beta}\bar{n}(y)\bar{n}_t(y) + \frac{\partial_t \gamma_1}{\beta}\bar{n}^2(y) \right) dy \\ + \frac{(1-f)}{\tilde{a}(x,t)}\chi_{(x_2,x_3)}(x) \left[\tilde{v}_a \frac{\varepsilon}{\beta^2}(1+\delta\bar{n})\bar{n}\left(2\gamma_1\bar{n}\bar{n}_t + \partial_t\gamma_1\bar{n}^2\right) \right]. \tag{3.41}$$

Multiplying (3.40) by the factor $\omega(x,t) = \exp\left(\int_0^x \frac{h_n(z,\bar{n}(z))}{\tilde{a}(z,t)}\, dz\right)$ and integrating, we get

$$\int_0^{L_{ij}} \exp\left(\int_{x_2}^y \frac{h_n(z,\bar{n}(z))}{a(z,t)}\, dz\right)\left(\frac{\tilde{D}}{\tilde{a}(y,t)}u_x(0) + \ell(y,t,\bar{n}(y),\bar{n}_t(y))\right) dy = 0.$$

This gives the following mass flux correction at $x = 0$ on the edge e_{ij}

$$\tilde{D}(u_{ij})_x(0,t) = -\frac{\int_0^{L_{ij}} \exp\left(\int_{x_2}^y \frac{h_n(z,\bar{n}_{ij}(z))}{\tilde{a}(z,t)}\, dz\right) \ell(y,t,\bar{n}_{ij}(y),(\bar{n}_{ij})_t(y))\, dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^y \frac{h_n(z,\bar{n}_{ij}(z))}{\tilde{a}(z,t)}\, dz\right)}{\tilde{a}(y,t)}\, dy}. \tag{3.42}$$

To obtain an explicit expression for $\tilde{D}(u_{ij})_x(L_{ij},t)$ we integrate equation (3.39) in $[x, L_{ij}]$ to get

$$\tilde{D}u_x(L_{ij}) - \tilde{a}(x,t)u_x(x) = \int_x^{L_{ij}} \left(\bar{n}_t(y) + 2\frac{\gamma_1}{\beta}\bar{n}(y)\bar{n}_t(y) + \frac{\partial_t\gamma_1}{\beta}\bar{n}^2(y)\right) dy \\ -(1-f)\chi_{(x_2,x_3)}(x)\left[(\tilde{v}_a(1+2\delta\bar{n})(1-\varepsilon\bar{m}) - \tilde{v}_r)u - \tilde{v}_a\frac{\varepsilon}{\beta}(1+\delta\bar{n})\bar{n}\left(2\gamma_1\bar{n}u - 2\frac{\gamma_1}{\beta}\bar{n}\bar{n}_t - \frac{\partial_t\gamma_1}{\beta}\bar{n}^2\right)\right].$$

We arrange equation (3.43) in the following form:

$$u_x(x) + \frac{h_n(x,\bar{n}(x))}{\tilde{a}(x,t)}u(x) = \frac{\tilde{D}}{\tilde{a}(x,t)}u_x(L_{ij}) + f(x,t,\bar{n}(x),\bar{n}_t(x)), \tag{3.43}$$

where

$$f(x,t,\bar{n}(x),\bar{n}_t(x)) = -\frac{1}{\tilde{a}(x,t)}\int_x^{L_{ij}} \left(\bar{n}_t(y) + 2\frac{\gamma_1}{\beta}\bar{n}(y)\bar{n}_t(y) + \frac{\partial_t\gamma_1}{\beta}\bar{n}^2(y)\right) dy \\ + \frac{(1-f)}{\tilde{a}(x,t)}\chi_{(x_2,x_3)}(x)\left[\tilde{v}_a\frac{\varepsilon}{\beta^2}(1+\delta\bar{n})\bar{n}\left(2\gamma_1\bar{n}\bar{n}_t + \partial_t\gamma_1\bar{n}^2\right)\right]. \tag{3.44}$$

Integrating equation (3.43) yields

$$\int_0^{L_{ij}} \exp\left(\int_0^y \frac{h_n(z,\bar{n}(z))}{\tilde{a}(z,t)}\, dz\right)\left(\frac{\tilde{D}}{\tilde{a}(y,t)}u_x(L) + f(y,t,\bar{n}(y),\bar{n}_t(y))\right) dy = 0$$

and finally

$$\tilde{D}(u_{ij})_x(L_{ij},t) = -\frac{\int_0^{L_{ij}} \exp\left(\int_{x_2}^y \frac{h_n(z,\bar{n}_{ij}(z))}{\tilde{a}(z,t)}\, dz\right) f(y,t,\bar{n}_{ij}(y),(\bar{n}_{ij})_t(y))\, dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^y \frac{h_n(z,\bar{n}_{ij}(z))}{\tilde{a}(z,t)}\, dz\right)}{\tilde{a}(y,t)}\, dy}. \tag{3.45}$$

Combining equation (3.37) and the explicit expressions (3.42)-(3.45) we recover the correct *feedback* mechanism and obtain the quasi-static *NTM* in the case of time-dependent parameters (3.6).

Remark 3.4.3. *Observe that the flux terms* (3.42)-(3.45) *depend explicitly on* $\partial_t\gamma_1$, λ_1 *and* λ_2 *through* (3.41), (3.44) *and* $\tilde{a}$. *Furthermore, the flux* (3.42) *encapsulates the contribution of the Dirichlet data on the feedback mechanism by means of* $\partial_t\bar{n}_{ij}$.

Remark 3.4.4. *Since in* (3.37) *we consider the contributions of the fluxes of* u_{ij} *and* u_{ji} *over the nodes* P_j *connected to node* P_i, *the equation for* N_i *depends on* N_j' *for all* $j \sim i$. *The coupling between the equations of the resulting system is therefore strengthened with respect to the NTM in Chapter 1, where the feedback mechanism along node* P_i *depends on* N_j *solely through* n_{ij}.

We now reformulate the fluxes (3.42)-(3.45) with the purpose of highlighting the dependencies of the *feedback* mechanism at node P_i on N_i' and N_j' for all $j \sim i$.

Recall that on the edge e_{ij} we can decompose the function $\partial_t n_{ij} =: q_{ij}$ in the following form

$$q_{ij}(x,t) = N_i'(t)q_{ij}^i(x,t) + N_j'(t)q_{ij}^j(x,t) + q_{ij}^0(x,t) \tag{3.46}$$

where q_{ij}^i, q_{ij}^j and q_{ij}^0 satisfy, respectively, (3.13), (3.14) and (3.15). Substitute the decomposition (3.46) in (3.41) on the edge e_{ij} and (3.44) on the edge e_{ji} to get

$$\begin{aligned}
\ell(x,t,\bar{n}_{ij},\partial_t\bar{n}_{ij}) = & \frac{1}{\tilde{a}(x,t)}\int_0^x \left(1 + 2\frac{\gamma_1}{\beta}n_{ij}(y)\right)\left(N_i'q_{ij}^i + N_j'q_{ij}^j + q_{ij}^0\right)\,dy \\
& + \frac{(1-f)}{\tilde{a}(x,t)}\chi_{(x_2,x_3)}(x)\tilde{v}_a\frac{2\varepsilon}{\tilde{\beta}^2}(1+\delta n_{ij})\gamma_1 n_{ij}^2\left(N_i'q_{ij}^i + N_j'q_{ij}^j + q_{ij}^0\right) \\
& + \frac{1}{\tilde{a}(x,t)}\int_0^x \frac{\partial_t\gamma_1}{\beta}\bar{n}_{ij}^2(y)\,dy + \frac{(1-f)}{\tilde{a}(x)}\chi_{(x_2,x_3)}(x)\tilde{v}_a\frac{\varepsilon}{\tilde{\beta}^2}(1+\delta n_{ij})n_{ij}^3\partial_t\gamma_1,
\end{aligned}$$

$$\begin{aligned}
f(x,t,\bar{n}_{ji},\bar{\partial}_t n_{ji}) = & -\frac{1}{\tilde{a}(x,t)}\int_x^L \left(1 + 2\frac{\gamma_1}{\beta}n_{ji}(y)\right)\left(N_i'q_{ji}^i + N_j'q_{ji}^j + q_{ji}^0\right)\,dy \\
& + \frac{(1-f)}{\tilde{a}(x,t)}\chi_{(x_2,x_3)}(x)\tilde{v}_a\frac{2\varepsilon}{\tilde{\beta}^2}(1+\delta n_{ji})\gamma_1 n_{ji}^2\left(N_i'q_{ji}^i + N_j'q_{ji}^j + q_{ji}^0\right) \\
& - \frac{1}{\tilde{a}(x,t)}\int_x^L \frac{\partial_t\gamma_1}{\beta}\bar{n}_{ji}^2(y)\,dy + \frac{(1-f)}{\tilde{a}(x)}\chi_{(x_2,x_3)}(x)\tilde{v}_a\frac{\varepsilon}{\tilde{\beta}^2}(1+\delta n_{ji})n_{ji}^3\partial_t\gamma_1.
\end{aligned} \tag{3.47}$$

The correction term on edge e_{ij} at node P_i is

$$
\begin{aligned}
\tilde{D}(u_{ij})_x(0,t) = &-\left(\frac{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)} \int_0^y \left(1+2\frac{\gamma_1}{\beta}n_{ij}\right) q_{ij}^i(z)\,dz\,dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy}\right. \\
&+\left.\frac{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)} (1-f)\chi_{(x_2,x_3)}(y)\tilde{v}_a\frac{2\varepsilon}{\tilde{\beta}^2}(1+\delta n_{ij})\gamma_1 n_{ij}^2 q_{ij}^i(y)\,dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy}\right) N_i'(t) \\
&-\left(\frac{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)} \int_0^y \left(1+2\frac{\gamma_1}{\beta}n_{ij}\right) q_{ij}^j(z)\,dz\,dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy}\right. \\
&+\left.\frac{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)} (1-f)\chi_{(x_2,x_3)}(y)\tilde{v}_a\frac{2\varepsilon}{\tilde{\beta}^2}(1+\delta n_{ij})\gamma_1 n_{ij}^2 q_{ij}^j(y)\,dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy}\right) N_j'(t) \\
&-\frac{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)} \left[\int_0^y \frac{\partial_t\gamma_1}{\beta}n_{ij}^2\,dz + (1-f)\chi_{(x_2,x_3)}\tilde{v}_a\frac{\varepsilon}{\tilde{\beta}^2}(1+\delta n_{ij})n_{ij}^3\partial_t\gamma_1\right]dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} \\
&-\frac{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)} \int_0^y \left(1+2\frac{\gamma_1}{\beta}n_{ij}\right) q_{ij}^0(z)\,dz\,dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} \\
&-\frac{\int_0^{L_{ij}} \exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right) \frac{(1-f)}{\tilde{a}(y,t)}\chi_{(x_2,x_3)}(y)\tilde{v}_a\frac{2\varepsilon}{\tilde{\beta}^2}(1+\delta n_{ij})\gamma_1 n_{ij}^2 q_{ij}^0(y)\,dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy},
\end{aligned}
\tag{3.48}
$$

while the contribution on edge e_{ji} at node P_i is

$$
\begin{aligned}
\tilde{D}(u_{ji})_x(L_{ji},t) = &\left(\frac{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^y \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)} \int_y^{L_{ji}} \left(1+2\frac{\gamma_1}{\beta}n_{ji}\right) q_{ji}^i(z)\,dz\,dy}{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^y \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} \right. \\
&- \left. \frac{\int_0^{L_{ji}} \exp\left(\int_{x_2}^y \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right) \frac{(1-f)}{\tilde{a}(y,t)} \chi_{(x_2,x_3)}(y)\tilde{v}_a \frac{2\varepsilon}{\beta^2}(1+\delta n_{ji})\gamma_1 n_{ji}^2 q_{ji}^i(y)\,dy}{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^y \frac{h_n(z,n_{ji}}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} \right) N_i'(t) \\
&+ \left(\frac{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^y \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)} \int_y^{L_{ji}} \left(1+2\frac{\gamma_1}{\beta}n_{ji}\right) q_{ji}^j(z)\,dz\,dy}{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^y \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} \right. \\
&- \left. \frac{\int_0^{L_{ji}} \exp\left(\int_{x_2}^y \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right) \frac{(1-f)}{\tilde{a}(y,t)} \chi_{(x_2,x_3)}(y)\tilde{v}_a \frac{2\varepsilon}{\beta^2}(1+\delta n_{ji})\tilde{\gamma}_1 n_{ji}^2 q_{ji}^j(y)\,dy}{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^y \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} \right) N_j'(t) \\
&+ \frac{\int_0^{L_{ji}} \exp\left(\int_{x_2}^y \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right) \left[\frac{1}{\tilde{a}(y,t)} \int_x^{L_{ji}} \frac{\partial_t\gamma_1}{\beta} n_{ji}^2\,dz - \frac{1-f}{\tilde{a}(y,t)}\chi_{(x_2,x_3)} v_a \frac{\varepsilon}{\beta^2}(1+\delta n_{ji}) n_{ji}^3 \partial_t \gamma_1\right] dy}{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^y \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} \\
&+ \left(\frac{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^y \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)} \int_y^{L_{ji}} \left(1+2\frac{\gamma_1}{\beta}n_{ji}\right) q_{ji}^0(z)\,dz\,dy}{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^y \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} \right. \\
&- \left. \frac{\int_0^{L_{ji}} \exp\left(\int_{x_2}^y \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right) \frac{(1-f)}{\tilde{a}(y,t)} \chi_{(x_2,x_3)}(y)\tilde{v}_a \frac{2\varepsilon}{\beta^2}(1+\delta n_{ji})\gamma_1 n_{ji}^2 q_{ji}^0(y)\,dy}{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^y \frac{h_n(z,n_{ji}}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} \right).
\end{aligned}
\tag{3.49}
$$

Reassuming, we can write (3.48) and (3.49) in the form

$$\tilde{D}(u_{ij})_x(0,t) = \mathcal{H}_{ij}^i(t)N_i'(t) + \mathcal{H}_{ij}^j(t)N_j'(t) + \mathcal{H}_{ij}^0, \tag{3.50}$$

$$\tilde{D}(u_{ji})_x(L_{ji},t) = \mathcal{K}_{ji}^j(t)N_j'(t) + \mathcal{K}_{ji}^i(t)N_i'(t) + \mathcal{K}_{ji}^0, \tag{3.51}$$

where we can identify the *feedback* effect due to the change of the Dirichlet data and the parameters γ_1, λ_1, λ_2 and F_τ. Here, the terms $\mathcal{H}$ derive from the flux of u_{ij} at $x = 0$ on the edge e_{ij}, while the terms $\mathcal{K}$ arise from the flux of u_{ji} at $x = L_{ji}$ on the opposite edge. The explicit expressions for the coefficients $\mathcal{H}$

and $\mathcal{K}$ are

$$\mathcal{H}_{ij}^{i}(t) := -\left(\frac{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)} \int_0^y \left(1+2\frac{\gamma_1}{\beta}n_{ij}\right) q_{ij}^{i}(z)\,dz\,dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} + \frac{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}(1-f)\chi_{(x_2,x_3)}(y)\tilde{v}_a\frac{2\varepsilon}{\tilde{\beta}^2}(1+\delta n_{ij})\gamma_1 n_{ij}^2 q_{ij}^{i}(y)\,dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy}\right), \tag{3.52}$$

$$\mathcal{H}_{ij}^{j}(t) := -\left(\frac{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)} \int_0^y \left(1+2\frac{\gamma_1}{\beta}n_{ij}\right) q_{ij}^{j}(z)\,dz\,dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} + \frac{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}(1-f)\chi_{(x_2,x_3)}(y)\tilde{v}_a\frac{2\varepsilon}{\tilde{\beta}^2}(1+\delta n_{ij})\gamma_1 n_{ij}^2 q_{ij}^{j}(y)\,dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy}\right), \tag{3.53}$$

$$\begin{aligned}\mathcal{H}_{ij}^{0}(t) := &-\frac{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)} \left[\int_0^y \frac{\partial_t\gamma_1}{\beta}n_{ij}^2\,dz + (1-f)\chi_{(x_2,x_3)}v_a\frac{\varepsilon}{\tilde{\beta}^2}(1+\delta n_{ij})n_{ij}^3\partial_t\gamma_1\right]dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} \\ &- \frac{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)} \int_0^y \left(1+2\frac{\gamma_1}{\beta}n_{ij}\right) q_{ij}^{0}(z)\,dz\,dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} \\ &- \frac{\int_0^{L_{ij}} \exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)\frac{(1-f)}{\tilde{a}(y,t)}\chi_{(x_2,x_3)}(y)\tilde{v}_a\frac{2\varepsilon}{\tilde{\beta}^2}(1+\delta n_{ij})\gamma_1 n_{ij}^2 q_{ij}^{0}(y)\,dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ij})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy},\end{aligned} \tag{3.54}$$

$$\begin{aligned}\mathcal{K}_{ji}^{j}(t) := &\frac{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)} \int_y^{L_{ji}} \left(1+2\frac{\gamma_1}{\beta}n_{ji}\right) q_{ji}^{j}(z)\,dz\,dy}{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} \\ &- \frac{\int_0^{L_{ji}} \exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right)\frac{(1-f)}{\tilde{a}(y,t)}\chi_{(x_2,x_3)}(y)\tilde{v}_a\frac{2\varepsilon}{\tilde{\beta}^2}(1+\delta n_{ji})\tilde{\gamma}_1 n_{ji}^2 q_{ji}^{j}(y)\,dy}{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy},\end{aligned} \tag{3.55}$$

$$
\begin{aligned}
\mathcal{K}^i_{ji}(t) :=& \frac{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)} \int_y^{L_{ji}} \left(1 + 2\frac{\gamma_1}{\beta} n_{ji}\right) q^i_{ji}(z)\,dz\,dy}{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} \\
&- \frac{\int_0^{L_{ji}} \exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right) \frac{(1-f)}{\tilde{a}(y,t)} \chi_{(x_2,x_3)}(y) \tilde{v}_a \frac{2\varepsilon}{\tilde{\beta}^2} (1+\delta n_{ji}) \gamma_1 n_{ji}^2 q^i_{ji}(y)\,dy}{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy},
\end{aligned}
\tag{3.56}
$$

$$
\begin{aligned}
\mathcal{K}^0_{ji} :=& \frac{\int_0^{L_{ji}} \exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right) \left[\frac{1}{\tilde{a}(y,t)} \int_x^{L_{ji}} \frac{\partial_t \gamma_1}{\beta} n_{ji}^2\,dz - \frac{1-f}{\tilde{a}(y,t)} \chi_{(x_2,x_3)} v_a \frac{\varepsilon}{\tilde{\beta}^2} (1+\delta n_{ji}) n_{ji}^3 \partial_t \gamma_1\right] dy}{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} \\
&+ \frac{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)} \int_y^{L_{ji}} \left(1 + 2\frac{\gamma_1}{\beta} n_{ji}\right) q^0_{ji}(z)\,dz\,dy}{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} \\
&- \frac{\int_0^{L_{ji}} \exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ji})}{\tilde{a}(z,t)}\,dz\right) \frac{(1-f)}{\tilde{a}(y,t)} \chi_{(x_2,x_3)}(y) \tilde{v}_a \frac{2\varepsilon}{\tilde{\beta}^2} (1+\delta n_{ji}) \gamma_1 n_{ji}^2 q^0_{ji}(y)\,dy}{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,n_{ji}}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy}.
\end{aligned}
\tag{3.57}
$$

The equation at node i becomes

$$
\begin{aligned}
Vol(i)\frac{d}{dt}\left(\left(1 + \frac{\gamma_1(i,t)N_i(t)}{\beta}\right) N_i(t)\right) =& \sum_{j\sim i} \left(-c_{ij} J_{ij}(0,t) + c_{ji} J_{ji}(L_{ji},t)\right) \\
-\sum_{j\sim i} \Big((c_{ji}\mathcal{K}^i_{ji}(t) - c_{ij}\mathcal{H}^i_{ij}(t))N_i'(t) \;&+ (c_{ji}\mathcal{K}^j_{ji}(t) - c_{ij}\mathcal{H}^j_{ij}(t))N_j'(t) + c_{ji}\mathcal{K}^0_{ji}(t) + c_{ij}\mathcal{H}^0_{ij}(t)\Big).
\end{aligned}
\tag{3.58}
$$

The LHS of (3.58) is

$$
Vol(i)\left(1 + 2\frac{\gamma_1(i,t)N_i(t)}{\beta}\right) N_i'(t) + Vol(i)\frac{\gamma_1'(i,t)N_i(t)}{\beta}
$$

and we finally obtain the equation

$$
\begin{aligned}
&\left(Vol(i)\left(1 + 2\frac{\gamma_1(i,t)N_i(t)}{\beta}\right) + \sum_{j\sim i}\left(c_{ji}\mathcal{K}^i_{ji}(t) - c_{ij}\mathcal{H}^i_{ij}(t)\right)\right) N_i'(t) + \sum_{j\sim i}(c_{ji}\mathcal{K}^j_{ji}(t) - c_{ij}\mathcal{H}^j_{ij}(t))N_j'(t) \\
&= \sum_{j\sim i}\left(-c_{ij}J_{ij}(0,t) + c_{ji}J_{ji}(L_{ji},t)\right) - \sum_{j\sim i}\left(c_{ji}\mathcal{K}^0_{ji}(t) + c_{ij}\mathcal{H}^0_{ij}(t)\right) - Vol(i)\frac{\gamma_1'(i,t)N_i(t)}{\beta}.
\end{aligned}
\tag{3.59}
$$

In matrix form:

$$
A(t)N'(t) = b(t), \quad A(t) \in \mathbb{R}^{h\times h}, \quad N(t), b(t) \in \mathbb{R}^h \text{ for all } t > 0 \tag{3.60}
$$

where

$$N(t) = (N_1(t), \dots, N_h(t)), \tag{3.61}$$

$$A_{ii}(t) = Vol(i)\left(1 + 2\frac{\gamma_1(t)N_i(t)}{\beta}\right) + \sum_{j\sim i}\left(c_{ji}\mathcal{K}^i_{ji}(t) - c_{ij}\mathcal{H}^i_{ij}(t)\right),$$

$$A_{ij}(t) = c_{ji}\mathcal{K}^j_{ji}(t) - c_{ij}\mathcal{H}^j_{ij}(t), \tag{3.62}$$

$$b_i(t) = \sum_{j\sim i}\left(-c_{ij}J_{ij}(0,t) + c_{ji}J_{ji}(L_{ji},t)\right) - \sum_{j\sim i}\left(c_{ji}\mathcal{K}^0_{ji}(t) + c_{ij}\mathcal{H}^0_{ij}(t)\right) - Vol(i)\frac{\gamma_1'(t)N_i(t)}{\beta},$$

and $J_{ij}(x,t) = -a(x,t)(n_{ij})_x(x,t) + h(x,t,n_{ij})$ for all $e_{ij} \in E_c$.

3.4.2 Mass balance

In this Section, we show that the global node system (3.60) obtained in Section 3.4.1 satisfies the mass balance (3.20). The evolution at node $i \in V$ is described by the local mass law

$$\begin{aligned} V_i(N_i' + M_i') = \underbrace{V_iF_\tau(i,t)}_{\tau \text{ production at } P_i} + \sum_{j\neq i}\Bigg(& \underbrace{Dc_{ij}(n_{ij})_x(0,t) - Dc_{ji}(n_{ji})_x(L_{ji},t)}_{\text{incoming mass flow at } P_i} \\ & - \underbrace{(C^i_{ij}(t) + C^i_{ji}(t))N_i'(t)}_{\text{feedback by } N_i \text{ variation at } P_i} - \underbrace{(B^i_{ij}(t) + B^i_{ji}(t))}_{\text{feedback by production and edge par. variation}}\Bigg). \end{aligned} \tag{3.63}$$

In view of (3.63), the decomposition (3.25) and (3.32), it is natural to define the terms B^i_{ij} and B^j_{ij} in (3.63) so that

$$C^i_{ij}N_i'(t) + B^i_{ij}(t) = -c_{ij}\tilde{D}(u_{ij})_x(0,t), \quad C^j_{ij}N_j'(t) + B^j_{ij}(t) = c_{ij}\tilde{D}(u_{ij})_x(L_{ij},t) \tag{3.64}$$

for all $e_{ij} \in E_c$, $t > 0$.

We must therefore show that B^i_{ij} and B^j_{ij} satisfy

$$C^i_{ij}N_i'(t) + C^j_{ij}N_j'(t) + B^i_{ij} + B^j_{ij} = c_{ij}\int_0^{L_{ij}}(\bar{n}_{ij} + \bar{m}_{ij})_t(x,t)\,dx \quad \text{for all } e_{ij} \in E_c,\ t > 0 \tag{3.65}$$

where

$$\begin{aligned} c_{ij}\int_0^{L_{ij}}(\bar{n}_{ij} + \bar{m}_{ij})_t(x,t)\,dx = {} & c_{ij}\left(\int_0^{L_{ij}} q_{ij}\,dx + \int_{(0,x_3)\cup(x_4,L_{ij})}\frac{2\gamma_1(i,j)\bar{n}_{ij}}{\beta}q_{ij}\,dx\right) \\ & + c_{ij}\int_{(0,x_3)\cup(x_4,L_{ij})}\frac{\partial_t\gamma_1(i,j)\bar{n}^2_{ij}}{\beta}\,dx, \end{aligned}$$

and

$$C^i_{ij}(t) := c_{ij}\left(\int_0^{L_{ij}} q^i_{ij}(x,t)\,dx + \int_{(0,x_3)\cup(x_4,L_{ij})}\frac{2\gamma_1(i,j)\bar{n}_{ij}}{\beta}q^i_{ij}(x,t)\,dx\right),$$

$$C^j_{ij}(t) := c_{ij}\left(\int_0^{L_{ij}} q^j_{ij}(x,t)\,dx + \int_{(0,x_3)\cup(x_4,L_{ij})}\frac{2\gamma_1(i,j)\bar{n}_{ij}}{\beta}q^j_{ij}(x,t)\,dx\right).$$

Recall that

$$\tilde{D}(u_{ij})_x(0,t) = -\frac{\int_0^{L_{ij}} \exp\left(\int_{x_2}^{y} \frac{h_n(z,\bar{n}_{ij}(z))}{\tilde{a}(z,t)}\,dz\right) \ell(y,t,\bar{n}_{ij},(\bar{n}_{ij})_t\,dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,\bar{n}_{ij}(z))}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy}, \tag{3.66}$$

and

$$\tilde{D}(u_{ij})_x(L_{ij},t) = -\frac{\int_0^{L_{ij}} \exp\left(\int_{x_2}^{y} \frac{h_n(z,\bar{n}_{ij}(z))}{\tilde{a}(z,t)}\,dz\right) f(y,t,\bar{n}_{ij},(\bar{n}_{ij})_t)\,dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,\bar{n}_{ij}(z))}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} \tag{3.67}$$

with

$$\begin{aligned}
\ell(x,t,\bar{n}_{ij},\partial_t\bar{n}_{ij}) &= \frac{1}{\tilde{a}(x,t)}\int_0^x \left(1+2\frac{\gamma_1}{\beta}\bar{n}_{ij}(y)\right)\left(N_i' q_{ij}^i + N_j' q_{ij}^j + q_{ij}^0\right)\,dy \\
&+ \frac{(1-f)}{\tilde{a}(x,t)}\chi_{(x_2,x_3)}(x)\tilde{v}_a\frac{2\varepsilon}{\tilde{\beta}^2}(1+\delta\bar{n}_{ij})\gamma_1\bar{n}_{ij}^2\left(N_i' q_{ij}^i + N_j' q_{ij}^j + q_{ij}^0\right) \\
&+ \frac{1}{\tilde{a}(x,t)}\int_0^x \frac{\partial_t\gamma_1(i,j)}{\beta}\bar{n}_{ij}^2(y)\,dy + \frac{(1-f)}{\tilde{a}(x)}\chi_{(x_2,x_3)}(x)\tilde{v}_a\frac{\varepsilon}{\tilde{\beta}^2}(1+\delta\bar{n}_{ij})\bar{n}_{ij}^3\partial_t\gamma_1(i,j),
\end{aligned}$$

$$\begin{aligned}
f(x,t,\bar{n}_{ij},\partial_t\bar{n}_{ij}) &= -\frac{1}{\tilde{a}(x,t)}\int_x^{L_{ij}} \left(1+2\frac{\gamma_1}{\beta}\bar{n}_{ij}(y)\right)\left(N_i' q_{ij}^i + N_j' q_{ij}^j + q_{ij}^0\right)\,dy \\
&+ \frac{(1-f)}{\tilde{a}(x,t)}\chi_{(x_2,x_3)}(x)\tilde{v}_a\frac{2\varepsilon}{\tilde{\beta}^2}(1+\delta\bar{n}_{ij})\gamma_1\bar{n}_{ij}^2\left(N_i' q_{ij}^i + N_j' q_{ij}^j + q_{ij}^0\right) \\
&- \frac{1}{\tilde{a}(x,t)}\int_x^{L_{ij}} \frac{\partial_t\gamma_1(i,j)}{\beta}\bar{n}_{ij}^2(y)\,dy + \frac{(1-f)}{\tilde{a}(x)}\chi_{(x_2,x_3)}(x)\tilde{v}_a\frac{\varepsilon}{\tilde{\beta}^2}(1+\delta\bar{n}_{ij})\bar{n}_{ij}^3\partial_t\gamma_1(i,j).
\end{aligned}$$

Hence we have

$$\begin{aligned}
&c_{ij}\tilde{D}(u_{ij})_x(L_{ij},t) - c_{ij}\tilde{D}(u_{ij})_x(0,t) \\
&= \frac{c_{ij}\int_0^{L_{ij}} \exp\left(\int_{x_2}^{y} \frac{h_n(z,\bar{n}_{ij}(z))}{\tilde{a}(z,t)}\,dz\right)\left[\ell(y,t,\bar{n}_{ij},(\bar{n}_{ij})_t) - f(y,t,\bar{n}_{ij},(\bar{n}_{ij})_t)\right]\,dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,\bar{n}_{ij}(z))}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} \\
&= \frac{c_{ij}\int_0^{L_{ij}} \exp\left(\int_{x_2}^{y} \frac{h_n(z,\bar{n}_{ij}(z))}{\tilde{a}(z,t)}\,dz\right)\left[\frac{1}{\tilde{a}(y,t)}\int_0^{L_{ij}}\left(1+2\frac{\gamma_1}{\beta}\bar{n}_{ij}(v)\right)\left(N_i' q_{ij}^i + N_j' q_{ij}^j + q_{ij}^0\right)\,dv\right]\,dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,\bar{n}_{ij}(z))}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} \\
&+ \frac{c_{ij}\int_0^{L_{ij}} \exp\left(\int_{x_2}^{y} \frac{h_n(z,\bar{n}_{ij}(z))}{\tilde{a}(z,t)}\,dz\right)\left[\frac{1}{\tilde{a}(y,t)}\int_0^{L_{ij}}\frac{\partial_t\gamma_1}{\beta}\bar{n}_{ij}^2(v)\,dv\right]\,dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,\bar{n}_{ij}(z))}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} \\
&= c_{ij}\int_0^{L_{ij}}\left(1+2\frac{\gamma_1(i,j)}{\beta}\bar{n}_{ij}(v)\right)\left(N_i' q_{ij}^i + N_j' q_{ij}^j + q_{ij}^0\right)\,dv + c_{ij}\int_0^{L_{ij}}\frac{\partial_t\gamma_1(i,j)}{\beta}\bar{n}_{ij}^2(v)\,dv \\
&= c_{ij}\int_0^{L_{ij}}(\bar{n}_{ij}+\bar{m}_{ij})_t(v,t)\,dv.
\end{aligned}$$

We can conclude that the correction terms (3.66) and (3.67) recover the correct mass balance.

3.4.3 Comparison with the feedback of Chapter 1

The decomposition (3.64) suggests that in the case of constant parameters γ_1, λ_1, λ_2 and F_τ, i.e. the scenario of Chapter 1, the effective correction terms (3.66) and (3.67) provide a more detailed description of the nodal *feedback* mechanism. In fact, we can write the contribution at node P_i arising from the edge e_{ij} as

$$\begin{aligned}
-c_{ij}\tilde{D}(u_{ij})_x(0,t) = \; & \underbrace{C^i_{ij}N'_i(t)}_{\text{feedback from Chapter 1}} - c_{ij} \underbrace{\frac{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,\bar{n}(z))}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)} \int_y^{L_{ij}} \left(1+2\frac{\gamma_1}{\beta}\bar{n}(z)\right) q^i_{ij}(z)\,dz\,dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,\bar{n}(z))}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} N'_i(t)}_{\text{new correction from node } P_i} \\
& + c_{ij} \underbrace{\frac{\int_0^{L_{ij}} \exp\left(\int_{x_2}^{y} \frac{h_n(z,\bar{n}(z))}{\tilde{a}(z,t)}\,dz\right) \frac{(1-f)}{\tilde{a}(y,t)}\chi_{(x_2,x_3)}(y)\tilde{v}_a\frac{2\varepsilon}{\tilde{\beta}^2}(1+\delta\bar{n})\gamma_1\bar{n}^2 q^i_{ij}(y)\,dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,\bar{n}(z))}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} N'_i(t)}_{\text{new correction from node } P_i} \\
& + c_{ij} \Bigg(\underbrace{\frac{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,\bar{n}(z))}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)} \int_0^{y} \left(1+2\frac{\gamma_1}{\beta}\bar{n}(z)\right) q^j_{ij}(z)\,dz\,dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,\bar{n}(z))}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy}}_{\text{new correction from node } P_j} \\
& + \underbrace{\frac{\int_0^{L_{ij}} \exp\left(\int_{x_2}^{y} \frac{h_n(z,\bar{n}(z))}{\tilde{a}(z,t)}\,dz\right) \frac{(1-f)}{\tilde{a}(y,t)}\chi_{(x_2,x_3)}(y)\tilde{v}_a\frac{2\varepsilon}{\tilde{\beta}^2}(1+\delta\bar{n})\gamma_1\bar{n}^2 q^j_{ij}(y)\,dy}{\int_0^{L_{ij}} \frac{\exp\left(\int_{x_2}^{y} \frac{h_n(z,\bar{n}(z))}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy}}_{\text{new correction from node } P_j} \Bigg) N'_j(t),
\end{aligned} \tag{3.68}$$

$$
\begin{aligned}
c_{ji}\tilde{D}(u_{ji})_x(L_{ji},t) = \quad & \underbrace{C^i_{ji}N_i'(t)}_{\text{feedback from Chapter 1}} \quad - c_{ji} \underbrace{\frac{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^y \frac{h_n(z,\bar{n}(z))}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)} \int_0^y \left(1+2\frac{\gamma_1}{\beta}\bar{n}(z)\right) q^i_{ji}(z)\,dz\,dy}{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^y \frac{h_n(z,\bar{n}(z))}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} N_i'(t)}_{\text{new correction from node } P_i} \qquad (3.69)\\
& - c_{ji} \underbrace{\frac{\int_0^{L_{ji}} \exp\left(\int_{x_2}^y \frac{h_n(z,\bar{n}(z))}{\tilde{a}(z,t)}\,dz\right) \frac{(1-f)}{\tilde{a}(y,t)} \chi_{(x_2,x_3)}(y)\tilde{v}_a \frac{2\varepsilon}{\beta^2}(1+\delta\bar{n})\gamma_1\bar{n}^2 q^i_{ji}(y)\,dy}{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^y \frac{h_n(z,\bar{n}(z))}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy} N_i'(t)}_{\text{new correction from node } P_i}\\
& + c_{ji} \left(\underbrace{\frac{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^y \frac{h_n(z,\bar{n}(z))}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)} \int_y^{L_{ji}} \left(1+2\frac{\gamma_1}{\beta}\bar{n}(z)\right) q^j_{ji}(z)\,dz\,dy}{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^y \frac{h_n(z,\bar{n}(z))}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy}}_{\text{new correction from node } P_j} \right.\\
& \left. \underbrace{- \frac{\int_0^{L_{ji}} \exp\left(\int_{x_2}^y \frac{h_n(z,\bar{n}(z))}{\tilde{a}(z,t)}\,dz\right) \frac{(1-f)}{\tilde{a}(y,t)} \chi_{(x_2,x_3)}(y)\tilde{v}_a \frac{2\varepsilon}{\beta^2}(1+\delta\bar{n})\gamma_1\bar{n}^2 q^j_{ji}(y)\,dy}{\int_0^{L_{ji}} \frac{\exp\left(\int_{x_2}^y \frac{h_n(z,\bar{n}(z))}{\tilde{a}(z,t)}\,dz\right)}{\tilde{a}(y,t)}\,dy}}_{\text{new correction from node } P_j} \right) N_j'(t),
\end{aligned}
$$

and observe both a reinforced relation between the *feedback* mechanism at node P_i and the rate of change of N_i and a newly introduced dependence on the rate of change of N_j for all $j \sim i$.

A numerical comparison between the two formulations is presented in Section 3.6.1, where we show that the novel *feedback* mechanism influences the behaviour of the system by inducing different dynamical features with respect to the *NTM* of Chapter 1.

3.5 Application to the case of Aβ dependent parameters

In the current Section we couple the Beta Amyloid system of Chapter 2 with the time-dependent *NTM* developed in Section 3.4. The concentrations of monomers, soluble oligomers and plaques of Beta Amyloid are defined on the *proximity* graph $G_p = (V, E_p)$, while the *connectivity* graph, $G_c = (V, E_c)$, accommodates intracellular soluble and insoluble Tau. Both networks share the same set of nodes V by exhibiting a different set of edges. This distinction reflects the different metric of spread of the proteins on the brain network. The weights of the *connectivity* graph, respectively the *proximity* graph, are denoted with c_{ij} and ω_{ij}.

3.5.1 The Model

Consider the following model for Aβ: let G_p be the *proximity* graph and f_i a probability measure on $[0,1]$ which satisfies

$$
\begin{cases} \partial_t f_{i,t} + (v[f_{i,t}]f_{i,t})_a = J[f_{i,t}], \\ f_{i,0} = f_i(0) \end{cases} \qquad i \in V, \tag{3.70}
$$

where

$$J[f_{i,t}] = \eta(t)\chi_H(t)\left\{\left(\int_{[0,1]} P(t,b,a)\,df_{i,t}(b)\right)\,da - df_{i,t}(a)\right\}. \tag{3.71}$$

The elliptic Aβ system is

$$\begin{cases} d_1\Delta u_1 - \sigma_1 u_1 + F_{A\beta}[f] + \Gamma_1 = 0, \\ d_2\Delta u_2 - \sigma_2 u_2 + \Gamma_2 = 0, & i \in V \\ -\sigma_3 u_3 + \Gamma_3 = 0, \end{cases} \tag{3.72}$$

where the monomers' source is

$$F_{A\beta}[f_{i,t}] = C_\mu \int_0^1 (\mu_0 + a)(1-a)\,df_{i,t}(a), \tag{3.73}$$

the rate of degeneration is

$$v[f_{i,t}](a,t) = C_G \int_{[0,1]} (b-a)^+\,df_{i,t}(b) + C_s(1-a)(u_2(i,t) - \bar{U}_2)^+, \tag{3.74}$$

and the reaction terms are given by

$$\begin{cases} \Gamma_1 = -u_1(a_{11}u_1 + a_{12}u_2) + k_1 u_3 \\ \Gamma_2 = a_{11}u_1^2 - a_{21}u_1u_2 + k_2u_3 \\ \Gamma_3 = -(\Gamma_1 + \Gamma_2) = u_1u_2(a_{12} + a_{21}) - (k_1 + k_2)u_3. \end{cases} \tag{3.75}$$

As in Chapter 2, we require that the model parameters satisfy

(i) $\sigma_1,\ \sigma_2,\ \sigma_3,\ a_{11},\ a_{12},\ a_{21}\ k_1,\ k_2,\ d_1,\ d_2,\ C_\mu,\ \mu_0, C_G,\ C_s$ are positive constants. The monomers' clearance parameter σ_1 is sufficiently large, i.e. $\sigma_1 > \bar{\sigma}_1$. The aggregation and fragmentation rates are symmetric: $a_{ij} = a_{ji}$, $k_1 = k_2$;

(ii) $\eta \in C([0,T])$, $\eta > 0$. P satisfies

$$P \in C([0,T]\times[0,1]^2), \quad P \geq 0, \tag{3.76}$$

$$\int_{[0,1]} P(t,b,a)\,da = 1 \text{ for } b \in [0,1],\ P(t,b,a) = 0 \quad \text{if } b > a \tag{3.77}$$

since impaired neurons do not recover, and it is Lipschitz continuous:

$$\exists L > 0 :\ |P(t'',b'',a'') - P(t',b',a')| \leq L(|b''-b'| + |a''-a'| + |t''-t'|), \tag{3.78}$$

for all $a', a'', b', b'' \in [0,1]$, $t',\ t'' \in [0,T]$.

Under the assumptions $(i) - (ii)$, by Theorem 2.3.1 there exists a unique solution (f, u_1, u_2, u_3) on $[0,T]$ in the sense of Definition 2.3.1 such that $u \in C^1([0,T])$ (by Section 2.7).

Consider now the *connectivity* graph G_c and let M_i, N_i be the concentration of insoluble and soluble Tau on the node $P_i \in V$. Let m_{ij}, n_{ij} be the concentration of insoluble and soluble Tau on the edge e_{ij}. In view of the previous sections, we require the following hypotheses on the *NTM* parameters:

(iii) $\gamma_1, \lambda_1, \lambda_2 \in C^1(\mathbb{R}^+)$, $\gamma_1 \geq 0$, $\lambda_1, \lambda_2 \in (0,1)$, $F_i \in C^1(\mathbb{R}^+)$ for all $i \in V$, $F_\tau \in C^1([0, L_{ij}] \times \mathbb{R}^+)$, $F_i, F_\tau \geq 0$ and $\exists C_\gamma, C_\lambda, C'_\lambda, C_F > 0$ such that

$$|\gamma_1|, |\partial_u \gamma_1| < C_\gamma \text{ on } \mathbb{R}^+, \quad C'_\lambda < \lambda_1, \lambda_2 < C_\lambda \text{ on } \mathbb{R}^+,$$

$$F_i(u), F_\tau(x,u) < C_F \text{ for all } x \in [0, L_{ij}],\ e_{ij} \in E_c,\ i \in V,\ u \in \mathbb{R}^+;$$

(iv) The parameters $D, f, \beta, \varepsilon, \delta, v_a, v_r$ are positive constants such that $A(t) \in GL_h(\mathbb{R})$ for all $t \in [0,T]$ and $\exists C_A > 0$ such that

$$\det A(t) > C_A \text{ for all } t \in [0,T].$$

In this Chapter, we suppose that soluble oligomers of Aβ (u_2) act by enhancing aggregation and diffusion of soluble Tau on the nodes and edges of the *connectivity* graph. In Section 3.3.1 we have shown that inserting time-dependent parameters in the equations on the edges of the *connectivity* graph requires a correction of the *feedback* mechanism introduced in Chapter 1 which substantially increases the complexity of the resulting equations on the nodes, as suggested by the calculation of Section 3.4.1.

Since u_2 is defined on the nodes of the *proximity* graph and since we assumed that the *connectivity* graph shares the same set of nodes, on e_{ij} we extend the definition of u_2 as a linear combination of the respective node concentrations

$$(u_2)_{ij}(x,t) = \left(1 - \tfrac{x}{L}\right) u_2(i,t) + \tfrac{x}{L} u_2(j,t) \quad \text{for } x \in (0, L_{ij}),\ t \geq 0$$

and define

$$\gamma_1(x,t;i,j) = \gamma_1((u_2)_{ij}(x,t)), \quad \lambda_k(x,t;i,j) = \lambda_k((u_2)_{ij}(x,t)),$$

where $\gamma_1,\ \lambda_k$ satisfy (iii) for $k = 1,2$.

The resulting equation for N_i at node $P_i \in V$ is

$$\left(Vol(i) \left(1 + 2\frac{\gamma_1(u_2(i))N_i(t)}{\beta} \right) + \sum_{j \sim i} \left(c_{ji}\mathcal{K}^i_{ji}(t) - c_{ij}\mathcal{H}^i_{ij}(t) \right) \right) N'_i(t) + \sum_{j\sim i} (c_{ji}\mathcal{K}^j_{ji}(t) - c_{ij}\mathcal{H}^j_{ij}(t)) N'_j(t)$$
$$= \sum_{j\sim i} \left(-c_{ij} J_{ij}(0,t) + c_{ji} J_{ji}(L_{ji}, t)\right) - \sum_{j \sim i} \left(c_{ji}\mathcal{K}^0_{ji}(t) + c_{ij}\mathcal{H}^0_{ij}(t) \right) - Vol(i) \frac{\gamma'_1(u_2(i)) u'_2(i) N_i(t)}{\beta}, \tag{3.79}$$

where $\mathcal{H}^i_{ij}$, $\mathcal{H}^j_{ij}$, $\mathcal{H}^0_{ij}$, $\mathcal{K}^j_{ji}$, $\mathcal{K}^i_{ji}$, and $\mathcal{K}^0_{ji}$ are defined, respectively, by (3.52), (3.53), (3.54), (3.55), (3.56), and (3.57), the flux J_{ij} is determined by the edge problem

$$\begin{cases} J_{ij}(x,t) = -a(x, u_2(i,j))(n_{ij})_x - h(x, u_2(i,j), n_{ij}), \\ (J_{ij})_x = F_\tau, \\ n_{ij}(0,t) = N_i(t), \quad n_{ij}(L_{ij}, t) = N_j(t), \end{cases}$$

and insoluble Tau at the nodes satisfies

$$M_i(t) = \frac{\gamma_1(i,t) N_i(t)^2}{\beta}, \quad i \in V. \tag{3.80}$$

Before stating the main result of this Section, we define the notion of solution of the Aβ-dependent *NTM*. Observe that the construction of the solution to the Aβ elliptic system (3.72) induces a restriction on the domain of definition of N_i and M_i for all $i \in V$.

Definition 3.5.1. *Let* $1 \leq i, j \leq h$. *Let, for all* i,

$$N_{i0} \geq 0,\ N_i \in C^1([0,T]);[0,\infty)),\ M_i \in C^1([0,T]);[0,\infty))$$

and, for all $i \neq j$ *such that* $c_{ij} > 0$,

$$n_{ij} \in C([0,L_{ij}] \times [0,T];[0,\infty)),\ m_{ij} \in L^\infty([0,L_{ij}] \times [0,T];[0,\infty)),\ J_{ij} \in C([0,L_{ij}] \times [0,T];\mathbb{R}).$$

Then $(M_i, N_i, m_{ij}, n_{ij})$ *is said to be a solution of the quasi-static* $A\beta$*-dependent NTM if equations* (3.79) *and* (3.80) *are satisfied, and*

$$\text{for all } t \geq 0: \quad \begin{cases} m_{ij}(t) = g(t, n_{ij}(t)) & \text{a.e. in } (0, L_{ij}) \setminus (x_3, x_4) \\ m_{ij}(t) = 0 & \text{in } (x_3, x_4) \\ J_{ij}(t) = -a(x, u_2(t))(n_{ij}(t))_x - h(x, u_2(t), n_{ij}(t)) & \text{in } \mathcal{D}'(0, L) \\ (J_{ij})_x = F_\tau, \\ n_{ij}(0,t) = N_i(t) \\ n_{ij}(L,t) = N_j(t). \end{cases} \tag{3.81}$$

If in addition the initial total mass of Tau is positive and bounded, i.e. if

$$0 < \mathcal{M}_0 = \sum_i \left(V_i(M_i(0) + N_{0i}) + \sum_{j \neq i} \int_0^L c_{ij}(m_{ij}(x,0) + n_{ij}(x,0))dx \right) < \infty, \tag{3.82}$$

we call $(M_i, N_i, m_{ij}, n_{ij})$ *a finite mass solution of the quasi-static* $A\beta$*-dependent NTM.*

In the following, we will prove the existence of a solution to the Aβ-dependent *NTM* combining the results of Chapter 1 and 2.

Theorem 3.5.1. *Let* $N_{i0} \geq 0$ *for all* $1 \leq i \leq h$. *Under the hypotheses* $(i) - (iv)$, *the quasi-static* $A\beta$*-dependent NTM possesses a unique solution in the sense of Definition 3.5.1.*

3.5.2 Mass balance

Inserting the production terms F_i and F_τ on the nodes and edges, respectively, violates the mass conservation property of Chapter 1.

Lemma 3.5.2. *Let* $N_{i0} \in [0,\infty)$ *for* $1 \leq i \leq h$. *If* $c_{ij} > 0$, *there exists a unique* $J \in \mathbb{R}$ *such that*

$$\begin{cases} a(x,u_2)n'(x) = -h(x,u_2,n(x)) - \int_0^x F_\tau(y,u_2)\,dy - J & \text{in } (0, L_{ij}), \\ n(0) = N_i,\ n(L) = N_j \end{cases} \tag{3.83}$$

has a solution $n = n_{ij}(0)$. *In addition* $n_{ij}(0)$ *is nonnegative and continuous in* $[0, L_{ij}]$.

Proof. The proof is based on Lemma 1.4.1 with the exception that the flux J_{ij} is not constant anymore on the edge. The equation on the edge is given by

$$(J_{ij})_x = F_\tau \tag{3.84}$$

which gives

$$J(x,t) = J(0,t) + \int_0^x F_\tau(y,u_2)\,dy =: J + \int_0^x F_\tau(y,u_2)\,dy. \tag{3.85}$$

Consider $J \in \mathbb{R}$ as a shooting parameter and consider the problem

$$\begin{cases} a(x,u_2)n'(x) = -h(x,u_2,n(x)) - \int_0^x F_\tau(y,u_2)\,dy - J & \text{in } (0,L_{ij}), \\ n(0) = N_i. \end{cases} \tag{3.86}$$

Observe that $n(x)$ is pointwise decreasing with respect to the parameter J, hence arguing as in the proof of Lemma 1.4.1 yields the result. □

It follows from Lemma 3.5.2 that the total initial mass of Tau is always finite.

Corollary 3.5.3. *Let $\mathcal{M}_0$ be the total initial mass, defined by* (3.82)*. Then $\mathcal{M}_0 < \infty$ and every solution of the quasi-static $A\beta$-NTM is a finite mass solution.*

Proof. The equations (3.79), (3.80) suggest the following global mass balance

$$\begin{aligned} \mathcal{M}(t) &:= \sum_{i\in V} Vol(i)\,(M_i + N_i) + \sum_{i\in V}\sum_{j\sim i} c_{ij}\int_0^{L_{ij}} (m_{ij}(x,t) + n_{ij}(x,t))\,dx \\ &= \sum_{i\in V} Vol(i)\int_0^t F_i(u_2(s))\,ds + \sum_{i\in V}\sum_{j\sim i} c_{ij}\int_0^t\int_0^{L_{ij}} F_\tau(x,u_2(s))\,dx\,ds. \end{aligned} \tag{3.87}$$

By (2.217) it follows that $u_2(i,t) \in [0, C_{\mu,\tilde\sigma}]$ for all $t \in [0,T]$ and $i \in V$, hence by continuity of F_τ and F_i for $i \in V$ and $e_{ij} \in E_c$ it follows that $\mathcal{M}(t) < \infty$ for all $t \in (0,T]$. □

Starting from a solution at given Dirichlet data we can perturb N_i and N_j to obtain a sufficiently close edge solution $\tilde n_{ij}$.

Lemma 3.5.4. *Let $t \geq 0$ be fixed. Let $\varepsilon_1 \geq \varepsilon_2 > 0$, $\gamma_2 > 0$, $N_i \in [-\varepsilon_2,\infty)$ for all $1 \leq i \leq h$, let $n_{ij} \in C([0,L])$ satisfy* (3.81) *for all $i \neq j$ such that $c_{ij} > 0$, and let $\mathcal{M}$, defined by* (3.82)*, be finite. Then there exists $\varepsilon_3 > 0$ which does not depend on i, j such that for all $\tilde N_i$ satisfying*

$$|\tilde N_i - N_i| \leq \varepsilon_3,$$

there exists a unique $\tilde n_{ij} \in C([0,L])$ which satisfies, for all $i \neq j$ such that $c_{ij} > 0$,

$$\begin{cases} -2\varepsilon_1 \leq \tilde n_{ij} & \textit{in } (0,L) \\ \left(a(x)(\tilde n_{ij})_x + h(x,\tilde n_{ij})\right)_x = -F_\tau(x,u_2) & \textit{in } \mathcal{D}'(0,L), \\ \tilde n_{ij}(0) = \tilde N_i,\ \tilde n_{ij}(L) = \tilde N_j. \end{cases} \tag{3.88}$$

Proof. We fix the edge e_{ij} and let $J \in \mathbb{R}$ be a shooting parameter. Consider the problem

$$\begin{cases} n' = -\frac{1}{a(x,u_2)}\left(J + h(x,n) + \int_0^x F_\tau(y,u_2)\,dy\right) & \text{for } x \in [0,L] \\ n(0) = \tilde N_i. \end{cases} \tag{3.89}$$

Since n is pointwise decreasing with respect to J, we can repeat the argument in Lemma 1.4.7 to obtain the existence for $\tilde n_{ij}$. The uniqueness will be proved in the following Section. □

3.5.3 A fixed point argument

In this Section, we prove the existence of a local solution to the Aβ-dependent *NTM*, following the lines of Chapter 1. The multiscale analysis of Section 3.4.1 yields a more precise description of the *feedback* mechanism with respect to the approximation provided in Chapter 1. However, the structure of the resulting problem is mathematically more complex. For example, the argument for the positivity result obtained in Section 1.6 cannot be repeated in this setting due to the intricate structure of the matrix A.

We introduce some continuity estimates for the edge variables n_{ij}, q^i_{ij}, q^j_{ij}, q^0_{ij}. Recall that q_{ij} satisfies

$$q_{ij}(x,t) = N_i'(t)q^i_{ij}(x,t) + N_j'(t)q^j_{ij}(x,t) + q^0_{ij}(x,t), \tag{3.90}$$

where $q^i_{ij}(x,t)$, $q^j_{ij}(x,t)$ and $q^0_{ij}(x,t)$, as functions of x satisfy, respectively,

$$\begin{cases} \left(a(x)(q^i_{ij})_x + \frac{\partial h(x,n_{ij})}{\partial n} q^i_{ij}\right)_x = 0 \quad \text{in } (0,L_{ij}) \\ q^i_{ij}(0,t) = 1, \quad q^i_{ij}(L,t) = 0 \end{cases} \tag{3.91}$$

$$\begin{cases} \left(a(x)(q^j_{ij})_x + \frac{\partial h(x,n_{ij})}{\partial n} q^j_{ij}\right)_x = 0 \quad \text{in } (0,L_{ij}) \\ q^j_{ij}(0,t) = 0, \quad q^j_{ij}(L,t) = 1 \end{cases} \tag{3.92}$$

$$\begin{cases} \left(a(x)(q^0_{ij})_x + \frac{\partial h(x,n_{ij})}{\partial n} q^0_{ij} + G(x,t,n_{ij})\right)_x + \frac{\partial F_\tau}{\partial t} = 0 \quad \text{in } (0,L_{ij}) \\ q^0_{ij}(0,t) = 0, \quad q^0_{ij}(L_{ij},t) = 0, \end{cases} \tag{3.93}$$

with

$$\begin{aligned} G(x,t,n_{ij}) &= b_1(x)\partial_t u_2(i,j)\lambda_1'(i,j)(n_{ij})_x + b_2(x)\partial_t u_2(i,j)\lambda_2'(i,j)(n_{ij})_x \\ &\quad + \frac{c(x)}{\beta} n^3_{ij}(1+\delta n_{ij})\partial_t u_2(i,j)\gamma_1'(i,j). \end{aligned} \tag{3.94}$$

A straightforward calculation yields the following explicit expressions for the feedback variables q^i_{ij}, q^j_{ij}, q^0_{ij}.

Lemma 3.5.5. *Let $t \geq 0$, $i \neq j$ and $c_{ij} > 0$. Let $N_i(t), N_j(t) \in [-\varepsilon_2, \infty)$ and $J_{ij}(t)$ be given numbers. Let $x \mapsto n_{ij}(x,t)$ be a Lipschitz continuous solution of*

$$\begin{cases} a(x)(n_{ij})_x(x,t) + h(x,n_{ij}) = -J_{ij}(t) \quad \textit{for a.e. } x \in [0,L] \\ -\varepsilon_1 < n_{ij}(x,t) \quad \forall x \in [0,L] \\ n_{ij}(0,t) = N_i(t), \; n_{ij}(L,t) = N_j(t), \end{cases} \tag{3.95}$$

and let q^i_{ij}, q^j_{ij} and q^0_{ij} be defined by (3.12). *Then*

$$q^i_{ij}(x,t) = e^{-\int_0^x \frac{h_n(s,n_{ij}(s,t))}{a(s)}ds} \left(\frac{e^{\int_0^L \frac{h_n(s,n_{ij}(s,t))}{a(s)}ds} \int_0^x \frac{e^{\int_0^y \frac{h_n(s,n_{ij}(s,t))}{a(s)}ds}}{a(y)}dy}{\int_0^L \frac{e^{\int_0^y \frac{h_n(s,n_{ij}(s,t))}{a(s)}ds}}{a(y)}dy} \right) \geq 0\,,$$

where h_n stands for $\frac{\partial h}{\partial n}$. Similarly, if $c_{ji} > 0$, we have that

$$q^i_{ji}(x,t) = e^{-\int_0^x \frac{h_n(s,n_{ji}(s,t))}{a(s)}ds} \left(1 - \frac{\int_0^x \frac{e^{\int_0^y \frac{h_n(s,n_{ji}(s,t))}{a(s)}ds}}{a(y)}dy}{\int_0^L \frac{e^{\int_0^y \frac{h_n(s,n_{ji}(s,t))}{a(s)}ds}}{a(y)}dy} \right) \geq 0$$

and

$$q_{ij}^0(x,t) = -e^{-\int_0^x \frac{h_n(z,n)}{a(z,t)}\,dz} \int_0^x \frac{e^{\int_0^y \frac{h_n(z,n)}{a(z,t)}\,dz}}{a(y,t)} \left(C + G(y,u_2(t),n_{ij}) + \int_0^y \partial_t F_\tau(z,u_2(t))\,dz \right) dy$$

where

$$C = -\frac{\int_0^{L_{ij}} \frac{e^{\int_0^y \frac{h_n(z,n)}{a(z,t)}\,dz}}{a(y,t)} \left(G(y,u_2(t),n_{ij}) + \int_0^y \partial_t F_\tau(z,u_2(t))\,dz \right) dy}{\int_0^{L_{ij}} \frac{e^{\int_0^y \frac{h_n(z,n)}{a(z,t)}\,dz}}{a(y,t)}\,dy}.$$

Observe that we do not control the sign of C and q_{ij}^0 without further hypotheses on the derivatives of the parameters (3.6).

Lemma 3.5.6. *Let $t \geq 0$ and $c_{ij} > 0$. Let $n_{ij}(t), \tilde{n}_{ij}(t) \in C([0,L])$ be such that*

$$-\varepsilon_1 < n_{ij}(t), \tilde{n}_{ij}(t) \quad \textit{in } [0,L].$$

If $n_{ij}(x,t)$ and $\tilde{n}_{ij}(x,t)$ satisfy (3.81)$_{3,4}$ *with given boundary conditions $(N_i(t), N_j(t))$, respectively $(\tilde{N}_i(t), \tilde{N}_j(t))$ contained in $[-\varepsilon_2, \infty)$ and $J_{ij}(t)$, respectively $\tilde{J}_{ij}(t)$, satisfy* (3.81)$_4$*, then there exists a constant C such that*

$$|n_{ij}(x,t) - \tilde{n}_{ij}(x,t)|,\ |J_{ij}(t) - \tilde{J}_{ij}(t)| \leq C\left(|N_i(t) - \tilde{N}_i(t)| + |N_j(t) - \tilde{N}_j(t)| \right). \tag{3.96}$$

Proof. Following the argument in Lemma 1.5.2 it suffices to observe that the transport term $h(x,u_2(t),n)$ is Lipschitz continuous in n uniformly in t by the boundedness of u_2 (which follows from (2.217)) and γ_1 by hypothesis (iii). □

The regularity properties of u_2 developed in Section 2.7 play a key role in the following Lemma, as they allow us to obtain uniform estimates.

Lemma 3.5.7. *Let $t \geq 0$ and $c_{ij} > 0$ and let $n_{ij}(t), \tilde{n}_{ij}(t) \in C([0,L])$ be as in Lemma 3.5.6. Let $q_{ij} = (n_{ij})_t$ and $\tilde{q}_{ij} = (\tilde{n}_{ij})_t$, and let $q_{ij}^i(t)$, $q_{ij}^j(t)$ and $q_{ij}^0(t)$ respectively $\tilde{q}_{ij}^i(t)$, $\tilde{q}_{ij}^j(t)$ and $\tilde{q}_{ij}^0(t)$ be defined by* (3.90)*. Then there exists a constant C such that*

$$|q_{ij}^i(x,t) - \tilde{q}_{ij}^i(x,t)|,\ |q_{ji}^i(t) - \tilde{q}_{ji}^i(t)|,\ \ |q_{ij}^0(x,t) - \tilde{q}_{ij}^0(x,t)| \leq C\left(|N_i(t) - \tilde{N}_i(t)| + |N_j(t) - \tilde{N}_j(t)| \right). \tag{3.97}$$

Proof. The result follows from the proof of Lemma 3.5.5 where we observe that $n \mapsto h_n(x,u_2(t),n)$ is Lipschitz continuous uniformly in time by the boundedness of u_2 ((2.217)) and γ_1 (iii). Concerning the estimate for q_{ij}^0, by Lemma 3.5.5 it follows that q_{ij}^0 is Lipschitz continuous in n uniformly in time since both $\partial_t u_2$ and γ_1' are bounded (see Section 2.7 and (iii)). □

We now proceed by defining the integral operator associated to the equations (3.79). Let $0 < \tau < T$ and consider the space $X_\tau := \{N \in C^0([0,\tau];\mathbb{R}^h)\}$. As in Chapter 1, we first show that the system admits a solution on a closed ball.

Theorem 3.5.8. *Let the hypotheses of Theorem 3.5.1 be satisfied. Then there exists $\tau > 0$ such that the quasi-static $A\beta$-dependent NTM possesses a unique solution which is defined for $t \in [0,\tau]$ and is not necessarily nonnegative.*

Proof. Let $N_{0i} \geq 0$ for all $i \in V$. Let $\rho > 0$ and

$$X_{\rho,\tau} := \{N \in C^0([0,\tau];\mathbb{R}^h); -\rho \leq N_i(t) - N_{0i} \leq \rho \text{ for all } i \in V, t \in [0,\tau]\}.$$

Let $(N_1, \dots, N_h) \in X_{\rho,\tau}$. By definition of $X_{\rho,\tau}$, N_i is uniformly bounded for all $i \in V$. By Lemma 3.5.2, there exists $n_{ij}(0)$ at initial time which satisfies (3.83) and the mass defined by (3.82) is finite. By Lemma 3.5.4 if ρ is small enough then there exists $n_{ij} \in C([0, L_{ij}] \times [0,\tau])$ which is uniformly bounded. By Lemma 3.5.7 and (iii) the terms $\mathcal{H}^i_{ij}(t)$, $\mathcal{H}^j_{ij}(t)$, $\mathcal{K}^i_{ji}(t)$, $\mathcal{K}^j_{ji}(t)$, $\mathcal{K}^0_{ji}(t)$ and $\mathcal{H}^0_{ij}(t)$ are uniformly bounded, which implies uniform boundedness of the coefficients of the matrix $A(t)$. Now by (iv) for all $t \in [0,\tau]$ there exists $A(t)^{-1} \in \mathbb{R}^{h\times h}$ and its coefficients are uniformly bounded. Indeed by the Cramer's rule we have

$$A(t)^{-1} = \frac{1}{\det A(t)} \text{adj}(A(t)) \tag{3.98}$$

where adj$(A(t))$ is the adjugate matrix of $A(t)$ whose entries are polynomials of degree $h-1$ in the coefficients of $A(t)$.

Based on the structure of system (3.60), we define the operator

$$\Phi(N(t)) = (\tilde{N}_1(t), \dots \tilde{N}_h(t)), \tag{3.99}$$

$$\tilde{N}_i(t) = N_{0i} + \int_0^t (\mathcal{A}_N(s) b(s, N(s)))_i \, ds,$$

where

$$\mathcal{A}_N \in C^0([0,\tau];\mathbb{R}^{h\times h}), \quad \mathcal{A}_N : t \longrightarrow A(t, N(t))^{-1}, \tag{3.100}$$

and we recall that

$$\begin{aligned} b_i(t, N_1(t), \dots, N_h(t)) &= \sum_{j\sim i} (-c_{ij} J_{ij}(0,t) + c_{ji} J_{ji}(L_{ji}, t)) \\ &- \sum_{j \sim i} \left(c_{ji}\mathcal{K}^0_{ji}(t) + c_{ij}\mathcal{H}^0_{ij}(t)\right) - Vol(i) \frac{u_2'(t)\gamma_1'(u_2(t))N_i(t)}{\beta}. \end{aligned} \tag{3.101}$$

Concerning the invariance property of Φ, we observe that

$$\begin{aligned} |\tilde{N}_i(t) - N_{0i}| &\leq \int_0^t |\mathcal{A}_N(s) b(s, N(s))_i| \, ds = \int_0^t \left| \sum_{j=1}^h A^{-1}_{ij}(s, N(s)) b_j(s, N(s)) \right| ds \\ &\leq t \sup_{s\in[0,t]} \sum_{j=1}^h \left| A^{-1}_{ij}(s, N(s)) b_j(s, N(s)) \right| \leq t \frac{C_\rho}{C_A} \end{aligned} \tag{3.102}$$

where the last inequality follows from (3.98), Lemma 3.5.6 and Lemma 3.5.7 with $\tilde{N}_i = \tilde{N}_j = 0$ and $(iii) - (iv)$. By finiteness of the initial mass and boundedness of the production terms F_τ, F_i, we can also choose τ small enough such that $t \mapsto \Phi(N)(t)$ is continuous on $[0,\tau]$. Therefore by (3.102) we have $\Phi(X_{\rho,\tau}) \subset X_{\rho,\tau}$ if τ is small enough.

Let $N^1, N^2 \in X_{\rho,\tau}$. We have

$$||\Phi(N^1(t)) - \Phi(N^2(t))||_{\mathbb{R}^h} \leq \int_0^t \left\| \mathcal{A}_{N^1}(s) b(s, N^1(s)) - \mathcal{A}_{N^2}(s) b(s, N^2(s)) \right\|_{\mathbb{R}^h} ds \tag{3.103}$$

$$\leq \int_0^t \left\| \mathcal{A}_{N^1}(s) \left(b(s, N^1(s)) - b(s, N^2(s))\right) \right\|_{\mathbb{R}^h} ds + \int_0^t \left\| \left(\mathcal{A}_{N^1}(s) - \mathcal{A}_{N^2}(s)\right) b(s, N^2(s)) \right\|_{\mathbb{R}^h} ds =: I_1 + I_2.$$

The integral I_1 rewrites as

$$\begin{aligned}
&\int_0^t \left\| A(s,N^1(s))^{-1}\left(b(s,N^1(s)) - b(s,N^2(s))\right)\right\|_{\mathbb{R}^h} ds \qquad (3.104)\\
&\leq \int_0^t \left\| A(s,N^1(s))^{-1}\right\|_2 \left\| b(s,N^1(s)) - b(s,N^2(s))\right\|_{\mathbb{R}^h} ds\\
&\leq \int_0^t \left\| A(s,N^1(s))^{-1}\right\|_F \left\| b(s,N^1(s)) - b(s,N^2(s))\right\|_{\mathbb{R}^h} ds\\
&\leq C_\rho \int_0^t \sqrt{\sum_{i,j=1}^h (A^{-1})^2_{ij}(s,N^1(s))} \left\| N^1(s) - N^2(s)\right\|_{\mathbb{R}^h} ds \leq t\frac{C_\rho}{C_A}\max_{s\in[0,\tau]}\left\| N^1(s) - N^2(s)\right\|_{\mathbb{R}^h},
\end{aligned}$$

where the last inequality follows from (3.98), Lemma 3.5.6, Lemma 3.5.7 and $(iii)-(iv)$. Concerning I_2, we have:

$$\begin{aligned}
&\int_0^t \left\| (\mathcal{A}_{N^1}(s) - \mathcal{A}_{N^2}(s))\, b(s,\tilde{N}^2(s))\right\|_{\mathbb{R}^h} ds \leq \int_0^t \left\| A^{-1}(s,N^1(s)) - A^{-1}(s,N^2(s))\right\|_2 \left\| b(s,N^2(s))\right\|_{\mathbb{R}^h} ds \qquad (3.105)\\
&= \int_0^t \left\| A^{-1}(s,N^1(s))\left[A(s,N^2(s) - A(s,N^1(s))\right] A^{-1}(s,N^2(s))\right\|_2 \left\| b(s,N^2(s))\right\|_{\mathbb{R}^h} ds\\
&\leq \int_0^t \left\| A^{-1}(s,N^1(s))\right\|_2 \left\| A(s,N^2(s) - A(s,N^1(s))\right\|_2 \left\| A^{-1}(s,N^2(s))\right\|_2 \left\| b(s,N^2(s))\right\|_{\mathbb{R}^h} ds\\
&\leq \frac{C_\rho}{C_A}\int_0^t \left\| A(s,N^2(s)) - A(s,N^1(s))\right\|_2 ds \leq \frac{C_\rho}{C_A}\int_0^t \left\| A(s,N^2(s)) - A(s,N^1(s))\right\|_F ds\\
&= \frac{C_\rho}{C_A}\int_0^t \sqrt{\sum_{i,j=1}^h \left(A_{ij}(s,N^2(s)) - A_{ij}(s,N^1(s))\right)^2} ds \leq t\frac{C_\rho}{C_A}\max_{s\in[0,\tau]}\left\| N^1(s) - N^2(s)\right\|_{\mathbb{R}^h}.
\end{aligned}$$

Combining (3.102), (3.104) and (3.105) we conclude that Φ is a contraction on $X_{\rho,\tau}$ is τ is sufficiently small. Hence we obtain a local solution $N \in C^0([0,\tau];\mathbb{R}^h)$ for the Aβ-dependent *NTM*. □

The local edge solution n we obtain through Theorem 3.5.8 exhibits the same positivity properties of Lemma's 1.6.1 and 1.6.2. However, the structure of the matrix A does not suggest a straightforward positivity result for N on the nodes as in Lemma 1.6.3.

Lemma 3.5.9. *Let $t \geq 0$ be fixed, let $\gamma_2 \geq 0$, $i \neq j$ and $c_{ij} > 0$. Let $N_i(t), N_j(t) \geq 0$ and $J_{ij} := J_{ij}(0,t)$ be given numbers and let $n_{ij} = n_{ij}(t) \in C([0,L_{ij}])$ satisfy* (3.81)*: $a(x,u_2)(n_{ij})_x + h(x,u_2,n_{ij}) = -J_{ij} - \int_0^x F_\tau(y,u_2)\,dy$ in $\mathcal{D}'(0,L_{ij})$ where $\int_0^{L_{ij}} F_\tau(y,u_2)\,dy > 0$.*

(i) If $J_{ij} = 0$, then $n_{ij}(x,t) > 0$ for $x \in [0,L_{ij}]$; in particular, $N_i(t) > 0$ and $N_j(t) > 0$;

(ii) If $J_{ij} > 0$, then $n_{ij}(x,t) > 0$ for $0 \leq x < L_{ij}$; in particular $N_j(t) > 0$;

(iii) If $J_{ij} < 0$, then $n_{ij}(x,t) > 0$ for $0 < x \leq L_{ij}$; in particular $N_i(t) > 0$.

In particular

$$n_{ij}(x,t) \geq 0 \quad \textit{for all } x \in [0,L_{ij}],\ t \geq 0. \qquad (3.106)$$

Proof. (i) Let $J_{ij} = 0$. Then $a(x, u_2)(n_{ij})_x = -\int_0^x F_\tau(y, u_2)\, dy \leq 0$. Arguing by contradiction we suppose that $n_{ij} = 0$ at some $y_0 \in (0, L_{ij})$. Since $h(x, u_2, 0) = 0$, $a(x, u_2)(n_{ij})_x \leq 0$ at $x = y_0$, whence $n_{ij} \leq 0$ in $(y_0, L_{ij}]$ and $n_{ij} < 0$ in $(y_1, L_{ij}]$ for some $y_0 < y_1 < L_{ij}$. Since $N_j \geq 0$ we have found a contradiction. If $N_i = 0$ then $n_{ij} \leq 0$ at some $y_0 \in (0, x_1)$, which is impossible.

The proof of (ii) is similar to the proof of (ii) in Lemma 1.6.1.

(iii) We consider the case (a): $J_{ij}(x) \leq 0$ for all $x \in [0, L_{ij}]$, (b): there exists $\bar{x}$ such that $J_{ij}(x) < 0$ at $[0, \bar{x})$ and $J_{ij}(x) > 0$ at $(\bar{x}, L_{ij}]$. The proof for (a) is similar to (ii).

(b): Arguing by contradiction, we suppose that $n_{ij} = 0$ at some $y_0 \in (0, L_{ij}]$. Then $a(y_0, u_2)(n_{ij})_x > 0$ at $x = y_0$ if $y_0 \in (0, \bar{x})$ and $a(y_0, u_2)(n_{ij})_x < 0$ at $x = y_0$ if $y_0 \in (\bar{x}, L_{ij}]$. Since $a(x, u_2)(n_{ij})_x \leq 0$ in $[\max\{\bar{x}, x_3\}, L_{ij}]$, $y_0 \in (0, \bar{x})$. Since $a(y_0, u_2)(n_{ij})_x > 0$ at $x = y_0$, $n_{ij} < 0$ for all $x \in [0, y_0)$, which contradicts the hypothesis $N_i \geq 0$. □

Recalling that the flux on the edge e_{ij} satisfies

$$J_{ij}(x,t) = J_{ij}(0,t) + \int_0^x F_\tau(y, u_2)\, dy, \quad F_\tau \geq 0,$$

we obtain the following:

Corollary 3.5.10. *Let $t \geq 0$ be fixed and $i \neq j$, $c_{ij} \neq 0$. Let $N_j(t) \geq 0$ and*

$$N_i(t) = 0.$$

Let $n_{ij}(t) \in C([0, L])$ satisfy $a(x, u_2)(n_{ij})_x + h(x, u_2, n_{ij}) = -J_{ij} - \int_0^x F_\tau(y, u_2)\, dy$ in $\mathcal{D}'(0, L_{ij})$ where $\int_0^{L_{ij}} F_\tau(y, u_2)\, dy > 0$. Then

(i) $J_{ji}(L_{ji}, t) \geq 0$ if $c_{ji} > 0$ and $J_{ij}(0, t) \leq 0$ if $c_{ij} > 0$;

(ii) if $N_j(t) > 0$, then $J_{ji}(L_{ji}, t) > 0$ if $c_{ji} > 0$ and $J_{ij}(0, t) < 0$ if $c_{ij} > 0$.

In particular, if $N_i(t) = 0$ the term $\sum_j (c_{ji} J_{ji}(L_{ji}, t) - c_{ij} J_{ij}(0, t))$ in the i^{th} coordinate of the vector b in (3.60) *is nonnegative for all i; it is strictly positive if there exists $j \neq i$ such that $N_j(t) > 0$ and $c_{ij} > 0$ or $c_{ji} > 0$.*

Remark 3.5.1. *In Chapter 1, Corollary 1.6.2 is sufficient to prove Lemma 1.6.3 and obtain positivity of the local solution. In this setting, let $N_{0i} \geq 0$ and N be a local solution to* (3.60) *such that $N(0) = N_0$. Suppose there exists $t_0 \in (0, \tau)$ such that $N_i(t_0) = 0$. The equation for N at node i yields*

$$\begin{aligned} N_i'(t_0) = A(t_0, N_i(t_0))^{-1} b(t_0) &= \sum_{j=1}^{h} (A^{-1})_{ij}(t_0, N_i(t_0)) b_j(t_0) \\ &= (A^{-1})_{ii}(t_0, N_i(t_0)) b_i(t_0) + \sum_{j \neq i} (A^{-1})_{ij}(t_0, N_i(t_0)) b_j(t_0) \end{aligned} \tag{3.107}$$

where

$$b_i(t_0) = \underbrace{\sum_{j \sim i} \left(-c_{ij} J_{ij}(0, t_0) + c_{ji} J_{ji}(L_{ji}, t_0)\right)}_{>0 \text{ by Corollary 3.5.10}} - \sum_{j \sim i} \left(c_{ji} \mathcal{K}_{ji}^0(t_0) + c_{ij} \mathcal{H}_{ij}^0(t_0)\right)$$

and

$$b_j(t_0) = \sum_{k\sim j} \left(-c_{jk} J_{jk}(0,t_0) + c_{kj} J_{kj}(L_{kj},t_0)\right) - \sum_{k\sim j} \left(c_{kj}\mathcal{K}^0_{kj}(t_0) + c_{jk}\mathcal{H}^0_{jk}(t_0)\right) - Vol(j)\frac{\gamma_1'(t_0)N_j(t_0)}{\beta}.$$

The behaviour of N_i' depends on the net flux at all nodes $j \in V$, the concentrations N_j, the edge feedback terms $\mathcal{K}^0_{kj}$, $\mathcal{H}^0_{jk}$ and the inverse of $A(t_0, N_i(t_0))$, therefore it is not straightforward to establish the expected positive sign of N in the current setting.

3.5.4 Global existence

By Theorem 3.5.8, the Aβ-dependent *NTM* has a local solution defined on the interval $[0,\tau]$. Its total mass is finite and bounded on $[0,\tau]$. We now extend the local solution to the entire interval $[0,T]$, where we recall that T is defined in Chapter 2. Let $[0,T_1)$ be the maximal interval of definition of N, where $T_1 < T$. By hypotheses $(iii) - (iv)$, the map $t \mapsto N_i'(t)$ is bounded for all $i \in V$, and therefore N can be extended to $[0,T_1]$. Applying the local existence argument of Theorem 3.5.8 at $t = T_1$, we can extend N on $[T_1,T_2)$ for some $T_2 \in (T_1,T)$, thus contradicting the maximality of $[0,T_1)$.

3.6 Numerical algorithms and experiments

The structure of the algorithm we implement to solve the time-dependent *NTM* is the same as in Chapter 1. The function `MassBalance` is expanded to include the integration of the equation (3.93)$_1$ and the calculation of the correction terms $\mathcal{H}$ and $\mathcal{K}$.

Algorithm 3: An algorithm for the *NTM*

Input : $(N_i(0))_{i=1}^h$
Output: $(N_i(t))_{i=1}^h$
for $k = 1,\dots,k_{end}$ **do**
  for $(i,j) \in E$ **do**
    $(n_{ij}(t^k), J_{ij}(t^k)) \leftarrow$ *FluxCalculator*$(N_i(t^k))$;
  end
  for $(i,j) \in E$ **do**
    $(q^i_{ij}(t^k), q^j_{ij}(t^k), q^0_{ij}(t^k)) \leftarrow$ *MassBalance*$(n_{ij}(t^k), J_{ij}(t^k))$;
    Calculate $\mathcal{H}^i_{ij}(t^k)$, $\mathcal{H}^j_{ij}(t^k)$, $\mathcal{K}^j_{ji}(t^k)$, $\mathcal{K}^i_{ji}(t^k)$, $\mathcal{H}^0_{ij}(t^k)$, $\mathcal{K}^0_{ji}(t^k)$;
  end
  Update $N_i(t^{k+1})$;
end

The nodal system for N (3.60) can be discretised through different approaches. We update $N_i(t^k)$ via the following procedure

$$\begin{cases} N(t^k) = N(t^{k-1}) + A(t^{k-1})^{-1} b(t^{k-1})\left(t^k - t^{k-1}\right), \\ N(t^0) = N_0, \end{cases} \qquad k = 1,\dots,k_T. \tag{3.108}$$

It follows that the computational cost (1.55) is augmented by the cost of solving the linear system $A(t^k)x = b(t^k)$ at each time step:

$$\mathcal{O}(\underbrace{k_{Newton} \cdot k_{ODE} N_X |E| N_T}_{\text{Edge problem}} + \underbrace{|V|^3 N_T}_{\text{Node problem}}). \tag{3.109}$$

The cost for the resolution of the linear system is theoretically assumed to be $O(|V|^3)$ since the matrix $A(t)$ does not exhibit an evident structure. However we adopt the standard MATLAB backslash operator function which takes advantage of symmetries in the problem and selects the numerical method according to the structure of the matrix. Observe that the corrective terms $\mathcal{H}$ and $\mathcal{K}$ are calculated using the explicit expressions obtained in Section 3.4.1. The integration of the equation for q_{ij}^0 is also straightforward thanks to its linear structure. The computational burden of the model is therefore carried by the `FluxCalculator` function, which executes a shooting procedure to solve the nonlinear equation for n_{ij}, and the linear system $Ax = b$.

3.6.1 Comparison of the different feedback models

We solve the *NTM* of Chapter 1 and the time-dependent *NTM* with constant parameters (3.6) to analyse the mathematical similarities and differences between the *feedback* mechanisms. All numerical simulations of the current Section were performed on the Department of Mathematics of the University of Rome Tor Vergata's high performance computing server, equipped with two 18-cores *Intel Xeon* 5220 CPUs (2.2 GHz, 36 cores total), 384 GB DDR4 RAM and Debian GNU/Linux as operating system.

We select a weighted directed 5-node network endowed with 15 edges generated with the MATLAB function `sprand`, which creates random matrices with uniformly distributed non-zero entries. The initial seeding node is selected by calculating the centrality *outdegree* measure of the nodes, that is, for each node $i \in V$ we calculate $\deg_{out}(i) := \sum_{j\sim i} c_{ij}$ and choose as seeding node one of the nodes exhibiting the highest $\deg_{out}$. Following the approach of [91], we simulate the models in the relevant cases of varying the strength of the diffusion barrier λ_1 and λ_2 and the aggregation rate γ_1. The remaining parameters are set as in Table 1.1. Specifically, to remove the singularity and avoid numerical instabilities, we set $\gamma_2 = 0$. The models are solved on the time scale of 6 months.

1. **Varying $\boldsymbol{\lambda_1}$ and $\boldsymbol{\lambda_2}$**

   Figure 3.1 shows the temporal evolution of the concentrations of total Tau ($Vol(i)\,(M_i + N_i)$) on each node of the graph. The time-dependent *NTM* generally exhibits a faster evolution than the standard *NTM*, as shown in Figure 3.1. This behaviour reflects the increased dynamical interaction between the node variables introduced by the new *feedback* corrections of Section 3.4.1. The simulation also suggests a modification of the final equilibrium: as illustrated in the first row of Figure 3.1, the nodal concentrations of the new model exhibit greater spatial variability at the final simulation time. In the same simulation, the qualitative behaviour also appears to be affected by the new *feedback* formulation, with curves losing their monotonic tendency and resulting in richer dynamics.

   As shown in [91], a reduction in the diffusion barrier parameters λ_1 and λ_2 results in a slower overall rate of Tau spreading on the network in both the original *NTM* and the new model, while reproducing the same spatial behaviour, thus showing that the *feedback* correction of Chapter 3 preserves the qualitative dependence of the original model on the diffusion barrier parameters.

2. **Varying $\boldsymbol{\gamma_1}$** Figures 3.2 and 3.3 show the effect of γ_1 on the models' evolution. As in the previous case, the overall rate of spreading of the new model is slightly faster than the original one, with a

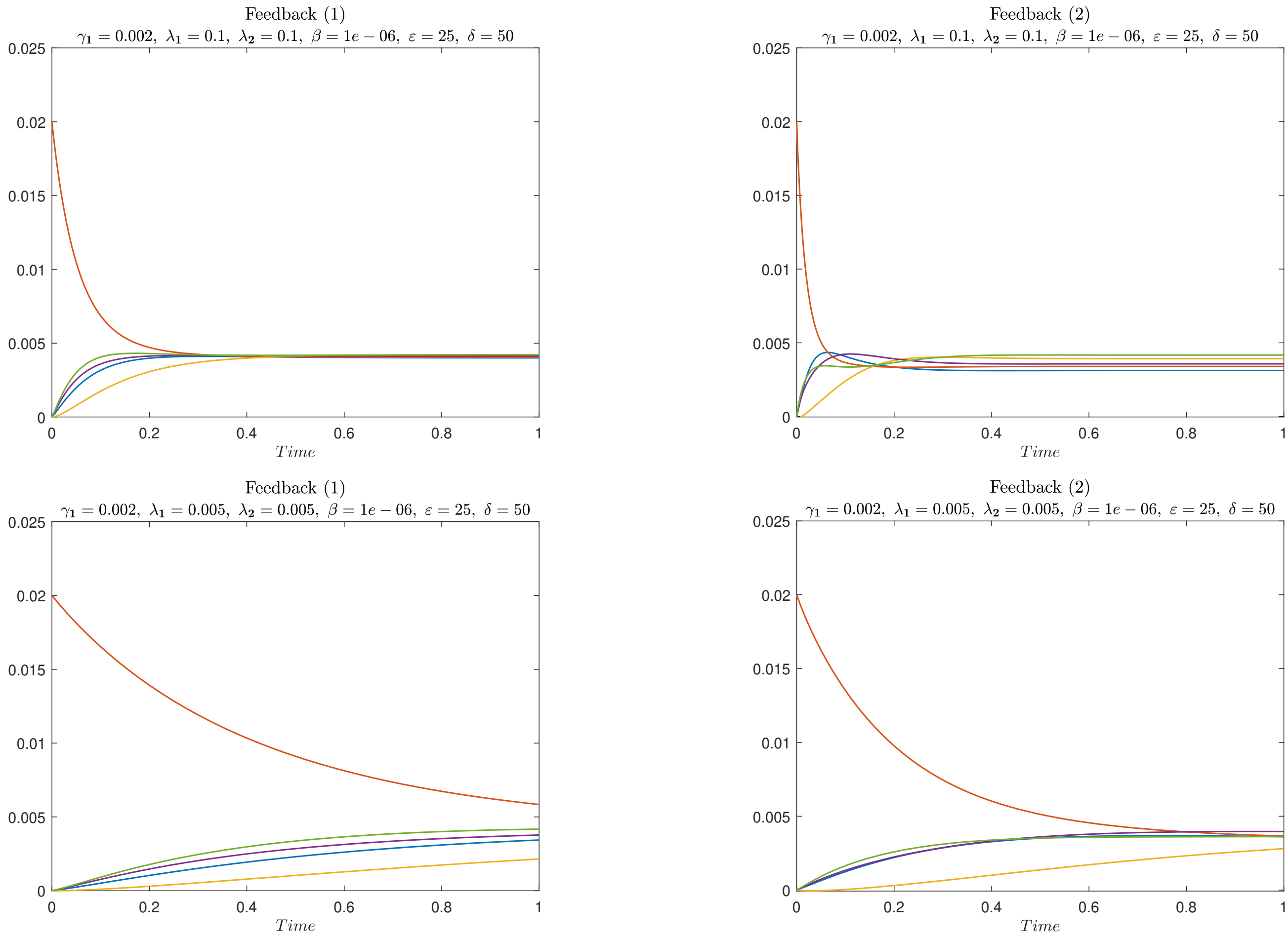

Figure 3.1: Comparison between the *NTM* with the *feedback* mechanism of Chapter 1 (1^{st} column) and Chapter 3 (2^{nd} column) with one seeding node. $Time = 1$ corresponds to $t = 6$ months. 1^{st} row: $\lambda_1 = \lambda_2 = 0.1$, 2^{nd} row: $\lambda_1 = \lambda_2 = 0.005$.

more pronounced effect in the case of $\gamma_1 = 0.001$. Moreover, the spatial spread of the associated equilibrium appears to be wider in the new *feedback* formulation.

Similarly to the effect observed when increasing λ_1 and λ_2, the rate of spread of Tau increases when reducing γ_1 from 0.008 to 0.001. The simulations show that the improved *feedback* mechanism preserves the effects of the aggregation rate γ_1 on the global dynamics of the model observed in [91].

3.6.2 Implementation details

In this Section, we discuss some numerical technicalities that validate the simulations showed in Section 3.6.

One of the main assumptions we needed to prove the existence of a solution to (3.79)-(3.80) is the invertibility of the matrix A. For each of the simulations of Section 3.6.1 we calculate the spectrum of A, here denoted by $\Lambda(A)$, at each time step and compute

$$\Sigma(A)(t) := \{|\lambda(t)|, \, \lambda(t) \in \Lambda(A(t))\}.$$

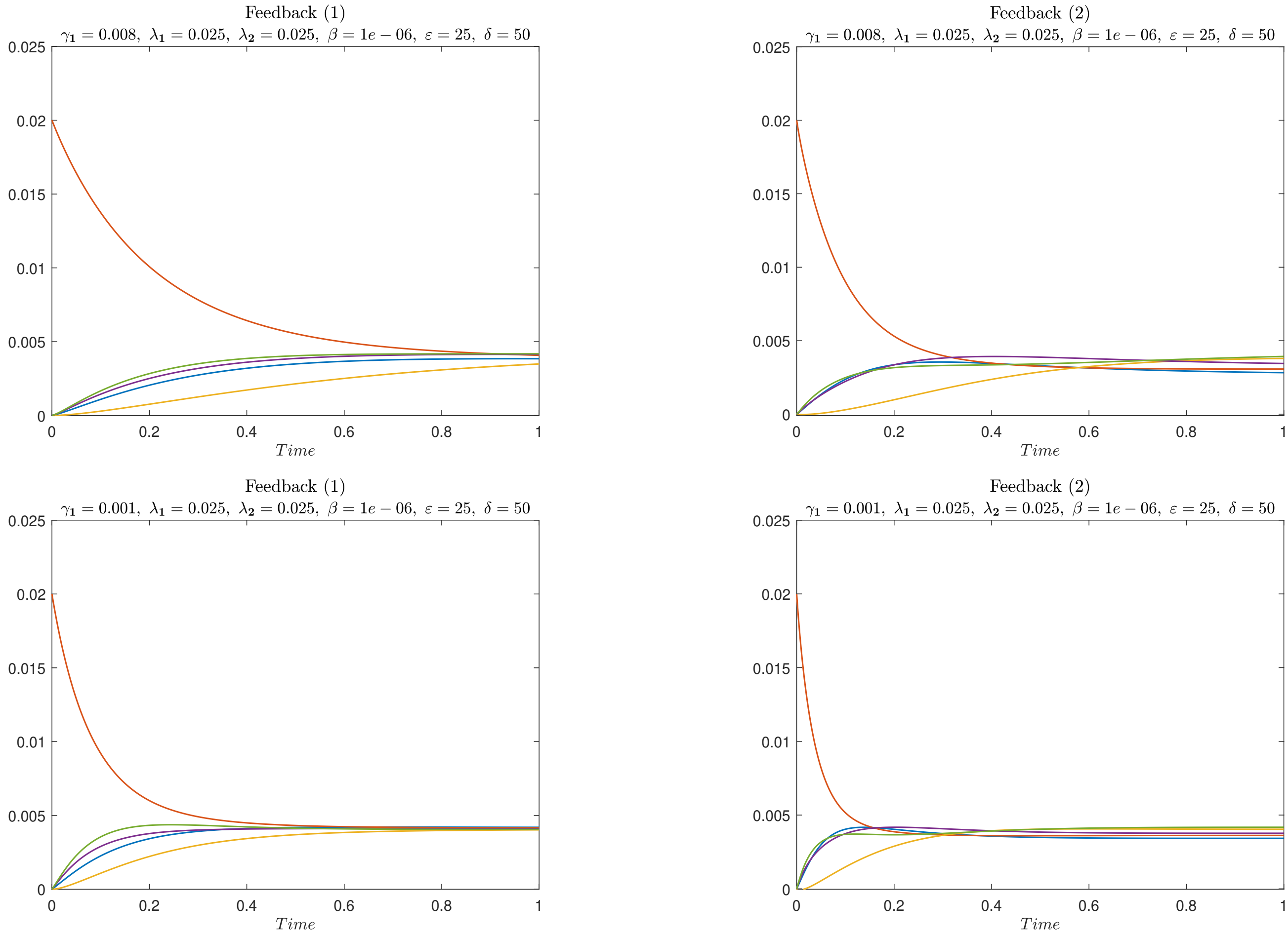

Figure 3.2: Comparison between the *NTM* with the *feedback* mechanism of Chapter 1 (1^{st} column) and Chapter 3 (2^{nd} column) with one seeding node. $Time = 1$ corresponds to $t = 6$ months. 1^{st} row: $\gamma_1 = 0.008$, 2^{nd} row: $\gamma_1 = 0.001$.

Figure 3.4 shows the temporal evolution of $\Sigma(A)$ in agreement with the hypothesis of $\det(A(t)) > 0$ for all $t \in [0, T]$.

We have previously observed that the main computational burden is related to solving the linear system $Ax = b$ and performing the shooting procedure on each edge of the network. We evaluate the error on the integration of system (3.60) by calculating the total network flux and showing that it satisfies

$$\sum_{i \in V} \sum_{j \sim i} c_{ji} J_{ji}(L_{ji}, t^k) - c_{ij} J_{ij}(0, t^k) = 0 \quad k = 1, \dots, k_T \tag{3.110}$$

where the RHS is zero because in the simulations of Section 3.6.1 we set $F_\tau = F_i \equiv 0$ and by calculating the residual associated to the nonlinear equation for n_{ij}:

$$r(t^k) := \max_{e_{ij} \in E_c} |\hat{n}_{ij}(L_{ij}, t^k; \hat{J}_{ij}(0, t^k)) - N_j(t^k)|, \quad k = 1, \dots, k_T, \tag{3.111}$$

where $\hat{n}_{ij}(L_{ij}, t^k; \hat{J}_{ij}(0, t^k))$ is the computed solution on the edge e_{ij} at time-step $t = t^k$ with flux at $x = 0$ equal to $\hat{J}_{ij}(0, t^k)$. Here, the quantity $\hat{J}_{ij}(0, t^k)$ is the shooting parameter obtained by solving the nonlinear equation $\hat{n}_{ij}(L_{ij}, t^k; \hat{J}_{ij}(0, t^k)) - N_j(t^k) = 0$, hence the definition of the residual $r(t^k)$ is consistent. After then, we calculate $\max_{k=1,\dots,k_{end}} r(t^k)$. The error calculations are reported in Tables 3.1 and 3.2.

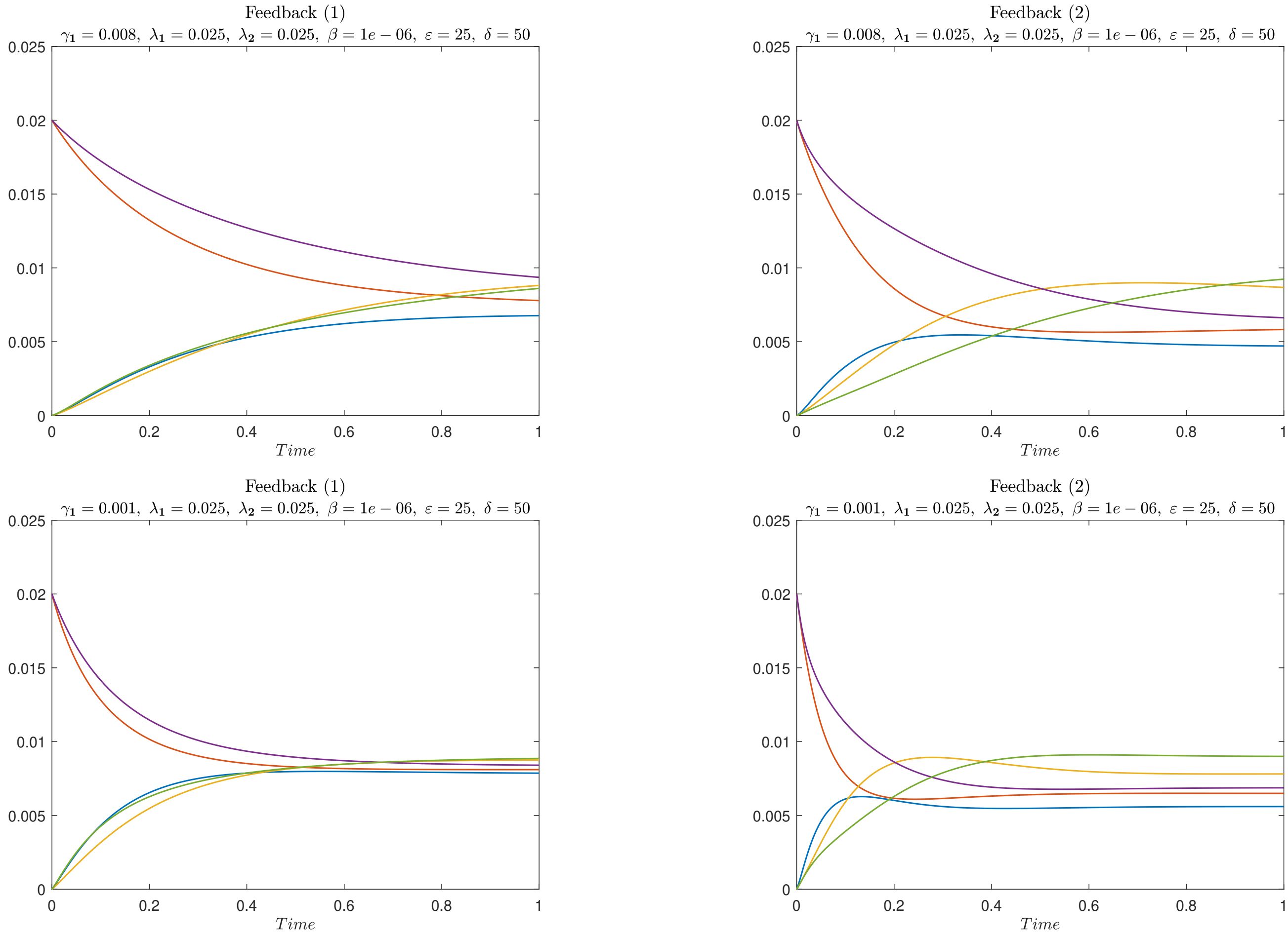

Figure 3.3: Comparison between the *NTM* with the *feedback* mechanism of Chapter 1 (1^{st} column) and Chapter 3 (2^{nd} column) with two seeding nodes. $Time = 1$ corresponds to $t = 6$ months. 1^{st} row: $\gamma_1 = 0.008$, 2^{nd} row: $\gamma_1 = 0.001$.

3.7 Limitations and future developments

In the present Chapter we considered the interaction between Beta Amyloid and Tau proteins by inserting time-dependent parameters in both the node and edge equations of the *NTM* developed in Chapter 1. While the presence of temporal evolving parameters at node level does not yield difficulties in establishing the model equations, the occurrence of dynamical processes along the edges induces a technical limitation in the formulation of the mass balance between each node and its incident edges. Admitting time-dependent parameters on the edge defines an additional term in the variation of the edge mass which cannot be split between the corresponding external nodes in a natural way, thus leaving an undefined nodal mass distribution in the quasi-static formulation of the model. In view of this limitation, since the

Residual					
Sim 1	Sim 2	Sim 3	Sim 4	Sim 5	Sim 6
9.9747×10^{-18}	1.1926×10^{-17}	4.7054×10^{-17}	9.9747×10^{-18}	9.9747×10^{-18}	3.8598×10^{-18}

Table 3.1: Computed residual as in Definition (3.111).

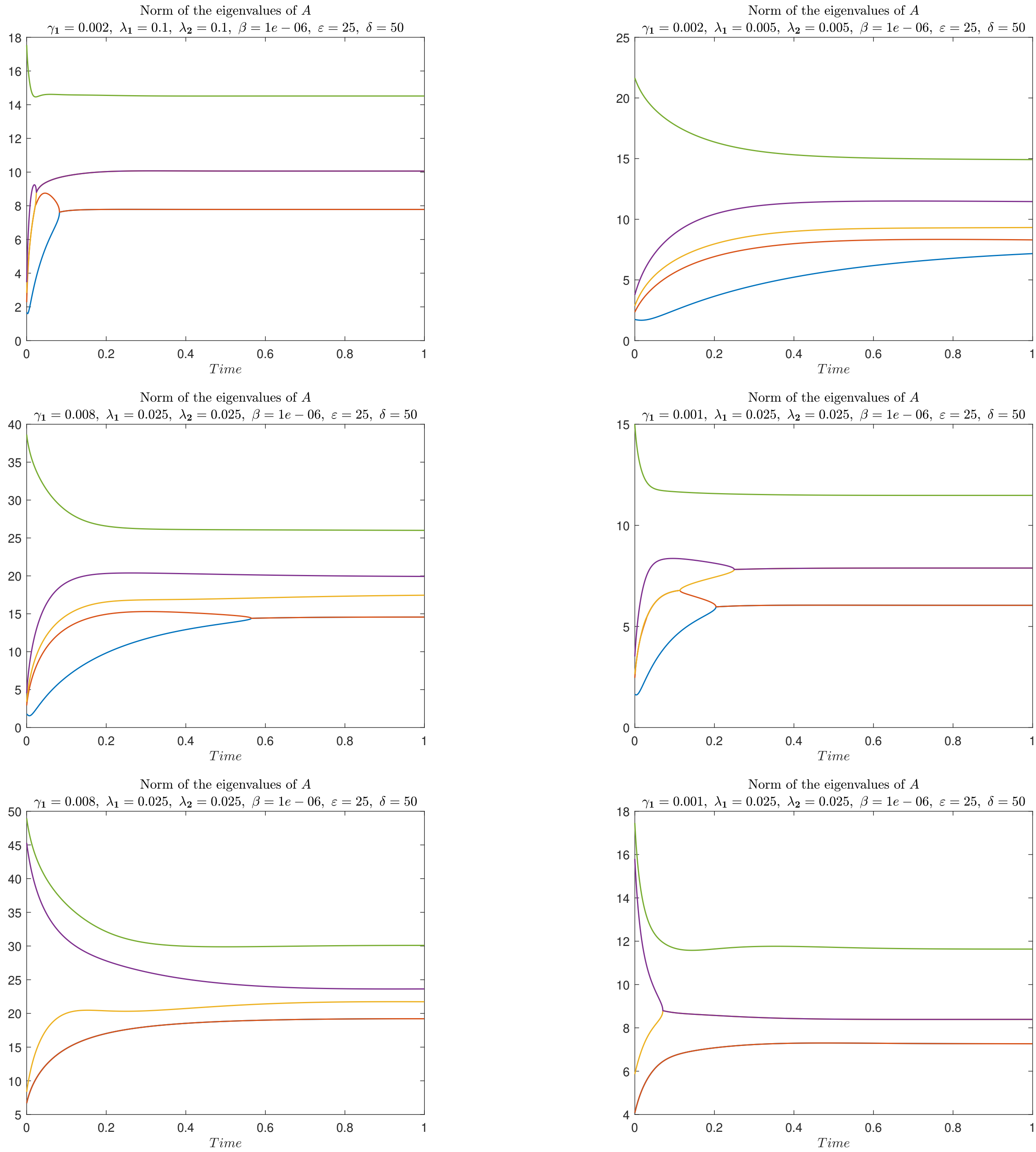

Figure 3.4: Evolution in time of the norm of the eigenvalues of A in each simulation.

equations of the full PDE-*NTM* are defined in the case of time-dependent parameters, we considered the effective time evolution of its solution by decomposing the edge profile n_{ij} as the sum of its evolving equilibrium and the "remainder" function u_{ij}. Formulating the PDE-*NTM* in this framework allowed us to correctly recover the time evolution of the flux of u_{ij}, which defines the *feedback* mechanism of the quasi-static model.

We developed a first approximation of the fluxes of u_{ij} at $x = 0$ and $x = L_{ij}$. The calculations

Total Network Flux					
Sim 1	Sim 2	Sim 3	Sim 4	Sim 5	Sim 6
2.0817×10^{-17}	8.3267×10^{-17}	1.1102×10^{-16}	5.5511×10^{-17}	4.1633×10^{-17}	8.3267×10^{-17}

Table 3.2: Computed net flux as in Definition (3.110).

we provided are formal and are based on the assumptions of fast convergence of u_{ij} to an equilibrium and vanishing terms of order $O(\phi_0)$ in the nonlinear equilibrium system associated to u_{ij}. Although the issue of recovering the exact limit remains to be addressed, these assumptions allowed us to obtain an explicit calculation of the *feedback* mechanism and investigate its dependence on the neighbouring nodal concentration of Tau.

The resulting system is a set of ODEs for the node concentrations N_i which are coupled by means of the net incoming flux $\sum_j c_{ji} J_{ji}(L_{ji}, t) - c_{ij} J_{ij}(0, t)$, as in Chapter 1, and the newly introduced dependence of the *feedback* mechanism at node P_i on the variation of N_j for all $P_j \sim P_i$. This behaviour portrays the action of neighbouring nodes on P_i and their effect is described by the matrix A.

We provided an application to the case of Aβ-dependent parameters by considering the model developed in Chapter 2. We assumed that soluble Aβ oligomers enhance Tau aggregation, hyperphosphorylation and spread by considering u_2-dependent parameters (3.6). In this setting, we proved the existence of a solution to the Aβ-*NTM* on the interval $[0, T]$. The existence argument is based on some *ad hoc* assumptions on the model parameters and variables. For example, by hypothesis (iv) we require uniform invertibility of the matrix A. Hence a further analysis should deal, for instance, with the estimate of the spectrum of A as a function of the parameters.

The purpose of this Chapter is to analyse the *feedback* mechanism problem in the case of time-dependent parameters and to provide a general theoretical framework to approximate the exact corrective terms yielded by the PDE-*NTM*. In terms of applicability of the model, we showed some numerical experiments highlighting a wide range of variability with respect to the model parameters. A comparison with the original *NTM* developed in Chapter 1 shows some differences in both the spatial and temporal evolution of the models, while preserving some of the dependencies analysed in [91]. Unlike the original *NTM*, the new model also does not exhibit evident positivity properties. A further drawback of the new *NTM* is the increased computational cost associated with solving the linear system in (3.60), suggesting the need for a refinement of the model algorithm and implementation.

From a mathematical point of view, the formal derivation of the “correct” feedback mechanism is important, but, in view of the serious drawbacks mentioned before, it is not clear if it is worthwhile to face the many questions which are left open, in particular the identification of numerous parameter values by comparison with real data and the possible extensions of the model which are of biological interest, such as the modelling of a reciprocal interaction between Aβ and Tau proteins and their involvement in inflammatory processes affecting the Alzheimer’s brain. Instead it seems to be more promising to change the model in an appropriate manner to avoid the feedback mechanisms. In the following Chapter we present a first proposal in this direction.

Chapter 4

A Release-Uptake Network-Transport Model

In this Chapter, we present a variation of the Network-Transport model (*NTM*) introduced in Chapter 1 by extending it to account for the processes of Tau Release and Uptake on the *connectivity* graph. These mechanisms establish a novel mass exchange dynamics between the edges and nodes of the network which is structurally different from the framework developed in Chapter 1. By applying the multiscale formalism introduced in Chapter 3, we show that the resulting quasi-static model does not exhibit a *feedback* phenomenon, which considerably simplifies both its mathematical analysis and its numerical simulations. These positive effects become even stronger when we describe the reciprocal interaction between Tau and Beta Amyloid by coupling the Release-Uptake *NTM* with the Aβ model developed in Chapter 2.

4.1 Introduction and biological setting

The spread of pathological Tau is a defining feature of tauopathies such as Alzheimer's disease and frontotemporal dementia. The propagation occurs in a prion-like fashion, which consists of an amplified action of an assembled toxic protein to induce the same a-physiological conformation in a protein assembly of the same type [37]. Prion-like propagation does not exert itself solely as passive diffusion along neuronal tracts but instead arises as a combination of *intracellular* transport and *transcellular* exchange between neurons. In particular, misfolded Tau can be released from affected neurons in the extracellular space and can be subsequently recruited by neighbouring cells [18],[37],[105], thus undergoing the processes of *release* and *uptake*.

Although the *Network Transport Model* introduced in Chapter 1 captures the large-scale diffusion of Tau pathology along the brain's structural connectivity, it represents Tau as a single species confined to neuronal connections. This formulation does not account for the extracellular phase of the Tau dynamics nor for the regulatory role of the neuronal plasma membrane, which mediates the exchange of Tau between the intracellular and extracellular compartments. However, the extracellular pool of Tau is progressively recognised as a critical mediator of disease progression. It facilitates the transneuronal propagation of misfolded species [96] and interacts with glial cells, initiating neuroinflammatory responses that may contribute to neuronal dysfunction [70].

In this Chapter, we introduce a new formulation of the *NTM* - the *Release-Uptake Network Transport Model* - which explicitly distinguishes between intracellular and extracellular Tau species and couples them through fluxes at the cell boundary. The model captures intracellular active transport, diffusion and aggregation-fragmentation dynamics along the edges of the *connectivity* graph, while extracellular spread and accumulation occur at the node level. The mass exchange between these compartments is mathematically described through Neumann-Robin-type boundary conditions involving intracellular and extracellular soluble Tau at the endpoint of each edge. This formulation identifies the release-uptake mechanism as a potential *bottleneck* of global Tau propagation and provides a general framework for analysing how molecular transport, aggregation and boundary exchange influence the evolution of Tau pathology on the brain.

The mathematical formulation of the model is developed in Section 4.2 together with a formal description of the mass transfer between nodes and edges in the quasi-static approximation. In addition to a variation of the boundary conditions for the edge problem, the model exhibits a further mathematical novelty consisting of the vanishing *feedback* mechanism. Assuming that the release-uptake process is a phenomenon occurring on the slow timescale, we show that in the quasi-static limit the mass exchange between nodes and edges is solely determined by the fluxes of intracellular Tau at the interface. The resulting model therefore simplifies the formulation of the *NTM* and reduces its mathematical and computational complexity.

In Section 4.3 we extend the model by coupling the Tau system with a model for Beta Amyloid on the *proximity* graph. We assume, as in Chapter 3, that soluble Beta Amyloid enhances Tau aggregation, diffusion and misfolding (for details, see Section 3.1). However, in this Chapter we deal with the synergistic interplay between the two proteins, thus assuming a bidirectional interaction. Specifically, we assume that the rate of neuronal degeneration depends on the concentration of extracellular soluble Tau [23]. Moreover, the release-uptake parameters governing Tau exchange across the cell membrane are modulated by soluble Aβ levels [104]. This coupling increases the mathematical complexity of the resulting model which requires a detailed analysis to prove the existence of a solution.

4.2 The Release-Uptake model for Tau

Let $G_c = (V, E_c)$ be the *connectivity* graph described in Chapter 1. In this Section, we introduce a new model for the spread of Tau protein on G_c as a variation of the standard *NTM* introduced in Chapter 1. The species we are concerned with are both intracellular and extracellular Tau. We first adopt a slightly different interpretation of the underlying network structure. The edges of the graph (i.e., white matter tracts of the brain) represent bundles of connected neurons with independent Tau dynamics, as in Chapter 1, and thus intracellular soluble and insoluble Tau are located on those connections. Conversely, nodes are considered to host extracellular soluble and insoluble Tau species and are identified with extracellular compartments. In view of this biological interpretation, we introduce a compartmentalisation of the edges characterised by distinct Tau dynamics. We distinguish three different segments:

(i) **Presyn. SD**: presynaptic somatodendritic compartment, $(0, x_1)$,

(ii) **AIS**: axon initial segment, (x_1, x_2),

(iii) **Axon**: axonal component, (x_2, L_{ij}),

where the interval $[0, L_{ij}]$ is identified with the edge e_{ij} for all $e_{ij} \in E_c$. This construction differs from the one introduced in [92] and adopted in Chapters 1 and 3 by the collapse of the synaptic and postsynaptic somatodendritic compartments at the endpoint node of each directed edge. This choice is consistent with the novel interpretation of the nodes of the network.

Here, we model the spread of intracellular Tau by means of active transport and passive diffusion and the aggregation and fragmentation at the edge level as in [91], [92]. The two species (*extra* and *intra* cellular) interact through the release of soluble intracellular Tau in the extracellular space and the uptake of soluble extracellular Tau at the cellular level. This mass exchange takes place along the node-edge boundary and mathematically it is modelled by means of Neumann-Robin-type boundary conditions on each edge. The processes of release and uptake of Tau are interpreted here as the bottleneck of the model dynamics. This assumption will prove to be essential to obtain the vanishing *feedback* mechanism in Section 4.2.1. Finally, we model intraregional accumulation, that is seeding of pathological Tau, through a suitable source term F_{ij}.

Let $m_{ij}(x,t)$ and $n_{ij}(x,t)$ denote the densities at time t per unit volume of insoluble and soluble intracellular pathological Tau, respectively, at the edge e_{ij}, where t refers to the slow time scale. $N_i(t)$ and $N_j(t)$ denote the density of extracellular soluble Tau at the vertices P_i and P_j. The equations for the edge variables (m_{ij}, n_{ij}) are

$$\begin{cases} (m_{ij})_t = -\Gamma(m_{ij}, n_{ij}, t) & \text{in } (0, L_{ij}), \\ \Gamma(m_{ij}, n_{ij}) = \beta m_{ij} - \gamma_1(t) n_{ij}^2 - \gamma_2(t) m_{ij} n_{ij}, \\ (n_{ij})_t = (a(x,t)(n_{ij})_x + h(x, m_{ij}, n_{ij}))_x + F_{ij} + \Gamma(m_{ij}, n_{ij}, t), \end{cases} \tag{4.1}$$

where

$$h(x, m_{ij}, n_{ij}) = \begin{cases} -(1-f)\left[v_a(1+\delta n_{ij})(1-\varepsilon m_{ij}) - v_r\right] n_{ij} & x \in (x_2, L_{ij}) \\ 0 & \text{otherwise} \end{cases}$$

and

$$a(x,t) = \begin{cases} D & \text{if } x \in (0, x_1) \\ D\lambda(t) & \text{if } x \in (x_1, x_2) \\ fD & \text{if } x \in (x_2, L_{ij}). \end{cases} \tag{4.2}$$

Consistently with the notation adopted in Chapter 3, the coefficients of the equations are expressed on the slow time scale. We define the flux of n_{ij} on the edge e_{ij} by

$$J_{ij}(x,t) = -a(x,t)(n_{ij})_x - h(x, n_{ij}, m_{ij}). \tag{4.3}$$

The exchange of soluble Tau between intracellular and extracellular space is modelled introducing the following boundary condition at the vertex-edge boundary $x = 0$ and $x = L_{ij}$:

$$\begin{cases} J_{ij}(0,t) = -\mu_{i,1}(t) n(0,t) + \mu_{i,2}(t) N_i(t), \\ J_{ij}(L_{ij},t) = \mu_{j,1}(t) n(L_{ij},t) - \mu_{j,2}(t) N_j(t) \end{cases} \quad t \geq 0, \tag{4.4}$$

where the parameters $\mu_{i,1}, \mu_{j,1} \geq 0$ govern the release of intracellular soluble Tau at the vertices P_i and P_j, respectively; similarly, the parameters $\mu_{i,2}, \mu_{j,2} \geq 0$ model the uptake of soluble extracellular Tau at the vertices P_i and P_j, respectively. In this Chapter, we assume a slow release-uptake dynamics, hence the coefficients $\mu_{i,k}$ are of order $O(1)$ on the slow time scale.

The edge equations (4.1) are coupled with the following ODE system on the nodes of G_c:

$$\begin{cases} M_i' = -\Gamma(M_i, N_i, t) \\ N_i' = \frac{1}{\mathrm{Vol}(i)} \sum_{j\sim i} \left(-c_{ij} J_{ij}(0,t) + c_{ji} J_{ji}(L_{ij},t)\right) + \Gamma(M_i, N_i, t) + F_i & \text{for } i \in V, \\ J_{ij} := -a(x,t)(n_{ij})_x + h(x, n_{ij}, m_{ij}) & \text{for } x \in [0, L_{ij}], \\ J_{ij}(0,t) = -\mu_{i,1}(t) n_{ij}(0,t) + \mu_{i,2}(t) N_i, \\ J_{ij}(L_{ij},t) = \mu_{j,1}(t) n_{ij}(L_{ij},t) - \mu_{j,2}(t) N_j. \end{cases} \tag{4.5}$$

The reaction term is

$$\Gamma(M, N, t) = \beta M - N(\gamma_1(t) N + \gamma_2(t) M). \tag{4.6}$$

Here we model the aggregation and diffusion parameters as time-dependent, as in Chapter 3, and introduce a new dynamical factor $\mu_{i,k}$ for $i \in V$ and $k = 1, 2$, by keeping a general formulation. In Section 4.2.1, we explicitly model the temporal evolution of these parameters as functions of soluble Beta Amyloid.

4.2.1 The quasi-static model

To correctly define a quasi-static approximation to (4.1)-(4.5), we must state the correct mass exchange of soluble tau between node i and edges e_{ij} and e_{ji} ($j \neq i$). In general, we have observed in Chapters 1 and 3 that this exchange is described by the flux contribution at all incoming and outgoing edges at a given node and the *feedback* mechanism arising from the variation of the Dirichlet boundary conditions on the edges. It is therefore natural to question whether this property continues to hold when considering a different type of boundary condition, that is (4.4). For this purpose, we adopt the decomposition introduced in (3.25) and show that in the case of slow *release-uptake* parameters $\mu_{i,k}$, the model does not exhibit any *feedback* phenomena.

In this Section, for simplicity we set $\gamma_2 \equiv 0$. Let $\phi_0 << 1$ be the proportion between the physical slow timescale and the fast one. We set:

$$\begin{aligned} &M_i(t) = g(N_i(t), t) + \phi_0 V_i(t) \quad i \in V, \\ &n_{ij}(x,t) = \overline{n}_{ij}(t) + \phi_0 u_{ij}(x,t) \quad e_{ij} \in E, \\ &m_{ij}(x,t) = g(\overline{n}_{ij}(x,t), t) + \phi_0 v_{ij}(x,t) \quad e_{ij} \in E. \end{aligned} \tag{4.7}$$

To simplify the notation, we erase the edge subscripts when dealing with edge variables. On the single edge $e_{ij} \in E$, we introduce the variables $\overline{n}_{ij}$ and $\overline{m}_{ij}$ as the solution to the *current equilibrium* problem

$$\begin{cases} J_{ij} := -a(x,t)(n_{ij})_x - h(x, n_{ij}, m_{ij}) \qquad \text{for } x \in [0, L_{ij}],\ e_{ij} \in E \\ (J_{ij})_x = F_{ij} \qquad \text{for } x \in [0, L_{ij}] \\ \Gamma(m_{ij}, n_{ij}, t) = 0 \\ J_{ij}(0,t) = -\mu_{i,1}(t)\bar{n}_{ij}(0,t) + \mu_{i,2}(t)N_i, \\ J_{ij}(L_{ij},t) = \mu_{j,1}(t)\bar{n}_{ij}(L_{ij},t) - \mu_{j,2}(t)N_j, \end{cases} \tag{4.8}$$

where $(N_i(t))_{i=1}^h$ is defined as the solution of system (4.5).

Since

$$g(n,t) = \frac{\gamma_1 n^2}{\beta}, \qquad g_n = 2\frac{\gamma_1}{\beta}n, \qquad g_t = \frac{\partial_t \gamma_1}{\beta}n^2,$$

and

$$\Gamma(m,n,t) = \beta m - \gamma_1(t)n^2,$$

we have that

$$\Gamma(m,n,t) = \Gamma(g(\overline{n}(t),t) + \phi_0 v(s), \overline{n}(t) + \phi_0 u(s), t) = \phi_0 \left(\beta v - 2\gamma_1(t)\bar{n}(t)u - \gamma_1(t)\phi_0 u^2\right). \tag{4.9}$$

Consider now the operator

$$
\begin{aligned}
&a(x,t)n_x + h(x,n,m)\\
&\quad= \phi_0 a(x,t)u_x + a(x,t)\overline{n}_x - (1-f)\chi_{(x_2,x_3)}\left[v_a(1+\delta(\overline{n}+\phi_0 u))(1-\varepsilon(\overline{m}+\phi_0 v)) - v_r\right](\overline{n}+\phi_0 u)\\
&\qquad + (1-f)\chi_{(x_2,x_3)}\phi_0[v_a\varepsilon v(1+\delta\bar{n})](\bar{n}+\phi_0 u)\\
&\qquad - (1-f)\chi_{(x_2,x_3)}\phi_0[v_a\delta u(1-\varepsilon\bar{m}-\varepsilon\phi_0 v)](\bar{n}+\phi_0 u)\\
&\quad= \phi_0 a(x,t)u_x + \underbrace{a(x,t)\overline{n}_x - (1-f)\chi_{(x_2,x_3)}[v_a(1+\delta\overline{n})(1-\varepsilon\overline{m}) - v_r]\overline{n}}_{=:-\overline{J}(x,t)}\\
&\qquad + \ (1-f)\chi_{(x_2,x_3)}\left(\phi_0 R_1^{u,v} + \phi_0^2 R_2^{u,v} + \phi_0^3 R_3^{u,v}\right)\\
&\quad=: -\bar{J}(x,t) - J_{ij}^{u,v}(x,t),
\end{aligned}
$$

where

$$
\begin{aligned}
R_1^{u,v} &:= -\left(v_a(1+2\delta\overline{n})(1-\varepsilon\overline{m}) - v_r\right)u + v_a(1+\delta\overline{n})\varepsilon\overline{n}v,\\
R_2^{u,v} &:= v_a\left(\varepsilon(1+2\delta\overline{n})uv - \delta(1-\varepsilon\overline{m})u^2\right),\\
R_3^{u,v} &:= v_a\delta\varepsilon u^2 v,\\
J_{ij}^{u,v}(x,t) &:= -\phi_0 a(x,t)u_x - (1-f)\chi_{(x_2,x_3)}\left(\phi_0 R_1^{u,v} + \phi_0^2 R_2^{u,v} + \phi_0^3 R_3^{u,v}\right).
\end{aligned}
$$

Finally we obtain

$$
\begin{aligned}
&(a(x,t)n_x + h(x,n,m))_x = -\bar{J}_x - (\bar{J}_{ij}^{u,v})_x\\
&\quad = -F_\tau + \phi_0(a(x,t)u_x)_x + \phi_0(1-f)\left[\chi_{(x_2,x_3)}\left(R_1^{u,v} + \phi_0 R_2^{u,v} + \phi_0^2 R_3^{u,v}\right)\right]_x,
\end{aligned}
\tag{4.10}
$$

where we have used that $\bar{n}$ satisfies the *current equilibrium* problem (4.8). According to the decomposition (4.7) and equations (4.5) - (4.9), we have

$$
\begin{aligned}
\phi_0 u_t &= -\overline{n}_t + n_t = -\overline{n}_t + (an_x - h(x,n,m))_x + F_\tau + \Gamma(\overline{m}+\phi_0 v, \overline{n}+\phi_0 u)\\
&= -\overline{n}_t + \phi_0(au_x)_x + \phi_0(1-f)\left[\chi_{(x_2,x_3)}\left(R_1^{u,v} + \phi_0 R_2^{u,v} + \phi_0^2 R_3^{u,v}\right)\right]_x\\
&+ \phi_0(\beta v - 2\gamma_1\bar{n}u - \gamma_1\phi_0 u^2),
\end{aligned}
$$

$$
\phi_0 v_t = -\overline{m}_t + m_t = -\frac{\partial_t\gamma_1\overline{n}}{\beta} - 2\frac{\gamma_1\overline{n}\,\overline{n}_t}{\beta} - \phi_0\left(\beta v - 2\gamma_1\overline{n}u - \gamma_1\phi_0 u^2\right). \tag{4.11}
$$

It follows that $(u,v) = (u_{ij}, v_{ij})$ satisfies the equations

$$
\begin{cases}
\phi_0 u_t = -\overline{n}_t + \phi_0(au_x)_x + \phi_0(1-f)\left[\chi_{(x_2,x_3)}\left(R_1^{u,v} + \phi_0 R_2^{u,v} + \phi_0^2 R_3^{u,v}\right)\right]_x\\
\qquad\quad +\phi_0(\beta v - 2\gamma_1\bar{n}u - \phi_0\gamma_1 u^2),\\
\phi_0 v_t = -\frac{\partial_t\gamma_1\overline{n}}{\beta} - 2\frac{\gamma_1\overline{n}\,\overline{n}_t}{\beta} - \phi_0\left(\beta v - 2\gamma_1\overline{n}u - \phi_0\gamma_1 u^2\right),\\
J_{ij}^{u,v}(x,t) := \phi_0 a(x,t)u_x - (1-f)\chi_{(x_2,x_3)}\left(\phi_0 R_1^{u,v} + \phi_0^2 R_2^{u,v} + \phi_0^3 R_3^{u,v}\right),\\
J_{ij}^{u,v}(0,t) = -\phi_0\mu_{i,1}(t)u_{ij}(0,t),\\
J_{ij}^{u,v}(L_{ij},t) = \phi_0\mu_{j,1}(t)u_{ij}(L_{ij},t).
\end{cases}
\tag{4.12}
$$

The function $t \mapsto V_i(t)$ satisfies

$$
\phi_0 V_i' = -\partial_t g(N_i) - \Gamma(g(N_i) + \phi_0 V_i, N_i)
$$

where

$$
\partial_t g(N_i) = \frac{\partial_t\gamma_1(t)}{\beta}N_i + \frac{2\gamma_1 N_i N_i'}{\beta},
$$

$$\Gamma(g(N_i) + \phi_0 V_i, N_i) = \beta \left(\frac{\gamma_1 N_i^2}{\beta} + \phi_0 V_i \right) - \gamma_1 N_i^2 = \beta \phi_0 V_i.$$

Hence we obtain the ODE

$$\phi_0 V_i' = -\frac{\partial_t \gamma_1(t)}{\beta} N_i - \frac{2\gamma_1 N_i N_i'}{\beta} - \phi_0 \beta V_i \quad i \in V. \tag{4.13}$$

Lastly, we reformulate the node equation for N_i. Recall that

$$N_i' = \frac{1}{Vol(i)} \sum_{j \neq i} \left(-c_{ij} J_{ij}(0,t) + c_{ji} J_{ji}(L_{ji},t)\right) + \Gamma(M_i, N_i, t) \tag{4.14}$$

$$= \frac{1}{Vol(i)} \sum_{j \neq i} \left(-c_{ij} J_{ij}(0,t) + c_{ji} J_{ji}(L_{ji},t)\right) + \Gamma\left(g(N_i) + \phi_0 V_i, N_i, t\right)$$

$$= \frac{1}{Vol(i)} \sum_{j \neq i} \left(-c_{ij} J_{ij}(0,t) + c_{ji} J_{ji}(L_{ji},t)\right) + \beta \phi_0 V_i.$$

Concerning the net incoming flux at node P_i, on the single edge e_{ij} we have

$$\begin{cases} J_{ij}(0,t) = -\mu_{i,1}(t)\bar{n}_{ij}(0,t) + \mu_{i,2}(t) N_i + J_{ij}^{uv}(0,t), \\ J_{ji}(0,t) = \mu_{i,1}(t)\bar{n}_{ji}(L_{ji},t) - \mu_{i,2}(t) N_i + J_{ji}^{uv}(L_{ji},t). \end{cases} \tag{4.15}$$

The resulting system is

$$\begin{cases} N_i' = \frac{1}{\mathrm{Vol}(i)} \sum_{j \neq i} \left[-c_{ij}(-\mu_{i,1}(t)\bar{n}_{ij}(0,t) + \mu_{i,2}(t) N_i) + c_{ji}(\mu_{i,1}(t)\bar{n}_{ji}(L_{ji},t) - \mu_{i,2}(t) N_i)\right] + F_i \\ + \frac{1}{\mathrm{Vol}(i)} \sum_{j \neq i} \left(-c_{ij} J_{ij}^{uv}(0,t) + c_{ji} J_{ji}^{uv}(L_{ji},t)\right) + \phi_0 \beta V_i, \quad i \in V, \\ M_i' = -\phi_0 \beta V_i, \quad i \in V, \\ \phi_0 u_t = -\overline{n}_t + \phi_0 (a u_x)_x + \phi_0 (1-f) \left[\chi_{(x_2,x_3)} \left(R_1^{u,v} + \phi_0 R_2^{u,v} + \phi_0^2 R_3^{u,v}\right)\right]_x \\ \qquad + \phi_0 (\beta v - 2\gamma_1 \bar{n} u - \phi_0 \gamma_1 u^2), \\ \phi_0 v_t = -\frac{\partial_t \gamma_1 \overline{n}}{\beta} - 2\frac{\gamma_1 \overline{n}\, \overline{n}_t}{\beta} - \phi_0 \left(\beta v - 2\gamma_1 \overline{n} u - \phi_0 \gamma_1 u^2\right), \\ \phi_0 V_i' = -\frac{\partial_t \gamma_1(t)}{\beta} N_i - \frac{2\gamma_1 N_i N_i'}{\beta} - \phi_0 \beta V_i \quad i \in V, \\ J_{ij}^{u,v}(0,t) = -\phi_0 \mu_{i,1}(t) u_{ij}(0,t), \\ J_{ij}^{u,v}(L_{ij},t) = \phi_0 \mu_{j,1}(t) u_{ij}(L_{ij},t), \quad e_{ij} \in E_c. \end{cases} \tag{4.16}$$

As in Chapter 3, ϕ_0 is a small parameter which represents the proportion of the physical timescales. The parameters D, β, γ_1, v_a and v_r are large constants of order $O(1/\phi_0)$ on the slow time scale. The function F_τ is of order $O(1/\phi_0)$ too, therefore the quantities

$$\tilde{D} = \phi_0 D, \quad \tilde{\beta} = \phi_0 \beta, \quad \tilde{\gamma}_1 = \phi_0 \gamma_1, \quad \tilde{v}_a = \phi_0 v_a, \quad \tilde{v}_r = \phi_0 v_r, \quad \tilde{F}_\tau = \phi_0 F_\tau$$

are all of order $O(1)$. We recall that

$$a(x,t) = \begin{cases} D & \text{in } (0, x_1) \\ D\lambda(t) & \text{in } (x_1, x_2) \\ fD & \text{in } (x_2, L_{ij}), \end{cases}$$

hence, it is also natural to introduce the function

$$\tilde{a} = \phi_0 a.$$

On the other hand, the release and uptake coefficients $\mu_{i,k}$ should not be rescaled as they are already of order $O(1)$ on the slow timescale. The equations (4.16) become

$$\begin{cases} N_i' = \frac{1}{\mathrm{Vol}(i)}\sum_{j\neq i}\left[-c_{ij}(-\mu_{i,1}(t)\bar{n}_{ij}(0,t)+\mu_{i,2}(t)N_i)+c_{ji}(\mu_{i,1}(t)\bar{n}_{ji}(L_{ji},t)-\mu_{i,2}(t)N_i)\right]+F_i \\ +\frac{1}{\mathrm{Vol}(i)}\sum_{j\neq i}\left(-c_{ij}J_{ij}^{uv}(0,t)+c_{ji}J_{ji}^{uv}(L_{ji},t)\right)+\tilde{\beta}V_i, \quad i\in V \\ M_i' = -\tilde{\beta}V_i, \quad i\in V \\ \phi_0 u_t = -\overline{n}_t + (\tilde{a}u_x)_x + (1-f)\left[\chi_{(x_2,x_3)}\left(\tilde{R}_1^{u,v}+\phi_0\tilde{R}_2^{u,v}+\phi_0^2\tilde{R}_3^{u,v}\right)\right]_x \\ \qquad +(\tilde{\beta}v - 2\tilde{\gamma}_1\bar{n}u - \phi_0\tilde{\gamma}_1 u^2), \\ \phi_0 v_t = -\frac{\partial_t\gamma_1\overline{n}}{\beta} - 2\frac{\gamma_1\overline{n}\,\overline{n}_t}{\beta} - \left(\tilde{\beta}v - 2\tilde{\gamma}_1\overline{n}u - \phi_0\tilde{\gamma}_1 u^2\right), \\ \phi_0 V_i' = -\frac{\partial_t\gamma_1(t)}{\beta}N_i - \frac{2\gamma_1 N_i N_i'}{\beta} - \tilde{\beta}V_i \quad i\in V, \\ J_{ij}^{u,v}(0,t) = -\phi_0\mu_{i,1}(t)u_{ij}(0,t), \\ J_{ij}^{u,v}(L_{ij},t) = \phi_0\mu_{j,1}(t)u_{ij}(L_{ij},t), \quad e_{ij}\in E_c, \end{cases} \tag{4.17}$$

where

$$\begin{aligned} \tilde{R}_1^{u,v} &:= -\left(\tilde{v}_a(1+2\delta\overline{n})(1-\varepsilon\overline{m})-\tilde{v}_r\right)u+\tilde{v}_a(1+\delta\overline{n})\varepsilon\overline{n}v, \\ R_2^{u,v} &:= \tilde{v}_a\left(\varepsilon(1+2\delta\overline{n})uv-\delta(1-\varepsilon\overline{m})u^2\right), \\ R_3^{u,v} &:= \tilde{v}_a\delta\varepsilon u^2 v. \end{aligned}$$

Since ϕ_0 is extremely small, we formally set $\phi_0 = 0$ in (4.17):

$$\begin{cases} -\overline{n}_t + (\tilde{a}u_x)_x + (1-f)\left[\chi_{(x_2,x_3)}\left(\tilde{R}_1^{u,v}+\phi_0\tilde{R}_2^{u,v}+\phi_0^2\tilde{R}_3^{u,v}\right)\right]_x \\ \qquad +(\tilde{\beta}v - 2\tilde{\gamma}_1\bar{n}u - \phi_0\tilde{\gamma}_1 u^2) = 0, \\ \left(\tilde{\beta}v - 2\gamma_1\overline{n}u\right) = -\frac{\partial_t\gamma_1\overline{n}}{\beta} - 2\frac{\gamma_1\overline{n}\,\overline{n}_t}{\beta}, \\ \tilde{\beta}V_i = -\frac{\partial_t\gamma_1(t)}{\beta}N_i - \frac{2\gamma_1 N_i N_i'}{\beta} \quad i\in V, \\ J_{ij}^{u,v}(0,t) = 0, \\ J_{ij}^{u,v}(L_{ij},t) = 0, \quad e_{ij}\in E_c. \end{cases} \tag{4.18}$$

This formal assumption implies that the flux contribution of the remainder term u_{ij} is null at the boundary, i.e. along the node-edge interface, meaning that the *Release-Uptake* variation to the *NTM* does not exhibit a *feedback* mechanism if the release-uptake coefficients are of order $O(1)$ on the slow time scale. This result substantially simplifies the framework of Chapter 1 since the resulting equation for N_i at node P_i is

$$Vol(i)\frac{d}{dt}\Big(\underbrace{g(N_i,t)}_{\overline{M}_i}+N_i\Big)(t) = \underbrace{\sum_{j\neq i}\left(-c_{ij}\bar{J}_{ij}(0,t)+c_{ji}\bar{J}_{ji}(L_{ji},t)\right)}_{\text{Net incoming flux at node } P_i}+Vol(i)F_i. \tag{4.19}$$

This simplification remarkably reduces the computational costs associated to (4.19) since the calculations of the terms $(n_{ij})_t$ needed in Chapters 1 and 3 to determine the *feedback* contributions are redundant in this setting and the computational burden is solely determined by the second-order elliptic equation for n_{ij}. The resulting model is therefore more practical and suitable from an application standpoint since computational efficacy is essential to perform large-scale simulations, parameter exploration and direct comparison with clinical data.

Observe that (4.19) resembles the standard network reaction-diffusion model, where the incoming fluxes $\bar{J}_{ij}(0,t)$ and $\bar{J}_{ji}(L_{ji},t)$ are defined by the entries of the Graph Laplacian matrix.

In the previous formal analysis we restricted our attention to the case $\gamma_2 \equiv 0$. However, repeating the calculations leading to (4.19) allowing $\gamma_2 \not\equiv 0$ shows that the structure of the resulting equations remains unchanged. In fact, the elimination of the *feedback* mechanism depends on the order of magnitude of $\mu_{i,k}$ rather than on the specific values of γ_2. Accordingly, in the following Sections we shall also include the case $\gamma_2 \not\equiv 0$.

4.2.2 Mass Balance

In this Section, we state some a priori results on the mass of the system. We recall that $(M_i, N_i, m_{ij}, n_{ij})$ satisfies, for all $i \in V$ and $e_{ij} \in E_c$

$$\begin{cases} \mathrm{Vol}(i)\,(M_i + N_i)'\,(t) = \sum_{j\sim i} \left(-c_{ij}J_{ij}(0,t) + c_{ji}J_{ji}(L_{ji},t)\right) + \mathrm{Vol}(i)F_i, \\ J_{ij} := -a(x,t)(n_{ij})_x - h(x,n_{ij},m_{ij}) \qquad \text{for } x \in [0,L_{ij}],\ e_{ij} \in E, \\ (J_{ij})_x = F_{ij} \qquad \text{for } x \in [0,L_{ij}], \\ J_{ij}(0,t) = -\mu_{i,1}(t)\bar{n}_{ij}(0,t) + \mu_{i,2}(t)N_i, \\ J_{ij}(L_{ij},t) = \mu_{j,1}(t)\bar{n}_{ij}(L_{ij},t) - \mu_{j,2}(t)N_j. \end{cases} \tag{4.20}$$

Let

$$\mathcal{M}_{node}(t) = \sum_{i\in V} \mathrm{Vol}(i)(M_i(t) + N_i(t)), \quad \mathcal{M}_{edge}(t) = \sum_{e_{ij}\in E_c} c_{ij} \int_0^{L_{ij}} (m_{ij}(x,t) + n_{ij}(x,t))\,dx.$$

The total mass satisfies

$$(\mathcal{M}_{node} + \mathcal{M}_{edge})'\,(t) = \sum_{e_{ij}\in E_c} c_{ij} \int F_{ij}(x,t)\,dx + \sum_{i\in V} \mathrm{Vol}(i)F_i(t). \tag{4.21}$$

By $(4.20)_3$ it follows that

$$\sum_{(i,j)\in E_c} c_{ij}(J_{ij}(L_{ij},t) - J_{ij}(0,t)) = \sum_{e_{ij}\in E} c_{ij} \int_0^{L_{ij}} F_\tau(x,t)\,dx, \tag{4.22}$$

hence by $(4.20)_1$ we have

$$\mathcal{M}'_{node}(t) = \sum_{e_{ij}\in E_c} c_{ij} \int F_{ij}(x,t)\,dx + \sum_{i\in V} \mathrm{Vol}(i)F_i(t) \tag{4.23}$$

and we conclude that the total edge mass $\mathcal{M}_{edge}$ is conserved.

In addition, in the case $F_i, F_{ij} \equiv 0$, the total mass on the nodes $\mathcal{M}_{node}$ is constant in time.

4.3 A combined model for Tau and Beta Amyloid

In this Section, we couple the *RU-Network-Transport model* developed in Section 4.2.1 with the Beta Amyloid model of Chapter 2. The equations for the Aβ model on the *proximity* graph are

$$\begin{cases} \partial_t f_{i,t} + (v[f_{i,t}]f_{i,t})_a = J[f_{i,t}], \\ f_{i,0} = f_i(0) \end{cases}, \quad i \in V, \tag{4.24}$$

$$\begin{cases} d_1 \Delta u_1(i,t) - \sigma_1 u_1(i,t) + F_{A\beta}[f_{i,t}] + \Gamma_1(u(i,t)) = 0, \\ d_2 \Delta u_2(i,t) - \sigma_2 u_2(i,t) + \Gamma_2(u(i,t)) = 0, \\ -\sigma_3 u_3(i,t) + \Gamma_3(u(i,t)) = 0, \end{cases} \qquad i \in V, \tag{4.25}$$

where the reaction terms are

$$\begin{cases} \Gamma_1 = -u_1(a_{11}u_1 + a_{12}u_2) + k_1 u_3 \\ \Gamma_2 = a_{11}u_1^2 - a_{21}u_1 u_2 + k_2 u_3 \\ \Gamma_3 = -(\Gamma_1 + \Gamma_2) = u_1 u_2(a_{12} + a_{21}) - (k_1 + k_2)u_3, \end{cases} \tag{4.26}$$

the signed measure $J[f_{i,t}]$ is

$$J[f_{i,t}] = \eta(t)\chi_H(t) \left\{ \left(\int_{[0,1]} P(t,b,a)\, df_{i,t}(b) \right) da - df_{i,t}(a) \right\}, \tag{4.27}$$

and the Aβ monomers' production is

$$F_{A\beta}[f_{i,t}] = C_\mu \int_0^1 (\mu_0 + a)(1-a)\, df_{i,t}(a), \quad i \in V,\, t > 0. \tag{4.28}$$

The degeneration rate for $f_{i,t}$ is defined as

$$v[f_{i,t}](a,t) = C_G \int_{[0,1]} (b-a)^+\, df_{i,t}(b) + C_s(1-a)(u_2(i,t) - \bar{U}_2)^+ + C_N(1-a)(N_i(t) - \bar{N}_i)^+ \tag{4.29}$$

where N_i denotes the concentration of extracellular Tau at node $i \in V$ and $\bar{N}_i > 0$ is a threshold value above which released Tau oligomers induce neuronal dysfunction and death [23].

Since the *connectivity* and *proximity* graphs share the same set of nodes but are endowed with different sets of edges, as in Chapter 3 we extend u_2 on every edge of the *connectivity* graph as a linear combination of the respective node concentrations

$$(u_2)_{ij}(x,t) = \left(1 - \tfrac{x}{L}\right) u_2(i,t) + \tfrac{x}{L} u_2(j,t) \quad \text{for } x \in (0, L_{ij}),\ t \ge 0.$$

The equation for the concentration of extracellular soluble Tau at node $i \in V$ is

$$\begin{aligned} &\left(1 + \frac{\gamma_1(i,t)N_i(2\beta - \gamma_2(i,t)N_i)}{(\beta - \gamma_2(i,t)N_i)^2}\right) \mathrm{Vol}(i) N_i' \\ &= \mathrm{Vol}(i) F_{i,\tau}(i,t) - \frac{\mathrm{Vol}(i) N_i^2}{\beta - \gamma_2(i,t)N_i} \left(\gamma_1'(i,t) + \frac{\gamma_1(i,t)\gamma_2'(i,t)N_i}{\beta - \gamma_2(i,t)N_i} \right) \\ &\quad + \sum_{j\sim i} c_{ji} J_{ji}(L_{ji},t) - c_{ij} J_{ij}(0,t) \end{aligned} \tag{4.30}$$

where the flux term satisfies for all $e_{ij} \in E_c$

$$\begin{cases} J_{ij}(x,t) = (a(x,u_2)n_{ij}(x,t))_x + h(x,n_{ij}(x,t),u_2), \quad x \in (0,L_{ij}) \\ (J_{ij})_x(x,t) = F_{ij,\tau}(x,t), \\ J_{ij}(0,t) = -\mu_{i,1}(u_2(i,t))n_{ij}(0,t) + \mu_{i,2}(u_2(i,t))N_i(t), \\ J_{ij}(L_{ij},t) = \mu_{j,1}(u_2(j,t))n_{ij}(L_{ij},t) - \mu_{j,2}(u_2(j,t))N_j(t), \\ m_{ij}(x,t) = g_m(t,n_{ij}(x,t)), \quad g_m(t,n) = \frac{\gamma_1(u_2(t))n^2}{\beta-\gamma_2(u_2(t))n^2}. \end{cases} \tag{4.31}$$

The extracellular insoluble Tau concentration is defined as

$$M_i(t) = \frac{\gamma_1(u_2(i,t))N_i^2(t)}{\beta - \gamma_2(u_2(i,t))N_i(t)}, \quad i \in V,\, t > 0. \tag{4.32}$$

The action of Aβ on extracellular Tau involves the u_2-dependence of both γ_1, γ_2 and λ as in Chapter 3 and the nodal Release-Uptake coefficients $\mu_{i,k}$, for $i \in V$ and $k = 1, 2$ [104].

As in Chapter 2, we require that the model parameters satisfy

(i) $\sigma_1,\, \sigma_2,\, \sigma_3,\, a_{11},\; a_{12},\, a_{21}\, k_1,\, k_2,\, d_1,\, d_2,\, C_\mu,\, \mu_0, C_G,\, C_s$ are positive constants. The monomers' clearance parameter σ_1 is sufficiently large, i.e. $\sigma_1 > \bar{\sigma}_1$. The aggregation and fragmentation rates are symmetric: $a_{ij} = a_{ji}$, $k_1 = k_2$;

(ii) $\eta \in C([0,T])$, $\eta > 0$. P satisfies

$$P \in C([0,T] \times [0,1]^2), \quad P \geq 0, \tag{4.33}$$

$$\int_{[0,1]} P(t,b,a)\, da = 1 \text{ for } b \in [0,1],\; P(t,b,a) = 0 \quad \text{if } b > a \tag{4.34}$$

since impaired neurons do not recover, and it is Lipschitz continuous:

$$\exists L > 0 :\; |P(t'',b'',a'') - P(t',b',a')| \leq L(|b''-b'| + |a''-a'| + |t''-t'|), \tag{4.35}$$

for all $a', a'', b', b'' \in [0,1]$, $t',\, t'' \in [0,T]$.

(iii) $\gamma_1, \gamma_2, \lambda \in C^1(\mathbb{R}^+)$, $\gamma_1, \gamma_2 \geq 0$, $\lambda \in (0,1)$, $F_{i,\tau} \in C^1(\mathbb{R}^+)$ for all $i \in V$, $F_{ij,\tau} \in C^1([0,L_{ij}] \times \mathbb{R}^+)$ for all $e_{ij} \in E_c$, $F_{i,\tau}, F_{ij,\tau} \geq 0$, $\mu_{i,k} \in C(\mathbb{R}^+)$ for all $i \in V$, $k = 1, 2$, $\mu_{i,k} \geq 0$ and $\exists C_\gamma, C'_\lambda, C''_\lambda, C_F, C_{ru} > 0$ such that

$$|\gamma_k|, |\partial_u \gamma_k|, |\partial^2_{uu}\gamma_k| < C_\gamma \text{ on } \mathbb{R}^+ \text{ for } k = 1,2, \quad C''_\lambda < \lambda < C'_\lambda \text{ on } \mathbb{R}^+, \tag{4.36}$$

$$F_{i,\tau}(u), F_{ij,\tau}(x,u) < C_F \text{ for all } x \in [0,L_{ij}],\; e_{ij} \in E,\; i \in V,\; u \in \mathbb{R}^+, \tag{4.37}$$

$$\mu_{i,k}(u), |\partial_u \mu_{i,k}(u)| < C_{ru} \text{ for all } i \in V,\; k = 1,2,\; u \in \mathbb{R}^+. \tag{4.38}$$

4.3.1 The main result

To state the main result of this chapter, we first introduce the definition of a solution for the quasi-static Aβ-Tau model introduced above. We denote by $X_{[0,1]}$ the space of probability measures on $[0,1]$ endowed with the 1-Wasserstein distance and by $\mathcal{M}(0,1)$ the space of signed Radon measures on $[0,1]$. We write

$$f \in \mathcal{L}(V; C([0,T]; X_{[0,1]})) \tag{4.39}$$

if $t \mapsto f_{i,t} \in C([0,T]; X_{[0,1]})$ for all $i \in V$ and

$$t \mapsto \int \rho(a) df_{i,t}(a) \tag{4.40}$$

is measurable as a function from $[0,T]$ to $\mathcal{M}(0,1)$ for all $\rho \in C([0,1])$ and $i \in V$.

We will denote distributional derivatives with ∂, ∇ and the standard Euclidean norm on $\mathbb{R}^{3h}$ with $|\cdot|$, when no other vector norm is under consideration. We may refer to the solution of system (4.25) as $u \in \mathbb{R}^{3h}$, where 3 is the number of species and h the number of nodes, or with $u_k \in \mathbb{R}^h$ for $k = 1,2,3$ as the vector of concentration of species k on the nodes.

Remark 4.3.1. *Observe that, as in Chapter 3, the $A\beta$ system* (4.25) *on the proximity graph does not require a prescription of the initial data since it is defined as the equilibrium solution to* (4.25) *with monomers' source* (4.28) *with $f_{i,t} = f_i(0)$; conversely, the RU-NTM is equipped with a given initial condition $N_i(0) = N_{i0} \geq 0$ where $N_{i0} < \beta/\gamma_2(u_2(i,0))$ if $\gamma_2(u_2(i,0)) > 0$.*

Definition 4.3.1. *A $5-$tuple (f, u_1, u_2, u_3) is a solution to* (4.24), (4.25),(4.30),(4.32) *if*

1. $f \in \mathcal{L}(V; C([0,T]; X_{[0,1]}))$; $u_k \in C([0,T], \mathbb{R}^h)$, $u_k(i) \geq 0$ *for all* $k = 1,2,3$ *and* $i = 1,\dots,h$, $N_i \in C^1\left([0,\infty); [0, \frac{\beta}{\gamma_2})\right)$, $M_i \in C^1([0,\infty); [0,\infty))$ *for all* $i = 1,\dots,h$ *and, for all* $i \neq j$ *such that* $c_{ij} > 0$, $n_{ij} \in C([0,L] \times [0,\infty); [0,\infty))$, $m_{ij} \in L^\infty([0,L] \times [0,\infty); [0,\infty))$, $J_{ij} \in C([0,\infty); \mathbb{R})$ *and* $n_{ij}(t) < \frac{\beta}{\gamma_2(u_2(t))}$ *a.e. in* $(0, L_{ij})$*;*

2. f *is a solution to* (4.24) *in a weak sense:*

$$\begin{aligned} \int_0^t \left(\int (\phi_s(a,s) + \phi_a(a,s) v_i(a,s)) df_{i,s}(a) + \int \phi(a,s) dJ_{i,s}(a) \right) ds \\ = \int \phi(\cdot, t)\, df_{i,t} - \int \phi(\cdot, 0)\, df_i(0) \end{aligned} \tag{4.41}$$

   for all $\phi \in C^1([0,1] \times [0,T])$ *and* $i = 1,\dots,h$*, where* v *is defined in* (4.29)*;*

3. (u_1, u_2, u_3) *satisfies the following graph equations:*

$$\begin{cases} d_1 \Delta u_1(t) - \sigma_1 u_1(t) + F[f(t)] + \Gamma_1(t) = 0, \\ d_2 \Delta u_2(t) - \sigma_2 u_2(t) + \Gamma_2(t) = 0, \\ -\sigma_3 u_3(t) + \Gamma_3(t) = 0, \end{cases} \tag{4.42}$$

   where $F[f]$ *and the reaction terms* Γ_k *are given by* (4.28) *and* (4.26)*;*

4. (M_i, N_i) *satisfies the equations* (4.30), (4.32) *and for all* $t \in [0,T]$ (m_{ij}, n_{ij}) *satisfies*

$$\begin{cases} J_{ij}(t) = (a(x,u_2) n_{ij}(t))_x + h(x, n_{ij}(t), u_2), \\ (J_{ij})_x(t) = F_{ij,\tau}(t), \quad \text{in } \mathcal{D}'(0, L_{ij}) \\ J_{ij}(0,t) = -\mu_{i,1}(u_2(i,t)) n_{ij}(0,t) + \mu_{i,2}(u_2(i,t)) N_i(t) \\ J_{ij}(L_{ij},t) = \mu_{j,1}(u_2(j,t)) n_{ij}(L_{ij},t) - \mu_{j,2}(u_2(j,t)) N_j(t), \\ m_{ij}(x,t) = g_m(t, n_{ij}(x,t)), \quad \text{in } (0, L_{ij}). \end{cases} \tag{4.43}$$

If in addition the initial total mass of Tau is positive and bounded, i.e. if

$$0 < \mathcal{M}_0 = \sum_i \left(\mathrm{Vol}(i)(M_i(0) + N_{0i}) + \sum_{j \neq i} \int_0^L c_{ij}(m_{ij}(x,0) + n_{ij}(x,0))dx \right) < \infty, \tag{4.44}$$

we call $(M_i, N_i, m_{ij}, n_{ij})$ a finite mass solution of the RU-NTM.

As we shall see in Section 4.6, (4.44) is always satisfied if $\gamma_2 \equiv 0$. If $\gamma_2(u_2(0)) > 0$, it follows from $(4.43)_5$ that $\mathcal{M}_0 < \infty$ if and only if $g_m(0, n_{ij}(0)) \in L^1(0, L_{ij})$ for all $i \neq j$ ($c_{ij} > 0$). Below we shall see that this is equivalent to requiring that $n_{ij}(0) < \frac{\beta}{\gamma_2(u_2(0))}$ in $(0, L_{ij})$ (Lemma 4.6.9); in addition by (4.37) the total Tau mass is uniformly bounded in time (Lemma 4.6.7).

The Chapter is devoted to the proof of the following result:

Theorem 4.3.1. *Let $0 \leq N_{i0} < \frac{\beta}{\gamma_2(u_2(i,0))}$ for all $i = 1, \dots, h$. Under the hypotheses $(i) - (iii)$, if for all $i \neq j$ such that $c_{ij} > 0$ there exists $n_{ij}(0) \in C\left([0, L_{ij}]; [0, \frac{\beta}{\gamma_2}]\right)$ which satisfies*

$$\begin{cases} n_{ij}(0) < \frac{\beta}{\gamma_2(0)} & \textit{a.e. in } (0, L_{ij}), \\ [a(x, u_2(0))(n_{ij})_x(0) + h(n_{ij}(0), u_2(0))]_x + F_{ij,\tau}(0) = 0 & \textit{in } \mathcal{D}'(0, L_{ij}), \\ -a(x, u_2(0))(n_{ij})_x(0) = -\mu_{i,1} n_{ij}(0) + \mu_{i,2} N_i(0) & \textit{at } x = 0, \\ -a(L_{ij}, u_2(0))(n_{ij})_x(L_{ij}, 0) - h(n_{ij}(0), u_2(0)) = \mu_{j,1} n_{ij}(0) + \mu_{j,2} N_j(0) & \textit{at } x = L_{ij}, \end{cases}$$

then the quasi-static $A\beta$-RU-NTM possesses a unique solution in the sense of Definition 4.3.1.

In the current Section, we develop the proof of Theorem 4.3.1 following the approach of the existence argument in Chapter 2 and extending it to include the coupled *Release-Uptake* Tau system. Hence we start analysing the characteristics problem issued by the Tau-dependent rate of degeneration $v[f]$ (4.29), followed by the study of the quasi-static Tau model (4.49)-(4.31)-(4.32). The approach we adopt for the latter problem resembles the proof of the main Theorem of Chapter 1, with the selection of new boundary conditions for the edge problem (i.e. the Release-Uptake conditions), u_2-dependent coefficients in both the edges and nodes of the *connectivity* graph and the subsequent time-varying singularity $n = \beta/\gamma_2(u_2(t))$.

For this purpose, we briefly recall the model equations: the measure $f_{i,t}$ satisfies the transport problem

$$\begin{cases} \partial_t f_{i,t} + (v[f_{i,t}] f_{i,t})_a = J[f_{i,t}], \\ f_{i,0} = f_i(0) \end{cases} \qquad i \in V, \tag{4.45}$$

with

$$J[f_{i,t}] = \begin{cases} \eta(t) \left[\left(\int_{[0,1]} P(t,b,a)\, df_{i,t}(b) \right) da - df_{i,t}(a) \right] & \text{if } i \in i_H \text{ and } t \in I_T, \\ 0 \quad \text{otherwise}, \end{cases}$$

i_H being the set of nodes of the network belonging to the brain hippocampal region. The Beta Amyloid concentrations satisfy

$$\begin{cases} d_1 \Delta u_1(i,t) - \sigma_1 u_1(i,t) + F_{A\beta}[f_{i,t}] + \Gamma_1(u(i,t)) = 0, \\ d_2 \Delta u_2(i,t) - \sigma_2 u_2(i,t) + \Gamma_2(u(i,t)) = 0, \\ -\sigma_3 u_3(i,t) + \Gamma_3(u(i,t)) = 0, \end{cases} \qquad i \in V, \tag{4.46}$$

where

$$F_{A\beta}[f_{i,t}] = C_\mu \int_0^1 (\mu_0 + a)(1-a)\, df_{i,t}(a), \quad i \in V,\, t > 0, \tag{4.47}$$

and

$$v[f_{i,t}](a,t) = C_G \int_{[0,1]} (b-a)^+ \, df_{i,t}(b) + C_s(1-a)(u_2(i,t) - \bar{U}_2)^+ + C_N(1-a)(N_i(t) - \bar{N}_i)^+. \tag{4.48}$$

The extracellular Tau model is

$$\begin{aligned}
&\left(1 + \frac{\gamma_1(u_2(i,t))N_i(2\beta - \gamma_2(u_2(i,t))N_i)}{(\beta - \gamma_2(u_2(i,t))N_i)^2}\right)\mathrm{Vol}(i)N_i' \\
&\quad = \mathrm{Vol}(i)F_{i,\tau}(i,t) - \frac{\mathrm{Vol}(i)N_i^2}{\beta - \gamma_2(u_2(i,t))N_i}\left(u_2'(i,t)\gamma_1'(u_2(i,t)) + \frac{\gamma_1(u_2(i,t))u_2'(i,t)\gamma_2'(u_2(i,t))N_i}{\beta - \gamma_2(i,t)N_i}\right) \\
&\qquad + \sum_{j\sim i} c_{ji}J_{ji}(L_{ji},t) - c_{ij}J_{ij}(0,t), \quad i \in V,
\end{aligned} \tag{4.49}$$

where for all $e_{ij} \in E_c$

$$\begin{cases}
J_{ij}(x,t,u_2) = (a(x,u_2)n_{ij}(x,t))_x + h(x,n_{ij}(x,t),u_2), & x \in (0,L_{ij}) \\
(J_{ij})_x(x,t,u_2) = F_{ij,\tau}(x,t), \\
J_{ij}(0,t) = -\mu_{i,1}(u_2(i,t))n_{ij}(0,t) + \mu_{i,2}(u_2(i,t))N_i(t), \\
J_{ij}(L_{ij},t,u_2) = \mu_{j,1}(u_2(j,t))n_{ij}(L_{ij},t) - \mu_{j,2}(u_2(j,t))N_j(t), \\
m_{ij}(x,t) = g_m(t,n_{ij}(x,t)), \quad g_m(t,n) = \frac{\gamma_1(u_2(t))n^2}{\beta - \gamma_2(u_2(t))n^2}.
\end{cases} \tag{4.50}$$

To simplify the notation, we will often write the equation for N_i in the form

$$\mathrm{Vol}(i)\,(M_i + N_i)' = \mathrm{Vol}(i)F_{i,\tau}(i,t) + \sum_{j\sim i} c_{ji}J_{ji}(L_{ji},t,u_2) - c_{ij}J_{ij}(0,t,u_2), \quad i \in V. \tag{4.51}$$

4.4 The Characteristics

Let $f \in \mathcal{L}(V; C([0,T]; X_{[0,1]}))$, $u \in C^0([0,T];\mathbb{R}^{3h})$ and $N \in C^0([0,T];\mathbb{R}^h)$. Consider the characteristics problem associated with (4.45)

$$\begin{cases}
\partial_t A_i(y,t) = v_i(A_i(y,t),t), \\
A_i(y,0) = y \in [0,1]
\end{cases} \quad i \in V. \tag{4.52}$$

Since $(N_1,\dots,N_h)$ belongs to a compact set $B \subset \mathbb{R}^h$, it is uniformly bounded by a constant $C = C(B)$. Arguing as in Section 2.5.1 or Remark 2.6.1, by (4.48) it follows that $a \mapsto v_i(a,t)$ is Lipschitz continuous uniformly in t for all $i \in V$, $t \mapsto v_i(a,t)$ is continuous for all $a \in [0,1]$, and therefore the problem (4.52) has a classical unique local solution which is continuous in $y \in [0,1]$ and such that $t \mapsto A_i(y,t)$ is increasing for all $y \in [0,1]$. Moreover, $0 \le A_i(y,t) \le A_i(1,t) = 1$ and

$$\partial_y A_i(y,t) = \exp\left(\int_0^t \partial_a v_i(A_i(y,s),s)\,ds\right) > 0. \tag{4.53}$$

The statement of Lemma 2.6.1 continues to hold:

Lemma 4.4.1. *Let $f \in \mathcal{L}(V; C([0,T]; X_{[0,1]}))$ be a solution to* (4.45) *and $A_i(y,t)$ a solution to* (4.52). *Then for all $i \in V$ and $t \in (0,T]$*

$$\operatorname{supp} f_{i,t},\ \operatorname{supp} J[f_{i,t}] \subseteq [A_i(0,t), 1]. \tag{4.54}$$

Proof. The proof follows from Lemma 2.6.1 by observing that $a \mapsto v_i(a,t)$ is Lipschitz continuous uniformly in t. □

The problem (4.45) translates in the construction of a probability measure $g_{i,t}$ such that $f_{i,t}$ is the push forward of $g_{i,t}$ through the action of A_i:

$$f_{i,t} = A_i \# g_{i,t}, \quad i \in V \tag{4.55}$$

where g and A satisfy

$$\begin{cases} \partial_t A_i(y,t) = C_G \int_{[0,1]} (A_i(\xi,t) - A_i(y,t))^+ \, dg_{i,t}(\xi) + C_s(1 - A_i(y,t))(u_2(i,t) - \bar{U}_2)^+ \\ \quad + C_N(1 - A_i(y,t))(N_i(t) - \bar{N}_i)^+, \\ \partial_t g_{i,t} = \eta(t)\chi_H \left[\partial_y A_i(y,t) \int P(t, A_i(\xi,t), A_i(y,t)) \, dg_{i,t}(\xi) \, dy - g_{i,t}(\xi)\right], \quad i \in V \\ d_1 \Delta u_1(t) - \sigma_1 u_1(t) + C_\mu \int_{[0,1]} (\mu_0 + A_i(\xi,t))(1 - A_i(\xi,t)) \, dg_{i,t}(\xi) + \Gamma_1(t) = 0, \\ d_2 \Delta u_2(t) - \sigma_2 u_2(t) + \Gamma_2(t) = 0, \\ -\sigma_3 u_3(t) + \Gamma_3(t) = 0, \\ \mathrm{Vol}(i) \left(M_i + N_i\right)'(t) = \mathrm{Vol}(i) F_{i,\tau}(i,t) + \sum_{j\sim i} c_{ji} \left[\mu_{i,1}(u_2(i,t)) n_{ji}(L_{ji},t) - \mu_{i,2}(u_2(i,t)) N_i(t)\right] \\ - \sum_{j \sim i} c_{ij} \left[-\mu_{i,1} n_{ij}(0,t) + \mu_{i,2}(u_2(i,t)) N_i(t)\right], \quad i \in V, \end{cases} \tag{4.56}$$

with initial boundary conditions

$$\begin{cases} g_{i,0} = f_i(0), \\ A_i(y,0) = y, \\ N_i(0) = N_{i0} \in [0, \beta/\gamma_2(u_2(i,0))[\end{cases} \qquad i \in V. \tag{4.57}$$

Definition 4.4.1. *A $6-$tuple (g, A, u_1, u_2, u_3, N) is a solution to* (4.56), (4.57) *if*

1. *$g \in \mathcal{L}(V; C([0,T]; X_{[0,1]}))$;*
2. *$A_i \in C([0,1] \times [0,T]; [0,1])$, $\partial_t A_i \in C([0,1] \times [0,T]; \mathbb{R})$ for all $i \in V$;*
3. *A_i satisfies* $(4.56)_1$ *and $A_i(y,0) = y$ for all $i \in V$ and $y \in [0,1]$;*
4. *$u_k \in C([0,T], \mathbb{R}^h)$, $u_k(i) \geq 0$ for all $k = 1,2,3$ and $i = 1, \dots, h$;*
5. *$N_i \in C^1\left([0,\infty); [0, \frac{\beta}{\gamma_2})\right)$, $M_i \in C^1([0,\infty); [0,\infty))$ for all $i = 1, \dots, h$ and, for all $i \neq j$ such that $c_{ij} > 0$, $n_{ij} \in C([0,L] \times [0,\infty); [0,\infty))$, $m_{ij} \in L^\infty([0,L] \times [0,\infty); [0,\infty))$, $J_{ij} \in C([0,\infty); \mathbb{R})$ and $n_{ij}(t) < \frac{\beta}{\gamma_2(u_2(t))}$ a.e. in $(0, L_{ij})$;*
6. *g is a solution to* $(4.56)_2$ *in a weak sense: for all $\phi \in C^1([0,1] \times [0,T])$*

$$\begin{aligned} &\int \phi(\cdot,t) \, dg_{i,t} - \int \phi(\cdot,0) \, df_i(0) - \int_0^t \left(\int (\phi_s(y,s) dg_{i,s}(y)\right) ds \\ &= \int_0^t \eta\chi_H \left[\int \phi(y,s) \partial_y A_i(y,s) \left(\int P(s, A_i(\xi,s), A_i(y,s)) \, dg_{i,s}(\xi)\right) dy \right. \\ &\qquad \left. - \int \phi(\xi,s) \, dg_{i,s}(\xi)\right] ds\,; \end{aligned} \tag{4.58}$$

7. (u_1, u_2, u_3) *satisfies the following graph equations:*

$$\begin{cases} d_1 \Delta u_1(t) - \sigma_1 u_1(t) + F[g(t)] + \Gamma_1(t) = 0, \\ d_2 \Delta u_2(t) - \sigma_2 u_2(t) + \Gamma_2(t) = 0, \\ -\sigma_3 u_3(t) + \Gamma_3(t) = 0, \end{cases} \tag{4.59}$$

where $F[g]$ *is defined in* (4.56)$_3$ *and the reaction terms* Γ_k *are given by* (4.26)*;*

8. (M_i, N_i) *satisfies*

$$\begin{aligned} \mathrm{Vol}(i)\left(M_i + N_i\right)'(t) &= \mathrm{Vol}(i) F_{i,\tau}(i,t) + \sum_{j\sim i} c_{ji}\left[\mu_{i,1}(u_2(i,t)) n_{ji}(L_{ji}, t) - \mu_{i,2}(u_2(i,t)) N_i(t)\right] \\ &\quad - \sum_{j\sim i} c_{ij}\left[-\mu_{i,1} n_{ij}(0,t) + \mu_{i,2}(u_2(i,t)) N_i(t)\right], \quad i \in V, \end{aligned}$$

where n_{ij} *is a solution to* (4.50).

The equivalence between the original problem and the characteristics reformulation in Chapter 2 follows from the regularity properties of A_i, which continue to hold in the current setting, therefore by Theorem 2.6.2 and Theorem 2.6.3 we have

Theorem 4.4.2. *Let* (A, g, u_1, u_2, u_3, N) *be a solution of* (4.56)-(4.57) *in* $[0, T]$. *Set*

$$f_{i,t} = A_i \# g_{i,t}, \quad \text{for all } t \in [0,T],\ i \in V.$$

Then (f, u_1, u_2, u_3, N) *is a solution to* (4.45)-(4.46)-(4.49).

Theorem 4.4.3. *Let* (f, u_1, u_2, u_3, N) *be a solution to* (4.45)-(4.46)-(4.49) *and* A *a solution to* (4.52). *Then there exists a measure* $g_{i,t}$ *such that*

$$f_{i,t} = A_i \# g_{i,t}, \quad \text{for all } t \in [0,T],\ i \in V$$

and (g, A, u_1, u_2, u_3, N) *is a solution to* (4.56)-(4.57).

We proceed by defining the contractive operator. Let $T > 0$ and

$$X_T := C^0([0,T] \times [0,1]; [0,1]^h) \times \mathcal{L}(V; C([0,T]; X_{[0,1]})) \times C^0([0,T]; \mathbb{R}^{3h}) \times C^0([0,T]; \mathbb{R}^h). \tag{4.60}$$

where $\mathcal{L}(V; C([0,T]; X_{[0,1]})) = \{f \in C([0,T]; X^h_{[0,1]}) : f_i \text{ is weakly* measurable}\}$ is endowed with the 1-Wasserstein distance. Let $(A, g, u, N) \in X_T$. We start with the characteristics problem

$$\begin{cases} \partial_t \tilde{A}_i(y,t) = \tilde{v}_i(\tilde{A}_i(y,t), t), \\ \tilde{A}_i(y,0) = y \in [0,1] \end{cases} \qquad i \in V, \tag{4.61}$$

$$\tilde{v}_i(a,t) = C_G \int_{[0,1]} (A_i(y,t) - a)^+ \, dg_{i,t}(y) + C_s(1-a)(u_2(i,t) - \bar{U}_2)^+ + C_N(1-a)(N_i(t) - \bar{\mathcal{N}}_i)^+ \geq 0 \tag{4.62}$$

and prove that it admits a solution $\bar{A}$. Then we define

$$d(F[g])_{i,t} = \eta \chi_H \left[\partial_y \bar{A}_i(y,t) \int P(t, \bar{A}_i(\xi,t), \bar{A}_i(y,t)) \, dg_{i,t}(\xi) \, dy - dg_{i,t}(y)\right] \tag{4.63}$$

and show that the problem

$$\begin{cases} \partial_t g_{i,t} = d(F[g])_{i,t}, \\ g_{i,0} = f_i(0) \end{cases} \tag{4.64}$$

has a solution $\bar{g}$ in the weak sense. Once we have defined $(\bar{A}, \bar{g})$, we can introduce the monomers' source

$$\tilde{F}[\bar{g}_{i,t}] = C_\mu \int (\mu_0 + \bar{A}_i(y,t))(1 - \bar{A}_i(y,t))\, d\bar{g}_{i,t}(y) \geq 0 \tag{4.65}$$

and, by Section 2.4 of Chapter 2, the elliptic problem

$$\begin{cases} d_1 \Delta \tilde{u}_1 - \sigma_1 \tilde{u}_1 + \tilde{F}[\bar{g}] + \Gamma_1 = 0, \\ d_2 \Delta \tilde{u}_2 - \sigma_2 \tilde{u}_2 + \Gamma_2 = 0, \\ -\sigma_3 \tilde{u}_3 + \Gamma_3 = 0, \end{cases} \qquad \sigma_k > 0 \quad k = 1,2,3, \quad \sum_{k=1}^{3} \Gamma_k(i) = 0 \quad i \in V, \tag{4.66}$$

has a unique non-negative solution $\bar{u}$. By proving that $u \in C^1([0,T];\mathbb{R}^{3h})$, we are then able to define the Tau aggregation functions $\gamma_1(\bar{u}_2), \gamma_1(\bar{u}_2)$, the diffusion barrier function $\lambda(\bar{u}_2)$ and the Release-Uptake terms $\mu_{i,k}(\bar{u}_2)$ and consider the *RU-NTM* given by

$$\begin{aligned} &\left(1 + \frac{\gamma_1(\bar{u}_2(i,t))N_i(2\beta - \gamma_2(\bar{u}_2(i,t))N_i)}{(\beta - \gamma_2(\bar{u}_2(i,t))N_i)^2}\right) \mathrm{Vol}(i) N_i \\ &\quad = \mathrm{Vol}(i) F_{i,\tau}(i,t) - \frac{\mathrm{Vol}(i) N_i^2}{\beta - \gamma_2(\bar{u}_2(i,t))N_i} \left(\bar{u}_2'(i,t)\gamma_1'(\bar{u}_2(i,t)) + \frac{\gamma_1(\bar{u}_2(i,t))\bar{u}_2'(i,t)\gamma_2'(\bar{u}_2(i,t))N_i}{\beta - \gamma_2(\bar{u}_2(i,t))N_i}\right) \\ &\qquad + \sum_{j \sim i} c_{ji} J_{ji}(L_{ji}, t) - c_{ij} J_{ij}(0,t), \quad i \in V, \\ &\qquad M_i(t) = \frac{\gamma_1(\bar{u}_2(i,t))N_i^2(t)}{\beta - \gamma_2(\bar{u}_2(i,t))N_i(t)}, \quad i \in V, \end{aligned} \tag{4.67}$$

$$\begin{cases} J_{ij}(x,t,\bar{u}_2) = (a(x,\bar{u}_2) n_{ij}(x,t))_x + h(x, n_{ij}(x,t), \bar{u}_2) \quad x \in (0, L_{ij}), \\ (J_{ij})_x(x,t,\bar{u}_2) = F_{ij,\tau}(x,t), \\ J_{ij}(0,t) = -\mu_{i,1}(\bar{u}_2(i,t)) n_{ij}(0,t) + \mu_{i,2}(\bar{u}_2(i,t)) N_i(t), \\ J_{ij}(L_{ij},t,\bar{u}_2) = \mu_{j,1}(\bar{u}_2(j,t)) n_{ij}(L_{ij},t) - \mu_{j,2}(\bar{u}_2(j,t)) N_j(t), \\ m_{ij}(x,t) = g_m(t, n_{ij}(x,t)), \quad g_m(t,n) = \frac{\gamma_1(t)n^2}{\beta - \gamma_2(t)n^2}. \end{cases} \tag{4.68}$$

Given a solution $\bar{N}$, we can finally define the operator on X_T

$$\mathcal{H}(A,g,u,N) = (\bar{A}, \bar{g}, \bar{u}, \bar{N}).$$

We start with problem (4.61)-(4.62).

Lemma 4.4.4. *Let $(A,g,u,N) \in X_T$. For all $i \in V$ set*

$$\tilde{v}_i(a,t) = C_G \int_{[0,1]} (A_i(y,t) - a)^+ \, dg_{i,t}(y) + C_s(1-a)(u_2(i,t) - \bar{U}_2)^+ + C_N(1-a)(N_i(t) - \bar{\mathcal{N}}_i)^+. \tag{4.69}$$

Then the problem

$$\begin{cases} \partial_t \tilde{A}_i(y,t) = \tilde{v}_i(\tilde{A}_i(y,t),t), \\ \tilde{A}_i(y,0) = y \in [0,1] \end{cases} \tag{4.70}$$

has a unique solution on $(0, T]$ *denoted by* $\bar{A}_i(y, t)$ *for all* $i \in V$*. The function* $y \mapsto \bar{A}_i(y, t)$ *is continuous and strictly increasing on* $[0, 1]$ *for all* $t \in [0, T]$*. Moreover* $\bar{A}_i([0, 1], t) = [\bar{A}_i(0, t), 1]$ *and* $\bar{A} \in C^0([0, T] \times [0, 1]; [0, 1]^h)$.

Proof. We need to prove that the map $(a, t) \mapsto \tilde{v}_i(a, t)$ is continuous and Lipschitz continuous in a uniformly in t. This implies existence of a unique local solution to problem (4.70) which is continuous in t and y. Then since $\tilde{v}_i(a, t) \geq 0$ for $a \in [0, 1]$, $t \mapsto \bar{A}_i(y, t)$ is increasing for all $y \in [0, 1]$, which implies $\bar{A}_i(0, t) \geq 0$ for all $i \in V$. Observe that $\tilde{v}_i(1, t) = 0$ for all $t \in [0, T]$, so $\bar{A}_i(1, t) = 1$ for all $t \in [0, T]$ and $i \in V$ as in Lemma 2.6.4.

Repeating the argument in Lemma 2.6.4 we also have

$$\partial_y \bar{A}_i(y, t) = \exp\left(\int_0^t \partial_a \tilde{v}_i(\bar{A}_i(y, s), s)\, ds\right) > 0 \quad \text{for } i \in V,\ y \in [0, 1],\ t \in [0, T] \tag{4.71}$$

hence $\partial_y \bar{A}_i(y, t)$ is bounded uniformly in t. Specifically $\bar{A}_i(y, t)$ is Lipschitz continuous in y uniformly in t for all $i \in V$.

To obtain Lipschitz continuity of $a \mapsto \tilde{v}_i(a, t)$ uniformly in t and continuity in t it suffices to observe that the term involving N_i satisfies these conditions. The remaining terms in $\tilde{v}_i$ are both continuous in t and Lipschitz continuous in a uniformly in t by the calculations of Lemma 2.6.4. □

We now consider the problem (4.64). The following result implies the existence of a unique solution to (4.64) and its proof can be obtained by repeating the argument in Lemma 2.6.5.

Lemma 4.4.5. *Let* $(A, g, u, N) \in X_T$ *and* $\bar{A}$ *the solution to* (4.61). *Let* $(F[g])_{i,t}$ *the signed measure on* $[0, 1]$ *defined as*

$$d(F[g])_{i,t} = \eta(t)\chi_H(t)\left[\partial_y \bar{A}_i(y, t) \int P(t, \bar{A}_i(\xi, t), \bar{A}_i(y, t))\, dg_{i,t}(\xi)\, dy - dg_{i,t}(y)\right], \tag{4.72}$$

for $i \in V,\ t \in [0, T]$*. Then for all* $i \in V$

1. *The equation*

$$\bar{g}_{i,t} = f_i(0) + \int_0^t (F[\bar{g}_{i,s}])\, ds \tag{4.73}$$

has a unique solution in $C([0, T]; X_{[0,1]})$ *for all* $i \in V$*, where the measure* $\int_0^t \mu(s)\, ds$ *is defined as* $\left(\int_0^t \mu(s)\, ds\right)(\mathrm{A}) = \int_0^t (\mu(s)(\mathrm{A}))\ ds$ *for any Borel set* $\mathrm{A} \subset [0, 1]$ *and* $\mu \in C([0, T], X_{[0,1]})$*;*

2. *The measure* $\bar{g}_{i,t}$ *is a weak solution to*

$$\begin{cases} \partial_t \bar{g}_{i,t} = \eta\chi_H\left[\partial_y \bar{A}_i(y, t) \int P(t, \bar{A}_i(\xi, t), \bar{A}_i(y, t))\, d\bar{g}_{i,t}(\xi)\, dy - \bar{g}_{i,t}(y)\right], \\ \bar{g}_{i,0} = f_i(0) \end{cases} \tag{4.74}$$

in the sense of (4.58).

By Lemmas 4.4.4 and 4.4.5 we have obtained the solutions $\bar{A}$ and $\bar{g}$. We proceed by defining the monomers' source

$$F[\bar{g}_{i,t}] := C_\mu \int_{[0,1]} (\mu_0 + \bar{A}_i(\xi, t))(1 - \bar{A}_i(\xi, t))\, d\bar{g}_{i,t}(\xi) \geq 0. \tag{4.75}$$

Remark 4.4.1. *By uniform boundedness of $t \mapsto u_2(i,t)$ and $t \mapsto N_i(t)$ it follows that $\tilde{v}_i$ is bounded, therefore $t \mapsto \bar{A}_i(y,t)$ is Lipschitz continuous uniformly in y and by the calculation in Remark 2.6.2 it follows that $t \mapsto F[\bar{g}_{i,t}]$ is Lipschitz continuous.*

By Remark 4.4.1 and Section 2.4 the elliptic graph system

$$\begin{cases} d_1\Delta u_1 - \sigma_1 u_1 + F[\bar{g}] + \Gamma_1 = 0, \\ d_2\Delta u_2 - \sigma_2 u_2 + \Gamma_2 = 0, \qquad\qquad i \in V, \\ -\sigma_3 u_3 + \Gamma_3 = 0, \end{cases} \tag{4.76}$$

exhibits a non negative solution $\bar{u} \in C([0,T];\mathbb{R}^{3h})$ which satisfies the mass balance

$$\sum_{k=1}^{3} \int_G \sigma_k u_k(i,t) = \int_G F[\bar{g}_{i,t}]. \tag{4.77}$$

4.5 Time regularity

To properly consider the problem (4.67)-(4.68) it is useful to show that $u \in C^1([0,T],\mathbb{R}^{3h})$. To this end, we shall adapt the arguments developed in Section 2.7 for u, where (A,g,u) is the global solution of the main problem of Section 2.6, to the solution of (4.76). The main idea is to first improve the time-regularity of $F[\bar{g}_{i,t}]$ obtained in Remark 4.4.1 and then show that $\bar{u}$ inherits the desired regularity property directly from its dependence on $F[\bar{g}_{i,t}]$.

Lemma 4.5.1. *Let $(A,g,u,N) \in X_T$. Let $\bar{A}$ and $\bar{g}$ be the solutions to* (4.70) *and* (4.74)*, respectively. The function $t \mapsto F[\bar{g}_{i,t}]$ satisfies*

$$\partial_t F[\bar{g}_{i,t}](t) = \mathcal{G}_i(t) \tag{4.78}$$

in the weak sense (4.58)*, where*

$$\begin{aligned} \mathcal{G}_i(t) = C_\mu \int (1-\mu_0 - 2\bar{A}_i(y,t))\tilde{v}_i(\bar{A}_i(y,t),t)\, d\bar{g}_{i,t}(y) \\ +C_\mu \eta(t)\chi_H(t) \int \left[(\mu_0 + \bar{A}_i(y,t))(1-\bar{A}_i(y,t))\partial_y \bar{A}_i(y,t) \left(\int P(t,\bar{A}_i(\xi,t),\bar{A}_i(y,t))\, d\bar{g}_{i,t}(\xi)\right)\right] dy \\ -C_\mu \eta(t)\chi_H(t) \int (\mu_0 + \bar{A}_i(y,t))(1-\bar{A}_i(y,t))\, d\bar{g}_{i,t}(y). \end{aligned}$$

Proof. As in Lemma 2.7.1, define $h_i(y,t) := (\mu_0 + \bar{A}_i(y,t))(1-\bar{A}_i(y,t))$. Since $t \mapsto \tilde{v}_i(y,t)$ is continuous for all $y \in [0,1]$ and $t \mapsto \bar{A}_i(y,t)$ is continuous by Lemma 4.4.4, the map $t \mapsto \partial_t \bar{A}_i(y,t) = \tilde{v}_i(\bar{A}_i(y,t),t)$ is continuous for all $y \in [0,1]$. This implies that $t \mapsto h_i(y,t) \in C^1([0,T])$ for all $y \in [0,1]$. Now let $\phi \in C^1([0,T])$. Repeating the same calculations as in Lemma 2.7.1 and applying Lemma 4.4.5 yields, for all $\phi \in C^1([0,T])$,

$$\begin{aligned}
\int_0^T \phi'(t)F[\bar{g}_{i,t}]\,dt = \phi(T)F[\bar{g}_{i,T}] - \phi(0)F[f_{i,0}] \qquad (4.79)\\
-C_\mu \int_0^T \eta(t)\chi_H(t)\phi(t) \int_{[0,1]} \Big[(\mu_0 + \bar{A}_i(y,t))(1-\bar{A}_i(y,t))\partial_y \bar{A}_i(y,t) \\
\left(\int P(t, \bar{A}_i(\xi,y), \bar{A}_i(y,t))\,d\bar{g}_{i,t}(\xi) \right) dy \Big]\,dt \\
+C_\mu \int_0^T \eta(t)\chi_H(t)\phi(t) \int_{[0,1]} (\mu_0 + \bar{A}_i(y,t))(1-\bar{A}_i(y,t))\,d\bar{g}_{i,t}(y)\,dt \\
-C_\mu \int_0^T \phi(t) \int_{[0,1]} (1-\mu_0 - 2\bar{A}_i(y,t))\tilde{v}_i(\bar{A}_i(y,t),t)\,d\bar{g}_{i,t}(y)\,dt.
\end{aligned}$$

□

Remark 4.5.1. *By Lemmas 4.4.4, 4.4.5 and 4.5.1, $\partial_t F[\bar{g}_{i,t}] \in L^\infty(0,T)$.*

The following result resembles the statement of Lemma 4.5.2. However the proof needs a slight modification since, by (4.69), $t \mapsto \tilde{v}_i(a,t)$ is not Lipschitz continuous.

Lemma 4.5.2. *Let $(A,g,u,N) \in X_T$. Let $\bar{A}$, $\bar{g}$ be the solutions to* (4.70) *and* (4.74)*, respectively. If $t \mapsto P(t,a,b)$ is Lipschitz continuous uniformly in (a,b), then $t \mapsto \partial_t F[\bar{g}_{i,t}]$ is continuous as a function from $[0,T]$ to $\mathbb{R}$.*

Proof. We recall that

$$\begin{aligned}
\partial_t F[\bar{g}_{i,t}] = C_\mu \int (1-\mu_0-2\bar{A}_i(y,t))\tilde{v}_i(\bar{A}_i(y,t),t)\,d\bar{g}_{i,t}(y) \\
+C_\mu \eta(t)\chi_H(t) \int \left[h_i(y,t)\partial_y \bar{A}_i(y,t) \int P(t,\bar{A}_i(\xi,t),\bar{A}_i(y,t))\,d\bar{g}_{i,t}(\xi) \right] dy \qquad (4.80)\\
-C_\mu \eta(t)\chi_H(t) \int (\mu_0 + \bar{A}_i(y,t))(1-\bar{A}_i(y,t))\,d\bar{g}_{i,t}(y),
\end{aligned}$$

where, as before, $h_i = (\mu_0 + \bar{A}_i(y,t))(1-\bar{A}_i(y,t))$.

Performing the change of variable $a = \bar{A}_i(y,t)$ as in Lemma 2.7.2, the integral in (4.80) becomes

$$\begin{aligned}
C_\mu \eta(t)\chi_H(t) \int \left[h_i(y,t)\partial_y \bar{A}_i(y,t) \int P(t,\bar{A}_i(\xi,t),\bar{A}_i(y,t))\,d\bar{g}_{i,t}(\xi) \right] dy \qquad (4.81)\\
= C_\mu \eta(t)\chi_H(t) \int \left[h_i(\bar{B}_i(a,t),t) \int P(t,\bar{A}_i(\xi,t),a)\,d\bar{g}_{i,t}(\xi) \right] da \\
= C_\mu \eta(t)\chi_H(t) \int \left[(\mu_0+a)(1-a) \int P(t,\bar{A}_i(\xi,t),a)\,d\bar{g}_{i,t}(\xi) \right] da.
\end{aligned}$$

We write

$$\begin{aligned}
\partial_t F[\bar{g}_{i,t}] = C_\mu \int (1-\mu_0-2\bar{A}_i(y,t))\tilde{v}_i(\bar{A}_i(y,t),t)\,d\bar{g}_{i,t}(y) \\
+C_\mu \eta(t)\chi_H(t) \int \left[(\mu_0+a)(1-a) \int P(t,\bar{A}_i(\xi,t),a)\,d\bar{g}_{i,t}(\xi) \right] da \\
-C_\mu \eta(t)\chi_H(t) \int h_i(y,t)\,d\bar{g}_{i,t}(y) =: I_1(t) + I_2(t) + I_3(t).
\end{aligned}$$

Let$(t_n)_{n\in\mathbb{N}}$ be a sequence such that $t_n \to t$ in $[0,T]$. Arguing as in the proof of Lemma 2.7.2, by the Lipschitz continuity of P and $t \mapsto \bar{A}_i(y,t)$ uniformly in y and the continuity of $\bar{g}_{i,t}$, it follows that $I_2(t_n) \to I_2(t)$ and $I_3(t_n) \to I_3(t)$ as $t_n \to t$.

We now write $I_1(t_n)$ as

$$\begin{aligned} I_1(t_n) = C_\mu \int &\big[(1-\mu_0 - 2\bar{A}_i(y,t_n))\tilde{v}_i(\bar{A}_i(y,t_n),t_n) \\ &-(1-\mu_0 - 2\bar{A}_i(y,t))\tilde{v}_i(\bar{A}_i(y,t),t)\big]\, d\bar{g}_{i,t_n}(y) \\ +C_\mu \int &(1-\mu_0 - 2\bar{A}_i(y,t))\tilde{v}_i(\bar{A}_i(y,t),t)\, d\bar{g}_{i,t_n}(y). \end{aligned} \tag{4.82}$$

The first integral in (4.82) gives

$$\begin{aligned} &C_\mu \int \big[(1-\mu_0 - 2\bar{A}_i(y,t_n))\tilde{v}_i(\bar{A}_i(y,t_n),t_n) \\ &-(1-\mu_0 - 2\bar{A}_i(y,t))\tilde{v}_i(\bar{A}_i(y,t),t)\big]\, d\bar{g}_{i,t_n}(y) \\ &\le C_\mu \int 2|\bar{A}_i(y,t_n)) - \bar{A}_i(y,t))|\tilde{v}_i(\bar{A}_i(y,t_n),t_n)\, d\bar{g}_{i,t_n}(y) \\ &+ C_\mu \int |1-\mu_0 - 2\bar{A}_i(y,t)|\, \big|\tilde{v}_i(\bar{A}_i(y,t_n),t_n) - \tilde{v}_i(\bar{A}_i(y,t),t)\big|\, d\bar{g}_{i,t_n}(y) \\ &\le \tilde{C}_\mu |t_n - t| + C_\mu(3+\mu_0)\int \big|\tilde{v}_i(\bar{A}_i(y,t_n),t_n) - \tilde{v}_i(\bar{A}_i(y,t),t)\big|\, d\bar{g}_{i,t_n}(y), \end{aligned} \tag{4.83}$$

where we have used that $t \mapsto \bar{A}_i(y,t)$ is Lipschitz continuous uniformly in y and the uniform boundedness of $\tilde{v}_i$. Now observe that, being continuous in $[0,1]\times[0,T]$, the map $(y,t)\mapsto \tilde{v}_i(y,t)$ is uniformly continuous, hence for all $\varepsilon > 0$ there exists $\delta > 0$ such that $\big|\tilde{v}_i(\bar{A}_i(y,t),t) - \tilde{v}_i(\bar{A}_i(y',t'),t')\big| < \varepsilon$ for all $|(y,t)-(y',t')| < \delta$. In particular for $y = y'$ it follows that

$$C_\mu(3+\mu_0)\int \big|\tilde{v}_i(\bar{A}_i(y,t_n),t_n) - \tilde{v}_i(\bar{A}_i(y,t),t)\big|\, d\bar{g}_{i,t_n}(y) \le C\varepsilon \int d\bar{g}_{i,t_n}(y) = C\varepsilon$$

provided that n is sufficiently large. Hence the integral term (4.83) satisfies

$$C_\mu \int \big[(1-\mu_0 - 2\bar{A}_i(y,t_n))\tilde{v}_i(\bar{A}_i(y,t_n),t_n) \; -(1-\mu_0 - 2\bar{A}_i(y,t))\tilde{v}_i(\bar{A}_i(y,t),t)\big]\, d\bar{g}_{i,t_n}(y) \to 0, \text{ as } t_n \to t.$$

Concerning the remaining term in $I_1(t_n)$, by narrow continuity of $t \mapsto \bar{g}_{i,t}$ we have

$$\begin{aligned} &\lim_{n\to\infty} C_\mu \int (1-\mu_0 - 2\bar{A}_i(y,t))\tilde{v}_i(\bar{A}_i(y,t),t)\, d\bar{g}_{i,t_n}(y) \\ &= C_\mu \int (1-\mu_0 - 2\bar{A}_i(y,t))\tilde{v}_i(\bar{A}_i(y,t),t)\, d\bar{g}_{i,t}(y). \end{aligned}$$

□

We conclude this Section with the main regularity result, whose proof is obtained *mutatis mutandis* from that of Lemma 2.7.3.

Lemma 4.5.3. *Let* $(A,g,u,N) \in X_T$ *and* $\bar{A}$, $\bar{g}$ *be the solutions to* (4.70), (4.74), *respectively. If* $t \mapsto P(t,a,b)$ *is Lipschitz continuous uniformly in* (a,b), *then* $t \mapsto \partial_t u(t)$ *is continuous as a function from* $[0,T]$ *to* $\mathbb{R}^{3h}$.

4.6 Existence for the Release-Uptake-NTM

Let $(A, g, u, N) \in X_T$ and $\bar{A}$, $\bar{g}$, $\bar{u}$ be solutions to (4.70), (4.74) and (4.76), respectively. To conclude the construction of the operator $\mathcal{H}$ on X_T, we need to show that the system

$$\begin{aligned}
&\left(1+\frac{\gamma_1(\bar{u}_2(i,t))N_i(2\beta-\gamma_2(\bar{u}_2(i,t))N_i)}{(\beta-\gamma_2(\bar{u}_2(i,t))N_i)^2}\right)\mathrm{Vol}(i)N_i' \qquad (4.84)\\
&\quad=\mathrm{Vol}(i)F_{i,\tau}(i,t)-\frac{\mathrm{Vol}(i)N_i^2}{\beta-\gamma_2(\bar{u}_2(i,t))N_i}\left(\bar{u}_2'(i,t)\gamma_1'(\bar{u}_2(i,t))+\frac{\gamma_1(\bar{u}_2(i,t))\bar{u}_2'(i,t)\gamma_2'(\bar{u}_2(i,t))N_i}{\beta-\gamma_2(\bar{u}_2(i,t))N_i}\right)\\
&\quad+\sum_{j\sim i}c_{ji}J_{ji}(L_{ji},t)-c_{ij}J_{ij}(0,t),\quad i\in V,\\
&\quad M_i(t)=\frac{\gamma_1(\bar{u}_2(i,t))N_i^2(t)}{\beta-\gamma_2(\bar{u}_2(i,t))N_i(t)},\quad i\in V,
\end{aligned}$$

$$\begin{cases}
J_{ij}(x,t,\bar{u}_2)=(a(x,\bar{u}_2)n_{ij}(x,t))_x+h(x,n_{ij}(x,t),\bar{u}_2) & x\in(0,L_{ij}),\\
(J_{ij})_x(x,t,\bar{u}_2)=F_{ij,\tau}(x,t),\\
J_{ij}(0,t,\bar{u}_2)=-\mu_{i,1}(\bar{u}_2(i,t))n_{ij}(0,t)+\mu_{i,2}(\bar{u}_2(i,t))N_i(t),\\
J_{ij}(L_{ij},t,\bar{u}_2)=\mu_{j,1}(\bar{u}_2(j,t))n_{ij}(L_{ij},t)-\mu_{j,2}(\bar{u}_2(j,t))N_j(t),\\
m_{ij}(x,t)=g_m(t,n_{ij}(x,t)),\quad g_m(t,n)=\frac{\gamma_1(u_2(t))n^2}{\beta-\gamma_2(u_2(t))n^2},
\end{cases}\tag{4.85}$$

associated to $(\bar{A}, \bar{g}, \bar{u})$ admits a solution on $[0, T]$ in the sense of Definition 4.4.1$_8$.

As in Chapter 1, both the edge and node equations exhibit a singularity at β/γ_2, which in principle is a dynamical quantity through its dependence on $\bar{u}_2$. Hence it is natural to require a condition of sub-criticality of N_i and n_{ij} for $i \in V$ and $e_{ij} \in E_c$, which we will prove in the following to be equivalent to the requirement of finite total mass. Since we assume the source terms on the nodes and edges of the network to be bounded, the latter property of the system turns out to be strictly related to the behaviour of the total mass at initial time.

We start by analysing the edge problem (4.85) at fixed time $t \geq 0$. We often suppress the time dependence and the edge subscripts to simplify the notation. Consider the shooting problem

$$\begin{cases}
J_x=F_{ij,\tau},\quad J=-an_x+h(x,n,g_m(n)) & \text{for } x\in[0,L],\\
J(0)=-\mu_{i,1}n(0)-\mu_{i,2}N_i,
\end{cases}\tag{4.86}$$

where $n(0) \geq 0$ is the shooting parameter and $g_m(n) = g_m(n, u_2(t))$. We look for a value of $n(0)$ for which the solution of (4.86) satisfies

$$n\geq 0\quad\text{in } [0,L]\quad\text{and}\quad J(L)=\mu_{j,1}n(L)-\mu_{j,2}N_j.\tag{4.87}$$

Lemma 4.6.1. *Let $x_1 \in (0, L]$ and let n_1 and n_2 be two non-negative solutions of* (4.86) *in* $[0, x_1]$, *with initial values $n_1(0)$ and $n_2(0)$. If $0 \leq n_1(0) < n_2(0)$, then $n_1 < n_2$ in* $[0, x_1]$.

Proof. Let J_1 and J_2 be the corresponding fluxes. Then $J_1(0) > J_2(0)$ and, since $J(x) = J(0) + \int_0^x F_{ij,\tau}$, $J_1(x) > J_2(x)$ for all $x \in [0, x_1]$. If there exists $\bar{x} \in (0, x_1]$ such that $n_1(\bar{x}) = n_2(\bar{x})$, since $h(x, 0, g_m(0)) = 0$, by the first order equation for n_1 and n_2 we have $a(\bar{x})(n_1 - n_2)_x(\bar{x}) < 0$, which is impossible. Hence we conclude that $n_1 < n_2$ in $[0, x_1]$. ☐

Corollary 4.6.2. *Given $N_i, N_j \geq 0$, there exists at most one non-negative solution of* (4.86)-(4.87).

Proof. Let n_1 and n_2 be two non-negative solutions. Then, for $k = 1, 2$,

$$J_k(L) = J_k(0) + \int_0^L F_{ij,\tau} \equiv J_k(0) + C,$$

whence

$$\mu_{j,1}n_k(L) - \mu_{j,2}N_j = -\mu_{i,1}n_k(0) + \mu_{i,2}N_i + C,$$

i.e.

$$\mu_{j,1}n_k(L) + \mu_{i,1}n_k(0) = \mu_{j,2}N_j + \mu_{i,2}N_i + C. \tag{4.88}$$

Arguing by contradiction we may assume without loss of generality that $n_1(0) < n_2(0)$. By Lemma 4.6.1, then also $n_1(L) < n_2(L)$, but this is in contradiction with (4.88). $\square$

In order to prove the existence of a solution of (4.86)-(4.87) we first consider the case that

$$\gamma_2(i) = 0 \text{ and } \gamma_2(i,j) = 0 \quad \text{ for all } i \in V,\ e_{ij} \in E_c. \tag{4.89}$$

In the following, we denote the condition (4.89) by $\gamma_2 \equiv 0$. We set

$$\mathcal{N} := \{n_0 \geq 0 : \text{ the solution of (4.86) with } n(0) = n_0 \text{ exists and is non-negative in } [0, L]\}.$$

Observe that $0 \in \mathcal{N}$ if and only if

$$N_i = N_j = 0 \quad \text{and} \quad F_{ij,\tau} \equiv 0 \text{ in } [0, L], \tag{4.90}$$

and in that case $n \equiv 0$ in $[0, L]$. Otherwise $0 \notin \mathcal{N}$ and, if $n(0) > 0$ is small enough, the solution of (4.86) crosses $n = 0$ at some point in $(0, L)$ and the solution of (4.86) is not globally defined in $[0, L]$. For example, if $N_i > 0$ is sufficiently large then $a(0)n_x(0) = \mu_{i,1}n(0) - \mu_{i,2}N_i << -\mu_{i,2}N_i < 0$.

Lemma 4.6.3. *There exists* $n^* > 0$ *such that* $n(0) \in \mathcal{N}$ *for all* $n(0) > n^*$.

Proof. Observe that $J(0) = -\mu_{i,1}n(0) + \mu_{i,2}N_i \to -\infty$ as $n(0) \to \infty$. Since $J_x = F_{ij,\tau}$ which is bounded, $S(n_0) := J(L; n_0) - \mu_{j,1}n(L; n_0) + \mu_{j,2}N_j \to -\infty$ as $n_0 \to \infty$, whence (4.86) has a solution $n > 0$ in $[0, L]$ if $n(0)$ is large enough. $\square$

Corollary 4.6.4. *There exists* $\underline{n}_0 \geq 0$ *such that*

$$\mathcal{N} = [\underline{n}_0, \infty),$$

and $\underline{n}_0 = 0$ *if and only if* (4.90) *is satisfied.*

Proof. By Lemma 4.6.3 the set $\mathcal{N}$ is non-empty and, by Lemma 4.6.1, it is an interval of the type $[\underline{n}_0, \infty)$. As we have observed above, $0 \in \mathcal{N}$ ($\Leftrightarrow$ $\underline{n}_0 = 0$) if and only if (4.90) is satisfied. $\square$

Lemma 4.6.5. *Let* $n \geq 0$ *be a solution of* (4.86) *in* $[0, L)$. *Then either* $n > 0$ *in* $[0, L)$ *or* (4.90) *is satisfied and* $n \equiv 0$ *in* $[0, L]$.

Proof. We must prove that $n > 0$ in $[0, L)$ if (4.90) is not satisfied. In that case $\underline{n}_0 > 0$. Arguing by contradiction we suppose that $n(x_0) = 0$ for some $x_0 \in (0, L)$.

Since $h(x, 0, g_m(0)) = 0$ and $n_x(x_0^-) \leq 0$, we have that $J(x_0^-) \geq 0$. Similarly, $J(x_0^+) \leq 0$. Since J is a continuous function, this implies that $J(x_0) = 0$. Since $J_x = F_\tau \geq 0$,

$$J \geq 0 \text{ in } (x_0, L), \quad J \leq 0 \text{ in } (0, x_0),$$

i.e., by the boundedness of h,

$$\begin{cases} Dn_x \le Cn & \text{in a right neighbourhood of } x_0 \\ n(x_0) = 0, \end{cases} \qquad \begin{cases} Dn_x \ge -Cn & \text{in a left neighbourhood of } x_0 \\ n(x_0) = 0. \end{cases}$$

Since $n \ge 0$ in $(0, L)$, it follows from Gronwall's Lemma that $n \equiv 0$ in a neigbourhood of x_0, and therefore $n \equiv 0$ in $[0, L]$. Indeed, if $Z(n) := \{x \in (0, L) : n(x) = 0\}$ then $Z(n)$ is a non-empty open set in $(0, L)$ by the argument above. Moreover, $Z(n)$ is closed by the continuity of n in $(0, L)$, hence $Z(n) = (0, L)$. □

Lemma 4.6.6. *Let $\gamma_2 \equiv 0$. Then problem* (4.86)-(4.87) *possesses at least one non-negative solution.*

Proof. Without loss of generality we may assume that $\underline{n}_0 > 0$. By Lemma 4.6.5, for all $n(0) \ge \underline{n}_0$ the solution of the shooting problem (4.86) satisfies

$$n > 0 \quad \text{in } [0, L).$$

By the definition of $\underline{n}_0$, there exists $x_0 \in (0, L]$ such that solution n of (4.86) vanishes at x_0 and necessarily $x_0 = L$:

$$n(0) = \underline{n}_0 \;\Rightarrow\; n(L) = 0.$$

Therefore

$$J(L) = -an_x(L) \ge 0, \qquad \mu_{j,1}n(L) - \mu_{j,2}N_j = -\mu_{j,2}N_j \le 0,$$

whence $J(L) \ge \mu_{j,1}n(L) - \mu_{j,2}N_j$ if $n(0) = \underline{n}_0$.

On the other hand, it easily follows from the proof of Lemma 4.6.3 that if $n(0) > \underline{n}_0$ is large enough, the solution of (4.86) satisfies $J(L) < \mu_{j,1}n(L) - \mu_{j,2}N_j$. Hence there exists $n(0) \ge \underline{n}_0$ such that the solution of (4.86) satisfies $J(L) = \mu_{j,1}n(L) - \mu_{j,2}N_j$. □

The uniqueness follows from the estimate (4.100) which will be proved in Lemma 4.6.12.

By hypothesis (4.37), if the initial mass is bounded, then the total mass of the system is bounded at all times and the structure of the equations yields the following mass balance.

Lemma 4.6.7. *Let $\gamma_2 \ge 0$, let $N_{0i} \in [0, \beta/\gamma_2(\bar{u}_2(i, 0)))$ for all $1 \le i \le h$ and let $(M_i, N_i, m_{ij}, n_{ij})$ be a finite mass solution of the quasi-static NTM in the sense of Definition 4.3.1$_4$. Then for all $t > 0$*

$$\mathcal{M}(t) = \mathcal{M}(0) + \sum_{i \in V} \int_0^t \mathrm{Vol}(i) F_{i,\tau}(t)\, dt + \sum_{(i,j) \in E_c} c_{ij} \int_0^t \int_0^{L_{ij}} F_{ij,\tau}(x, t)\, dx\, dt > 0, \tag{4.91}$$

where $0 < \mathcal{M}_0 < \infty$ is the total initial mass defined by (4.93).

4.6.1 Sub-critical behaviour

We now consider the case of $\gamma_2 \not\equiv 0$.

Remark 4.6.1. *The condition $N_i < \beta/\gamma_2(i)$, $N_j < \beta/\gamma_2(j)$ is not sufficient to guarantee a subcritical behaviour for n_{ij} on the edge e_{ij}. For example, let $F_{ij,\tau} \equiv 0$ and suppose $\mu_{i,1} << \mu_{i,2}$, $\mu_{j,1} << \mu_{j,2}$. We have*

$$J(0) = J(L_{ij}) \Rightarrow \mu_{i,1}n(0) + \mu_{j,1}n(L_{ij}) = \mu_{i,2}N_i + \mu_{j,2}N_j.$$

Selecting $N_i \lesssim \frac{\beta}{\gamma_2}$ and $N_j \lesssim \frac{\beta}{\gamma_2}$ implies that at least one of $n(0)$ and $n(L_{ij})$ must be supercritical, i.e. $n(0) \ge \frac{\beta}{\gamma_2(i)}$ or $n(L_{ij}) \ge \frac{\beta}{\gamma_2(j)}$.

As in Chapter 1, we relax the nonnegativity of n and consider the problem

$$\begin{cases} -\varepsilon_1 \leq n_{ij} < \frac{\beta}{\gamma_2} & \text{a.e. in } (0, L_{ij}) \\ -\varepsilon_2 \leq N_i, N_j, \quad N_i < \beta/\gamma_2(i), N_j < \beta/\gamma_2(j), & \\ (J_{ij})_x(x, t, \bar{u}_2) = F_{ij,\tau}(x, t), & \text{in } \mathcal{D}'(0, L_{ij}), \\ J_{ij}(0, t) = -\mu_{i,1}(\bar{u}_2(i, t))n_{ij}(0, t) + \mu_{i,2}(\bar{u}_2(i, t))N_i(t), & \\ J_{ij}(L_{ij}, t) = \mu_{j,1}(\bar{u}_2(j, t))n_{ij}(L_{ij}, t) - \mu_{j,2}(\bar{u}_2(j, t))N_j(t). & \end{cases} \tag{4.92}$$

We state some natural properties of the advective term h and the function g_m which defines the edge insoluble Tau concentration.

Lemma 4.6.8. *Let $g_m(n, t)$ and $h(x, n, \bar{u}_2(t))$ be defined by* (4.85)$_5$ *and* (4.2) *and let $\varepsilon_1 > 0$. Then $\partial_n g_m > 0$ in $(0, \frac{\beta}{\gamma_2})$, $g(n, \bar{u}_2(t)) \to \infty$ as $n \to \frac{\beta}{\gamma_2}$ for all $t \geq 0$, and there exists $C > 0$ such that*

$$h,\ \tfrac{\partial h}{\partial n} \geq -C \text{ in } (0, L_{ij}) \times (-\varepsilon_1, \tfrac{\beta}{\gamma_2}) \times \mathbb{R}^+, \qquad h,\ \tfrac{\partial h}{\partial n},\ \tfrac{\partial^2 h}{\partial^2 n} \in L^\infty_{\text{loc}}([0, L] \times [-\varepsilon_1, \tfrac{\beta}{\gamma_2}) \times \mathbb{R}^+).$$

The following result ensures that, in the case of $\gamma_2 \not\equiv 0$, the condition of finite total mass is equivalent to the subcritical behaviour of n.

Lemma 4.6.9. *Let $t \geq 0$ be fixed and $\gamma_2 \not\equiv 0$. Let $\varepsilon_1 \geq \varepsilon_2 > 0$, $N_i \in \left[-\varepsilon_2, \frac{\beta}{\gamma_2(\bar{u}_2(i))}\right)$ for all $1 \leq i \leq h$, and let $n_{ij} \in C([0, L_{ij}])$ satisfy* (4.92) *for all $i \neq j$ such that $c_{ij} > 0$. If*

$$\mathcal{M} := \sum_{i \in V} \left(\mathrm{Vol}(i)(N_i + g_m(N_i, \bar{u}_2)) + \sum_{j \neq i} c_{ij} \left(\int_0^L n_{ij} + g_m(n_{ij}, \bar{u}_2)\, dx \right) \right), \tag{4.93}$$

then

$$\begin{aligned} \mathcal{M} < \infty \ &\Leftrightarrow\ g_m(n_{ij}, \bar{u}_2(i, j)) \in L^1(0, L_{ij})\ \forall\, e_{ij} \in E_c \\ &\Leftrightarrow\ n_{ij} < \tfrac{\beta}{\gamma_2(\bar{u}_2(i,j))} \text{ in } [0, L]\ \forall\, e_{ij} \in E_c. \end{aligned} \tag{4.94}$$

Setting $t = 0$, we obtain the following characterization of initial data with finite mass:

Corollary 4.6.10. *Let $\gamma_2 \not\equiv 0$ and $N_{0i} \in [0, \beta/\gamma_2(\bar{u}_2(i, 0))$ for all $1 \leq i \leq h$. Let $n_{ij}(0) \in C([0, L_{ij}])$ satisfy, for all $i \neq j$ such that $c_{ij} > 0$,*

$$\begin{cases} 0 \leq n_{ij}(0) < \frac{\beta}{\gamma_2(\bar{u}_2(i,j,0))} & \text{a.e. in } (0, L_{ij}) \\ \left(a(x, \bar{u}_2(i, j, 0))(n_{ij}(0))_x + h(x, n_{ij}(0), \bar{u}_2(i, j, 0))\right)_x + F_{ij,\tau}(0) = 0 & \text{in } \mathcal{D}'(0, L_{ij}) \\ J_{ij}(0, 0) = -\mu_{i,1}(\bar{u}_2(i, 0))n_{ij}(0, 0) + \mu_{i,2}(\bar{u}_2(i, 0))N_{i0}, & \\ J_{ij}(L_{ij}, 0) = \mu_{j,1}(\bar{u}_2(j, 0))n_{ij}(L_{ij}, 0) - \mu_{j,2}(\bar{u}_2(j, 0))N_{j0}. & \end{cases} \tag{4.95}$$

Let $\mathcal{M}_0$ be defined by (4.93) *at $t = 0$. Then*

$$\mathcal{M}_0 < \infty \ \Leftrightarrow\ g_m(n_{ij}(0), \bar{u}_2(i, j, 0)) \in L^1(0, L_{ij}) \ \Leftrightarrow\ n_{ij}(0) < \tfrac{\beta}{\gamma_2(\bar{u}_2(i,j,0))} \text{ in } [0, L_{ij}].$$

Proof of Lemma 4.6.9. By (4.85)$_5$, the first equivalence in (4.94) is immediate, so it remains to prove the second one. Since ($\Leftarrow$) is obvious, we only prove the implication ($\Rightarrow$).

For simplicity, we drop the dependencies of $\bar{u}_2$ on i, j and t. Let $g(n_{ij}, \bar{u}_2) \in L^1((0, L_{ij}))$. We fix $i \sim j$ and set $n = n_{ij}$. Since $h(x, n, \bar{u}_2) = 0$ if $x \notin [x_2, L_{ij}]$, from the first order equation for n on $(0, x_2)$ it follows that

$$-a(x, \bar{u}_2)n_x = -\mu_{i,1}(\bar{u}_2)n(0) + \mu_{i,2}(\bar{u}_2)N_i + \int_0^x F_{ij,\tau}\, dy.$$

Hence by hypothesis (4.36), (4.37) and (4.38) and by definition of a it follows that n is Lipschitz continuous in $[0, x_2]$. Suppose there exists $\xi \in [0, L_{ij}]$ such that $n(\xi) = \frac{\beta}{\gamma_2(\bar{u}_2(\xi))}$. Then the behaviour of g_m as $n \to \beta/\gamma_2(\bar{u}_2(\xi))$ implies that $\xi \notin [0, x_2]$.

If $n(\xi) = \frac{\beta}{\gamma_2(\bar{u}_2(\xi))}$ for some $\xi \in (x_2, L_{ij}]$, it follows from Lemma 4.6.8 and the hypothesis (4.36) that

$$\lim_{x \to \xi^-} h(n(x), \bar{u}_2(x)) = \infty,$$

hence by the equation for n we have

$$a(x, \bar{u}_2)n_x = -h(x, n, \bar{u}_2) - J(x) \to -\infty, \text{ as } x \to \xi^-$$

which is impossible.

The proof of the local existence of a solution to (4.84) is based on the construction of a contraction. To properly define a contractive operator we fix a suitable space X_τ and, since we assume a finite total initial mass, Corollary (4.6.10) yields an edge solution n_{ij} at time $t = 0$ for all edges and $(N_1, \ldots, N_h) \in X_\tau$, which is subcritical. That solution is then locally extended to $[0, \tau]$ by Lemma 4.6.11, where τ is sufficiently small to guarantee a subcritical behaviour.

Lemma 4.6.11. *Let $t \geq 0$ be fixed. Let $\varepsilon_1 \geq \varepsilon_2 > 0$, $\gamma_2 \not\equiv 0$, $N_i \in \left[-\varepsilon_2, \frac{\beta}{\gamma_2(i)}\right)$ for all $1 \leq i \leq h$, let $n_{ij} \in C([0, L])$ satisfy* (4.92) *for all $i \sim j$ and let $\mathcal{M}$, defined by* (4.93)*, be finite. Then there exists $\varepsilon_3 > 0$ which does not depend on i, j such that for all $\tilde{\gamma}_k \geq 0$, $\tilde{\lambda} \in (0, 1)$, $\tilde{F}_{ij,\tau} \geq 0$, $\tilde{\mu}_{i,k} \geq 0$ and for all $\tilde{N}_i < \beta/\tilde{\gamma}_2(i)$ satisfying*

$$|\tilde{\gamma}_k - \gamma_k|, |\tilde{\lambda} - \lambda|, |\tilde{F}_{ij,\tau} - F_{ij,\tau}|, |\tilde{\mu}_{i,k} - \mu_{i,k}|, |\tilde{N}_i - N_i| \leq \varepsilon_3,$$

there exists a unique $\tilde{n}_{ij} \in C([0, L_{ij}])$ which satisfies, for all $i \neq j$ such that $c_{ij} > 0$,

$$\begin{cases} -2\varepsilon_1 \leq \tilde{n}_{ij} < \frac{\beta}{\tilde{\gamma}_2(i,j)}, & \text{in } (0, L_{ij}), \\ -(a(x, \tilde{\lambda})(\tilde{n}_{ij})_x + h(x, \tilde{n}_{ij}, \tilde{\gamma}_1, \tilde{\gamma}_2))_x = \tilde{F}_{ij,\tau}(x, t), & \text{in } \mathcal{D}'(0, L_{ij}), \\ J_{ij}(0, t) = -\tilde{\mu}_{i,1}(i, t)\tilde{n}_{ij}(0, t) + \tilde{\mu}_{i,2}(i, t)\tilde{N}_i(t), \\ J_{ij}(L_{ij}, t) = \tilde{\mu}_{j,1}(j, t)\tilde{n}_{ij}(L_{ij}, t) - \tilde{\mu}_{j,2}(j, t)\tilde{N}_j(t). \end{cases} \tag{4.96}$$

Proof. Consider the shooting problem

$$\begin{cases} -(a(x, \tilde{\lambda})n_x + h(x, n, \tilde{\gamma}_1, \tilde{\gamma}_2))_x = \tilde{F}_{ij,\tau}(x, t), & x \text{ in } (0, L_{ij}) \\ J(0) = -\tilde{\mu}_{i,1}(i, t)n(0) + \tilde{\mu}_{i,2}(i, t)\tilde{N}_i(t). \end{cases} \tag{4.97}$$

By Corollary 4.6.10 we can apply the argument in Lemma 4.6.6 to obtain a sub-critical solution n associated to the parameter set $(N_i, N_j, \gamma_1, \gamma_2, \lambda, \mu_{i,k}, F_{ij,\tau})$. By the continuous dependence of n on the parameters and the monotonicity of J in $n(0)$, we obtain that for some perturbation of the parameters $(\tilde{N}_i, \tilde{N}_j, \tilde{\gamma}_1, \tilde{\gamma}_2, \tilde{\lambda}, \tilde{\mu}_{i,k}, \tilde{F}_{ij,\tau})$ there exists a solution $\tilde{n} \geq -2\varepsilon_1$ to (4.96) which satisfies $\tilde{J}(L) = \tilde{\mu}_{j,1}\tilde{n}(L) - \tilde{\mu}_{j,2}\tilde{N}_j$ provided that the perturbation is sufficiently small, i.e.

$$|\tilde{\gamma}_k - \gamma_k|, |\tilde{\lambda} - \lambda|, |\tilde{F}_{ij,\tau} - F_{ij,\tau}|, |\tilde{\mu}_{i,k} - \mu_{i,k}|, |\tilde{N}_i - N_i|, |\tilde{N}_j - N_j| \leq \varepsilon_{ij}.$$

Since the number of edges is finite, we define $\varepsilon_3 = \min_{i \sim j} \varepsilon_{ij} > 0$. □

4.6.2 A fixed point argument

In this Section, we provide a local solution to the *RU-NTM*. We will then prove its nonnegativity and extend it to the interval $[0, T]$. The main tool we need to construct the contractive operator is a uniform estimate for the edge solution n_{ij}.

Lemma 4.6.12. *Let $t \geq 0$ and $c_{ij} > 0$. Let $n_{ij}(t), \tilde{n}_{ij}(t) \in C([0, L_{ij}])$ be such that*

$$-\varepsilon_1 < n_{ij}(t), \tilde{n}_{ij}(t) < \beta/\gamma_2(\bar{u}_2(i,j,t)) \quad \textit{in } [0, L_{ij}].$$

If $n_{ij}(x,t)$ and $\tilde{n}_{ij}(x,t)$ satisfy (4.92)$_{3,4,5}$ *with boundary conditions*

$$\begin{cases} J_{ij}(0,t) = -\mu_{i,1}(u_2(i,t))n_{ij}(0,t) + \mu_{i,2}(u_2(i,t))N_i(t), \\ J_{ij}(L_{ij},t) = \mu_{j,1}(u_2(j,t))n_{ij}(L_{ij},t) - \mu_{j,2}(u_2(j,t))N_j(t), \end{cases} \tag{4.98}$$

$$\begin{cases} \tilde{J}_{ij}(0,t) = -\mu_{i,1}(u_2(i,t))\tilde{n}_{ij}(0,t) + \mu_{i,2}(u_2(i,t))\tilde{N}_i(t), \\ \tilde{J}_{ij}(L_{ij},t) = \mu_{j,1}(u_2(j,t))\tilde{n}_{ij}(L_{ij},t) - \mu_{j,2}(u_2(j,t))\tilde{N}_j(t), \end{cases} \tag{4.99}$$

where $J_{ij}(t)$ and $\tilde{J}_{ij}(t)$ are the fluxes of n_{ij} and $\tilde{n}_{ij}$, respectively. Then there exists a constant C such that

$$|n_{ij}(x,t) - \tilde{n}_{ij}(x,t)| \leq C \left(|N_i(t) - \tilde{N}_i(t)| + |N_j(t) - \tilde{N}_j(t)| \right). \tag{4.100}$$

Proof. The fluxes J_{ij} and $\tilde{J}_{ij}$ satisfy

$$(J_{ij} - \tilde{J}_{ij})_x = 0 \quad \Rightarrow \quad J_{ij}(x) - \tilde{J}_{ij}(x) = \text{ constant } =: J_\omega. \tag{4.101}$$

We set $\omega = n_{ij} - \tilde{n}_{ij}$. By the mean value theorem, ω satisfies the equation

$$-\left(a(x,\bar{u}_2)\omega_x + b(x,\bar{u}_2)\,\omega\right) = J_\omega. \tag{4.102}$$

where $b = 0$ in $(0, x_2)$ and, if $x_2 < x < L_{ij}$, $b(x,\bar{u}_2) = \frac{\partial h}{\partial n}(x, \nu(x,t), \bar{u}_2)$ for some function $\nu(x,t) \in [-\varepsilon_1, \max_{x,t} \beta/\gamma_2(x,t))$. The quantity J_ω satisfies

$$J_\omega = -\mu_{i,1}\omega(0) + \mu_{i,2}(N_i - \tilde{N}_i) = \mu_{j,1}\omega(L_{ij}) - \mu_{j,2}(N_j - \tilde{N}_j). \tag{4.103}$$

Integrating equation (4.102) on $[0, L_{ij}]$ gives

$$\omega(L_{ij}) = \omega(0)e^{-\int_0^{L_{ij}} \frac{b}{a}\,dy} - J_\omega e^{-\int_0^{L_{ij}} \frac{b}{a}\,dy} \int_0^{L_{ij}} \frac{e^{\int_0^y \frac{b}{a}\,dz}}{a(y,\bar{u}_2)}\,dy. \tag{4.104}$$

By (4.103) and (4.104) it follows that

$$\omega(0) = \frac{\mu_{i,2}(N_i - \tilde{N}_i) - J_\omega}{\mu_{i,1}} \tag{4.105}$$

therefore

$$\omega(0) = \frac{\mu_{i,2}}{\mu_{i,1}}(N_i - \tilde{N}_i) - \frac{\mu_{j,1}}{\mu_{i,1}}\omega(0)e^{-\int_0^{L_{ij}} \frac{b}{a}\,dy} + \frac{\mu_{j,1}}{\mu_{i,1}}J_\omega e^{-\int_0^{L_{ij}} \frac{b}{a}\,dy} \int_0^{L_{ij}} \frac{e^{\int_0^y \frac{b}{a}\,dz}}{a(y,\bar{u}_2)}\,dy + \frac{\mu_{j,2}}{\mu_{i,1}}(N_j - \tilde{N}_j). \tag{4.106}$$

Now by (4.103) we rearrange (4.106) to get

$$\left(1+\frac{\mu_{j,1}}{\mu_{i,1}}e^{-\int_0^{L_{ij}}\frac{b}{a}\,dy}+\mu_{j,1}e^{-\int_0^{L_{ij}}\frac{b}{a}\,dy}\int_0^{L_{ij}}\frac{e^{\int_0^y\frac{b}{a}\,dz}}{a(y,\bar{u}_2)}\,dy\right)\omega(0) \tag{4.107}$$
$$=\frac{\mu_{i,2}}{\mu_{i,1}}(N_i-\tilde{N}_i)+\frac{\mu_{j,2}}{\mu_{i,1}}(N_j-\tilde{N}_j)+\frac{\mu_{j,1}\mu_{i,2}}{\mu_{i,1}}e^{-\int_0^{L_{ij}}\frac{b}{a}\,dy}\int_0^{L_{ij}}\frac{e^{\int_0^y\frac{b}{a}\,dz}}{a(y,\bar{u}_2)}\,dy\,(N_i-\tilde{N}_i).$$

Integrating the equation for ω yields

$$\omega(x)=\omega(0)e^{-\int_0^x\frac{b}{a}\,dy}-J_\omega e^{-\int_0^x\frac{b}{a}\,dy}\int_0^{L_{ij}}\frac{e^{\int_0^y\frac{b}{a}\,dz}}{a(y,\bar{u}_2)}\,dy \quad \text{for } x\in(0,L_{ij}],$$

hence by (4.103), (4.107) and the uniform bound on h and h_n given by Lemma 4.6.8 we obtain the desired estimate. □

We now set up the fixed point argument to prove existence of a finite mass local solution which in principle is not necessarily non-negative.

Theorem 4.6.13. *Let $\gamma_2\geq 0$ and let the hypotheses of Theorem 4.3.1 be satisfied. Then there exists $\tau>0$ such that the Release-Uptake NTM possesses a unique solution which is defined for $t\in[0,\tau]$ and is not necessarily non-negative.*

Proof. Let $N_{i0}\in\left[0,\frac{\beta}{\gamma_2(\bar{u}_2(i,0))}\right)$ for $i\in V$ and let $\delta>0$, $\tau\in(0,T]$. We set

$$X_{\delta,\tau}=\{(N_1,N_2,\dots,N_h);\ N_i\in C([0,\tau]),\ N_{i0}-\delta\leq N_i(t)\leq N_{i0}+\delta<\tfrac{\beta}{\gamma_2(\bar{u}_2(i,t))}\text{ for all } i,t\}.$$

In particular we have that, by Theorem 2.4.1, the uniform bound on $\bar{u}_2$ given by (4.77) and (4.36),

$$N_i(t)\leq C_{\delta,\tau}:=\max_{1\leq k\leq h}N_{k0}+\delta<\max_{1\leq k\leq h,\,0\leq t\leq\tau}\tfrac{\beta}{\gamma_2(\bar{u}_2(k,t))}\quad\text{if } (N_1,N_2,\dots,N_h)\in X_{\delta,\tau}, \tag{4.108}$$

for all $t\in[0,\tau]$ and $i\in V$. So let $(N_1,\dots,N_h)\in X_{\delta,\tau}$ and $i\sim j$. By Lemma 4.6.6 (if $\gamma_2\equiv 0$) and the hypothesis of Theorem 4.3.1 and Corollary 4.6.10 (if $\gamma_2\not\equiv 0$), for all $e_{ij}\in E_c$ there exists $n_{ij}(0)\in C([0,L_{ij}];\left[0,\frac{\beta}{\gamma_2(\bar{u}_2(i,j,0))}\right)$ which satisfies the edge problem (4.95) at $t=0$. By Lemma 4.6.11 and the continuity of both $\bar{u}_2$ (Theorem 2.4.1) and the parameters ((4.36), (4.37), (4.38)), if δ and τ are sufficiently small, then for all $e_{ij}\in E_c$ there exists $n_{ij}\in C([0,L_{ij}]\times[0,\tau])$ such that for all $x\in[0,L_{ij}]$ and $t\in[0,\tau]$,

$$n_{ij}(x,t)<\tfrac{\beta}{\gamma_2(\bar{u}_2(x,t))} \tag{4.109}$$

and, for all $t\in[0,\tau]$,

$$\begin{cases}(a(x)(n_{ij}(x,t))_x+h(x,n_{ij}(x,t),\bar{u}_2(x,t)))_x=F_{ij}(t) & \text{in } (0,L_{ij}),\\ -[a(x,\bar{u}_2(x,t))n_{ij}(x,t)]_x=-\mu_{i,1}n(0,t)+\mu_{i,2}N_i(t) & \text{at } x=0,\\ -[a(x,\bar{u}_2(x,t))n_{ij}(x,t)+h(x,n_{ij}(x,t),\bar{u}_2(x,t))]_x=\mu_{j,1}n(L_{ij},t)-\mu_{j,2}N_j(t) & \text{at } x=L_{ij}.\end{cases} \tag{4.110}$$

We define the following operator Φ on $X_{\delta,\tau}$

$$
\begin{aligned}
&\Phi(N_1,\dots,N_h) = (\tilde N_1,\dots,\tilde N_h),\\
&\tilde N_i(t) = N_i(0) + \int_0^t \frac{\sum_{j\neq i}(c_{ji}J_{ji}(L_{ji},s) - c_{ij}J_{ij}(0,s))}{\mathrm{Vol}(i)\left(1+\frac{\gamma_1 N_i(s)(2\beta-\gamma_2(\bar u_2(i,s))N_i(s))}{(\beta-\gamma_2(\bar u_2(i,s))N_i(s))^2}\right)}\,ds\\
&+\int_0^t \frac{F_{i,\tau}(s)}{\left(1+\frac{\gamma_1 N_i(s)(2\beta-\gamma_2(\bar u_2(i,s))N_i(s))}{(\beta-\gamma_2(\bar u_2(i,s))N_i(s))^2}\right)}\,ds\\
&-\int_0^t \frac{\frac{N_i^2(s)}{\beta-\gamma_2(\bar u_2(i,s))N_i(s)}\left(\bar u_2'(i,s)\gamma_1'(\bar u_2(i,s)) + \frac{\gamma_1(\bar u_2(i,s))\bar u_2'(i,s)\gamma_2'(\bar u_2(i,s))N_i(s)}{\beta-\gamma_2(\bar u_2(i,s))N_i(s)}\right)}{\left(1+\frac{\gamma_1 N_i(s)(2\beta-\gamma_2(\bar u_2(i,s))N_i(s))}{(\beta-\gamma_2(\bar u_2(i,s))N_i(s))^2}\right)}\,ds \quad (t\in[0,\tau]),
\end{aligned}
$$

where $J_{ij} = -(a(x,\bar u_2)(n_{ij})_x + h(x,n_{ij},\bar u_2))$. To simplify the notations, we write

$$
\begin{aligned}
r_i(s) &= \left(1+\frac{\gamma_1 N_i(s)(2\beta-\gamma_2(\bar u_2(i,s))N_i(s))}{(\beta-\gamma_2(\bar u_2(i,s))N_i(s))^2}\right),\\
\mathcal P_i(s) &= \left(\bar u_2'(i,t)\gamma_1'(\bar u_2(i,t)) + \frac{\gamma_1(\bar u_2(i,t))\bar u_2'(i,t)\gamma_2'(\bar u_2(i,t))N_i}{\beta-\gamma_2(\bar u_2(i,t))N_i}\right),
\end{aligned}
\tag{4.111}
$$

which yields

$$
\begin{aligned}
\tilde N_i(t) &= N_i(0) + \int_0^t \sum_{j\neq i}\frac{(c_{ji}J_{ji}(L_{ji},s) - c_{ij}J_{ij}(0,s))}{\mathrm{Vol}(i)r_i(s)}\,ds + \int_0^t \frac{F_i(s) - \frac{N_i^2(s)}{\beta-\gamma_2(\bar u_2(i,s))N_i}\mathcal P_i(s)}{r_i(s)}\,ds\\
&= N_i(0) + \int_0^t \sum_{j\neq i}\frac{\mu_{i,1}(\bar u_2(i,s))\left[c_{ij}n_{ij}(0,s) + c_{ji}n_{ji}(L_{ji},s)\right]}{\mathrm{Vol}(i)r_i(s)}\,ds\\
&\quad - \int_0^t \sum_{j\neq i}\frac{\mu_{i,2}(\bar u_2(i,s))(c_{ij}+c_{ji})N_i(s)}{\mathrm{Vol}(i)r_i(s)}\,ds + \int_0^t \frac{F_i(s) - \frac{N_i^2(s)}{\beta-\gamma_2(\bar u_2(i,s))N_i}\mathcal P_i(s)}{r_i(s)}\,ds.
\end{aligned}
$$

First we observe that we can choose δ such that $r_i(s)\ge c>0$. Indeed, considering r_i as a function of N, on the admissible domain $(-\infty,\beta/\gamma_2((\bar u_2(i,s)))$ we have

$$
\begin{aligned}
&r_i(N_i(s)) = 0 \iff \gamma_2(\bar u_2(i,s)) < \gamma_1(\bar u_2(i,s)) \text{ and}\\
&N_i(s) = \frac{\beta\left(\gamma_2(\bar u_2(i,s)) - \gamma_1(\bar u_2(i,s)) + \sqrt{\gamma_1(\bar u_2(i,s))(\gamma_1(\bar u_2(i,s)) - \gamma_2(\bar u_2(i,s))}\right)}{\gamma_2(\bar u_2(i,s))\left[\gamma_2(\bar u_2(i,s)) - \gamma_1(\bar u_2(i,s))\right]} =: \boldsymbol{N_i}(s) < 0,
\end{aligned}
$$

and $r_i(N_i)>0$ if $N_i\ge 0$. It can be easily checked that $\boldsymbol{N}_i(s)\in\left(-\infty,-\frac{\beta}{2\gamma_1(\bar u_2(i,s))}\right]$ whenever $\gamma_2(\bar u_2(i,s))\le\gamma_1(\bar u_2(i,s))$ and that $r_i(s)>0$ if $\gamma_2(\bar u_2(i,s))\ge\gamma_1(\bar u_2(i,s))$. By the uniform bound on $\bar u_2$ (4.77) and (4.36), $\boldsymbol{N}_i(s) < -\frac{\beta}{2C_\gamma}$ and we can choose $\delta>0$ small enough that $r_i(N_i(s))>0$ for $N_i(s)\in\left[-\delta,\frac{\beta}{\gamma_2(\bar u_2(i,s))}\right)$, for example by taking $\delta<\frac{\beta}{2C_\gamma}$.

Observe that by (4.36) and Lemma 4.5.3 the maps $t\mapsto r_i(t)$, $t\mapsto\mathcal P_i(t)$ are bounded for all $i\in V$. By the continuous dependence of n_{ij} on N_i and N_j (Lemma 4.6.12), $t\mapsto n_{ij}(x,t)$ is bounded uniformly in

x. By (4.37), (4.38) and Lemma 4.6.11 we can choose $\tau > 0$ so small that $\tilde{N}_i$ is continuous for all $i \in V$ and $(\tilde{N}_1, \dots \tilde{N}_h) \in X_{\delta,\tau}$, and therefore $\Phi(X_{\delta,\tau}) \subset X_{\delta,\tau}$. A straightforward calculation based on Lemma 4.6.12 shows that Φ is a contraction on $X_{\delta,\tau}$, hence we obtain a local solution of the *Release-Uptake NTM* on $[0, \tau]$ whose coordinate N_i takes values on $\left[-\delta, \min_{s\in[0,\tau]} \frac{\beta}{\gamma_2(\bar{u}_2(i,s))}\right)$. □

In the next section we shall prove that the solution is non-negative for $0 \le t \le \tau$.

4.6.3 Positivity Properties

In this section we prove some a priori estimates which ensure non negativity of finite mass solutions of the *Release-Uptake NTM*.

We consider the problem for n_{ij} on the edge e_{ij} at a fixed time $t \ge 0$, where $i \sim j$, $N_i(t)$ and $N_j(t)$ are given real numbers belonging to $\left[0, \frac{\beta}{\gamma_2(\bar{u}_2(i,t))}\right)$, $\left[0, \frac{\beta}{\gamma_2(\bar{u}_2(j,t))}\right)$ respectively.

Lemma 4.6.14. *If $N_i = 0$ for some $i \in V$, then the incoming flux at node i satisfies*

$$\sum_{j\sim i} c_{ji}J_{ji}(L_{ji}) - c_{ij}J_{ij}(0) = \sum_{j\sim i} c_{ji}\mu_{i,1}n_{ji}(L_{ji}) + c_{ij}\mu_{i,1}n_{ij}(0) \ge 0 \tag{4.112}$$

and

$$\sum_{j\sim i} c_{ji}J_{ji}(L_{ji}) - c_{ij}J_{ij}(0) > 0 \text{ if there exists } j \sim i \text{ s.t. } N_j > 0. \tag{4.113}$$

Proof. (4.112) follows from the non negativity of the edge solution. Let $j \sim i$ such that $N_j > 0$ and consider the edge (i, j). We have

$$J_{ij}(0) = -\mu_{i,1}n_{ij}(0), \quad J_{ij}(L_{ij}) = \mu_{j,1}n_{ij}(L_{ij}) - \mu_{j,2}N_j.$$

If $J_{ij}(0) = 0$ then $n_{ij}(0) = 0$ and Lemma 4.6.5 implies $n_{ij} \equiv 0$ in $[0, L_{ij}]$, $N_i = N_j = 0$ and $F_{ij} \equiv 0$, which is impossible. Therefore $n_{ij} > 0$ in $[0, L_{ij})$ and $J_{ij}(0) < 0$. □

Lemma 4.6.15. *Let $(N_i(t))_{i\in V}$ be a solution of* (4.84). *If the total initial mass satisfies $\mathcal{M}(0) > 0$ then $N_i(t) > 0$ for all $i \in V$ and $t > 0$.*

Proof. By contradiction, assume there exist $t > 0$ and $i \in V$ such that $N_i(t) = 0$. By (4.84) and Lemma 4.6.14

$$\mathrm{Vol}(i)N_i'(t) = \mathrm{Vol}(i)F_i + \sum_{j\sim i} c_{ji}J_{ji}(L_{ji}, t) - c_{ij}J_{ij}(0, t) \tag{4.114}$$

$$= \mathrm{Vol}(i)F_i + \sum_{j\sim i} c_{ji}\mu_{i,1}n_{ji}(L_{ji}) + c_{ij}\mu_{i,1}n_{ij}(0) \ge 0. \tag{4.115}$$

By definition of (i, t) and the continuity in time of F_i, n_{ij} and n_{ji} for $j \sim i$, we have

$$N_i'(t) = 0 \quad \Rightarrow \quad F_i(t) = 0, \quad n_{ji}(L_{ji}) = n_{ij}(0) = 0, \quad j \sim i. \tag{4.116}$$

Therefore, Lemma 4.6.5 implies that

$$N_j(t) = 0 \quad \text{for all } j \sim i, \tag{4.117}$$

hence repeating the argument above for $j \sim i$ yields

$$N_j'(t) = 0 \Rightarrow F_j(t) = 0, \quad n_{kj}(L_{kj}) = n_{jk}(0) = 0 \text{ and } N_k(t) = 0 \text{ for all } k \sim j. \tag{4.118}$$

Now iterating the argument on the connected component of i, i.e. the entire set V, we get

$$N_i(t) = 0, \quad F_i(t) = 0 \quad \text{ for all } i \in V, \quad n_{ij}(0) = n_{ij}(L_{ij}) = 0 \quad \text{ for all } (i,j) \in E, \tag{4.119}$$

which, together with the definition of $(M_i)_{i\in V}$, implies that the total mass of tau in the nodes at time t is zero. Moreover, by Lemma 4.6.5 and the definition of $(m_{ij})_{(i,j)\in E}$, the total edge mass is zero, hence we have

$$\mathcal{M}(t) = 0, \tag{4.120}$$

which clearly leads to a contradiction because the total mass satisfies

$$\mathcal{M}(t) = \mathcal{M}(0) + \sum_{i\in V} \int_0^t \mathrm{Vol}(i) F_i(t)\, dt + \sum_{(i,j)\in E} c_{ij} \int_0^t \int_0^{L_{ij}} F_{ij}(x,t)\, dx\, dt > 0. \tag{4.121}$$

□

4.6.4 Global Existence

By Theorem 4.6.13, the *Release-Uptake NTM* has a local solution, defined in an interval $[0,\tau]$, where $\tau \leq T$. If $\gamma_2 \equiv 0$, its total mass is and finite by Corollary 4.6.6 and Lemma 4.6.7 and $N_i(t) \geq 0$ for all $t \in [0,\tau]$ and $1 \leq i \leq h$ (by Lemma 4.6.15). If $\gamma_2 \not\equiv 0$, its total mass is finite at $t = 0$ (by hypothesis) and remains finite in $(0,\tau]$ (by Lemma 4.6.7); in addition, N_i and n_{ij} are subcritical in $[0,\tau]$ (by Lemma 4.6.9) and $N_i(t) \geq 0$ for all $t \in [0,\tau]$, $e_{ij} \in E_c$ and $1 \leq i \leq h$ (by Lemma 4.6.15).

We now show that $\tau = T$. Suppose that $[0,\tau^*)$ is the maximal interval of definition of N_i for all $i \in V$, where $\tau^* < T$. By hypothesis (4.36), (4.37), (4.38), the uniform bound on $\bar{u}_2$ (2.14) and Lemma 4.6.12, there exists a constant $C_\delta > 0$ such that $|N_i'(t)| < C_\delta$ for all $t \in [0,\tau^*)$, and therefore N_i can be extended on $[0,\tau^*]$ and it continues to be subcritical for all $i \in V$. Moreover, $N_i(\tau^*) \geq 0$ for all $i \in V$ and the total mass of the system at time $t = \tau^*$ is finite, hence by the local existence result above it can be continued on an interval $[\tau^*, \tau^{**})$ with $\tau^* < \tau^{**} < T$, thus contradicting the maximality of $[0,\tau^*)$.

4.7 Local Existence for the $A\beta$-Release-Uptake-NTM

In Sections 4.4, 4.5 and 4.6 we have defined the operator $\mathcal{H}$ on X_T as

$$\mathcal{H}(A,g,u,N) = (\bar{A},\bar{g},\bar{u},\bar{N}), \tag{4.122}$$

where

$$X_T := C^0([0,T]\times[0,1];[0,1]^h) \times \mathcal{L}(V; C([0,T];X_{[0,1]})) \times C^0([0,T];\mathbb{R}^{3h}) \times C^0([0,T];\mathbb{R}^h). \tag{4.123}$$

The current Section is devoted to prove existence of a fixed point of $\mathcal{H}$ on X_T, following the approach of [14] and Chapter 2.

We recall that, given $(A,g,u,N) \in X_T$, $\bar{A}$ is a solution to the problem

$$\begin{cases} \partial_t \tilde{A}_i(y,t) = \tilde{v}_i(\tilde{A}_i(y,t),t), \\ \tilde{A}_i(y,0) = y \in [0,1] \end{cases} \qquad i \in V, \tag{4.124}$$

$$\tilde{v}_i(a,t) = C_G \int_{[0,1]} (A_i(y,t)-a)^+ \, dg_{i,t}(y) + C_s(1-a)(u_2(i,t)-\bar{U}_2)^+ + C_N(1-a)(N_i(t)-\bar{\mathcal{N}}_i)^+ \geq 0. \quad (4.125)$$

$\bar{g}$ is then defined as a solution to

$$\begin{cases} \partial_t g_{i,t} = d(F[g])_{i,t}, \\ g_{i,0} = f_i(0) \end{cases} \quad (4.126)$$

where

$$d(F[g])_{i,t} = \eta \chi_H \left[\partial_y \bar{A}_i(y,t) \int P(t, \bar{A}_i(\xi,t), \bar{A}_i(y,t)) \, dg_{i,t}(\xi) \, dy - dg_{i,t}(y) \right]. \quad (4.127)$$

$\bar{u}$ is the vector of concentrations of Beta Amyloid satisfying the elliptic equations

$$\begin{cases} d_1 \Delta \tilde{u}_1 - \sigma_1 \tilde{u}_1 + \tilde{F}[\bar{g}] + \Gamma_1 = 0, \\ d_2 \Delta \tilde{u}_2 - \sigma_2 \tilde{u}_2 + \Gamma_2 = 0, \\ -\sigma_3 \tilde{u}_3 + \Gamma_3 = 0, \end{cases} \quad (4.128)$$

issued by the monomers' source

$$\tilde{F}[\bar{g}_{i,t}] = C_\mu \int (\mu_0 + \bar{A}_i(y,t))(1 - \bar{A}_i(y,t)) \, d\bar{g}_{i,t}(y) \geq 0. \quad (4.129)$$

Finally, $\bar{N}$ is the concentration of soluble extracellular Tau and it satisfies

$$\begin{aligned} &\left(1 + \frac{\gamma_1(\bar{u}_2(i,t))N_i(2\beta - \gamma_2(\bar{u}_2(i,t))N_i)}{(\beta - \gamma_2(\bar{u}_2(i,t))N_i)^2}\right) \mathrm{Vol}(i) N_i' \quad (4.130)\\ &\quad = \mathrm{Vol}(i) F_{i,\tau}(i,t) - \frac{\mathrm{Vol}(i) N_i^2}{\beta - \gamma_2(\bar{u}_2(i,t))N_i} \left(\bar{u}_2'(i,t)\gamma_1'(\bar{u}_2(i,t)) + \frac{\gamma_1(\bar{u}_2(i,t))\bar{u}_2'(i,t)\gamma_2'(\bar{u}_2(i,t))N_i}{\beta - \gamma_2(\bar{u}_2(i,t))N_i} \right), \\ &\quad + \sum_{j \sim i} c_{ji} J_{ji}(L_{ji},t) - c_{ij} J_{ij}(0,t), \quad i \in V, \\ &\quad M_i(t) = \frac{\gamma_1(\bar{u}_2(i,t))N_i^2(t)}{\beta - \gamma_2(\bar{u}_2(i,t))N_i(t)}, \quad i \in V, \end{aligned}$$

$$\text{for all } e_{ij} \in E_c : \begin{cases} J_{ij}(x,t,\bar{u}_2) = (a(x,\bar{u}_2)n_{ij}(x,t))_x + h(x, n_{ij}(x,t), \bar{u}_2) \quad x \in (0, L_{ij}), \\ (J_{ij})_x(x,t,\bar{u}_2) = F_{ij,\tau}(x,t), \\ J_{ij}(0,t) = -\mu_{i,1}(\bar{u}_2(i,t))n_{ij}(0,t) + \mu_{i,2}(\bar{u}_2(i,t))N_i(t), \\ J_{ij}(L_{ij},t,\bar{u}_2) = \mu_{j,1}(\bar{u}_2(j,t))n_{ij}(L_{ij},t) - \mu_{j,2}(\bar{u}_2(j,t))N_j(t), \\ m_{ij}(x,t) = g_m(t, n_{ij}(x,t)), \quad g_m(t,n) = \frac{\gamma_1(t)n^2}{\beta - \gamma_2(t)n^2}. \end{cases} \quad (4.131)$$

In the following, we will prove that $\mathcal{H}$ is invariant on $X_{\rho,\tau}$ if τ is small enough. As in [14] and Chapter 2, by the Kantorovich-Rubinstein duality [4] for $\mathcal{W}_1$, $\mathcal{H}$ is a contraction only on its image $\mathcal{H}(X_{\rho,\tau}) \subset X_{\rho,\tau}$, which in principle is not a complete space, hence we need to adapt the fixed-point argument by proving the continuity of $\mathcal{H}$ as a map from $X_{\rho,\tau}$ with the standard metric topology to the same space endowed with a weaker topology. In particular, we refer to $\mathcal{T}_d$ as the metric topology of $X_{\rho,\tau}$ and to $\mathcal{T}$ as the weaker topology on $X_{\rho,\tau}$ obtained by endowing the characteristics space $C([0,1] \times [0,\tau]; \mathbb{R}^h)$ with the L^1 topology on $[0,1] \times [0,\tau]$.

For the reader's convenience, we recall the hypotheses on the model parameters.

(i) $\sigma_1,\ \sigma_2,\ \sigma_3,\ a_{11},\ a_{12},\ a_{21}\, k_1,\ k_2,\ d_1,\ d_2,\ C_\mu,\ \mu_0, C_G,\ C_s$ are positive constants. The monomers' clearance parameter σ_1 is sufficiently large, i.e. $\sigma_1 > \bar{\sigma}_1$. The aggregation and fragmentation rates are symmetric: $a_{ij} = a_{ji}$, $k_1 = k_2$;

(ii) $\eta \in C([0,T])$, $\eta > 0$. P satisfies

$$P \in C([0,T] \times [0,1]^2), \quad P \geq 0, \tag{4.132}$$

$$\int_{[0,1]} P(t,b,a)\, da = 1 \text{ for } b \in [0,1],\ P(t,b,a) = 0 \quad \text{if } b > a \tag{4.133}$$

since impaired neurons do not recover, and it is Lipschitz continuous:

$$\exists L > 0 :\ |P(t'',b'',a'') - P(t',b',a')| \leq L(|b''-b'| + |a''-a'| + |t''-t'|), \tag{4.134}$$

for all $a', a'', b', b'' \in [0,1]$, $t',\ t'' \in [0,T]$.

(iii) $\gamma_1, \gamma_2, \lambda \in C^1(\mathbb{R}^+)$, $\gamma_1, \gamma_2 \geq 0$, $\lambda \in (0,1)$, $F_{i,\tau} \in C^1(\mathbb{R}^+)$ for all $i \in V$, $F_{ij,\tau} \in C^1([0,L_{ij}] \times \mathbb{R}^+)$ for all $e_{ij} \in E_c$, $F_{i,\tau}, F_{ij,\tau} \geq 0$, $\mu_{i,k} \in C(\mathbb{R}^+)$ for all $i \in V$, $k = 1,2$, $\mu_{i,k} \geq 0$ and $\exists C_\gamma, C'_\lambda, C''_\lambda, C_F, C_{ru} > 0$ such that

$$|\gamma_k|, |\partial_u \gamma_k|, |\partial^2_{uu}\gamma_k| < C_\gamma \text{ on } \mathbb{R}^+ \text{ for } k = 1,2, \quad C''_\lambda < \lambda < C'_\lambda \text{ on } \mathbb{R}^+, \tag{4.135}$$

$$F_{i,\tau}(u), F_{ij,\tau}(x,u) < C_F \text{ for all } x \in [0,L_{ij}],\ e_{ij} \in E,\ i \in V,\ u \in \mathbb{R}^+, \tag{4.136}$$

$$\mu_{i,k}(u), |\partial_u \mu_{i,k}(u)| < C_{ru} \text{ for all } i \in V,\ k = 1,2,\ u \in \mathbb{R}^+. \tag{4.137}$$

Theorem 4.7.1. *Let $\rho > 0$ fixed and $\mathcal{H}$ defined by* (4.122). *Let $N_0 \in \mathbb{R}^h$ such that the total mass of system* (4.130) *at initial time is finite. If $\tau > 0$ is sufficiently small then $\mathcal{H}(X_{\rho,\tau}) \subset X_{\rho,\tau}$,*

$$\mathcal{H}(A_n, g_n, u_n, N_n) \to H(A,g,u,N) \text{ in } \mathcal{T} \quad \text{as } (A_n, g_n, u_n, N_n) \to (A,g,u,N) \text{ in } \mathcal{T}_d,$$

and $\mathcal{H}$ is a contraction on $\mathcal{H}(X_{\rho,\tau})$.

Proof. We start by showing the invariance of $\mathcal{H}$ on X_τ if τ is small enough. By (4.124)

$$\begin{aligned} |\bar{A}_i(y,t) - y| &= |\bar{A}_i(y,t) - \bar{A}_i(y,0)| \\ &= C_G \int_0^t \int (A_i(\xi,s) - \bar{A}_i(y,s))^+\, dg_{i,s}(\xi)\, ds \\ &\quad + C_S \int_0^t (1 - \bar{A}_i(y,s))(u_2(i,s) - \bar{U}_2)^+\, ds \\ &\quad + C_S \int_0^t (1 - \bar{A}_i(y,s))(N_i(s) - \bar{\mathcal{N}}_i)^+\, ds \\ &\leq C_G \int_0^t \int (A_i(\xi,s) - \bar{A}_i(y,s))^+\, dg_{i,s}(\xi)\, ds \ + C_\rho t \end{aligned} \tag{4.138}$$

where we have used that u_2 and N_i are uniformly bounded in time. By Gronwall's Lemma we obtain

$$|\bar{A}_i(y,t) - y| \leq C_\rho t e^{C_G t} \to 0 \text{ as } t \to 0^+ \quad \text{for all } i \in V,\ y \in [0,1]. \tag{4.139}$$

The calculation in (2.221) implies $|\bar{u}_k(i,t) - (u_0)_k(i)| \to 0$ as $t \to 0^+$ for all $i \in V$ and $k = 1,2,3$. By Lemma 4.4.5, $g_{i,t} \in C([0,\tau]; X_{[0,1]})$ and therefore $g_{i,t} \to f_i(0)$. It remains to show that, for all $i \in V$, $||\bar{N}_i(t) - N_{i0}|| \to 0$ as $t \to 0^+$. Since the initial mass of system (4.130) is finite and the production terms $F_{i,\tau}$, $F_{ij,\tau}$ are bounded by (4.136), there exists $C_{\mathcal{M}} > 0$ such that $0 \le \bar{N}_i(t) \le C_{\mathcal{M}}$ and by Lemma 4.6.12 the respective edge solution satisfies $0 \le \bar{n}_{ij} \le C_{\mathcal{M}}$ for all $e_{ij} \in E_c$. Moreover, adopting the notation (4.111), $r_i(s) \ge 1$ and it is bounded by (4.135) and the estimate on $\bar{N}_i$. Observe that by the proof of Theorem 4.3.1 there exists $\delta > 0$ such that $\bar{N}_i(t) \le N_{i0} + \delta < \min_{s\in[0,\tau]} \frac{\beta}{\gamma_2(\bar{u}_2(i,s))}$ for all $t \in [0,\tau]$. This estimate, coupled with the uniform bound on $\bar{u}_2$ and (4.135), implies that $|\mathcal{P}_i| < C_\delta$ for some $C_\delta > 0$. By (4.112) it follows that

$$\begin{aligned}|\bar{N}_i(t) - N_{i0}| \le& \int_0^t \sum_{j\neq i} \frac{\mu_{i,1}(\bar{u}_2(i,s))\left[c_{ij}\bar{n}_{ij}(0,s) + c_{ji}\bar{n}_{ji}(L_{ji},s)\right]}{\mathrm{Vol}(i) r_i(s)}\, ds \\ &+ \int_0^t \sum_{j\neq i} \frac{\mu_{i,2}(\bar{u}_2(i,s))(c_{ij}+c_{ji})\bar{N}_i(s)}{\mathrm{Vol}(i) r_i(s)}\, ds + \int_0^t \frac{\left|F_i(s) - \frac{\bar{N}_i^2(s)}{\beta - \gamma_2(\bar{u}_2(i,s))N_i}\mathcal{P}_i(s)\right|}{r_i(s)}\, ds \\ &\le \frac{C_{ru}}{\mathrm{Vol}(i)} C_{\mathcal{M}}\, t + \frac{C_{ru}}{\mathrm{Vol}(i)} C_{\mathcal{M}} \sum_{j\sim i}(c_{ij}+c_{ji})\, t + C_F C_\delta t \to 0 \text{ as } t \to 0^+ \text{ for all } i \in V.\end{aligned} \tag{4.140}$$

As in Section 2.6, we proceed by proving the $(\mathcal{T}_d, \mathcal{T})$ continuity of $\mathcal{H}$. Let $((A_n, g_n, u_n, N_n))_n$ be a sequence in $X_{\rho,\tau}$ such that $(A_n, g_n, u_n, N_n) \to (A, g, u, N)$ in $(X_{\rho,\tau}, \mathcal{T}_d)$ as $n \to \infty$. We have to show that $(\bar{A}_n, \bar{g}_n, \bar{u}_n, \bar{N}) \to (\bar{A}, \bar{g}, \bar{u}, \bar{N})$ in $(X_{\rho,\tau}, \mathcal{T})$. It follows from Lemma 4.4.4 that $\bar{A}_i^n$ and $\bar{A}_i$ are bounded uniformly in $i \in V, t \in [0,T]$ and $n \in \mathbb{N}$, therefore by the dominated convergence theorem, if $\bar{A}_i^n - \bar{A}_i \to 0$ a.e. in $[0,1] \times [0,T]$ for all $i \in V$, then $(\bar{A}_n, \bar{g}_n, \bar{u}_n, \bar{N}_n) \to (\bar{A}, \bar{g}, \bar{u}, \bar{N})$ in $(X_{\rho,\tau}, \mathcal{T})$. Repeating the calculations in (2.224), we obtain

$$\begin{aligned}|\bar{A}_i^n(y,t) - \bar{A}_i(y,t)| \le\ & C_G \int_0^t \int \left|(A_i^n(\xi,s) - \bar{A}_i^n(y,s))^+ - (A_i(\xi,s) - \bar{A}_i(y,s))^+\right| dg_{i,s}^n(\xi)\, ds \\ &+ C_G \int_0^t \int \left|(A_i(\xi,s) - \bar{A}_i(y,s))^+\right| d(g_{i,s}^n - g_{i,s})(\xi)\, ds \\ &+ C_S \int_0^t \left|(1 - \bar{A}_i^n(y,s))\left[(u_2^n(i,s) - \bar{U}_2)^+ - (u_2(i,s) - \bar{U}_2)^+\right]\right| ds \\ &+ C_S \int_0^t \left|\bar{A}_i^n(y,s) - \bar{A}_i(y,s)\right| (u_2(i,s) - \bar{U}_2)^+\, ds \\ &+ C_N \int_0^t \left|(1 - \bar{A}_i^n(y,s))\left[(N_i^n(s) - \bar{\mathcal{N}}_i)^+ - (N_i(s) - \bar{\mathcal{N}})^+\right]\right| ds \\ &+ C_S \int_0^t \left|\bar{A}_i^n(y,s) - \bar{A}_i(y,s)\right| (N_i(s) - \bar{\mathcal{N}}_i)^+\, ds =: I_1 + I_2 + I_3 + I_4 + I_5 + I_6.\end{aligned}$$

Since $(A_n, g_n, u_n, N_n), (A, g, u, N) \in X_{\rho,\tau}$, we have that $\max_{[0,\tau]} ||u_n(\tau) - u(\tau)||_{\mathbb{R}^{3h}}, \max_{[0,\tau]} ||N^n(\tau) - N(\tau)||_{\mathbb{R}^h} \le \mathrm{diam}(X_{\rho,\tau}) = 2\rho$, therefore we can easily bound I_3, I_4, I_5 and I_6 as in the proof of Theorem 2.6.6:

$$|I_3|, |I_5| \le C_\rho\, t\, d((A_n, g_n, u_n, N_n), (A, g, u, N)) \tag{4.141}$$

$$|I_4|, |I_6| \le C_\rho \int_0^t \left|\bar{A}_i^n(y,s) - \bar{A}_i(y,s)\right| ds. \tag{4.142}$$

By (2.228) we get

$$
\begin{aligned}
|\bar{A}_i^n(y,t) - \bar{A}_i(y,t)| \le \tilde{C}_\rho \int_0^t \left|\bar{A}_i^n(y,s) - \bar{A}_i(y,s)\right| \, ds \\
+ C\, t\, d((A_n, g_n, u_n, N_n), (A, g, u, N)) + I_2
\end{aligned}
\tag{4.143}
$$

whence by Gronwall's inequality

$$
|\bar{A}_i^n(y,t) - \bar{A}_i(y,t)| \le (C\, t\, d((A_n, g_n, u_n, N_n), (A, g, u, N)) + I_2)\, e^{\tilde{C}_\rho t}, \tag{4.144}
$$

where $I_2 \to 0$ by the dominated convergence theorem (the details are stated in the proof of Theorem 2.6.6).

It remains to show that $\mathcal{H}$ is a contraction on $\mathcal{H}(X_{\rho,\tau}$. Let $(A^1, g^1, u^1, N^1),\ (A^2, g^2, u^2, N^2) \in \mathcal{H}(X_{\rho,\tau})$. The characteristics satisfy

$$
\begin{aligned}
|\bar{A}_i^1(y,t) - \bar{A}_i^2(y,t)| \le \big(C\, \tau\, d((A^1, g^1, u^1, N^1), (A^2, g^2, u^2, N^2)) \\
+ C_G \int_0^\tau \int \left|(A_i^2(\xi,s) - \bar{A}_i^2(y,s)^+\right| \, d(g_{i,s}^1 - g_{i,s}^2)\, ds\Big)\, e^{\tilde{C}_\rho \tau}.
\end{aligned}
\tag{4.145}
$$

By Lemma 4.4.4, since $(A^2, g^2, u^2, N^2) \in \mathcal{H}(X_{\rho,\tau})$, the functions $\xi \mapsto A_i^2(\xi,s)$, $\xi \mapsto \bar{A}_i^2(\xi,s)$ are Lipschitz continuous uniformly in s, therefore

$$
\begin{aligned}
|\bar{A}_i^1(y,t) - \bar{A}_i^2(y,t)| &\le \left(C\, \tau\, d((A^1, g^1, u^1, N^1), (A^2, g^2, u^2, N^2)) + C_G \int_0^\tau \mathcal{W}_1(g_{i,s}^1, g_{i,s}^2)\, ds\right) e^{\tilde{C}_\rho \tau} \\
&\le \tilde{C} \tau d((A^1, g^1, u^1, N^1), (A^2, g^2, u^2, N^2)),
\end{aligned}
\tag{4.146}
$$

for all $i \in V,\ t \in [0,\tau]$. By Lemma 2.6.5 it follows that

$$
\mathcal{W}_1(\bar{g}_{i,t}^1, \bar{g}_{i,t}^2) \le C\tau \max_{t \in [0,\tau]} \mathcal{W}_1(\bar{g}_{i,t}^1, \bar{g}_{i,t}^2) \le C\tau d((A^1, g^1, u^1, N^1), (A^2, g^2, u^2, N^2)), \tag{4.147}
$$

for all $i \in V,\ t \in [0,\tau]$.

Concerning the u component, we observe that the calculations in (2.234) are based on the mass balance

$$
\sum_{k=1}^{3} \sum_{i \in V} \sigma_k \bar{u}_k(i,t) = \sum_{i \in V} F_{A\beta}(i,t), \quad t \ge 0,
$$

where $F_{A\beta}$ does not explicitly depend on N, hence the arguments (2.234) and (2.235) may be repeated verbatim to obtain

$$
|\bar{u}_k^1(i,t) - \bar{u}_k^2(i,t)| \le C\tau d((A^1, g^1, u^1, N^1), (A^2, g^2, u^2, N^2)) \tag{4.148}
$$

for all $i \in V,\ k = 1,2,3,\ t \in [0,\tau]$.

Lastly, we need to show that the N component of $\mathcal{H}$ is contractive. The following calculations are slightly technical due to the structure of the ODE system for $\bar{N}$. The most complicated terms are those depending on $\bar{u}_2'$. In fact, we have proved the existence of $\bar{u}_2$ in Section 2.2.2 applying the implicit function theorem, which does not produce an explicit expression for the solution. As observed in Section 4.5, the expression for $\bar{u}_2'$ depends on both $\partial_t F[\bar{g}_t]$ and the Jacobian of the nonlinear elliptic system, where the latter is not straightforward to handle analytically. For this purpose we shall adopt some linear algebra tools to control the quantities involving that matrix, similarly to the proof of Theorem 3.5.8 in Chapter 3.

We denote by $\bar{n}_{ij}^k$ the edge solution of (4.131) associated to the soluble Tau concentrations $\bar{N}_i^k, \bar{N}_j^k$ on the edge e_{ij} for $k=1,2$. We refer to the maps r_i and $\mathcal{P}_i$ evaluated at $(\bar{N}_i^k, \bar{u}_2^k(i))$ with r_i^k and $\mathcal{P}_i^k$ for all $i \in V$ and $k=1,2$. Let $i \in V$ and $t \in (0,\tau]$. By Theorem 4.6.13 and Section 4.6.4, we have

$$
\begin{aligned}
|\bar{N}_i^1(t) - \bar{N}_i^2(t)| \leq \int_0^t \sum_{j\sim i} &\left| \frac{\mu_{i,1}(\bar{u}_2^1)\left(c_{ij}\bar{n}_{ij}^1(0,s) + c_{ji}\bar{n}_{ji}^1(L_{ji},s)\right)}{\mathrm{Vol}(i) r_i^1(s)} - \frac{\mu_{i,1}(\bar{u}_2^2)\left(c_{ij}\bar{n}_{ij}^2(0,s) + c_{ji}\bar{n}_{ji}^2(L_{ji},s)\right)}{\mathrm{Vol}(i) r_i^2(s)} \right| ds \qquad (4.149)\\
&+ \int_0^t \sum_{j\sim i} \left| \frac{\mu_{i,2}(\bar{u}_2^1)(c_{ij}+c_{ji})\bar{N}_i^1(s)}{\mathrm{Vol}(i) r_i^1(s)} - \frac{\mu_{i,2}(\bar{u}_2^2)(c_{ij}+c_{ji})\bar{N}_i^2(s)}{\mathrm{Vol}(i) r_i^2(s)} \right| ds\\
&+ \int_0^t \left| \frac{F_i(\bar{u}_2^1)}{r_i^1(s)} - \frac{F_i(\bar{u}_2^2)}{r_i^2(s)} \right| ds + \int_0^t \left| \frac{(\bar{N}_i^1)^2(s)}{\beta - \gamma_2(\bar{u}_2^1)\bar{N}_i^1(s)} \mathcal{P}_i^1(s) - \frac{(\bar{N}_i^2)^2(s)}{\beta - \gamma_2(\bar{u}_2^2)\bar{N}_i^2(s)} \mathcal{P}_i^2(s) \right| ds\\
&= J_1 + J_2 + J_3 + J_4.
\end{aligned}
$$

We start by estimating the integral J_1. By Theorem 4.6.13 it follows that $\bar{N}^k$ is non-negative and $r_i^k \geq 1$ for $k=1,2$. We obtain

$$
\begin{aligned}
J_1 &\leq \frac{1}{\mathrm{Vol}(i)} \int_0^t \sum_{j\sim i} \left|\mu_{i,1}(\bar{u}_2^1) - \mu_{i,1}(\bar{u}_2^2)\right| r_i^2(s) \left(c_{ij}\bar{n}_{ij}^1(0,s) + c_{ji}\bar{n}_{ji}^1(L_{ji},s)\right) ds \qquad (4.150)\\
&+ \frac{1}{\mathrm{Vol}(i)} \int_0^t \sum_{j\sim i} \mu_{i,1}(\bar{u}_2^2) \left| r_i^2(s)\left(c_{ij}\bar{n}_{ij}^1(0,s) + c_{ji}\bar{n}_{ji}^1(L_{ji},s)\right) - r_i^1(s)\left(c_{ij}\bar{n}_{ij}^2(0,s) + c_{ji}\bar{n}_{ji}^2(L_{ji},s)\right)\right| ds\\
&\leq \frac{C_{\rho,\gamma,ru}}{\mathrm{Vol}(i)} \max_{[0,\tau]} |\bar{u}_2^1(i,s) - \bar{u}_2^2(i,s)|\, \tau + \frac{C_{ru}}{\mathrm{Vol}(i)} \int_0^t \sum_{j\sim i} |r_i^2(s) - r_i^1(s)| \left(c_{ij}\bar{n}_{ij}^1(0,s) + c_{ji}\bar{n}_{ji}^1(L_{ji},s)\right) ds\\
&+ \frac{C_{ru}}{\mathrm{Vol}(i)} \int_0^t \sum_{j\sim i} r_i^1(s) \left| c_{ij}(\bar{n}_{ij}^1(0,s) - \bar{n}_{ij}^2(0,s)) + c_{ji}(\bar{n}_{ji}^1(L_{ji},s) - \bar{n}_{ji}^2(L_{ji},s))\right| ds\\
&\leq \frac{C_{\rho,\gamma,ru}}{\mathrm{Vol}(i)} \tau\, d((A^1,g^1,u^1,N^1),(A^2,g^2,u^2,N^2)) + \frac{C_{\rho,\gamma,ru}}{\mathrm{Vol}(i)} \int_0^t |\bar{N}_i^1(s) - \bar{N}_i^2(s)|\, ds\\
&+ \frac{C_{\rho,\gamma,ru}}{\mathrm{Vol}(i)} \int_0^t \sum_{j\sim i} \left(|\bar{N}_i^1(s) - \bar{N}_i^2(s)| + |\bar{N}_j^1(s) - \bar{N}_j^2(s)|\right) ds\\
&\leq \frac{C_{\rho,\gamma,ru}}{\mathrm{Vol}(i)} \tau\, d((A^1,g^1,u^1,N^1),(A^2,g^2,u^2,N^2)) + \frac{C_{\rho,\gamma,ru}}{\mathrm{Vol}(i)} \int_0^t \max_{j\in V} |\bar{N}_j^1(s) - \bar{N}_j^2(s)|\, ds
\end{aligned}
$$

where we have used that γ_1, γ_2 and $\mu_{i,1}$ are Lipschitz continuous by (4.135), (4.137), the estimate from Lemma 4.6.12 and (4.148). Observe that, by (4.100), the terms $\bar{n}_{ij}^1(0,s) - \bar{n}_{ij}^2(0,s)$ and $\bar{n}_{ji}^1(L_{ji},s) - \bar{n}_{ji}^2(L_{ji},s)$ depend simultaneously on the quantities $\bar{N}_i^1 - \bar{N}_i^2$ and $\bar{N}_j^1 - \bar{N}_2^j$. Consequently, the evolution at each node is coupled to that of its neighbours and one can not apply Gronwall's inequality independently for each node i as in the previous estimates.

A straightforward calculation similar to (4.150) yields

$$
J_2 \leq \frac{C_{\rho,\gamma,ru}}{\mathrm{Vol}(i)} \tau d((A^1,g^1,u^1,N^1),(A^2,g^2,u^2,N^2)) + \frac{C_{\rho,\gamma,ru}}{\mathrm{Vol}(i)} \int_0^t \max_{j\in V} |\bar{N}_j^1(s) - \bar{N}_j^2(s)|\, ds. \qquad (4.151)
$$

By hypothesis (4.136), F_i is Lipschitz continuous, and therefore

$$J_3 \leq C_{F_\tau,\rho,\gamma,ru}\tau d((A^1,g^1,u^1,N^1),(A^2,g^2,u^2,N^2)) + C_{F_\tau,\rho,\gamma,ru}\int_0^t \max_{j\in V}|\bar{N}_j^1(s)-\bar{N}_j^2(s)|\,ds. \tag{4.152}$$

The term J_4 requires some attention since it depends on $u_2'(i,t)$, which has been proved in Section 4.5 to be continuous. We recall that

$$\mathcal{P}_i(s) = \bar{u}_2'(i,t)\gamma_1'(\bar{u}_2(i,t)) + \frac{\gamma_1(\bar{u}_2(i,t))\bar{u}_2'(i,t)\gamma_2'(\bar{u}_2(i,t))\bar{N}_i}{\beta-\gamma_2(\bar{u}_2(i,t))\bar{N}_i}.$$

The integral J_4 rewrites as

$$\begin{aligned} J_4 &\leq \int_0^t \frac{(\bar{N}_i^1)^2(s)}{\beta-\gamma_2(\bar{u}^1)\bar{N}_i^1(s)}\left|\mathcal{P}_i^1(s)-\mathcal{P}_i^2(s)\right|\,ds + \int_0^t |\mathcal{P}_i^2(s)|\left|\frac{(\bar{N}_i^1)^2(s)}{\beta-\gamma_2(\bar{u}_2^1)\bar{N}_i^1(s)} - \frac{(\bar{N}_i^2)^2(s)}{\beta-\gamma_2(\bar{u}_2^2)\bar{N}_i^2(s)}\right|\,ds \qquad (4.153)\\ &\leq \int_0^t \frac{(\bar{N}_i^1)^2(s)}{\beta-\gamma_2(\bar{u}^1)\bar{N}_i^1(s)}\left|\mathcal{P}_i^1(s)-\mathcal{P}_i^2(s)\right|\,ds + C_{\rho,\gamma}\tau d((A^1,g^1,u^1,N^1),(A^2,g^2,u^2,N^2))\\ &+ C_{\rho,\gamma}\int_0^t |\bar{N}_i^1(s)-\bar{N}_i^2(s)|\,ds, \end{aligned}$$

where the last inequality follows from (4.135), (4.148) and Lemma 4.5.3. Specifically, by Remark 4.5.1 we have $\partial_t F_{A\beta}^k \in L^\infty(0,\tau)$ and by Lemma 4.5.3 the time derivative of $\bar{u}_2^k(i,t)$ is bounded on $[0,\tau]$ for $k=1,2$ and $i\in V$.

The quantity $|\mathcal{P}_i^1(t)-\mathcal{P}_i^2(t)|$ satisfies

$$\begin{aligned} \left|\mathcal{P}_i^1(t)-\mathcal{P}_i^2(t)\right| &\leq |(\bar{u}_2^1)'(i,t)|\left|\gamma_1'(\bar{u}_2^1(i,t))-\gamma_1'(\bar{u}_2^2(i,t))\right| + |\gamma_1'(\bar{u}_2^2(i,t))|\left|(\bar{u}_2^1)'(i,t)-(\bar{u}_2^2)'(i,t)\right| \qquad (4.154)\\ &+\left|\frac{\gamma_1(\bar{u}_2^2(i,t))(\bar{u}_2^2)'(i,t)\gamma_2'(\bar{u}_2^2(i,t))\bar{N}_i^2}{\beta-\gamma_2(\bar{u}_2^2(i,t))\bar{N}_i^2} - \frac{\gamma_1(\bar{u}_2^1(i,t))(\bar{u}_2^1)'(i,t)\gamma_2'(\bar{u}_2^1(i,t))\bar{N}_i^1}{\beta-\gamma_2(\bar{u}_2^1(i,t))\bar{N}_i^1}\right|\\ &\leq C_{\rho,\gamma}|\bar{u}_2^1(i,t)-\bar{u}_2^2(i,t)| + C_\gamma\left|(\bar{u}_2^1)'(i,t)-(\bar{u}_2^2)'(i,t)\right|\\ &+\left|\frac{\gamma_1(\bar{u}_2^2(i,t))(\bar{u}_2^2)'(i,t)\gamma_2'(\bar{u}_2^2(i,t))\bar{N}_i^2}{\beta-\gamma_2(\bar{u}_2^2(i,t))\bar{N}_i^2} - \frac{\gamma_1(\bar{u}_2^1(i,t))(\bar{u}_2^1)'(i,t)\gamma_2'(\bar{u}_2^1(i,t))\bar{N}_i^1}{\beta-\gamma_2(\bar{u}_2^1(i,t))\bar{N}_i^1}\right|. \end{aligned}$$

From Lemma 4.5.3 we have

$$(\bar{u}^k)'(t) = C_{\sigma_1}(J^k(t))^{-1}J^k(0)(\partial_t F_{A\beta}^k[\bar{g}_{1,t}],\partial_t F_{A\beta}^k[\bar{g}_{2,t}],\ldots,\partial_t F_{A\beta}^k[\bar{g}_{h,t}],0,\ldots,0)^T, \quad t\in[0,\tau],\ k=1,2 \tag{4.155}$$

where $J^k(t)$ is the Jacobian of the nonlinear system associated with $\bar{u}^k$. The global existence argument of Section 2.4 implies that the matrix is invertible uniformly in $[0,\tau]$. Specifically, we solved the equation for u_3 and then localised the eigenvalues of the Jacobian in the set $\{z\in\mathbb{C} : \Re(z)<0\}$. By (2.62) and (2.63), we can easily obtain a uniform lower bound for $\min_{\lambda\in\Lambda(J^k(t))}|\lambda|$, hence for the determinant of $J^k(t)$. We also recall that, by Lemma 4.5.2, the time derivative of $F_{A\beta}^k[\bar{g}_{i,t}]$ is given by

$$\begin{aligned} \partial_t F_{A\beta}^k[\bar{g}_{i,t}] &= C_\mu\int(1-\mu_0-2\bar{A}_i^k(y,t))\tilde{v}_i(\bar{A}_i^k(y,t),t)\,d\bar{g}_{i,t}^k(y) \qquad (4.156)\\ &+C_\mu\eta(t)\chi_H(t)\int\left[(\mu_0+a)(1-a)\int P(t,\bar{A}_i^k(\xi,t),a)\,d\bar{g}_{i,t}^k(\xi)\right]da\\ &-C_\mu\eta(t)\chi_H(t)\int(\mu_0+\bar{A}_i^k(y,t))(1-\bar{A}_i^k(y,t))\,d\bar{g}_{i,t}^k(y) \end{aligned}$$

for $k = 1, 2$.

We now proceed to estimate the term $|(\bar{u}_2^1)'(i,t) - (\bar{u}_2^2)'(i,t)|$.

$$||(\bar{u}^1)'(t) - (\bar{u}^2)'(t)||_{\mathbb{R}^{3h}} \leq C_{\sigma_1} \left\|(J_1(t))^{-1} - (J_2(t))^{-1}\right\|_2 \left\| J_1(0) \begin{pmatrix} \partial_t F^1_{A\beta}[\bar{g}_{1,t}] \\ \partial_t F^1_{A\beta}[\bar{g}_{2,t}] \\ \vdots \\ \partial_t F^1_{A\beta}[\bar{g}_{h,t}] \\ 0 \\ \vdots \\ 0 \end{pmatrix} \right\|_{\mathbb{R}^{3h}} \tag{4.157}$$

$$+ C_{\sigma_1} \left\|(J_2(t))^{-1}\right\|_2 \left\| J_1(0) \begin{pmatrix} \partial_t F^1_{A\beta}[\bar{g}_{1,t}] \\ \partial_t F^1_{A\beta}[\bar{g}_{2,t}] \\ \vdots \\ \partial_t F^1_{A\beta}[\bar{g}_{h,t}] \\ 0 \\ \vdots \\ 0 \end{pmatrix} - J_2(0) \begin{pmatrix} \partial_t F^2_{A\beta}[\bar{g}_{1,t}] \\ \partial_t F^2_{A\beta}[\bar{g}_{2,t}] \\ \vdots \\ \partial_t F^2_{A\beta}[\bar{g}_{h,t}] \\ 0 \\ \vdots \\ 0 \end{pmatrix} \right\|_{\mathbb{R}^{3h}}$$

$$\leq C_{\sigma_1} \left\| J_1(t)^{-1} \left[J_2(t) - J_1(t)\right] J_2(t)^{-1} \right\|_2 \left\|\partial_t F^1_{A\beta}[\bar{g}^1_t]\right\|_{\mathbb{R}^h} + C_{\sigma_1} \left\|J_2(t)^{-1}\right\|_2 \left\|\partial_t F^2_{A\beta}[\bar{g}^2_t] - \partial_t F^1_{A\beta}[\bar{g}^1_t]\right\|_{\mathbb{R}^h}.$$

The last inequality follows from the structure of $J_k(0)$. Indeed, $J_k(0)$ is block upper triangular with block in position $(1,1)$ given by $-I_h$. We can easily estimate the term $\left\|J_k(t)^{-1}\right\|_2$ by observing that its coefficients are uniformly bounded. Indeed by the Cramer's rule we have

$$J_k(t)^{-1} = \frac{1}{\det J_k(t)} \mathrm{adj}(J_k(t)) \tag{4.158}$$

where $\mathrm{adj}(J_k(t))$ is the adjugate matrix of $J_k(t)$ whose entries are polynomials of degree $3h-1$ in the coefficients of $J_k(t)$. The bound given by (4.77) on $\bar{u}^k$ and the uniform invertibility imply $\left\|J_k(t)^{-1}\right\|_2 \leq \left\|J_k(t)^{-1}\right\|_F \leq C_\sigma$ for $k = 1, 2$ and $t \in [0, \tau]$. By Remark 4.5.1, the estimate (4.157) gives

$$\begin{aligned} ||(\bar{u}^1)'(t) - (\bar{u}^2)'(t)||_{\mathbb{R}^{3h}} &\leq C_{\sigma_1, F_{A\beta}} \left\|J_2(t) - J_1(t)\right\|_2 + C_{\sigma_1} \left\|\partial_t F^2_{A\beta}[\bar{g}^2_t] - \partial_t F^1_{A\beta}[\bar{g}^1_t]\right\|_{\mathbb{R}^h} \\ &=: A + B. \end{aligned} \tag{4.159}$$

The first term yields

$$\begin{aligned} A^2 &\leq C^2_{\sigma_1, F_{A\beta}} \left\|J_2(t) - J_1(t)\right\|_F^2 = C^2_{\sigma_1, F_{A\beta}} \sum_{i,j=1}^{3h} \left[(J_2)_{ij}(t) - (J_1)_{ij}(t)\right]^2 \\ &\leq C^2_{\sigma_1, F_{A\beta}} \max_{i \in V, k=1,2,3} \left(\bar{u}^1_k(i,t) - \bar{u}^2_k(i,t)\right)^2 \leq C d((A^1, g^1, u^1, N^1), (A^2, g^2, u^2, N^2))^2 \end{aligned} \tag{4.160}$$

since the coefficients of J_1 and J_2 are polynomials in the Aβ concentrations $\bar{u}^1_k(i,t)$ and $\bar{u}^2_k(i,t)$, respectively, of degree at most 1 (the matrix entries are detailed in (2.55)). To quantify the term B, let $i \in V$ and

$t \in [0, \tau]$. By (4.156), it follows that

$$\begin{aligned}\left|\partial_t F^2_{A\beta}[\bar{g}^2_{i,t}] - \partial_t F^1_{A\beta}[\bar{g}^1_{i,t}]\right| \le C_\mu \bigg| &\int (1-\mu_0 - 2\bar{A}^2_i(y,t))\tilde{v}_i(\bar{A}^2_i(y,t),t)\, d\bar{g}^2_{i,t}(y) \\ - &\int (1-\mu_0 - 2\bar{A}^1_i(y,t))\tilde{v}_i(\bar{A}^1_i(y,t),t)\, d\bar{g}^1_{i,t}(y)\bigg| \\ + C_\mu \eta(t)\chi_H(t) \int (\mu_0 + a)(1-a) &\left|\int P(t, \bar{A}^2_i(\xi,t),a)\, d\bar{g}^2_{i,t}(\xi) - \int P(t,\bar{A}^1_i(\xi,t),a)\, d\bar{g}^1_{i,t}(\xi)\right| da \\ + C_\mu \eta(t)\chi_H(t) &\left|\int (\mu_0 + \bar{A}^2_i(y,t))(1-\bar{A}^2_i(y,t))\, d\bar{g}^2_{i,t}(y) - \int (\mu_0 + \bar{A}^1_i(y,t))(1-\bar{A}^1_i(y,t))\, d\bar{g}^1_{i,t}(y)\right|.\end{aligned} \tag{4.161}$$

By Lemma 4.69, $a \mapsto \tilde{v}_i(a,t)$ is Lipschitz continuous uniformly in t. Moreover, $(A^k, g^k, u^k, N^k) \in \mathcal{H}(X_{\rho,\tau})$ and therefore the map $y \mapsto (1-\mu_0 - 2\bar{A}^k_i(y,t))\tilde{v}_i(\bar{A}^k_i(y,t),t)$ is Lipschitz continuous uniformly in t. This yields

$$\begin{aligned} &C_\mu \left|\int (1-\mu_0 - 2\bar{A}^2_i(y,t))\tilde{v}_i(\bar{A}^2_i(y,t),t)\, d\bar{g}^2_{i,t}(y) - \int (1-\mu_0 - 2\bar{A}^1_i(y,t))\tilde{v}_i(\bar{A}^1_i(y,t),t)\, d\bar{g}^1_{i,t}(y)\right| \\ &\le C_\rho \int |\bar{A}^2_i(y,t) - \bar{A}^1_i(y,t)|\, d\bar{g}^2_{i,t}(y) + \int |1-\mu_0 - 2\bar{A}^1_i(y,t)|\tilde{v}_i(\bar{A}^1_i(y,t),t)\, d(\bar{g}^2_{i,t} - \bar{g}^1_{i,t})(y) \\ &\le C\tau d((A^1,g^1,u^1,N^1),(A^2,g^2,u^2,N^2)) + C\mathcal{W}_1(\bar{g}^2_{i,t}, \bar{g}^1_{i,t}).\end{aligned} \tag{4.162}$$

Arguing as in (4.162), by the Lipschitz continuity of P and $y \mapsto \bar{A}^k_i(y,t)$ uniformly in t we can conclude that for all $i \in V$ and $t \in [0,\tau]$

$$\left|\partial_t F^2_{A\beta}[\bar{g}^2_{i,t}] - \partial_t F^1_{A\beta}[\bar{g}^1_{i,t}]\right| \le Cd((A^1,g^1,u^1,N^1),(A^2,g^2,u^2,N^2)). \tag{4.163}$$

Reassuming, we have proved that

$$||(\bar{u}^1)'(t) - (\bar{u}^2)'(t)||_{\mathbb{R}^{3h}} \le Cd((A^1,g^1,u^1,N^1),(A^2,g^2,u^2,N^2)) \tag{4.164}$$

and therefore

$$\begin{aligned}\left|\mathcal{P}^1_i(t) - \mathcal{P}^2_i(t)\right| \le\ & Cd((A^1,g^1,u^1,N^1),(A^2,g^2,u^2,N^2)) \\ &+ \left|\frac{\gamma_1(\bar{u}^2_2(i,t))(\bar{u}^2_2)'(i,t)\gamma_2'(\bar{u}^2_2(i,t))\bar{N}^2_i}{\beta - \gamma_2(\bar{u}^2_2(i,t))\bar{N}^2_i} - \frac{\gamma_1(\bar{u}^1_2(i,t))(\bar{u}^1_2)'(i,t)\gamma_2'(\bar{u}^1_2(i,t))\bar{N}^1_i}{\beta - \gamma_2(\bar{u}^1_2(i,t))\bar{N}^1_i}\right|.\end{aligned} \tag{4.165}$$

A straightforward calculation on the remaining term of (4.165) shows that, by (4.164), (4.135) and the uniform bound on $(\bar{u}^k_2)'$

$$\left|\mathcal{P}^1_i(t) - \mathcal{P}^2_i(t)\right| \le C_1 d((A^1,g^1,u^1,N^1),(A^2,g^2,u^2,N^2)) + C_2\left|\bar{N}^2_i(t) - \bar{N}^1_i(t)\right|. \tag{4.166}$$

From (4.149), (4.150), (4.151), (4.152), (4.153) and (4.166) we obtain for all $t \in [0,\tau]$

$$\max_{i\in V}\left|\bar{N}^1_i(t) - \bar{N}^2_i(t)\right| \le C_1\tau d((A^1,g^1,u^1,N^1),(A^2,g^2,u^2,N^2)) + C_2\int_0^t \max_{i\in V}\left|\bar{N}^1_i(s) - \bar{N}^2_i(s)\right| ds \tag{4.167}$$

hence by Gronwall's inequality

$$\max_{i\in V} \left|\bar{N}_i^1(t) - \bar{N}_i^2(t)\right| \le C_1 \tau d((A^1, g^1, u^1, N^1), (A^2, g^2, u^2, N^2))e^{C_2 t} \tag{4.168}$$

for all $t \in [0, \tau]$. Combining (4.146), (4.147), (4.148), (4.168) we conclude that $\mathcal{H}$ is a contraction on $\mathcal{H}(X_{\rho,\tau})$ if τ is sufficiently small. $\square$

The local existence on $[0, \tau]$ follows from Proposition 4.8 in [14].

4.7.1 Global Existence

To extend the solution to the whole interval $[0, T]$, suppose that $[0, \tau^*)$ is the maximal interval. We recall that the Aβ monomers' source is uniformly bounded

$$F_{A\beta}[g_{i,t}] = C_\mu \int (\mu_0 + A_i(y,t))(1 - A_i(y,t))\, dg_{i,t}(y) \le C \quad \text{for all } i \in V, t \in [0, t^*), \tag{4.169}$$

hence by (4.77) it follows that

$$|u_k(i,t)| \le \tilde{C} \quad \text{for } t \in [0, \tau^*),\ i \in V,\ k = 1, 2, 3. \tag{4.170}$$

Moreover, by the mass balance of the *Release-Uptake NTM* (Lemma 4.6.7),

$$|N_i(t)|, |n_{ij}(x,t)| \le \mathcal{M} \quad \text{for } t \in [0, \tau^*),\ e_{ij} \in E_c,\ i \in V,\ x \in [0, L_{ij}]. \tag{4.171}$$

By (4.170) and (4.171), $v_i(A_i(y,t),t)$ is bounded uniformly in t, therefore $t \mapsto A_i(y,t)$ is Lipschitz continuous. By Lemma 4.4.4, $y \mapsto A_i(y,t)$ is Lipschitz continuous uniformly in t. Moreover, by Lemma 4.4.5, $t \mapsto g_{i,t} \in X_{[0,1]}$ is Lipschitz continuous, therefore both can be extended with continuity to $[0, \tau^*]$ and the limit $\lim_{t\to\tau^*} A_i(y,t) = A_i(y, \tau^*)$ is Lipschitz continuous in y. By Remark 4.4.1, $t \mapsto F[g_{i,t}]$ is Lipschitz continuous. Now repeating the argument leading to (4.148) we obtain that $t \mapsto u \in \mathbb{R}^{3h}$ is Lipschitz continuous. By (4.130), (4.170) and (4.171) it follows that N_i' is bounded on $[0, \tau^*)$, and therefore both can be extended to $[0, \tau^*]$. We have thus proved that $[0, \tau^*)$ is not maximal, contradicting the definition of τ^*.

4.8 Numerical algorithms and experiments

In this Section, we describe the algorithm implementing the *Release-Uptake NTM* and present some numerical simulations we ran on the mouse brain network extracted from [68]. For each simulation, we report the error estimates for the implementation of the model throughout the 12 month time range. The MATLAB code is available at https://github.com/Raj-Lab-UCSF/NTM_ru/tree/main/Transport_Network_Neumann.

4.8.1 Implementation details

The implementation of the *Release-Uptake NTM* (4.20) follows that of Sections 1.8 and 3.6. We select an inhomogeneous time grid $0 = t^1 \le t^2 \le \cdots \le t^{k_{end}} = T$ and, given the concentrations $N_i(t^k)$ for $i = 1, \dots, h$, we solve the problem $(4.20)_{2,3,4,5}$ on each edge of the *connectivity* graph. For this purpose, we introduce an inhomogeneous spatial grid on the interval $[0, L_{ij}]$ for every $e_{ij} \in E_c$. For simplicity, we set $L_{ij} = L_{\ell m}$ for all $e_{ij}, e_{\ell m} \in E_c$. The edge problem for (n_{ij}, J_{ij}) is solved through a shooting argument, as detailed in Section 4.6. We start by solving the problem

$$\begin{cases} a(x)n_x + h(x,n) = -J(0) + \int_0^x F(y)\,dy, \\ J(0) = -\mu_{i,1}n(0) + \mu_{i,2}N_i, \end{cases} \tag{4.172}$$

by calculating n as a function of the shooting parameter $n(0)$, i.e. $\tilde{n}(x, n(0))$, via an Implicit Euler scheme on the first compartment $(0, x_1)$. Then, starting from $\tilde{n}(x_1, n(0))$, the solution $\tilde{n}$ is extended on the entire interval $(0, L_{ij})$ by requiring continuity at the compartments' interfaces. Ultimately, the edge profile n and its flux are obtained by solving the problem

$$\text{find } n(0) \in \mathbb{R}^+ \text{ s.t.} \quad \tilde{J}(L_{ij}) - \mu_{j,1}\tilde{n}(L_{ij}, n(0)) + \mu_{j,2}N_j = 0, \tag{4.173}$$

where $\tilde{J}$ denotes the flux of $\tilde{n}$. This procedure is performed by the *FluxCalculator* function. Having computed the fluxes at time $t = t^k$, we update the concentrations N_i at the time step $t = t^{k+1}$ via a discretisation of the node equations $(4.20)_1$ obtained through an Explicit Euler scheme. The shooting procedure is computed by means of the MATLAB functions `fsolve` and `ODE45`.

In terms of computational burden, the dominating operation is the resolution of the shooting problem (4.173) since the calculation of the edge term $\partial_t n$, an essential step in Chapter 1, is redundant in this model due to the vanishing *feedback* mechanism.

The network adjacency is extracted from the mouse mesoscale connectome (MCA) from the Allen Institute for Brain Science [68], which is endowed with 426 nodes and 65644 edges. For further details on the definition of the network, see [91]. The remaining parameters are set as in Tables 4.3 and 4.4. The simulations are run in parallel using the computational resources provided by the University of California, San Francisco.

As in Chapter 3, we calculate the residual $r_{ij}(t^k)$ associated to (4.173) for each edge and time step of the simulations and we report the quantity $\max_{e_{ij},k} r_{ij}(t^k)$ in Table 4.1. By (4.23), we also calculate for each simulation the relative error

$$err(t^k) = \frac{|\mathcal{M}_{node}(t^k) - \mathcal{M}_{node}(0)|}{\mathcal{M}_{node}(0)} \tag{4.174}$$

in the case $F_i, F_{ij} \equiv 0$ and

$$err(t^k) = \frac{|\mathcal{M}_{node}(t^k) - \Big(\mathcal{M}_{node}(0) + t^k \sum_{e_{ij}\in E_c} L_{ij}F_{ij} + t^k \sum_{i\in V} \mathrm{Vol}(i)F_i\Big)|}{\mathcal{M}_{node}(0) + t^k \sum_{e_{ij}\in E_c} L_{ij}F_{ij} + t^k \sum_{i\in V} \mathrm{Vol}(i)F_i} \tag{4.175}$$

in the case $F_i = F_{ij} \equiv F > 0$. In Table 4.2 we report the value of $\max_{k=1,\dots,k_{end}} err(t^k)$. It is worth noticing that the global network error on the entire time-grid is affected by two main contributions. First, we observe that, with respect to the numerical simulations presented in Section 3.6 where the model is implemented on a synthetic small network, the size of the graph is extremely larger due to its empirical origin. This results in an increase in the global accumulation error. Secondly, the discretisation scheme adopted for the node equations is extremely sensitive to the time step selected, therefore a possible approach to increase preciseness is the selection of an higher order implicit scheme on the nodes, which in turn would require a larger computational time. Concerning the residual associated with (4.173), we observe that the edge problem exhibits a larger error with respect to the case of Dirichlet boundary conditions in Section 3.6. This property is due to the nature of the shooting function defined in (4.173), which exhibits a large first derivative near the solution $n(0)$ in the parameter range we set (see, for example, Figure 4.1). Clearly, this behaviour affects the preciseness of the calculation of Newton's method iteration needed to solve the shooting problem.

Residual				
Sim 1	Sim 2	Sim 3	Sim 4	Sim 5
2.7452×10^{-9}	1.3246×10^{-9}	3.5623×10^{-11}	2.3472×10^{-8}	1.077×10^{-11}
Sim 6	Sim 7	Sim 8	Sim 9	Sim 10
9.9461×10^{-10}	9.3612×10^{-8}	1.1635×10^{-7}	2.3476×10^{-8}	3.4299×10^{-8}

Table 4.1: Computed residual as in Definition (4.172).

Mass Error				
Sim 1	Sim 2	Sim 3	Sim 4	Sim 5
3.1176×10^{-2}	5.0776×10^{-2}	1.6046×10^{-4}	5.3695×10^{-2}	7.6312×10^{-2}
Sim 6	Sim 7	Sim 8	Sim 9	Sim 10
2.0996×10^{-2}	8.6078×10^{-6}	9.8254×10^{-5}	2.5067×10^{-4}	3.8038×10^{-4}

Table 4.2: Computed mass error as in Definition (4.174)-(4.175).

Algorithm 4: An algorithm for the *RU-NTM*

Input : $(N_i(0))_{i=1}^h$
Output: $(N_i(t))_{i=1}^h$

```
for k = 1, ..., k_end do
    for (i, j) ∈ E do
        (n_ij(t^k), J_ij(t^k)) ← FluxCalculator(N_i(t^k));
    end
    Update N_i(t^{k+1});
end
```

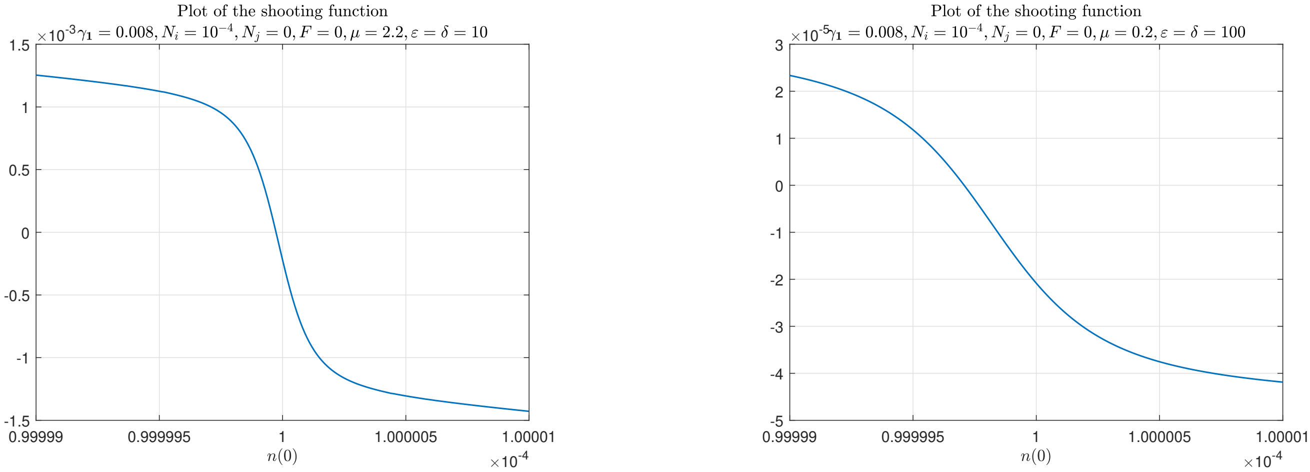

Figure 4.1: Behaviour of the shooting function near the solution $n(0)$.

4.8.2 Numerical simulations

In this Section, we present some numerical results obtained by implementing the *Release-Uptake-NTM*. Being the first computational analysis of the model, we assume that the parameters are not time-dependent and that $\gamma_2 = 0$ to reduce numerical instabilities. We follow the approach of [91] and simulate the model in four relevant cases: varying the aggregation rate γ_1, the source of pathological Tau at the edge level F_{ij} the degree of directionality bias δ and ε and the novel release-uptake parameters $\mu_{i,k}$. As a case study, we assume that the release and uptake processes occur at the same rate, meaning that $\mu_{i,1} = \mu_{i,2}$ for all $i \in V$.

1. **Varying γ**

   Figure 4.2 shows the temporal evolution of the concentrations N_i at each node of the network with different selections for γ_1, while Figure 4.3 shows the spatial disposition of Tau and the related heat-map. The plots suggests that the rate of spread of extracellular Tau is increased when γ_1 is smaller, as already observed in the original *NTM* [91].

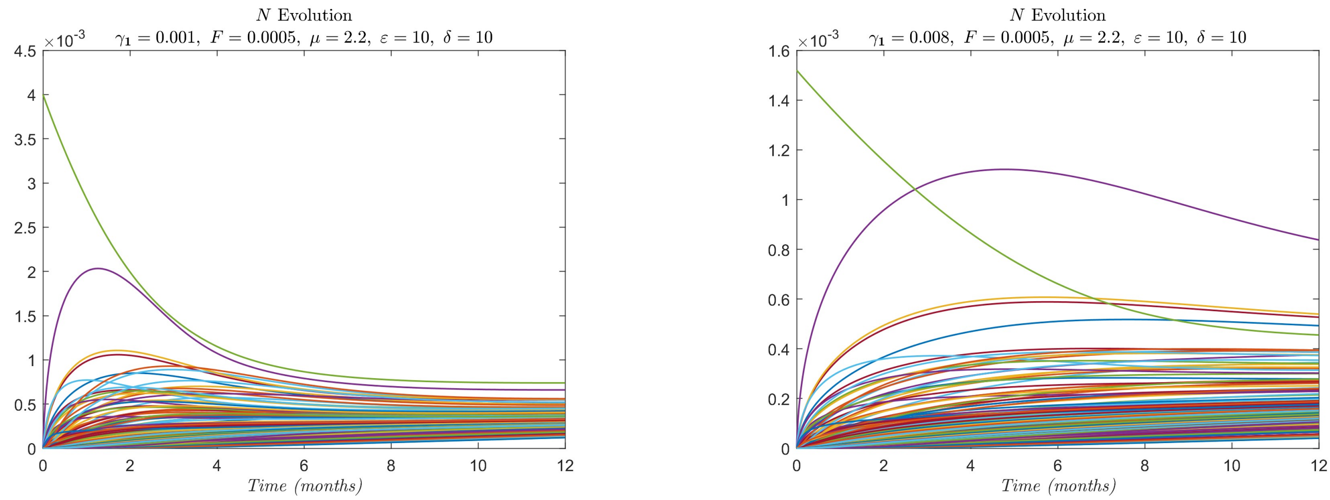

Figure 4.2: Time evolution of the concentration of N on the nodes, (a) $\gamma_1 = 0.001$, (b) $\gamma_1 = 0.008$.

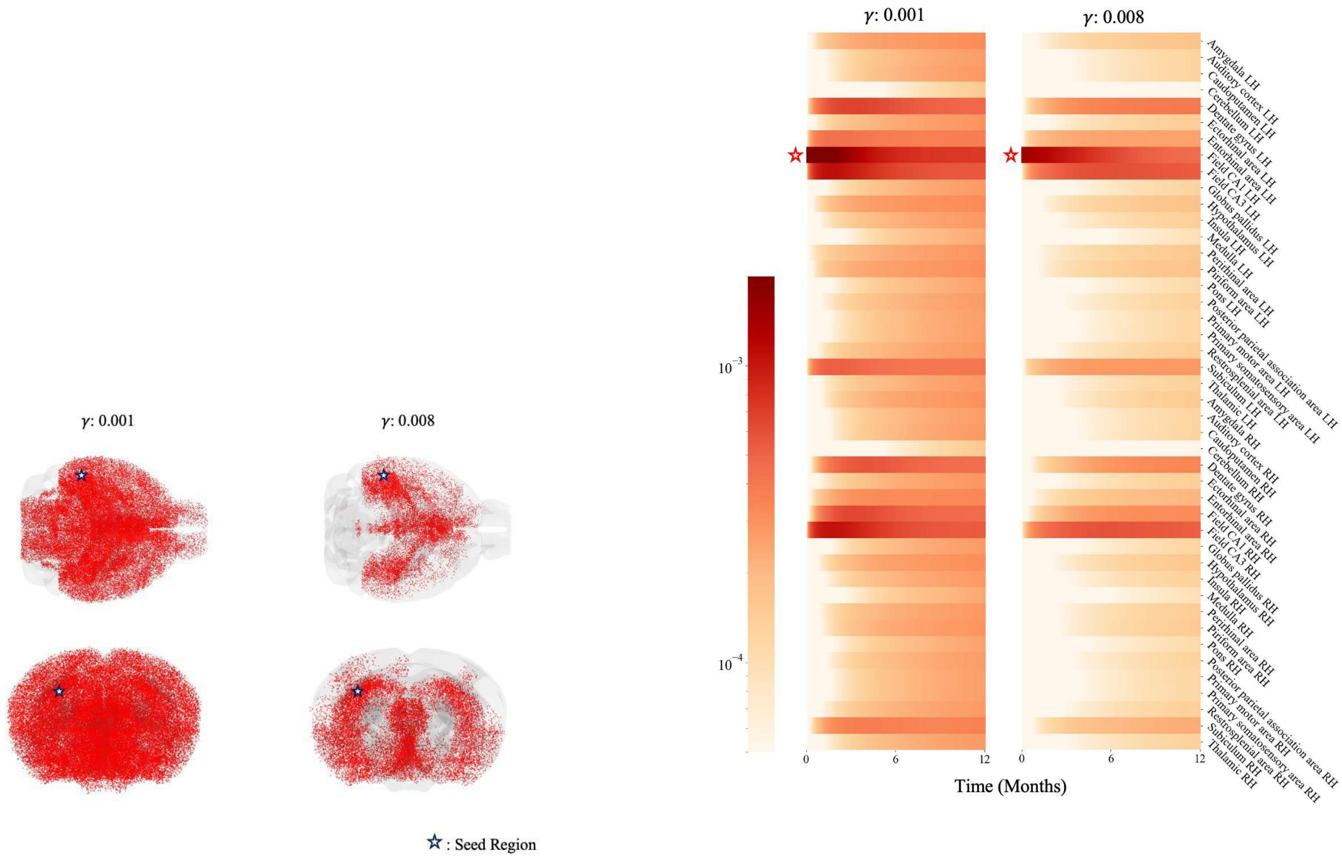

Figure 4.3: (a) Spatial disposition of extracellular Tau at time $t = 6$ months in the case $\gamma_1 = 0.001$ (first column) and $\gamma_1 = 0.008$ (second column). (b) Heat-map of extracellular Tau on the network in the case $\gamma_1 = 0.001$ (first column) and $\gamma_1 = 0.008$ (second column).

2. **Varying $\boldsymbol{F_{ij}}$**

   Figure 4.4 shows the dynamics of the model under different selections for the pathological seeding rate F_{ij} on the edges. The spatial distribution of Tau along the network is portrayed in Figure 4.5. The effect of the soluble intracellular Tau source is to increase the concentration of soluble extracellular Tau on the network.

3. **Varying $\boldsymbol{\mu}$** Figure 4.6 represents the time evolution of extracellular Tau on the network with different selections for the release-uptake parameters. Here, for simplicity we choose $\mu_{i,1} = \mu_{i,2} =: \mu$ for all $i \in V$. Figure 4.7 and 4.8 show the respective heat-map and spatial distribution on the network. The simulations confirm the main model hypothesis of the Release-Uptake process as the bottleneck of extracellular Tau evolution in the *RU-NTM*. In fact, smaller values of μ are associated to a slower overall dynamics on the network.

4. **Varying $\boldsymbol{\delta}$ and $\boldsymbol{\varepsilon}$** Figure 4.9, 4.10 and 4.11 show the behaviour of extracellular Tau on the network in the Anterograde and Retrograde bias, i.e. scenarios in which the edge mass flux agrees with the directionality of the edge (Ant.) or disagrees (Ret.). The bias is encoded in the selection of the parameters δ and ε, which influence the direction of the advective velocity on the single edge. While the temporal evolution seems to be unaffected, the spatial disposition of extracellular Tau

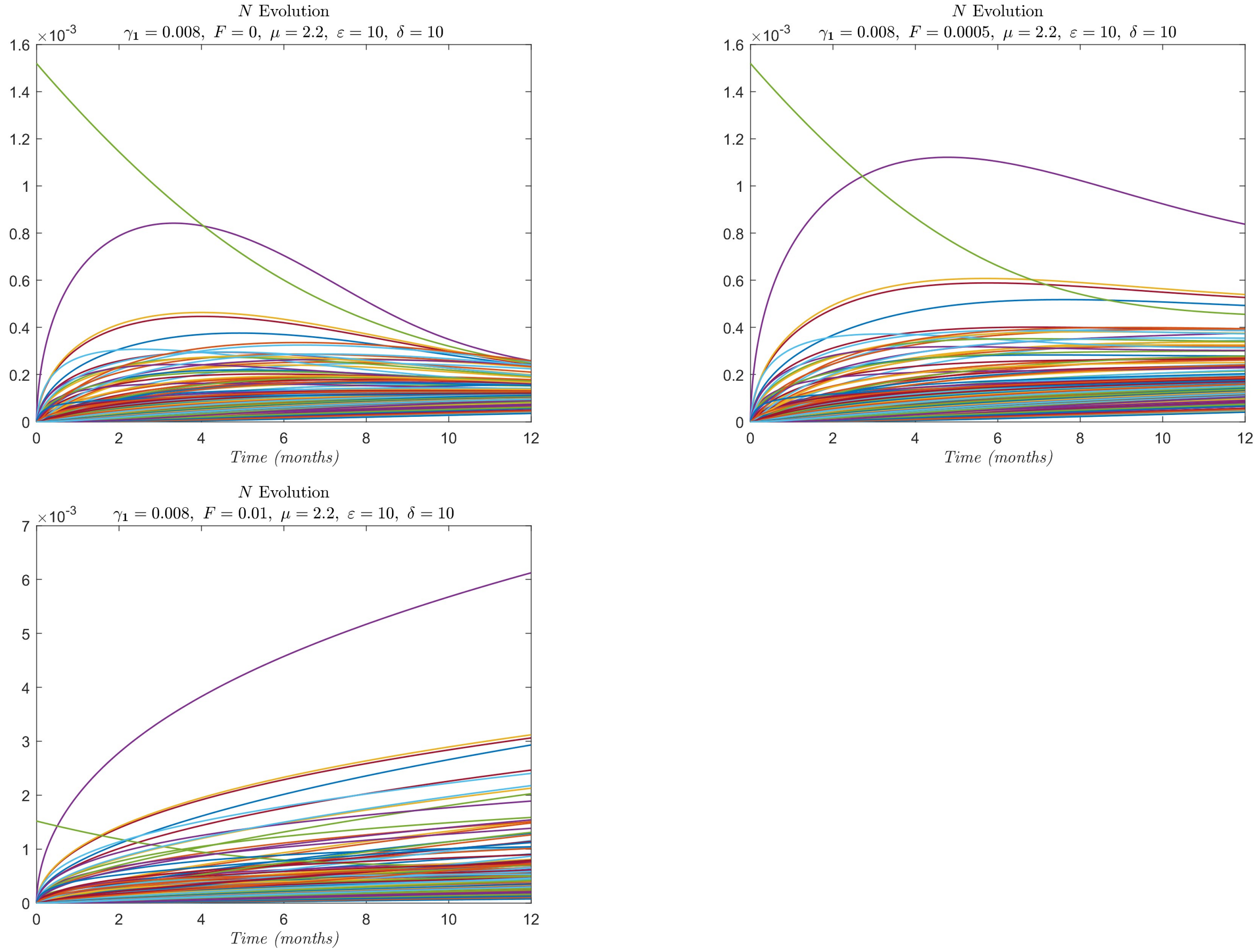

Figure 4.4: Time evolution of the concentration of N on the nodes, (a) $F_{ij} = 0$, (b) $F_{ij} = 0.0005$, (c) $F_{ij} = 0.01$.

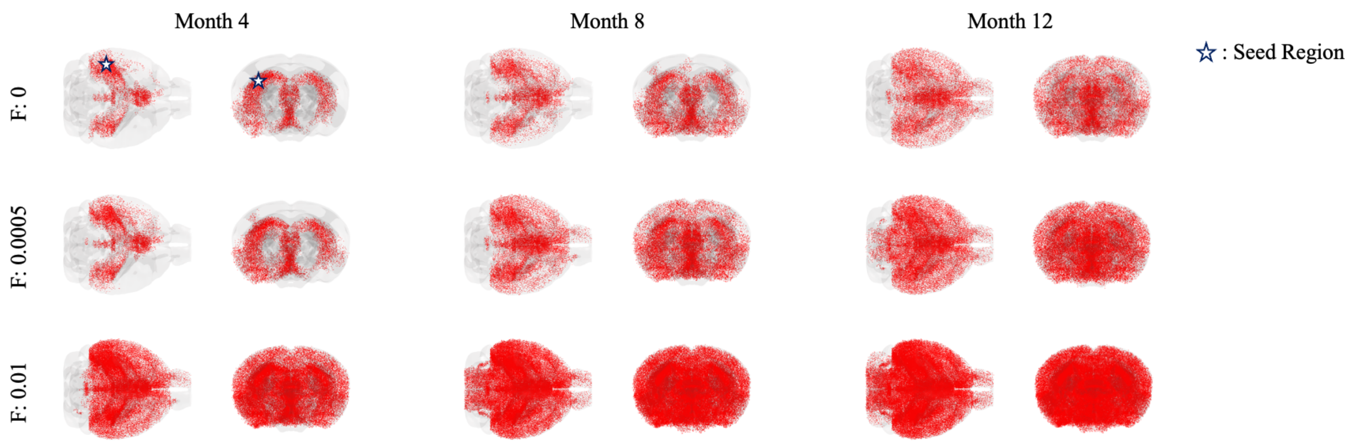

Figure 4.5: Spatial disposition of extracellular Tau on the network. First row: $F_{ij} = 0$, second row: $F_{ij} = 0.0005$, third row: $F_{ij} = 0.01$.

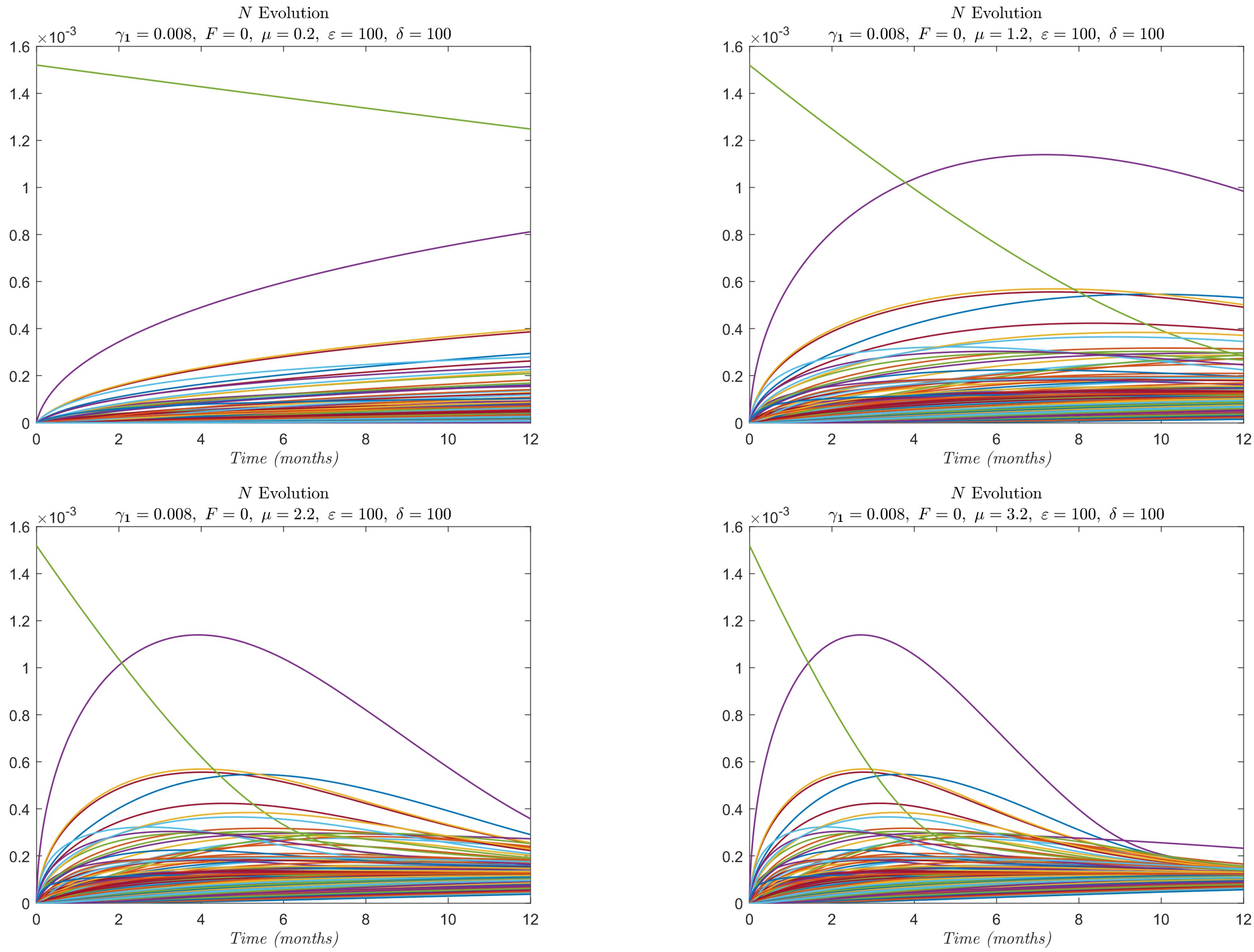

Figure 4.6: Time evolution of the concentration of N on the nodes, first row: $\mu = 0.2$, $\mu = 1.2$, second row: $\mu = 2.2$, $\mu = 3.2$.

on the network is differentiated in the Ant. vs Ret. bias as shown in the heat-map in Figure 4.10. Clearly this effect is due to the different edge flux configuration (Figure 4.11). In the Retrograde case, Tau is strongly localised in the seeding (starred) region, compared to the Anterograde case. The latter shows a more persistent Tau load in the *Field CA3* (left hemisphere) and the *Field CA3* (right hemisphere), regions exhibiting smaller Tau concentrations in the Retrograde setting. Therefore the *Release-Uptake NTM* preserves the macroscopic properties related to the flux biases (Ant. vs Ret.) of the original *NTM* [91].

4.9 Limitations and future developments

In the present Chapter, we proposed a variation of the *NTM* introduced in Chapter 1 to account for intracellular and extracellular Tau species on the *connectivity* graph. The novelty of the *Release-Uptake NTM* consists in the description of the release-uptake mechanism involving Tau along the neuronal cell membrane, which is technically encapsulated by the Neumann-Robin boundary conditions at each edge of the network. Prescribing the exact flux at each endpoint of the edges implies a remarkable simplification of

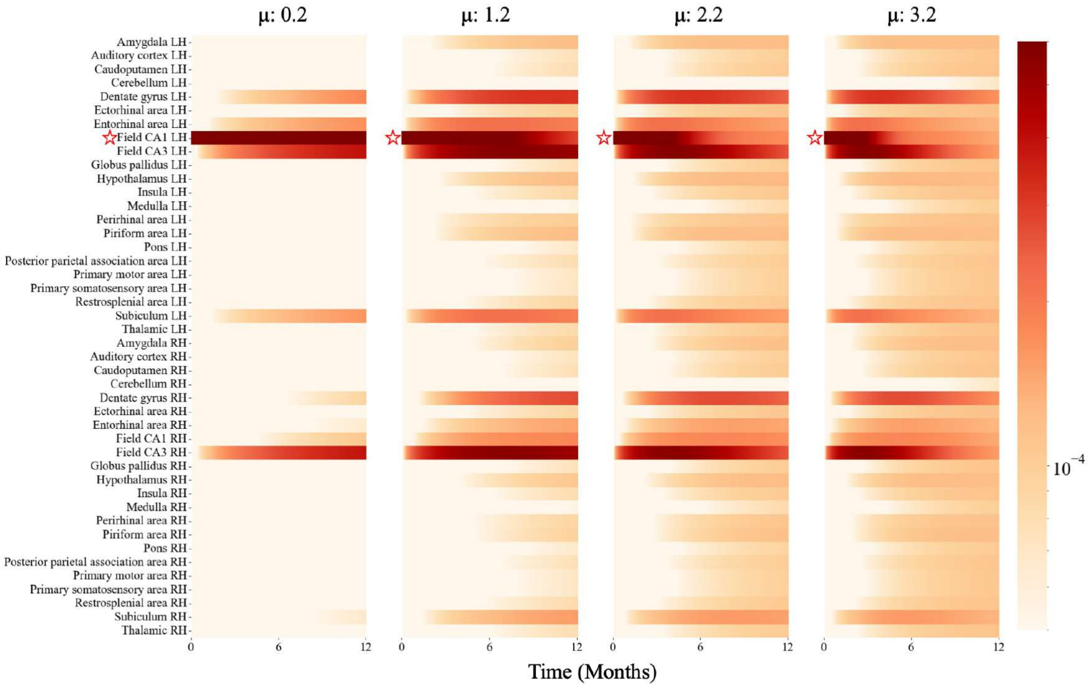

Figure 4.7: Heat-map of extracellular Tau on the network in the case $\mu = 0.2$ (first column), $\mu = 1.2$ (second column), $\mu = 2.2$ (third column) and $\mu = 3.2$ (fourth column). The starred region represents the initial seeding area.

the original model since the mass exchange dynamics at each node consists of the unique contribution of the net incoming flux on the incident edges. The resulting model is therefore more practical from a mathematical standpoint. Moreover, the flexibility of the original *NTM* to incorporate new processes validates it as a general framework.

The interaction between Beta Amyloid and Tau is modelled in a two-way fashion to account for the enhancement of Tau aggregation, diffusion and release-uptake under the action of soluble Aβ and the increase in the rate of spread of the pathology induced by Tau on f. We proved existence of a solution to the coupled system following the approach of [14] and extending the contraction space to include the extracellular Tau variable. In view of the explicit equation for N_i, we consider the time regularity result of Section 2.7 and adapt it to the current setting. The proof differs from the main theorem of Chapter 2 in the analysis of the *Release-Uptake NTM* for fixed parameters (Section 4.6) and the study of the contractive operator on X_T (Section 4.7).

The resulting Tau system recovers the positivity properties of the original *NTM*, unlike the time-dependent model of Chapter 3. Computationally, the elimination of the *feedback* implies a considerable reduction in the costs associated with the implementation of the model. In view of the large scale of the brain network, this represents a remarkable practical improvement for future parameter inference and comparison with human data.

Although neuroinflammation is not explicitly modelled in the present work, incorporating extracellular Tau produces a more biologically realistic framework for the *NTM* and provides a flexible foundation for future extensions that could integrate inflammatory or glial-mediated effects.

A further limitation of the model is the localisation of the release-uptake process. Intracellular Tau

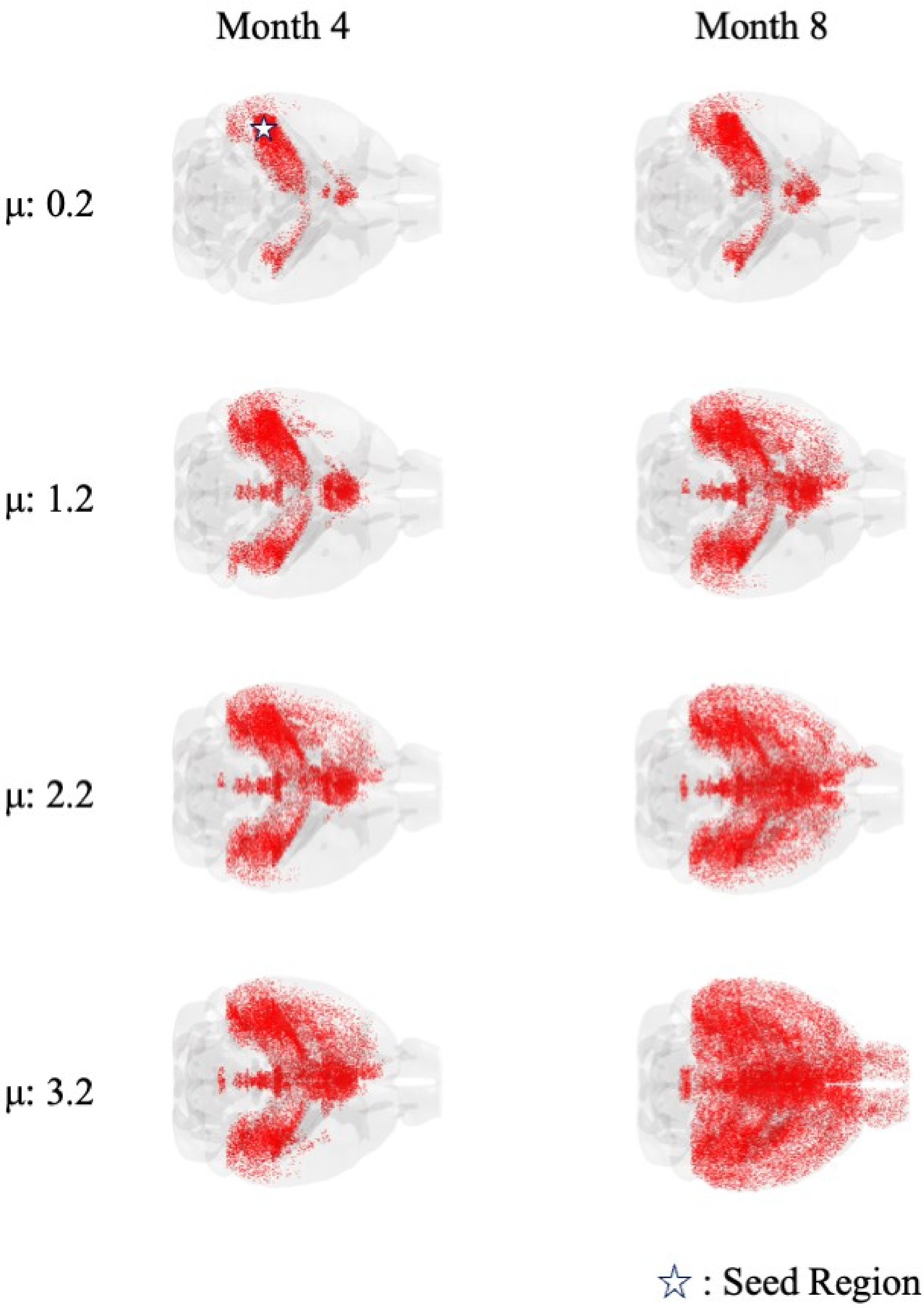

Figure 4.8: Spatial disposition of extracellular Tau at time $t = 4$ months (first column) and $t = 8$ months (second column).

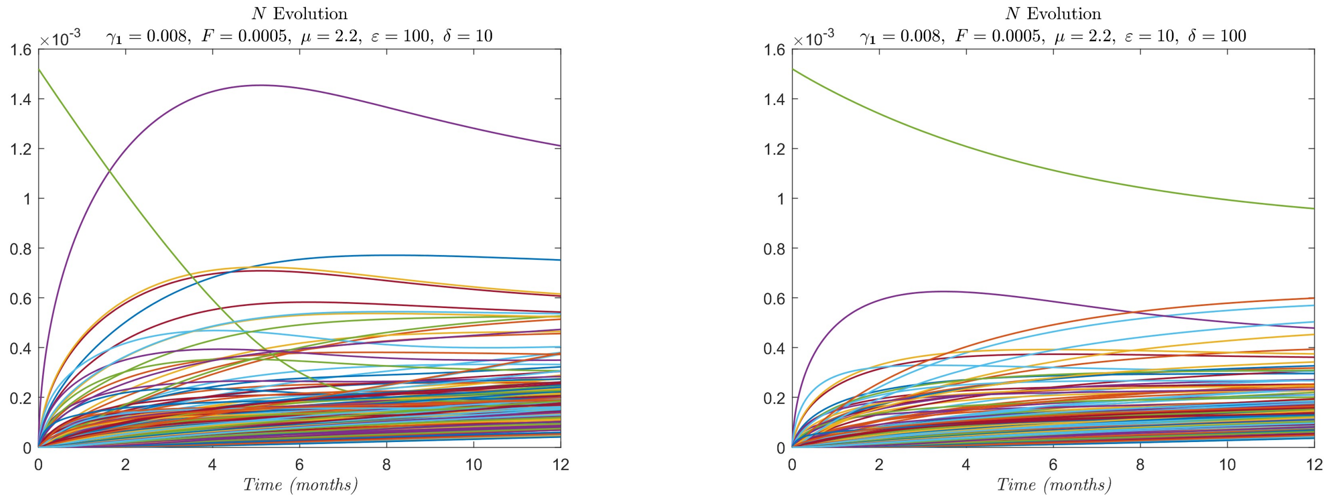

Figure 4.9: Time evolution of the concentration of N on the nodes, (a) $\delta = 10$, $\varepsilon = 100$, (b) $\delta = 100$, $\varepsilon = 10$.

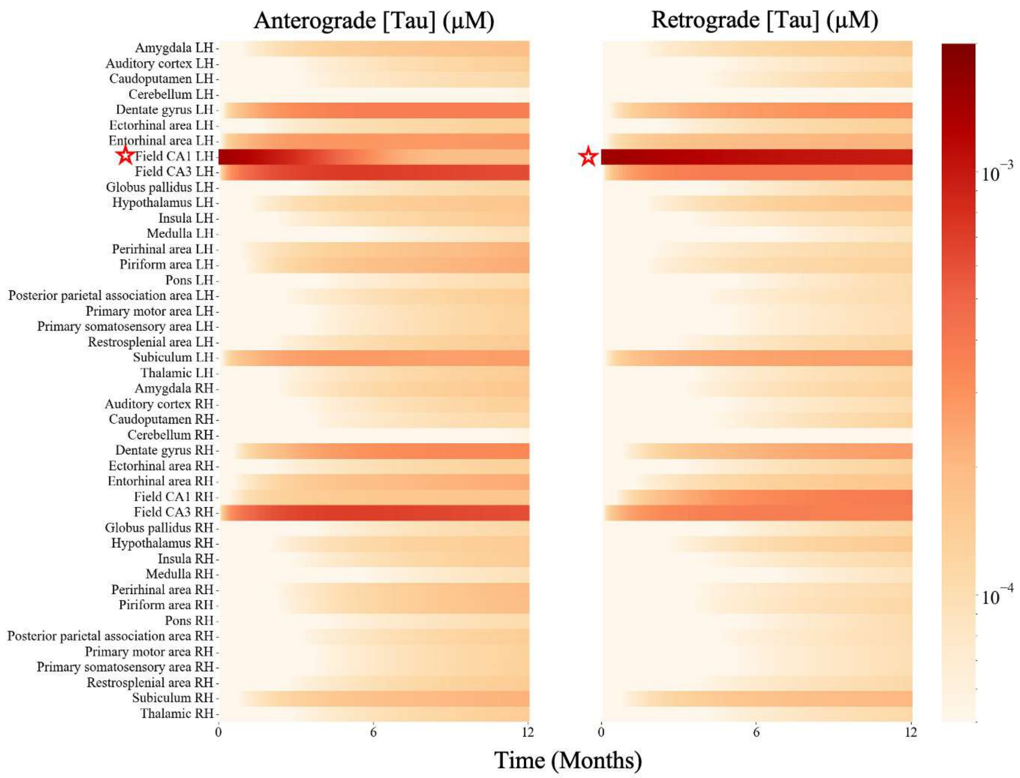

Figure 4.10: Heat-map of extracellular Tau in the Anterograde and Retrograde bias. Ret. bias: $\delta = 10$, $\varepsilon = 100$, Ant. bias: $\delta = 100$, $\varepsilon = 10$. The starred region represents the initial seeding area.

is in fact released at the end point of the respective edge and subsequently confined to the extracellular compartment corresponding to the respective node. The recruitment of Tau in the same way takes place locally from the node towards the incident edges, following the pathways of the underlying network. However, an interesting scenario could be the case of release-uptake between edges and nodes that are not directly incident, but simply neighbouring, thus allowing Tau spread in a "non local" manner.

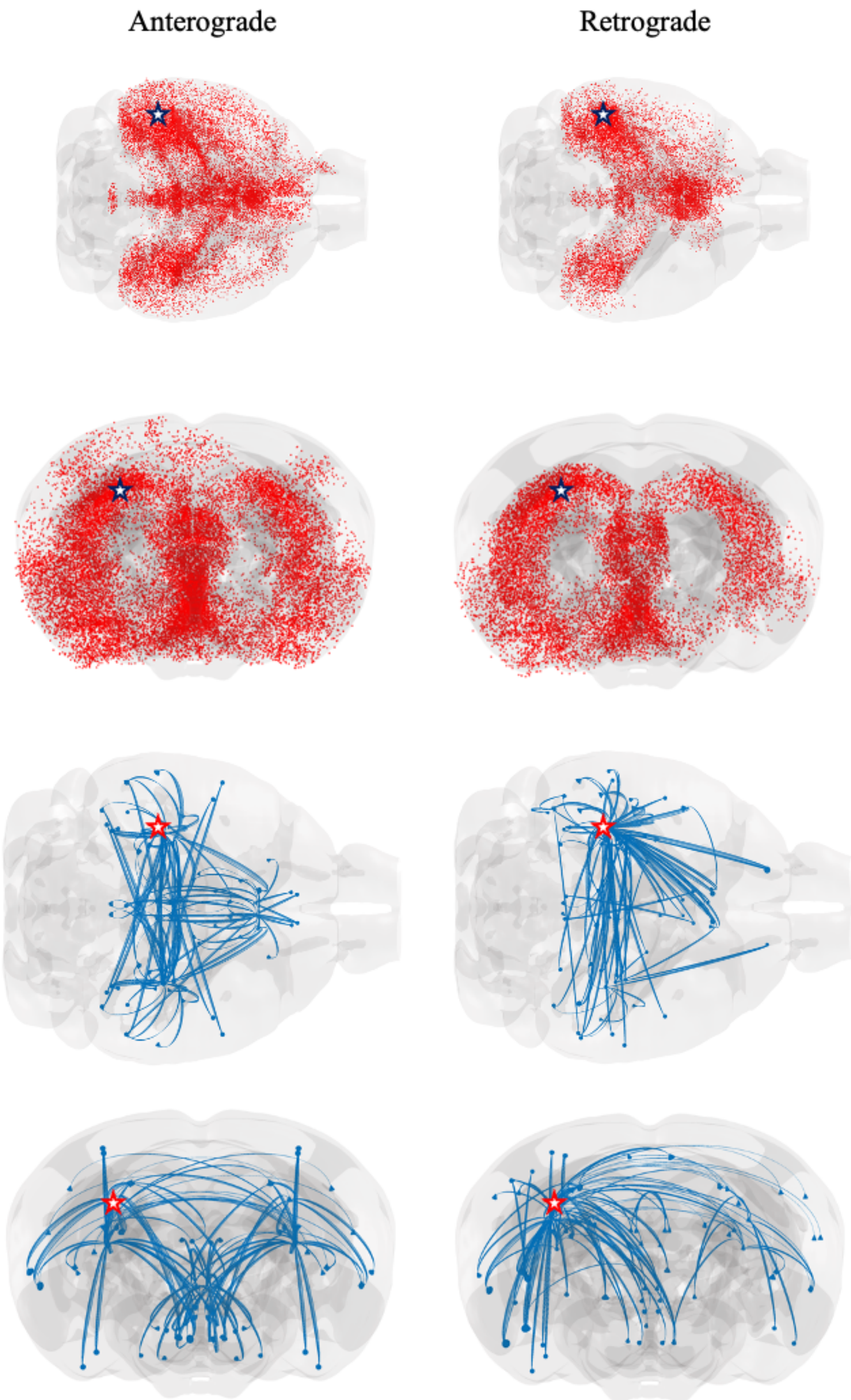

Figure 4.11: Spatial disposition of extracellular Tau (in red) on the network and its (upper 10%) fluxes (in blue) between different regions at time $t = 6$ months. Retrograde bias: $\delta = 10$, $\varepsilon = 100$, Anterograde bias: $\delta = 100$, $\varepsilon = 10$. The starred point represents the initial seeding region.

Symbol	Description	Remark
f	Diffusing fraction of n	0.7
β	Fragmentation rate of m	Unimolecular process by which $m \rightarrow n$ (10^{-6})
γ_1	Aggregation rate, $n + n$	Bimolecular process by which $n \rightarrow m$ ([0.001,0.008])
δ	Ant. vel. enhancement factor	Effect modulated by n ([10,100])
ϵ	Ret. vel. enhancement factor	Effect modulated by m ([10,100])
λ	Diffusivity barrier, AIS	Reduces the rate of diffusion within AIS (0.025)
$\mu_{i,1}$	Release of n at P_i	([0.2,3.2])
$\mu_{j,1}$	Release of n at P_j	([0.2,3.2])
$\mu_{i,2}$	Uptake of N at P_i	([0.2,3.2])
$\mu_{j,2}$	Uptake of N at P_j	([0.2,3.2])
F_{edge}	Production of n on the edge	([0,0.01])
F_{node}	Production of N on the node	([0,0.01])

Table 4.3: List of parameters and the respective ranges explored. Ant. = anterograde, ret. = retrograde, conc. = concentration, vel. = velocity., AIS = axon initial segment.

Symbol	Description	Remark
D	Theoretical diffusivity of n	Estimated to be 12 μm^2/s*
v_a	Native ant. transport velocity of n	Estimated to be 0.7 μm/s*
v_r	Native ret. transport velocity of n	Estimated to be 0.7 μm/s*

Table 4.4: List of parameters of the Release-Uptake *NTM*. The values were estimated from previous experimentally derived estimates [57]. The parameters have been taken as global, regionally invariant constants, as in Chapter 1.

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