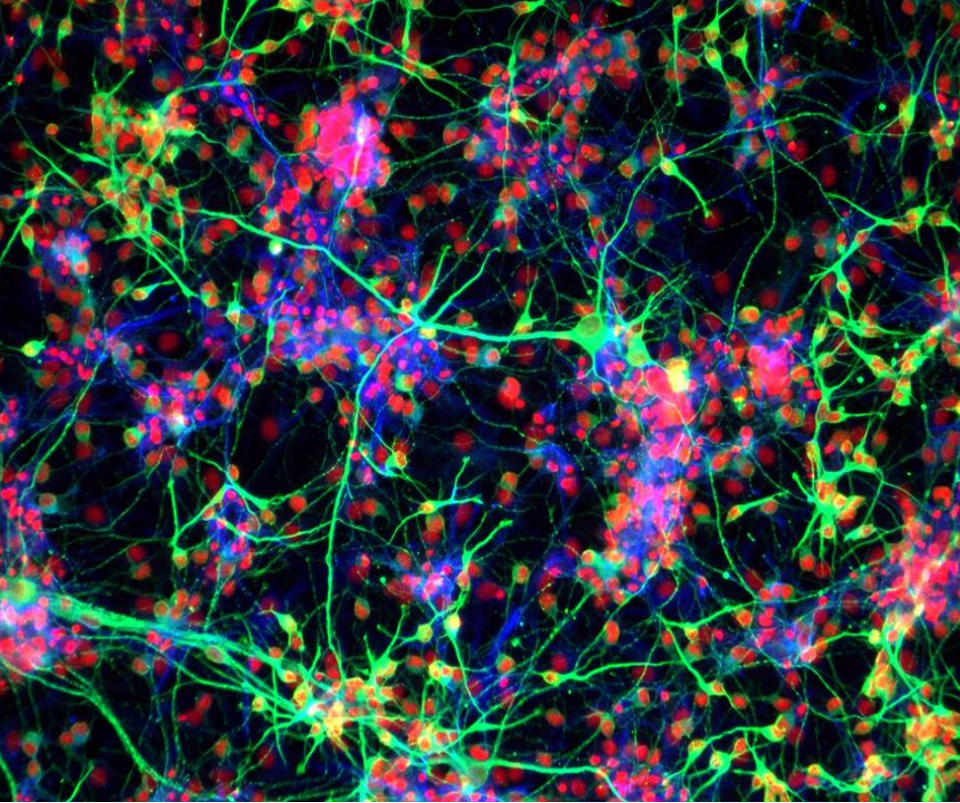




INCA-ABACO
Università di Roma Tor Vergata
22 marzo 2016

**Matematica e
modelli biomedici,
un cammino
appena iniziato**

Roberto Natalini

Istituto per le Applicazioni del Calcolo

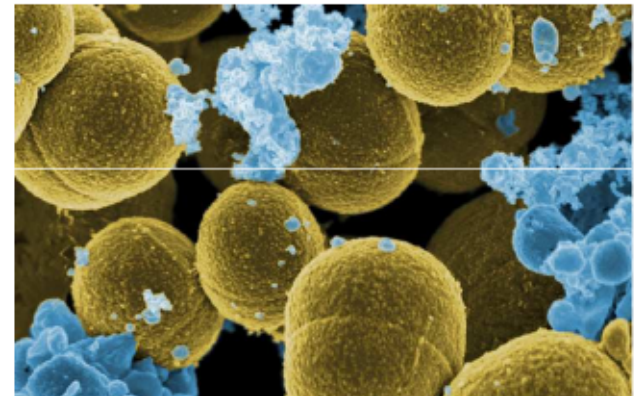
Consiglio Nazionale delle Ricerche



Mathematics Is Biology's Next Microscope, Only Better; Biology Is Mathematics' Next Physics, Only Better

Joel E. Cohen

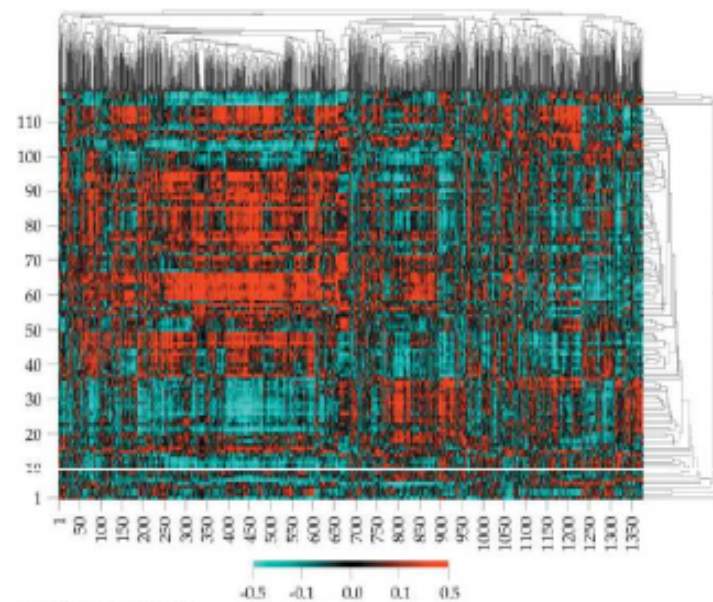
Il microscopio alla fine del XVII secolo provocò una rivoluzione facendo conoscere i microorganismi che prima erano invisibili.



La matematica oggi fornisce nuovi tipi di microscopio. Permette di vedere strutture e processi altrimenti inaccessibili.

La biologia ha bisogno della matematica

La biologia studia l'emergere di strutture complesse da un'enorme quantità di individui eterogenei e per farlo avrà bisogno della matematica



DOI: 10.1371/journal.pbio.0020450.g003

Figure 3. Clustered Image Map of Gene Expression-Drug Activity Correlations

La matematica si sviluppa grazie alla biologia

La biologia è la nuova fisica dei matematici. Pone dei problemi di una complessità incomparabile. Vi sono tra i 3 e i 20 milioni di specie viventi.

Alcune interazioni del passato tra matematica e biologia

Struttura per età delle popolazioni	Eulero	1760
Equazione logistica per la popolazione	Verhulst	1838
Equilibrio in genetica delle popolazioni	Hardy-Weinberg	1908
Dinamica di interazione tra le specie	Lotka-Volterra	1925-1931
Onde viaggianti in genetica	Fisher, Kolmogorov	1937
Morfogenesi	Turing	1952
Modello del segnale nel neurone	Hodgkin-Huxley	1952

Settori in cui oggi la matematica contribuisce alla biologia

Funzionamento della cellula	Capire le catene di reazioni chimiche che avvengono nel citoplasma e nel nucleo. Trasporto del segnale chimico.
Genomica	Sequenziamento del DNA
Espressione genica	Come avviene l'interazione tra geni e proteine
Geometria e topologia delle macromolecole	Le proteine sono caratterizzate non solo dalla composizione, ma anche dalla geometria che permette di nascondere o esibire certe proprietà
Fisiologia	Modellizzare il funzionamento degli organi, accoppiando la biologia, alla fisica, meccanica, idrodinamica etc...(polmoni, cuore, flusso sanguigno).
Neurobiologia	Trasmissione dei segnali nervosi. Manca una teoria del funzionamento del cervello.
Biologia delle popolazioni	Come si evolvono, si muovono e interagiscono le diverse popolazioni.
Filogenetica	Come ricostruire l'evoluzione all'indietro confrontando i diversi patrimoni genetici.

Argomenti di oggi

Livello intracellulare

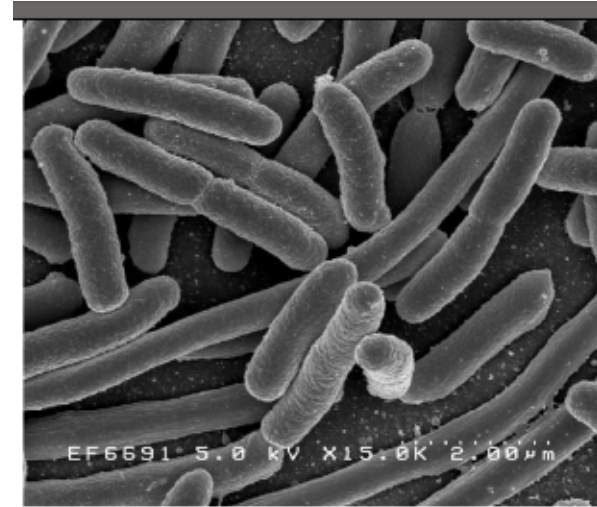
Trasporto di segnali nella cellula

Trasporto di vaccini nella cellula

Movimenti cellulari

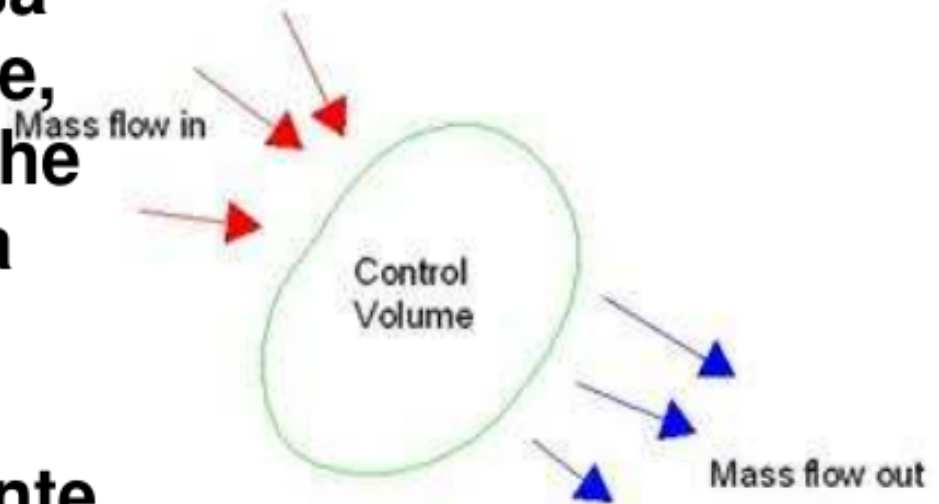
La chemotassi

Sviluppo di cellule staminali



Come nasce un modello macroscopico

Nell'ipotesi che la massa (proteine, fluidi, cellule, ...) si conservi, si ha che la variazione di massa nel tempo in un certo volume è uguale al flusso di massa entrante meno quello uscente.

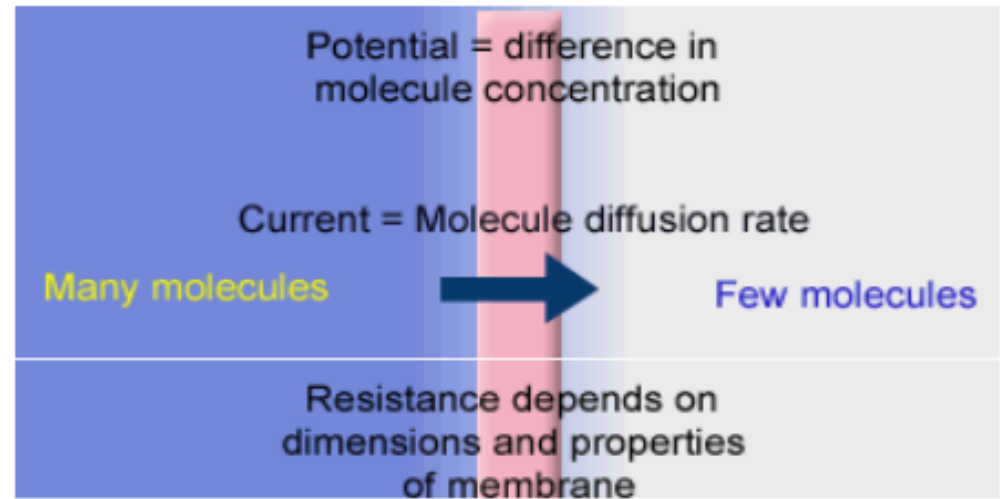


$$\partial_t u + \operatorname{div} F = 0$$

Determinare il FLUSSO (I): la Legge di Fick

Il flusso di materia (proteine, liquidi, batteri) trasportata verso l'esterno è proporzionale al gradiente della concentrazione.

D è la diffusività. Il segno “–” indica che la materia si sposta da una concentrazione più alta verso quella più bassa

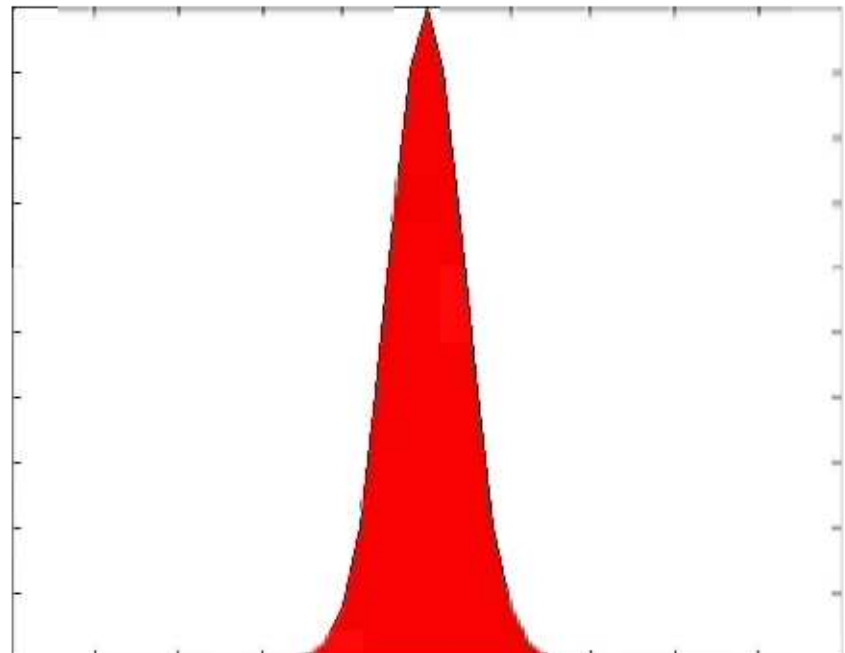


$$F = -D \nabla u$$

Modelli diffusivi

- Equazione del calore
(interpretazione
probabilistica)
- Reazione diffusione
- Traveling waves, Turing
instabilities, pattern
formation.
Prototipo: Eq. Fisher-
Kolomogorov

$$\partial_t U = \Delta U + f(U)$$

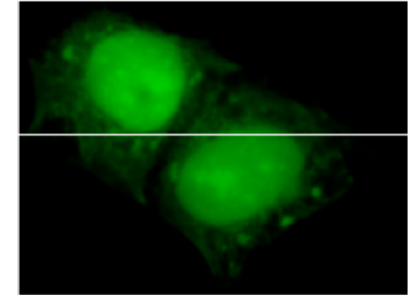


Applicazione: trasporto di segnali intracellulari

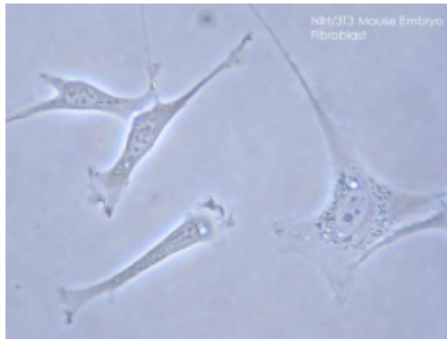
(A. Cangiani, R. Natalini, in collab. con P. Lavia)

Che cos'è un segnale?

PROTEINE FATTE DA ALTRE CELLULE (ES. ORMONI)
AGENTI ESTERNI (BATTERI, VIRUS)
ALCUNE SOSTANZE CHIMICHE SEMPLICI (CALCIO)



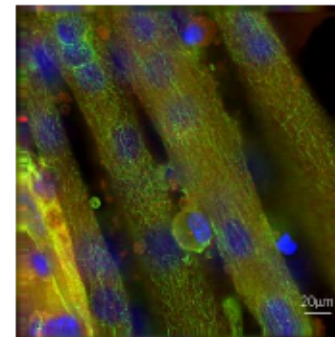
I segnali determinano l'attivazione di pochi geni che segnano il destino della cellula



FIBROBLASTO



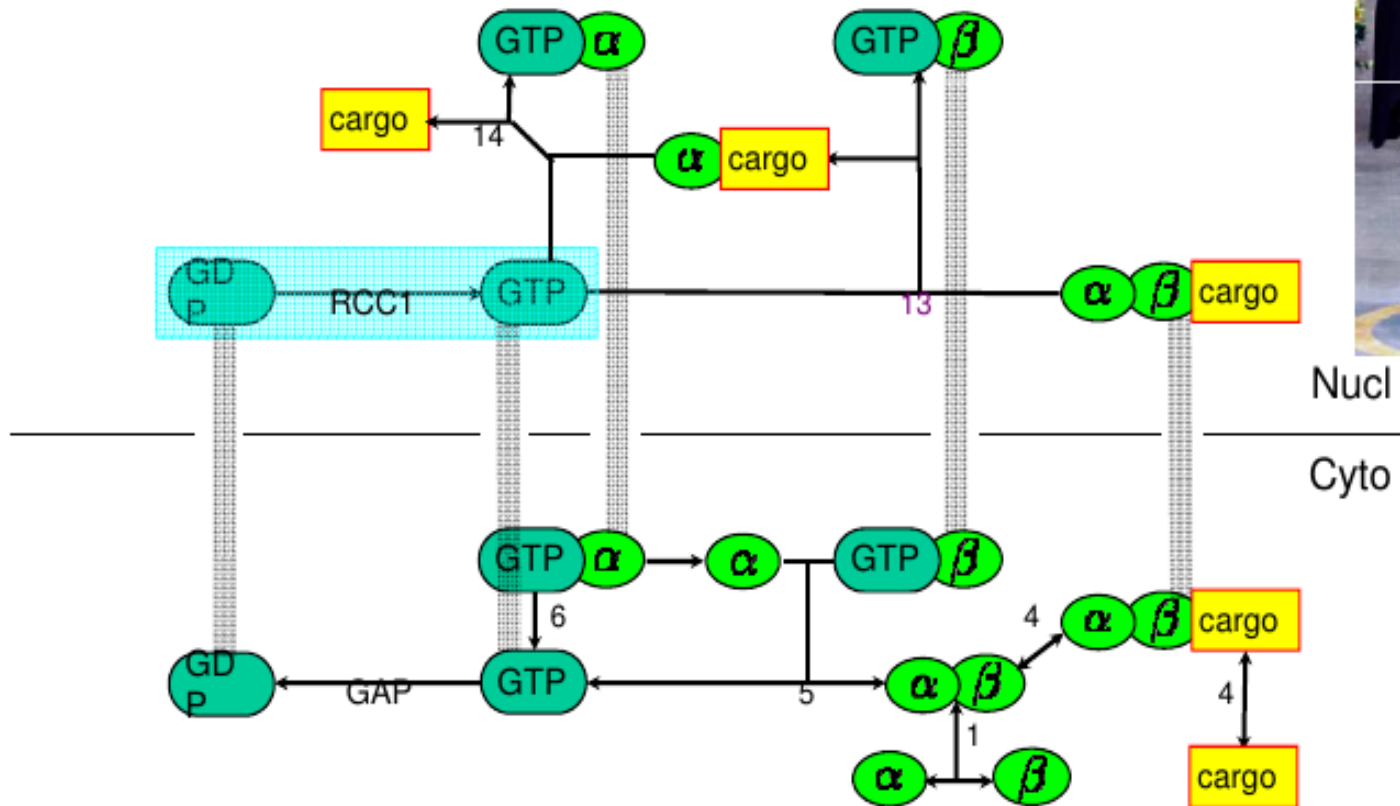
NEURONE



MIOTUBI

Meccanismo di trasporto della Ran

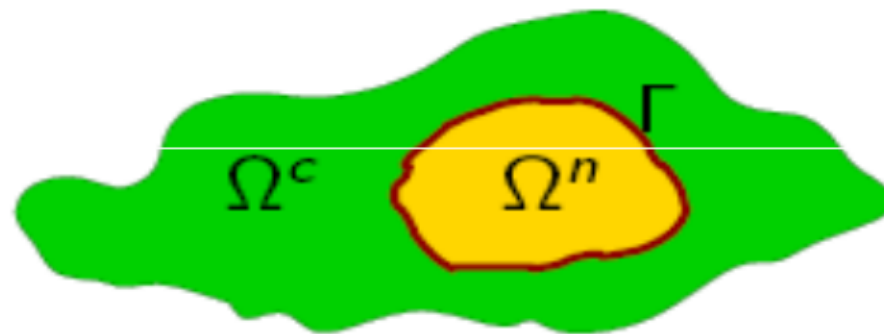
Gunter Blobel, Nobel
Biomedicina, 1999



Modelli matematici del trasporto

Modelli a compartimenti: equazioni differenziali ordinarie

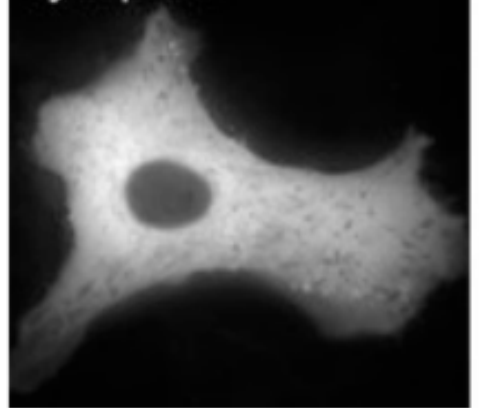
Modelli spaziali: alle derivate parziali



Γ = nuclear membrane.

Il sistema di trasporto della Ran

cytoplasm



(Citoplasma)

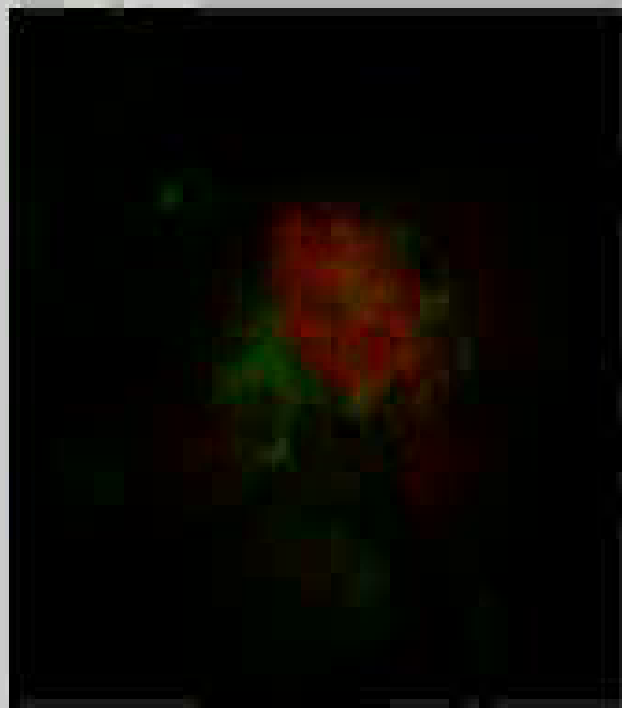
$$\left\{ \begin{array}{l} \frac{\partial R_t}{\partial t} = d_r \Delta R_t - m_1(R_t) - r_1(R_t, T) + r_{-1}(T_r), \\ \frac{\partial R_d}{\partial t} = d_r \Delta R_d + m_1(R_t), \\ \frac{\partial T_r}{\partial t} = d_{tr} \Delta T_r + r_1(R_t, T) - r_{-1}(T_r), \\ \frac{\partial C}{\partial t} = d_c \Delta C - r_2(C, T), \\ \frac{\partial T}{\partial t} = d_t \Delta T - r_1(R_t, T) + r_{-1}(T_r) - r_2(C, T), \\ \frac{\partial T_c}{\partial t} = d_{tc} \Delta T_c + r_2(C, T) - r_a(T_c, D) + r_d(D_c), \\ \frac{\partial D_c}{\partial t} = -\nabla \cdot (\mathbf{b} D_c) + r_a(T_c, D) - r_d(D_c), \\ \frac{\partial D}{\partial t} = d_d \Delta D - r_a(T_c, D) + r_d(D_c), \end{array} \right.$$

(Nucleo)

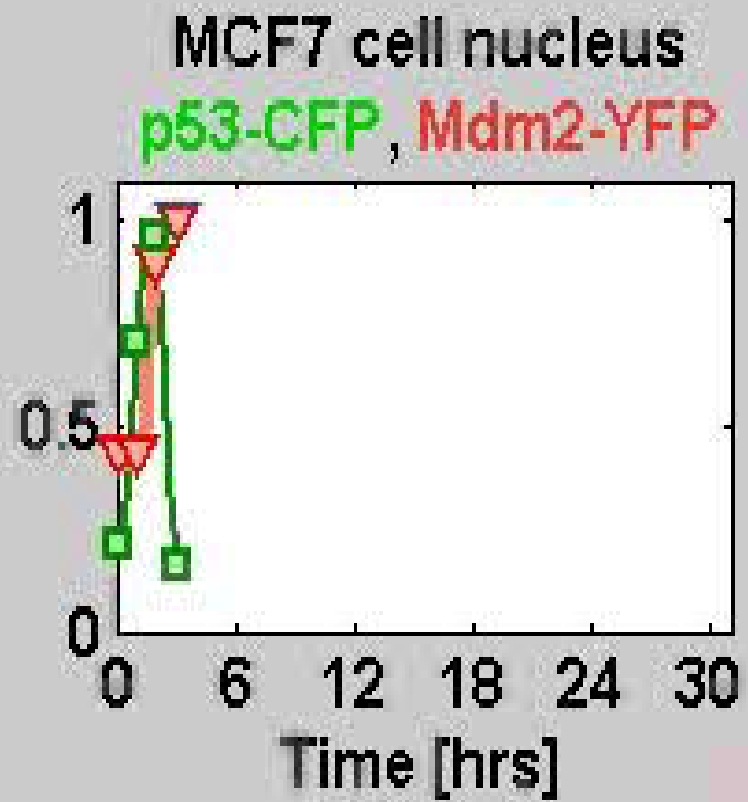
$$\left\{ \begin{array}{l} \frac{\partial R_t}{\partial t} = d_r \Delta R_t + m_2(R_d) - r_1(R_t, T) + r_{-1}(T_r) - r_3(R_t, T_c), \\ \frac{\partial R_d}{\partial t} = d_r \Delta R_d - m_2(R_d), \\ \frac{\partial T_r}{\partial t} = d_{tr} \Delta T_r + r_1(R_t, T) - r_{-1}(T_r) + r_3(R_t, T_c), \\ \frac{\partial C}{\partial t} = d_c \Delta C + r_3(R_t, T_c), \\ \frac{\partial T}{\partial t} = d_t \Delta T - r_1(R_t, T) + r_{-1}(T_r), \\ \frac{\partial T_c}{\partial t} = d_{tc} \Delta T_c - r_3(R_t, T_c), \end{array} \right.$$

**+ CONDIZIONI DI TRASMISSIONE
SULLA MEMBRANA NUCLEARE**

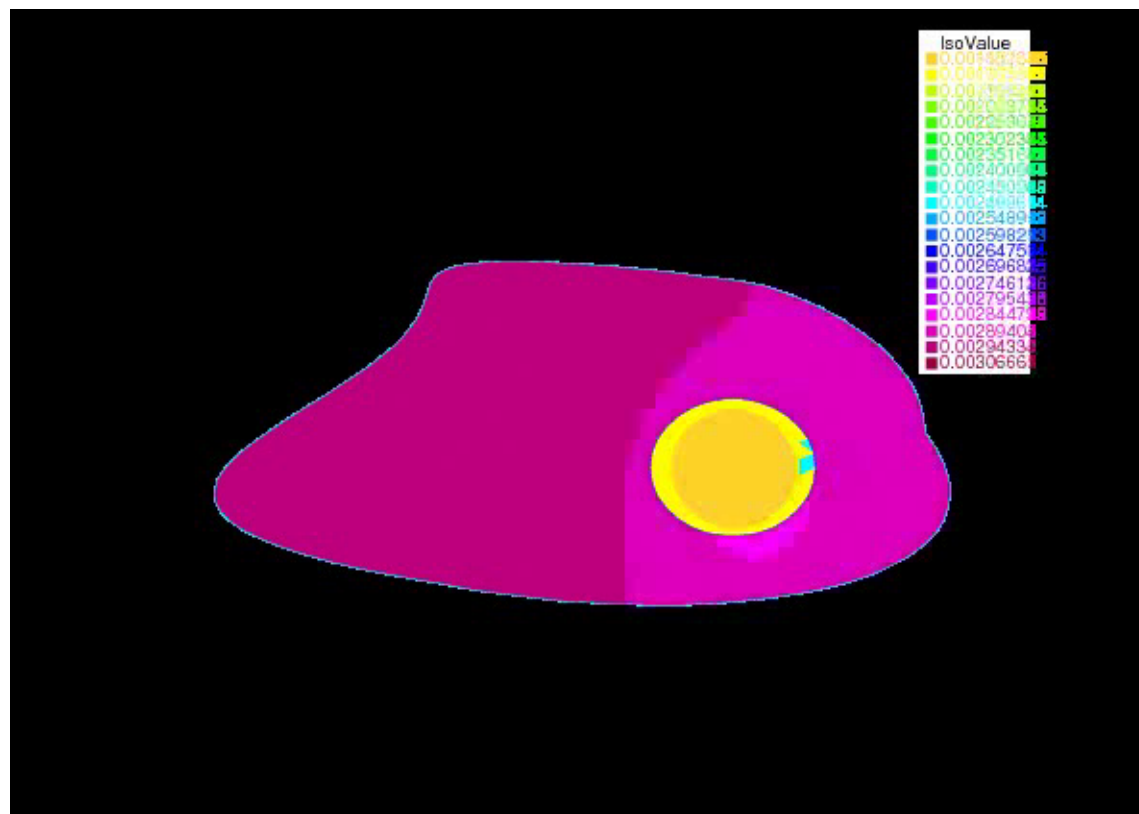
La proteina anti-tumori: la p53



Time: 3 hrs



La simulazione numerica

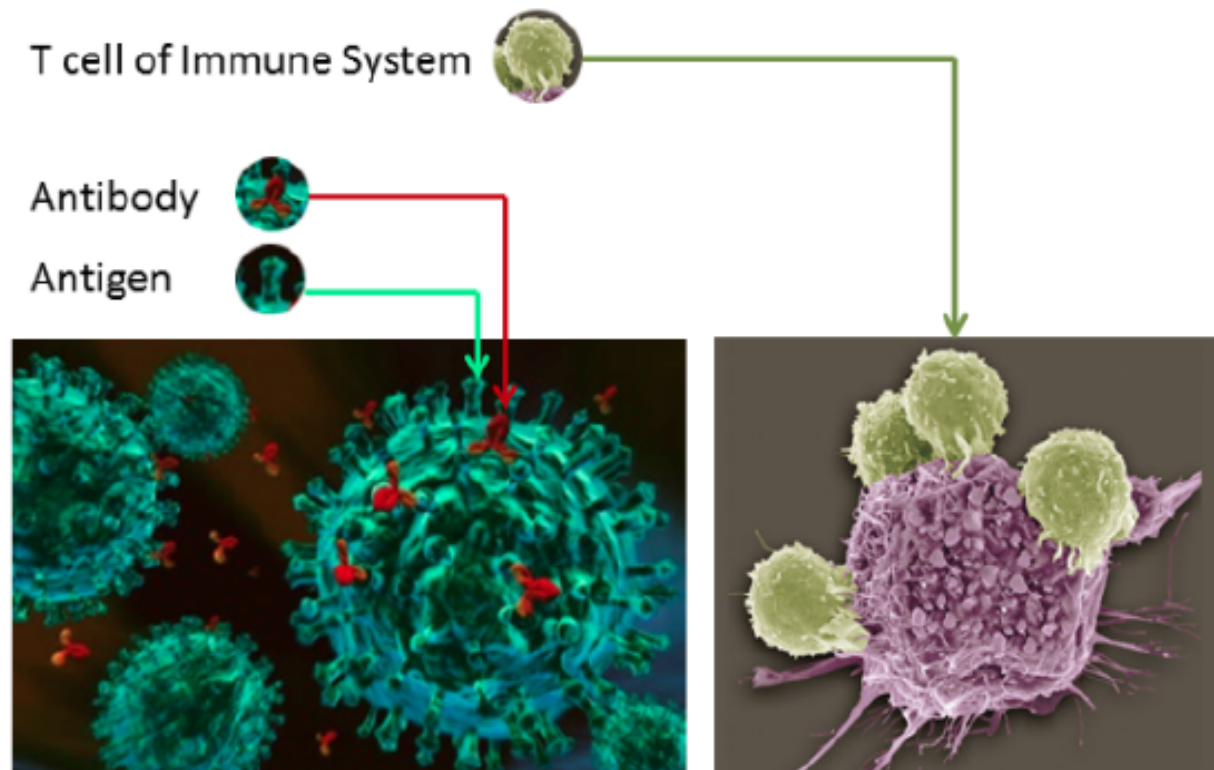


Cancer cells

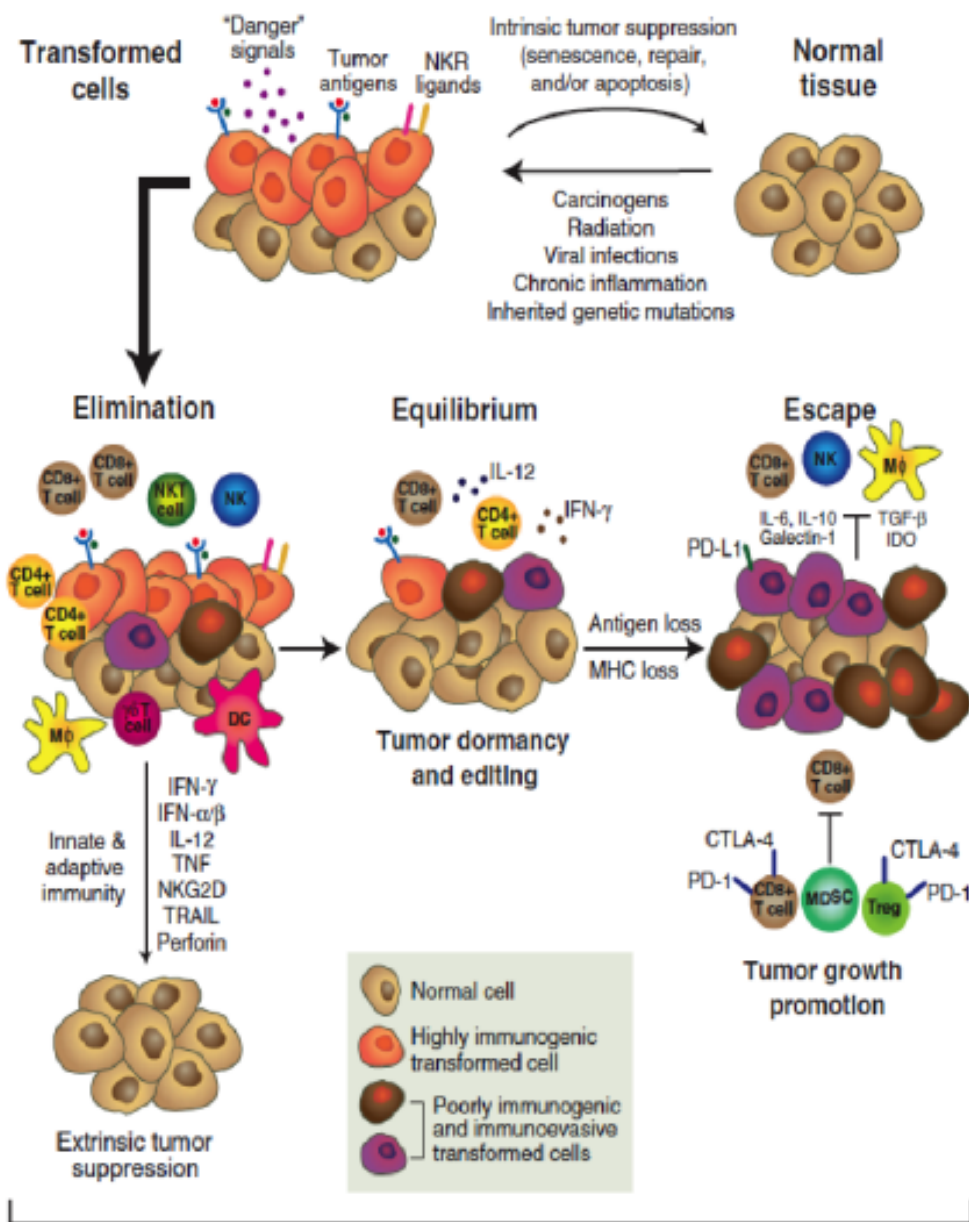
The cancer cells present some antigens on their surface.

An antigen (**antibodies generator**) is any substance that triggers the production of antibodies when it is introduced into the body or when it appears on the surface of the cancer cells.

Antigens are usually attacked by the immune systems. When the antigens are produced by our organism (as in a cancer), they elude the immune system which does not attack them.



Cancer and Immune Response



MECHANISM OF ACTION

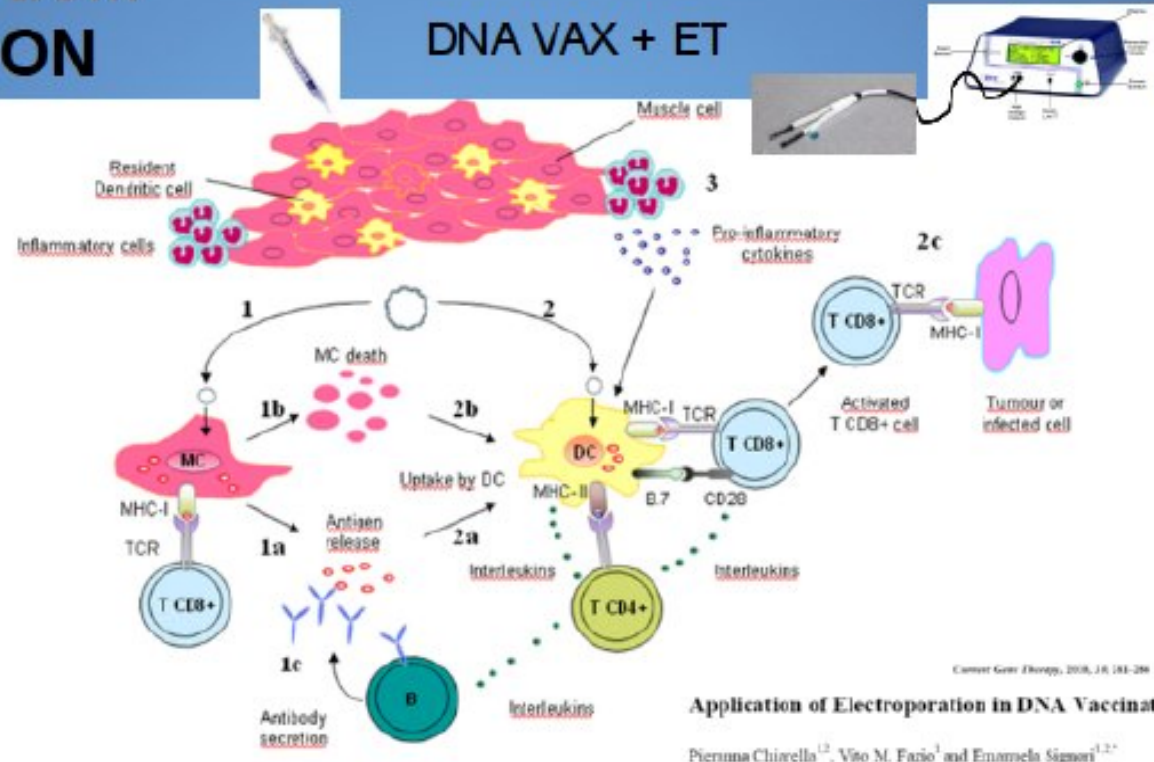


Figure 1. Intramuscular administration of the DNA vaccine followed by electrotransfer.

The plasmid vaccine encoding the target antigen enters muscle cells (MC) or resident dendritic cells (DC). 1) The target antigen is released by the MC after synthesis in the endoplasmic reticulum (1a) or through MC death (1b). 2) DC is able to present to T CD8+ cell the antigen released by MC via MHC-II or MHC-I (cross presentation) or the same DC, after DNA plasmid uptake, proceeds directly to presentation through MHC-I. The vaccine can induce both humoral (1c) and cellular immune response against the target antigen (2c) and this response is enhanced by recruitment of inflammatory cells and secretion of pro-inflammatory cytokines at the site of plasmid electrotransfer (3).

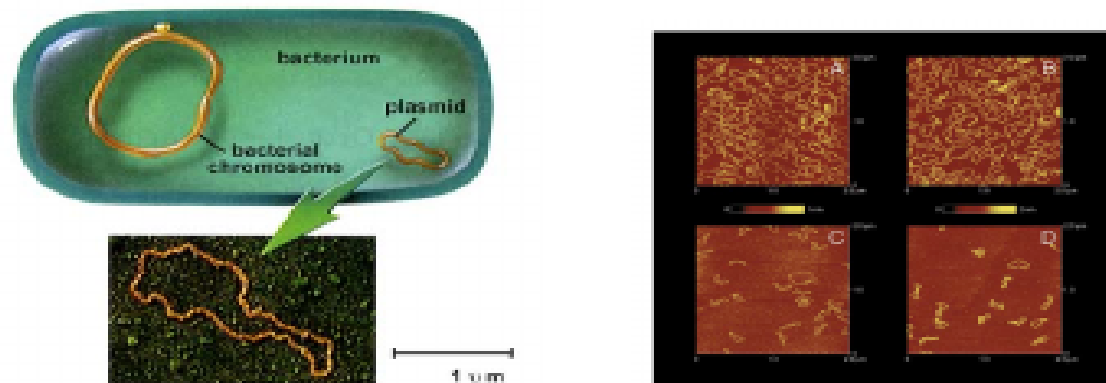
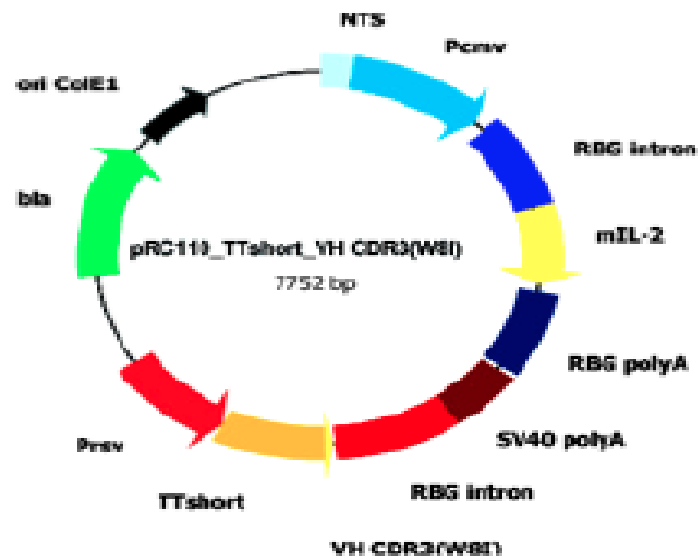
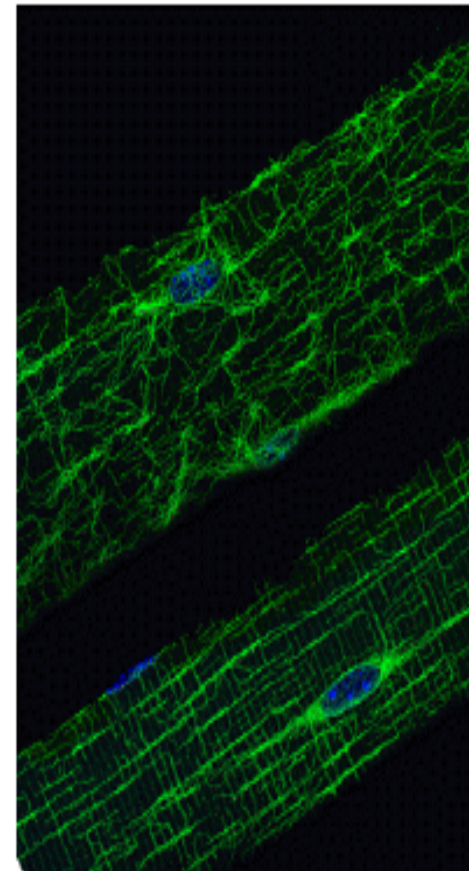
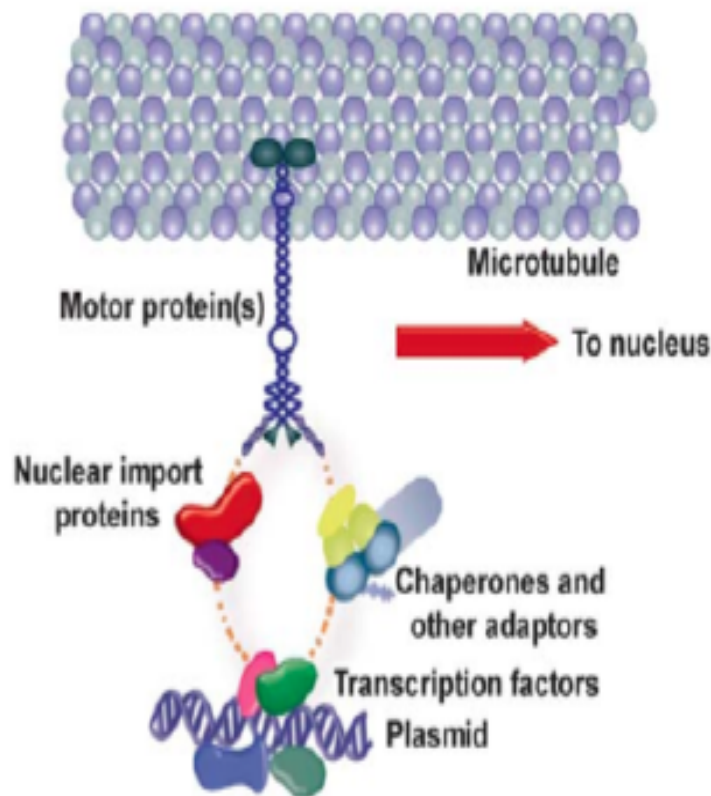


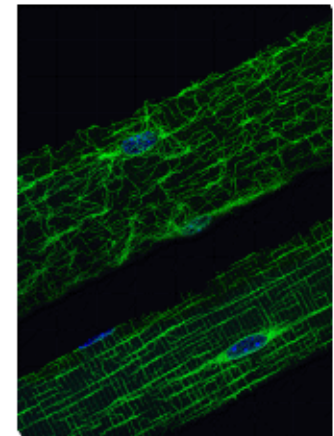
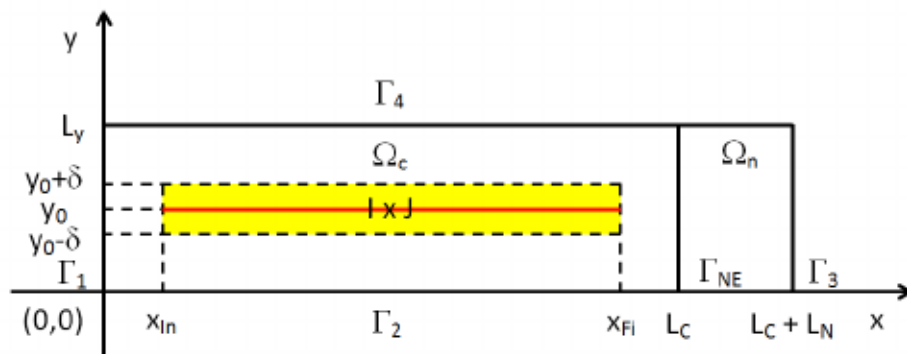
Figure : Plasmids: at left, bacteria plasmid; at right, culture of plasmids.



Microtubules are one component of the cytoskeleton.

Dynein (motor protein) moves along microtubule and it transports large molecules near the nucleus.





$I \times J$ attraction area of microtubule with $I = [x_{In}, x_{Fi}]$ and $J = [y_0 - \delta, y_0 + \delta]$.

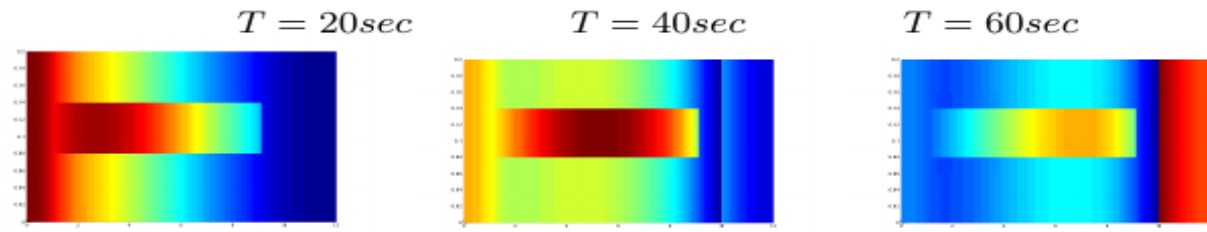


Figure : Spatial distribution of the cargo concentration and its complexes on the action of diffusion and MT. The permeability on the nuclear envelope is considered.

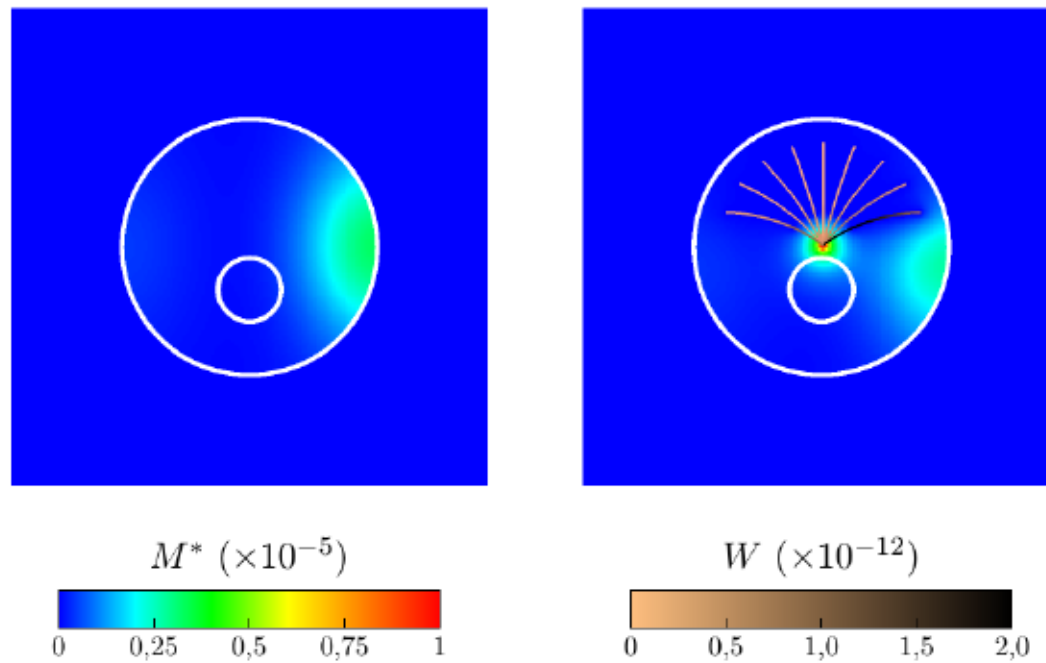
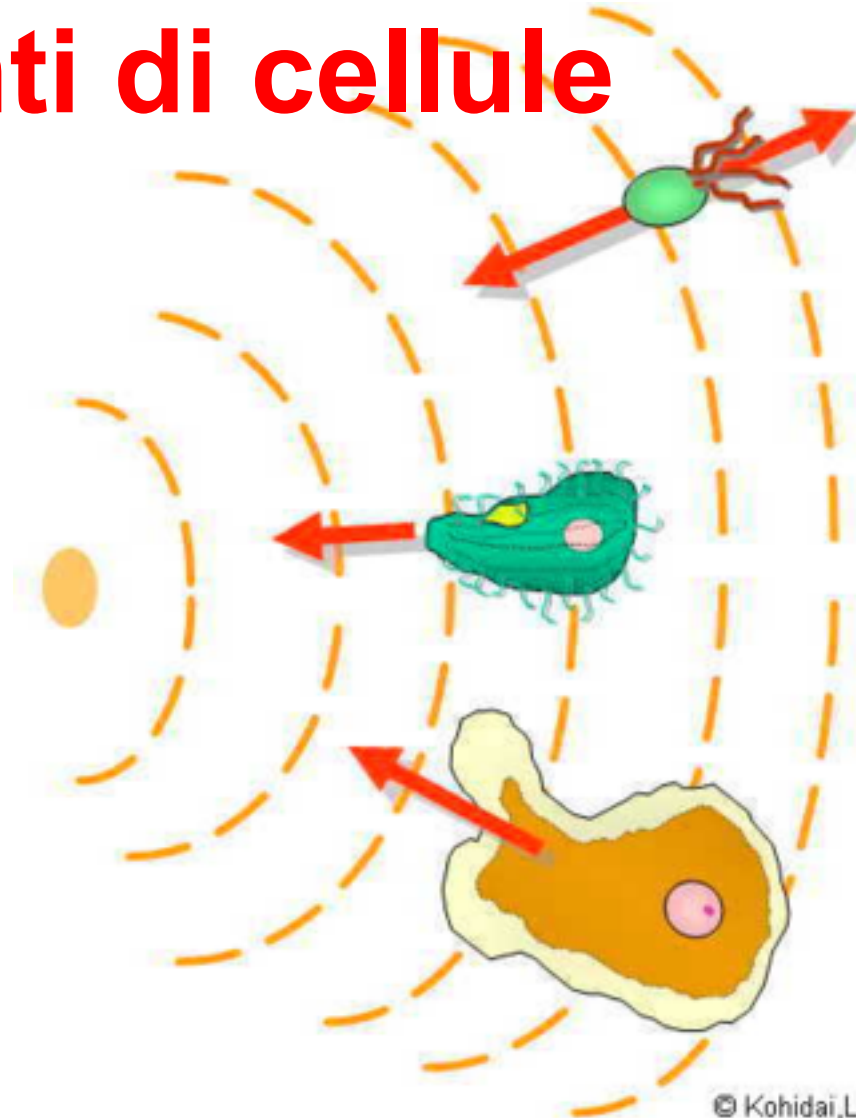


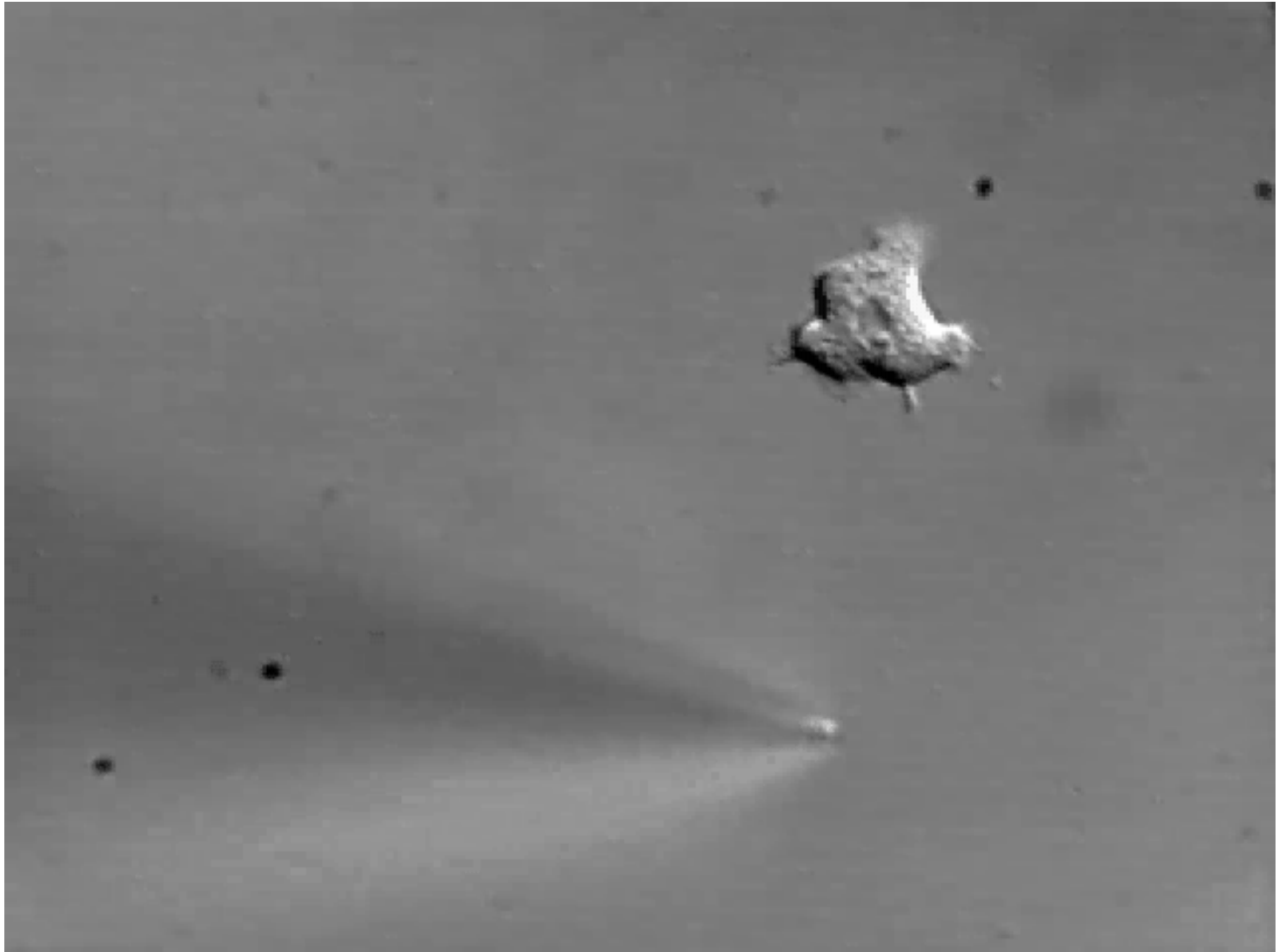
Figure : Spatial repartition of plasmids concentration at $t = 10\text{ s}$ in simulations with and without microtubules

Chemiotassi: movimenti di cellule (oppure organi o altra entità biologica) che sentono e rispondono ad un fattore chimico (e si muovono direzionalmente)

Movimenti di cellule

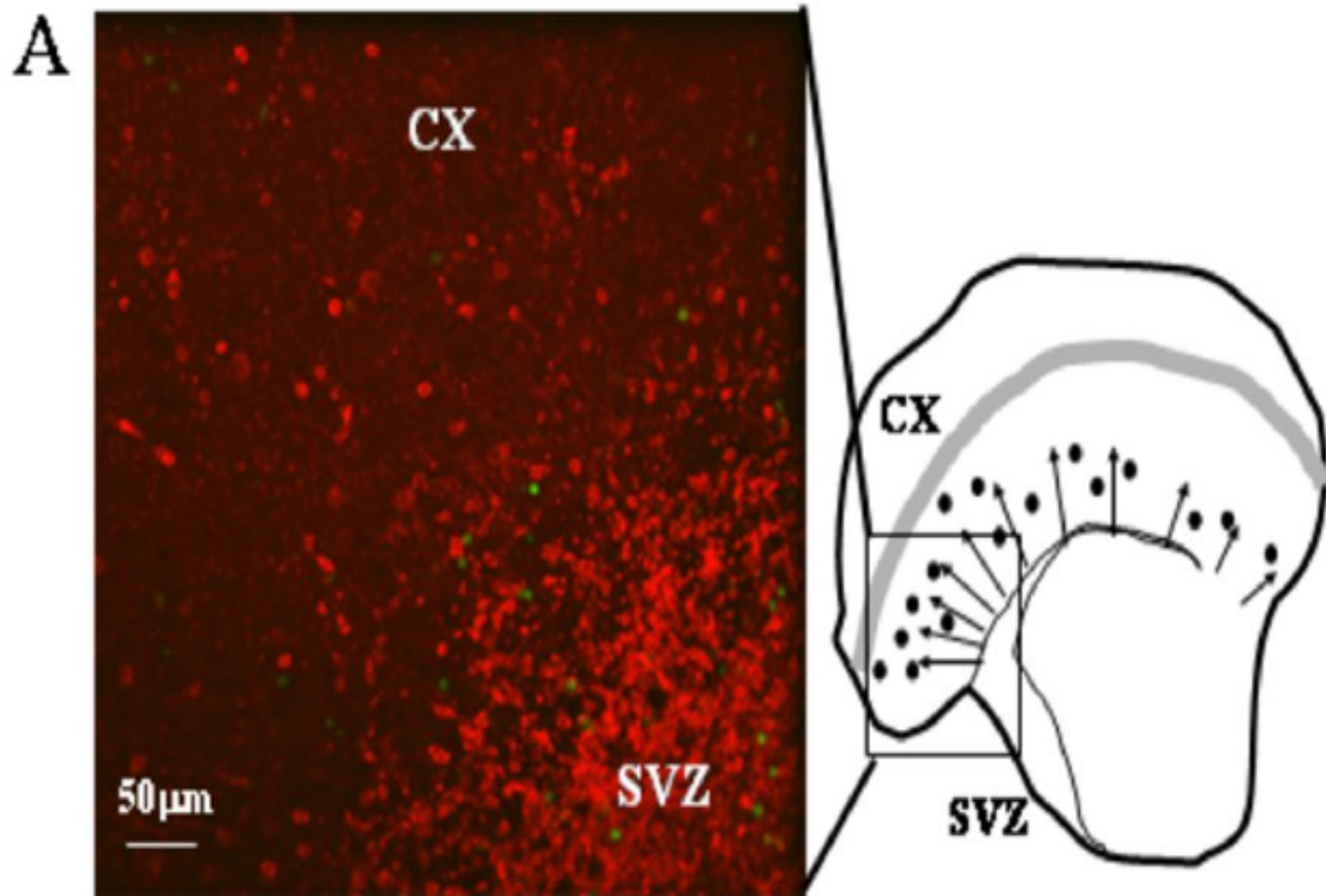


Il movimento dell'ameba

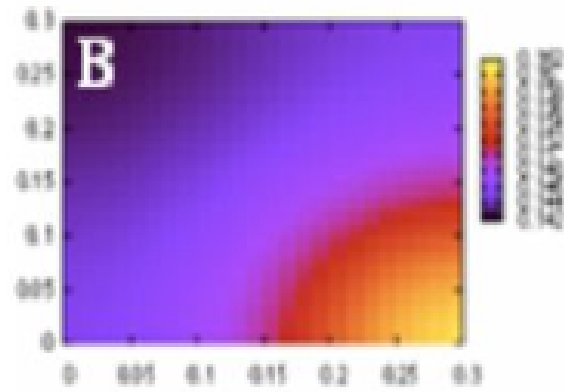


Movimento di cellule staminali cerebrali

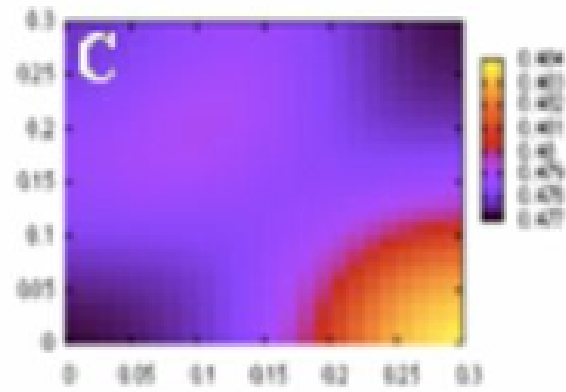
con F. Cavaliere, C. Volonté, F. Castiglione, M. Biani, D. Vergni



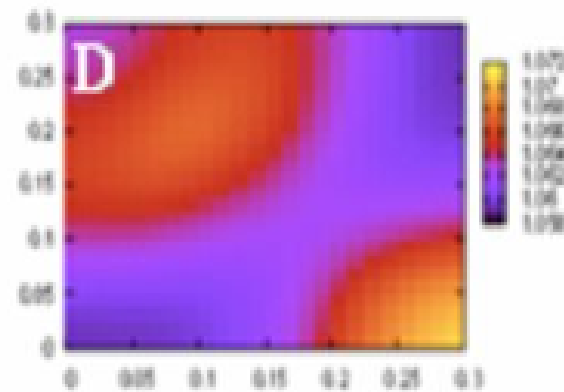
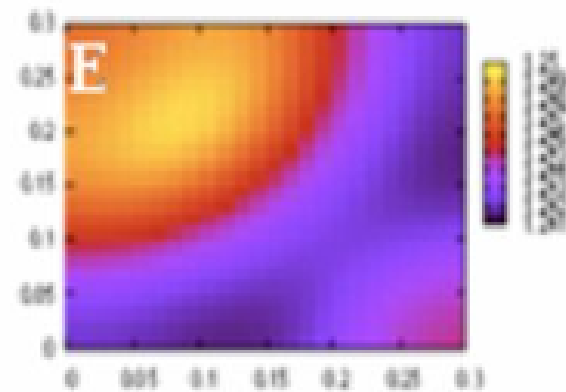
Senza
farmaco



QCD



Con
farmaco

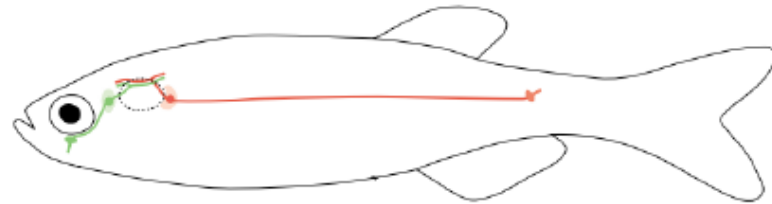
**OGD/PPADS**

Lateral line

A fundamental sensory system present in fish and amphibians.

Large variety of behaviours:

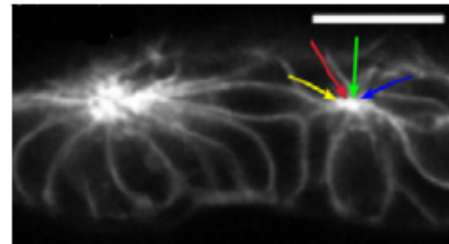
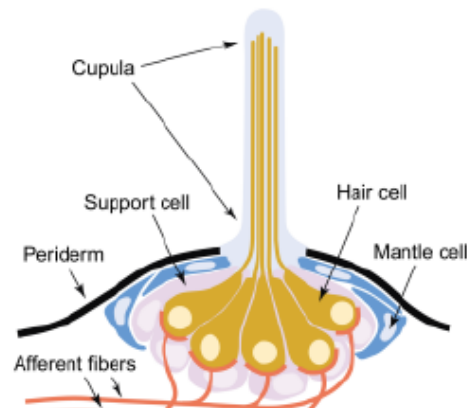
- detect movement and vibration in the surrounding water;
- prey and predator detection;
- school swimming.



Neuromasts

Main sensory organs of the lateral line, embedded in the body surface in a rosette-shaped pattern: 1–2 sensory hair cells in the centre, surrounded by other support cells (8–12 cells).

Neuromasts extend a ciliary bundle into the water, which detect movement in the surrounding environment.

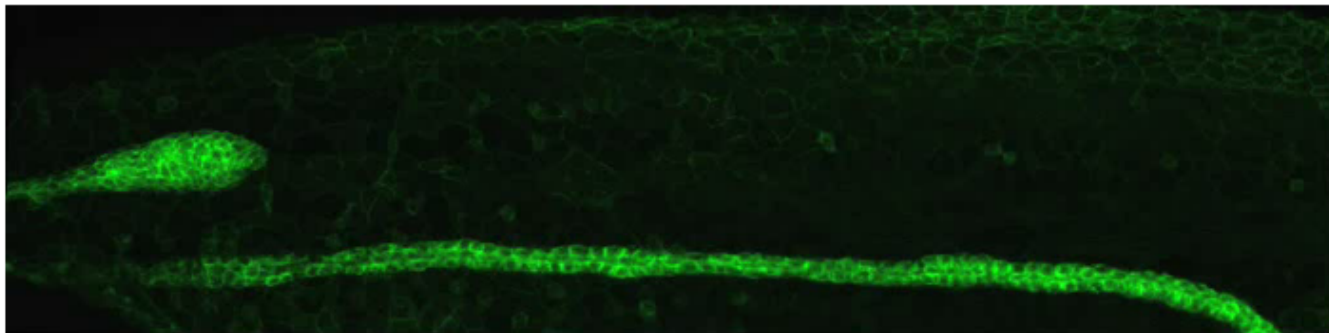


Experimental observations

An initial elongated group (80-100 cells) of mesenchymal cells (***primordium***), with a *trailing region* near the head and a *leading region* towards the future tail of the embryo.

Two primary mechanisms in the morphogenesis process:

- 1 a collective cell migration guided by a haptotactic signal, with constant velocity of about $69 \mu\text{m h}^{-1}$;
- 2 a process of differentiation in the trailing region that induces a *mesenchymal–epithelial transition* and causes the neuromasts assembly and their detachment.



[Movie zebrafish \(Gilmour et al, 2006\).](#)

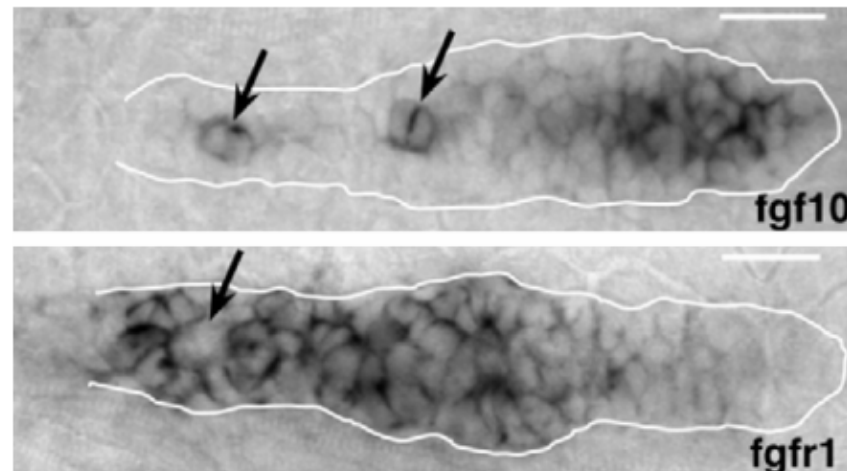
Neuromasts assembly

Two main factors:

- 1 *fibroblast growth factors* **FGF3–FGF10**, strongly chemotactic;
- 2 receptor **FGFR**.

Experimental observations on the FGF activity

- 1 FGF3 and FGF10 are substantially **equivalent** (robustness of the system);
- 2 FGF and FGFR are **mutually exclusive**.

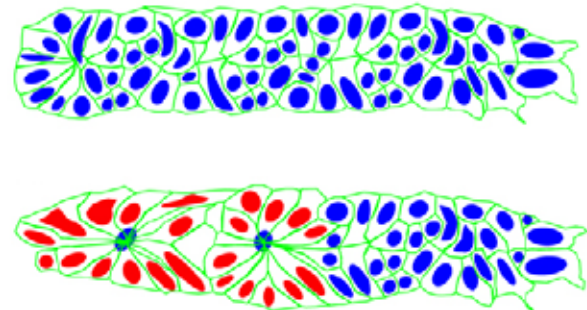


Leader to follower differentiation

- **leader** mesenchymal cells: produce FGF but the receptor FGFR is not activated;
- **follower** epithelial cells: activate FGFR, but do not produce FGF.

Cyclic mechanism

- 1 at the beginning, all cells are leader;
- 2 leader–follower differentiation (MET transition) produces rosette-shaped structures (proto-neuromasts);
- 3 neuromasts deposition.



Three sufficient conditions for the leader–follower transition

- 1 a low level of SDF-1a (trailing zone is preferred for transition);
- 2 a high level of FGF;
- 3 a **lateral inhibition** effect (*leader/follower transition favored by a low number of neighboring cells*).

The basic mathematical model

$\mathbf{X}_i(t)$: position of the i -th cell;

$\varphi_i(t)$: switch variable for the i -th cell ($\varphi_i = 0, 1$ resp. follower-leader);

$f(\mathbf{x}, t)$: concentration of FGF (equivalent FGF3 and FGF10);

$s(\mathbf{x}, t)$: concentration of SDF-1a;

$$\left\{ \begin{array}{l}
 \text{acceleration } i\text{-th cell} \\
 \underbrace{\ddot{\mathbf{X}}_i}_{\text{acceleration } i\text{-th cell}} = \underbrace{\alpha \mathbf{F}_1(\nabla s)}_{\text{haptotaxis}} + \underbrace{\gamma(1 - \varphi_i) \mathbf{F}_1(\nabla f)}_{\text{chemotaxis}} + \underbrace{\mathbf{F}_2(\dot{\mathbf{X}})}_{\text{alignment}} + \underbrace{\mathbf{F}_3(\mathbf{X})}_{\text{attraction/repulsion}} \\
 \quad \quad \quad - \underbrace{[\mu_F + (\mu_L - \mu_F)\varphi_i] \dot{\mathbf{X}}_i}_{\text{damping}}, \\
 \\
 \text{leader-follower state} \\
 \underbrace{\varphi_i}_{\text{leader-follower state}} = \begin{cases} 0, & \text{if } \underbrace{\delta F_1(s)}_{\text{SDF conc.}} - \underbrace{[k_F + (k_L - k_F)\varphi_i] F_1(h(f))}_{\text{FGF conc.}} + \underbrace{\lambda \Gamma(n_i)}_{\text{lateral inhib.}} \leq 0, \\ 1, & \text{otherwise,} \end{cases} \\
 \\
 \text{FGF rate in time} \\
 \underbrace{\partial_t f}_{\text{FGF rate in time}} = \underbrace{D \Delta f}_{\text{diffusion}} + \underbrace{\xi F_4(\mathbf{X})}_{\text{production}} - \underbrace{\eta f}_{\text{molecular degradation}}, \\
 \\
 \text{SDF rate in time} \\
 \underbrace{\partial_t s}_{\text{SDF rate in time}} = - \underbrace{\sigma s F_5(\mathbf{X})}_{\text{degradation}},
 \end{array} \right.$$

Numerical assessment of stability of a N -rosette.

Dynamical simulation on a perturbed configuration of the steady solution:

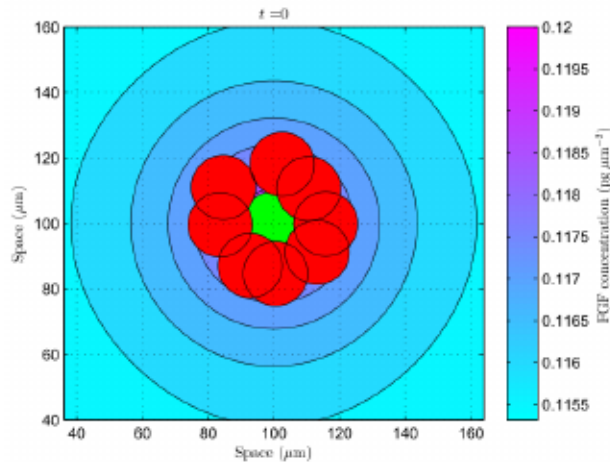


Figure : A perturbed 8-rosette

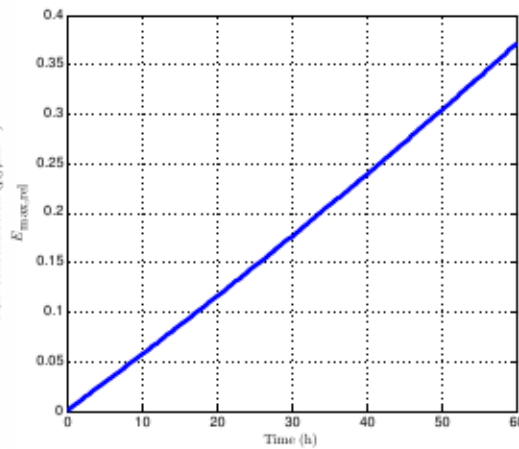


Figure : $\max_i \|\mathbf{X}_i(t) - \mathbf{X}_{i0}\| / R$

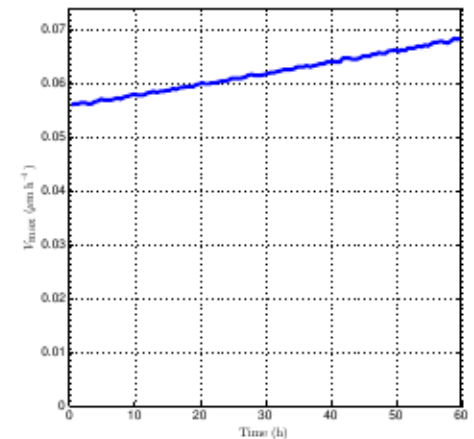
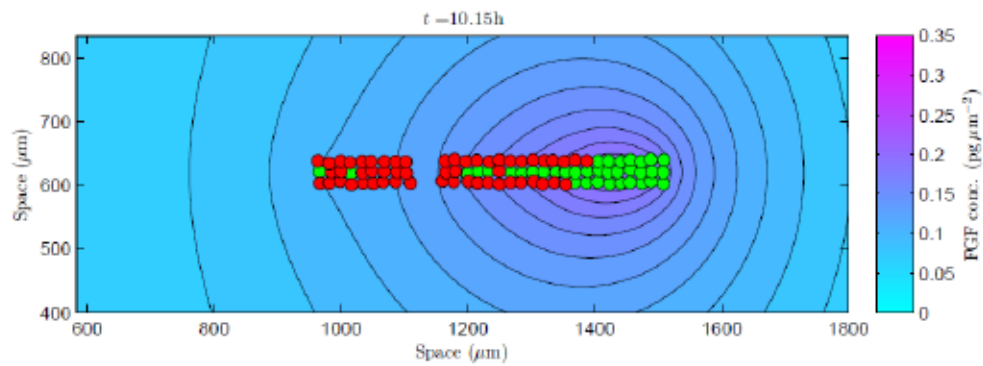
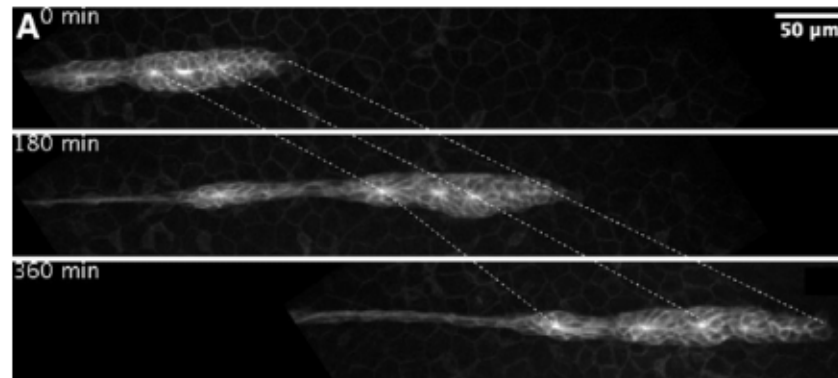


Figure : $\max_i \|\dot{\mathbf{X}}_i(t)\|$

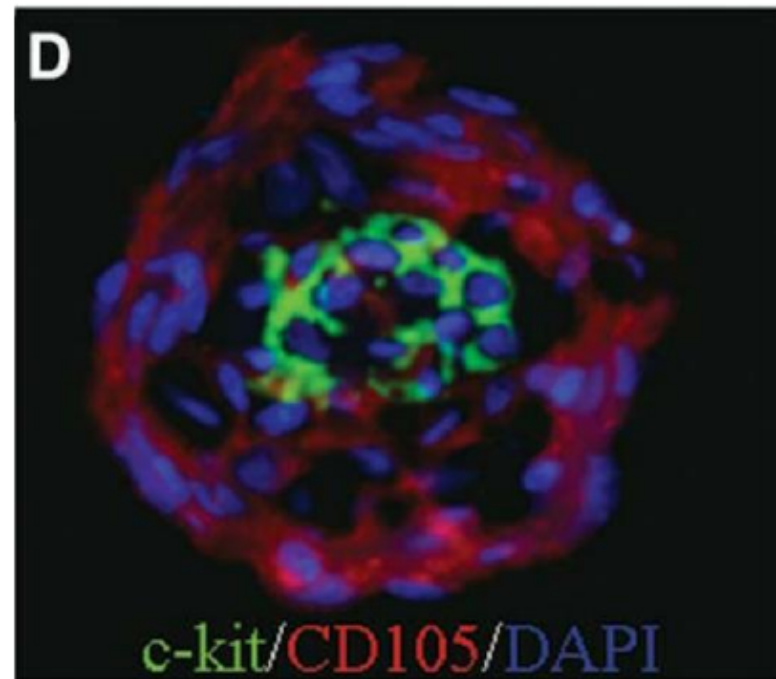
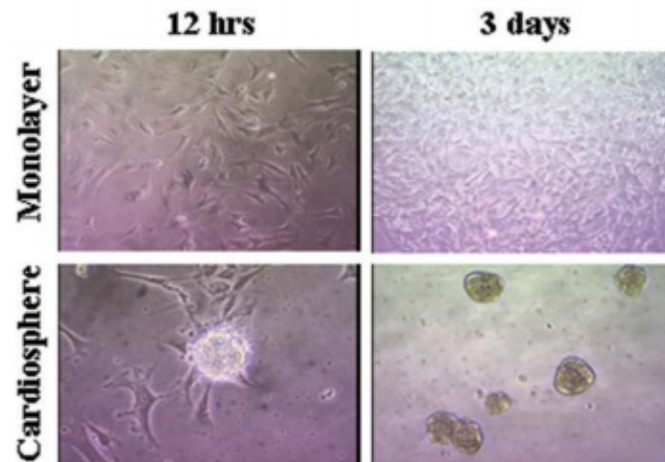
Numerical simulation

Dynamical model



Parameters estimates

Cardiac stem cells and the growth of cardiospheres



Cardiac stem cells and the growth of cardiospheres

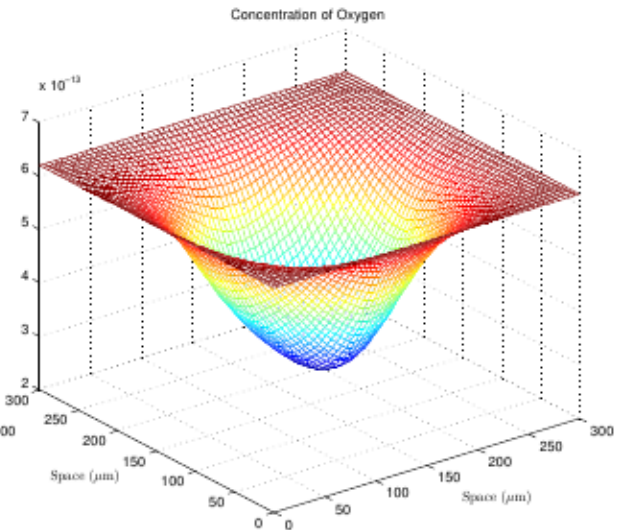
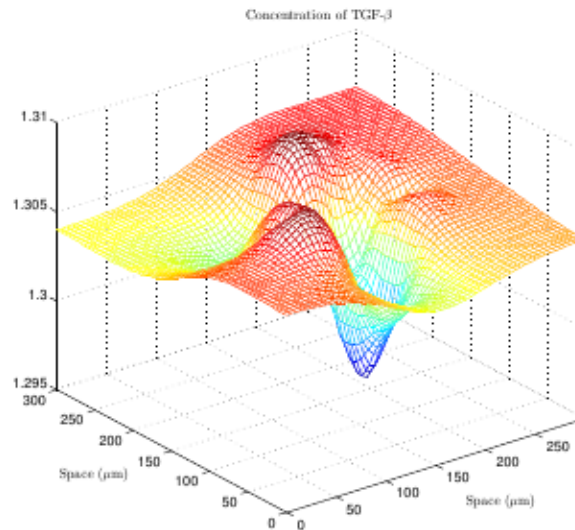
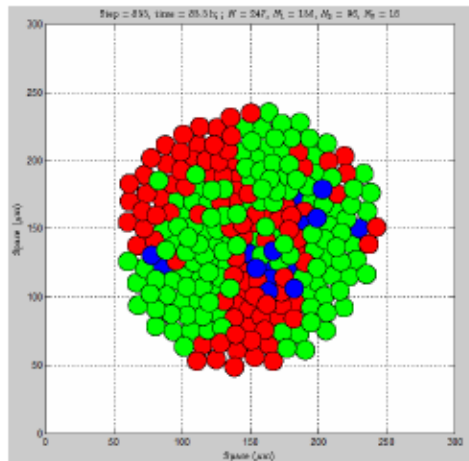
A hybrid model

$$\ddot{X}_i = \sum_{\substack{j=1 \\ j \neq i}}^N K(r_{ij}) - \mu \dot{X}_i + \alpha \mathcal{F}(\nabla S(X_i)) \quad (2)$$

μ is a friction coefficient for unit mass due to the adhesion to the substrate, and $K(r_{ij})$ the attraction-repulsion force for unit mass between i-th and j-th cell defined as:

$$K(r_{ij}) := \begin{cases} -k_1 \left(\frac{1}{\|r_{ij}\|} - \frac{1}{R_1} \right) \frac{r_{ij}}{\|r_{ij}\|}, & \|r_{ij}\| \leq R_1 \\ k_2 (\|r_{ij}\| - R_1) \frac{r_{ij}}{\|r_{ij}\|} & R_1 < \|r_{ij}\| \leq R_2 \end{cases} \quad (3)$$

Cardiac stem cells and the growth of cardiospheres



Cardiac stem cells and the growth of cardiospheres

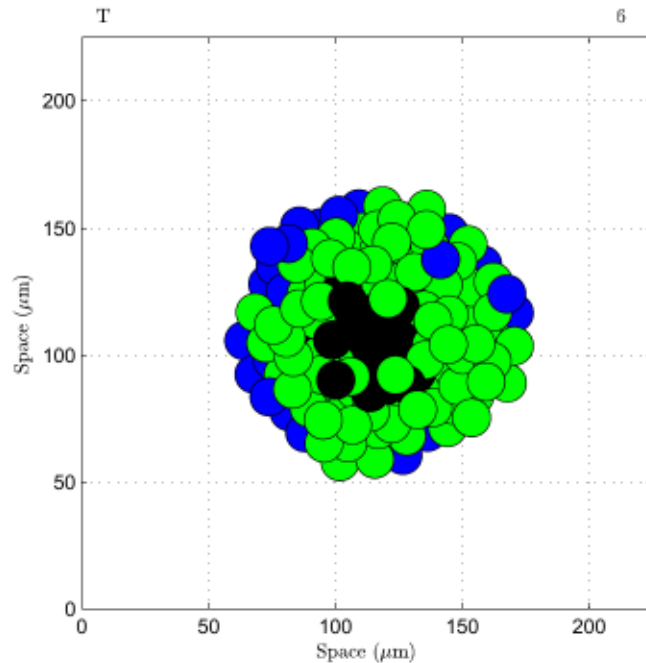


Figure : Growth after 72 hours with 5% of oxygen

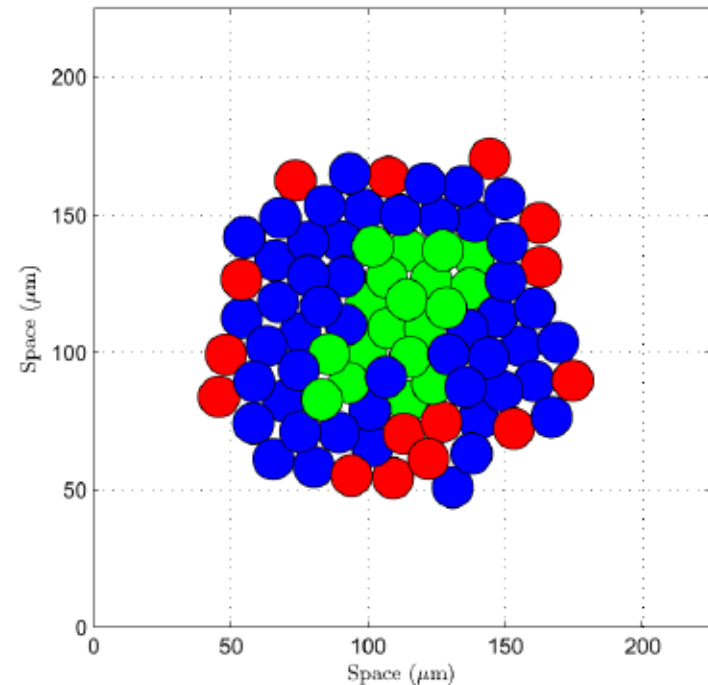
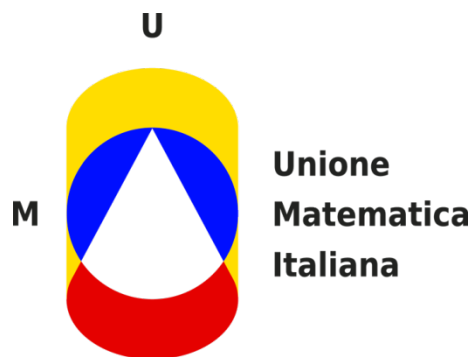
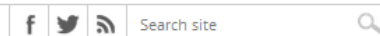


Figure : Growth after 72 hours with 21% of oxygen



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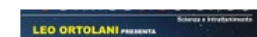
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