Multiscale Methods to Model Complex Multicellular Systems

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Partial Differential Equations in Biology

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Workgroup on Complex Dynamical Systems

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"To those who do not know mathematics, it is difficult to get across a real feeling as to the beauty, the deepest beauty, of nature. If you want to learn about nature, to appreciate nature, it is necessary to understand the language that she speaks in". (Richard Feynman)

In evidence:

Address by the President Obama at the National Academy of Sciences annual meeting (April 27, 2009)

Nicola Bellomo's Shanks Lecture (Vanderbilt University, Nashville TN, USA, May 2009)

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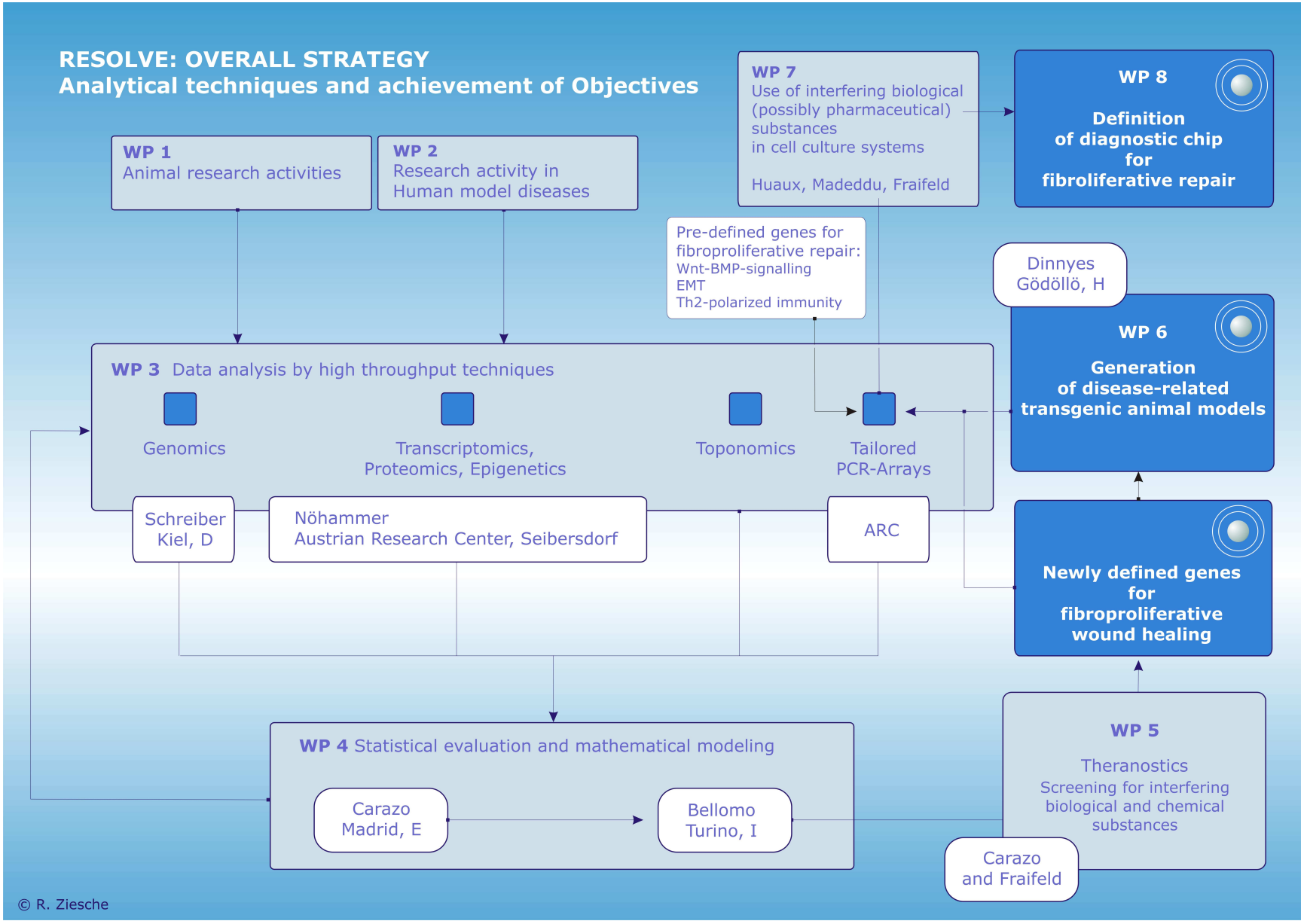

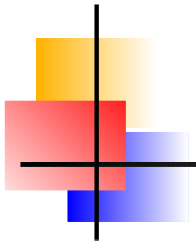

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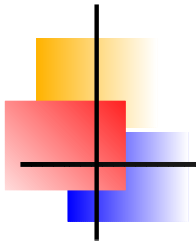

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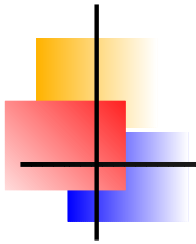

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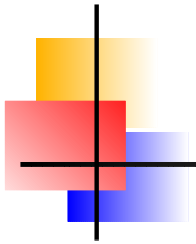

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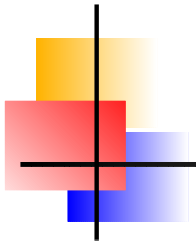

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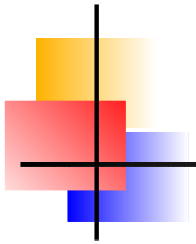

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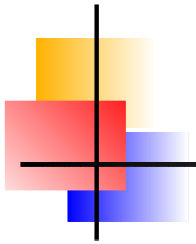
Six critical changes in cell physiology that characterize malignant cancer growth. These six changes - self-sufficiency in growth signals, insensitivity to anti-growth signals, evading apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis, all incorporate some aspect of genetic mutation and evolutionary selection leading to malignant progression. Indeed, it is well accepted that the onset of cancer occurs through a sequence of genetic mutations and evolutionary selection leading to malignancy, a concept not yet well addressed through mathematical modeling.



I - From Biology to Mathematics: Complexity

FIVE KEY CHARACTERISTICS OF LIVING SYSTEMS

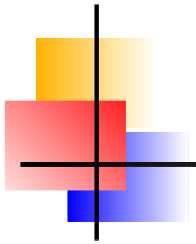
I HETEROGENEOUS EXPRESSION OF STRATEGIC ABILITY: depends on the position and state of the surrounding entities and on environmental conditions.

II EVOLVE IN TIME AND LEARN Darwinian Mutations caused by successive, rapid, selections of entities which become resistent to environmental actions.

III MODIFY THE LAWS OF CLASSICAL MECHANICS Moreover, in some cases, generate proliferative/destructive events.

IV HETEROGENEITY OF COMPONENTS Multicellular systems contain from millions to a few copies of each of thousands of different components, each with specific interactions (differently from the physical systems).

V MULTISCALE ASPECTS Biological systems are multiscale: events at the cellular scale depend on the dynamics of the molecular scale.



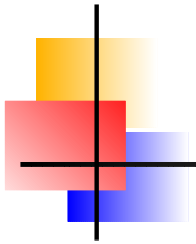
From Biology to Mathematics: System Biology, Module's Theory

• REDUCING COMPLEXITY BY DECOMPOSING THE OVERALL SYSTEM INTO SEVERAL INTERACTING SUBSYSTEMS.

• SYSTEMS BIOLOGY (Woose, 2004): aims to develop a system-level understanding of biological systems by means of a set of principles and methodologies that links the behaviors of molecules to system characteristics and functions.

• MODULE'S THEORY (Hartwell et all., 1999): decomposing the overall system into several interacting subsystems, each of them characterized by a lower order of complexity.

• FUNCTIONAL SUBSYSTEM: a collection of entities, which have the ability to express the same ability regarded as a scalar variable. The whole system is constituted by several interacting functional subsystems.



From Biology to Mathematics: Multiscale Aspects

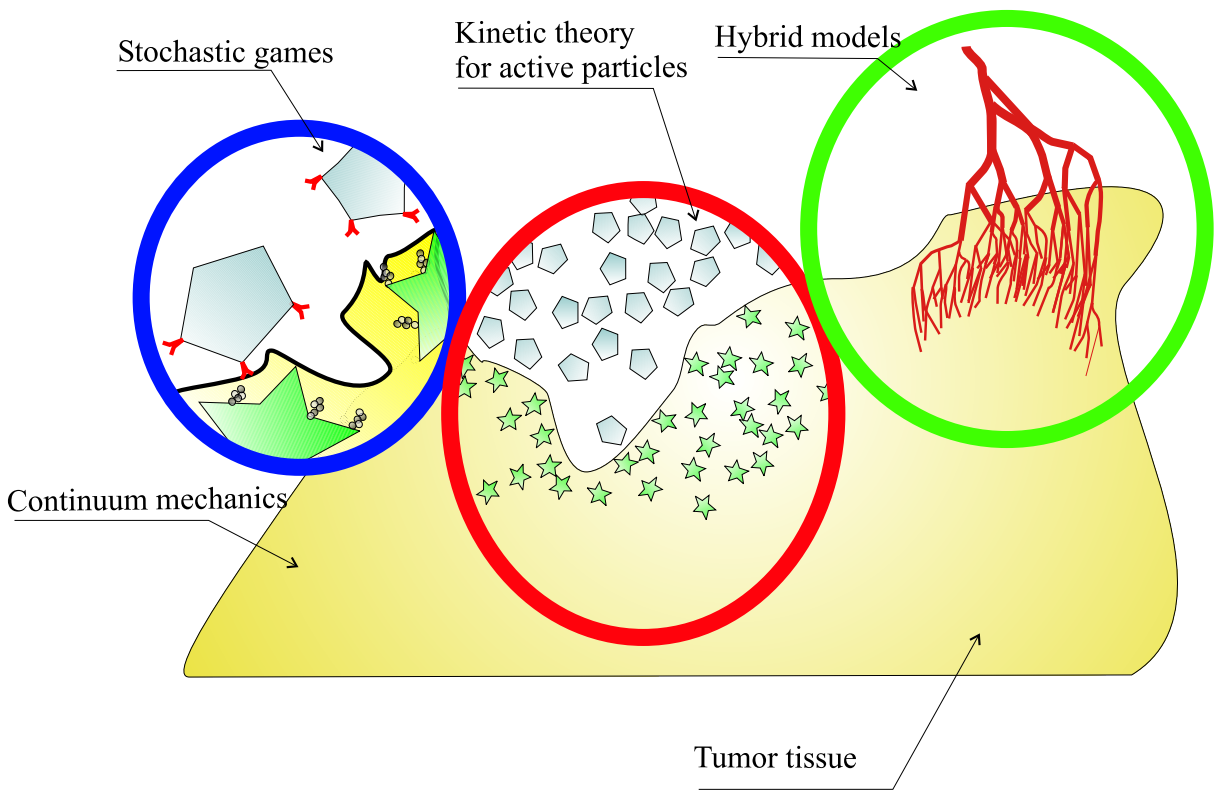
THE SUB-CELLULAR SCALE: The evolution of a cell is regulated by the genes contained in its nucleus. Receptors on the cell surface can receive signals which can activate or suppress genes (uncontrolled cell proliferation, or cell death- so-called apoptosis)

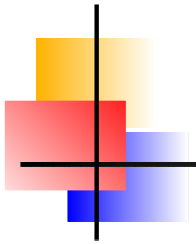
THE CELLULAR SCALE: cell-cell interactions are key elements at all stages of tumor formation (tumor cells-host cells, or among tumor cells-tumor cells, tumor cells-immune cells).

THE MACROSCOPIC SCALE: the growth of tumor cells, if not stopped by the cell-cell interactions will form a mass characterized by *three zones*: an external proliferating layer, an intermediate layer in which there are clusters of quiescent tumor cells, and an inner zone with necrotic cells. Angiogenic process is often described macroscopically.

From Biology to Mathematics: From Biology to Mathematics

MULTISCALE REPRESENTATION OF TUMOR GROWTH: gene interactions (*stochastic games*), cells (*kinetic theory*), tissues (*continuum mechanics*), mixed (*hybrid models*).





From Biology to Mathematics: Five Key Questions

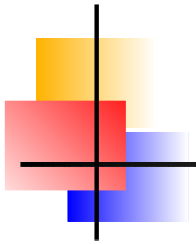
1. *Can mathematics contribute to reduce the complexity of the overall system by reducing it into suitable subsystems?*

2.*Can mathematics offer tools suitable to describe complex biological systems and, and specifically, cancer phenomena?*

3. *How the dynamics at the molecular and cellular scales can be described by mathematical equations which include the modeling of interactions between micro and macro environments?*

4. *How the dynamics at the molecular scale is transferred to the scale of cells including mutations, competition with the immune system and reaction to therapeutical actions?*

5. *How far the state-of-the-art is from the development of a multiscale biological-mathematical theory of cancer phenomena?*

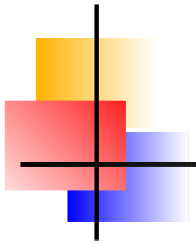


From Biology to Mathematics: From a Dilemma to a Challenge to Mathematicians

Dilemma: *Should mathematics attempt to reproduce experiments by equations whose parameters are identified on the basis of empirical data? Or, in alternative, mathematics should develop new structures, hopefully a new theory, suitable to capture the complexity of the biological phenomena and finally basing experiments on theoretical foundations?*

Personal opinion: *The conflict is not wise considering that both conceptual approaches should march together. However, the idea of describing complex systems by simple mathematics it is too naive. Indeed, the reproduction of experiments is not related to the true essence of biology.*

Challenges for applied mathematicians: *Mathematical problems generated by applications of models to real biological problems are very difficult.*



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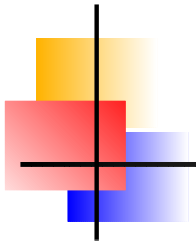


The Kinetic Theory for Active Particles

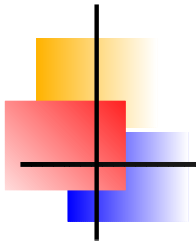
• The system is constituted by a large number of interacting entities, called ***active particles*** organized into n interacting functional subsystems labeled by the indexes $i = 1, \ldots, n$.

• The variable charged to describe the state of each particles is called ***microscopic state***, which is denoted by the variable $\mathbf{w} = \{\mathbf{x}\,,\ \mathbf{v}\,,\ u\}$, where $\mathbf{x} \in D_{\mathbf{x}}$ is ***position***, $\mathbf{v} \in D_{\mathbf{v}}$ is ***mechanical state***, e.g. linear velocity, and $u \in D_u$ is the ***biological function*** or ***activity***.

• The description of the overall state of the system is defined by the distribution function f_i, called ***generalized distribution function***

$$f_i = f_i(t, \mathbf{x}, \mathbf{v}, u) \quad [0, T] \times D_{\mathbf{x}} \times D_{\mathbf{v}} \times D_u \ \rightarrow \ \mathbb{R}_+ \,,$$

$f(t, \mathbf{x}, \mathbf{v}, u)\, d\mathbf{x}\, d\mathbf{v}\, du$ denotes the number of active particles whose state, at time t, is in the elementary volume of the space of microscopic states.



The Kinetic Theory for Active Particles

Macroscopic quantities (given by weighted moments). For instance the ***local size*** of the i^{th} functional subsystem

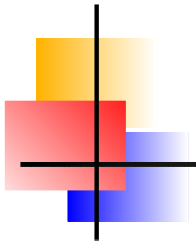
$$\nu[f_i](t,\mathbf{x}) = \int_{D_\mathbf{v}\times D_u} f_i(t,\mathbf{x},\mathbf{v},u)\,d\mathbf{v}\,du\,,$$

Focusing on activity terms, the ***local activation*** is computed as follows:

$$a_j[f_i](t,\mathbf{x}) = \int_{D_\mathbf{v}\times D_u} u_j\, f_i(t,\mathbf{x},\mathbf{v},u)\,d\mathbf{v}\,du\,,$$

while the ***local activation density*** is given by:

$$a_j^d[f_i](t,\mathbf{x}) = \frac{a_j[f_i](t,\mathbf{x})}{\nu[f_i](t,\mathbf{x})} = \frac{1}{\nu[f_i](t,\mathbf{x})}\int_{D_\mathbf{v}\times D_u} u_j\, f_i(t,\mathbf{x},\mathbf{v},u)\,d\mathbf{v}\,du.$$



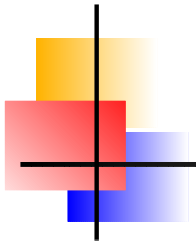
The Kinetic Theory for Active Particles

DERIVATION OF MATHEMATICAL STRUCTURES

The derivation of the evolution equation for the $f_i s$ is obtained by a balance for net flow of active particles in the elementary volume of the space of the microscopic state by transport and interactions. The following following active particles are involved in the interactions:

- ***Test*** particles with microscopic state $(\mathbf{x}, \mathbf{v}, u)$, at the time t, and distribution function is $f = f(t, \mathbf{x}, \mathbf{v}, u)$.
- ***Field*** particles with microscopic state $(\mathbf{x}^*, \mathbf{v}^*, u^*)$, at the time t, and distribution function is $f^* = f(t, \mathbf{x}^*, \mathbf{v}^*, u^*)$.
- ***Candidate*** particles with microscopic state $(\mathbf{x}_*, \mathbf{v}_*, u_*)$, and distribution function is $f_* = f(t, \mathbf{x}_*, \mathbf{v}_*, u_*)$.

Conservative interactions: particles modify their microscopic state;
Non conservative interactions: proliferation or destruction of particles in their microscopic state.



The Kinetic Theory for Active Particles

THE MATHEMATICAL STRUCTURES

The mathematical framework refers to the evolution in time and space of the test particle f_i

$$\frac{df_i}{dt}\, d\mathbf{x}\, d\mathbf{v} = \Big(G_i[\mathbf{f}] - L_i[\mathbf{f}] + S_i[\mathbf{f}] \Big)\, d\mathbf{x}\, d\mathbf{v}\,,$$

where interactions of candidate and test particles refers to the field particles and $\mathbf{f} = \{f_i\}_{i=1}^n$. Moreover,

• $G_i[\mathbf{f}]$ denotes the ***gain*** of candidate particles into the state $\mathbf{x}\,\mathbf{v}, u$ of the test particle;

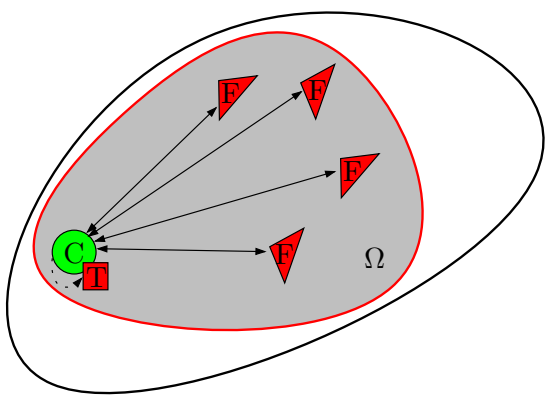
• $L_i[\mathbf{f}]$ models the ***loss*** of test particles;

• $S_i[\mathbf{f}]$ models ***proliferation/destruction*** of test particles in their microscopic state.

The Kinetic Theory for Active Particles: The interactions

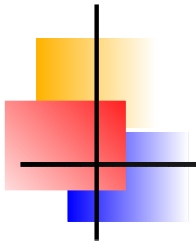
Interactions involve candidate particles of the h^{th} population with field particles of the k^{th} population:

H.2.1. The candidate and test particles in $\mathbf{x}$, with state $\mathbf{v}_*, u_*$ and $\mathbf{v}, u$, respectively, interact with the field particles in $\mathbf{x}^*$, with state $\mathbf{v}^*, u^*$ located in its interaction domain Ω, $\mathbf{x}^* \in \Omega$.



H.2.2. Interactions are weighted by a suitable term $\eta_{hk}[\rho](\mathbf{x}^*)$, that can be interpreted as an ***interaction rate***, which depends on the local density in the position of the field particles.

H.2.3. The distance and topological distribution of the intensity of the interactions is weighted by a function $p_{hk}(\mathbf{x}, \mathbf{x}^*)$ such that:
$\int_\Omega p_{hk}(\mathbf{x}, \mathbf{x}^*)\, d\mathbf{x}^* = 1.$



The Kinetic Theory for Active Particles

H.2.4. The candidate particle modifies its state according to the probability density $\mathcal{A}$ defined as follows:

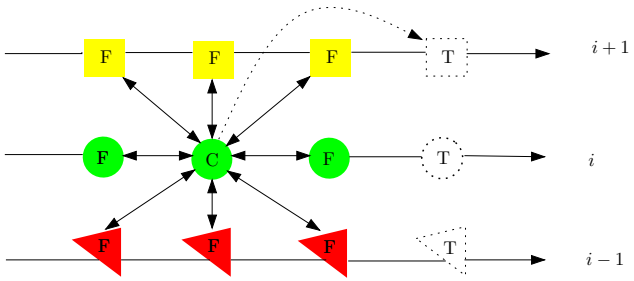
$$\mathcal{A}_{hk}(\mathbf{v}_* \to \mathbf{v},\, u_* \to u | \mathbf{v}_*, \mathbf{v}^*, u_*, u^*)\,,$$

where $\mathcal{A}$ denotes the probability density that a candidate particles with state $\mathbf{v}_*, u_*$ reaches the state $\mathbf{v}, u$ after an interaction with the filed particles with state $\mathbf{v}^*, u^*$, while the test particle looses its state $\mathbf{v}$ and u after interactions with field particles with velocity $\mathbf{v}^*$ and activity u^*.

H.2.5. The test particle, in $\mathbf{x}$, can proliferate, due to encounters with field particles in $\mathbf{x}^*$, with rate $\mu^i_{hk}(\mathbf{x}, \mathbf{x}^*)$, which denotes the proliferation rate into the functional subsystem i, due the encounter of particles belonging the functional subsystems h and k. Destructive events can occur only within the same population with rate $\mu^i_{ik}(\mathbf{x}, \mathbf{x}^*)$.

The Kinetic Theory for Active Particles

Cells during proliferation can move from one population to the other.



Remark. The following factorization:

$$\mathcal{A}_{hk}(\cdot) = \mathcal{B}_{hk}(u_* \to u,\, |u_*, u^*) \times \mathcal{C}_{hk}(\mathbf{v}_* \to \mathbf{v}\,|\mathbf{v}_*, \mathbf{v}^*, u_*, u^*)\,,$$

can be used in a variety of applications.

$\mathcal{A}$, $\mathcal{B}$, and $\mathcal{C}$ are, for positive defined f, probability densities:

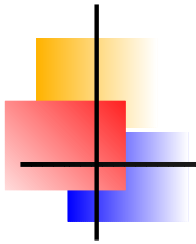
$$\int_{D_{\mathbf{v}}\times D_u} \mathcal{A}_{hk}(\mathbf{v}_* \to \mathbf{v},\, u_* \to u\,|\mathbf{v}_*, \mathbf{v}^*, u_*, u^*)\, d\mathbf{v}\, du = 1\,, \quad \forall\ \mathbf{v}_*, \mathbf{v}^*\ u_*, u^*.$$

$$\int_{D_u} \mathcal{B}_{hk}(u_* \to u,\, |u_*, u^*)\, du = \int_{D_{\mathbf{v}}} \mathcal{C}_{hk}(\mathbf{v}_* \to \mathbf{v}\,|\mathbf{v}_*, \mathbf{v}^*, u_*, u^*)\, d\mathbf{v} = 1.$$

The Kinetic Theory for Active Particles: General Framework

$$
\begin{aligned}
&\left(\partial_t + \mathbf{v}\cdot\partial_{\mathbf{x}}\right) f_i(t,\mathbf{x},\mathbf{v},u) \\
&= \left[\sum_{j=1}^{n}\left(G_{ij}[\mathbf{f}] - L_{ij}[\mathbf{f}]\right) + \sum_{h=1}^{n}\sum_{k=1}^{n} S^i_{hk}[\mathbf{f}]\right](t,\mathbf{x},\mathbf{v},u) \\
&= \int_{\Lambda} \eta_{ij}[\rho_j](t,\mathbf{x}^*) p_{ij}(\mathbf{x},\mathbf{x}^*)\, \mathcal{B}_{ij}(u_* \to u | u_*, u^*)\, \mathcal{C}_{hk}(\mathbf{v}_* \to \mathbf{v}\,|\mathbf{v}_*,\mathbf{v}^*,u_*,u^*) \\
&\times f_i(t,\mathbf{x},\mathbf{v}_*,u_*) f_j(t,\mathbf{x}^*,\mathbf{v}^*,u^*)\, d\mathbf{v}_*\, d\mathbf{v}^*\, du_*\, du^*\, d\mathbf{x}^*\,, \\
&- f_i(t,\mathbf{x},\mathbf{v}) \int_{\Gamma} \eta_{ij}[\rho_j](t,\mathbf{x}^*) p_{ij}(\mathbf{x},\mathbf{x}^*)\, f_j(t,\mathbf{x}^*,\mathbf{v}^*,u^*)\, d\mathbf{v}^*\, du^*\, d\mathbf{x}^* \\
&+ \int_{\Gamma\times D_u} \eta_{hk}[\rho_k](t,\mathbf{x}^*) p_{hk}(\mathbf{x},\mathbf{x}^*)\, \mu^i_{hk}(u_*,u^*) \\
&\times f_h(t,\mathbf{x},\mathbf{v},u_*) f_k(t,\mathbf{x}^*,\mathbf{v}^*,u^*)\, d\mathbf{v}^*\, du_*\, du^*\, d\mathbf{x}^*\,,
\end{aligned}
$$

where $\Lambda = \Omega \times D^2_{\mathbf{v}} \times D^2_u$,, $\Gamma = \Omega \times D_{\mathbf{v}} \times D_u$.



The Kinetic Theory for Active Particles: Open Systems

Modeling macroscopic actions means the identification of the term $K_i = K_i(t, \mathbf{x}, u)$ supposed to be a known function of its arguments. The action K_i acts over the variable u for each functional subsystem. The resulting equation, for $i = 1, \ldots, n$ is as follows:

$$(\partial_t + \mathbf{v} \cdot \partial_{\mathbf{x}})\ f_i(t, \mathbf{x}, \mathbf{v}, u) + \partial_u \left(K_i(t, \mathbf{x}, u)\, f_i(t, \mathbf{x}, \mathbf{v}, u)\right) = J_i[\mathbf{f}].$$

Modeling microscopic actions means modeling of functional subsystems generated by the outer system. Their representation can be delivered by the distribution functions:

$$g_r(t, \mathbf{x}, w)\,, \qquad r = 1, \ldots, m\,, \qquad w \in D_w = D_u.$$

depending on time, space and on a variable w modeling the activity of the outer functional subsystem.

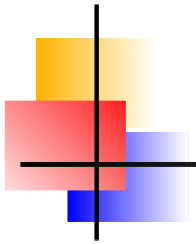
The Kinetic Theory for Active Particles: The Framework

$$(\partial_t + \mathbf{v}\cdot\partial_{\mathbf{x}})\ f_i(t,\mathbf{x},\mathbf{v},u) = J_i[\mathbf{f}](t,\mathbf{x},\mathbf{v},u) + Q_i[\mathbf{f},\mathbf{g}](t,\mathbf{x},\mathbf{v},u)\,,$$

$$Q_i[\mathbf{f},\mathbf{g}] = \sum_{j=1}^{r} C^e_{ir}[\mathbf{f},\mathbf{g}](t,\mathbf{x},\mathbf{v},u) + \sum_{h=1}^{n}\sum_{r=1}^{n} S^e_{hr}(i)[\mathbf{f},\mathbf{g}](t,\mathbf{x},\mathbf{v},u)\,,$$

$$\begin{aligned} C^e_{ij}[\cdot] \quad &= \quad \int_\Lambda \eta^e_{ij}[\rho_j](t,\mathbf{x}^*)p^e_{ij}(\mathbf{x},\mathbf{x}^*)\,B_{ij}(u_*\to u|u_*,u^*)C_{hk}(\mathbf{v}_*\to\mathbf{v}\,|\mathbf{v}_*,\mathbf{v}^*,u_*,u^*) \\ &\times \quad f_i(t,\mathbf{x},\mathbf{v}_*,u_*)g_r(t,\mathbf{x}^*,\mathbf{v}^*,w^*)\,d\mathbf{v}_*\,d\mathbf{v}^*\,du_*\,dw^*\,d\mathbf{x}^*\,, \\ &- \quad f_i(t,\mathbf{x},\mathbf{v})\int_\Gamma \eta^e_{ij}[\rho_j](t,\mathbf{x}^*)p^e_{ij}(\mathbf{x},\mathbf{x}^*)\,g_r(t,\mathbf{x}^*,\mathbf{v}^*,w^*)\,d\mathbf{v}^*\,dw^*\,d\mathbf{x}^*. \end{aligned}$$

$$\begin{aligned} S^e_{hk}(i)[\cdot] \quad &= \quad \int_{\Gamma\times D_u} \eta^e_{hk}[\rho_k](t,\mathbf{x}^*)p_{hk}(\mathbf{x},\mathbf{x}^*)\,\mu^e_{hk}(i)(u_*,u^*) \\ &\times \quad f_h(t,\mathbf{x},\mathbf{v},u_*)g_k(t,\mathbf{x}^*,\mathbf{v}^*,u^*)\,d\mathbf{v}^*\,du_*\,dw^*\,d\mathbf{x}^*\,, \end{aligned}$$



The Kinetic Theory for Active Particles

• η^e_{hk} models the encounter rates between the k^{th} external action with state w^* and the h^{th} ***candidate particle*** with state u_*.

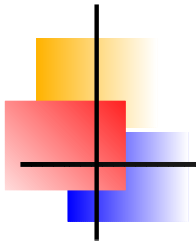
• $B^e_{ij}(u_* \to u, v^*)$ denotes the probability density that the candidate particle the i^{th} population with state u_*, h falls into the state u of the same population due to interactions with the j^{th} action with state w^*.

• $C^e_{ij}(\mathbf{v}_* \to \mathbf{v}|\mathbf{v}_*, \mathbf{v}^*, u_*, w^*)$ models the velocity dynamics, conditioned by the activity of the interacting pairs.

• $\mu^e_{hk}(i)(u_*, v^*; u)$ models the net proliferation into the i^{th} population, due to interactions, which occur with rate η_{hk}, of the ***candidate*** particle of the population h^{th} with state u_* with the k^{th} action with state v^*.

The Kinetic Theory for Active Particles

$$
\begin{aligned}
\partial_t f_i(t,u) \quad &+ \quad \mathcal{F}_i(t)\,\partial_u f_i(t,u) = J_i[\mathbf{f}](t,u) + Q_i[\mathbf{f}](t,u) \\
&= \quad \sum_{j=1}^{n} \int_{D_u \times D_u} \eta_{ij}(u_*,u^*)\mathcal{B}_{ij}(u_*,u^*;u) f_i(t,u_*) f_j(t,u^*)\,du_*\,du^* \\
&- \quad f_i(t,u) \sum_{j=1}^{n} \int_{D_u} \eta_{ij}(u,u^*) f_j(t,u^*)\,du^* \\
&+ \quad \sum_{h=1}^{n}\sum_{k=1}^{n} \int_{D_u \times D_u} \eta_{hk}(u_*,u^*)\mu^i_{hk}(u,u^*) f_h(t,u_*) f_k(t,u^*)\,du_*\,du^*\,, \\
&+ \quad \sum_{r=1}^{m} \int_{D_u \times D_v} \eta^e_{ij}(u_*,v^*)\mathcal{C}_{ij}(u_*,v^*;u) f_i(t,u_*) g_r(t,u^*)\,du_*\,dv^* \\
&- \quad f_i(t,u) \sum_{r=1}^{m} \int_{D_v} \eta^*(u,v^*) g_r(t,v^*)\,dv^* \\
&+ \quad \sum_{h=1}^{r}\sum_{r=1}^{m} \int_{D_u} \int_{D_u} \eta^e_{hk}(u_*,v^*)\mu^e_{hk}(i)(u_*,v^*;u) f_h(t,u_*) g_r(t,v^*)\,du_*\,dv^*\,,
\end{aligned}
$$



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Part I - From Biology to Mathematics - Complexity and Multiscale Issues

Part II - The Mathematical Kinetic Theory for Active Particles

Part III - **Modeling Keloid Formation, Progression, Mutations, and Immune System Competition**

Part IV - From Microscopic to Macroscopic

Modeling Keloid Formation, Progression, Mutations, and Immune System Competition

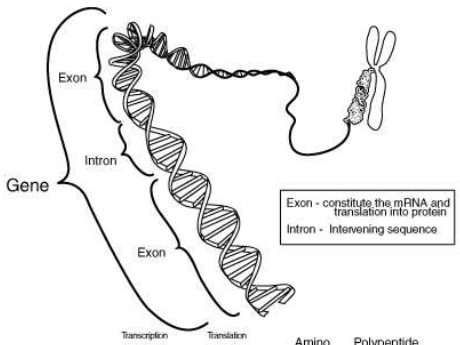
Gene: a union of genomic sequences encoding a coherent set of potentially overlapping functional products (GERSTEIN ET AL, *Genome Research* **17** (2007) 669-681).

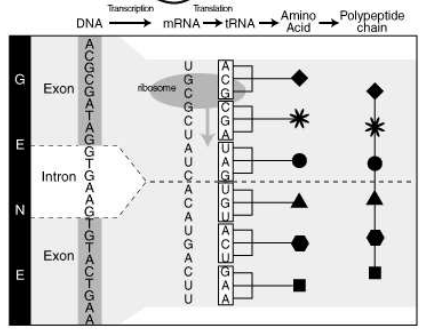
Gene Mutation: a permanent change in the DNA sequence that makes up a gene (a normal allele is changed to a rare and abnormal variant):

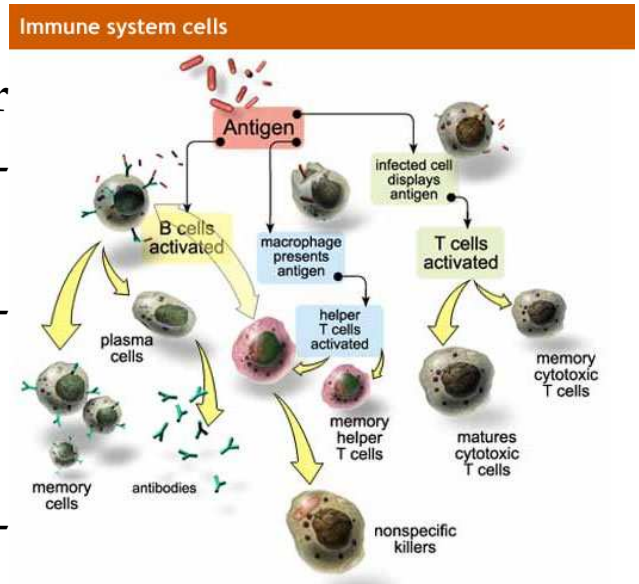
- Hereditary (germline): inherited from a parent;
- Acquired (somatic): acquired during a person lifetime (physical or chemical exogenous agents, mistake during DNA replication), e.g. Tumor.

Immune System: a complex of cells (leukocytes or white blood cells) and molecules which provides a defense against pathogenic agents

- Capability of distinguishing between "self" and "non-self" entities;
- Learning;
- Memory of previous encounters with foreign "non-self" agents.



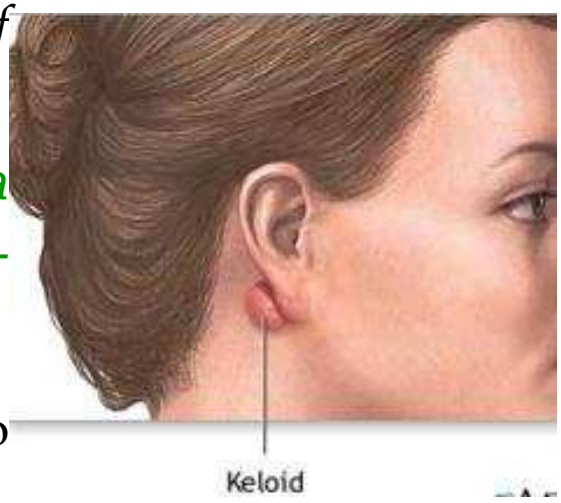




(Source: the Human Immune Response System www.uta.edu/chagas/images/immunSys.jpg)

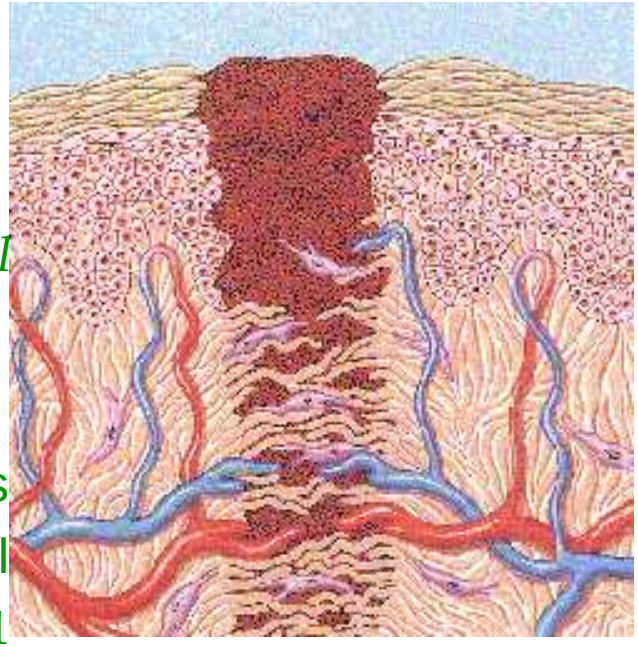
Modeling Keloid Formation, Progression, Mutations, and Immune System Competition

Keloid: *Dermal tumor that forms during a protracted wound healing process characterized by increased deposition of extracellular matrix by fibroblast cells*



D WOLFRAM ET AL, *Hypertrophic scars and keloids–a review of their pathophysiology, risk factors, and therapeutic management, Dermatol Surg.* **35** *(2009) 171-81.*

Triggering Causes: remain elusive and there is no satisfactory treatment for this disorder.



Medical Hypotheses:

- Viruses:

P. ALONSO ET AL, Keloids: A viral hypothesis, *Medical Hypotheses*, **70** (2008) 156-166.

- Genetic Susceptibility and Mutations:

M. NASSIRI ET AL, Gene expression profiling reveals alteration of caspase 6 and 14 transcripts in normal skin of keloid-prone patients, *Arch Dermatol Res.*, **301** (2009) 183-188.

Modeling Keloid Formation, Progression, Mutations, and Immune System Competition

CELL SUBSYSTEMS, ACTIVITY, AND DISTRIBUTION FUNCTIONS

Cell Subsystems	Activity	Distribution Function
Normal Fibroblasts (NFc)	Proliferation	$f_1(t,u)$
Activated Viruses (AV)	Aggressiveness	$f_2(t,u)$
Keloid Fibroblasts (KFc)	Proliferation	$f_3(t,u)$
Malignant (Mc)	Progression	$f_4(t,u)$
Immune System (ISc)	Activation	$f_5(t,u)$

Modeling Keloid Formation, Progression, Mutations, and Immune System Competition

Parameter	Biological Meaning
α	Heterogeneity rate of (KFc)
β	Proliferation rate of (KFc)
β_i	Proliferation rate of (ISc)
δ	Destruction rate of (AV) and (Mc) by (ISc)
δ_i	Destruction rate of (ISc) by (AV) and (Mc)
γ	Mutation rate of (NFc) in (KFc)
λ	Mutation rate of (KFc) in (Mc)
ϵ	Scale factor

Modeling Keloid Formation, Progression, Mutations, and Immune System Competition

INTERACTIONS AND PARAMETERS

	Interactions	(NFc)	(AV)	(KFc)	(Mc)	(ISc)
(NFc)	Proliferative	$\varepsilon^2\beta$				
	Destructive		$-\varepsilon\delta$			
	Transitive	$\varepsilon\gamma$	γ			
(AV)	Conservative	$\varepsilon\alpha$				
	Proliferative	$\varepsilon\beta$				$\varepsilon\beta$
	Destructive					$-\delta$
(KFc)	Conservative		α			
	Proliferative	β	β			
	Destructive		$-\varepsilon^2\delta$			$-\varepsilon^2\delta$
	Transitive		λ			
(Mc)	Conservative		$\varepsilon^2\alpha$			
	Proliferative		$\varepsilon\beta$			
	Destructive					$-\delta$
(ISc)	Proliferative		β_i	$\varepsilon^2\beta_i$	β_i	
	Destructive		δ_i	$-\varepsilon^2\delta_i$	δ_i	

Modeling Keloid Formation, Progression, Mutations, and Immune System Competition

THE MATHEMATICAL MODEL

$$
\begin{cases}
\partial_t f_1 = \varepsilon\Big(\varepsilon\,\beta\displaystyle\int_0^\infty f_1(t,u)\,du - \delta\int_0^\infty f_2(t,u)\,du\Big) f_1(t,u)\,, \\[2ex]
\partial_t f_2 = \Big(\varepsilon\beta\displaystyle\int_0^\infty [f_1(t,u)+f_5(t,u)]\,du - \delta\int_0^\infty f_5(t,u)\,du\Big) f_2(t,u) - f_2(t,u)\int_0^\infty f_1(t,u)\,du \\
\qquad +f_2(t,u-\epsilon\,\alpha)\displaystyle\int_0^\infty f_1(t,u)\,du\,, \\[2ex]
\partial_t f_3 = \Big(\beta\displaystyle\int_0^\infty f_1(t,u)\,du - (1-\beta+\varepsilon^2\delta)\int_0^\infty f_2(t,u)\,du\Big) f_3(t,u) - \varepsilon^2\delta\, f_3(t,u)\displaystyle\int_0^\infty f_5(t,u)\,du \\
\qquad +f_3(t,u-\alpha)\displaystyle\int_0^\infty f_2(t,u)\,du + \gamma\Big(\epsilon\int_0^\infty f_1(t,u)\,du + \int_0^\infty f_2(t,u)\,du\Big) f_1(t,u)\,, \\[2ex]
\partial_t f_4 = \Big((\varepsilon\beta-1)\displaystyle\int_0^\infty f_2(t,u)\,du - \delta\int_0^\infty f_5(t,u)\,du\Big) f_4(t,u) + \lambda\, f_3(t,u)\displaystyle\int_0^\infty f_2(t,u)\,du \\
\qquad +f_4(t,u-\varepsilon^2\alpha)\displaystyle\int_0^\infty f_2(t,u)\,du\,, \\[2ex]
\partial_t f_5 = \beta_i\Big(\displaystyle\int_0^\infty [f_2(t,u)+f_4(t,u)]\,du + \varepsilon^2\int_0^\infty f_3(t,u)\,du\Big) f_5(t,u) - \delta_i\, f_5(t,u)\displaystyle\int_0^\infty u\, f_2(t,u)\,du \\
\qquad -\delta_i\Big(\displaystyle\int_0^\infty u\, f_4(t,u)\,du + \varepsilon^2\int_0^\infty u\, f_3(t,u)\,du\Big) f_5(t,u).
\end{cases}
$$

Initial Conditions and Fixed Parameters

INITIAL CONDITIONS:

- The number of Normal Fibroblasts in the wound is equal to the number of Activated Virus, i.e. $f_1(0,u) = f_2(0,u)$;
- ISc have reached the wound (sentinel level), $f_5(0,u)$;
- Keloid Fibroblasts and Mc are not initially present, $f_3(0,u) = f_4(0,u) = 0$.

PARAMETERS IN EVERY SIMULATIONS:

- The mutation rate of the Normal Fibroblasts to Keloid Fibroblasts is not negligible ($\gamma = 0.4$);
- The destructive ability of the ISc is quite low ($\delta = 0.3$);
- The non-self cells have an intermediate ability to inhibit the response of the ISc ($\delta_i = 0.5$);
- The scale factor is $\epsilon = 0.5$.

THE VALUES OF THE PARAMETERS α, β, β_i, AND λ ARE SET CASE-WISE.

Sensitivity Analysis of the Parameter α

PARAMETERS:

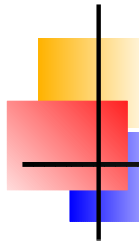
- Weak Keloid Fibroblasts proliferation ($\beta = 0.4$);
- Low proliferation of the ISc ($\beta_i = 0,35$);
- The probability that Keloid Fibroblasts become Mc is not negligible ($\lambda = 0.5$).

EXPECTED ASYMPTOTIC BEHAVIOUR:

Increasing amplification of the heterogeneity phenomena of the non-self entities, and correspondingly increase the chances to develop malignant effects.

TEST CASES:

- Simulations for values of $\alpha \in [0, 0.35]$;
- Simulations for values of $\alpha \in (0.35, 0.5]$;
- Simulations for values of $\alpha \in (0.5, 1]$.



Modeling Keloid Formation, Progression, Mutations, and Immune System Competition

Simulations for Values of $\alpha \in [0, 0.35]$

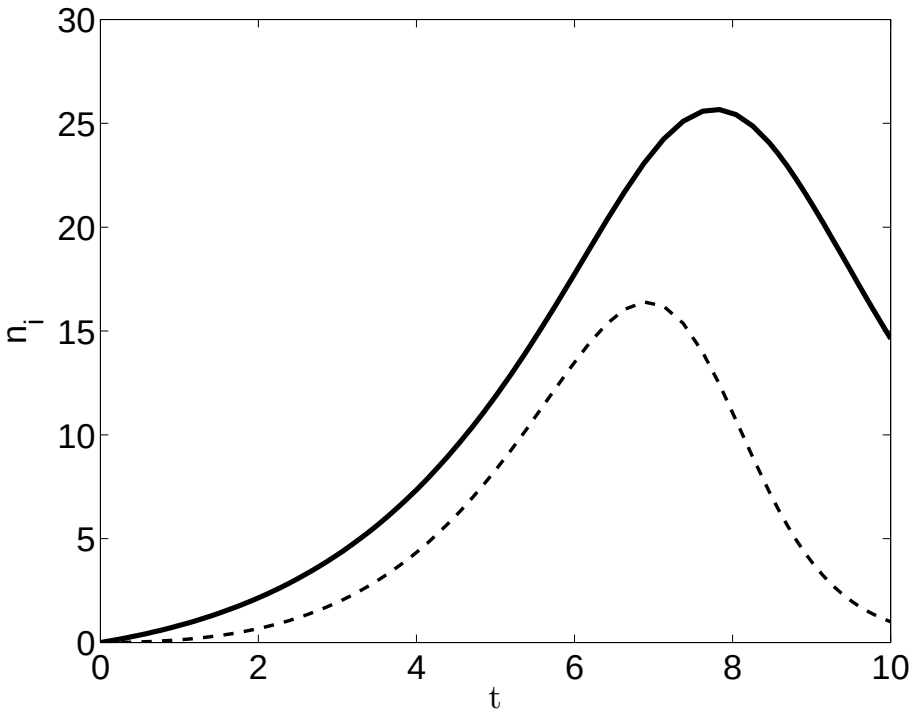


Figure 1: Time evolution of the densities of Keloid Fibroblasts (solid line) and of Mc (dashed line) for $\alpha = 0.3$. The low magnitude of the progression rate never allows the number of Mc to overcome the number of Keloid Fibroblasts

Modeling Keloid Formation, Progression, Mutations, and Immune System Competition

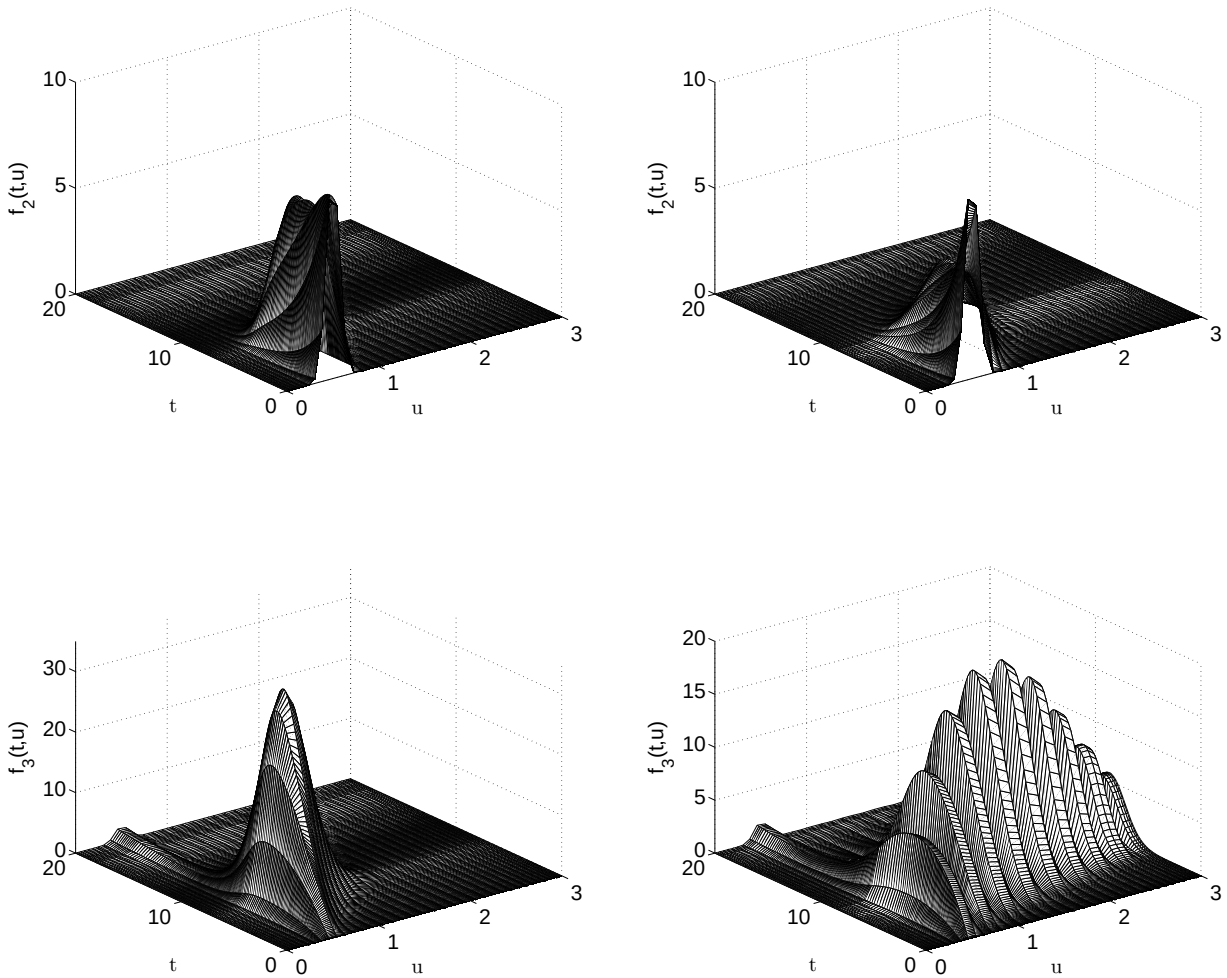


Figure 2: The distribution functions of AV (top panels) and Keloid Fibroblasts (bottom panels) for $\alpha = 0.1$ and $\alpha = 0.3$.

Modeling Keloid Formation, Progression, Mutations, and Immune System Competition

Simulations for Values of $\alpha \in [0, 0.35]$

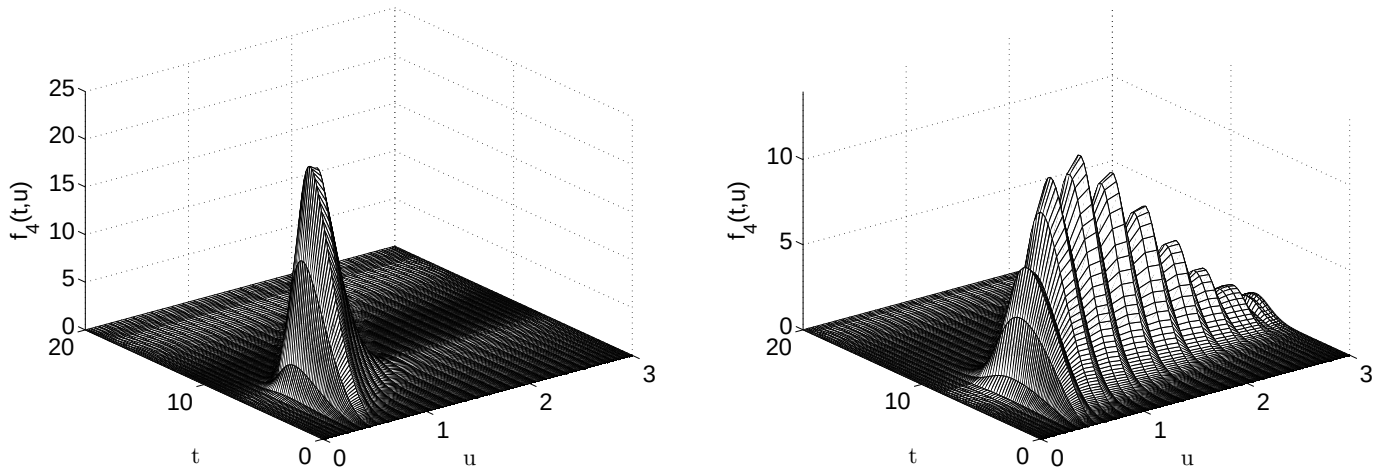


Figure 3: The distribution function of the Mc for $\alpha = 0.1$ (left panel) and $\alpha = 0.3$ (right panel).

BIOLOGICAL INTERPRETATION:

These simulations may represent the failure of the normal wound healing process where, because of the low number of non-self entities with a high level of heterogeneity, the ISc would avoid the formation of keloid and malignant effects.

Modeling Keloid Formation, Progression, Mutations, and Immune System Competition

Simulations for Values of $\alpha \in (0.35, 0.5]$

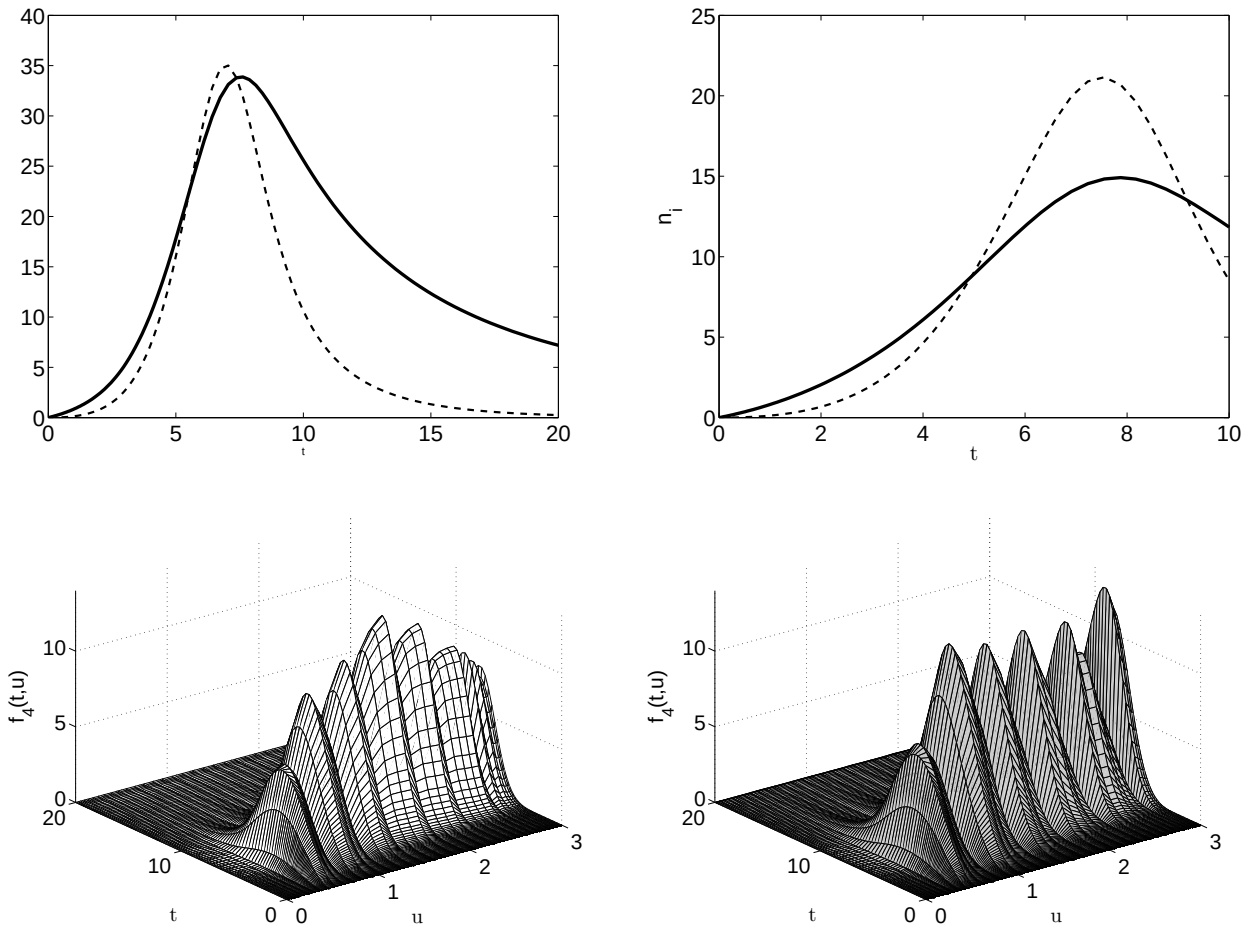


Figure 4: Time evolution of Keloid Fibroblasts (solid line) and of Mc (dashed line) for $\alpha = 0.4$ and $\alpha = 0.5$ (t.p). Distribution function of Mc (b.p.).

Modeling Keloid Formation, Progression, Mutations, and Immune System Competition

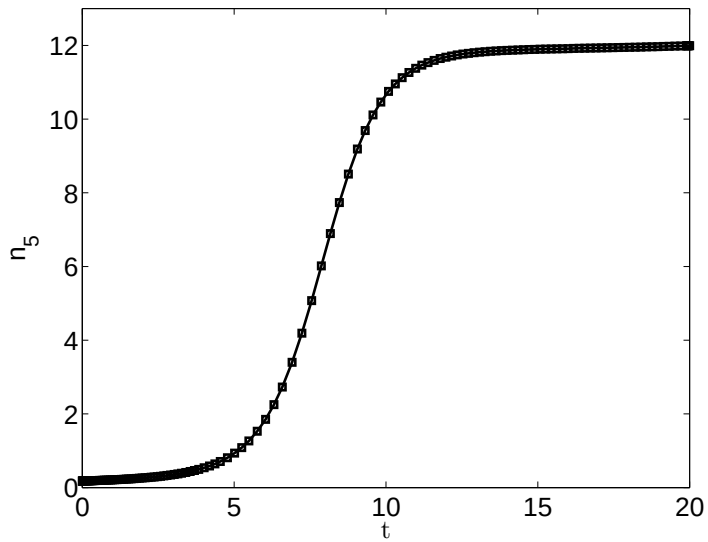


Figure 5: Time evolution of the density of the ISc for $\alpha = 0.5$.

BIOLOGICAL INTERPRETATION:

These simulations may represent a failure of the normal wound healing process where the keloid formation, which depends on how long it takes the ISc to deplete the Keloid Fibroblasts , would prevail malignant effects.

Modeling Keloid Formation, Progression, Mutations, and Immune System Competition

Simulations for Values of $\alpha \in (0.5, 1]$

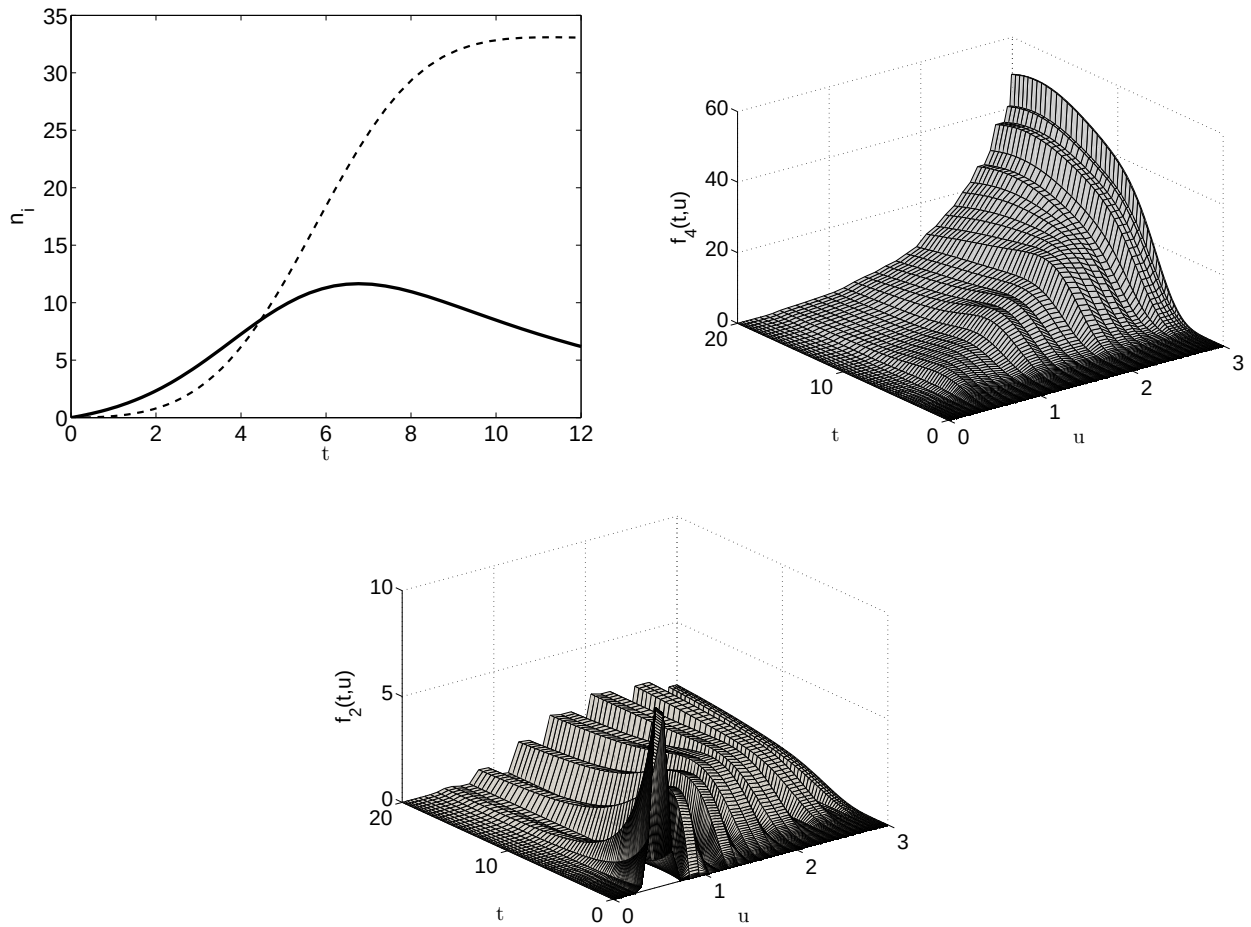


Figure 6: Time evolution of KFc (solid line) and Mc, $\alpha = 0.8$. Distribution function of Mc and AV.

Sensitivity Analysis of the Parameter β_i

Fixed Parameters:

Letting the magnitude of the parameters so that a high manifestation of heterogeneity and aggressiveness is manifest specifically setting $\alpha = 0.8$, $\beta = 0.4$, $\lambda = 0.5$.

Expected Asymptotic Behaviour:

It is expected that increasing values of β_i produce a higher activation of the immune system and sequently a more efficient ability to contrast the non-self cells.

Test Cases:

- Simulations for $\beta_i = 0$;
- Simulations for $\beta_i \in]0, 0.55]$;
- $\beta_i \in]0.55, 1]$.

Modeling Keloid Formation, Progression, Mutations, and Immune System Competition

Simulations for $\beta_i \in]0.55, 1]$

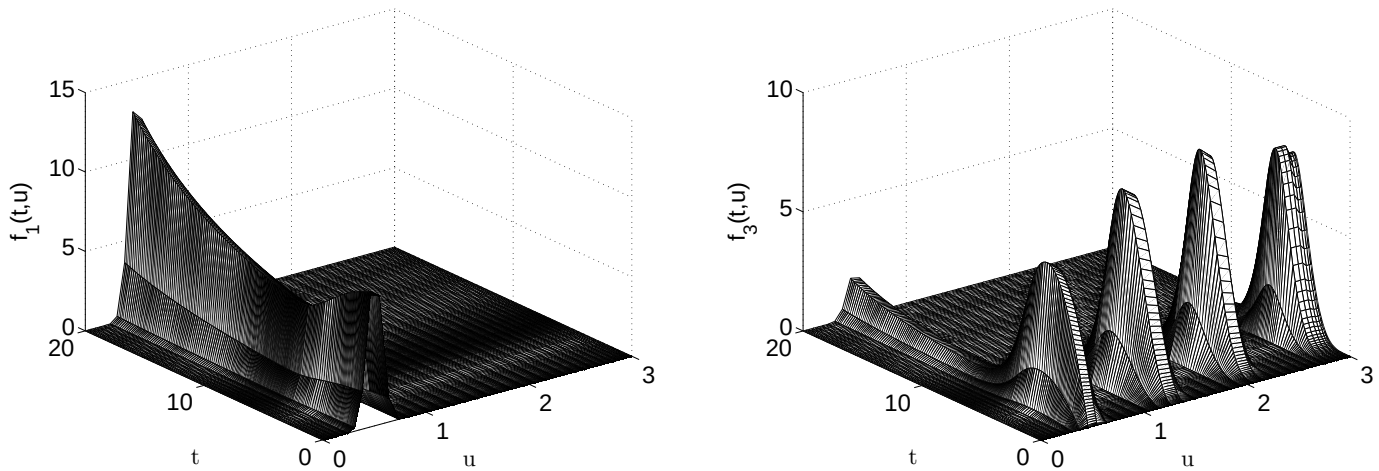


Figure 7: Distribution function of the NFc and Keloid Fibroblasts for $\beta_i = 0.8$.

BIOLOGICAL INTERPRETATION:

The immune system prevents the formation of malignant tumors, but the genetic susceptibility of the patient does not avoid the possibility of the keloid formation.

Modeling Keloid Formation, Progression, Mutations, and Immune System Competition

Simulations for $f_1(0,u) = g_{10}(u)$, $f_2(0,u) = g_0(u)$, and $f_5(0,u) = g_1(u)$

This assumption means that the Activated Viruses have not reached the wound ($n[f_2](0) = 0$) and after the injury the number of Normal Fibroblasts is greater than the number of the ISc, namely $n[f_5](0) < n[f_1](0)$.

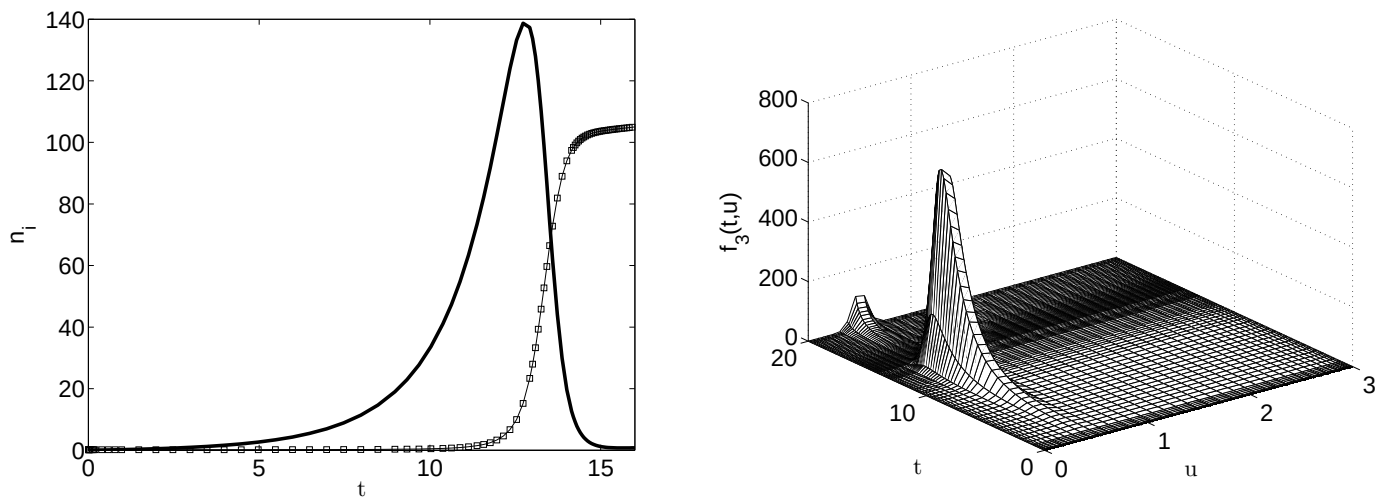


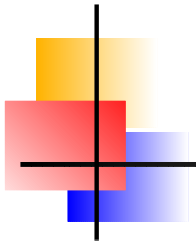
Figure 8: Time evolution of the Keloid Fibroblasts and Isc and the distribution function of Keloid Fibroblasts .

Simulations Summary

Fixed Parameters	Free Parameter	Simulation Results and Biological Interpretation
$\beta = 0.4$ $\beta_i = 0.35$ $\gamma = 0.4$ $\lambda = 0.5$ $\delta_I = 0.5$ $\delta = 0.3$ $\epsilon = 0.5$	$\alpha = 0.2$	Onset of Keloid Fibroblasts and Mc Mc never overcome Keloid Fibroblasts Low number of the high activity non-self cells Depletion of the Mc and Activated Viruses by ISc Normal Fibroblasts proliferates again
	$\alpha = 0.5$	Mc overcome Normal Fibroblasts High activity levels for Keloid Fibroblasts and Mc Low number of the Activated Viruses with high activity Normal Fibroblasts are not able to proliferate Partial depletion of the low activity non-self cells
	$\alpha = 0.8$	Mc overcome Keloid Fibroblasts more and more High proliferation of Activated Viruses High number of the high activity non-self cells Inhibition of the ISc after competition Destruction of the Normal Fibroblasts

Simulations Summary

Fixed Parameters	Free Parameter	Simulation Results and Biological Interpretation
$\beta = 0.4$ $\alpha = 0.8$ $\gamma = 0.4$ $\lambda = 0.5$ $\delta_I = 0.5$ $\delta = 0.3$ $\epsilon = 0.5$	$\beta_i = 0$	Untrammeled increasing of the non-self cells High levels of proliferation of the Activated Viruses and Keloid Fibroblasts High levels of progression of the Mc Total inhibition of the ISc Destruction of Normal Fibroblasts
	$\beta_i = 0.8$	Depletion of the non-self entities by ISc Revival of the Proliferation of the Normal Fibroblasts Rebirth of Keloid Fibroblasts because genetic susceptibility



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Part II - The Mathematical Kinetic Theory for Active Particles

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Part IV **- From Microscopic to Macroscopic**

From Microscopic to Macroscopic

•N.B., A. BELLOUQUID, J. NIETO, AND J. SOLER, *Complexity and Mathematical Tools Toward the Modelling of Multicellular Growing Systems*, 20, (2010) . Let us

consider a stochastic perturbation in velocity of the whole system,

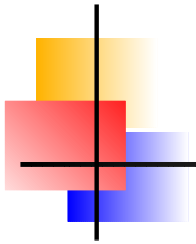
$$(\partial_t + \mathbf{v}\cdot\nabla_{\mathbf{x}})\ f_i = \nu_i\,\mathcal{L}_i[f_i] + J_i[\mathbf{f}] + Q_i[\mathbf{f},\mathbf{g}]\,,$$

• ν_i is the turning rate or turning frequency, hence $\tau_i = \frac{1}{\nu_i}$ is the mean run time.

• The linear transport term describes the dynamics of biological organisms modelled by a velocity-jump process,

$$\mathcal{L}_i[f_i] = \int_{D_{\mathbf{v}}} \Big(T_i(\mathbf{v}^*\to\mathbf{v})f_i(t,\mathbf{x},\mathbf{v}^*,u) - T_i(\mathbf{v}\to\mathbf{v}^*)f_i(t,\mathbf{x},\mathbf{v},u)\Big)\,d\mathbf{v}^*\,,$$

where $T_i(\mathbf{v}^*\to\mathbf{v})$ is, for the i^{th} subsystem, the probability kernel for the new velocity $\mathbf{v}\in D_{\mathbf{v}}$ assuming that the previous velocity was $\mathbf{v}^*$.



From Microscopic to Macroscopic

The hypotheses on the turning operators L_i are as follows:

H.1. Each turning operator L_i satisfies the following solvability conditions:

$$\int_{D_{\mathbf{v}}} L_i[f]\, d\mathbf{v} = \int_{D_{\mathbf{v}}} \mathbf{v} L_i[f]\, d\mathbf{v} = 0. \tag{1}$$

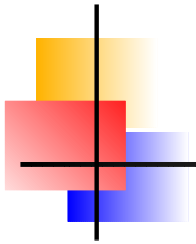
H.2. There exists a unique function

$$M^i_{\rho,\mathbf{U}} \in L^1(D_{\mathbf{v}}, (1+|\mathbf{v}|)\, d\mathbf{v}),$$

for all $\rho \geq 0$ and $\mathbf{U} \in D_{\mathbf{v}}$, verifying

$$L_i(M^i_{\rho,\mathbf{U}}) = 0, \quad \int_{D_{\mathbf{v}}} M^i_{\rho,\mathbf{U}}(\mathbf{v})\, d\mathbf{v} = \rho, \quad \int_{D_{\mathbf{v}}} \mathbf{v}\, M^i_{\rho,\mathbf{U}}(\mathbf{v})\, d\mathbf{v} = \rho\, \mathbf{U}.$$

Here, variables t, x and u act as parameters. These hypotheses allow to derive macroscopic scale hyperbolic systems.



From Microscopic to Macroscopic

Let us consider a *hyperbolic scaling* formally corresponding to the following choice of scale:

$$t \to \varepsilon\, t\,, \quad x \to \varepsilon\, x \quad \Rightarrow \quad t\,\nu = \frac{1}{\varepsilon}\,,$$

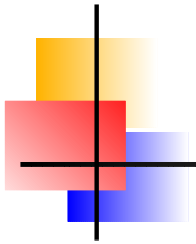
which produces the following non-dimensional model:

$$\varepsilon\,(\partial_t + \mathbf{v}\cdot\nabla_{\mathbf{x}})\; f_i^\varepsilon = L_i[f_i^\varepsilon] + \varepsilon^{q_i}\, J_i^\varepsilon[\mathbf{f}^\varepsilon] + \varepsilon\, Q_i^\varepsilon[\mathbf{f}^\varepsilon, \mathbf{g}], \qquad i = 1,2,3,4,$$

The closed system interaction operator is scaled as follows

$$J_i^\varepsilon[\mathbf{f}^\varepsilon] = \sum_{j=1}^{4} \Big(G_{ij}[\mathbf{f}^\varepsilon] - L_{ij}[\mathbf{f}^\varepsilon] \Big)(t,\mathbf{x},\mathbf{v},u) + \varepsilon^{\delta_i} \sum_{j=1}^{4}\sum_{k=1}^{4} S_{jk}^i[\mathbf{f}^\varepsilon],$$

where we have retained the same notation for the non-dimensional gain G_{ij}, lost L_{ij} and proliferative/destructive S_{jk}^i term.



From Microscopic to Macroscopic

The hyperbolic macroscopic behavior is deduced from the limit $\varepsilon \to 0$. First, taking $\varepsilon = 0$ we formally obtain $L_i[f_i^0] = 0$, so each f_i^0 verifies the conditions of hypothesis **H.2.** Then, we have four limiting distributions of the form $f_i^0 = M_{\rho_i^0, \mathbf{U}_i^0}$ corresponding to our four subsystems, and we have to study the equations satisfied by the equilibrium variables ρ_i^0 and $\mathbf{U}_i^0$. To do that, integration over $\mathbf{v}$ yields:

$$
\begin{aligned}
&\partial_t \rho_i^\varepsilon + \operatorname{div}(\rho_i^\varepsilon \mathbf{U}_i^\varepsilon) \\
&\quad = \varepsilon^{q_i - 1} \sum_{j=1}^{4} \int_{D_\mathbf{v}} \Big(G_{ij}[\mathbf{f}^\varepsilon] - L_{ij}[\mathbf{f}^\varepsilon] \Big) d\mathbf{v} + \varepsilon^{q_i + \delta_i - 1} \sum_{j=1}^{4} \sum_{k=1}^{4} \int_{D_\mathbf{v}} S_{jk}^i[\mathbf{f}^\varepsilon] d\mathbf{v} \\
&\quad + \varepsilon^{q_i - 1} \sum_{j=1}^{m} \int_{D_\mathbf{v}} \Big(G_{ij}^e[\mathbf{f}^\varepsilon] - L_{ij}^e[\mathbf{f}^\varepsilon] \Big) d\mathbf{v} + \varepsilon^{q_i + \delta_i - 1} \sum_{j=1}^{m} \int_{D_\mathbf{v}} S_{ij}^e[\mathbf{f}^\varepsilon, \mathbf{g}] d\mathbf{v}.
\end{aligned}
$$

From Microscopic to Macroscopic

Analogous calculations for the momentum equation yield:

$$\partial_t(\rho_i^\varepsilon \mathbf{U}_i^\varepsilon) + \mathrm{Div}\Big(\int_{D_\mathbf{v}} \mathbf{v} \otimes \mathbf{v}\, f_i^\varepsilon \, d\mathbf{v}\Big)$$

$$= \varepsilon^{q_i-1} \sum_{j=1}^{4} \int_{D_\mathbf{v}} \mathbf{v}\Big(G_{ij}[\mathbf{f}^\varepsilon] - L_{ij}[\mathbf{f}^\varepsilon]\Big) d\mathbf{v} + \varepsilon^{q_i+\delta_i-1} \sum_{h=1}^{4}\sum_{k=1}^{4} \int_{D_\mathbf{v}} \mathbf{v}\, S_{hk}^i[\mathbf{f}^\varepsilon] d\mathbf{v}$$

$$+ \quad \varepsilon^{q_i-1} \sum_{j=1}^{m} \int_{D_\mathbf{v}} \mathbf{v}\Big(G_{ij}^e[\mathbf{f}^\varepsilon] - L_{ij}^e[\mathbf{f}^\varepsilon]\Big) d\mathbf{v} + \varepsilon^{q_i+\delta_i-1} \sum_{j=1}^{m} \int_{D_\mathbf{v}} \mathbf{v} S_{ij}^e[\mathbf{f}^\varepsilon, \mathbf{g}] d\mathbf{v}.$$

Moreover we use the pressure tensor P_i^0 as a measure of the statistical variation in velocity around the expected mean velocity $\mathbf{U}_i^0$,

$$P_i^0(t,x,u) = \int_{D_\mathbf{v}} (\mathbf{v} - \mathbf{U}_i^0) \otimes (\mathbf{v} - \mathbf{U}_i^0)\, f_i^0 \, d\mathbf{v}.$$

$$\int_{D_\mathbf{v}} \mathbf{v} \otimes \mathbf{v}\, M_{\rho_i^0, \mathbf{U}_i^0}\, d\mathbf{v} = P_i^0 + \rho_i^0\, (\mathbf{U}_i^0 \otimes \mathbf{U}_i^0).$$

From Microscopic to Macroscopic

Perturbation of the equilibrium $f_i = M^i_{\rho_i^0, \mathbf{U}_i^0} + \varepsilon h_i$, with $\mathbf{M} = \{M^i_{\rho_i^0, \mathbf{U}_i^0}\}_{i=1}^4$:

$$\partial_t \rho_i^0 + \mathrm{div}(\rho_i^0 \mathbf{U}_i^0) = O(\varepsilon^{q_i})$$

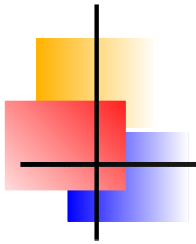
$$+\varepsilon^{q_i-1} \sum_{j=1}^{4} \int_{D_{\mathbf{v}}} \Big(G_{ij}[\mathbf{M}] - L_{ij}[\mathbf{M}] \Big) d\mathbf{v} + \varepsilon^{q_i+\delta_i-1} \sum_{j=1}^{4} \sum_{k=1}^{4} \int_{D_{\mathbf{v}}} S^i_{jk}[\mathbf{M}] d\mathbf{v}$$

$$+\varepsilon^{q_i-1} \sum_{j=1}^{m} \int_{D_{\mathbf{v}}} \Big(G^e_{ij}[\mathbf{M}, \mathbf{g}] - L^e_{ij}[\mathbf{M}, \mathbf{g}] \Big) d\mathbf{v} + \varepsilon^{q_i+\delta_i-1} \sum_{j=1}^{m} \int_{D_{\mathbf{v}}} S^e_{ij}[\mathbf{M}, \mathbf{g}] d\mathbf{v},$$

$$\partial_t (\rho_i^0 \mathbf{U}_i^0) + \mathrm{Div}\Big(\int_{D_{\mathbf{v}}} \mathbf{v} \otimes \mathbf{v}\, M_{\rho_i^0, \mathbf{U}_i^0}\, d\mathbf{v} \Big) = O(\varepsilon^{q_i})$$

$$+\varepsilon^{q_i-1} \sum_{j=1}^{4} \int_{D_{\mathbf{v}}} \mathbf{v} \Big(G_{ij}[\mathbf{M}] - L_{ij}[\mathbf{M}] \Big) d\mathbf{v} + \varepsilon^{q_i+\delta_i-1} \sum_{h=1}^{4} \sum_{k=1}^{4} \int_{D_{\mathbf{v}}} \mathbf{v}\, S^i_{hk}[\mathbf{M}] d\mathbf{v}$$

$$+\varepsilon^{q_i-1} \sum_{j=1}^{m} \int_{D_{\mathbf{v}}} \mathbf{v} \Big(G^e_{ij}[\mathbf{M}, \mathbf{g}] - L^e_{ij}[\mathbf{M}, \mathbf{g}] \Big) d\mathbf{v} + \varepsilon^{q_i+\delta_i-1} \sum_{j=1}^{m} \int_{D_{\mathbf{v}}} \mathbf{v} S^e_{ij}[\mathbf{M}, \mathbf{g}] d\mathbf{v}.$$



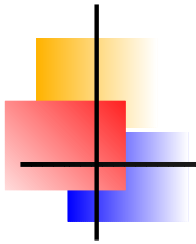
From Microscopic to Macroscopic

Case 1. $\delta_i \geq 0$ and $q_i > 1$: This is the simple conservative hyperbolic system:

$$\begin{cases} \partial_t \rho_i^0 + \operatorname{div}(\rho_i^0 \mathbf{U}_i^0) = 0, \\ \\ \partial_t(\rho_i^0 \mathbf{U}_i^0) + \operatorname{Div}\big(\rho_i^0(\mathbf{U}_i^0 \otimes \mathbf{U}_i^0) + P^0\big) = 0. \end{cases}$$

Case 2. $\delta_i > 0$ and $q_i = 1$: In this case we preserve a source term related to conservative actions, and therapy actions into the closed system:

$$\begin{cases} \partial_t \rho_i^0 + \operatorname{div}(\rho_i^0 \mathbf{U}_i^0) = \sum_{j=1}^4 \int_{D_{\mathbf{v}}} \Big(G_{ij}[\mathbf{M}] - L_{ij}[\mathbf{M}]\Big) d\mathbf{v} \\ \qquad\qquad + \sum_{j=1}^m \int_{D_{\mathbf{v}}} \Big(G_{ij}^e[\mathbf{M}, \mathbf{g}] - L_{ij}^e[\mathbf{M}, \mathbf{g}]\Big) d\mathbf{v}, \\ \\ \partial_t(\rho_i^0 \mathbf{U}_i^0) + \operatorname{Div}\big(\rho_i^0(\mathbf{U}_i^0 \otimes \mathbf{U}_i^0) + P^0\big) = \sum_{j=1}^4 \int_{D_{\mathbf{v}}} \mathbf{v}\Big(G_{ij}[\mathbf{M}] - L_{ij}[\mathbf{M}]\Big) d\mathbf{v} \\ \qquad\qquad + \sum_{j=1}^m \int_{D_{\mathbf{v}}} \mathbf{v}\Big(G_{ij}^e[\mathbf{M}, \mathbf{g}] - L_{ij}^e[\mathbf{M}, \mathbf{g}]\Big) d\mathbf{v}. \end{cases}$$



From Microscopic to Macroscopic

Case 3. $\delta_i = 0$ and $q_i = 1$: In this last case we preserve all the macroscopic information about the closed system, including proliferative, destructive interactions, and therapy actions:

$$
\begin{cases}
\partial_t \rho_i^0 + \operatorname{div}(\rho_i^0 \mathbf{U}_i^0) = \displaystyle\sum_{j=1}^{4} \int_{D_{\mathbf{v}}} \Big(G_{ij}[\mathbf{M}] - L_{ij}[\mathbf{M}] + \sum_{k=1}^{4} S_{jk}^{i}[\mathbf{M}] \Big) d\mathbf{v} \\
\qquad\qquad + \displaystyle\sum_{j=1}^{m} \int_{D_{\mathbf{v}}} \Big(G_{ij}^{e}[\mathbf{M}, \mathbf{g}] - L_{ij}^{e}[\mathbf{M}, \mathbf{g}] + S_{ij}^{e}[\mathbf{M}, \mathbf{g}] \Big) d\mathbf{v}, \\
\partial_t (\rho_i^0 \mathbf{U}_i^0) + \operatorname{Div}\big(\rho_i^0 (\mathbf{U}_i^0 \otimes \mathbf{U}_i^0) + P^0\big) \\
\qquad\qquad = \displaystyle\sum_{j=1}^{4} \int_{D_{\mathbf{v}}} \mathbf{v} \Big(G_{ij}[\mathbf{M}, \mathbf{g}] - L_{ij}[\mathbf{M}, \mathbf{g}] + \sum_{k=1}^{4} S_{jk}^{i}[\mathbf{M}] \Big) d\mathbf{v} \\
\qquad\qquad\qquad + \displaystyle\sum_{j=1}^{m} \int_{D_{\mathbf{v}}} \mathbf{v} \Big(G_{ij}^{e}[\mathbf{M}, \mathbf{g}] - L_{ij}^{e}[\mathbf{M}, \mathbf{g}] + S_{ij}^{e}[\mathbf{M}, \mathbf{g}] \Big) d\mathbf{v}.
\end{cases}
$$

From Microscopic to Macroscopic

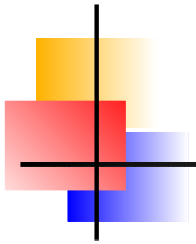
Theorem *Let* $\mathbf{f}^\varepsilon$ *verify*

$$\|\mathbf{f}^\varepsilon\|_{C(0,\infty;L^p(D_{\mathbf{x}}\times D_{\mathbf{v}}\times D_u))^4} \leq C < \infty$$

for some $p > 2$*, and such that each* f_i^ε *converges pointwise. We also assume that the microscopic state space has finite measure and that the probability densities* $\mathcal{B}_{jk}$*,* $\mathcal{C}_{jk}$*,* $\mathcal{B}^e_{jk}$ *and* $\mathcal{B}^e_{jk}$ *are bounded functions while the interactions rates* η_{ij} *and* η^e_{ij}*, intensity rates* p_{ij} *and* p^e_{ij} *and proliferation/destruction rates* μ^i_{ij} *are all square integrable with respect to their variables. Finally, we assume that* $\mu^1_{i,j}$ *and* $\mu^2_{i,j}$ *are continuous. Then, the pointwise limit of* $\mathbf{f}^\varepsilon$ *is the vector valued function* $\mathbf{M} = \{M^i_{\rho_i^0,\mathbf{U}_i^0}\}_{i=1}^4$ *given by hypothesis H.2. with*

$$\rho_i^0 = \lim_{\varepsilon\to 0}\rho[f_i^\varepsilon], \qquad \mathbf{U}[f_i^0] = \lim_{\varepsilon\to 0}\mathbf{U}_i^\varepsilon,$$

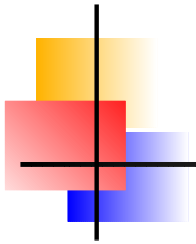
i.e., the weak and pointwise limits of the local density velocity of f_ε*. Moreover, in the three regimes introduced above, the limiting densities* ρ_i^0 *and velocities* $\mathbf{U}_i^0$ *verify the three case considered above.*



From Microscopic to Macroscopic

• Possibly, the mathematical structure we have seen refers a new class of equations. A rigorous framework is delivered for the derivation of models, when a mathematical description of cell interactions can be derived, by phenomenological interpretation, from empirical data. On the other hand, only when the above interactions are delivered by a theoretical interpretation delivered within the framework of biological sciences, then we may talk about a ***biological-mathematical theory***.

• The various theoretical approaches known in the literature postulate probabilistic models of gene expression, while gene interactions among genes and with the outer environments should be taken into account. Considering that a robust theory is not yet available, a conjecture is here proposed developing at the molecular scale some ideas already exploited at the cellular scale. This conjecture is proposed in what follows at a preliminary stage still waiting to be properly developed.



From Microscopic to Macroscopic

The interaction scheme from the lower to the higher scale can be represented as follows:

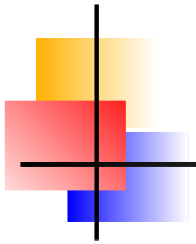
$$\Big[\mathcal{L}\,\varphi = \mathcal{N}[\varphi,\varphi] + \mathcal{M}[\varphi,\psi]\Big] \quad \rightarrow \quad \Big[\mathcal{L}\,\mathbf{f} = J[\mathbf{f}] + \mathcal{Q}[f,\varphi]\Big]\,,$$

that corresponds to the following dynamics:

• The evolution of the system at the lower scale is determined by the interaction between active particles within the population, and with particles of the outer environment.

• The evolution of the system at the higher scale is determined by the interaction between active particles, of both populations among themselves, and, for each of them, with particles of the lower system.

• A simplified approach consists in modelling the parameters of the equation at the cellular scale using the distance $d(\varphi,\varphi_0)$ of the distribution φ form the initial distribution φ_0.



From Microscopic to Macroscopic

Let us now consider the coupling with the lower scale, where the overall state is defined by the distribution function of gene expression:

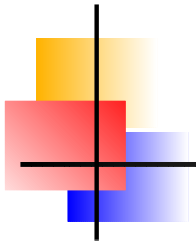
$$\varphi = \varphi(t, v) \; : \quad [0, T] \times D_v \; \rightarrow \; \mathbf{R}_+ \, ,$$

over the microscopic state $v \in D_v$ of the interacting entities regarded as active particles.

The system at the lower scale interacts with the outer environment, that has the ability of modifying the gene expression by an action of the type

$$\psi = \psi(t, v) \; : \; [0, T] \times \mathcal{D} \; \rightarrow \; \mathbf{R}_+ \, , \qquad \int_0^{\mathrm{T}} \int_{\mathcal{D}} \psi(\mathrm{t}, \mathrm{v}) \, \mathrm{dv} \, \mathrm{dt} \leq \mathrm{M} \, ,$$

for some constant M.



From Microscopic to Macroscopic

$$\begin{cases} \partial_t n = \mathrm{div}_{\mathbf{x}} \left(D_n \dfrac{n \nabla_{\mathbf{x}} n}{\sqrt{n^2 + \frac{D_n^2}{c^2} |\nabla_{\mathbf{x}} n|^2}} - n\chi \dfrac{\nabla_{\mathbf{x}} S}{\sqrt{1 + |\nabla_{\mathbf{x}} S|^2}} \right) + H(n, S), \\ \\ \partial_t S = \nabla_{\mathbf{x}} (D_S \cdot \nabla_{\mathbf{x}} S) + K(n, S), \end{cases}$$

where n and S denote, respectively, the density of the cells and of the chemoattractant