A Kinetic approach to Darwinian Dynamics

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Part I - The Complexity Features of Living Systems

From **Wikipedia**, the free encyclopedia:

Complex systems present problems both in mathematical modelling and philosophical foundations.
The study of complex systems represents a new approach to science that investigates how relationships between parts give rise to the collective behaviors of a system and how the system interacts and forms relationships with its environment.
....
The key problems of complex systems are difficulties with their formal modelling and simulation. From such a perspective, in different research contexts complex systems **are defined on the basis of their different attributes**.

Part I - The Complexity Features of Living Systems

N.Bellomo, H. Berestycki, F. Brezzi, and J.P. Nadal, *Mathematics and Complexity in Life and Human Sciences*, Mathematical Models and Methods in Applied Sciences, 2010.

N.Bellomo, *Modelling Complex Living Systems. A Kinetic Theory and Stochastic Game Approach*, (Birkhauser-Springer, Boston, 2008).

N.N. Taleb, *The Black Swan: The Impact of the Highly Improbable*, 2007.

G. Jona Lasinio , *La Matematica come Linguaggio delle Scienze della Natura,*
- Life represents and advanced stage of an evolutive and selective process. It seems to me difficult understanding living entities without considering their historical evolution. Population dynamics is based on a rather primitive mathematical theory, on the other hand it should explain the emergence of individual living entities by selection.

Part I - The Complexity Features of Living Systems

Five Common Features and Sources of Complexity

1. Ability to express a strategy: Living entities are capable to develop specific ***strategies*** and *organization abilities* that depend on the state of the surrounding environment.

2. Heterogeneity: The ability to express a strategy is not the same for all entities.

3. Learning ability: Living systems receive inputs from their environments and have the ability to learn from past experience.

4. Interactions: Interactions nonlinearly additive and involve immediate neighbors, but in some cases also distant particles.

5. Darwinian selection and time as a key variable: All living systems are evolutionary. For instance birth processes can generate individuals more fitted to the environment, who in turn generate new individuals again more fitted to the outer environment.

Emerging Behaviors and Model Validation

i) Models should be derived within mathematical structures suitable to include the aforesaid common features of living, hence complex, systems;

ii) The first step toward the validation of models consists in verifying that they describe quantitative results delivered in quasi steady states (corresponding to experiments) as an output of the dynamics at the micro-scale, without artificially inserting them into the model;

iii) The second step toward the validation of models consists in verifying that they describe, at least at a qualitative level, emerging collective behaviors observed in reality.

Evolutionary Dynamics

The tentative to link

cancer modeling to **evolutionary biology**

is one of the most challenging frontiers of the mathematical biology at the moment.

Populations of Reproducing Individuals Evolve

Genes, cells, ideas change over time but they do not evolve

Main Ingredients of Evolutionary Dynamics

Reproduction

Selection

Mutation

Random Drift

Spatial Movement

Main Ingredients of Evolutionary Dynamics

Reproduction:
to make copies of themselves

Selection:
different types of individuals compete each other -
the final output is a choice

Mutation:
to generate different types that can be evaluated in
the selection process (biological novelty and diversity)

Selection:

selection operates whenever different types of individuals reproduce at different rates

Mutation:

mutations are errors during reproduction - they arises when reproduction is not perfectly accurate

Fitness Landscape

Genotype of an organism: is the genomic sequence of the organism

Phenotype of an organism: is given by its shape, behavior, performance and any kind of ecological interaction
It determines the fitness (i.e. the reproduction rate) of the organism

There is a mapping from genotype to phenotype

There is another mapping from phenotype to fitness

The fitness landscape is a convolution of these two mappings

Evolutionary Game Theory

Game Theory: mathematical theory to study human behavior in strategic and economic decisions

Interaction between two players

how to maximize the payoff in a game given that no one knows what the other will do - rationality

Evolutionaty Game Theory: individuals have fixed strategies and they interact randomly with other individuals - no rationality

Evolutionary Game Theory

The payoff is interpreted as fitness

Success in the game is translated into reproductive success

Strategies that do well reproduce faster

Strategies that do poorly are outcompeted:
natural selection

Cooperation (prisoner's dilemma)

Evolutionary progress often requires the cooperation of simpler parts that are already available
Ex: replicating molecules had to cooperate to form the first cells

Cooperation: the donor pays a cost and the recipient gets a benefit

In evolutionary biology, cost and benefit are measured in terms of reproductive success

Open problem: how natural selection can lead from competition to cooperation

Natural selection choose defection: specific mechanisms are needed to favor cooperation

Finite populations

Stocastic formulation to describe:

- neutral drift: in a finite population with several different types, without mutations, eventually all but one type will be extinct

and

- neutral evolution: Evolutionary biologists typically distinguish two main types of natural selection: purifying selection, which acts to eliminate deleterious mutations; and positive (Darwinian) selection, which favors advantageous mutations. Positive selection can, in turn, be further subdivided into directional selection, which tends toward fixation of an advantageous allele, and balancing selection, which maintains a polymorphism. The neutral theory of molecular evolution predicts that purifying selection is ubiquitous, but that both forms of positive selection are rare, whereas not denying the importance of positive selection in the origin of adaptations.

Evolutionary dynamics of cancer

- Cancer is a disease of multicellular organism

- Cancer is a breakdown of cellular cooperation

- Cells continuously receive signals from other cells telling them that they are doing all right

- If these signal fail to arrive, then the default program for a cell is to commit suicide

- Apoptosis (programmed death) is d defense mechanism against cancer

- Cancer progression can be seen as a destructive evolution

- Mutation: any genetic modification in the differentiated cells

Evolutionary dynamics of cancer

- Cancer results if the equilibrium between cell birth and death is shifted toward uncontrolled proliferation

- During cell division there is a small probabilty that a mistake will be made during DNA replication

- The mutation might confer a fitness advantage, a fitness disadvantage or might not change the reproductive rate :
all of these mutations can represent steps towards cancer and are therefore disadvantageous for the organism

Cancer Immunoediting

The immune system plays at least three distinct roles in preventing cancer:

i) It protects the host against viral infection and hence suppresses virus-induced tumors;

(ii) it prevents the establishment of an inflammatory environment that facilitates tumorigenesis by eliminating pathogens and by prompt resolution of inflammation;

(iii) it eliminates tumor cells in certain tissues because nascent transformed cells often co-express ligands for activating receptors on innate immune cells and tumor antigens that are recognized by immune receptors on lymphocytes of the adaptive immune system. Cancer cells express antigens that differentiate them from their nontransformed counterparts

The Cancer Immunoediting Hypothesis

The cancer immunoediting process, in its most complex embodiment, proceeds sequentially through three distinct phases

- elimination

- equilibrium

- escape

Elimination

The elimination phase is best described as an updated version of cancer immunosurveillance:

the innate and adaptive immune systems work together to detect the presence of a developing tumor and destroy it before it becomes clinically apparent

coordinated and balanced activation of both innate and adaptive immunity is needed to protect the host against a developing tumor

If tumor cell destruction goes to completion, the elimination phase represents an endpoint of the cancer immunoediting process (but the elimination phase has not yet been directly observed in vivo)

the immune components required for effective elimination of any given tumor are dependent on specific characteristics of the tumor, such as how it originated (spontaneous versus carcinogen-induced), its anatomic location, and its rate of growth

Equilibrium

Rare tumor cell variants may survive the elimination phase and enter the equilibrium phase:

- the adaptive immune system prevents tumor cell outgrowth and also sculpts the immunogenicity of the tumor cells

- equilibrium can be the longest phase of the cancer immunoediting process perhaps extending throughout the life of the host

- it may represent a second stable endpoint of cancer immunoediting

- in equilibrium, the immune system maintains residual tumor cells in a functional state of dormancy, a term used to describe latent tumor cells that may reside in patients for decades before eventually resuming growth as either recurrent primary tumors or distant metastases

- equilibrium thus represents a type of tumor dormancy in which outgrowth of occult tumors is specifically controlled by immunity

Escape

Tumor cells that have acquired the ability to circumvent immune recognition and/or destruction emerge as progressively growing, visible tumors

progression from equilibrium to the escape phase can occur:

- because the tumor cell population changes in response to the immune systems editing functions

and/or

- because the host immune system changes in response to increased cancer-induced immunosuppression or immune system deterioration

The end result is the generation via a Darwinian selection process of poorly immunogenic tumor cell variants that become invisible to the immune system and thus acquire the capacity to grow progressively

Escape

Alternatively, escape may result from the establishment of an immunosuppressive state within the tumor microenvironment

Tumor cells can promote the development of such a state by producing immunosuppressive cytokines such as vascular endothelial growth factor (VEGF), transforming growth factorb (TGF-b), galectin, or indoleamine 2,3-dioxygenase (IDO) and/or by recruiting regulatory immune cells that function as the effectors of immunosuppression

Part II - On the Representation of the System

Identification of the **functional subsystems**: tumor cells are distinguished according to their progressive hallmarks, while the immune cells are characterized by the capability to recognize specific hallmarks.

1. $i = 1$ labels epithelial cells, whose selected function is the ability, supposed uniform for all cells, to feed proliferative phenomena. Proliferative events can generate cells with the same phenotype, but also cells with different phenotype toward the onset of cancer cells. It is supposed that the organism is a source of epithelial cells, so that their quantity can be regarded as constant in time;
2. $i = 2$ labels cells, generated by the first functional subsystem, that have the ability to thrive in a chronically inflamed micrenvironment;
3. $i = 3$ denotes the functional subsystem of cells, generated by the previous subsystem, that have the ability to evade the immune recognition;
4. $i = 4$ refers to cells that have acquired the ability of suppressing the immune reaction;

Identification of the **functional subsystems**

1. $i = 5$ labels cells of the innate immune system which have the ability to acquire, by a learning process, the capacity of contrasting the development of cancer cells;
2. $i = 6$ labels cells generated by the innate immune system, which have acquired the ability of contrasting the development of cancer cells labelled by $i = 2$, i.e. cancer cells from the first hallmark;
3. $i = 7$ labels cells of the immune system generated from the previous two subsystems, which have acquired the ability of contrasting the development of cancer cells labelled by $i = 3$, i.e. cancer cells from the second hallmark;
4. $i = 8$ labels cells of the immune system generated from the previous three subsystems, which have acquired the ability of contrasting the development of cancer cells labelled by $i = 4$, i.e. cancer cells from the third hallmark.

Bellouquid A., De Angelis E., Knopoff D., From the Modeling of the Immune Hallmarks of Cancer to a Black Swan in Biology, M3AS, 23, (2013) 949–978.

E. De Angelis, On the mathematical theory of post-Darwinian mutations, selection, and evolution, M3AS, 24, (2014) 2723–2742.

Part II - On the Representation of the System

Discrete representation of the activity variable:

$$I_u = \{0 = u_1, ..., u_j, ..., u_m = 1\},$$

with $u_j < u_{j+1}$, for $j = 1, \ldots m-1$. This variable is heterogeneously distributed and we assume that increasing values of the activity correspond to an increasing ability of the subsystem to express its biological function.
The overall state of the system is described by the **discrete probability distribution function**

(1) $$f_{ij} = f_{ij}(t), \quad i = 1, ..., 8\,, \quad j = 1, ..., m.$$

The index i labels each subsystem, j labels the activity variable, and $f_{ij}(t)$ represents the number of active particles from functional subsystem i that, at time t, have the state u_j. Therefore,

(2) $$n_i[f](t) = \sum_{j=1}^{m} f_{ij}(t), \quad i = 1, ..., 8$$

Part II - On the Representation of the System

The balance equation can be summarized as follows:

$$\frac{df_{ij}}{dt}(t) = C_{ij}[f](t) + P_{ij}[f](t) - D_{ij}[f](t) - L_{ij}[f](t), \tag{3}$$

for $i = 1, ..., 8$ and $j = 1, ..., m$, where J_{ij}, C_{ij}, P_{ij}, D_{ij} and L_{ij} are suitable operators acting over the whole set of probability densities. Specifically,

$C_{ij}[f](t)$ is the net flux, at time t, into the state u_j of the functional subsystem i, due to conservative interactions that only modify the micro-state;

$P_{ij}[f](t)$ is the gain, at time t, into the state u_j of the functional subsystem i, due to proliferative events;

$D_{ij}[f](t)$ is the loss, at time t, in the state u_j of the functional subsystem i, due to destructive events;

$L_{ij}[f](t)$ is the natural relaxation of the immune system at time t and in the state u_j of the functional subsystem i, to a given healthy state.

Part II - On the Representation of the System

The terms appearing in the right-hand side of the evolution equation (3) can now be detailed according to the following expressions:

$$C_{ij}[f] = \sum_{k=1}^{n}\sum_{p=1}^{m}\sum_{q=1}^{m} \eta_{ik}[f]\, \mathcal{B}_{ik}^{pq}(j)[f]\, f_{ip}\, f_{kq} - f_{ij} \sum_{k=1}^{n}\sum_{q=1}^{m} \eta_{ik}[f]\, f_{kq}, \tag{4}$$

$$P_{ij}[f] = \sum_{h=1}^{n}\sum_{k=1}^{n}\sum_{p=1}^{m}\sum_{q=1}^{m} \eta_{hk}[f]\, \mu_{hk}^{pq}(ij)[f]\, f_{hp}\, f_{kq}, \tag{5}$$

$$D_{ij}[f] = f_{ij} \sum_{k=1}^{n}\sum_{q=1}^{m} \eta_{ik}[f]\, \nu_{ik}^{jq}[f]\, f_{kq}, \tag{6}$$

for $i = 1, ..., 8$ and $j = 1, ..., m$, and

$$L_{ij}[f] = \lambda\,(f_{ij} - f_{ij}^{0}), \tag{7}$$

for $i = 5, \ldots 8$ and $j = 1, ..., m$, namely, in the natural relaxation terms of the evolution equations for the populations of the immune system, we have chosen as healthy state the initial value of the distributions, say f_{ij}^{0}.

Part II - On the Representation of the System

Denoting by the abbreviation hp-particle the meaning of particle belonging to the h-th functional subsystem with state u_p:

• η_{hk} is the encounter rate between the hp-candidate particle with the kq-field particle. It is assumed that it depends on the ability of interacting cells to recognize each other based on the distance between their states and distribution functions.

• $\mathcal{B}_{ik}^{pq}(j)$ is the transition probability density that the ip-candidate particle falls into the state j of the same functional subsystem after an interaction with a kq-field particle

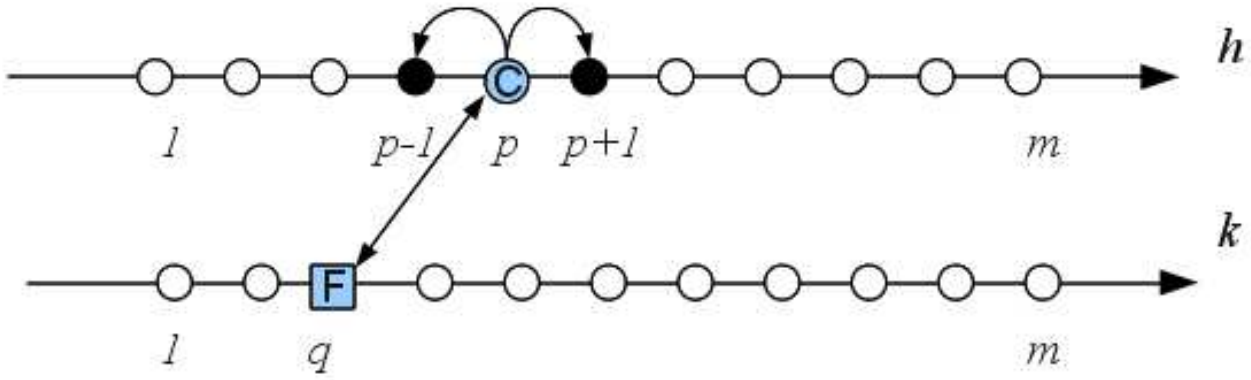


Figure 1: Dynamics of conservative interactions. A candidate particle from sybsystem h with state u_p can experiment a conservative interaction with a field particle from subsystem k. The output of the interaction can be u_{p-1}, u_p or u_{p+1}, depending on the kind of interaction the two are undergoing.

• $\mu_{hk}^{pq}(ij)$ models the net proliferation rate into the ij-state, due to interactions, occurring with rate η_{hk}, between the hp-candidate particle the kq-field particle.

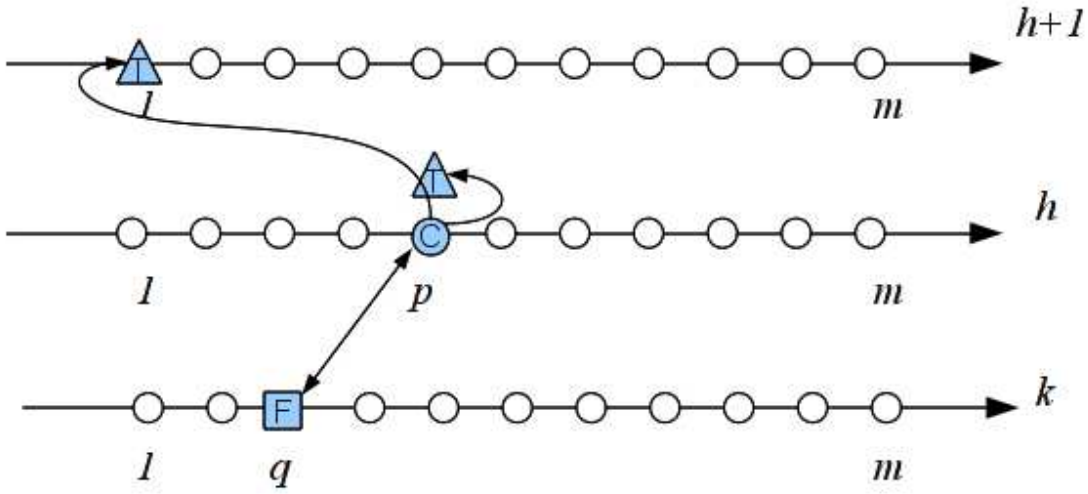


Figure 2: Dynamics of proliferative interactions. A candidate particle (mother cell) of functional subsystem h, by interacting with a field particle from population k, can proliferate a daughter cell, belonging either to the same functional subsystem with same state, or eventually to the following functional subsystem with the lowest activity value.

Interactions can induce net proliferative events, which may generate, although with small probability, a daughter cell that presents genetic modifications with respect to the mother cell.

In some cases, these different cells represent the first mutation toward the onset of cancer cells. If these cells have the ability to overcome the immune defence, then further mutations can occur toward progression and hallmarks of cancer.

The modeling approach is based on the idea that these mutations occur with higher probability when progression increases. The general framework is that of mutations and Darwinian selection.

• ν_{ik}^{jq} models the net destruction rate into the ij-state, due to interactions, occurring with rate η_{ik} between the ij-test particle and the kq-field particle. Interactions can induce net destructive events in the sense that the immune system has the ability to kill a cancer cell.

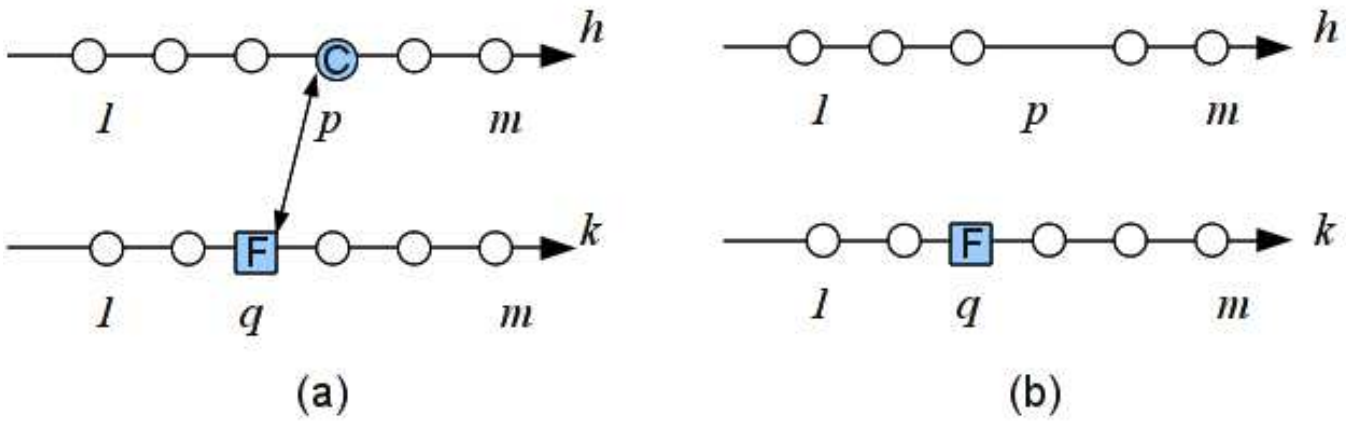


Figure 3: Dynamics of destructive interactions. A candidate particle from functional subsystem h with state u_p, interacting with a field particle from population k with state u_q, figure (a), can undergo a destructive action which occurs within the same state of the candidate particle, figure (b).

Part II - Modeling Strategy

• ***Encounter rate.*** The modeling of the encounter rate η_{hk} needs to take into account the specific functions and expressions of cells, also related to a learning process. Only encounters which lead to progression, mutations, and proliferation will be considered, being referred to a (positive) value η_0. This dimensionless parameter, small with respect to one, corresponds to interactions within the subsystem of epithelial cells, and can be included into the time scale. Taking into account the dependence of the encounter rate on the distance between the distribution functions, as already mentioned in section 2.3, we first introduce

$$(8)\quad \Psi_{hk}[f] = \begin{cases} \exp\left(-\tau \dfrac{||f_h - f_k||}{||f_h|| + ||f_k||}\right), & ||f_h||, ||f_k|| \neq 0, \qquad \tau > 0, \\ \\ 0, & ||f_h|| = ||f_k|| = 0, \end{cases}$$

for each pair of functional subsystems $(h,\, k)$.

Part II - Modeling Strategy

- *Encounter rate of functional subsystems* $h = 1, 2, 3, 4$ *with* $k = 1$. The rate of encounters between tumor and epithelial cells, increases with the hallmark h, as progressive hallmarks correspond to increasing activation to search nutrients for increasing proliferation:

(9) $$\eta_{h1} = \eta_0 \, h \, \Psi_{h1}[f], \quad \forall \; h = 1, 2, 3, 4.$$

On the other hand, it is assumed to be equal to zero for encounters involving only cancer cells: $\eta_{hk} = 0, \forall \; h, k = 2, 3, 4.$

- *Encounter rate of functional subsystems* $h = 5, 6, 7, 8$ *with* $k = 1, 2, 3, 4.$ Immune cells have the ability to identify cancer cells only if they have acquired, after a learning process, this specific ability. The following assumption is proposed:

(10) $$\eta_{hk} = \sigma \, \eta_0 \, \Psi_{hk}[f], \qquad \sigma > 0,$$

for each pair
$(h, \; k) = (5, 2), (6, 2), (6, 3), (7, 2), (7, 3), (7, 4), (8, 2), (8, 3), (8, 4).$

Part II - Modeling Strategy

• ***Transition probability density.*** Progression phenomena refer to an increasing activity within the same functional subsystem. This dynamics is modeled by the terms $\mathcal{B}_{ik}^{pq}(j)$. Only interactions with encounter rate different from zero are considered:

- *Interactions involving functional subsystems* $h = 1, 2, 3, 4$ *with* $k = 1$. Epithelial and cancer cells can increase their state only after an interaction with epithelial cells. Probability of transition is assumed to decrease with the activity state of the candidate particle:

$$\mathcal{B}_{h1}^{pq}(j) = \begin{cases} \alpha\,(1-u_p), & j = p+1, \quad \alpha > 0, \\ 1-\alpha\,(1-u_p), & j = p, \\ 0, & \text{otherwise.} \end{cases} \tag{11}$$

Part II - Modeling Strategy

- *Interactions of functional subsystem* $h = 1$ *with* $k = 2, 3, 4$. Epithelial cells are assumed to feed progression of cancer cells without changing their own state: $\mathcal{B}_{1k}^{pq}(p) = 1$.

- *Interactions of functional subsystems* $h = 5, 6, 7, 8$ *with* $k = 2, 3, 4$. Immune cells acquire progressively the ability to identify functional subsystems of tumor cells. As a consequence, immune cells may increase their state and the probability of progression decreases with increasing p-th state:

$$\mathcal{B}_{52}^{pq}(j) = \mathcal{B}_{62}^{pq}(j) = \mathcal{B}_{73}^{pq}(j) = \mathcal{B}_{84}^{pq}(j) = \begin{cases} \alpha\,(1 - u_p), & j = p + 1, \\ 1 - \alpha\,(1 - u_p), & j = p, \\ 0, & \text{otherwise.} \end{cases} \tag{12}$$

- *Interactions between cancer cells from* $h = 2, 3, 4$ *with* $k = 5, 6, 7, 8$. It is assumed that these types of interactions do not induce biological events to cancer cells.

Part II - Modeling Strategy

• ***Mutation events.*** These are rare events, related to the rate η_{hk}, where generation of a daughter cell occurs in a functional subsystem different from that of the mother cells. This event is modeled by the term $\mu_{hk}^{pq}(ij)$, where $i = h + 1$ with output into the state $j = 1$:

- *Mutations from cancer subsystems* $h = 1, 2, 3$. These are related to encounters with the first functional subsystem $k = 1$:

$$\mu_{h1}^{pq}(ij) = \begin{cases} \varepsilon_1 \, u_p, & i = h+1, \, j = 1, \quad \varepsilon_1 > 0, \\ 0, & \text{otherwise.} \end{cases} \tag{13}$$

Part III - Modeling Strategy

- *Mutations from immune subsystems* $h = 5, 6, 7$. These are related to an increasing capability of the immune cells to recognize a specific hallmark:

$$\mu_{52}^{pq}(6j) = \begin{cases} \varepsilon_{26}\, u_p, & j = 1, \quad \varepsilon_{26} > 0, \\ 0, & \text{otherwise.} \end{cases} \tag{14}$$

$$\mu_{63}^{pq}(7j) = \begin{cases} \varepsilon_{27}\, u_p, & j = 1, \quad \varepsilon_{27} > 0, \\ 0, & \text{otherwise.} \end{cases} \tag{15}$$

$$\mu_{74}^{pq}(8j) = \begin{cases} \varepsilon_{28}\, u_p, & j = 1, \quad \varepsilon_{28} > 0, \\ 0, & \text{otherwise.} \end{cases} \tag{16}$$

Part II - Modeling Strategy

• ***Proliferative events.*** Proliferation occurs within the same functional subsystem with rate η_{hk} being modeled by the term $\mu_{hk}^{pq}(ij)$, where $i = h$ and $j = p$:

- *Proliferation in cancer subsystems* $h = 2, 3, 4$. Proliferation increases with the hallmarks of cancer cells, due to the resulting deregulated proliferation program which is an acquired capability of tumor cells:

$$\mu_{h1}^{pq}(hj) = \begin{cases} \beta_1\, h\, u_p, & j = p, \quad \beta_1 > 0 \\ 0, & \text{otherwise.} \end{cases} \tag{17}$$

- *Proliferation in immune cells subsystems* $h = 6, 7, 8$. Immune cells proliferate due to encounters with cells up to the identified tumor subsystems:

$$\mu_{hk}^{pq}(hj) = \begin{cases} \beta_2, & j = p, \quad \beta_2 > 0 \\ 0, & \text{otherwise.} \end{cases} \tag{18}$$

for each pair $(h,\, k) = (6, 2), (7, 2), (7, 3), (8, 2), (8, 3), (8, 4)$.

Part III - Modeling Strategy

• ***Destruction rate.*** Destructive terms concern only cancer and immune cells. Immune cells have the ability to suppress cancer cells that are identified by them. It is assumed that this ability increases with increasing activity of immune cells:

(19) $$\nu_{26}^{pq} = \nu_{27}^{pq} = \nu_{28}^{pq} = \nu_{37}^{pq} = \nu_{38}^{pq} = \nu_{48}^{pq} = \gamma\, u_q, \quad \gamma > 0.$$

Encounter rates are symmetric: $\eta_{hk} = \eta_{kh}, \forall\ h, k, p, q$. However, the other interaction terms do not have this property due to lack of reversibility.

Part III - Modeling Strategy

The biological meaning of the parameters introduced in the model are here summarized: η_0, σ, τ: refer to interaction rates

α: is a parameter of the probability density in conservative progressions

$\varepsilon_1, \varepsilon_{26}, \varepsilon_{27}, \varepsilon_{28}$: model the mutation rate for cancer and immune cells

β_1, β_2: model the proliferation rate for cancer and immune cells

γ: refers to suppression rate

λ: refers to the relaxation of the immune system

Part II - Qualitative Analysis

Initial value problem:

$$\text{(20)} \qquad \begin{cases} \dfrac{df_{ij}(t)}{dt} = J_{ij}[f](t), \\ \\ f_{ij}(0) = f^0_{ij}, \end{cases}$$

where $J_{ij}[f](t) = C_{ij}[f](t) + P_{ij}[f](t) - D_{ij}[f](t) - L_{ij}[f](t)$, for $i = 1, ..., n$ and $j = 1, ..., m$, and $f = \{f_{ij}\}$,
M_{nm} be the set of real $n \times m$ matrixes with the 1-norm

$$\text{(21)} \qquad \| f \|_1 = \sum_{i=1}^{n} \sum_{j=1}^{m} |f_{ij}|, \qquad f = \{f_{ij}\} \in M_{nm}.$$

$X = C_b([0, +\infty); M_{nm})$ be the linear space of the matrix-valued bounded and continuous functions $f = f(t) : [0, +\infty) \to M_{nm}$ equipped with the infinity norm $\| f \|_\infty = \sup_{t \in [0, +\infty)} \| f \|_1$.
$(X, \| \cdot \|_\infty)$ is a real Banach space

Assumption H.1. In section 2.3, $\mathcal{B}_{ik}^{pq}(j)$ is defined as a transition probability density, and this implies that is such that

$$\sum_{j=1}^{m} \mathcal{B}_{ik}^{pq}(j)[f] = 1, \quad \forall i,k = 1,...,n\,, \quad \forall p,q = 1,...,m.$$

Assumption H.2. There exists $C_\eta > 0$ such that

$$0 < \eta_{ik}[f] \leq C_\eta, \quad \forall i,k = 1,...,n.$$

Assumption H.3. Both the encounter rate $\eta_{ik}[f]$ and the transition probability $\mathcal{B}_{ik}^{pq}(j)[f]$ satisfies that there exist constants L_1, L_2 such that:

$$(22) \qquad \mid \eta_{ik}[f] - \eta_{ik}[g] \mid \leq L_1 \frac{\parallel g_i - f_i \parallel + \parallel g_k - f_k \parallel}{\parallel g_i \parallel}, \quad \forall f,g \in M_{nm},$$

and

$$(23) \mid \mathcal{B}_{ik}^{pq}(j)[f] - \mathcal{B}_{ik}^{pq}(j)[g] \mid \leq L_2 \frac{\parallel g_i - f_i \parallel + \parallel g_k - f_k \parallel}{\parallel g_i \parallel}, \quad \forall f,g \in M_{nm},$$

for all $i,k = 1,.....,n$ and $j,p,q = 1,....m$.

Part III - Qualitative Analysis

Theorem:
Let Assumptions H.1, H.2, H.3 hold, and let $f_0 \in M_{nm}$.
Then there exists T such that if $t \leq T$, there exists a strictly positive constant a such that the problem (20) admits a unique non-negative global solution $f \in X_T$ satisfying the following estimate:

(24) $$\| f(t) \|_1 \leq a \| f_0 \|_1, \quad t \in [0, T].$$

The smallness condition on the initial condition can be avoided by using the parameter λ large enough and the result can be stated as follows:

Part III - Qualitative Analysis

Theorem:
Let Assumptions H.1, H.2, H.3 hold, and let $f_0 \in M_{nm}$. Then there exists λ^0 such that if $\lambda \geq \lambda^0$, there exists a strictly positive constant a such that the problem (20) admits a unique non-negative global solution $f \in X$ satisfying the following estimate:

(25) $$\| f(t) \|_1 \leq a \| f_0 \|_1, \quad t \in (0, \infty).$$

Part III - Qualitative Analysis

Coming back to our model, i.e. Eq.s (3)-(7) and $n = 8$, due to the fact that we have $L_{ij}[f](t) = 0$ for $i = 1, \ldots, 4$ and $\forall j = 1, ..., m$, we obtain the following local existence theorem:

Let Assumptions H.1, H.2, H.3 hold, and let $f_0 \in M_{nm}$. Then there exists T such that if $t \leq T$, there exists a strictly positive constant a such that the problem (20) admits a unique non-negative global solution $f \in X_T$ satisfying the following estimate:

(26) $$\| f(t) \|_1 \leq a \| f_0 \|_1, \quad t \in [0, T].$$

Part IV - Emerging Behaviors

A preliminary numerical analysis:

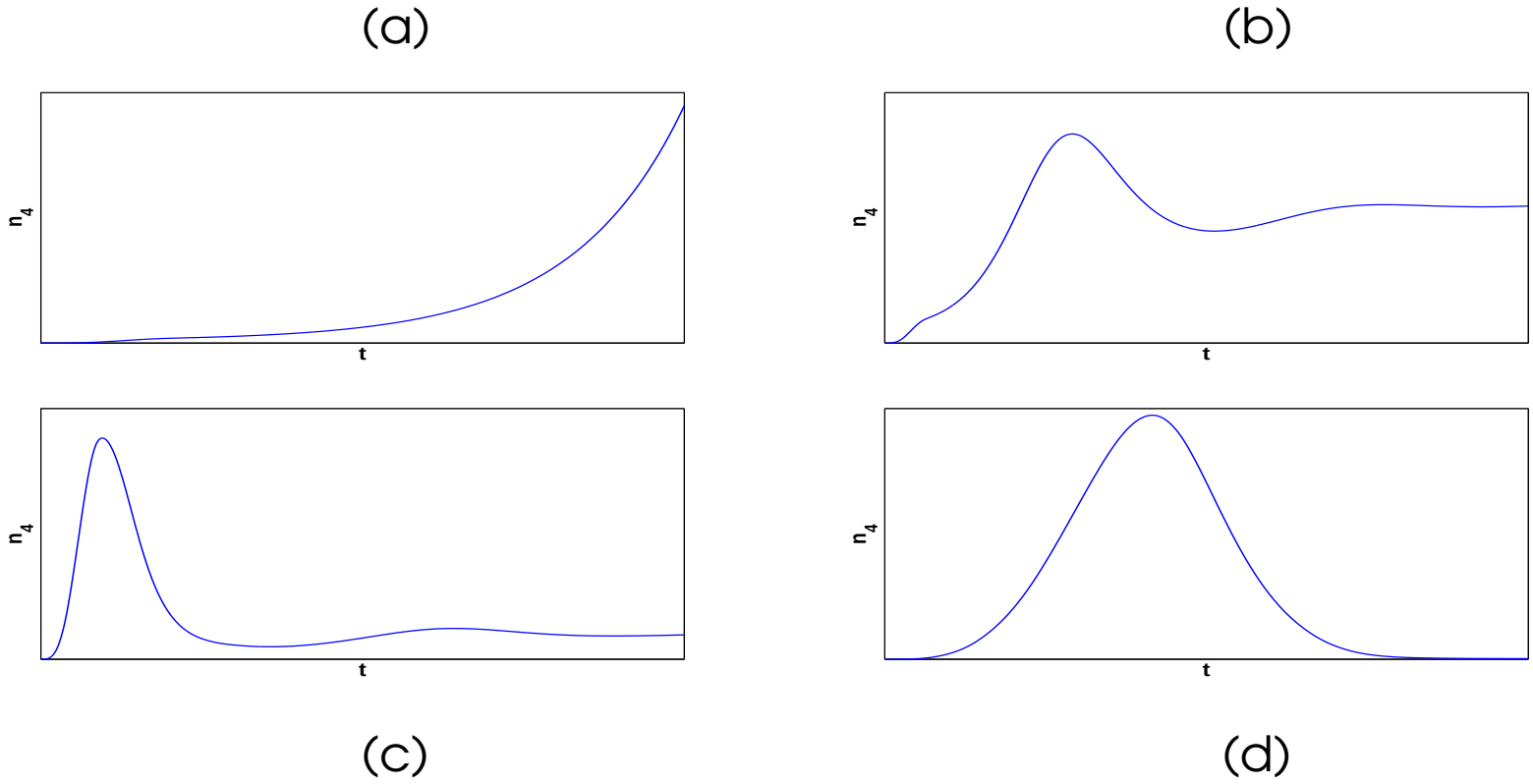
ε_1: model the mutation rate for cancer subsystems h = 1, 2, 3 related to encounters with the first functional subsystem k = 1

ε_{28}: model the mutation rate for immune cells from h=7 to h=8

if there exists a critical value $\varepsilon_c = \frac{\varepsilon_1}{\varepsilon_{28}}$ such that for $\varepsilon < \varepsilon_c$ the immune system has the ability to prevent the growth of cancer cells, namely cells of the fourth functional subsystem, while for $\varepsilon > \varepsilon_c$ the opposite behavior is depicted.

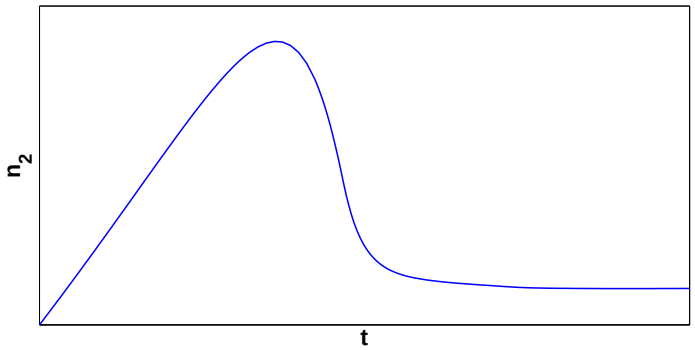
The objective of the simulations aims at depicting the following emerging behaviors: *cancer cells cannot be suppressed for low values of the said parameter. Therefore these will end up to aggregate into compact multicellular structures, while for high values immune cells have the ability to learn the presence of cancer cells, which are progressively depleted.*

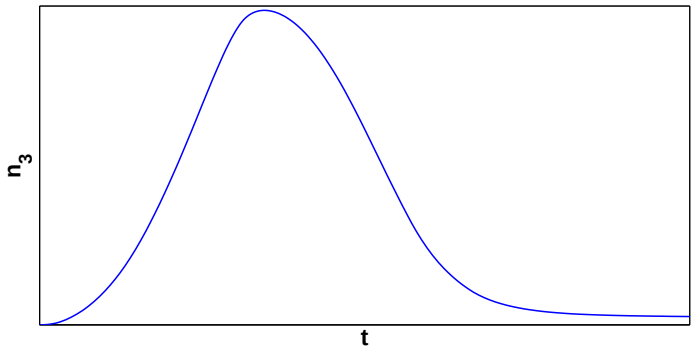
Part IV - Emerging Behaviors



Evolution of the density of functional subsystem 4 for different (increasing) values of parameter ε_{28}: number density of cancer cells of the last hallmark have an increasing behavior (a), as the immune cell is not able to deplete them, while an asymptotic value is reached for increasing value (c): a latent situation is reached. Finally, for greater values cancer cells are suppressed (d).

Part IV - Emerging Behaviors





Number density of preceding hallmarks after a temporary increase decay due to the selection of cells of the highest hallmark.

The **rare event** is the growth of cancer cells, which is generated by a mutation into the highest hallmarks where the immune cells have not anymore the ability to identify the presence of cancer cells and suppress them. As we have seen, it is a Darwinian selective process ruled by cellular properties, and specifically on the mutation rate. Hence the **rare event** is related to a mutation that is already a rare event which can cause disaster for the vertebrate carrier of such mutation.

Living entities/outer environment

A further development:

an analysis of the interactions between living entities and the **external environment** surrounding them

More fitted entities can proliferate and expand, while less fitted ones may slowly disappear

The dynamics generates the extinction of some populations and the survival of others. In some cases, survival might even mean an excess of proliferation, as occurs in genetic diseases

Interactions can, in some cases, also modify the evolution of the environment: it is expected that some of the said new subsystems may disappear due to their limited adaptability to the other subsystems, while some of them may develop by taking advantage of the others.

Living entities/outer environment

Referring to the phenomenological description presented before, let us consider a large system of individuals called active particles with their individual state called activity:
this corresponds to genotype-phenotype expression.

The individuals corresponding to the same expressions are assembled into functional subsystems, where the common tract is viewed as a functional expression that aims at survivance.

The activity within the population is the micro-state, which is heterogeneously distributed, while the description of the overall state of the system is delivered by suitable distribution functions over the said micro-state.

Living entities/outer environment

Representation of the **inner system**:
The inner system is constituted by active particles and is decomposed into functional subsystems labeled by the subscripts i = 1, . . . , n, each related to a different activity corresponding to different phenotype expressions: f_i

Representation of the **outer system**:
The outer system is constituted by agents, called active agents, and is decomposed into agents functional subsystems labeled by the subscript j = 1, . . . , n, each identified by a different activity corresponding to an ability to interact with the activity of each functional subsystem of the inner system, for instance ability to acquiring feeding and environmental well being: g_j

Living entities/outer environment

A formal mathematical structure defines the balance of the number of active particles and agents in the elementary volume of the space of the micro-state as follows:

$$
(27)\quad \begin{cases} \partial_t f_i(t,u) = C_i[\mathbf{f}](t,u) + P_i[\mathbf{f},\mathbf{g}](t,u) - \lambda_i[f_i](f_i - \widetilde{f}_i)(t,u), \\ \\ \partial_t g_j(t,w) = C_j^e[\mathbf{g}](t,w) + P_j^e[\mathbf{g},\mathbf{f}](t,w) - \lambda_j^e[g_j](g_j - \widetilde{g}_j)(t,w), \end{cases}
$$

where C_i and C_j^e (P_i and P_j^e) model the net flux of particles that, due to conservative (proliferative/destructive) interactions, fall into the elementary volume $[u, u+du]$ and $[w, w+dw]$ of each functional subsystem of active particles and agents, respectively, while λ_i and λ_j^e refer the natural decay of each functional subsystem toward a level distribution.

Living entities/outer environment

$\rightarrow$ The micro-scale interactions are modeled by theoretical tools of game theory: **consensus, competition, learning, escaping**

$\rightarrow$ Interaction rules are generally governed by a **distance** between the interacting particles or agents:
– models often assume that such a distance is constant in time or evolves according to well prescribed rules

– recent studies on the dynamics of wealth distribution have proposed models where the distance evolves in time related to competitions at the macro-scale level

– this feature induces significant modifications of the emerging behaviors foreseen by models

– therefore an additional analysis focused on its influence of Darwinian dynamics is definitely worth to be studied

Living entities/outer environment

An efficient way to investigate the predictive ability of models refers to their ability to depict a variety of **emerging behaviors**, which can be observed at a qualitative level

Some of the emerging behaviors can be classified as **rare and not predictable** event: the need of including this type of investigation in Darwinian dynamics is referring to the onset and development of cancer cells, namely to their evolutionary features

An important focus refers to the detection of early signals (early-warning signals for critical transitions), which allow to understand when these specific events can appear in time

What mathematical models should foresee

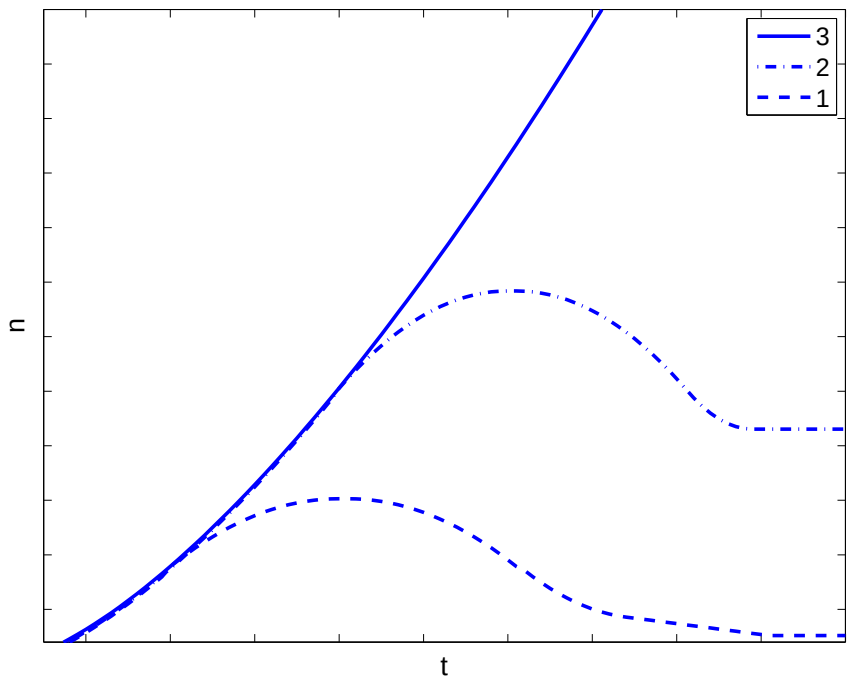
The validation of models of the dynamics of living, hence complex, systems is based on their ability to predict emerging behaviors:

1. Starting from the dynamics of the inner and outer systems, interactions should lead to modifications of the probability distribution over the activity variable of each system.
2. New subsystems are generate by this interaction. The following asymptotic behaviors should be foreseen:
   i) Progressive suppression, might be after an initial growth, of the subsystems which are not well fitted with respect to the environment;
   ii) Asymptotic equilibrium with the environment such that the number of individuals in each functional subsystem remains constant.
3. Indefinite growth of the size (number) in one or more functional subsystem.

Here each behavior corresponds to a different population related to successive mutations.

The ordinate reports the number density where in the first mutation the number density can even tend to zero after an initial growth, after the second mutation an asymptotic value is reached, while the third one shows a monotone growth.

The first and second mutation show the effect of the immune system, while the third one shows that the immune system has lost its ability as mutated cells have acquired the ability to escape the immune defence



Here the dynamics when the outer environment can act, by means of specific, therapeutical actions which improve the ability of immune cells to "learn" the presence of mutated cancer cells. Then, the action of the immune system can even deplete cells in advanced mutations

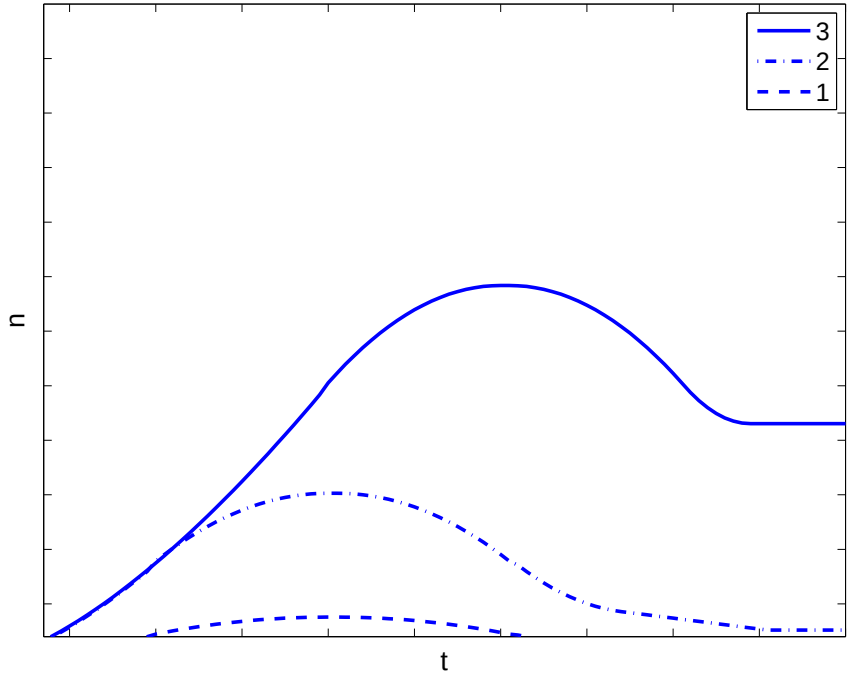


Figure 4: Evolution of a number density corresponding to successive mutations, taking into account the outer environment.

What is still missing ?

A complete multiscale analysis where the micro-scale, namely that of cells selected for the modeling approach, is linked to the dynamics at the lower molecular scale of cells as well as to the macro-scale of tissues.

A research perspective:

aspects of Darwinian dynamics similar to those studied in the preceding sections can be observed, and hence modeled, also in fields different from those of biology such as economy and social sciences.
In fact, modern approaches aim at understanding the role of human behaviors at the micro-scale on the overall dynamics of systems being aware that individual, in some cases irrational, behaviors can induce large deviations.