On the mathematical theory of living systems II: The interplay between mathematics and system biology

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\section*{ABSTRACT}

This paper aims at showing how the so-called mathematical kinetic theory for active particles can be properly developed to propose a new system biology approach. The investigation begins with an analysis of complexity in biological systems, continues with reviewing a general methodology to reduce complexity and furnishes the mathematical tools to describe the time evolution of such systems by capturing all their features.

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\section*{1. Aims and plan of the paper}

The emerging area of system biology aims at understanding biological systems at system level [1].

For this relatively new field of biology, the behavior of a system cannot be explained by its components alone but it is necessary to examine the cellular dynamics and the mechanism processes. Thus, in order to understand biological systems, the interactions between components need to be studied and the way in which they give rise to the behavior of the whole system has to be analyzed.

The aim of this paper is to propose a new system biology approach, by means of the kinetic theory for active particles [2]. In a recent paper [3], a critical analysis of the development of this theory has been presented, with the aim to capture the peculiar characteristics of the evolution of living systems, possibly toward a mathematical theory of evolution. This goal can be achieved by transferring the phenomenological analysis offered by anthropologists [4–6] into the formal description offered by equations derived within the framework of mathematical sciences.

The critical discussion that followed [3] has put in evidence [7–12] that the interplay between mathematics and biology should be focused on the complexity features of living systems. In other words, mathematics should be able to retain, as far as possible, this crucial aspect. The latter appears as an obliged passage to pursue the objective of what is considered one of the greatest scientific revolutions that will hopefully characterize this century, namely the mathematical formalization of biology [13]. This effort definitely needs a great deal of research activity and human energy considering that it has to overcome the conceptual difficulties of the lack of first principles, as critically analyzed in various papers ([14–16] among others).

Although the present state-of-the-art is still far from the aforementioned ambitious objective, any contribution, to even small progresses in that direction, is a challenging opportunity for applied mathematicians. This is the objective of this paper, that is devoted to design a modeling approach and to identify the mathematical tools that can be achieved to deal with it.

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The sequential steps of the approach, as we shall see, are the following.

(i) Assessment of the complexity features of biological systems in general, followed by the development of a mathematical structure suitable to retain the aforementioned features.
(ii) Identification of the scales that are appropriate to represent the specific system under consideration.
(iii) Development of a system biology approach, whose first step is the decomposition of the overall system into functional subsystems.
(iv) Derivation of the mathematical tools suitable to model, at each scale, the dynamics of the functional subsystems.
(v) Modeling the interactions among the various components of the overall system, taking into account the networks and the multiscale aspects of their connection.

The above project follows [17], where general topics on complexity and mathematical tools were presented. The contents are organized as follows. Section 2 is devoted to the identification of the complexity features of living, and hence complex, systems. Section 3 reports the mathematical structure given by the kinetic theory for active particles [2] able to model such kind of systems and examines its consistency with the aforementioned key features. Section 4 focuses on the main objective of this paper, that is to propose the guidelines to develop a modeling approach for biological systems. Hence, at first a general methodology to reduce the complexity is presented, and then appropriate mathematical tools are introduced. Section 5 critically analyzes discrete setting of the variables at the microscopic scale. The aim is twofold, namely, as a computational tool and as an approach to model genetic mutations. Section 6 looks ahead to research perspectives starting from a deep insight to multiscale issues and following by some speculations related to conceivable paths to develop a mathematical theory for biological systems.

2. On the complexity of biological systems

Biological systems are very different from the physical ones. In fact, while the latter are composed by many copies of few elements, the former ones are constituted by a large variety of components: biological systems contain from millions to a few copies of each of thousands of different elements, and this is one of the most important characteristic of such systems.

They are constituted by living entities which have the ability to develop a specific strategy and an organizing ability, depending on the state of the surrounding environment. This strategy can be expressed without the application of any external organizing principle and depends on the search of individuals for their best fitness, sometimes just for their survival. In various cases such a skill evolves in time. In fact, living systems receive inputs from the environment and have the ability to learn from past experience, in order to adapt themselves to the changing-in-time external conditions [6]. This strategy is not the same for all entities. Indeed, heterogeneity characterizes a great part of living systems. Interacting entities can appear and behave different to many extent, even though they share the same molecular structure, for instance due to different phenotype expression generated by the same genotype. Moreover, living entities typically operate out-of-equilibrium. For example, a constant struggle against the environment is developed to remain in a particular out-of-equilibrium state, namely stay alive [18].

Interactions contribute to the development of the aforementioned strategy. These are nonlinear and involve immediate neighbors, but in some cases also distant entities. This is what happens at the level of cells, which have the ability to communicate by signaling and can choose different observation paths within networks that evolve in time. Living entities play a game at each interaction with an output that is technically related to their strategy often associated to the surviving and the adaptation ability.

The presence of this strategy produces mutations and selections given by destructive and/or proliferative events. Moreover, all living systems are evolutionary: birth processes can generate individuals that fit better the outer environment, which in turn generate new ones fitting better and better.

In conclusion, such kind of systems present a great complexity and if we want to model them we must handle this aspect. From a mathematical point of view, the complexity is translated in a large number of variables, and hence in a large number of equations able to describe the overall system. On the other hand, this implies an high computational effort. Consequently, to model such kind of systems at first we have to reduce this complexity.

An additional difficulty arises when we observe that the study of biological systems needs a multiscale approach. For instance, the dynamics at the molecular (genetic) level determines the cellular behaviors; moreover, the structure of macroscopic tissues depends on such dynamics.

In the following section, we will see that a modeling approach for these kind of systems is actually possible. As already mentioned, the first step will be to reduce complexity, while the second one will be to specialize a mathematical structure able to model such systems.

3. On the kinetic theory for active particles

This section deals with the mathematical approach we follow to describe the evolution in time of the biological systems under consideration. More precisely, the mathematical method we will adopt is that suggested by the kinetic theory for active particles, briefly the KTAP theory.
Introduced in [2] and further developed in [19,20], such a theory allows to model living systems characterized by the following five features.

(i) The system is made up of a large number of interacting entities, called active particles, whose physical microscopic state is described by a set of variables. Among the others, a variable called activity represents the individual ability to express a specific strategy.

(ii) The activity variable is heterogeneously distributed over the active particles. This means that the entities can differ even if they have the same structure. Interactions modify the state of the particles, while the strategy they express can be modified by the shape of their heterogeneous distribution.

(iii) Interactions involve not only immediate neighbors (short range interactions) but also the distant ones (long range interactions). Indeed, living systems communicate each other directly or through media. Consequently, each entity interacts with all the others in a domain whose elements are able to communicate. In some cases, such a domain is identified with the visibility zone, in other cases with a communication network.

(iv) Interactions are complex, namely the overall output of the game that an active particle plays with the ones lying in its interaction domain is not the linear superposition of its separated interactions with all of them, but a complex combination whose form depends on the strategy that all particles can develop.

(v) The output of the game modifies the activity of interacting particles and may also generate, in the proliferative process, particles with a different structure (for instance, entities with a different phenotype).

The KTAP theory has been applied by various authors to model complex systems in life sciences, for instance in immune competition [21–25], social dynamics [26], spread of epidemics [27,28], interpretation of clinical data [29], and many others. These modeling approaches are based on linearly additive interactions but recently the modeling of nonlinear interactions has been investigated [30] and applied to vehicular traffic [31] and crowd dynamics [32].

In order to model living systems, the KTAP theory requires at first that all particles expressing the same strategy are organized in the same functional subsystem. Consequently, the system under consideration is divided into subsystems that, from now on, we assume to be in number of $n$. For each of them, a probability distribution function is introduced

$$f_i = f_i(t, u) : [0, T] \times D_u \rightarrow \mathbb{R}, \quad i = 1, \ldots, n$$

(3.1)

where the index $i$ denotes the subsystem and $u \in D_u$ is the activity variable. The quantity $f_i(t, u)du$ represents the number of particles whose state, at time $t$, is in the elementary volume $[u, u + du]$ and consequently,

$$v_i(t) = \int_{D_u} f_i(t, u) du, \quad i = 1, \ldots, n$$

(3.2)

gives the number of active particles in the $i$-th subsystem. Moreover if $f_i$ is known, the following quantities [33], called activation and activation density, respectively,

$$a_i = a[f_i](t) = \int_{D_u} u f_i(t, u) du, \quad A_i = A[f_i](t) = \frac{a[f_i](t)}{v_i(t)}$$

(3.3)

can be evaluated.

If the system is subject to external actions applied by $m$ agents, the KTAP theory suggests to introduce, in addition to $f_i$, the distribution functions

$$g_k = g_k(t, u) : [0, T] \times D_u \rightarrow \mathbb{R}, \quad k = 1, \ldots, m$$

to model the action from the outer environment. The external agents, whose action is supposed to be known, are regarded as a specific population with the ability to interact with active particles of the inner system and influencing their state.

In the following subsection, we shall give the equations describing the time evolution of the distribution functions $f_i$ and in Section 3.2 we will see the reasons why the proposed mathematical structure is able to model the biological system.

We conclude this paragraph by examining some properties of the inner and outer interactions we will consider. Interactions involve three different types of particles, namely test, candidate and field particles with activity $u$, $u_*$, and $u^*$, respectively and work as follows: candidate particles can acquire in probability the state of the test particle after an interaction with field particles, while test particles lose their state. Moreover, we assume that interactions are non-linear, involve only particles which are in the interaction domain $D_u$ of the test particle and can be both conservative (i.e. they modify only the state of the particles) and non-conservative (i.e. they produce proliferative and/or destructive events).

3.1. Mathematical structures

The mathematical structure able to describe the time evolution of the distribution functions $f_i$ consists in the following system of partial integro-differential equations [34]:

$$\partial_t f_i(t, u) = Q[u][f] = f_i[\mathbf{f}](t, u) + J^u[f, \mathbf{g}](t, u), \quad i = 1, \ldots, n,$$

(3.4)
where \( f = (f_1, \ldots, f_n) \) and \( g = (g_1, \ldots, g_m) \) are the distribution function vectors of the active particles and of the external agents, respectively, \( Q_f[f] \) is the net flux of particles that fall into the elementary volume \( [u, u + du] \) of the space of the microscopic states and \( j^f[f, g] \) and \( j^g[f, g] \) model the interactions of particles within the closed system and with the outer ones, respectively.

The formal expression of the terms appearing at the right-hand side of system (3.4) is:

\[
j_{ij}[f](t, u) = C_{ij}[f](t, u) + P_{ij}[f](t, u)
\]

with

\[
C_{ij}[f](t, u) = \sum_{j=1}^{n} \int_{D_u \times D_u} \eta_{ij}(u_+, u^*|f(t, u_+), f_j(t, u^*)) B_{ij}(u_+ \rightarrow u|u_+, u^*, A_i(t)) f_i(t, u_+) f_j(t, u^*) \, du_+ \, du^* - f_i(t, u) \sum_{j=1}^{n} \int_{D_u} \eta_{ij}(u, u^*|f(t, u), f_j(t, u^*)) f_j(t, u^*) \, du^*,
\]

\[
P_{ij}[f](t, u) = \sum_{h=1}^{n} \sum_{j=1}^{n} \int_{D_u \times D_u} \eta_{ij}(u_+, u^*|f_i(t, u_+), f_j(t, u^*)) \mu_{ij}^u(u_+) \rightarrow u|u_+, u^*, A_i(t)) f_i(t, u_+) f_j(t, u^*) \, du_+ \, du^*,
\]

and

\[
j_{ij}^g[f, g](t, u) = C_{ij}^g[f, g](t, u) + P_{ij}^g[f, g](t, u),
\]

with

\[
C_{ij}^g[f, g](t, u) = \sum_{k=1}^{m} \int_{D_u \times D_w} \eta_{ik}^g(u_+, \omega^*|f_i(t, u_+), g_k(t, \omega^*)) C_{ik}(u_+ \rightarrow u|u^*, \omega^*, A_k(t)) f_i(t, u_+) g_k(t, \omega^*) \, du_+ \, dw^* - f_i(t, u) \sum_{k=1}^{m} \int_{D_u} \eta_{ik}^g(u, \omega^*|f_i(t, u), g_k(t, \omega^*)) g_k(t, \omega^*) \, dw^*,
\]

\[
P_{ij}^g[f, g](t, u) = \sum_{h=1}^{n} \sum_{k=1}^{m} \int_{D_u \times D_w} \eta_{ik}^g(u_+, \omega^*|f_i(t, u_+), g_k(t, \omega^*)) \times v_{ik}^g(u_+, \omega^*|u^*, \omega^*, A_k(t)) f_i(t, u_+) g_k(t, \omega^*) \, du_+ \, dw^*,
\]

where

- \( \eta_{ij} \) is the encounter rate between the candidate particle of the i-th functional subsystem and the field particle of the j-th functional subsystem;
- \( \eta_{ik}^g \) is the encounter rate between the candidate particle of the i-th functional subsystem and the k-th field agent;
- \( B_{ij} \) is the probability density that the candidate particle of the i-th subsystem with state \( u_+ \) falls into the state \( u \) after an interaction with a field particle of the j-th functional subsystem;
- \( C_{ik} \) is the probability density that the candidate particle of the i-th functional subsystem falls into the state \( u \) after an interaction with the k-th field agent;
- \( \mu_{ij}^u \) models the net proliferation into the i-th functional subsystem, due to interactions, occurring with rate \( \eta_{ij} \), between the candidate particle of the i-th population and the field particle of the j-th subsystem;
- \( v_{ik}^g \) models the net proliferation into the i-th functional subsystem, due to interactions, occurring with rate \( \eta_{ik}^g \), between the candidate particle of the h-th population and the k-th field agent.

**Remark 3.1.** The terms \( C_{ij}[f] \) and \( C_{ij}^g[f, g] \) model the number conservative inner and outer interactions, respectively, while the terms \( P_{ij}[f, g] \) and \( P_{ij}^g[f, g] \) model the non-conservative inner and outer interactions, respectively.

**Remark 3.2.** The above mathematical structures can be regarded as an extension of those proposed in [20]. Here the approach includes the modeling of proliferative/destructive events, as well as the interaction with external agents acting at the microscopic scale. Specific expressions of the interaction terms will be reported in Section 4.

### 3.2. Consistency with complexity features of biological systems

The mathematical structure (3.4) provides the framework to model large systems of living interacting entities. The aim of this subsection is to explain the way in which such a structure is able to model the complexity features of the biological systems presented in Section 2. To this end, we review those issues and try to understand how they are captured by the mathematical structure proposed above.

- **The complexity generated by a large variety of components** is reduced by dividing the system into subsystems that have the ability to express collectively a certain strategy identified by the scalar variable \( u \). Of course, the decomposition depends on the type of investigation that is carried out [33].
• **Strategy and organization ability** are modeled by the activity variable $u$. The activity is heterogeneously distributed and depends on the distribution function $f_i$.

• **The modeling of inner (and outer) interactions** is delivered by the terms $\eta_{ij}$, $B_{ij}$ and $\mu_{ij}$ ($\eta_{ik}$, $C_{ik}$, $\mu_{ik}$), which correspond to the encounter rate, the output of conservative interactions, and the output of proliferative and/or destructive events, respectively;

• **Mutations and selections** are generated during the proliferation and are related to genetic mixing or errors. The selection is natural as the active particles that are best fitted to the environment survive and proliferate, in some cases with prevalence with respect to the other particles [3].

• **Multiscale essence** is a key issue in understanding how far a mathematical model is from a mathematical theory of living systems. In fact, modeling of the terms that describe interactions at the microscopic scale is generally obtained by a purely phenomenological approach. On the other hand, it should instead be related to the dynamics at the microscopic scale as documented in [35].

### 4. On a system biology approach

Methods of system biology aim at looking at any overall biological system as an assembly of interconnected subsystems, each of them being modeled by a suitable set of equations. The dynamics of the system is delivered by a set of interconnected equations. In principles, this approach should lead to a quantitative predictive description where mathematical tools can play an important role [36].

A conceptual basis is offered by the so-called **theory of modules** by Hartwell [18]. This theory has been re-visited, from the mathematical modeling point of view, in [33] focusing on multicellular systems described by the kinetic theory for active particles summarized in Section 3. In particular, as we have seen, the term functional subsystem is used as an alternative to the term module, while the component of a module are called active particles.

Both biologists and applied mathematicians consider this strategy a challenging objective still far from being exhaustively treated. Definitely, recent studies in the field of genomic sciences [37] have given very important contributions toward the understanding of the dynamics at the molecular scale. However, a unified, somehow robust, approach does not yet exist.

This section aims at offering some guidelines toward the aforementioned objective based also on an appropriate use of the mathematical tools presented in the preceding section. The approach proposed in the following does not naively claim to be exhaustive. It aims at bringing a conceptual contribution to a fascinating, however difficult, topic. Therefore, two specific issues are selected and treated in two subsections: the first one offers some speculations on the criteria to decompose the overall system, while the second one focuses on additional mathematical tools.

#### 4.1. Decomposition rules toward reducing complexity

This subsection presents some perspective ideas on the rules to be followed on the decomposition of the overall system into subsystems characterized by a lower level of complexity.

The concept of **functional subsystem** was proposed in [33] for multicellular systems and subsequently used in various papers, e.g. [3,38], where this term identifies a collection of cells that have the ability to express collectively a certain strategy identified by a scalar variable. The concept can be generalized to the lower molecular scale by grouping genes, whose expression collectively generates a certain phenotype [39].

It is worth stressing that the link between a functional subsystem and its activity depends also on the specific phenomena that aims at being analyzed. Moreover, considering that the various subsystems are linked in networks, the modeling approach needs dealing also with their interactions, whose intensity is heterogeneously distributed among the particles of the same functional subsystem. Therefore, the representation of the system by a probability distribution, as we have seen in Section 2, appears consistent with the real behavior of the system under consideration.

The dynamics within each functional subsystem needs to be related to that at the lower molecular scales. Indeed, the major challenge is to model, at the macroscopic level, the behavior of biological systems in terms of components revealed by molecular biology. Therefore, more than one scale is necessary for each subsystem. Moreover, the mathematical approach should consider the fact that the derivation of biological tissue models is related to the lower cellular scale, and consequently the organization of functional subsystem into organs needs to be treated. An additional problem is the interaction between subsystems, which can act in different ways, for instance as boundary conditions or as external inputs.

The present state-of-the-art does not yet allow to treat efficiently the aforementioned mathematical problems. However, some preliminary promising results have been proposed and can be properly developed. An important one is that the methods reviewed in [3] consider that living systems evolve in time due also to Darwinian type selections that occur at the cellular scale [40,41], while differential games can generate, under suitable assumptions, Bellman type nonlinear elliptic equations [42]. This implies that macroscopic models, such as models of tissues, should include this time dependent feature. Further, the aforementioned selection may generate the onset of new cell populations and consequently additional macroscopic models, or the depletion of some of them existing at the beginning. This evolution can be contrasted or favored by the presence of external actions either from the environment or from therapeutical actions. However, mathematics still needs to be properly developed toward the aforementioned ambitious aim.
4.2. Mathematical tools

A first step consists in specializing the mathematical structure proposed in Section 3.1 by giving a modeling approach for each of the terms appearing in (3.4). Let us first consider the term $\eta_{ij}$. Intuitively, it depends on the distance $d_{ij}$ of the considered active particles, in the sense that increasing values of $d_{ij}$ correspond to decreasing values of $\eta_{ij}$. Hence, we propose to model it in the following way

$$\eta_{ij}(u_*, u^*[f_i, f_j]) = \eta_{ij}^0 e^{-cd_{ij}(u_*, u^*[f_i, f_j])},$$

(4.1)

where $\eta_{ij}^0$ is the initial encounter rate, $c$ is a positive constant and

$$d_{ij}(u_*, u^*[f_i, f_j]) = d_{1,ij}(u_*, u^*) + d_{2,ij}(u_*, u^*[f_i, f_j]) + d_{3,ij}(u_*, u^*),$$

(4.2)

where $d_{1,ij}(u_*, u^*) = |u_* - u^*|$ is the distance between the activity of the involved particles; $d_{2,ij}(u_*, u^*[f_i, f_j]) = \|f_i - f_j\|$ is the distance between the distribution functions of the involved particles in a suitable norm $\|\cdot\|$, and $d_{3,ij}(u_*, u^*) = |u_* - E(u^*)|$ is the distance between the activity of the candidate particle of the $i$-th subsystem and the mean value of the activities of the field particles.

Analogously, the term $\eta_{ik}^*$ can be modeled as

$$\eta_{ik}^*(u_*, u^*[f_i, g_k]) = \eta_{ik}^0 e^{-cd_{ik}(u_*, u^*[f_i, g_k])},$$

(4.3)

where $c$ is still a positive constant, $\eta_{ik}^0$ is the initial encounter rate while $d_{ik}$ denotes the distance between a particle of the $i$-th subsystem and the $k$-th external agent. The function $d_{ik}$ is defined as in (4.1) with $g_k$ and $u^*$ in place of $f_j$ and $u^*$, respectively.

Let us now consider the term $B_{ij}$, which represents the probability density that the candidate particle of the $i$-th subsystem, when interacting with a field particle of the $j$-th functional subsystem, changes its state characterized by the action $u_*$ into the new one corresponding to the action $u$. In this paragraph, we discuss some issue concerning the way in which the methods of game theory can be used to design the coupling matrix $B_{ij}$.

Classical game theory was introduced to design a mathematical theory of human behavior in strategic decisions [43]. After some pioneering application to biological sciences [44–46], a seminal paper by Maynard Smith and Price [47] introduced the game theory in evolutionary system biology for the first time. For a comprehensive introduction to game theory and its applications to biological evolutionary dynamics we refer to the recent books [48,49] and references therein.

Game theory typically analyzes the interaction between two (or more) agents (players). Each player chooses a strategy in order to maximize his payoff, where the payoff can have different meanings in different contexts. For instance, in systems biology it can be assumed to coincide with whatever phenotype’s fitness (e.g., rate of reproduction).

Normally, a game is described by:

- a set $I = \{1, 2, \ldots, n\}$ of players;
- a set $S_i$ of strategies for each player $i \in I$. The set $s = (s_1, \ldots, s_n)$, with $s_i \in S_i$ ($i = 1, \ldots, n$) is a strategy profile for the game;
- a payoff function $\pi_i : S \rightarrow \mathbb{R}$ for each player $i = 1, \ldots, n$, where $S$ is the set of all strategy profiles. In other words, $\pi_i(s)$ is the payoff of player $i$ when the strategy profile $s$ is chosen.

In the case of two-players/two-strategies game, the previous setting reads as follows. Let $I = \{1, 2\}$ be the set of players and assume that each player can choose between two strategies denoted as $A$ and $B$. The set of strategy profiles is:

$$S = \{\{A, A\}, \{A, B\}, \{B, A\}, \{B, B\}\}.$$ 

On $S$ we have to define two different payoff functions $\pi_1$ and $\pi_2$ relative to the two players $i = 1, 2$:

$$\pi_1(\{A, A\}) = a, \quad \pi_1(\{A, B\}) = b, \quad \pi_1(\{B, A\}) = c, \quad \pi_1(\{B, B\}) = d;$$

$$\pi_2(\{A, A\}) = a, \quad \pi_2(\{A, B\}) = c, \quad \pi_2(\{B, A\}) = b, \quad \pi_2(\{B, B\}) = d.$$ 

This special case can be conveniently synthesized in the payoff matrix:

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>B</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

The meaning is the following. Each row of the matrix refers to a strategy of player 1, each column to a strategy of player 2. If player 1 plays $A$ against $A$ he gets $a$; if 1 plays $A$ against $B$ he gets $b$; if 1 plays $B$ against $A$ he gets $c$ and so on. Games strategies relative to the previous example are called pure strategies. More interesting in our context is the case of mixed strategies. A mixed strategy for the $i$-th player is a probability distribution over its set $S_i$ of pure strategies. Consider, to simplify, the case of $n$ players $(1 = 1, \ldots, n)$ each having two pure strategies $A$ and $B$, labeled by the index $h = 1, 2$. A mixed strategy for
player $i$ is a vector $x_i$ in the 2-dimensional euclidean space $\mathbb{R}^2$, its $h$-th coordinate $x_{ih} \in [0, 1]$ being the probability assigned by $x_i$ to the player’s $h$-th pure strategy.

Traditionally, game theory considers each player as “rational”, in the sense that he assumes that his opponent behaves in a certain way, and then he acts accordingly to maximize his payoff. In order to apply the basic tools of game theory to our modeling problem, we are forced to relax this assumption. Let us consider a population of players (functional subsystems) interacting in a game. Each functional subsystem has its own strategy, and interacts randomly with all other subsystems. The payoffs of all these encounters are added up, and the success in the game is translated in an increased fitness of the subsystem (for example, into reproductive success).

When trying to apply methods from game theory to our modeling problem, we have to consider interactions between a candidate particle, having activity $u_*$ and belonging to the $i$-th functional subsystems, and a field particle, having activity $u^*$ and belonging to the $j$-th functional subsystem, that is, a two-players game. Each “player” expresses a two-fold mixed strategy, with the payoff related to the probability that an encounter ends with a transition $u_* \rightarrow u$ in the activity variable. To be more specific, the payoff function can be represented as follows:

\[
\begin{array}{cccccc}
\ldots & i & j & \ldots \\
\ldots & \ldots & \ldots & \ldots & \ldots & \ldots \\
i & \ldots & B_{ji} & \ldots & \ldots & \ldots \\
\ldots & \ldots & \ldots & \ldots & \ldots & \ldots \\
j & \ldots & B_{ij} & \ldots & \ldots & \ldots \\
\ldots & \ldots & \ldots & \ldots & \ldots & \ldots 
\end{array}
\]  

(4.4)

where we indicated, with abuse of notation, with the same labels $i$ and $j$ both the functional subsystems (players) and the relative strategies they adopt in the interaction. Observe that since the entries of the matrix (4.4) are probabilities of transition from a state activity to a (possibly) different one, the quantities $B_{ij}$ are real numbers in the interval $[0, 1]$ and satisfy the normalization condition $\sum_{j=1}^{n} B_{ij} = 1$ ($i = 1, \ldots, n$).

The above reasonings lighten the analogies and differences between the standard game theory and the kinetic theory of active particles. First, each functional subsystem develops a function that implies a strategy whose aim is to assert its own task. Consequently, such strategies are qualitatively different among different subsystems. The strategy expressed by each subsystem depends, also quantitatively, on other subsystems with which it interacts, on the state activity $u_*$ of the subsystem’s components and on the activity $u^*$ of the interacting individuals. The idea of using a mixed strategy game reflects in the dependence of the payoff terms on the frequency of agent particles in each subsystem. In this way, the expected payoff of each strategy depends on the distribution functions $f_i$, and the interactions become nonlinear and nonlinearly additive. This point results in extreme relevance in the applications to system biology.

**Remark 4.1.** The functional subsystem defines the interactions’ typology, whereas the strategy depends also on the interactions themselves.

**Remark 4.2.** Once the states (distribution functions) of interacting individuals have been prescribed, the process output is known only in probability. We define these ones as *doubly stochastic* interactions, inasmuch both the states of interacting elements are random variables and the dynamics is a random map.

**Remark 4.3.** The treatment of the term $\mu_{ij}$ in (3.7) is similar though more complex. It is worth observing that the interactions mediated by the latter term also influence those related to the term $B_{ij}$, since they modify the number of interacting individuals.

Analogous reasonings can be applied to interactions between particles of the inner system and agents of the outer system. Methods of game theory are able to furnish pieces of information concerning the dynamics of strategies played by the interacting functional subsystems. Particularly interesting are the existence of equilibria or evolutionarily stable strategies. Roughly speaking, the interacting subsystems play a strategy that happens to be a Nash equilibrium if neither one can increase its payoff by deviating from that strategy. The concept of evolutionarily stable strategy (ESS), introduced in [47], is more strictly related to biological evolution. A strategy is evolutionary stable if a whole population using that strategy cannot be invaded by a small group of mutant genotype. It appears clear that these concepts are someway connected with the local and possibly global interaction dynamics portrait, in this way furnishing a way to introduce information on in-time behavior of living systems.

5. **Discretization and computing**

This section analyzes the problem of using continuous or discrete variables in connection both with modeling and computational purposes.

Focusing on the literature in the field of biology, the paper by Greller et al. [50], concerning the modeling of cancer onset and growth, identifies different stages of cancer cells from normal to cells with metastatic competence through pre-neoplastic and proliferative states. The authors put in evidence the problem of selecting a discrete or continuous activity
variable. However, the answer to this difficult question cannot immediately given. A partial answer is offered by the paper of Hanahan, and Weinberg [51] concerning the pathways toward cancer progression. This important paper has been here interpreted by an approach where different stages of mutations are translated in an onset of new functional subsystems. This is a partial answer to the issue under consideration as the selection of a discrete or continuous variable within each subsystem is still looking for a conceptual guideline.

Let us consider, before dealing with this specific problem, the simply technical problem of constructing a discrete system toward computing. More precisely, let us consider the more complex case where \( u \in \mathbb{R}^+ \) is defined over an unbounded domain. Moreover, we consider the case of closed systems defined by (3.4), where \( f_i^u = 0 \) and \( C_i \) and \( P_i \) are defined in (3.6) and (3.7), respectively.

According to the Sinc method we consider a partition of the set \([0, a]\) of the activity variable \( u \) with the following \( m \) collocation points

\[
u_j = \frac{j - 1}{h}, \quad h = \frac{a}{m - 1}, \quad \text{for} \quad j \in \{1, 2, \ldots, m\}.
\]

The interpolation of the distribution function is as follows:

\[
f_i^m(t, u) = \sum_{j=1}^{m} S_j(u, h) f_j(t), \quad \forall i = 1, \ldots, n
\]

where

\[
S_j(u, h) = \frac{h}{\pi (u - (j - 1)h)} \sin \left( \frac{\pi}{h} (u - (j - 1)h) \right),
\]

are the Sinc functions such that \( S_j(u, h) = \delta_k \) where \( \delta_k \) is the Kronecker delta.

Quadratures provide macroscopic quantities. For instance, the local density and the first order moment, called local activation, are approximated by the following quadrature rule:

\[
\int_0^a f_i(t, u) \, du \simeq \sum_{j=1}^{m} f_j(t), \quad \forall i = 1, \ldots, n
\]

\[
\int_0^a u f_i(t, u) \, du \simeq \sum_{j=1}^{m} w_j f_j(t), \quad w_j = \int_0^a u S_j(u, h) \, du.
\]

Subsequently, suitable interpolation and quadrature rules allow us to obtain a system of ordinary differential equations which define the evolution of the distribution functions \( f_i \) in the nodes \( u_j \), namely \( f_j(t) = f_i(t, u_j) \). The formal structure is as follows:

\[
\frac{d}{dt} f_j(t) = J_i(\{f_j\})(t),
\]

where finite sums, replacing integrals, appear in the right-hand-side term.

The collocation scheme that has been just described is certainly useful for the applications and simulations. It can be improved by taking advantage of the contents of [52] and therein cited bibliography. Moreover, it can be technically generalized to include external actions, for instance medical treatments [53,54]. However, it is important stressing that using discrete variables is not only finalized to computing, but also to a deeper understanding of biological complexity. In fact the collocation points can be identified by mutation stages. Therefore, the finite sums correspond to transitions toward discrete states and not to approximations of integrals. This basically means that the contents of Section 4 has to be properly revisited according to this specific interpretation.

6. Looking ahead

A deep understanding of the multiscale evaluative features of biological systems is a preliminary step toward the development of a system biology approach. In fact, the decomposition of the overall system needs to be related to the representation scales chosen for the mathematical modeling of each subsystem. Moreover, living systems evolve in time due also to Darwinian type selection that occurs at the cellular scale. This implies that macroscopic models, such as models of tissues, should include this time dependent feature. Further, the aforementioned selection may generate the onset of new cell populations and consequently additional macroscopic models, or the depletion of some of them existing at the origin. This evolution can be contrasted or favored by the presence of external actions either from the environment or from therapeutical actions. This section aims at showing how the mathematical tools reported in Section 3 can be properly developed to treat such problem.

The multiscale aspects of biological systems imply that the dynamics at the higher scale is influenced by the lower scales, namely the parameters of models at the high scale, cellular or tissue, have to be computed by the dynamics at the lower scale.
This paper has been mainly focused on the understanding of the dynamics at the lower scale with the aim of extracting the basic concepts of the organization of biological behaviors in view of their structuring into a new system biology approach. These reasoning can be made more precise by selecting the cellular scale as the basis to transfer the information from the lower molecular scale to that of tissues and organs. There exists a well-settled literature concerning the derivation of macroscopic models of tissues as documented in recent papers [55,56], where the most relevant contributions in the field are reported. The common feature of the various papers analyzed in this paper consists in developing suitable asymptotic methods for the equations obtained by perturbation of the spatially homogeneous case by a stochastic velocity jump process. This technique was introduced in [57] and applied in [58] also to the case of multicellular systems undergoing proliferative and/or destructive interactions. Different parabolic and/or hyperbolic scaling leads to different classes of tissue models where biological activities and interactions introduce source terms that are generated both by mutations and proliferative events. This approach has been successful in the derivation proposed in [34] of the celebrated Keller and Segel model [59,60]. Further practical applications are critically analyzed in [61], while conceptual paths are treated in [62].

However, these results leave open the problem of modeling the link with the lower molecular scale. Some perspective ideas can be given toward the ambitious aim of modeling the aforementioned complex interplay. The following sequential steps are proposed in agreement with mathematical approach presented in the preceding sections.

(i) Families of genes are selected and grouped into functional subsystems which can potentially have an impact with the specific analysis under consideration.

(ii) The activity variable for each subsystem is selected as the ability to produce over and lower expression of proteins.

(iii) The dynamics mentioned in (ii) needs to be modeled in connection with the interactions involving the different functional subsystems at the molecular scale and their interaction with the outer environment.

(iv) Interactions between functional subsystems at the molecular scale and those at the higher cellular scale activate or repress the biological functions expressed at the cellular scale. This dynamics can be activated or deactivated by external actions.

This brief presentation does not naively claim to be exhaustive. As a matter of fact, the aforementioned guidelines simply represent a research project, as complex as ambitious it may appear, still to be developed.

Various hints toward research perspectives have been given in the preceding section. However, the major research perspective consists in developing a deep analysis of the topic treated in Section 4, namely the link between game theory and the stochastic games presented in this paper within the general framework of the kinetic theory for active particles. Using discrete variables, as we have seen in Section 5, we can contribute to this aim.

References


