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Review

Complexity analysis and mathematical tools towards the modelling of living systems ☆

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Abstract

This paper is a review and critical analysis of the mathematical kinetic theory of active particles applied to the modelling of large living systems made up of interacting entities. The first part of the paper is focused on a general presentation of the mathematical tools of the kinetic theory of active particles. The second part provides a review of a variety of mathematical models in life sciences, namely complex social systems, opinion formation, evolution of epidemics with virus mutations, and vehicular traffic, crowds and swarms. All the applications are technically related to the mathematical structures reviewed in the first part of the paper. The overall contents are based on the concept that living systems, unlike the inert matter, have the ability to develop behaviour geared towards their survival, or simply to improve the quality of their life. In some cases, the behaviour evolves in time and generates destructive and/or proliferative events.

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1. Motivations and plan of the paper

The kinetic theory of active particles, hereafter sometimes abbreviated as KTAP, is a mathematical method that has been developed to model the dynamics of large living systems. The theory applies to complex systems constituted by living entities interacting in space or along networks; normally, the knowledge of the dynamics of a few entities does not straightforwardly lead to a description of the dynamics of the overall system.

In details, this mathematical theory can be applied to systems characterized by the following common features:

(i) The system is constituted by a large number of interacting entities, called *active particles*, whose microscopic state, in addition to geometrical and mechanical variables, also includes an additional variable, called *activity*, which represents the individual ability to express a specific strategy. Living systems have the ability to develop behaviour that cannot only be explained by the classical mechanics laws, and, in some cases, can generate proliferative and/or destructive processes. Such behaviour is not simply an individual and isolated expression, but generally depends on interaction with all the other individuals.

(ii) The activity variable is heterogeneously distributed over the active particles, while the overall state of the system is described by a probability distribution function over the microscopic state of the particles. Interactions modify the state of the interacting entities, while the strategy they express may can be modified by the shape of their heterogeneous distribution.

(iii) Interactions occur not only through contact, but can also be distributed in space as well as along networks. Generally, living systems communicate with each other either directly or through media. As a consequence each entity interacts with all the other entities that are in a domain where they are able to communicate with each other. In some cases, such a domain is identified by the visibility zone, while in other cases by a communication network.

At present, we simply recall that the theory has been profitably applied to model complex systems such as the onset of cancer and competition with the immune system [27–29], traffic flow [51,60], social systems [31,32], psychological interactions [19,42], politics [92,93].

The books [30] and [13] provide useful references, where specific applications, i.e. immune competition, social systems, vehicular and crowd dynamics, are reported together with various refinements of the mathematical tools.

Moreover, the idea of using a two scale approach [20,21,44,45], has been proposed in order to consider the multiscale aspects, which are an inner feature of several complex systems.

This paper is divided into two parts, the first one is focused on the mathematical tools of the kinetic theory of active particles, while the second part provides a review of a variety of applications in life sciences, namely developments of system biology towards modelling epidemics on complex networks, modelling complex social systems, traffic, crowds and swarms. The contents are not limited to a survey of existing results. Several indications concerning research perspectives are given in both parts, focused on the methodology and applications, respectively. The paper is organized in seven more sections.

- Section 2 deals with some conceptual aspects that are preliminary to the derivation of the mathematical tools. The first aspect is the decomposition of the overall system, in order to reduce its complexity, into functional subsystems by a suitable development of the theory of functional modules by Hartwell [73] revisited in the field of biological sciences [27], and in the field of behavioural economy [3,4]. This decomposition involves the analysis of scaling problems.
- Section 3 deals with the derivation of mathematical tools for systems with homogeneously distributed activity variable. The first step consists in the modelling of interactions at the individual level of active particles, where the output of the interaction is determined by stochastic games. Subsequently, a mathematical framework is derived, using the modelling of microscopic interactions, by a suitable balance equation in the elementary space of the microscopic states. Such a framework can act as a paradigm for the derivation of specific models.
- Section 4 develops the same analysis in the case of systems with heterogeneously distributed activity. Again, the final objective consists in the derivation of suitable frameworks, which act as background paradigm for the derivation of specific models.
- Section 5 proposes a bridge between the mathematical structures described in the preceding sections and the various applications treated in the subsequent ones. Various aspects of the general modelling approach are critically analyzed and conceivable applications are examined. This section can be regarded as a methodological introduction to the applications developed in the subsequent sections.
- Section 6 deals with modelling and perspective ideas on applications of the theory to the modelling of complex systems where the velocity variable has no relevant physical meaning in the assessment of the state of the interacting particles. Specifically, this section deals with two applications. The first one is focused on social systems within a framework and specifically on opinion formation. The second application has the aim of at showing how a mathematical interpretation of systems biology can be properly developed to model the evolution of epidemics with virus mutations. This section also outlines some perspective ideas concerning interactions within complex networks.
- Section 7 deals with the modelling of systems where the space and the velocity variables have a relevant physical meaning in the assessment of the state of the interacting particles. The applications are focused on crowds, and swarms. A critical analysis of the existing literature on the modelling of traffic shows how the approach can be properly developed to model animal flocks. This topic represents a fascinating frontier for applied mathematics. The literature in the field is quite limited, while this section provides various hints on modelling. In fact, this section, unlike the previous ones, is mainly focused on research perspectives rather than on a detailed review of existing results.
- Section 8 proposes a critical analysis, which also takes advantage of the models presented in the preceding sections, of various common features of complex systems. It deals with the ability of the mathematical tools to take into account these features, while research perspectives are indicated looking at a *mathematical theory for complex living systems*. This challenging objective means that such a theory should be valid not only for specific systems but also for a broader variety of systems. Particularly important is the use of multiscale methods to link the different scales that characterize the system which is object of modelling.

It is worth stressing that the mathematical kinetic theory of active particles cannot be regarded as a straightforward generalization of the classical kinetic theory, because of the different way of decomposing the system and modelling interactions. However, under suitable simplification and *ad hoc* assumptions, it can be shown, see paper [7], that the classical model of the kinetic theory [97] can be viewed as a particular case of the theory developed in this paper. This paper is focused on the modelling of living systems, however suitable developments of KTAP's methods can be applied also to model large systems of interacting particles such as mixtures [63], suspensions with continuous particle size distribution [41].

On the other hand, some connections can be identified with methods that apply agent methods related to the derivation of master equations [8,103]. Many results obtained by physicists now have a rigorous background, among others Talagrand [105]. However, the equilibrium and dynamical properties of such systems are far from being fully understood from a mathematical point of view.

2. Functional subsystems, scaling, and representations

This section deals with some preliminary aspects that are needed for the mathematical formalization, which will be the subject of the next two sections. We refer to a large system of interacting entities that can be precisely defined borrowing from [13] the following definitions:

- The interacting entities are called *active particles*, and are characterized by mechanical variables, and also by a suitable *function* that they express. This function is called *activity*.

Living systems, particularly in biology (e.g. multicellular systems), are constituted by different types of active particles, therefore several different functions are expressed. The activity variable and its distribution play a relevant role in determining the output of interactions. Generally, the activity variable is heterogeneously distributed among particles, which have the ability to express the same function with different intensities. The same reasonings can be extended to crowds and swarms, where interacting individuals organize their strategy according to heterogeneously distributed personal abilities.

This is a relevant source of complexity. Furthermore, living systems, unlike most inert matter systems are characterized by the presence of a variety of components. In some cases, this number can be so large that the complexity of the analytical and computational methods developed for modelling cannot be effectively applied. Therefore, it is useful to reduce it by decomposing the system into suitable functional subsystems following well defined rules. According to some conceptual ideas proposed in the field of behavioural economy [3,4], the following definition can be given:

- A *functional subsystem* is a collection of active particles, which have the ability to express the same *activity*, which is regarded as a scalar variable. The whole system is constituted by several interacting functional subsystems.

Generally, the link between a functional subsystem and its activity also depends on the specific phenomena that has to be analyzed. Therefore, the decomposition into functional subsystems is a flexible approach that can be adapted to each particular investigation. Moreover, considering that the various subsystems are linked in networks, the modelling approach also needs to deal also with their interactions.

The modular approach by Hartwell [73] already allows complexity to be reduced by decomposing biological systems into several interacting subsystems. In fact, this approach can possibly be considered the first fundamental contribution to system biology [113]. Hartwell's theory has been re-visited in paper [27] which focused on multicellular systems described by the kinetic theory of active particles [30]. Hartwell's modules are identified by cell populations, that have the ability to express a certain behaviour collectively, which is the same in each module and has to be identified by a scalar variable.

It is worth stressing, with reference to [3], see also paper [27], that the decomposition method can be regarded as a tool to reduce complexity. In fact, active particles in each module, which is regarded as a functional subsystem, are not of the same type, while they express the same strategy collectively. Therefore, the modelling approach needs to assess a certain number of activities, while the functional subsystems correspond to each of these activities.

Generally, complex systems are constituted by interacting components distributed in space, in some cases constrained along networks. Each component is constituted by several interacting entities. This aspect generates remarkable difficulties in the modelling approach: among others, the need to describe the interactions that involve the various components. The scale (microscopic or macroscopic) suitable to describe each component may not be the same for all of them.

This topic can be clarified by giving a definition of representation scales. In fact, systems of real world are generally constituted by several interacting elements. This implies that mathematical models need to be designed at their typical observation and representation scales.

The *microscopic scale* corresponds to modelling the evolution of the variable that is suitable to describe the physical state of each single element. An alternative to the above approach can be developed when the system is constituted by a large number of elements and it is possible to obtain suitable locally in space averages of their state in an elementary space volume ideally tending to zero. In this case, the modelling refers to the *macroscopic scale*, namely to the evolution of locally averaged quantities, called *macroscopic variables*.

The above two scales are generally sufficient to model the evolution of inert matter systems. On the other hand, living systems need the addition of models derived at lower scales. For instance, the microscopic scale in biology corresponds to cells, while the dynamics of cells depends on the dynamics at the lower *molecular scale*, namely the scale of genes. In some cases, the complexity of the system induces the use of even a larger scale, the *super-macroscopic* scale, which corresponds to population dynamics [9,98,112], that, in simpler cases, does not include an internal structure.

The above scaling corresponds to different classes of equations. Generally, models designed at the microscopic scale are stated in terms of ordinary differential equations, while models at the macroscopic scale are generally stated in terms of partial differential equations. The modelling is developed within the framework of deterministic causality principles unless some external noise is added. This means that once a cause is given, the effect is deterministically identified.

The motivations to use the macroscopic scale instead of the microscopic one are also related to the practical objective of reducing complexity. For instance, when systems involve a large number of interacting elements, the number of equations of the model may be too large to be computationally tractable. Moreover, macroscopic quantities are often of practical interest; therefore, it is convenient to deal with equations involving these variables directly.

The approach of the *kinetic theory of active particles* [13] is completely different; the microscopic scale is used to model the interactive dynamics among active particles, while the overall state of the whole system is described by the probability distribution over the microscopic state. The microscopic state also includes non-mechanical variables, called *activity*.

Jager and Segel [91] published the first paper to introduce the concept of activity variable in the microscopic state of living entities. Their aim was to model the social dynamics of populations of insects on the basis of the empirical data suggested by Hogeweg and Hesper [83]. Subsequently, these models were generalized to the modelling of immune competition [26] and to various fields of applied sciences [6].

In short, the following issues need to be carefully treated in the modelling approach:

- Two scales are, in some cases, necessary to derive models in a functional subsystem, for instance models at microscopic and sub-microscopic scale. The interaction between the models at different scales needs to be transferred to the higher scale since the information comes from the lower scale.
- The various models in a network correspond, in some cases, to different scales. Therefore, it is necessary to derive models at the higher scale from the corresponding description delivered at the lower scale.
- Multiscale interactions can also occur between the sub-microscopic and macroscopic scales, within the same functional subsystem, as documented in paper [44].

The above issues are well known in biology, see for instance the two-scale representation for multicellular systems [21], as well as the derivation of macroscopic equations from the underlying description at the microscopic level [2,14,15,56,64,67,69].

The difficulty of dealing with mathematical aspects in life sciences has been well documented in the paper by May [94], Hartwell et al. [73], Herrero [81], Reed [102]. This is due to the lack of paradigms and conservation laws, which characterize most inert matter systems. An additional problem, as already mentioned, is the multiscale essence of all living systems.

Finally, it is worth stressing that the above reasonings are focused on, but not limited, to living systems, considering that the lower scale also plays a relevant role in the case of inert matter. For instance, in the case of classical particles, the *interaction potential* modelling the exchange of forces between a pair of particles depends on their inner structure, which, however, is assumed to be constant in time.

Let us now consider, after the above preliminary reasonings, the mathematical representation of a large system constituted by active particles belonging to different functional subsystems. The physical microscopic state of the particles is identified by a variable that is suitable to describe their state, while the overall state of the whole system is described by a probability distribution over the microscopic state of the particles.

Some definitions are given in view of the mathematical treatment developed in the next sections.

- The physical variable charged to describe the state of each active particle is called *microscopic state*, and is constituted by the *geometrical microscopic state*, the *mechanical microscopic state*, and the *activity*, which may have a different meaning for each particular system.
- The space of the states of the active particles is called *microscopic state space*. When the active particles are points of the Euclidean space, the position $\mathbf{x}$ of each active particle is the geometrical microscopic state, while the mechanical microscopic state is the velocity $\mathbf{v}$.
- The description of the overall state of the functional subsystem is defined by the distribution function f_i, which in the case of representation by points, is as follows

$$f_i = f_i(t, \mathbf{x}, \mathbf{v}, u), \quad [0, T] \times D_{\mathbf{x}} \times D_{\mathbf{v}} \times D_u \to \mathbb{R}^+ = [0, +\infty[, \tag{1}$$

where $i = 1, \ldots, n$ identifies the specific subsystem. The function f_i is called *generalized distribution function* and is such that $f_i(t, \mathbf{x}, \mathbf{v}, u)\, d\mathbf{x}\, d\mathbf{v}\, du$ denotes the number of active particles whose state, at time t, is in the elementary volume of the space of microscopic states for each subsystem. The whole domain of the microscopic states is defined by $D_{\mathbf{x}} \times D_{\mathbf{v}} \times D_u$.

The following particular case can be considered:

(i) If the number of active particles is constant in time, then the distribution function can be normalized with respect to such a number and consequently is a probability density.

(ii) If the distribution over the activity variable is constant in time, namely it is not modified by interactions, f_i can be written as follows:

$$f_i = f_i(t, \mathbf{x}, \mathbf{v}) P_i(u), \tag{2}$$

where P_i is a probability density over the state u. As a particular case, if the activity is the same for all particles ($u = u_0$) of a subsystem, using Dirac's notation of the delta function, one has:

$$f_i = f_i(t, \mathbf{x}, \mathbf{v}) \delta(u - u_0). \tag{3}$$

If the number of particles is constant in time, the distribution function can be normalized with respect to such a number and acquire the structure of a probability density. Moreover, it can be technically shown how the knowledge of the distribution function (or probability density) (1) leads, under suitable integrability conditions, to the calculations of macroscopic quantities for each subsystem. In what follows we refer, for simplicity of notations, to the relatively simpler case (1), while generalizations to enlarged definitions of the microscopic state are simply matter of analogous calculations. In details, if $\mathbf{f} = \{f_i\}_1^n$ is known, macroscopic gross variables can be computed, under obvious integrability properties, as moments weighted by the above distribution function. In particular, the *local size* of the ith functional subsystem is given by:

$$\nu[f_i](t, \mathbf{x}) = \int_{D_{\mathbf{v}} \times D_u} f_i(t, \mathbf{x}, \mathbf{v}, u)\, d\mathbf{v}\, du. \tag{4}$$

The local initial size of the ith functional subsystem, at $t = 0$, is denoted by n_{i0}, while the local size for all functional subsystem is denoted by n_0, and is given by

$$n_0[\mathbf{f}_0](\mathbf{x}) = \sum_{i=1}^{n} n_{i0}(\mathbf{x}), \tag{5}$$

where $\mathbf{f}_0 = \mathbf{f}(t = 0, \mathbf{x}, \mathbf{v}, u)$ denotes the initial distribution for the set of all subsystems.

The integration over $D_{\mathbf{x}}$ gives the *total size* of the ith subsystem:

$$N_i(t) = \int_{D_{\mathbf{x}}} \nu_i(t, \mathbf{x})\, d\mathbf{x}, \tag{6}$$

which can depend on time due to the role of proliferative or destructive interactions, as well as to the flux of particles through the boundaries of the volume. The *total size* $N = N(t)$ of all subsystems is given by the sum of all N_i.

It is worth stressing, in view of the applications dealt with in Section 7, that active particles have a dimension, therefore a maximal packing density ν_M can be defined corresponding to full contact of all particles. Local density and all distribution functions can be normalized with respect to such a density. In particular, a dimensionless density ρ can be defined as follows:

$$\rho_i(t,\mathbf{x}) = \frac{\nu[f_i](t,\mathbf{x})}{\nu_M}. \tag{7}$$

Marginal densities refer either to the generalized distribution over the mechanical state

$$f_i^m(t,\mathbf{x},\mathbf{v}) = \int_{D_u} f_i(t,\mathbf{x},\mathbf{v},u)\,du, \tag{8}$$

or to generalized distribution over the microscopic activity:

$$f_i^a(t,u) = \int_{D_\mathbf{x}\times D_\mathbf{v}} f_i(t,\mathbf{x},\mathbf{v},u)\,d\mathbf{x}\,d\mathbf{v}. \tag{9}$$

First order moments provide either *linear mechanical macroscopic* quantities or *linear activity macroscopic* quantities. For instance, the mass velocity of particles, at the time t in the position $\mathbf{x}$, is defined by

$$\mathbf{U}[f_i](t,\mathbf{x}) = \frac{1}{\nu[f_i](t,\mathbf{x})} \int_{D_\mathbf{v}\times D_u} \mathbf{v} f_i(t,\mathbf{x},\mathbf{v},u)\,d\mathbf{v}\,du. \tag{10}$$

Focusing on activity terms, linear moments related to each ith component of the system are computed as follows:

$$a_j[f_i](t,\mathbf{x}) = \int_{D_\mathbf{v}\times D_u} u_j f_i(t,\mathbf{x},\mathbf{v},u)\,d\mathbf{v}\,du, \tag{11}$$

while the *local activation density* is given by

$$a_j^d[f_i](t,\mathbf{x}) = \frac{a_j[f_i](t,\mathbf{x})}{\nu[f_i](t,\mathbf{x})} = \frac{1}{\nu[f_i](t,\mathbf{x})} \int_{D_\mathbf{v}\times D_u} u_j f_i(t,\mathbf{x},\mathbf{v},u)\,d\mathbf{v}\,du. \tag{12}$$

Global quantities are obtained integrating over space. A different interpretation can be given for each of the above quantities. Large values of $a_j[f_i]$ may be due to large number of particles with relatively small values of the activity, but also to small number of particles with relatively large values of the activity, while $a_j^d[f_i]$ allows to identify the size of the mean value of the activation.

Similar calculations can be developed for higher order moments if motivated by some interest for the applications. For instance, *local quadratic activity* can be computed as second order moments:

$$e[f_i](t,\mathbf{x}) = \int_{D_\mathbf{v}\times D_u} u^2 f_i(t,\mathbf{x},\mathbf{v},u)\,d\mathbf{v}\,du, \tag{13}$$

while the *local quadratic density* is given by:

$$\varepsilon[f_i](t,\mathbf{x}) = \frac{e[f_i](t,\mathbf{x})}{\nu[f_i](t,\mathbf{x})} = \frac{1}{\nu[f_i](t,\mathbf{x})} \int_{D_\mathbf{v}\times D_u} u^2 f_i(t,\mathbf{x},\mathbf{v},u)\,d\mathbf{v}\,du. \tag{14}$$

The mathematical structures derived in next sections and the applications reviewed in Sections 6 and 7 refers to particular representations. Among others: the physical meaning of $e[f_i]$ and $\varepsilon[f_i]$ stands for the energy and energy density expressed by the activity variable, the detailed meaning depends (as in the case of linear momenta) on the specific system under consideration. It is an important quantity as it can play a role in the strategy developed by the active particles. For instance, the strategy developed by the active particles may substantially change, when the energy passes a certain threshold.

– The *microscopic state is identified only by the activity variable*. Namely, space and velocity variables are not significant to describe the microscopic state of the active particles. In this case, the overall state of the system is described by the distribution function $f_i(t,u)$ over the activity variable only.
– The *microscopic state is identified only by the space and activity variables*. Namely, the velocity variable is not significant to describe the microscopic state, while it is important knowing the localization of the active particles, but not their velocity. Therefore, the representation is given by $f_i(t,\mathbf{x},u)$.

The above two cases need to be distinguished from the spatially homogeneous description with constant probability density distribution over the velocity variable. The system is still described by the distribution function $f_i(t,u)$, but the velocity variable has a role in the modelling of the system.

Various systems in life sciences are characterized by the fact that the microscopic state is identified by a discrete variable rather that a continuous one. For instance, this situation occur in traffic flow modelling [60], where the low number of individuals (vehicles) weakens the assumption of the continuity of the distribution function. Let us consider a system of active particles organized in n interacting subsystems, where both space and velocity variables may be discrete due to modelling requirements.

Let us consider first the case of a velocity variable belonging to the set:

$$I_{\mathbf{v}} = \{\mathbf{v}_1, \ldots, \mathbf{v}_r, \ldots, \mathbf{v}_R\}, \tag{15}$$

with components $\mathbf{v}_r$, $r = 1, \ldots, R$. The distribution function is defined as follows:

$$f_i(t,\mathbf{x},\mathbf{v}) = \sum_{r=1}^{R} f_i^r(t,\mathbf{x})\,\delta(\mathbf{v}-\mathbf{v}_r), \tag{16}$$

where the space variable remains continuous, and $f_i^r(t,\mathbf{x}) = f_i(t,\mathbf{x},\mathbf{v}_r)$. Analogously, if also the space variable is discrete and belongs to the set:

$$I_{\mathbf{x}} = \{\mathbf{x}_1, \ldots, \mathbf{x}_s, \ldots, \mathbf{x}_S\}, \tag{17}$$

with components $\mathbf{x}_s$, $s = 1, \ldots, S$, the distribution function is defined as follows:

$$f_i(t,\mathbf{x},\mathbf{v}) = \sum_{r=1}^{R}\sum_{s=1}^{S} f_i^{rs}(t)\delta(\mathbf{x}-\mathbf{x}_s)\,\delta(\mathbf{v}-\mathbf{v}_r), \tag{18}$$

where $f_i^{sr}(t) = f_i(t,\mathbf{x}_s,\mathbf{v}_r)$.

Moments are obtained still according to the method we have seen above, simply replacing integration over the velocity variable by finite sums. Calculations are technical and are not repeated here.

3. Mathematical tools for homogeneous activity distribution

This section deals with the derivation of mathematical structures suitable to describe the evolution of large systems of interacting active particles belonging to different functional subsystems. The derivation is developed in the case of homogeneous (or constant) distribution over the activity variable, namely when the activity variable is the same for all particles. Interactions modify the mechanical variables, for instance position and velocity, while their activity is not modified. Still, the activity variable has a remarkable role on the dynamics of the interactions.

Let us first consider the case of one functional subsystem only, the generalization to several interaction subsystems is, as we shall see, immediate. Interactions, at the time t, refer to three types of particles:

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

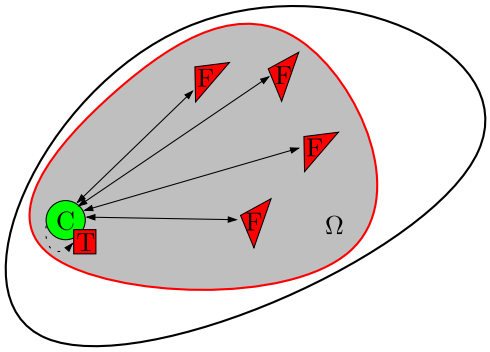

Fig. 1. The candidate particle C interacts with the field particles F, which are within its interaction domain Ω, and develops a strategy based of the states and localization of the particles F. Subsequently the particle modifies its microscopic state.

Two different types of interactions are considered: *conservative interactions*, when particles modify their microscopic state, and *non-conservative interactions*, when interactions generate proliferation or destruction of particles in their microscopic state.

The mathematical framework refers to the evolution in time and space of the test particle. The derivation for f is based on the following balance of equations in the elementary volume of the phase space:

$$\frac{df}{dt}\,d\mathbf{x}\,d\mathbf{v} = \big(G[f] - L[f] + S[f]\big)\,d\mathbf{x}\,d\mathbf{v}, \tag{19}$$

where interactions of candidate and test particles refers to the field particles, and:

$G[f]$ denotes the *gain* of candidate particles into the state $(\mathbf{x}, \mathbf{v})$;
$L[f]$ models the *loss* of test particles with state $(\mathbf{x}, \mathbf{v})$;
$S[f]$ models *proliferation/destruction* of test particles.

Therefore, a basic aspect of the characterization of the above equation is the modelling of interactions among particles. The approach proposed in this section is a technical development of that proposed in paper [60] for the specific case of vehicular flow modelling. Bearing all above in mind, the modelling is developed on the basis of the following assumptions:

H.3.1. The candidate and/or test particles in $\mathbf{x} \in \Omega$, with velocity $\mathbf{v}_*$ and $\mathbf{v}$, respectively, interact with the field particles in $\mathbf{x}^*$, with velocity $\mathbf{v}^*$ located in its interaction domain Ω, $\mathbf{x}^* \in \Omega = \Omega(x)$ (see Fig. 1).

H.3.2. Interactions are weighted by a suitable term $\eta[\rho](t, \mathbf{x}^*)$, that can be interpreted as an *interaction rate*, which depends on the local density ρ in the position $\mathbf{x}^*$ of the field particles.

H.3.3. The distance and topological distribution of the intensity of the interactions is weighted by a function $w = w(\mathbf{x}, \mathbf{x}^*)$ such that:

$$\int_{\Omega} w(\mathbf{x}, \mathbf{x}^*)\,d\mathbf{x}^* = 1. \tag{20}$$

H.3.4. The candidate particle f_* modifies its velocity $\mathbf{v}_*$ according to the probability density denoted by $\mathscr{A}(\mathbf{v}_* \to \mathbf{v}|\mathbf{v}, \mathbf{v}^*)$, which represents the probability that a candidate particle, with velocity $\mathbf{v}_*$, reaches, in the same position, the velocity $\mathbf{v}$ after an interaction with a field particle with velocity $\mathbf{v}^*$. The density satisfies the following property:

$$\int_{D_{\mathbf{v}}} \mathscr{A}(\mathbf{v}_* \to \mathbf{v}|\mathbf{v}_*, \mathbf{v}^*)\,d\mathbf{v} = 1, \quad \forall \mathbf{v}_*, \mathbf{v}^* \in D_{\mathbf{v}}, \tag{21}$$

while the test particle looses its state $\mathbf{v}$ after interactions with field particles with velocity $\mathbf{v}^*$. In general, $\mathscr{A}$ is not consistent with conservation of momentum and energy. In fact the presence of an activity variable (although the same for all active particles) implies the onset of a behaviour, which modifies the classical conservation laws.

H.3.5. The candidate particle, in $\mathbf{x}$, can proliferate, or be destroyed, with net birth/death rate $\mu(\mathbf{x}, \mathbf{x}^*)$, due to encounters with field particles in $\mathbf{x}^*$.

The derivation of the mathematical framework is obtained by replacing the expression of the gain and loss terms into Eq. (18), where the total derivative of the distribution function has to be written using the transport with velocity $\mathbf{v}$.

The result derived by Assumptions H.3.1–3.5 is, in absence of external field, as follows:

$$(\partial_t + \mathbf{v} \cdot \partial_{\mathbf{x}}) f(t, \mathbf{x}, \mathbf{v}) = \big(G[f] - L[F] + S[f]\big)(t, \mathbf{x}, \mathbf{v}), \tag{22}$$

where

$$G[f] = \int_{\Lambda} \eta[\rho](t, \mathbf{x}^*) w(\mathbf{x}, \mathbf{x}^*) \mathscr{A}(\mathbf{v}_* \to \mathbf{v} | \mathbf{v}_*, \mathbf{v}^*) f(t, \mathbf{x}, \mathbf{v}_*) f(t, \mathbf{x}^*, \mathbf{v}^*)\, d\mathbf{x}^*\, d\mathbf{v}_*\, d\mathbf{v}^*, \tag{23}$$

$$L[f] = f(t, \mathbf{x}, \mathbf{v}) \int_{\Gamma} \eta[\rho](t, \mathbf{x}^*) w(\mathbf{x}, \mathbf{x}^*) f(t, \mathbf{x}^*, \mathbf{v}^*)\, d\mathbf{x}^*\, d\mathbf{v}^*, \tag{24}$$

and

$$S[f] = f(t, \mathbf{x}, \mathbf{v}) \int_{\Gamma} \eta[\rho](t, \mathbf{x}^*) w(\mathbf{x}, \mathbf{x}^*) \mu(\mathbf{x}, \mathbf{x}^*) f(t, \mathbf{x}^*, \mathbf{v}^*)\, d\mathbf{x}^*\, d\mathbf{v}^*, \tag{25}$$

where $\Lambda = \Omega \times D_{\mathbf{v}} \times D_{\mathbf{v}}$ and $\Gamma = \Omega \times D_{\mathbf{v}}$.

As we shall see, some models are such that the density $\mathscr{A}$ is conditioned also by the distribution function of the field particle.

The generalization to a system of several interacting functional subsystems is immediate. It is simply necessary to include interactions of active particles for a large system of n functional subsystems labelled by the index $i = 1, \ldots, n$. Technical calculations yield:

$$(\partial_t + \mathbf{v} \cdot \partial_{\mathbf{x}}) f_i(t, \mathbf{x}, \mathbf{v}) = \sum_{j=1}^{n} \big(G_{ij}[\mathbf{f}] - L_{ij}[\mathbf{f}] + S_{ij}[\mathbf{f}]\big)(t, \mathbf{x}, \mathbf{v}), \tag{26}$$

where

$$G_{ij}[\mathbf{f}] = \int_{\Lambda} \eta_{ij}[\rho_j](t, \mathbf{x}^*) w_{ij}(\mathbf{x}, \mathbf{x}^*) \mathscr{A}_{ij}(\mathbf{v}_* \to \mathbf{v} | \mathbf{v}_*, \mathbf{v}^*) f_i(t, \mathbf{x}, \mathbf{v}_*) f_j(t, \mathbf{x}^*, \mathbf{v}^*)\, d\mathbf{x}^*\, d\mathbf{v}_*\, d\mathbf{v}^*, \tag{27}$$

$$L_{ij}[\mathbf{f}] = f_i(t, \mathbf{x}, \mathbf{v}) \int_{\Gamma} \eta_{ij}[\rho_j](t, \mathbf{x}^*) w_{ij}(\mathbf{x}, \mathbf{x}^*) f_j(t, \mathbf{x}^*, \mathbf{v}^*)\, d\mathbf{x}^*\, d\mathbf{v}^*, \tag{28}$$

and

$$S_{ij}[\mathbf{f}] = f_i(t, \mathbf{x}, \mathbf{v}) \int_{\Gamma} \eta_{ij}[\rho_j](t, \mathbf{x}^*) w_{ij}(\mathbf{x}, \mathbf{x}^*) \mu_{ij}(\mathbf{x}, \mathbf{x}^*) f_j(t, \mathbf{x}^*, \mathbf{v}^*)\, d\mathbf{x}^*\, d\mathbf{v}^*. \tag{29}$$

An interesting development refers to modelling the dynamics of particles, which move from a functional subsystem to another one, as sketched in Fig. 2 (these transitions can be induced both by conservative and proliferative events, see [21]). In this case the mathematical structure is developed as follows:

$$(\partial_t + \mathbf{v} \cdot \partial_{\mathbf{x}}) f_i(t, \mathbf{x}, \mathbf{v}) = \sum_{h=1}^{n} \sum_{k=1}^{n} \big(G^i_{hk}[\mathbf{f}] + S^i_{hk}[\mathbf{f}]\big)(t, \mathbf{x}, \mathbf{v}) - \sum_{j=1}^{n} L_{ij}[\mathbf{f}](t, \mathbf{x}, \mathbf{v}), \tag{30}$$

where

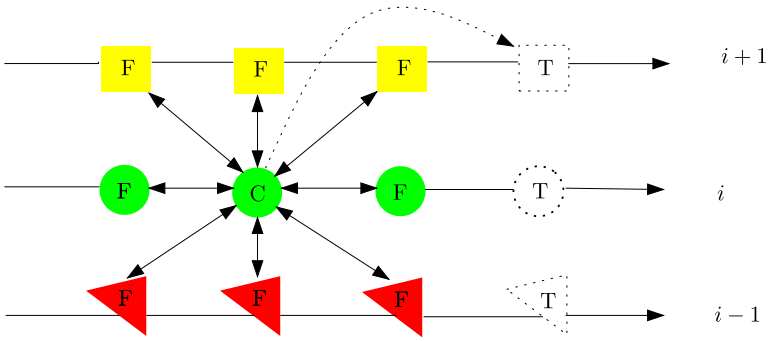

Fig. 2. Transition with change of population. The candidate particle C of the i subsystem interacts with field particles modifies its microscopic state and shift into different functional subsystem.

$$G^i_{hk}[\mathbf{f}] = \int_\Lambda \eta_{hk}[\rho_k](t,\mathbf{x}^*) w_{hk}(\mathbf{x},\mathbf{x}^*) \mathscr{A}_{hk}(\mathbf{v}_* \to \mathbf{v}, h \to i | \mathbf{v}_*, \mathbf{v}^*) f_h(t,\mathbf{x},\mathbf{v}_*) f_k(t,\mathbf{x}^*,\mathbf{v}^*)\, d\mathbf{x}^*\, d\mathbf{v}_*\, d\mathbf{v}^*, \tag{31}$$

and

$$S^i_{hk}[\mathbf{f}] = f_h(t,\mathbf{x},\mathbf{v}) \int_\Gamma \eta_{hk}[\rho_k](t,\mathbf{x}^*) w_{hk}(\mathbf{x},\mathbf{x}^*) \mu^i_{hk}(\mathbf{x},\mathbf{x}^*) f_k(t,\mathbf{x}^*,\mathbf{v}^*)\, d\mathbf{x}^*\, d\mathbf{v}^*, \tag{32}$$

where $\mathscr{A}^i_{hk}(\mathbf{v}_* \to \mathbf{v}, h \to i | \mathbf{v}_*, \mathbf{v}^*)$ and $\mu^i_{hk}(\mathbf{x},\mathbf{x}^*)$ denote, respectively, the probability density of transition into the state $(\mathbf{x},\mathbf{v})$ of the functional subsystem i, and the proliferation/destruction net birth/death rate into the functional subsystem i, due to the encounter with the particles belonging the functional subsystems h and k.

Bearing all above in mind, let us consider the representation analyzed in Section 2, where the velocity variable belongs to the set $I_{\mathbf{v}}$ defined in (15), with components $\mathbf{v}_r$, $r = 1,\dots,R$, while the distribution function is defined in (16), and the space variable remains continuous. Let $f^r(t,x) = f(t,x,v_r)$ and $\mathbf{f}_{I_v}$ be the vector whose components are $f^r(t,x)$, for $r = 1,\dots,R$. In this case the probability density defined in (20) has to be replaced by a discrete density $\mathscr{A}_{pq}(v_p \to v_r) = \mathscr{A}_{pq}(p \to r)$ such that

$$\sum_{r=1}^{R} \mathscr{A}_{pq}(p \to r) = 1, \quad \forall p,q = 1,\dots,R, \tag{33}$$

where $\mathscr{A}_{pq}$ denotes the probability density that a candidate particle with velocity $\mathbf{v}_p$ modifies, in the same position, its state into $\mathbf{v}_r$ after an interaction with a field particle with velocity $\mathbf{v}_q$. This density can be conditioned by the distribution function of the candidate particle.

Technical calculations, in absence of proliferative and/or destructive events, analogous to those we have seen above, yield:

$$(\partial_t + \mathbf{v}_r \cdot \partial_{\mathbf{x}}) f^r(t,\mathbf{x}) = \big(G^r[\mathbf{f}_{I_v}] - L^r[\mathbf{f}_{I_v}]\big)(t,\mathbf{x}), \tag{34}$$

where

$$G^r[\mathbf{f}_{I_v}] = \sum_{p=1}^{R} \sum_{q=1}^{R} \int_\Omega \eta[\rho](t,\mathbf{x}^*) w(\mathbf{x},\mathbf{x}^*) \mathscr{A}_{pq}(p \to r) f^p(t,\mathbf{x}) f^q(t,\mathbf{x}^*)\, d\mathbf{x}^*, \tag{35}$$

and where

$$L^r[\mathbf{f}_{I_v}] = f^r(t,\mathbf{x}) \sum_{q=1}^{R} \int_\Omega \eta[\rho](t,\mathbf{x}^*) w(\mathbf{x},\mathbf{x}^*) f^q(t,\mathbf{x}^*)\, d\mathbf{x}^*. \tag{36}$$

Analogous reasonings and structures can be developed in the case of discrete space variables, which can be seen either as a discrete variable or as a method to identify functional subsystems.

The frameworks proposed in this section refer to a system, which does not interact with the outer environment. These actions are often necessary in modelling systems in life sciences. This topic is dealt with in the next section referring to heterogeneous systems and later focusing with specific applications.

4. Mathematical tools for heterogeneous activity systems

This section is focused on the modelling of systems of active particles when interactions modify both mechanical and activity variable. The guidelines to derive a mathematical framework are those followed in Section 3. Namely, the modelling of stochastic, topological games is developed and, subsequently, the evolution equation for the distribution function over the state of the particles is derived using a balance of particles in the elementary volume of the space of the microscopic states.

In principles, the above program is simply a technical development of the methods used in Section 3. However, rather than looking for a very general structure, it is useful, for modelling purposes [13], looking for suitable specializations. Therefore, let us focus on systems such that:

Conjecture 4.1. *Interactions modify the activity variable according to the topological stochastic games introduced in Section 3, however independently on the distribution of the velocity variable, modification of the velocity of the interacting particles depends also on the activity variable.*

The above conjecture is based on the idea that particles develop an individual strategy that depends on the activity expressed by the other particles, but not by the velocity distribution.

Let us now focus (in the case of one functional subsystem) on the interactions of a candidate or a test particle in $\mathbf{x}$ (with velocities $\mathbf{v}_*$, $\mathbf{v}$, and activity u_*, u, respectively) with the field particles in $\mathbf{x}^*$, with velocity $\mathbf{v}^*$ and activity u^* located in its interaction domain Ω, namely $\mathbf{x}^* \in \Omega$. We assume, as in Section 3, that interactions are weighted by the term $\eta[\rho](t, \mathbf{x}^*)$ interpreted as an *interaction rate*, while the distance and topological distribution of the intensity of the interactions is weighted by the function $w = w(\mathbf{x}, \mathbf{x}^*)$. In details, the following assumption characterizes these interactions:

H.4.1. The candidate particle modifies its state according to the probability density $\mathscr{A}$, which has the following factorization:

$$\mathscr{A}(\mathbf{v}_* \to \mathbf{v}, u_* \to u|\mathbf{v}_*, \mathbf{v}^*, u_*, u^*) = \mathscr{B}(u_* \to u|u_*, u^*)\mathscr{C}(\mathbf{v}_* \to \mathbf{v}|\mathbf{v}_*, \mathbf{v}^*, u_*, u^*), \tag{37}$$

where $\mathscr{A}$ denotes the probability density that a candidate particles with state $(\mathbf{v}_*, u_*)$ reaches the state $(\mathbf{v}, u)$ after an interaction with the field 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^*.

The quantities defined in Assumption H.4.1 are probability densities, therefore the following properties hold true:

$$\int\limits_{D_\mathbf{v} \times D_u} \mathscr{A}(\mathbf{v}_* \to \mathbf{v}, u_* \to u|\mathbf{v}_*, \mathbf{v}^*, u_*, u^*)\, d\mathbf{v}\, du = 1, \quad \forall \mathbf{v}_*, \mathbf{v}^* \in D_\mathbf{v},\ \forall u_*, u^* \in D_u, \tag{38}$$

while after the factorization (36):

$$\int\limits_{D_u} \mathscr{B}(u_* \to u|u_*, u^*)\, du = 1, \quad \forall u_*, u^* \in D_u, \tag{39}$$

and

$$\int\limits_{D_\mathbf{v}} \mathscr{C}(\mathbf{v}_* \to \mathbf{v}|\mathbf{v}_*, \mathbf{v}^*, u_*, u^*)\, d\mathbf{v} = 1, \quad \forall \mathbf{v}_*, \mathbf{v}^* \in D_\mathbf{v},\ \forall u_*, u^* \in D_u. \tag{40}$$

Equating, analogously to the approach of the preceding section, the total variation of f in the elementary volume of the space of the microscopic states yields:

$$(\partial_t + \mathbf{v}\cdot\partial_{\mathbf{x}})\, f(t,\mathbf{x},\mathbf{v},u) = \big(G[f] - L[f] + S[f]\big)(t,\mathbf{x},\mathbf{v},u), \tag{41}$$

where

$$G[f] = \int\limits_{\Lambda\times D_u\times D_u} \eta[\rho](t,\mathbf{x}^*)w(\mathbf{x},\mathbf{x}^*)\mathscr{B}(u_*\to u|u_*,u^*)\mathscr{C}(\mathbf{v}_*\to\mathbf{v}|\mathbf{v}_*,\mathbf{v}^*,u_*,u^*) \times f(t,\mathbf{x},\mathbf{v}_*,u_*)f(t,\mathbf{x}^*,\mathbf{v}^*,u^*)\,d\mathbf{x}^*\,d\mathbf{v}_*\,d\mathbf{v}^*\,du_*\,du^*, \tag{42}$$

$$L[f] = f(t,\mathbf{x},\mathbf{v},u)\int\limits_{\Gamma\times D_u} \eta[\rho](t,\mathbf{x}^*)w(\mathbf{x},\mathbf{x}^*)f(t,\mathbf{x}^*,\mathbf{v}^*,u^*)\,d\mathbf{x}^*\,d\mathbf{v}^*\,du^*, \tag{43}$$

and

$$S[f] = f(t,\mathbf{x},\mathbf{v},u)\int\limits_{\Gamma\times D_u} \eta[\rho](t,\mathbf{x}^*)\mu(\mathbf{x},\mathbf{x}^*,u_*,u^*)w(\mathbf{x},\mathbf{x}^*)f(t,\mathbf{x}^*,\mathbf{v}^*,u^*)\,d\mathbf{v}^*\,du^*\,d\mathbf{x}^*. \tag{44}$$

Of course, if Conjecture 4.1 is not applied, one has simply to suppress the factorization and leave the more general expression of $\mathscr{A}$ instead of the product of $\mathscr{B}$ and $\mathscr{C}$. The conjecture can be simply used for modelling purposes. As already mentioned these densities can, in some specific cases, be conditioned by the distribution function of the field particles.

The generalization to the case of several interacting subsystems, as well as to systems with discrete velocities, is technical. One has to consider interactions with all functional subsystems, in the first case, and with all discrete velocities, in the second case, precisely as we have seen in Section 3. Detailed calculations are reported only in the general case, which includes transition from one functional subsystem to an other. The corresponding mathematical structure, with meaning of notations analogous to that we have seen in Section 3, is as follows:

$$(\partial_t + \mathbf{v}\cdot\partial_{\mathbf{x}})\, f_i(t,\mathbf{x},\mathbf{v},u) = J_i[\mathbf{f}] = \sum_{h=1}^{n}\sum_{k=1}^{n}\big(G^i_{hk}[\mathbf{f}] + S^i_{hk}[\mathbf{f}]\big)(t,\mathbf{x},\mathbf{v},u) - \sum_{j=1}^{n} L_{ij}[\mathbf{f}](t,\mathbf{x},\mathbf{v},u), \tag{45}$$

where

$$G^i_{hk}[\mathbf{f}] = \int\limits_{\Lambda\times D_u\times D_u} \eta_{hk}[\rho_k](t,\mathbf{x}^*)w_{hk}(\mathbf{x},\mathbf{x}^*)\mathscr{B}_{hk}(u_*\to u, h\to i|u_*,u^*) \times \mathscr{C}_{hk}(\mathbf{v}_*\to\mathbf{v}|\mathbf{v}_*,\mathbf{v}^*,u_*,u^*)f_h(t,\mathbf{x},\mathbf{v}_*,u_*)f_k(t,\mathbf{x}^*,\mathbf{v}^*,u^*)\,d\mathbf{x}^*\,d\mathbf{v}_*\,d\mathbf{v}^*\,du_*\,du^*, \tag{46}$$

$$S^i_{hk}[\mathbf{f}] = \int\limits_{\Gamma\times D_u\times D_u} \eta_{hk}[\rho_k](t,\mathbf{x}^*)w_{hk}(\mathbf{x},\mathbf{x}^*)\mu^i_{hk}(\mathbf{x},\mathbf{x}^*,u_*,u^*)f_h(t,\mathbf{x},\mathbf{v},u_*) \times f_k(t,\mathbf{x}^*,\mathbf{v}^*,u^*)\,d\mathbf{x}^*\,d\mathbf{v}^*\,du_*\,du^*, \tag{47}$$

and

$$L_{ij}[\mathbf{f}] = f_i(t,\mathbf{x},\mathbf{v},u)\int\limits_{\Gamma\times D_u} \eta_{ij}[\rho_j](t,\mathbf{x}^*)w_{ij}(\mathbf{x},\mathbf{x}^*)f_j(t,\mathbf{x}^*,\mathbf{v}^*,u^*)\,d\mathbf{x}^*\,d\mathbf{v}^*\,du^*. \tag{48}$$

Specific models, for instance the modelling of immune competition in multicellular systems [30], motivate to study the particular cases in which active particles have a velocity distribution that is constant in time and that is not modified by interactions. Moreover the distribution of particles is uniform in space. In this case, the only interactions that play a role are those involving the activity variable. Therefore, performing the integration with respect to the velocity variable in Eqs. (40)–(43) yields:

$$\partial_t f(t,u) = \eta_0\int\limits_{D_u\times D_u} \mathscr{B}(u_*\to u|u_*,u^*)f(t,u_*)f(t,u^*)\,du_*\,du^* - \eta_0 f(t,u)\int\limits_{D_u}\big[1-\mu(u,u^*)\big]f(t,u^*)\,du^*. \tag{49}$$

Focusing on the more general case of Eqs. (44)–(47), the following structure is obtained:

$$\partial_t f_i(t,u) = \sum_{h=1}^{n}\sum_{k=1}^{n} \int_{D_u\times D_u} \eta_{hk}[\rho_k]\mathscr{B}_{hk}(u_* \to u, h \to i\,|u_*,u^*)\, f_h(t,u_*)\, f_k(t,u^*)\, du_*\, du^*$$
$$+ \sum_{h=1}^{n}\sum_{k=1}^{n} \int_{D_u\times D_u} \eta_{hk}[\rho_k]\mu^i_{hk}(u_*,u^*;u)\, f_h(t,u_*)\, f_k(t,u^*)\, du_*\, du^*$$
$$- f_i(t,u)\sum_{k=1}^{n}\int_{D_u} \eta_{ik}[\rho_k] f_k(t,u^*)\, du^*. \tag{50}$$

The case (44) can be generalized to models with discrete velocities, calculations are not repeated. On the other hand, it is useful showing that the same calculations can be developed also for the discretization of the activity variable as follows: $I_u = \{u_1,\ldots,u_r,\ldots,u_R\}$. Technical calculations, for a one functional subsystem only and supposing that the transition probability density depends on the distribution function, yield:

$$\partial_t f^r(t) = J[\mathbf{f}_{I_u}] = \eta_0 \sum_{p=1}^{R}\sum_{q=1}^{R} \mathscr{B}_{pq}(p\to r) f^p(t) f^q(t) - \eta_0 f^r(t)\sum_{q=1}^{R} f^q(t), \tag{51}$$

where $\mathbf{f}_{I_u}$ denotes the vector of all distribution functions $f^r(t) = f(t,u=u_r)$ corresponding to the discrete value u_r and $\mathscr{B}_{pq}(p\to r)$ denotes the probability density that a candidate particle with state u_p modifies its state into u_r after an interaction with a field particle with state u_q. This term $\mathscr{B}_{pq}(p\to r)$ is such that:

$$\sum_{r=1}^{R}\mathscr{B}_{pq}(p\to r) = 1, \quad \forall p,q = 1,\ldots,R. \tag{52}$$

It is worth observing that some models are such that the dependent variables $\mathbf{x}$ and $\mathbf{v}$ have not a real physical meaning in the sense of mechanical sciences. This aspect induces further technical modifications of the mathematical structure. For instance, the modelling of the term η may include dependence on the state of the interacting active particles.

The above modelling approach, used in the case of closed system, can be generalized to open systems where interactions with the outer environment occur. The mathematical framework reported in the following refers to [17] and is limited to the case of absence of actions on the mechanical variables, and population transition only in the case of proliferation. Further generalizations, such as those of the applications in Section 6, are technical.

The modelling approach takes into account the action of external agents, which may act, for each functional subsystem, either at the macroscopic scale on the variable u, or at the microscopic scale on the distribution function f_i. *Macroscopic actions* are identified by 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:

$$(\partial_t + \mathbf{v}\cdot\partial_{\mathbf{x}}) f_i(t,\mathbf{x},\mathbf{v},u) + \partial_u\big(K_i(t,\mathbf{x},u) f_i(t,\mathbf{x},\mathbf{v},u)\big) = J_i[\mathbf{f}], \tag{53}$$

where $J_i[\mathbf{f}]$ is defined as in (45).

Modelling *external actions at the microscopic scale* means representing functional subsystems of the outer system by the distribution functions:

$$g_r\big(t,\mathbf{x},u^e\big), \quad r = 1,\ldots,n,\ u^e \in D_u \tag{54}$$

given as known functions of space and the variable u^e modelling the activity of the outer functional subsystem. The domain of u^e has been assumed to coincide with that of u.

The action of the outer system generates a dynamics analogous to that of the inner system, namely the modification of the activity variable for each functional subsystem, transition from one subsystem to the other, and proliferative/destructive events. Therefore, referring to [17] for details, the following mathematical structure is derived:

$$(\partial_t + \mathbf{v}\cdot\partial_{\mathbf{x}})\, f_i(t,\mathbf{x},\mathbf{v},u) = J_i[\mathbf{f}](t,\mathbf{x},\mathbf{v},u) + Q_i[\mathbf{f},\mathbf{g}](t,\mathbf{x},\mathbf{v},u), \tag{55}$$

where $J_i[\mathbf{f}]$ is defined as in (45) and the operator Q_i corresponds to interactions to the action of the outer system corresponding to the distribution functions g_r. Particular expressions are given in Section 6.

5. Some reasoning on the modelling approach

The mathematical tools derived in Sections 3 and 4 can be used, and further developed, to model complex systems in life sciences. Before dealing with specific applications, it is worth analyzing the main guidelines to be followed towards this target. A concise introduction to the applications of the next sections is given here to indicate their specific complexity features, that have to be taken into account in the modelling approach. Let us consider, among several ones, the following topics:

(i) Decomposition into functional subsystems;
(ii) Complexity and modelling of interactions focused on mutations and interactions along networks;
(iii) Selection of the appropriate mathematical structure for modelling;
(iv) Specific objectives of the modelling approach.

These issues are dealt with focusing on the applications treated in the next sections, which have been selected also on the basis of their peculiar physical differences.

The mathematical tools we are talking about can be used to deal with a great variety of complex systems, however, in some specific cases, they can be further developed for a deeper understanding of the system under consideration.

Bearing all above in mind, let us consider the problem of the *decomposition into functional subsystems*. As we have seen, the first step towards the treatment of complexity consists in decomposing the overall system into functional subsystems. This strategy allows to reduce the number of variables that characterize the system itself. In some cases, this number is so large that it is difficult, say impossible, to deal with the modelling approach. The decomposition allows to reduce the number of variables to the essential ones, which are specifically related to the objective of the modelling strategy. However, this simplification of physical reality is successful only when it is able to select the variables, which have an effective role in the dynamics that is object of investigation. For instance, the role of the space variable is essential in some specific cases, while in other cases, the space variable can be used to identify the functional subsystem rather than having the classical role in mechanics, namely position of the active particle.

The subsequent step of the modelling approach is the selection of the appropriate mathematical structures among the various ones we have seen in the preceding sections. This matter requires a deep analysis on the complexity of the system attempting to provide an answer to the following questions:

– Is the activity variable heterogeneously distributed and do interactions modify this distribution?
– Do space and velocity variables play a role in the dynamics of the system?
– Does the space distribution of interacting entities affect the strategy developed by them and, hence, the output of the interaction?
– Can rapid mutations of the system modify the ability of interacting entities to express their strategy and, in some cases, generate mutations from one functional subsystem to the other?

An answer to the above queries can be given referring to specific systems and, in particular, to those dealt with in the next sections. For instance, the modelling of opinion formation in homogeneous media, analyzed in the next section (Section 6.1), does not need the space and velocity variables considering that communications through fast media essentially reduce the role of space. On the other hand, if the communication is developed through networks, the space variable plays an important role, while the modelling approach needs further development of mathematical tools.

Still remaining at the example of opinion formation, the space can be viewed as the *localization* of groups of individuals, which are characterized by different ways of receiving and forwarding messages finalized to modify opinions. In this case, the space variable is used to identify different functional subsystems, where the activity variable is the same for all of them, however interactions rules among active particles differ from system to system. Interactions

may occur homogeneously in space, but also along networks identified by different localizations. The modelling needs to take into account different interaction rules related to the topological distribution of the network.

A further aspect to be taken into account is that the modelling rules may change in time for various reasons. For instance, interacting particles can shift from one functional subsystem to an other due to their natural evolution, or the interaction rules may change due according to the overall state of the system. Therefore, the selection of the appropriate mathematical framework has to be specifically referred to the characteristics of the system. This is the case of the application dealt with in Section 6.1, where functional subsystems are identified by group of individuals affected by a virus, which mutates. These mutations can generate shift from one population to the other. Different interaction rules correspond to mutations of the virus.

Sections 3 and 4 presented a variety of mathematical frameworks, which can be subsequently selected with direct reference to each specific system. For instance, if the heterogeneity phenomena for the activity variables are negligible, the tools of Section 3 are sufficient, otherwise methods of Section 4 have to be considered. In general, living systems are characterized by an heterogeneous distribution of the activity variable. However, an homogeneous distribution activity is often assumed as a simplification of physical reality as in the classical modelling approach of vehicular traffic [25].

An additional aspect of the modelling approach is the selection of the use of continuous or discrete variables and the need of considering, or not, mutations. Subsequently, the modelling approach can be focused on the so-called *tables of interaction rules* and *tables of games*, which are specific of the particular system under consideration. These rules can, in some cases, be modified by environmental conditions, for instance, as we shall see in Section 7, when moving from normal to panic conditions in crowds and swarms modelling.

Let us now finally reason on what one can expect from a mathematical model of a complex system. Generally, mathematical models of the inert matter are requested to reproduce both qualitatively and quantitatively empirical data. Moreover, a successful model should reproduce different empirical situations. Far more challenging are the requirements referred to complex living systems, where models are required to reproduce, at least at a qualitative level, emerging collective behaviours, which cannot be directly related to the dynamics of a few entities. Therefore, mathematical models should show emerging behaviours and analyze how these behaviours depend on the parameters of the model as well as on the data that characterize the statement of mathematical problems generated by the application of the model to real physical conditions.

The following sections attempt to enlighten the above considerations focusing on specific applications. Their presentation follows the same guidelines for all of them. Specifically, a brief phenomenological description of the physical system that is object of modelling is followed by the selection of the mathematical structure to be used towards modelling. Subsequently, a survey of the existing literature is referred to these mathematical frameworks, while a critical analysis focused on further developments concludes each section.

It is worth stressing that the contents of the next sections does not naively claim to give an answer to all above queries. The existing literature only provides some preliminary answers, while the aim of this paper also consists at looking at new research developments. Perspective ideas are given in the last section.

6. Modelling complex systems in space homogeneity

This section is devoted to applications where KTAP methods can be developed to model complex systems in life sciences, which are characterized by the following common properties:

(i) The activity variable is heterogeneously distributed over the interacting active particles.
(ii) Active particles can shift from one functional subsystem to the other.
(iii) The velocity and space variables have not a relevant physical meaning in the assessment of the microscopic state.
(iv) Active particles are subject to an external action, which modifies their activity.

Two specific classes of systems are reviewed in the following subsections. The first one concerns social dynamics and opinion formations, while the second one refers to the onset and developments of epidemics with virus mutations. The review is proposed using a common style of presentation: a survey of the existing literature, the assessment of the mathematical structures, a description of specific models, followed by a brief comment on the results of the simulations. The first class of models is based on a structure with discrete activity variable, while continuous variables

are used for the second class of models. The mathematical structures, that act as paradigms for the derivation of models, may need minor modifications with respect to those proposed in Sections 3 and 4.

6.1. On the complexity of social systems and opinion formation

KTAP methods have been applied to model social and/or economical systems where the individual behaviour can possibly have a remarkable role in the overall dynamics of the system. This endeavour has been defined by several scientists as *behavioural economy*, and refers to social systems in a broad sense. Some analogies can be identified with the dynamics of opinion formation, and more in general, with psychological interactions.

Several attempts to combine social sciences and mathematical modelling can be found in the literature. The main branches are agent-based models [10] and social networks [66,68], and [111]. *Agent-based models* are computational models in which interactions among individual (agents) are modelled to understand the emerging behaviour of the macroscopic overall system starting from the microscopic dynamics of each agent. These models have been used to describe a great variety of phenomena of recent times, like the growth of Internet, the arise and diffusion of terrorism, the formation of traffic jams, the onset of financial crisis, the spread of epidemics and social segregation. Notice that all the phenomena listed above are strongly affected by individual or particles interaction and behaviour. The study of *social networks* [71] is receiving growing attention, focusing on their role in determining and constraining social and economical behaviour.

A systematic approach to applications to social dynamics and opinion formation by KTAP methods has been introduced by Bertotti and Delitala [31–34]. Further developments and applications to behavioural economy are given by papers [3] and [4], where the concept of *functional subsystem* has been proposed to identify group of interest, which collectively express the same purpose, or strategic objective, modelled by the activity variable.

This decomposition allows to subdivide a large system into various interacting subsystems identified by the activity they express. Consequently, the overall complexity is reduced, but new mathematical difficulties arise due to the multiscale aspects; in fact, interactions among subsystems, which occur at a larger scale, have to be added to the interactions among the active particles [4]. This feature is analogous to what happens in biology, where the functions expressed by cells are determined by the dynamics at the molecular scale. Therefore, interactions among cells refer to functions expressed by the dynamics at a lower scale (genes, proteins, etc.). This two scale interactions also occur in social, political, and economical systems, as critically analyzed in the last section of this paper.

Bearing all above in mind, let us now introduce the mathematical structures developed in [31] and [34], which allow us to introduce some models both of social dynamics and opinion formations. In this context, the activity variable can attain a finite number of values $I_u = \{u_1, \ldots, u_r, \ldots, u_R\}$, where $u_i \in [0, 1]$ refers to the opinion or the social state of the individuals. R represents the finite number of activity states. The functional subsystem is constituted by individuals; interactions modify only the state of the individuals, but do not generate proliferative and/or destructive events.

Let $\mathbf{f} = \{f^r(t)\}$ and $\mathbf{g} = \{g^r(t)\}$ represent the discrete probability densities that model, for $r = 1, \ldots, R$, respectively, the probability distribution over the activity state and the effect of an external action. $g^r(t) = g(t, u_r)$ is the (known in time) normalized distribution of the external agents, sustaining the rth activity state, and satisfies the following condition:

$$\sum_{r=1}^{R} g_r(t) = 1, \quad \forall t \geqslant 0. \tag{56}$$

The mathematical structure, that is used for the modelling, refers to Eqs. (51) and (55) as follows:

$$\begin{aligned} \partial_t f^r(t) = {} & \sum_{p=1}^{R}\sum_{q=1}^{R} \eta^{pq} \mathscr{B}_{pq}(p \to r) f^p(t) f^q(t) - f^r(t) \sum_{q=1}^{R} \eta^{rq} f^q(t) \\ & + \sum_{p=1}^{R}\sum_{q=1}^{R} \varepsilon^{pq} \mathscr{C}_{pq}(p \to r) f^p(t) g^q(t) - f^r(t) \sum_{q=1}^{R} \varepsilon^{rq} g^q(t), \end{aligned} \tag{57}$$

where the encounter rates η^{pq} and ε^{pq} are supposed to depend on the state of the interacting entities; $\mathscr{B}_{pq}(p \to r)$ has been defined in Section 4; the term $\mathscr{C}_{pq}(p \to r)$ denotes the probability density that a candidate particle with state u_p

modifies its state into u_r after an interaction with an external action, which acts as a field particle, with state w_q. Moreover, $\mathscr{C}_{pq}(p \to r)$, according to its property of probability density, satisfies the following condition:

$$\sum_{r=1}^{R} \mathscr{C}_{pq}(p \to r) = 1, \quad \forall p, q = 1, \ldots, R. \tag{58}$$

The above mathematical structures have been used in the above cited papers [3,4,31–33], and [34]. Two specific models of social dynamics and opinion formations are selected among the above cited ones, and are briefly described in the following with the aim at showing the practical application of KTAP's methods to derive models in life sciences. The first one refers to closed systems, while the second one to open systems. In both cases, we consider one functional subsystem only. Interactions of several subsystems are dealt with in [3] and [4].

Let us introduce the *social dynamics model* proposed in [32], which concerns a society in which individuals, distinguished by their social state (wealth), described by u, undergo competitive and/or cooperative interactions in absence of external actions. The wealth is assessed by social classes whose number R is a parameter of the model. Interactions are modelled by the terms $\mathscr{B}_{pq}(p \to r)$, which define the so-called *table of the games*. The modelling is developed by taking into account the following behaviours:

- The output of interactions, for *individuals with sufficiently close social states*, is such that individuals with the higher social position improve their state, while those in the lower position decrease their state (competitive behavior);
- The output of interactions, for *individuals with not sufficiently close social states*, is such that individuals with the lower social state improve their state, while those in the higher state decrease it (altruistic or cooperative behaviour);
- The parameter m, attaining any integer value between 0 and $R - 1$, models the critical distance, referred to R, between social classes, and separates the competitive from the altruistic behaviour;
- The global wealth $Q = \sum_i u_i f_i$ is preserved.

The detailed expression of the various terms of the table is given in [32]. The qualitative analysis and simulations of the initial value problem aim at showing the role of the parameters and of the initial conditions on the asymptotic behaviour of the solutions, with special attention to the existence and stability of equilibrium configurations.

The mathematical problem is well-posed, namely the solution is proved to exist unique and positive. The dependence of the asymptotic (in time) scenarios on the initial wealth of the system has been studied focusing on special values of the parameters R and m. The qualitative analysis has been limited to "low-dimensional" cases, namely $R = 5$ and $m = 2$. In this case, it has been proved that asymptotically stable equilibrium solutions exist for each value of the initial available wealth Q_0. However, a systematic computational analysis confirms the results obtained by the qualitative analysis for the above particular case also for general choice of the parameters. Simulations show the following:

- A unique equilibrium configuration exists for fixed value of the initial wealth Q_0, which is preserved along the evolution; such an equilibrium configuration with each component different from zero (internal equilibrium) is asymptotically stable for general initial condition. The shape of equilibrium configuration depends on Q_0.
- Large values of Q_0, greater than the critical value $Q_0 = 0.5$, correspond to a trend of the population to a distribution with a number of wealthy individuals larger than the number of poor individuals. The opposite trend is described for small values of Q_0, lower than the critical value $Q_0 = 0.5$.
- The trend for values of Q_0 greater than the critical value $Q_0 = 0.5$ is contrasted by large values of the parameter m, while it is increased for small values of the parameter m. The trend that appears for small values of Q_0, lower than the critical value $Q_0 = 0.5$, is increased by large values of the parameter m, while it is contrasted for small values of the parameter m.

These results are in agreement with the evidence that *the dynamics of a society also depends on the global available wealth*, namely the asymptotic behaviour of a rich country may substantially differ from the one of a poor country,

although the social organization that controls the distribution of the wealth is the same. In other words, the same social organization cannot be applied to both poor and rich countries otherwise it ends up with enlarging social distances.

Let us now consider the model, proposed in [33], which describes the *evolution of opinion distribution within a population* in the presence of external actions (called leaders or persuaders). The number of opinions is identified by the parameter R, while the activity variable u is the opinion of the individuals, and the interactions lead to modifications of opinion. Interactions are modelled by the terms $\mathscr{B}_{pq}(p \to r)$ and $\mathscr{C}_{pq}(p \to r)$, namely the *table of the games*. Their modelling takes into account the following opposite behaviours:

- *Compromise-like processes*: If two individuals have opinions initially sufficiently close, the opinion of the two involved individuals may become closer and closer due to interactions;
- *Boredom-like processes*: A portion of individuals tends to adopt a new opinion (close to the original one) when meeting other individuals who think, about a specific topic, the same way as they do.

The detailed expression of the various terms of the table is given in [33]. Qualitative analysis and simulations aim at showing the role of the external actions on the asymptotic behaviour of the solutions, focused on existence, shape, and stability of equilibrium configurations. A brief summary of results given below refers to papers [33,34], and [35]. Specifically, the qualitative of the initial value problem is developed by methods analogous to those we have seen above for the model of social dynamics and leads to similar results. Namely, the mathematical problem is well posed for general initial data, while for low number of opinions, namely $R = 3$, it has been proved the existence of a unique equilibrium configuration, which is asymptotically stable in the case of persuaders with action constant in time [33]. Moreover, the existence of a globally attractive periodic solution has been proved in [34] for the case of periodic-in-time actions of the persuaders. Clustering of opinions has been analyzed in [35] for special choice of parameters. Simulations confirm the results given by the approach proposed in [55], motivated and supported by the empirical data of opinion formation. Specifically, starting from a generic distribution of opinions over the individuals in a group, empirical data show that, depending on the topology of the interactions and on the "open-mindness" of the individuals, the consensus emerges on one single opinion, or, if the individuals are more "closed-minded", on more different opinions.

6.2. On the modelling of epidemics with virus mutations

The mathematical literature on epidemics has been developed by several authors using either ordinary differential equations or partial differential equations with internal structure. The research activity is documented in various books [62,98,106,112], as well as in the review paper [49], and therein cited bibliography.

KTAP mathematical methods can be used to model the heterogeneous distribution of the intensity of epidemics with virus mutations and competition with the immune and specific therapies. The application follows the guidelines offered by the pioneer paper [59], subsequently developed in [57].

The modelling refers to a large system constituted by several interacting individuals: they initially are in a healthy state, then become carriers of a virus, which in turn progressively evolves toward more aggressive states and eventually mutates into new forms. Interactions between individuals may cause infections and the transition of the individuals from one pathological state to another.

The system may be decomposed into n populations of interacting individuals, labelled by the subscript i ($i = 1, \ldots, n$) and regarded as functional subsystems. The following populations are considered: $i = 1$, which denotes healthy individuals whose microscopic state models the susceptibility to contract the pathological state; $i = 2$, which denotes individuals healthy carriers of the virus, whose microscopic state models the infectivity of the virus; $i = 3, \ldots, n$ that denote the individuals affected by the virus at the first and subsequent stages, whose microscopic state models the progression of both the infectivity and the pathological state.

The overall state for each population is described by the distribution function f_i over the microscopic state normalized with respect to the number N_{01} of individuals belonging to the population $i = 1$ at the time $t = 0$. The therapeutical actions on the individuals of different populations are described by the distribution functions $\mathbf{g}(t, u^e) = \{g_i(t, u^e)\}$ with $i = 1, \ldots, n$, over the microscopic state related to the level of the pathology: g_i is normalized, as well as f_i, with respect to the number N_{01}. A simplified assumption is the following: $g_i(t, u^e) = \zeta_i(t)\varphi_i(u^e)$ where $\varphi_i = \varphi_i(u^e)$ models the intrinsic properties of the therapy acting on the individuals of the ith population, and $\zeta_i(t)$ is the intensity of

the application over time. The factorization indicates the different effects due to the time length and to the typology of the therapeutical treatment. Moreover, the distribution function $g_i(t,u^e)$ is defined over the same domain as $f_i(t,u)$.

The therapeutical action has different effects according to the specific population of the individuals which undergo the treatment. In general, it induces a regression of the pathological state, which could possibly result, for individuals belonging to the populations $i \geqslant 3$, in a transition to a different population, characterized by a lower intensity of the pathology. The corresponding mathematical structure is similar to (50) where the interaction rate between individuals does not depend on the densities but on the populations of the interacting individuals. In addition, as in (55), the presence of the external actions is included. Specifically, it writes:

$$\begin{aligned}\partial_t f_i(t,u) = {} & \sum_{h=1}^{n}\sum_{k=1}^{n} \int_{\mathbb{R}^+\times\mathbb{R}^+} \eta_{hk}\mathscr{B}_{hk}(u_* \to u, h \to i|u_*,u^*) f_h(t,u_*) f_k(t,u^*)\,du_*\,du^* \\ & - f_i(t,u)\sum_{k=1}^{n}\int_{\mathbb{R}^+}\eta_{ik} f_k(t,u^*)\,du^* \\ & + \sum_{h=1}^{n}\sum_{k=1}^{n}\zeta_k(t)\int_{\mathbb{R}^+\times\mathbb{R}^+}\mu_{hk}\big(u_*,u^{e*}\big)\mathscr{C}_{hk}\big(u_*\to u,h\to i|u_*,u^{e*}\big) f_h(t,u_*)\varphi_k\big(u^{e*}\big)\,du_*\,du^{e*} \\ & - f_i(t,u)\sum_{k=1}^{n}\zeta_k(t)\int_{\mathbb{R}^+}\mu_{ik}\big(u,u^{e*}\big)\varphi_k\big(u^{e*}\big)\,du^{e*}. \end{aligned} \tag{59}$$

A specific model with 4 populations has been proposed in [57] to model the progression of the virus toward more aggressive states, corresponding to:

- $n = 1$: normal (healthy) individuals,
- $n = 2$: individuals carrier of the pathology,
- $n = 3$, $n = 4$: individuals with the first and second stage of mutations of the virus.

The modelling of the external actions is simply referred to the action of the immune system. Specifically, all distribution functions $g_i(t,u^e)$ are assumed to be characterized by a constant intensity and by an exponential decay with respect to the activity u^e.

The table of the games has been modelled assuming that:

- The probability of infection increases when the intensity of the pathological state and virus mutations increase, and correspondingly the action of the immune system decreases.
- Individuals in a certain population can shift to an higher one, due to evolution of the virus.

A detailed description of the above assumptions are given in [57], where the interested reader is addressed for a deeper insight into this topic.

Simulations are obtained by solving the initial value problem for Eq. (59), which is "well posed", as documented in [57]. Various interesting phenomena are reproduced by the dynamics described by the model: in particular, the empirical evidence, see for instance [62], of the emergence in time of individuals carriers of virus at the most aggressive stage, and eventually carriers of new more aggressive pathology related to the virus mutations. This phenomenon may be related to a Darwinian type evolution, which leads to the selection of the most fitting (aggressive) type of virus. The immune system plays an active role in contrasting the virus and selecting the most fitting one.

In details, simulations have been developed in the following cases:

(i) *Absence of the action of the immune system*: The model describes the progressive evolution of the epidemics towards higher pathological cases. The heterogeneity of distribution of the progression of viruses over the population is well depicted in [57]. Moreover, the mutation into a new type of virus is highlighted with graphs showing the increase of individuals affected by virus at different mutation stages.

(ii) *Presence of the action of the immune system, still not yet sufficient to deplete the pathology*: The action of the immune system is able to contrast partially the progression, and, therefore, the onset of the progressing state is only partially reduced. Simulations show that the immune system is able to contrast the less aggressive components of the virus, but is not able to contrast the virus in the individuals affected by the virus at the more aggressive stages.

(iii) *Presence of the action of the immune system sufficient to deplete completely the pathology*: The different action of the immune system is obtained by increasing the values of the parameters that characterize the defense ability of the immune system.

It is worth stressing that in this model the defense of the immune system is applied by two specific actions: the intensity of the action and the ability to identify the progression state of the virus. On the other hand, the progression state of the virus evolves in time while the identification ability decays with increasing progression. Therefore, it follows that the action of the immune system, if not sufficient after a suitable short time, may become not any longer effective.

6.3. Critical analysis

The two classes of models reviewed in the preceding section identify suitable examples of complex systems, where the KTAP methods can be applied to model systems where space and velocity do not play a relevant role in the identification of the microscopic state of the active particles. Further developments of the modelling approach require additional analysis focused on the role of the space variable, whose discretization can be used to identify geographical regions related to functional subsystems. Generally, regions are linked in networks, and this aspect should be taken into account to model interactions among individuals.

The case of evolution of epidemics appears to be technically different considering that interactions among individuals are possible only within regions, while migrations can occur from one region to the other with space diffusion of the epidemics. Therefore, research activity can be focused on further developments of the model reviewed in Section 6.2 to include this type of dynamics. The generalization can possibly include birth and death events that occur in most biological systems.

According to the above reasonings, it can be stressed that the mathematical structures reported in Sections 3 and 4 may offer a useful reference framework. However, applications generally need, as we have seen, further technical developments to capture the specificity of each system under consideration.

7. Modelling complex system in space heterogeneity

This section deals with a review of models, derived using KTAP's methods, of complex systems where active particles are heterogeneously distributed in space. More in details, models refer to vehicular traffic, pedestrian crowds, and swarms.

Methods of the generalized kinetic theory have been applied to model vehicular traffic since the pioneer book by Prigogine and Hermann [100], who arguably were the first ones to introduce the use of a mathematical approach to model systems of non-classical particles. Subsequently, various developments have been produced by applied mathematicians and physicists as documented in the review papers [22,74,87]. A modelling approach specifically based on the mathematical structures proposed in Section 4 has been proposed in [60], and subsequently developed by various authors as we shall see in Section 7.1. The objective of the modelling consists in reproducing quantitatively empirical data and depicting behaviours that are observed at a qualitative level such as bottleneck, jumps formation and emerging cluster of vehicles. Moreover, a model should include parameters, possibly in a limited number, that can be technically identified.

Mathematical modelling of pedestrian crowd has been mainly developed at the microscopic scale [75,76], and at the macroscopic scale [23,80,84,108]. Methods of the kinetic theory of active particles can be properly developed to model crowd dynamics following the guidelines offered by this paper as we shall see in Section 7.2. However, this research line is still at an early stage.

Modelling the dynamics of swarms represents a challenging research objective for applied mathematicians. It is still a perspective considering that at the moment the literature in the field is limited to various reasonings that are

still preliminary to a detailed modelling approach. Section 7.3 reports about this topics. Therefore, the contents of this section gradually move from a review of the existing literature to challenging perspectives. The special issue [18] provides additional bibliographical citations on crowd and flock modelling.

7.1. On the modelling of vehicular traffic

Motivations to use KTAP's methods to model vehicular traffic are offered by the criticisms raised in Daganzo's paper [54], where the heterogeneous distribution of the quality of the driver-vehicle subsystem is stressed in contrast with the existing literature, where this aspect is substantially ignored. Moreover, paper [54] also criticizes the assumption of continuity of the distribution function over the microscopic state of vehicles considering that the number of interacting entities is not large enough to justify this assumption.

The second criticism is taken into account in [51] and [60], where the granular nature of traffic is modelled by kinetic type models with discrete velocities. Therefore, the overall state of the system is described by a discrete probability distributions over groups of vehicles with velocity within a certain velocity range. Specifically, it is observed that vehicles travelling along a road do not span with continuity the whole set of admissible velocities; rather, they tend to move in clusters, which can be identified and distinguished from each other by a discrete set of velocity values. The discretization creates cells in the velocity space for vehicles whose velocity belongs to these cells.

The first step of the modelling approach consists in the assessment of the mathematical representation. Referring to paper [60], the modelling is developed taking into account the following assumptions:

- The traffic flow is along a road in which only the longitudinal motion is explicitly accounted (lateral displacement are not physically considered).
- The individual state of vehicles is delivered by dimensionless quantities, namely position $x \in [0, 1]$, referred to the length of the vehicle, and velocity $v \in [0, 1]$, referred to the maximal velocity V_ℓ that can be reached by an isolated vehicle.
- As in (15), the velocity variable is discretized into the set: $I_v = \{v_1 = 0, \ldots, v_r, \ldots, v_R = 1\}$.
- The overall state of the system is delivered by the discrete distribution function $f^r = f(t, x, v_r)$, $r = 1, \ldots, R$, that naturally implies that the number of vehicles with a velocity larger than V_ℓ can be neglected. The function weighting the interactions over the visibility zone on front of the driver is indicated as $\omega(x, x^*)$.
- Interactions are binary, but non-localized: an interaction length is introduced, which defines a visibility zone for each vehicle. The final outcome on the speed of the candidate vehicle is then determined by a weighted average of the interactions with all of the field vehicles in its visibility zone.
- The flux of vehicles depends on the road conditions.

Under the above assumptions, a finite number of velocity classes is identified, and the distribution function f can be written as a linear combination of R Dirac functions

$$f(t, x, v) = \sum_{r=1}^{R} f^r(t, x)\delta(v - v_i).$$

Accordingly, macroscopic quantities are obtained by weighted sums. For instance, mass density and flow are given by:

$$\rho(t, x) = \sum_{r=1}^{R} f^r(t, x), \tag{60}$$

and

$$q(t, x) = \sum_{r=1}^{R} v_r f^r(t, x) = \rho(t, x)\,\xi(t, x), \tag{61}$$

where ξ is the mean velocity. Analogous calculations can be performed for second order quantities such as energy and velocity variance.

The mathematical structure used for the modelling is a technical particularization of the ones we have seen in Section 4, Eqs. (33), (34) and (35). Specifically:

$$\begin{aligned}\partial_t f^r(t,x) + v_r \partial_x f^r(t,x) &= J[\mathbf{f}_{I_v}](t,x)\\ &= \sum_{p=1}^{R}\sum_{q=1}^{R}\int_{\Omega} \eta[\rho](t,x^*) w(x,x^*) \mathscr{A}_{pq}(p\to r)[\rho](t,x^*) f^p(t,x) f^q(t,x^*)\,dx^*\\ &\quad - f^r(t,x)\sum_{q=1}^{R}\int_{\Omega}\eta[\rho](t,x^*) f^q(t,x^*)\,dx^*, \end{aligned} \tag{62}$$

where $\mathbf{f}_{I_v}$ denotes the vector of all $f(t,x,v_r)$, $\eta[\rho]$ defines the rate of interaction between vehicles, and $\mathscr{A}_{pq}(p\to r)[\rho]$ defines the so-called *table of games*, which models the microscopic interactions among the vehicles by giving the probability that a vehicle with speed v_p adjusts its velocity to v_r after an interaction with a vehicle travelling at speed v_q. The table of games $\mathscr{A}$ is modelled by assuming that the interactions among the vehicles are affected by the macroscopic conditions of traffic through the local density ρ. Moreover, $\mathscr{A}$ satisfies the additional requirements:

$$\mathscr{A}_{pq}(p\to r)[\rho](t,x^*) \geqslant 0, \qquad \sum_{r=1}^{R}\mathscr{A}_{pq}(p\to r)[\rho](t,x^*) = 1, \quad \forall p,q\in\{1,\dots,R\}, \tag{63}$$

and for all $\rho\in[0,1]$.

The model considered in [60] is obtained following the four key points:

- The rate η of the interactions among the vehicles is inversely proportional to the mean free space locally found along the road estimated via the quantity $1-\rho$ (recalling $\rho=1$ represents the road capacity) with $\rho\in[0,\,1)$.
- The weight function is uniform in the visibility zone of the driver.
- A phenomenological parameter $\alpha\in[0,1]$ is incorporated in the table of the games, whose lower and higher values are related to bad and good road conditions respectively.
- The table of games is derived assuming that low vehicles are attracted by fast vehicles, while fast vehicles are obliged to slow down when interacting with slow ones if they are unable to pass by. Moreover, the probability of modifying the velocity (both acceleration and deceleration) linearly increases with the quality of the road, and decreases with the density; it reaches the maximal value for $\alpha=1$ and $\rho=0$.

The qualitative analysis developed in the spatially homogeneous case in [60] shows the well-posedness of the initial value mathematical problem of the model. Moreover, it is proved the existence of at least one equilibrium point in a suitable positively invariant set. The uniqueness of a stable equilibrium point is proved only for particular cases corresponding to low number of velocities ($R=3$).

Simulations in the spatially homogeneous case confirm and generalize the results of the qualitative analysis. Moreover, they show that the model quantitatively depicts, in steady uniform conditions, the empirical data critically analyzed by Kerner [85] as they are represented in the velocity diagram, namely mean velocity versus density at equilibrium. The result, precisely as in [85], shows that the velocity keeps it maximal value until ρ reaches a critical value ρ_c, subsequently it shows a rapid localized decrease followed by a smooth decay to zero when ρ tends to one.

Simulations in the spatially non-homogeneous case have shown a variety of emerging behaviours that are empirically observed. In details, several phenomena are highlighted:

- *Formation of a queue* due to the accumulation of incoming vehicles behind a pre-existing group of motionless vehicles. Starting with an initial condition where all distribution functions are set to zero except the one corresponding to the first velocity, which is assumed constant, simulations show the expected enlargement of the plateau due to a backward propagation of the queue toward the inflow boundary, with a nearly constant maximum value of the density located in the rear part of the group of vehicles. The opposite phenomenon is also shown with a slow down-flowing of the vehicles from the right boundary, with a progressive emptying of the queue.
- *Bottleneck and the effect on the traffic* of a variation in the maximum density allowed along the road. This situation may arise as a consequence of a reduction in the number of lanes available to the vehicles, or more in general

because of a narrowing of the roadway, and is usually referred to as a bottleneck. As in the previous problem, formation and backward propagation of a queue are observed.

- *Cluster merging* when overtaking is forbidden. This may be due, for instance, to very bad road conditions or to some sort of special limitations imposed on the traffic, and it can be formally obtained by setting $\alpha = 0$ in the table of games. The result is that vehicles simply tend to maintain their current speed, until they reach other slower vehicles when they are forced to slow down to the velocity of the leaders and to queue, no matter how much free space is actually available on the road. Simulations in this case show also the formation of *stop-and-go waves* in the rear cluster as a reaction to the velocity transitions occurring immediately after the encounter with the front one. These waves, that finally smooth out as the velocity within the rear cluster becomes uniform, are reproduced thanks to the dislocation of the interactions, which forces the leading vehicles of the rear cluster to realize first the need for slowing down while approaching the front cluster.

It is worth stressing that the above model is characterized by one parameter only, corresponding to the quality of the road-environment outer system. Moreover, simulations show that, in homogeneous situations, increasing values of α correspond to increasing values of ρ_c. The above relation between α and ρ_c suggested the practical identification of α by direct measurement of ρ_c, see [38].

The above modelling approach has been further developed in some recent papers. For instance, Bonzani and Gramani in [37] analyze multilane flows, where each lane represent a different functional subsystem, and confirm the predictive ability of emerging behaviours delivered by the model. Moreover, Gramani [72] analyzes the role of the activity variable, in the simplest assumption of constant probability distribution over such a variable, and confirms the empirical observations by Kerner [86]. Specifically, it is shown that the velocity diagram and the speed variance versus density for a constant distribution of the activity variable are as those depicted by model [60] and that the largest values of fluctuations are localized corresponding to transition from free to congested flow.

The analysis of [72] is limited to the case of constant, with respect to time, probability distribution of the activity variable. The distribution is only modified by interactions among vehicles and depends on local density conditions. This perspective idea can be applied to the discrete velocity model of paper [72] where the distribution function includes the activity variable, namely:

$$f(t,x,v,u) = \sum_{r=1}^{R} \delta(v - v_r) f^r(t,x,u), \tag{64}$$

by considering, as in Eq. (37) of Section 4, the transition probability density $\mathscr{A}$ to be given by the product of the density corresponding to variation of velocity $\mathscr{C}$ and that corresponding to variation of activity $\mathscr{B}$. The former is modelled as in [72], where a measure of the quality is given by the product of α per u, while the latter corresponds to a mixing dynamics on the activity. A possible modelling choice for the mixing dynamics is such that the behaviour of the driver-vehicle micro-system tends to a common value with increasing density; specifically, when the density increases the behavioural differences decrease, while in jam conditions all vehicles show the same behaviour.

The main issue to be remarked is that this perspective idea of modelling the heterogeneous behaviour of the driver-vehicle micro-system is necessary to explain emerging behaviours that are empirically observed.

7.2. Some reasonings about crowds modelling

Modelling of crowd dynamics, similarly to the approach used for vehicular traffic, can be developed at the three representation scales corresponding to individual dynamics (microscopic), locally averaged (macroscopic) quantities, and statistical distribution over the microscopic state (statistical scale).

The literature in the field is almost limited to the approach at the microscopic scale as documented by the activity developed by Helbing and coworkers, among various papers [75,76]. The approach at the macroscopic scale has been settled by Hughes [84], and subsequently developed by various authors [23,24,50,77,78], by means of classical methods of continuum mechanics based on the use of mass and momentum conservation equations properly closed by phenomenological models modelling the relation of the acceleration term, or mean velocity, to local flow conditions. Recently, paper [99] has considered discrete-time modelling by means of a family of measures, which provide an estimate of the space occupancy by pedestrians in time.

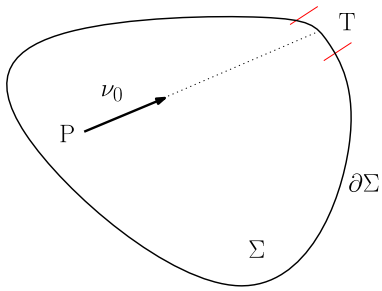

Fig. 3. Geometry of the crowd domain.

The interest in this type of modelling is not purely speculative, for instance the papers by Venuti et al. [108–110], are focused on the modelling of the interactions between crowds and lively footbridges and related structural analysis. Moreover, Helbing studies the panic conditions and evacuation problems [77], while detailed calculations of pilgrim's Jamarat bridge, where overcrowding is the cause of frequent accidents, have been developed by Coscia and Canavesio in [50], and by Helbing and coworkers [79].

This section aims at showing how the mathematical structures proposed in the preceding sections can be used to model crowd dynamics in bounded domains whose geometry is represented in Fig. 3. Only a few guidelines are given in the following to be properly developed within an appropriate research project.

Let us consider a distribution function of the type $f = f(t, \mathbf{x}, \mathbf{v})$ where the activity is assumed to be constant i.e. assuming that individuals behave in the same way, and the space variable is dimensionless being divided by the characteristic length ℓ of the domain Σ, while the velocity is divided by the maximal velocity V_ℓ that can be reached by an isolated individual.

The mathematical structure to be used for modelling is as follows:

$$\begin{aligned}\partial_t f(t,\mathbf{x},\mathbf{v}) + \mathbf{v}\cdot\partial_{\mathbf{x}} f(t,\mathbf{x},\mathbf{v}) &= J[f](t,\mathbf{x},\mathbf{v})\\ &= \int_\Lambda \eta[\rho](t,\mathbf{x}^*)w(\mathbf{x},\mathbf{x}^*)\mathscr{A}(\mathbf{v}_*\to\mathbf{v}|\mathbf{v}_*,\mathbf{v}^*)[\rho]f(t,\mathbf{x}_*,\mathbf{v}_*)f(t,\mathbf{x}^*,\mathbf{v}^*)\,d\mathbf{v}_*\,d\mathbf{v}^*\,d\mathbf{x}^*\\ &\quad - f(t,\mathbf{x},\mathbf{v})\int_\Gamma \eta[\rho](t,\mathbf{x}^*)w(\mathbf{x},\mathbf{x}^*)f(t,\mathbf{x}^*,\mathbf{v}^*)\,d\mathbf{v}^*\,d\mathbf{x}^*,\end{aligned} \tag{65}$$

where all quantities appearing in this equation have been defined in Section 3 and the transition density function $\mathscr{A}$ is assumed to depend on the local density.

A necessary preliminary observation is that a crowd generally has a target, therefore some geometrical notations are necessary to identify it. Let us consider a crowd moving in a two-dimensional domain Σ with boundary $\partial\Sigma$. The geometry is represented in Fig. 3, which shows an outlet zone corresponding to evacuation, for instance a point T of the boundary corresponding to the exit. The geometry can be further modified by inserting internal obstacles and an inlet zone. Therefore, given a target point $T = (x_T, y_T)$ inside Σ, the pedestrian direction is identified by the unit vector from $P = (x, y)$ to the target T:

$$\boldsymbol{v}_0(x,y) = \frac{x - x_T}{\sqrt{(x-x_T)^2 + (y-y_T)^2}}\boldsymbol{i} + \frac{y - y_T}{\sqrt{(x-x_T)^2 + (y-y_T)^2}}\boldsymbol{j}, \tag{66}$$

where $\boldsymbol{i}$ and $\boldsymbol{j}$ are two unit orthogonal vectors in a two-dimensional domain.

The modelling problem consists in the characterization of the terms η, w, $\mathscr{A}$, while the mathematical problem needs, in addition to the initial condition, also the statement of boundary conditions, unless the modelling refers to crowds in unbounded domains. Some reasonings are here briefly proposed focusing on the differences between traffic and crowd modelling. Moreover, the implications of the onset of panic conditions are considered.

– The modelling of the interaction rates can be developed similarly to the case of vehicular traffic, namely by increasing the interaction rate with increasing local density.

– The assumption that the weight w decays with the distance is not a general rule. Indeed, different contexts (e.g. a match at a stadium, the pilgrims location, the escape from fire, etc.) lead to different pedestrian behaviour; for instance clustering phenomena do not always follow the same rules as attraction, and repulsion depends on the specific strategies expressed by the individuals composing the crowd.
– Panic conditions modify the dynamics of interactions in various ways, for instance by increasing quantitatively the interaction rate and by disregarding the target in favor of clustering.
– The statement of boundary conditions must be carefully developed, taking into account the active particles leaving $\partial\Sigma$ and those moving to $\partial\Sigma$. This topic is dealt with in [58] by suitable development of methods of the classical kinetic theory.

The above essential indications have to be regarded, as already mentioned, as preliminary hints to develop a specific research program.

7.3. Can mathematics deal with the modelling of the beautiful shapes of swarms?

Modelling of swarms is an attractive research perspective, which is motivated not only by the difficulty of this objective, but also by the observation of the beauty of the shapes formed by birds, which appear in the sky during spring and autumn periods. Analogous phenomena are, however, observed in various living systems such as fishes, which try to escape the attack of a predator; or cells, which aggregate forming particular, smooth or irregular, shapes, see [40,82]. The mathematical literature in the field does not yet offer sufficiently formalized results able to lead to predictions delivered by solutions of mathematical equations. Therefore, this subsection reports only some perspective ideas that can be hopefully transferred into a mathematical approach.

Preliminarily, it is worth indicating some specific features of the dynamics of swarms including a critical analysis of various technical difficulties that have to be tackled in dealing with the modelling of swarms:

(i) Interactions between active particles of a swarm are in three space coordinates, while those of particles of a crowds are defined in two space coordinates.
(ii) The domain occupied by the swarm evolves in time; the map from the initial configuration Σ_0 to the configuration at time t, Σ_t has to be computed by the solution of a free boundary conditions, where the initial condition included the initial shape of the domain Σ_0.
(iii) Generally, swarms refer to animal behaviours, which differ from population to population and that can be modified by external actions that can induce panic. Namely, a swarm in normal conditions has a well defined objective, for instance reaching a certain zone starting from a localization. However, panic conditions can modify the overall strategy to pursue this objective, which is consequently modified.
(iv) In all cases, a swarm has the ability to express a common strategy, which is a non-linear elaboration of all individual contributions, generated by each individuals based on the microscopic state of all other individuals.
(v) The dynamics of interactions differs in the various zones of the swarm. For instance, from the border to the center of Σ. Stochastic behaviours are an essential characteristics of the dynamics.
(vi) The above mentioned strategy includes a clustering ability (flocking) that prevents the fragmentation of Σ_t. Moreover, when a fragmentation of Σ_t occurs, the clustering ability induces an aggregation.
(vii) The concept of swarm can be extended to various types of micro organisms and ultimately to cells in a multicellular system. In this case the strategy expressed by the interacting entities depends on the biological functions that characterize the population. Moreover, the modelling approach should include proliferative and/or destructive events.

The mathematical literature on swarm modelling is very limited with respect to that related to traffic and crowds. Moreover, although the scaling and representation is analogous, different modelling approaches have been proposed in the literature. Among others, stochastic differential equations [2], macroscopic equations derived from stochastic perturbation of individual dynamics [48,56], modelling swarming patterns [43,65,107], and flocking phenomena [63], [52] and [53].

Summarizing, the modelling approach should take into account that fluctuations are an intrinsic feature of the systems under consideration. Moreover, it is worth mentioning that recent studies [11] conjecture, on the basis of

empirical data, that some systems of animal world develop a common strategy based on interactions depending on topological rather than metric distances. This definitely is a valuable suggestion to be used towards modelling. In general a swarm has the ability to express a collective intelligence that is generated by a cooperative strategy [36,111]. The interested reader can find further details on the subject in [95] and [104].

A deep insight on emerging strategies needs to be specifically referred to the type of individuals composing the swarm [12,61]. Heterogeneity of individual behaviours plays an important role in the dynamics of swarms of cells in biology [21], where several complex events, such as proliferative/destructive events or mutations, may arise in short time intervals.

Stochastic behaviours of swarms suggest to modify the governing mathematical structure. A conceivable approach, worth to be properly investigated, is the following:

$$\partial_t f(t,\mathbf{x},\mathbf{v}) + \mathbf{v}\cdot\partial_{\mathbf{x}} f(t,\mathbf{x},\mathbf{v}) = J[f](t,\mathbf{x},\mathbf{v}) + \frac{1}{\tau}\mathscr{L}(t,\mathbf{x},\mathbf{v}), \tag{67}$$

where the term

$$\mathscr{L}[f] = \int_{D_{\mathbf{v}}} \big[T(\mathbf{v},\mathbf{v}_*;\mathbf{x})\, f(t,\mathbf{x},\mathbf{v}_*) - T(\mathbf{v}_*,\mathbf{v};\mathbf{x})\, f(t,\mathbf{x},\mathbf{v})\big]\, d\mathbf{v}_*, \tag{68}$$

models a linear velocity-jump process, where τ is the mean run time, hence ν is the turning rate or turning frequency, and $T(\mathbf{v},\mathbf{v}_*;\mathbf{x})$ is the probability kernel for the new velocity $\mathbf{v}\in D_{\mathbf{v}}$ assuming that the previous velocity was $\mathbf{v}_*$. This corresponds to the assumption that individuals choose any direction with bounded velocity. Specifically, the set of possible velocities is denoted by $D_{\mathbf{v}}$, where $D_{\mathbf{v}}\subset\mathbb{R}^3$, and it is assumed that $D_{\mathbf{v}}$ is bounded and spherically symmetric (i.e. $\mathbf{v}\in D_{\mathbf{v}} \Rightarrow -\mathbf{v}\in D_{\mathbf{v}}$). Such a kernel can be assumed to depend on the localization within Σ_t.

The above indications need to be regarded as a very preliminary step towards the development of models suitable to describe the complex dynamics of the system under consideration. Possibly, research project can be developed by using the kinetic theory methods reviewed in the preceding sections, where the modelling of the interaction terms should take into account the qualitative indications given above.

8. Looking forward

The contents of this paper have been proposed in two parts. The first part is focused on mathematical tools of the KTAP developed to model living systems. The second one has shown, by means of specific applications, how these tools can be applied to derive mathematical models for systems, where the dynamics of a few entities does not straightforwardly generate that of the whole system. Emerging collective behaviour does not appear to be related to the individual dynamics and not even to the dynamics of a few entities. Indeed the strategy developed by the interacting individuals depends on their density and topological distribution.

Although the KTAP methods appear to be appropriate to modelling a broad variety of systems belonging to different fields of life sciences, looking forward to further developments can take advantage of an additional critical analysis. Therefore, this final section attempts to give an answer to the following two specific questions which can be posed among others:

(i) Are complex systems characterized by common features, and, if so, is it reasonable to ask oneself if it is possible to extract some common features for all of them? Consequently, do the mathematical structures reported in Sections 3 and 4 have the ability to set them into a mathematical framework?
(ii) Considering that complex systems can be observed and represented at different scales, how can the KTAP methods deal with this multiscale issue?

The following two subsections deal with the above queries, while the third one provides some hints for future research.

8.1. Common features of complex systems focused on mathematical structures

Let us consider the identification of the common features that characterize complex living systems, and also focused on some specific applications, with the aim of showing how the KTAP theory can deal with them. The following issues have been selected:

- *Expression of strategic ability*: Living systems have the ability to express an individual strategy that modifies laws of classical mechanics and, in some cases, generates proliferative and/or destructive processes. As a consequence, the state of the interacting entities should include variables that are suitable to describe the strategy they express. This aspect is dealt with by introducing an *activity variable*, which modifies the dynamics at the microscopic level according to the strategy developed by interactions with other active particles.
- *Complexity induced by a large number of variables*: Most of the systems under consideration need the use of a large number of variables to define their overall state. This aspect specifically refers to the activity variable. Therefore, the number of equations needed by the modelling approach may be too large to be practically treated. The mathematical approach is such that the selection of the activity variable corresponds to the decomposition of the overall system into functional subsystems, whose elements collectively express a specific strategy.
- *Heterogeneity*: The expression of strategy is heterogeneously distributed. Consequently, the dynamics of the system is stochastic, namely the deterministic expression of a reductionistic approach should be replaced by a stochastic representation with random variables.
  KTAP methods take into account this aspect within the framework of a conjecture of factorization of the probability density that models interactions into the densities that modify the activity variable and that modify the velocity. In several cases, heterogeneity is an important characteristic of complex systems. For instance, in vehicular traffic flow, it can explain the transition from free to congested flow by a remarkable increase of the velocity variance [85,86]. This aspect has been only considered in recent literature, while the traditional approach was based on the assumption of homogeneous activity variable.
- *Interactions*: Interactions modify the state of the active particles according to the strategy they express, on the basis of the space and state distribution of the other particles. The strategy can be modified by the shape of their distribution. Therefore, the output depends on the overall state of the interacting particles. Generally, elementary laws of classical mechanics are violated. Interactions can occur not only by contact, but also be distributed in space as well as within networks. In fact, living systems have the ability to communicate either directly or through the use of media.
  The modelling approach is such that each active particle interacts with all the other particles that are in a suitable domain, which, in some cases, is identified by the visibility zone, while in other cases by a network where interactions occur. Active particles play a game at each interaction and the output is technically related to the ability they have to develop a certain strategy. Given a certain input, the output cannot, in general, be deterministically identified, namely the behaviour of particles is randomly distributed and the output of the interaction is random.
- *Distance and topology*: Interactions may not be homogeneous in space, considering that interacting entities can, in some cases, choose different observation paths. Moreover, the distance is not simply geometric, considering that interacting entities have the ability to identify localization at a great distance and may even privilege it with respect to localization at short distance.
  The modelling takes into account the role of the topological distribution of the active particle, which plays a role when communication among entities selects specific paths and directions. An important consequence is that interactions do not involve pairs of entities, but a number of entities and their geometrical distribution.
- *Mutations and evolution*: An additional aspect that has to be considered is that, in some cases, the specific properties of living systems evolve in time. This evolution may even correspond to real mutations with substantial modification of the interaction rules related to mutated entities [1].
  This is a delicate issue that has only been partially considered in the mathematical approach we have reviewed. In fact, mutations are taken into account by the probability that an active particle falls into a new population with mutated characteristics.

8.2. Multiscale aspects and interactions

Generally, complex systems are constituted by interacting components, which eventually correspond to functional subsystems distributed in space, and, in some cases, constrained by networks. Each component is constituted by several interacting active particles. Therefore, the modelling approach needs to describe the interactions that involve the various components, in addition to those of the particles of different functional subsystems. An additional technical difficulty is that the scale (microscopic or macroscopic) that is suitable to describe each component may not be the same for all of them. Bearing all this in mind, different types of interactions have to be considered:

(i) Interactions between subsystems at the same scale, both of which have been modelled by the KTAP methods. This type of interaction has been considered, for instance, in immune competition e.g. [88,89].
(ii) Interactions between subsystems at different relative scales, both of which have been modelled by the KTAP methods. An example is that of the modelling of the interactive dynamics of genes and cells in biology [20,21].
(iii) Interactions between subsystems at different scales, one modelled by macroscopic equations and the other by KTAP methods. This aspect has been considered by Ajmone Marsan in the field of behavioural economy [5].

It should be observed that the concept of *microscopic scale* is independent on the size of the interacting entities, but it is related to the fact that each entity is modelled as a whole. Therefore, interactions of type (i) and (ii) occur at the microscopic scale, although the size of particles is different for interactions (ii). Dealing with this matter implies that the mathematical structures reported in this paper need to be further developed to take into account that one subsystem can act over another due to macroscopic variables as observed in different life sciences fields, see for instance [20] and [5]. It is essential to deal with this delicate problem in the case of (iii)-type interactions, see [44,45].

The above topics highlight a challenging research perspective, where the above cited literature represents only an introductory contributions that is still open to further developments. Dealing with these issues means taking into account the derivation of macroscopic equations from the underlying description at the microscopic level. Some literature on this topic has already been cited, among others [16,46,47,64,67,69]. However, the development of asymptotic methods, in some way analogous to those of the classical kinetic theory [97], need *ad hoc* assumptions that limit the full generality of the mathematical result. Applied mathematicians are engaged in the challenging task of developing methods, which are valid without such *a priori* assumptions.

8.3. Perspectives

Various research perspectives have already been indicated in this section as well as in preceding sections, focusing both on the derivation of mathematical structures and modelling topics. KTAP's methods can deal with several aspects of complex systems, however not all of them. For instance, the modelling approach to mutations is only at a preliminary stage, and further developments are still needed.

An additional characteristic of complex systems is their learning ability. This aspect could possibly be considered within the term $\mathscr{B}$ assuming that the variation of activity, namely $u_* \to u$ corresponds to a learning process due to interactions with different active particles. This topic, which still has to be properly developed, introduces an interesting research perspective in the modelling of cognitive sciences, e.g. [39] and [101].

The most important perspective, according to the authors' bias, is related to the derivation of the terms $\mathscr{A}$, $\mathscr{B}$, $\mathscr{C}$, μ, and η, which can be modelled on the basis of a phenomenological analysis of the subsystem. A robust theory may be possibly be developed to obtain these quantities. This challenging target could be pursued after having specialized the specific system that is subject of the modelling. The approach of [21] suggests extracting, in the case of multicellular systems, the above quantities from the underlying description at the lower scale of genes.

The essential idea is that suitable moments of the variable at the low scale identify the activity variable at the high scale. Heterogeneity is induced by the different behaviour of the particles at the low scale. Hopefully, this approach can be generalized to broad variety complex systems. It can take advantage of research activities in the field of biological sciences, where the dynamics at the low scale is related to inheritance, mutations, and evolution [70,90,96], and [1]. Possibly, this approach can be generalized to a broader variety of complex systems.

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