What is life?
A perspective of the mathematical kinetic theory of active particles

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Abstract

The modeling of living systems composed of many interacting entities is treated in this paper with the aim of describing their collective behaviors. The mathematical approach is developed within the general framework of the kinetic theory of active particles. The presentation is in three parts. Firstly, we derive the mathematical tools, subsequently, we show how the method can be applied to a number of case studies related to well defined living systems, and finally, we look ahead to research perspectives.

Keywords: active particles, collective learning, complexity, crowd dynamics, evolutionary economics, multiscale problems, kinetic theory, virus pandemics

AMS Subject Classification: 92C60, 92D30

To the memory of Pietro Greco - 20-04-1955 — 18-12-2020

1 Aims and plan of the paper

This paper is devoted to the presentation and critical analysis about a new class of mathematical tools which claim to describe some important features of living systems composed of many interacting entities. The presentation is not limited to theory, but also to applications due to their contribution to enlighten the bridge between mathematics and real systems. In addition, a critical analysis is a key feature of each section looking ahead to further development of the theory.

The main difficulty is that living systems do not relay on a field theory to guide the mathematical approach. This concept is well understood in biology as critically analyzed by various authors [101, 119, 131]. More in general, the same reasonings can be addressed to all fields of sciences devoted to the study of living systems. A hint is given in Chapter 7 of [23], where the authors replace the definition *soft sciences* with that of *science of living systems*. This vision gives to mathematics an essential role towards a unified vision of all sciences which goes beyond any classification from soft to hard. Indeed, it is a first step to develop a strategy to take into account that, in the case of the living matter, the approach is not supported, as mentioned, by a field theory [14, 23].

The strategy consists in replacing the field theory by a mathematical structure (say a mathematical theory) suitable to capture, as far as it is possible, the complexity features of living systems. This structure defines the conceptual framework for the derivation of models in a broad variety of fields, for instance social dynamics, financial markets, dynamics of multicellular systems, immune competition, individual and collective learning, and the modeling of large systems of self-propelled particles such as crowds and swarms.

The first part of our paper is devoted to the derivation of theoretical tools in view of the aforementioned theory which includes some new ideas, with respect to those proposed in [23], according to a more general vision of active particle methods. Subsequently, we present a selection of applications focused on the modeling of dynamics of living systems which can be modeled by the theoretical tools presented in the first part of the paper. The selection accounts for different features of models with special attention to the role of space dynamics by showing how space can have an influence over the collective behavior of the whole system. Finally, we look ahead to research perspectives also based by a critical (and self-critical) analysis which closes each section with the aim of enlightening how far the mathematical tools proposed in our paper succeed in chasing the mythical objective of designing a mathematical theory of living systems.

Section 2 is devoted to design a strategy towards the derivation of mathematical tools to model systems composed of many living interacting entities, where their collective dynamics are generated by interactions among the said entities and the external environment. The strategy essentially consists in selecting the key complexity features of living systems to be captured into a general differential structure suitable to potentially describe them. This structure is further specialized into the class of systems object of the modeling approach.

In Section 3, we transfer the aforementioned strategy into mathematical structures which are derived within the general framework of the so-called *kinetic theory of active particles*, are deemed to take the place of the field theories available to support the derivation of models for physical systems of the inert matter. These structures provide the conceptual framework for the derivation of models which are obtained by insertion of the mathematical description of interactions.

Section 4 presents a review of applications of the mathematical theory presented in the preceding sections. The survey refers to the following topics: collective learning, behavioral crowd dynamics, virus pandemics, and evolutionary economics. This section also briefly reports about the so-called *mathematical theory of behavioral swarms* introduced in [33] and applied, in [114], to modeling the dynamics of prices. This approach derives dynamical systems corresponding to pseudo-Newtonian frameworks. The survey of applications is limited to very recent years with the aim of enlightening new ideas on the modeling of interactions as a key step towards the mathematical description of behavioral systems.

Section 5 reports a critical analysis focused on challenging research perspectives towards as the key strategy to further development of mathematical tools as well as to modeling complex systems in real life.

2 A strategy towards modeling living systems

This section is devoted to the design of a general strategy towards the modeling of the collective dynamics of large systems of interacting living entities. The quest towards this challenging objective is in three steps, each of them treated in the following subsections. Firstly, we present a general conceptual-philosophical framework, subsequently a strategy is set out in view of mathematical formalizations, lastly a critical analysis is proposed, focusing on a suitable interpretation of the scaling problem, to make operative the strategy towards an appropriate selection of mathematical tools.

2.1 Conceptual framework

A conceptual framework is proposed in this subsection with the aim of providing a support towards the derivation of the modeling strategy. This strategy is also based on some scientific works selected according to the authors' perspective accounting for their contribution that help understanding the complex interactions between mathematical sciences and the dynamics of living systems.

• **Erwin Schrödinger (1887–1961)** looked for a physical theory, where cells modify their state due to interactions with other cells [137]. Schrödinger's pioneering ideas chased a systems approach motivated by the study of mutations (some of them also induced by external actions such as radiations). We can argue that one of his intuitions was that that the dynamics at the level of cells is driven by the dynamics at the molecular scale. This concept is nowadays the most important hint of the interactions between mathematics and biology, where understanding the link between the dynamics at the molecular scale of genes and the functions expressed at the level of cells is a key passage to achieve the derivation of a bio-mathematical theory. The following sentence from [137]:

> *Living systems have the ability to extract entropy to keep their own at low levels*

identifies ability of living systems to develop a their own strategy. Hence the concept of *active particles* was already introduced.

• **Lee Hartwell (born 1938)**, Nobel Laureate in 2001, firmly indicates [96] that the mathematical approach to the description of the dynamics of the inert matter cannot be straightforwardly applied to living systems:

> *Biological systems are very different from the physical or chemical systems of the inanimate matter. In fact, although living systems obey the laws of physics and chemistry, the notion of function or purpose differentiate biology from other natural sciences. Indeed, cells are not molecules, but have a living dynamic induced by the lower scale of genes and is organized into organs.*

This statement, in [96], directly looks forward a challenging research perspective whose first step consists in acknowledging that the mathematics used for the inert matter fails when applied to the living matter.

Between these two milestones, some specific models have been proposed to describe the dynamics of the aforementioned class of dynamical systems by methods somehow inspired by the mathematical kinetic theory and by the Boltzmann equation in particular [61]. For instance Prigogine and Hermann developed an approach to describe the dynamics of vehicular traffic on highways [130]. An important feature of this model is that the car-driver subsystem is viewed as an active particle whose ability is heterogeneously distributed, while the overall state of the system is defined by a probability distribution over micro-scale state. A deep study of the heterogeneity properties has been clearly identified by the structures proposed in[128].

Methods from the kinetic theory, have been subsequently developed by various authors, for instance on the modeling of the social dynamics of families of insects in [105], or of the immune competition between cancer and immune cells [29]. These pioneering papers have been followed by a vast literature mainly developed in this century. A review and a critical analysis on kinetic theory methods is postponed to the next section specifically devoted to transfer the concepts of this section into a mathematical theory. Here we simply indicate the sharp critical analysis presented in[11] which enlightens the conceptual differences between the classical kinetic theory and that referred to active particles.

living systems are evolutionary in that first they are subject to dynamic change, deriving from both internal and external forces, or interactions, second they are subject to some form of selection, weak or strong according to the configuration of the system. Notably, selection is not necessarily efficient because it might also select on the ground of other attributes distinct from efficiency. This pseudo-darwinian feature does not belong, as we shall see, to biology only, but it characterizes all living systems. These include systems in economics and sociology, where the dynamic, driven by learning, includes mutations and selection.

The awareness of Hartwell's legacy motivates a quest towards the search of a rational to chase the objective of the derivation of a mathematical theory of living systems by going far beyond the classical methods valid for the inert matter. A preliminary contribution to this challenging objective is delivered by the answer to three key questions presented in the following.

• **KQ1: What is complexity?** *Complexity viewed as a barrier.* Imagine a world correctly described in mathematical and logical terms. That would make realistic the Leibniz dream (free translation from Latin language):

> *In the future, when an issue is controversial, it will not be necessary to dispute between two philosophers but between two subjects able in computations. It will suffice them to keep the abacus into their hands, sit down, and say each other – in a friendly way – start making calculations*, [118].

Unfortunately (or luckily?), two hard constraints preclude the actual achievement of a world so entirely known to allow such exciting solutions.

- The so-called chaos in dynamical systems, whose apparently-random states of disorder and irregularities are often governed by deterministic laws (that are highly sensitive to initial conditions);

- The phenomenon of complexity, namely the emergence of entirely new properties at any new level of aggregation.

Arguably, Leibnitz was not aware of the existence of them. Therefore, we might pose to ourself the following question: *from where to start understanding complexity?* In Aristotle, complexity seems opposed to simplicity as a matter of lifestyle. In Latin, the world *complexus* means what is woven together.

In the 40s of the last century, von Neumann was working with automata and their complexity, but: *he described his own concept of complexity as "vague, unscientific and imperfect"* (from McMullin, 2000).

If we jump to the 60s of the last century, we have the Kolmogorov complexity, defined as a measure: given an object, e.g., a piece of text, the length of the shortest computer program (in a predetermined programming language) that produces the same object as output.

Beautiful, but again it is not a reply to our search about what complexity is. The concept was there, but missing a clear interpretation and definition, confused with the a-scientific and anti-reductionist holism, i.e., the idea that we should view many systems (physical, biological, social, our body, etc.) as wholes, not merely as collections of parts. Sure, but then what? So, neither holism nor simple reductionism, but with Nobel Laureate Philip Anderson (born 1923), in 1972 the "More is different" clarification [10]:

> *(p.393) The reductionist hypothesis may still be a topic for controversy among philosophers, but among the great majority of active scientists I think it is accepted without questions. The workings of our minds and bodies, and of all the animate or inanimate matter of which we have any detailed knowledge, are assumed to be controlled by the same set of fundamental laws (...) The main fallacy in this kind of thinking is that the reductionist hypothesis does not by any means imply a "constructionist" one (...) The constructionist hypothesis breaks down when confronted with the twin difficulties of scale and complexity. The behavior of large and complex aggregates of elementary particles, it turns out, is not to be understood in terms of a simple extrapolation of the properties of a few particles. Instead, at each level of complexity entirely new properties appear (...).*

Often, complexity is related to biological systems, however this is a narrow vision as complexity is everywhere in our world [19]. In particular, the focus of our paper goes over various topics including evolutionary economics referring to the conceptual framework in [78], where it is given evidence of the role of complexity in economical systems. The following quotation from Nobel Prize in economy Herbert Simon has been extracted from [138] and reported in [78] to enlighten the initial step towards linking economy to the theory of complexity.

> *Roughly by a complex system I mean one made up of a large number of parts that interact in a non-simple way. In such systems, the whole is more than the sum of the parts, not in an ultimate metaphysical sense, but in the important pragmatic sense that, given the properties of the parts and the laws of their interaction, it is not a trivial matter to infer the properties of the whole.*

At this end, as a key milestone towards the development of a mathematical theory, it is necessary to transfer the aforementioned general concepts to an assessment of the relevant complexity features by answering to the second key question.

KQ2: Which are the main complexity features of living system? A mathematical theory of living system should arguably attempt to capture the complexity feature of living systems [23, 14]. Therefore, the answer to this question aims at contributing to the key objective of our paper. Without naively claiming that our reply can be exhaustive, our proposal for a selection of five key features is as follows:

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

2. Heterogeneity: The ability to express a strategy is not the same for all entities as *expression of heterogeneous behaviors* is a common feature of a great part of living systems.

3. Nonlinearity of interactions: Interactions are nonlinearly additive and nonlocal as they may involve entities that are not immediate neighbors.

4. Learning ability: Living systems receive inputs from the environments and have the ability to learn from past experience. Accordingly, the strategy they develop evolves in time.

5. Darwinian mutations and selection: All living systems are evolutionary, as interactions can generate, by birth of aggregations, new entities that are increasingly fitted to the environment, who in turn generate new entities again more fitted to the environment.

KQ3: What is the black swan? The expression *black swan* has been introduced to denote an unpredictable events which are far away from those generally observed by repeated empirical evidence. Let us report the definition by Taleb [143]:

> *A Black Swan is a highly improbable event with three principal characteristics: It is unpredictable; it carries a massive impact;*

and, after the fact, we concoct an explanation that makes it appear less random, and more predictable, than it was.

Actually, the concept of the *black swan* is associated to the concept of *not predictable event* or, negatively *not predicted event*, but we wish stressing that we want to refer this concept to the ability of mathematical models to provide all possible scenarios including events which are unlikely to be anticipated. This vision has a well defined implication on the modeling approach which should not include, in the model, any artificial relaxation term suggested by observed data rather than by interactions. Indeed, this is a key issue towards the derivation of a mathematical theory of living systems to be carefully tackled in the following.

2.2 From philosophical thoughts to figurative fantasy

Let us now leave the various concepts presented until now and give some space to our fantasy. A free interpretation in[35] suggests that the *Metamorphosis-III* by Cornelis Escher:

$$https://arthive.com/it/escher/works/200075\ Metamorphosis$$

depicts most of the aforementioned complexity features, for instance the collective strategy by which a village with houses with almost uniform shapes is gradually transformed into an heterogeneous village which includes architectures with different shapes.

We can observe that the evolution is selective as shown by the transition from essential shapes to an organized village, where all available spaces are exploited to include an increasing population. The presence of a church, that takes an important part of the space and a somehow key position, indicates the presence of a cultural evolution. This might even reflect a multiscale dynamic. In fact, it results from the interplay between the micro-scale of individuals and the macro-scale of the village.

In addition, the last part of Metamorphosis-III shows a sudden change from a peaceful village to a chess plate which represents a battle between two antagonist armies. If we hide this part, we should admit that it is a sudden change which is not predicted by early signal. The third key question specifically refers to this topic. We firstly notice that the village exists in reality (it is in the Mediterranean coast immediately on the south of the village of Amalfi), then we pose the following question: *Does the tower truly exists?*

The answer is that the real village looks at the sea, while the tower cannot be observed looking at it from right to left by an observer who faces the the sea from the village, as shown on the upper picture of Figure 1. On the other hand, an observer placed on the rear of the village can observe a tower on the cape in the lower picture of Figure 1.

Figure 1: Different visions of the village Atrani on Amalfi-coast

The Metamorphosis represents a figurative example of the practice of tessellation primarily used for architecture and decoration. Tessellation has also been used in mathematical applications since it is a case in which the gradual movement from one regular geometric form to the subsequent one can create a cascade effect. Indeed regular over-imposed behaviors or patterns, when moving, can create a complex multidimensional artefact, such us in the Metamorphosis. Complex multi-dimensionality out of regular geometric structures is common also in biology: take the case of beehives or Roman cauliflower.

So far, the Metamorphosis teaches us that different visions of the same object can be represented into one unified collective representation. Indeed, this is one of the specific features of complex systems. If now we leave some additional freedom to our fantasy, the tower can be interpreted as an early signal that an extreme event is going to happen. The various changes in the picture can be interpreted as predictable emerging behaviors, while the last one appears as a non-predictable event. Escher has gone through the experience of two world wars, where peaceful villages transformed into a battlefield between the two armies of the chess plate.

2.3 On a strategy towards modeling living systems

This subsection proposes a modeling strategy that copes with the absence of a field theory when dealing with living matter. This strategy motivates replacing the definition *soft sciences* by *science of living systems*. Indeed, the strategy we propose consists in replacing the field theory by a mathematical structure (say a mathematical theory) suitable to capture, as far as it is possible, the complexity features of living systems. This structure defines the conceptual framework for the derivation of models which are obtained by inserting models of interactions into the structure itself. In more details, the sequential steps of the strategy can be summarized as follows:

1. *Understanding the links* between the dynamics of living systems and their *complexity features*;

2. *Subdivision into subsystems:* The overall system can be divided into so-called *functional subsystems*, in short FSs, which share common objectives and strategy.

3. *Derivation of a general mathematical structure*, consistent with the aforesaid features, with the aim of offering the *conceptual framework* toward the derivation of specific models;

4. *Design of specific models* corresponding to well defined classes of systems by implementing the said structure with suitable models of individual-based, micro-scale, interactions;

5. *Validation of models* by quantitative comparison of the dynamics predicted by them against empirical data. Models are required to reproduce qualitatively emerging behaviors.

This strategy, which leads to a modeling rationale, is represented in figure 2 which indicates, by a flow-chart, how the observation of the real system moves to models, which only approximate, physical reality and, consequently, need to be validated. Some additional remarks contribute to further enlightening the flow chart.

• *Multiscale aspects:* Modeling must be *multiscale*, as the dynamic at the large scale depends on the dynamics at the low scales. For instance, the functions expressed by a cell are determined by the dynamics at the molecular (genetic) level.

• *Role of the environment:* The environment evolves in time, in several cases also due to interactions with the internal living system.

• *Large deviations:* Emerging behaviors may present large deviations. In this case, small deviations in the input create large deviations in the output.

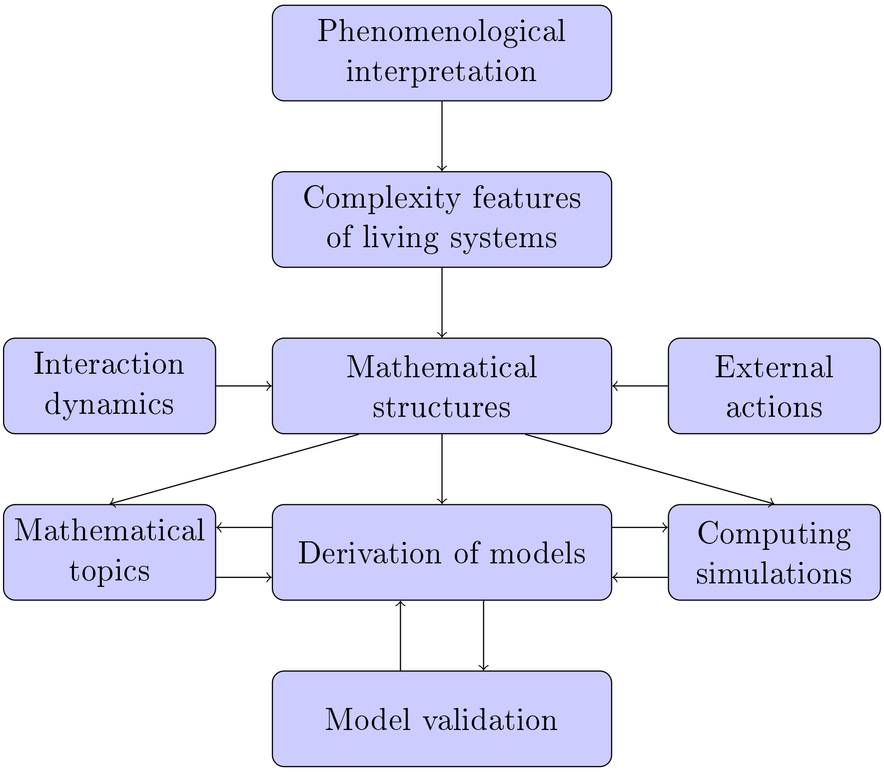

Figure 2: Modeling strategy

• *Individuals within a certain FS can aggregate into groups of affinity:* Communications and subsequent dynamics can take advantage (or disadvantage) from the said aggregation by creating a new communication network.

2.4 The scaling problem

The representation and modeling of dynamical systems can be developed at three representation scales, namely *microscopic* (individual based), *macroscopic* (hydrodynamical), and at the intermediate *mesoscopic* (kinetic) scales. In the kinetic theory approach, the dependent variable is a distribution function over the microscopic state of the individuals.

Our study refers to the collective dynamics of several heterogeneous interacting individuals. Heterogeneity, which affects interactions, motivates the selection of the kinetic theory approach as the most appropriate towards modeling. In fact, it can naturally account for heterogeneity and stochastic interactions [23]. On the other hand, the number of interacting entities is not, in most cases, large enough to justify continuity assumption of the aforementioned distribution function. This key difficulty cannot be hidden and has to be carefully treated in the derivation of the mathematical structure, bearing in the mind that technical developments of models of the classical kinetic theory cannot be straightforwardly applied to living systems. For instance, the celebrated Boltzmann equation is based on the assumption of a rarefied flow where only binary, short range, interactions occur, while interactions in the Vlasov equations are distributed in the whole space which is not the case of living systems, where the domain of interactions refers both to sensitivity and visibility of individuals. In addition, interactions of classical particles preserve mechanical quantities, namely mass, momentum, and energy, while these properties are often lost in the case of living systems.

The mathematical theory reported in the next section is grounded on methods of the kinetic theory consistently with the strategy proposed in this section, but, considering the developments imposed by the complexity features of living systems. This selection should be critically examined as none of the scales, standing alone, is sufficient to depict the dynamics of the class of systems under consideration. Indeed, a multiscale vision is necessary and it is a key feature of a mathematical theory of living systems. Therefore, various reasonings on this vision are going to be a constant presence in the next sections.

The contents of the next sections is mainly focused on the kinetic theory of active particles, in short the KTAP approach. However, we are aware that the rationale proposed in the following can be referred to other formal structures, for instance, Fokker Plank approach [88, 125], agent methods [89], statistical physics of living particles [99, 100], evolutionary dynamics [124].

3 Towards a mathematical theory of living systems

We show, in this section, how the strategy proposed in Section 2 can be transferred into a *mathematical theory*, where this term is used to refer to mathematical structures suitable to capture, as far as it is possible, the complexity features of living systems. The study is mainly focused on the kinetic theory of active particles, where individual entities, called *active particles* (in short a-particles), interact across networked populations. The micro-scale state of a-particles includes, in addition to mechanical variables, also a variable, called *activity*, which models the behavioral ability of the individual entities. According to the authors' perspective, the kinetic theory approach appears to be the most appropriate to be selected without hiding the key difficulty consisting in that the number of interacting entities is not large enough to fully justify the continuity assumption of the distribution function.

As mentioned, there exists a well established literature on this topic which starts from those we have indicated as pioneering research works [29, 105, 128, 130]. We specifically refer to the book [23] and, in addition, we include some recent developments mainly motivated by specific applications. In more details, the theory is presented in Subsection 3.1, additional reasonings on modeling interactions and networks are proposed in Subsection 3.2 referring also to the key problems posed in [47], while a critical analysis is proposed in Subsection 3.3 to enlighten how much the theory is consistent with the conceptual approach of Section 2 and how further research activity should be developed.

3.1 The mathematical theory of active particles

We focus on the collective dynamics of large systems of a-particles. Living entities, at each interaction, play a game with an output that depends on their strategy often related to surviving and adaptation abilities. Interactions are modeled by theoretical tools of stochastic game theory which are characterized as follows:

- Stochastic game theory deals with entire populations of players, where strategies with higher payoff might spread over each population by learning related to individual based and between each individual and the collectivity interactions.

- The strategy expressed by individuals, i.e. a-particles, is heterogeneously distributed over the micro-states of players which include both mechanical and activity variables.

- Players are modeled as stochastic variables linked to a distribution function over the micro-state. The payoff is heterogeneously distributed over players as well, and it might be motivated by "rational" or even "irrational" strategies.

- The payoff depends on the actions of the co-players as well as on the frequencies of interactions. Both quantities can depend on the probability state of the system.

- Interactions are nonlocal and nonlinearly additive in a way that the dynamics of the whole system is not straightforwardly determined by the dynamics of a few entities.

A qualitative description of phenomenological examples of interactions is as follows:

1. *Competitive (dissent):* One of the interacting a-particles increases its status by taking advantage of the other which is forced to decrease its status. Competition brings advantage to only one of them.

2. *Cooperative (consensus):* The interacting a-particles exchange their status, i.e. a-particles with higher state decrease it, while the others with lower state increase it. All a-particles show a trend to share their micro-state.

3. *Learning:* One of the two a-particles modifies, independently from the other, the micro-state. It learns by reducing the distance between them.

4. *Hiding-chasing:* One of the two attempts to increase the overall distance from the other, which in turn tries to reduce it.

5. *Mixed competitive-cooperative:* A-particles do not share the same strategy, but some of them act competitively whereas some others cooperatively.

If the dynamics of interaction depends on space, the following geometrical quantities, and related properties, must be introduced:

- *Visibility domain:* Ω_v which is the domain within which an a-particle can see the others.

- *Sensitivity domain:* Ω_s which is the domain within which an a-particle can feel the presence of the other a-particles. If $\Omega_s \subseteq \Omega_v$, then interactions occur within Ω_s. If $\Omega_v \subseteq \Omega_s$, then interactions occur within Ω_v. The interaction domain Ω is defined as the intersection between Ω_v and Ω_s.

- *The size of the sensitivity domain* Ω_s depends on the amount of information which can be received by an a-particle, hence Ω_s depends on the distribution function. The theory proposed in [20] suggests that the size of Ω_s depends on a critical density, namely a critical number of particles. The mathematical formalization in [32] indicates how Ω_s is related to the velocity direction and visibility angle of each a-particle.

The overall system is subdivided into n FSs whose state is defined by the distribution function

$$f_i = f_i(t, \mathbf{x}, \mathbf{v}, \mathbf{u}) \, : [0, T] \times \Sigma \times D_{\mathbf{v}} \times D_{\mathbf{u}} \longrightarrow R_+, \qquad i = 1, \ldots, n, \tag{1}$$

where Σ is the domain where a-particles are located, and $D_{\mathbf{u}}$ and $D_{\mathbf{v}}$ denote the domains of the variables $\mathbf{u}$ and $\mathbf{v}$, respectively. The following a-particles are supposed to be involved, for each functional subsystem, in the interactions:

• *Test* particles of the i-th functional subsystem with microscopic state, at time t, delivered by the variable $(\mathbf{x}, \mathbf{v}, \mathbf{u})$, whose distribution function is $f_i = f_i(t, \mathbf{x}, \mathbf{v}, \mathbf{u})$. The test particle is assumed to be representative of the whole system.

• *Field* particles of the k-th functional subsystem with microscopic state, at time t, defined by the variable $(\mathbf{x}^*, \mathbf{v}^*, \mathbf{u}^*)$, whose distribution function is $f_k = f_k(t, \mathbf{x}^*, \mathbf{v}^*, \mathbf{u}^*)$.

• *Candidate* particles, of the h-th functional subsystem, with microscopic state, at time t, defined by the variable $(\mathbf{x}_*, \mathbf{v}_*, \mathbf{u}_*)$, whose distribution function is $f_h = f_h(t, \mathbf{x}_*, \mathbf{v}_*, \mathbf{u}_*)$.

Let us now consider short range interactions, when particles interact within an interaction domain Ω generally small with respect to the domain Σ containing the whole system; and let us use the term i-particle to denote a particle in the i–th functional subsystem. Bearing in mind that a precise definition and computing of Ω still needs to be given, the theory states that the modeling of interactions is delivered by the following quantities:

• *Interaction rate for conservative dynamics:* $\eta_{hk}[\mathbf{f}](\mathbf{x}, \mathbf{v}_*, \mathbf{u}_*, \mathbf{x}^*, \mathbf{v}^*, \mathbf{u}^*)$, which models the frequency of the interactions between a candidate h-particle with state $\mathbf{x}, \mathbf{v}_*, \mathbf{u}_*$ and a field k-particle with state $\mathbf{x}^*, \mathbf{v}^*, \mathbf{u}^*$. Analogous expression is used for interactions between test and field particles.

• *Interaction rate for non-conservative dynamics:* $\mu_{hk}[\mathbf{f}](\mathbf{x}, \mathbf{v}_*, \mathbf{u}_*, \mathbf{x}^*, \mathbf{v}^*, \mathbf{u}^*)$, is analogous to η_{hk}, but corresponding to proliferative and destructive interactions.

• *Transition probability density:* $\mathcal{C}^i_{hk}[\mathbf{f}](\mathbf{v}_* \to \mathbf{v},\, \mathbf{u}_* \to \mathbf{u} \,|\, \mathbf{x}, \mathbf{v}_*, \mathbf{u}_*, \mathbf{x}^*, \mathbf{v}^*, \mathbf{u}^*)$, which denotes the probability density that a candidate h-particle, with state $\mathbf{x}, \mathbf{v}_*, \mathbf{u}_*$, ends up into the state of the test particle of the i-th FS after an interaction with a field k-particle.

• *Proliferative term:* $\mathcal{P}^i_{hk}[\mathbf{f}](\mathbf{v}_* \to \mathbf{v},\, \mathbf{u}_* \to \mathbf{u} \,|\, \mathbf{x}, \mathbf{v}_*, \mathbf{u}_*, \mathbf{x}^*, \mathbf{v}^*, \mathbf{u}^*)$, which models the proliferative events for a candidate h-particle, with state $\mathbf{x}, \mathbf{v}_*, \mathbf{u}_*$, into the i-th functional subsystem after interaction with a field k-particle with state $\mathbf{x}^*, \mathbf{v}^*, \mathbf{u}^*$.

• *Destructive term:* $\mathcal{D}_{ik}[\mathbf{f}](\mathbf{x}, \mathbf{v}, \mathbf{u}, \mathbf{x}^*, \mathbf{v}^*, \mathbf{u}^*)$, which models the rate of destruction for a test i-particle in its own functional subsystem after an interaction with a field k-particle with state $\mathbf{x}^*, \mathbf{v}^*, \mathbf{u}^*$.

These quantities can be viewed in terms of rates by multiplying their interaction rate with the terms modeling transition, proliferative, and destructive events. Hence we have *transition rate:* $\eta_{hk}[\mathbf{f}]\, \mathcal{C}^i_{hk}[\mathbf{f}]$, *proliferation rate:* $\mu_{hk}[\mathbf{f}]\, \mathcal{P}^i_{hk}[\mathbf{f}]$, and *destruction rate:* $\mu_{ik}[\mathbf{f}]\, \mathcal{D}_{ik}[\mathbf{f}]$.

Mathematical structures are obtained by number balance of a-particles within an elementary volume of the space of microscopic states, mechanics and activity, of particles

Variation rate of the number of active particles

= *Inlet flux rate by conservative interactions*

−*Outlet flux rate by conservative interactions*

+*Inlet flux rate by proliferative interactions and mutations*

−*Outlet flux rate by destructive interactions and mutations.*

This balance relation corresponds to the following general structure:

$$(\partial_t + \mathbf{v}\cdot\partial_{\mathbf{x}})\ f_i(t,\mathbf{x},\mathbf{v},\mathbf{u}) = \big(\mathcal{C}_i - \mathcal{L}_i + \mathcal{P}_i - \mathcal{D}_i\big)[\mathbf{f}](t,\mathbf{x},\mathbf{v},\mathbf{u}), \tag{2}$$

where the various terms $\mathcal{C}_i, \mathcal{L}_i, \mathcal{P}_i$ and $\mathcal{D}_i$ can be formally expressed, consistently with the definition of the interaction terms.

Remark 3.1. *A commonly applied assumption is that the terms $\mathcal{P}^i_{hk}$ and $\mathcal{D}_{ik}$ depend, in addition to $\mathbf{f}$, only on the activity variables, namely $\mathcal{P}^i_{hk}[\mathbf{f}](\mathbf{u}_* \to \mathbf{u}|\mathbf{u}_*,\mathbf{u}^*)$ and $\mathcal{D}_{ik}[\mathbf{f}](\mathbf{u},\mathbf{u}^*)$. This assumption is used in the equations below.*

In the spatially homogeneous case, the mathematical structure is specialized as follows:

$$\begin{aligned}
\partial_t f_i(t,\mathbf{u}) &= \Big(\mathcal{C}_i[\mathbf{f}] - \mathcal{L}_i[\mathbf{f}] + \mathcal{P}_i[\mathbf{f}] - \mathcal{D}_i[\mathbf{f}]\Big)(t,\mathbf{u}) \\
&= \sum_{h,k=1}^{n} \int_{D_\mathbf{u}\times D_\mathbf{u}} \eta_{hk}[\mathbf{f}](\mathbf{u}_*,\mathbf{u}^*)\, \mathcal{C}^i_{hk}[\mathbf{f}]\,(\mathbf{u}_* \to \mathbf{u}|\mathbf{u}_*,\mathbf{u}^*)\, f_h(t,\mathbf{u}_*) f_k(t,\mathbf{u}^*)\, d\mathbf{u}_*\, d\mathbf{u}^* \\
&\quad - f_i(t,\mathbf{u}) \sum_{k=1}^{n} \int_{D_\mathbf{u}} \eta_{ik}[\mathbf{f}](\mathbf{u},\mathbf{u}^*)\, f_k(t,\mathbf{u}^*)\, d\mathbf{u}^* \\
&+ \sum_{h,k=1}^{n} \int_{D_\mathbf{u}\times D_\mathbf{u}} \mu_{hk}[\mathbf{f}](\mathbf{u}_*,\mathbf{u}^*) \mathcal{P}^i_{hk}[\mathbf{f}]\,(\mathbf{u}_* \to \mathbf{u}|\mathbf{u}_*,\mathbf{u}^*)\ f_h(t,\mathbf{u}_*) f_k(t,\mathbf{u}^*)\, d\mathbf{u}_*\, d\mathbf{u}^* \\
&\quad - f_i(t,\mathbf{u}) \sum_{k=1}^{n} \int_{D_\mathbf{u}} \mu_{ik}[\mathbf{f}](\mathbf{u},\mathbf{u}^*)\, \mathcal{D}_{ik}(\mathbf{u},\mathbf{u}^*) f_k(t,\mathbf{u}^*)\, d\mathbf{u}^*.
\end{aligned} \tag{3}$$

The same calculations, in the spatially inhomogeneous case, correspond to Eq. (2), where the interaction terms are given by:

$$\begin{aligned}
\mathcal{C}_i &= \sum_{h,k=1}^{n} \int_{\Omega\times D_\mathbf{u}\times D_\mathbf{u}\times D_\mathbf{v}\times D_\mathbf{v}} \eta_{hk}[\mathbf{f}](\mathbf{w}_*,\mathbf{w}^*)\, \mathcal{C}^i_{hk}[\mathbf{f}](\mathbf{v}_* \to \mathbf{v},\ \mathbf{u}_* \to \mathbf{u}|\mathbf{w}_*,\mathbf{w}^*) \\
&\qquad \times f_h(t,\mathbf{x},\mathbf{v}_*,\mathbf{u}_*) f_k(t,\mathbf{x}^*,\mathbf{v}^*,\mathbf{u}^*)\, d\mathbf{x}^*\, d\mathbf{v}_*\ d\mathbf{v}^*\, d\mathbf{u}_*\, d\mathbf{u}^*,
\end{aligned} \tag{4}$$

$$\mathcal{L}_i = f_i(t,\mathbf{x},\mathbf{v},\mathbf{u}) \sum_{k=1}^{n} \int_{\Omega\times D_\mathbf{v}\times D_\mathbf{u}} \eta_{ik}[\mathbf{f}](\mathbf{w},\mathbf{w}^*)\, f_k(t,\mathbf{x}^*,\mathbf{v}^*,\mathbf{u}^*)\, d\mathbf{x}^* d\mathbf{v}^*\, d\mathbf{u}^*, \tag{5}$$

$$\begin{aligned}
\mathcal{P}_i &= \sum_{h,k=1}^{n} \int_{\Omega\times D_\mathbf{u}\times D_\mathbf{u}\times D_\mathbf{v}\times D_\mathbf{v}} \mu_{hk}[\mathbf{f}](\mathbf{w}_*,\mathbf{w}^*)\, \mathcal{P}^i_{hk}[\mathbf{f}]\,(\mathbf{u}_* \to \mathbf{u}|\mathbf{u}_*,\mathbf{u}^*) \\
&\qquad \times f_h(t,\mathbf{x},\mathbf{v}_*,\mathbf{u}_*) f_k(t,\mathbf{x}^*,\mathbf{v}^*,\mathbf{u}^*)\, d\mathbf{x}^*\, d\mathbf{v}_*\, d\mathbf{v}^*\, d\mathbf{u}_*\, d\mathbf{u}^*,
\end{aligned} \tag{6}$$

$$\begin{aligned}
\mathcal{D}_i &= f_i(t,\mathbf{x},\mathbf{v},\mathbf{u}) \sum_{k=1}^{n} \int_{\Omega\times D_\mathbf{v}\times D_\mathbf{u}} \mu_{ik}[\mathbf{f}](\mathbf{w},\mathbf{w}^*)\, \mathcal{D}_{ik}[\mathbf{f}](\mathbf{u},\mathbf{u}^*) \\
&\qquad \times f_k(t,\mathbf{x}^*,\mathbf{v}^*,\mathbf{u}^*)\, d\mathbf{x}^*\, d\mathbf{v}^*\, d\mathbf{u}^*,
\end{aligned} \tag{7}$$

where $\mathbf{w}$, $\mathbf{w}_*$ and $\mathbf{w}^*$ denote the microscopic states $(\mathbf{x}, \mathbf{v}, \mathbf{u})$, $(\mathbf{x}, \mathbf{v}_*, \mathbf{u}_*)$ and $(\mathbf{x}^*, \mathbf{v}^*, \mathbf{u}^*)$, respectively. Detailed calculations, which are not repeated here, indicate how Ω can be computed when the sensibility area Ω_s is given by an arc of circle, with radius R_s around the velocity direction. Then, if the visibility arc, symmetric or non-symmetric, is known, R_s is referred to the critical number of a-particles necessary to provide a sufficient information.

Further developments of the structures (2)–(7) will be outlined in the next two subsections referring to a critical analysis on the limits and possible extensions of these structures. Here, we just anticipate some technical remarks that can contribute to enlighten the properties of these mathematical structures in view of derivation of models:

- The use of distribution functions, rather than probability densities, as dependent variables accounts for a dynamics with a variable number of a-particles due to birth and loss processes.

- Mutations can be modeled by birth processes which can generate entities (gain) more fitted to the environment, who in turn might generate new entities again more fitted to the outer environment. Selection can be modeled by death (loss) of entities less fitted to the environment.

- Two types of interactions are taken into account: *micro-micro* or *micro-macro*, where the term *macro* corresponds to macroscopic quantities obtained by weighted averaging of the distribution function.

Some explicative figures can enlighten the role of interactions by distinguishing the differences between the case of space homogeneity and that of space dynamics. In more details:

– Figure 3 represents two a-particles moving with velocity $\mathbf{v}$ that define the visibility domain, while the sensitivity domain depend on the local density. The figure "A" on the left shows the case of a visibility domain (blue contour) greater than the sensitivity domain (red contour), so that visibility is sufficient to allow to acquire the full necessary information. The figure "B" on the left shows the opposite case, namely a visibility domain (blue contour) smaller than the sensitivity domain (red contour), so that lack of visibility reduces the necessary information.

– Figure 4 shows various models of interaction dynamics related to a scalar activity variable. It is shown how the activity variable can be modified by interaction with an other a-particle cooperative and competitive interactions are considered, while in the chasing-hiding dynamics both a-particles modify their state toward the same direction by attempting to keep the distance.

Remark 3.2. *Dimensionless variables are used, where the cartesian components of the position* $\mathbf{x}$ *are referred to a characteristic length* ℓ *of the system, while* v_i *has been referred to the limit velocity* v_M *which can be reached by*

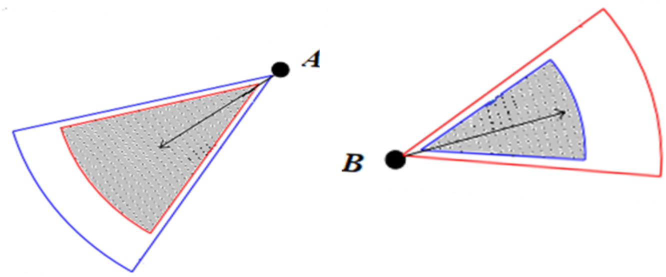

Figure 3: Sensitivity and interaction domains

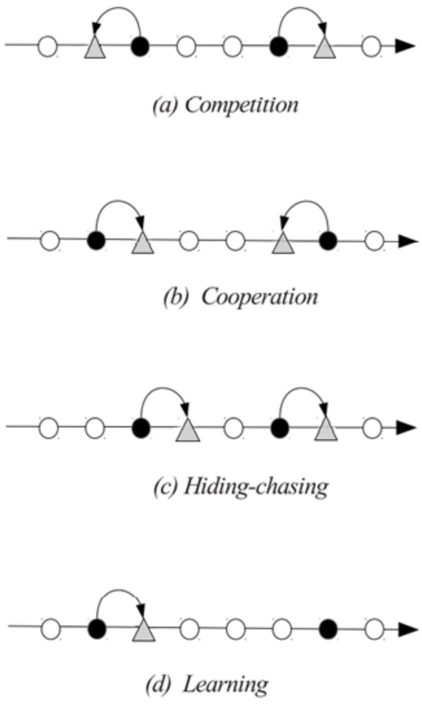

Figure 4: Cooperation, dissent, hiding chasing, learning

the fastest particle. In particular, if the system is localized in a bounded domain Σ, the positive constant ℓ is the diameter of the circle containing Σ, while if the system moves in an unbounded domain, ℓ is simply referred to the domain Σ_0 containing the particles at $t = 0$.

Remark 3.3. *Simulations need the statement of mathematical problems by defining initial and boundary conditions to be properly referred to the general structure (2), specialized into specific models. The mathematical structure includes first order derivative with respect to both time and space. Therefore, the initial conditions are defined by f_i at $t = 0$ and $\mathbf{x} \in \Sigma$, namely $f_i(t = 0, \mathbf{x} \in \Sigma, \mathbf{v} \in D_{\mathbf{v}}, \mathbf{u} \in D_{\mathbf{u}})$, while boundary conditions might be defined by a model suitable to describe how a-particle leave the wall $\partial\Sigma$ after having reached it. In addition, the presence of the wall modifies the trajectories of the a-particles as these try to avoid the wall, see the study of human crowds in [15].*

3.2 On the modeling of interactions and dynamical networks

The mathematical formalization of the interaction terms which appear in Eqs.(3.1)–(3.7) is the key passage to derive models of real world applications. Hence, it is worth developing further reasonings on the rationale to be followed in their modeling. In doing so, we will also refer to the contents of the book [47], where the authors propose, in the closing section, six key problems which are brought to the attention of scientists, as challenging research perspectives. We will quote three of them referring to some aspects of the modeling of interactions and networks.

> ***BL1:*** *We know that people are affected by their positions in networks, but we do not have a variety of models of how people create their networks. We also do not have good models for network's change and evolution.*
>
> ***BL2:*** *There are lots of models that show how groups arrive at consensus but no generally accepted model of how groups become polarized or how two groups can become more and more different and possibly hostile.*
>
> ***BL3:*** *Regarding networks and homophily, birds of a feather flock together, but people are influenced by those they like. Both these processes result in the same outcome (similar people together in groups), but there is no standard accepted way of separating these two processes.*

We do claim that the mathematical tools reviewed in this section provide a definite answer to these key problems which also refer also to the modeling of social interactions and to the dynamics of endogenous networks. Therefore, some indications are given in the following, that may be properly developed within a specific future research program.

• The key problem by **BL1** focuses on endogenous, dynamical, networks [120, 141]. Exogenous, time independent, networks have been studied in [112, 113] within the framework of the KTAP theory by a modeling approach that includes migration dynamics across nodes. Interactions consider not only the dynamics within each node, but also between active particles in the nodes and the network viewed as a whole. A different approach is required to develop the dynamics of model aggregation in endogenous networks, where nodes are created by affinity features. Some perspective ideas in [14] suggest that, in the case of space homogeneity, the dynamics is driven by the distance between the interacting entities for both micro-micro and micro-macro interactions. Some reasonings are here proposed focusing on space dependent systems.

Let us consider interactions within the same FS, and let us call d_{pq} the *metric distance* between a p-particle and a q-particle and φ_{pq} the corresponding *social distance*, where the notations p and q correspond, respectively, to state p and q, respectively. The metric distance can be taken as a weighted sum of all specific distances, namely mechanical $||\mathbf{x}_p - \mathbf{x}_q||$ and $||\mathbf{v}_p - \mathbf{v}_q||$, activity $||\mathbf{u}_p - \mathbf{u}_q||$, and probability state $||f_p - f_q||$, where $|| \cdot ||$ denotes a selected norm in a linear space. Then, we can introduce the concept of *social state* as a weighted sum of the norm of all components of the state of a-particles. This calculation is meaningful if all components of the state variable are in a dimensionless form with values in a finite range.

The technical problem consists in modeling, firstly d_{pq} and subsequently the decay rule of φ_{pq}. A simple way of modeling d_{pq}^{hk} is that suggested in [14], namely by a weighted sum of all metric distance of the components of the micro-state and of the metric distance between the distribution functions of the interacting pairs, while a simple way of referring φ to d is as follows:

$$\varphi_{pq} = \varphi_0\big(- \exp(-\sigma \, d_{pq})\big), \qquad \sigma > 0,$$

as the link between the two distances is that φ decays as d increases. Interactions are significant if the q-particle is placed in the sensitivity domain of the p-particle, while $\varphi = 0$ if the position of the q-particle does not belong to this sensitivity domain.

A conjecture worth to be studied is that the overall FS creates an endogenous network nodes obtained by discrete values of the aforementioned social distance. Then each node of the endogenous network acts as a functional subsystem.

• Focusing on the key problems **BL2** and **BL3**, the remark in [47] that a great part of the literature is devoted to modeling consensus dynamics [47], however heterogeneous [6]. On the other hand, different types of interactions should be considered, is definitely correct. This problem was already considered in [7]. Therein, it is suggested that both consensus and dissent are present in an heterogeneous population depending on a social distance between interacting a-particles. More in general, we can argue that different types of coexistence should be investigated as an additional heterogeneity feature of behavioral systems. The key problem also refers to the behavioral way by which individuals interact.

Some models to describe social dynamics in populations have been developed under the assumption that either consensus or opposition take place depending on the social distance [34, 70, 71]. This dynamics explains how radicalization phenomena mentioned in **BL2** show up. Further, it is a feature to be taken into account in crowd dynamics, where rational (leaders) and irrational behaviors might be contextually present. However, a systematic study has not yet been carried out. A more general approach might be developed by assuming that the interaction term $\mathcal{C}^i_{hk}[\mathbf{f}]$ in (3.4) is not modeled by only one of the qualitative interactions reported in Fig. 4, but by a convex combination of two different types of interactions, for instance consensus and dissent,

$$\mathcal{C}^i_{hk}[f_h, f_k] = \psi[f_h, f_k]\mathcal{A}^i_{hk}[f_h, f_k] + \big(1 - \psi[f_h, f_k]\big)\mathcal{B}^i_{hk}[f_h, f_k]. \tag{8}$$

Indeed, further study would be necessary towards the modeling of the term ψ which separates the two different of dynamic.

3.3 Critical analysis

The structures defined in (3.2)–(3.7) permit one to derive mathematical models once the various interaction terms $\eta, \mu, \mathcal{C}, \mathcal{P}, \mathcal{D}$ are modeled on the basis of a phenomenological-theoretical interpretation of each specific system object of the study. However, a detailed analysis of the qualitative properties of these structures is necessary to verify their ability to capture the complexity features identified by answering to the key question KQ2, posed in Section 2, within the modeling framework depicted in the flow chart of Figure 1.

Bearing all above in the mind, let us focus on each of the selected key features, and discuss to what extend the mathematical theory can account for them. The study of this problem refers also to specific applications.

• *Ability to express a strategy:* This ability is modeled by the activity variable, which is a *behavioral variable*. If the activity is a vector, then all components may affect each other. When the model includes both behavioral and mechanical variables, a commonly shared opinion is that the mechanical dynamic is influenced by individual behaviors. An example of the first case is given by the dynamic of idiosyncratic learning which affects the skill in market sharing [28], while an example of the second case appears in crowd dynamics [31] as the strategy by which walkers move and select trajectories depends on their emotional state. The motion of cells follows analogous rules, namely the motion is often a function of biological, in some case heterogeneous, properties [140].

• *Heterogeneity:* The use of the distribution function over the activity, that is the dependent variable of the model, naturally accounts for the heterogeneous behavior of a-particles within each FS. Subdivision into different FSs can also be referred to certain types of heterogeneity as in the case of endogenous frameworks.

• *Nonlinear interactions:* The output of interactions is generally nonlinearly additive with respect to the inputs. In addition, it can also depend on the distribution functions of the interacting a-particles. As an example, models of opinion formation include the sensitivity of a-particles not only to individual a-particles, but also to first order moments. This type of dynamic characterizes, for instance, aggregation into political opinions as individual attitudes are modified not only by individual based interactions, but also by groups [7].

• *Learning ability:* Individual entities learn from past experience [54, 55, 56]. As a consequence, the rules by which a-particles interact is modified by the level of learning heterogeneously acquired by each individual. The applications treated in the next Section 4 include this type of interactions.

• *Darwinian mutations and selection:* All living systems are evolutionary, as birth processes can generate entities more fitted to the environment. These, in turn, may generate new entities again more fitted to the outer environment. An immediate application appears in the immune competition in cancer dynamics, where several mutations generate cancer cells [93, 95, 150], while the immune system evolves by learning to produce selection [122].

The general structure of all interaction terms can potentially model all features that have been reported above. However, although we have verified that the mathematical structures derived by the kinetic theory of active particles can capture the complexity features of living systems, additional key problems have to be considered to validate the mathematical theory. Some of the said key problems may be suggested by the applications treated in Section 4. Here, we simply mention some topics which deserved further reasonings, for instance:

Collective behaviors may present *large deviations* that might lead to non-predictable events i.e. to the so-called *black swan*. A critical issue consists in understanding how large deviations can be considered a black swan or simply a consequence of the fragility of the system [13].

Individual entities often show a trend to aggregate *into groups of affinity* which generate endogenous networks modifying the rules of interaction and, consequently, the interactions' outcome.

The assumption of continuity of the distribution function is justified only by the involvement of a very large number of a-particles. Discrete distributions can be used as shown in [23], but also pseudo Newtonian frameworks can be developed as shown in Section 4.

Different types of dynamics can be captured by the activity variable. A modeling approach might search for a hierarchy as in the case of crowd dynamics, where pedestrians firstly exchange their emotional state and subsequently develop a walking strategy [15].

Non-symmetric interactions and lack of information: Figure 3 shows that visibility domain can reduce the sensitivity domain, whenever $\Omega_v \subset \Omega_v$. In this case, the a-particles receives a limited, in some cases even asymmetric information. As a consequence the strategy by which the a-particle expresses one's activity might not be sufficient to achieve rationality.

Various other key problems are suggested by the applications reported in Section 4, where the cornerstone of all application is the search for a *multiscale vision* which is the key passage towards a mathematical theory of living systems.

4 Applications looking ahead to modeling perspectives

This section presents a review and critical analysis of the mathematical theory proposed in Section 3, with special emphasis on applications. In that section, it has been shown how mathematical models can be derived by inserting specific models of micro-scale interactions into differential structures specifically selected for each system under consideration.

This paper goes beyond [35] as in these recent years important developments of the theory have been proposed spurred by applications. We select five topics which, according to the authors' perspective, present features that deserve attention in view of future extensions of the theory. In more details, the presentation consider the following applications: collective learning, human crowds, immune competition and diseases spreading, evolutionary economics, and behavioral swarms. The presentation includes some sample simulations.

As we shall see, the survey of applications already includes some reasonings on possible modeling perspectives which are not simply technical developments, but need to be viewed as motivations and hints towards furthers steps in the quest towards a mathematics for living systems. Accordingly, this section motivates the contents of the last section which looks forward to further steps along the complex path proposed in our paper.

4.1 Collective learning dynamics

The definition *collective learning* is used to denote the dynamics by which an individual learns a well defined knowledge, or even a well defined skill, from a population of interacting individuals. In more details, the following definition can guide the modeling approach [58]:

> *Collective learning is a social process of cumulative knowledge, based on a set of shared rules and procedures which allow individuals to coordinate their actions in search for problem solutions.*

Within this framework we stress that collective learning is an *interactive process*, where the transfer of knowledge is induced by interactions which occur in the individual's mind as a social and participatory process and that increases his mental knowledge [129, 148].

In addition, collective learning is *lastly cumulative*, as it accumulates over time. A specific example is the *social learning*, originated with the development of psychology sciences, which occurs when the individual learns new behaviors (as specific skills) and concepts from others [21, 136], see also [116].

The collective learning process, that takes place within a system of interacting individuals, is characterized by the following sequential steps:

1. **Perception**: Each individual possesses a perception domain defined in the space of the microscopic states. It is the domain within which the presence of other individuals is perceived with a different intensity that can depend, for instance, on a *social distance*, namely the distance between the activity variables of the test and field a-particles. Accordingly, the modeling approach should first define the interaction domain and, subsequently, a metrics to estimate the said distance.

2. **Interactions and learning**: Individuals may increase, by interactions, the level of their knowledge, that is a positive defined quantity. Both binary and multiple interactions should be considered. Networks, both exogenous and endogenous, can enhance the learning dynamics. Also in this respect a suitable metric should be chosen in order to quantify the amount of learning acquired over time.

3. **From learning to behavioral dynamics:** *Learning* can act as a preparatory step preceding and conditioning other dynamics [53]. For instance, *collective learning* followed by a specific *social dynamic*. In this case, the *activity* variable is a vector defined by two components: $\mathbf{w} = \{u, v\}$, where u is the component that characterizes the level of *learning* and v is the *social* component whose dynamic is also induced by u.

Methods of the kinetic theory of active particles have been proposed in [54, 56] with application to modeling scholar learning [48]. Further developments have been treated in [53], where the modeling of the interaction between learning and different dynamics were investigated. An interesting modeling perspective refers to the dynamics of heritages [45].

In more details, the application treated in [54] refers to learning dynamics in the spatially homogeneous case, specifically to collective learning in a classroom. In more details, three different cases are considered:

Case (a) corresponds to the traditional teaching approach, which assumes that students only attend lectures of the teacher.

Case (b) in which students are engaged in collaborative work forming groups of two individuals. The groups are homogeneous and the members of each group are selected among students having similar initial achievements.

Case (c), where the students are organized in groups as in case (b), but the groups are heterogeneous and the members are chosen at random.

As for the *transition probability densities* we must distinguish two types of dynamics:

• *For the student-teacher interaction* the probability for a student to learn is proportional to the level of knowledge of the teacher. The subsequent increase of knowledge is a uniform random variable given by a fraction of what he/she does not know.

• *For the student-student interaction* the probability for a student to learn is proportional to the product of his level of ignorance and the level of knowledge of the interaction partner. The subsequent increase of knowledge is a uniform random variable given by a fraction of what he does not know. The probability for a student to keep his level of knowledge is proportional to the level of knowledge itself.

The application shows that the level of knowledge of a student not only increases, but also can decrease, which is not unexpected. Indeed, inappropriate teaching material, lack of attention of the students, disordered discussions, misunderstandings and so on, may result in unlearning. Furthermore, the performance of low level students may be enhanced when they form groups with better students, although this improvement is obtained at the expense of the achievements of their colleagues.

The kinetic theory modeling offers deeper insights into system dynamics by naturally providing the time evolution of the density distribution functions of each group of students, while the subdivision into functional subsystems allows to investigate how the different types of students interact.

Let's conclude this subsection by some remarks, selected according to the authors' perspective, looking ahead to research perspectives: :

1. *Nonlinear interactions*: Nonlinearity of interactions at the micro-scale means that the output of interactions could depend not only on the

microscopic state of the interacting entities, but also on the probability distribution functions of the functional subsystems to which they belong.

2. *Mutations and selection*: Post-Darwinian dynamics consisting in mutations followed by selection plays an important role in biology. An analogous dynamic appears in social systems, where new groups may be generated, for instance, by the aggregation of different groups. These, subsequently, may either expand or disappear due a competition somehow mediated by the external environment.

3. *From learning to behavioral dynamics:* Collective learning is almost always followed by a subsequent dynamic, where individual behaviors depend on the level of learning which is heterogeneously achieved in a population.

We mention two case studies, treated in the next subsections, where learning dynamic precede a subsequent dynamic.

In *crowd dynamics in the presence of epidemics*, the awareness of the risk of contagion can pervade crowds moving in venues of a territory. This feeling, which is learned by interactions with other individuals, modifies individual trajectories in the search of paths through low density areas, but paying the price of increasing, with respect to the trajectories in absence of such awareness, to reach a target. This topic has been introduced in [111], within the framework of models of behavioral-social crowd dynamics [31, 110], accounting for recent studies on the pandemic by virus COVID-19 [25].

analogous phenomena appear in the modeling of the *motion of cells*, where interactions firstly define the biological function expressed by various cell populations and subsequently express a motion strategy [140].

In the analysis of *technological learning and industrial dynamics*, learning might be represented as the process of accumulation of knowledge of heterogeneous firms, competing to increase their market shares. Knowledge is idiosyncratic but its level and distribution influence the overall collective population dynamics of firms.

4.2 Vehicular traffic and human crowds

The modeling and simulation of vehicular traffic and human crowds by the kinetic theory approach is a very active research area involving challenging analytical problems and potentially leading to novel applications [23].

The kinetic theory modeling of vehicular traffic trace back to the pioneering works [130, 128], and a review of the most recent contributions on this research area, including human crowds, is given in [8]. The modeling of interactions by density dependent rules have been firstly introduced in [68] and in [64]. In both works it has been assumed that the speed of vehicles can only take a finite number of velocities, but the grid of discrete velocities is different in the two cases, namely it is a fixed grid in [68] whereas it depends on the density in [64]. Further developments of this pivotal idea have been given in [84, 85], while a qualitative analysis and numerical study of the initial value problem has been carried out in [37].

The modeling of human crowds accounting for nonlinear interactions between pedestrians has been started in [24] and further extended by various authors as reported in [8]. See also [80, 81, 110, 111, 109]. In [110], the kinetic model presented in [30] is further developed to study the dynamics in bounded domains with obstacles. In [111], such model is coupled to a disease contagion model inspired from the work on emotional contagion in [44], while in [109] it is further extended to account for the propagation of stress conditions in time and space.

The control of crowds is studied in [9] by means of the social influence of leaders, namely trained personnel that may guide pedestrians to egress from complex environment whose connectivity is not known or modified by incidents. Beside its theoretical interest, this topic is of practical importance as it may significantly contribute to crowd management in emergency situations where overcrowding may cause fatal accidents.

More recently, focus has been put on accounting for human psychology in the modeling of the social dynamic in crowds [31, 44] as the literature on safety problems clearly indicates that crisis management can take advantage of models that account for human behaviors [132, 133, 134, 135, 151]. In these studies, interacting pedestrians modify their psychological status and, in turn, the walking strategy. The emotional states significantly affects the overall crowd dynamics in extreme real-life situations such as a peaceful demonstration that turns violent and the spreading of panic in emergency evacuations.

A closely related problem is that of epidemics spread. An hybrid approach, that couples a kinetic model of crowd dynamics with one of contagion spreading, has been proposed in [111]. In spite of the similarity between models that deal with evacuation and virus transmission a remarkable difference must be pointed out. In the former the key social state is the level of stress whereas in the latter is the level of awareness. The resultant pedestrians' behavior is completely different in the two cases. The level of stress promotes aggregation of walkers and leads to the herd behavior under panic conditions [117]. By contrast, the level of awareness pushes pedestrians to follow social distancing guidelines.

The research program on these challenging topics has just started, and many contributions are still to come due to the many complex aspects of human psychology as well as the inherent system heterogeneity. A multiscale framework, like the one proposed in [15] for the modeling of human crowds, needs to be formulated because, for practical applications, the crowd must be describe at all the three possible modeling scales (i.e. microscopic, mesoscopic, macroscopic) by a consistent approach, namely models must be derived at each scale using the same principles and similar parameters.

It is foreseeable that the main objective of the future computational modeling of human crowds is the development of a simulation platform in support to urban planners and/or crisis managers [26]. This platform may consider to simulate a mixed traffic consisting of cars, trams, and pedestrians, and lead to optimize the flow of vehicles over networks of roads in cities by defining optimal transportation policies, improve the management of safety problems, such as emergency evacuation, and/or the design of buildings.

Furthermore, such a platform can be used in training crisis managers as it allows to explore scenarios triggered by different courses of action. This "what-if" analysis is crucial for elaborating optimal procedures, especially for dealing with emergency conditions. Note that the platform can also be designed to create virtual and augmented-reality applications that further enhance the training capability. A major issue in developing this kind of platform is the modeling of interactions between heterogeneous agents and the capability to fully capture the geometrical complexity of the network where the dynamic is studied. In this respect, the platform needs to be developed within a system approach to crowd dynamics that also includes the modeling of how the crowd behavior modifies in extreme situations.

4.3 From the immune competition to modeling virus pandemics

Modeling the immune competition between cancer and immune cells ended up with the first class of models derived within a mathematical theory of active particles [39]. This research line has been further developed in [38] to account for mutations and selection of tumor cells as well as for the learning ability of the immune system, while the modeling of the role of macrophages has been developed in [79]. The book [122] is a useful reference to understand the complex dynamics in immunology, while the book [150] provides a precious description of cancer biology. The pioneering paper [66], devoted to the modeling of virus mutations followed by a learning dynamics, provides some ideas which can be developed towards a modeling approach to depict the complex mutation-learning dynamics specifically referred to COVID-19.

The modeling of the dynamics of the corona-virus requires, as shown in [25], a multiscale approach beyond deterministic population dynamics, as contagion occurs at the high scale of individuals depending on the viral charge inside each individual whose dynamics is at smaller scales determined by the competition between virus particles and the immune system. In addition, spatial dynamics and interactions are important features to be considered, as the dynamics are generated by nonlocal interactions and transportation devices. In the following, some reasonings about a number of research perspectives are presented.

Heterogeneity: Most epidemiological models are based on averaged large population behaviors over a given calendar time. In particular, compartmental models (starting from the celebrated model by Kermack and McKendrick [108]) use mean-field approximations. However, these models involve complex parameters that depend on many factors, which makes it difficult to predict how a change of a single environmental, demographic or epidemiological condition will affect the whole population. Moreover, these models are not valid if the population size is small-to-medium, as happens in some spatial domains (neighborhoods, stations, schools, etc.) that are very relevant in the dynamics around the development of an epidemic. Including heterogeneity, in the formulation of epidemiological models, improves their predictive and explanatory power and applicability. For instance, [102, 103] are valuable references that consider heterogeneity in populations described by compartmental models.

Some infections need modeling heterogeneity. For instance, during the COVID-19 crisis, the number of tested positive cases has shown to be a very widespread variable. However, its real usefulness is limited since it is highly dependent on testing capacity. Accordingly, [2, 3] propose to include the presence of different heterogeneous sub-populations, like hospitalizations, ICU admissions and deceased in order to have a better overview of the situation, obtaining very good forecasts through the so-called SHARUCD model. Kinetic models are also useful to deal with heterogeneity. The multiscale kinetic theory approach developed in [25] accounts for individual reactions to the infection and pandemic events heterogeneously distributed over the population. In addition, kinetic models let the population be divided into social, age, immune and/or gender groups, what may give specific answers to several questions arising in public health. Interactions between a pandemic with production systems [94] and with human psychological fragility [86] are problems of great general interest.

Spatial dynamics and propagation of infectious diseases: When it comes to assessing particular responses to specific outbreaks, studying how the proximity of people plays a role in the diffusion of a disease and what can be done in crowded areas and mass gatherings is crucial to give targeted responses. Crowd and epidemiological modeling have so far been treated as separated fields of research, with a very few attempts to link them together [50, 106, 111].

In order to study the propagation of an epidemic through the development of mathematical models of crowd dynamics, a deep understanding of how risk awareness spreads and how it triggers a diffusion of coping strategies is needed [1]. Moreover, an accurate representation of the spread over larger territories, like an entire city, leads to consider multi-scale, multi-layer networks [82, 127].

Different approaches can be used to model and simulate the spatial propagation of contagion within a set of active particles. From a continuous kinetic approach coupling the ideas presented in Section 5.2 with contagion dynamics [50, 109, 111], to Agent-Based modeling (see e.g. [144] for an interactive tool to study contagion dynamics, or [62] for an agent-based simulation of vaccination policies), without losing sight of contagion over graphs or networks [115, 147]. The approach shall be carefully selected, based on the system under study and on the objectives of each specific research.

Within host dynamics: The discussion above deals so far with disease transmission at the scale of an epidemic. However, it is also useful to describe disease processes at the microscopic scale, namely the spread of a viral or bacterial infection among a population of target cells, resulting in the so-called *in-host* models. Some recommended readings on this topic are [39, 122, 123], together with the review [63] and references therein, which introduce essentials on cell biology and immunology.

For respiratory diseases that cause damage to the lungs, like COVID-19, models should describe the dynamics of the viral load which might lead to different asymptotic trends between full recovery and death by overload and even material corruption of the lung. A description of the dynamics of the lung in order to detect those areas which are more susceptible to stretch overload in the pulmonary parenchyma is provided in [59]. Recent contributions in this topic are given in [104], which presents an interactive COVID-19 tissue simulator of viral dynamics of SARS-CoV-2 in a layer of epithelium and several sub-models (such as single-cell response, pyroptosis death model, tissue-damage model, lymph-node model and immune response), and [149] which develops a community-driven SARS-CoV-2 tissue simulator.

Multiscale aspects: It is plain that modeling ought to be developed within a multiscale approach, as the contagion dynamics should be treated at the scale of individuals, while the state of each single individual (healthy, infectious, etc.) depends on the dynamics at the micro-scale of cells related by the within-host competition between pathogens (e.g., viral particles or bacteria) and the immune system. Both scales constantly interact and that is probably one of the key features of the model presented in [25]. This coupling, as well as heterogeneity of populations, lead to variety of research perspectives accounting for immunization and vaccination programs, see [60, 87].

4.4 From behavioral to evolutionary economics

The very first application to modeling social dynamics by the kinetic theory methods arguably belongs to the pioneering paper [105], while the kinetic theory of active particles was applied in [40, 41, 42, 43] to opinion formation and wealth policy, by using scalar discrete activity variables. Further studies have followed in the field of behavioral and political economy, as examples [69, 70, 71, 73, 72]. This research activity refers to the stream of behavioral economics [145, 146].

Recent advancements moved from behavioral and collective population dynamics to model the footprints of evolutionary processes in economic dynamics by means of the kinetic theory of active particles, in short the KTAP approach, which includes both continuous and discrete distribution in the space of micro-states. In order to address the modeling of evolving economies, the capitalist system has to be understood as characterized by processes of endogenous self-sustained growth, punctuated by small and big crises. The following statement, from page 83 of [139], enlightens the underlying modeling scope:

> *Industrial mutation – if I may use the biological term – that incessantly revolutionizes the economic structure from within, incessantly destroying the old one, incessantly creating a new one. This process of Creative Destruction is the essential fact about capitalism.*

In modern capitalism, business firms are a central locus of the efforts to advance technologies, develop new products and operate new production processes [74]. In this respect the application of the KTAP approach to evolutionary dynamics as started with the modeling of *firm-level behaviors*. The key patterns meant to capture firm-level attributes and their interaction (see [28, 78, 76]) include:

– Persistently heterogeneity in firm characteristics nested in competitive environments that shape their individual economic fate and, collectively, the evolution of the forms of industrial organization.

– The process through which heterogeneous firms compete, let us call it Schumpeterian competition, on the basis of the products and services they offer and obviously their prices, and get selected - with some firms growing, some declining, some going out of business, some new ones always entering.

– Such processes of competition and selection are continuously fueled by the activities of innovation, adaptation, imitation by incumbent firms and by entrants.

More specifically, the approach developed in [28] restricts to the following dynamics:

1. *Learning* or empirically the *within effect* capturing idiosyncratic innovation, imitation, changes in technique of production;

2. *Selection* or empirically the *between effect* capturing market interactions where more competitive firms gain at the expense of less competitive ones.

In addition, the approach in [28] considers two functional subsystems which are nested into a hierarchical structure:

1. **Subsystem 1: Evolutionary landscape:** It represents the dynamics of learning to which firms are subject to. It is meant to capture the arrival of new technologies, new ideas, new organizational practices. It evolves *independently* from firm interactions, and it follows a *continuous growth* process. In economic terms, it represents the evolution of the technological frontier.

2. **Subsystem 2: Evolutionary landscape and endogenous system of interactions:** It comprises two distinct levels of interactions: one which determines the advancement of knowledge of each individual firm through the action of the first Subsystem, the second which entails the competition in the market arena among heterogeneous firms in terms of knowledge level.

Starting from the results in [28], the following lines of research might be pursued:

• *Imitation, entry, exit:* A first line of advancement with respect to the application of the KTAP to evolutionary economics entails the modeling of imitation, entry and exit dynamics applied to firms [75]. Imitation across firms represents the possibility to include forms of knowledge transmission occurring between pairs, say similar firms in the innovation space, which might acquire competencies and capabilities from other firms, and not simply from the exogenous innovation dynamics lead by Subsystem 1. Including imitation patterns might allow also to consider mutation, say from being a bad toward being a good firm in terms of the overall activity rate. With reference to selection, currently the modeling approach has stuck with a constant number of firms, however selection occurs also at the fringe and it is affected by exit, say mortality of firms. Additionally, entry of new types of firms, and particularly their attributes in terms of learning capacity is crucially important to shape the overall selection dynamics. Finally, entry of new firms might occur in the same sector or even in other sectors of activity.

• *From single sector to multi-sector dynamics:* Firms producing similar products are said to belong to the same sector of activity. Sectors are in general defined in terms of the produced output, say automotive versus food versus pharmaceutical sectors. Indeed, a big chunk of the evolution of modern capitalism has occurred by means of the arrival of new sectors of activity introducing long-term effects of structural change with some sectors gaining product and labor shares and some others declining [142]. A further evolution of the KTAP modeling approach toward evolutionary economics entails the introduction of multi-sector spaces of competitions, by means of parallel hierarchical Subsystems 1, as outlined above, each of one characterized by its internal knowledge evolution, but competing among them in terms of Subsystem 2 not only in terms of their internal efficiency but also of desirability of the produced product. The introduction of a multi-sector perspective would entail the specification of consumption dynamics shaping the overall evolution of each sector.

• *Network structure:* Neither firms nor sectors of activity are monads: in order to operate production activity, firms require to buy intermediate production goods from their peers that might be other firms in the same sector of activity or even in different ones. In economics, the phenomenon is labeled under the notion of value chain or vertical integrated structure [126], implying that each producer relies on a chain of suppliers of goods, and itself is the supplier of other firms. The integration of the KTAP with a network structure of firms, whose links represent the flows of knowledge or goods will allow to model one of the most important feature of contemporary capitalism and to allow to study how structures of relations *among* peers *along* the chain differently affect the selection process. Underlying conditions leading to virtuous or vicious chains might be studied.

• *Exploiting the multi-scale approach: from firms to sectors to the macro-economy:* Together with flexibility and heterogeneity, the other fundamental attribute of the KTAP approach is being multi-scale. The multi-scale structure brings enormous benefits to study economic processes which in general are stratified and are not isomorphic to different levels of aggregation [77]. A future modeling advancement would be to insert, on top of a multi-product structure, a third upper subsystem represented by the overall macro-economy, including all sectors and being endowed by its own *activity functions*. The macroeconomic Subsystems would be particularly relevant to study policy effects which are conducted at the macro-level.

4.5 Behavioral swarms

The assumption of the continuity of the distribution functions, that is the dependent variable of the mathematical structures derived in Section 3, has been critically analyzed in that section. This hypothesis breaks down if the number of interacting a-particles is not sufficiently high, in some sense still to be defined, to justify it. This conceptual difficulty motivates the search of alternative approaches suitable to tackle this key problem.

A simple approach consists in substituting the continuous distribution over the micro-state by a discrete one so that each node of the discrete micro-scale variable represents the number of particles in a certain domain of the space of the microscopic states. This approach has been applied in a variety of real world applications, for instance vehicular traffic [37, 64, 84], social dynamics [41] and evolutionary economics [28]. However, the problem of selecting the discrete nodes, which may depend on the local density [64], is still open.

Alternative frameworks can be found in the literature, examples include agent methods with application to sociophysics [89], lattice Boltzmann with application to pattern formation in biology [67], and behavioral swarms [33]. The third approach has been recently proposed based on the idea that the classical theory of swarms can be developed to account for a behavioral dynamics by inserting in the micro-state of the interacting individuals the activity variable [33]. The authors have used the definition *behavioral swarms* to identify this specific feature of their mathematical approach.

A classical reference for the swarm dynamics is the pioneering paper by Cucker and Smale [65], where the collective behaviors of interacting mechanical self-propelled particles is studied within a pseudo-Newtonian framework. This paper has motivated a huge literature on the modeling, qualitative analysis, and computational applications of the mathematical theory of swarms e.g. [97, 98]. Interactions produce accelerations, where inertia is hidden in the interaction parameters rather than being explicitly taken into account. The mathematical literature in the field has been reviewed and critically analyzed in Sections 5 and 6 of [8], see also [83].

The original model [65] describes the temporal evolution of the mechanical variables (positions and momentum) of the individual entities, but unlike in the modeling of the collective dynamics of biological and social complex systems, one needs to take into account internal variables such as temperature, spin and excitation, to list a few [91, 92]. These pioneering papers have motivated the overall contents of [33], where mathematical structures have been derived to model the dynamics of both social and mechanical variables according to a hierarchy by which individuals firstly modify their activity variable and subsequently develop their movement in space by mechanical rules driven by the activity. Hence, individual entities are viewed as a-particles. The examples treated in [33] show how each individual firstly learn, from the surrounding a-particles in their sensitivity area, how the velocity directions can be selected and subsequently develop their movement strategy. Selection refers to a fixed number of a-particles according to the conjecture proposed in [20].

The theory proposed in [33] is somehow inspired by some applications of the theory to social and economical problems [4, 17, 18, 27]. As mentioned, it consists in the derivation of differential structures which, consistently with the paradigms proposed in Section 2, describe the interactive dynamics of the activity and mechanical variables. These structures have been applied to the modeling of price dynamics in open markets where sellers and buyers undergo non-symmetric interactions [27, 114] and in the behavioral dynamics of swarms [33], where it is shown how the modeling of collective learning in real swarms modifies the collective behavior with respect to that in absence of learning.

The approach of behavioral swarms is a very recent proposal and we cannot yet state that a complete theory is presently available, as important topics should still be developed. For instance, we refer to the dynamics across functional subsystems and the modeling of mutations followed by selections. This specific dynamics is important not only in the modeling of biological systems, for instance multicellular systems in cancer phenomena [150] and the immune competition[122], but also in social-economical systems, where pseudo-Darwinian dynamics are observed in various cases, where active particles mutate and can be selected with some analogy with biological systems.

4.6 Additional reasonings

The review of applications presented in this section is essentially descriptive, however each application has been followed by simulations suitable to provide a quantitative description of the predictive ability of models. A brief description with focus on emerging behaviors is given below looking ahead to validation of models which are required to reproduce all emerging behaviors that are observed in real systems.

1. Models of collective learning[54, 56] were applied to learning in a classroom and, in addition, as a preliminary dynamic in all following applications. Emerging behaviors show the difference between collective and individual learning.

2. Propagation of virus infection were shown in crowd dynamics [111], while the role of stress induced by perception of danger has been shown in[31].

3. Modeling of virus pandemics has shown the in-host immune competition between virus and immune cells can enhance the collective spread of the epidemics[25]. An interesting behavior is shown in the modeling of virus' variations, where new variants progressively replace the original less aggressive virus[36].

4. Simulations developed in [28] show how idiosyncratic learning of technological progress can lead to a monopole of a limited number of enterprizes followed by disappearance of the others.

5. The mathematical theory of behavioral swarms was followed quantitative results on a dynamics where individual in a swarm perceive the movement of the neighborhood individual and develop an individual strategy that modifies the collective dynamics [33].

The aim of simulations is not limited to provide quantitative results, as it can also investigate emerging collective behaviors that is the first step towards the validation of models. Indeed, the collective dynamics of living systems often shows emerging behaviors which preserve the qualitative behavior for different initial conditions although quantitatively sensitive to small variation of parameters.

It is worth noticing that a common feature of all applications is that the collective dynamics is an output of the interaction between different dynamics. In this case, the activity variable is a vector, while the interaction follows a certain hierarchy of dynamics. For instance in the case of the interaction between firms and markets, firms firstly develop an idiosyncratic learning of technological growth, while market sharing is a consequence. This dynamics has been studied in the case of space homogeneity, while in crowd dynamics the interactions involves, firstly, social interactions, while walking dynamics follows being influenced by the social awareness acquired by each individual by means of a collective learning within the crowd.

Additional common features characterized all examples proposed in this section. Some of them are selected in the following and are referred to the specific models treated in the applications proposed in this section. Specifically: *Action of the external environment*; *Competition among a-particles*; and *Mutation and selection*. The interested reader can be rapidly recognize the above five features in the various class if models treated in this section. The next section. which is devoted to research perspectives, will add further reasonings on modeling and developments of the mathematical structures.

5 Perspectives towards a mathematical theory of living systems

In this paper, we have, proposed and critically analyzed a mathematical theory which aims at describing, by a differential system, the complex dynamics of systems composed by many interacting living entities. The rationale to achieve this objective were presented in Section 2, the mathematical structures and tools was developed in Section 3, while various applications were reviewed in Section 4.

As already stressed, further developments of the mathematical theory are needed to pursue the challenging objective posed in this paper, namely providing an answer to the key question posed in the title, namely *What is life?* posed within the framework of mathematical sciences.

Accordingly, this last section is devoted to select a number of research perspectives which can contribute to the design of a mathematics of living systems. In more details, the following topics have been selected on the basis of the authors' past experience and present vision:

1. Modeling pseudo-Darwinian dynamics.

2. Multiscale vision, representation, and dynamics.

3. Reasonings on agent methods referred to the KTAP theory.

These topics are treated in the following subsections, while the closure focuses on the mythical, however worth to be chased, objective indicated in the title of our paper. For each topic, firstly, we provide a qualitative description. Subsequently, we verify how far the approach of the mathematical theory can capture the specific dynamics under consideration. Finally, possible developments of the aforementioned mathematical theory are considered.

5.1 Pseudo-Darwinian mutations and selection

All living systems evolve in time and generate, from a certain genotype, a sequence of phenotypes that are modification of the original one. According to the general framework proposed in our paper, the description of an evolutionary system starts with a number of FSs which, due to mutations and selection, changes in time to include new FSs generated by mutations, while other FSs, less fitted to the environment, disappear by selection.

This dynamics is well known in biology, as it often corresponds to the onset of phenotypes that generate genetic diseases, for instance cancer [150]. However, we can observe the presence of pseudo-Darwinian mutations and selection in a broad variety, if not all, living systems. As an example, the need of including this type of dynamics in the modeling of systems in evolutionary and behavioral economics is motivated in [12] from the very first chapters.

In more details, this topic is treated in [75, 78], consistently with the interpretation of the interaction between firms and open markets mediated by the ability of firms to learn new skills in the design and production of goods. The dynamics, as shown in [28], may lead to the selection of firms which may even aggregate, while other firms may disappear due to their loss to capture the market.

The mathematical structures (3.2)–(3.7) show how this dynamics can be described, at formal level, by the terms C^i_{hk} and P^i_{hk} which model, respectively, conservative and proliferative dynamics, while selection is described by the destructive term D^i_{hk}. All different types of dynamics account for the interaction with the external environment that can promote both mutations and selection. Alternative approaches have been developed by nonlinear dynamical systems with mutations and selection [57].

The key problem of KTAP methods consists in the modeling of these terms accounting for both internal features and interaction with the external environment and/or specific actions. The mathematical structures (3.2)–(3.7) have been derived at the microscopic scale by a statistical representation consistent with the system's heterogeneity. A conjecture, worth to be studied, is that the rules by which a-particles interact may be induced by the dynamics of interaction at a submicroscopic scale. As an example, in biology the functions expressed by a cell are determined by the dynamics at the molecular (genetic) level, while in the case of firms the internal staff organization determines the dynamics of each firm. Various examples of evolutionary systems can be found also in social systems, as an example, the dynamics of cultural evolution [45].

As an additional example concerns the dynamics of a virus pandemic in a complex interconnected world [25] which shows how the contagion can diffuse in a crowd, where the awareness of the contagion is heterogeneously distributed. Subsequently, a within host competition between virus and immune systems develops inside the lung of infected individuals. The study of this interaction depicts useful scenarios of hospitalization, recovery and death, by a multiscale approach, where the dynamics of individuals depends on the dynamics at smaller scales inside each individual.

An interesting research perspective, definitely worth to be studied, consists in understanding the interplay between the dynamics at the two scales. A reasonable assumption is that, similar mathematical tools can be used for both scales albeit if referred to different variables and interactions. Then, the coupling should explain how the output from the lower scale affects the higher scale.

5.2 On a multiscale vision

The modeling of complex systems always needs a *multiscale approach*, where the dynamics at the large scale must be properly related to the dynamics at the low scales. This features appears also in the interactions as some of the models reviewed in Section 4 include not only *micro-scale interactions*, but also *micro-macro interactions* that occur between particles and FSs viewed as a whole being represented by their mean value.

All systems are multiscale, where we can identify the micro-scale (individual based) and macro-scale (hydrodynamics). Kinetic theory methods provide a statistical representation of micro-scale entities when the overall system is constituted of a large number of interacting entities, in our case a-particles. A general vision of *multiscale methods* consists firstly, in modeling individual based interactions, which are used to derive models at the micro-scale; subsequently, these models are used to derive kinetic type models, namely at the mesoscopic scale. The third step consists in developing asymptotic or averaging methods which lead to macro-scale models by letting this parameter to zero under reasonable physical assumptions.

This micro-macro derivation corresponds to the sixth problem posed by David Hilbert for classical particles in physics. Possible generalizations to a-particles systems are treated in [51, 52]. Specific applications have been developed referring to crowd dynamics [22] and biology as reviewed in [52]. The key difficulty, well defined in [11], is the fact that living systems leave far from equilibrium which makes highly difficult the search for pseudo-Maxwellian distribution as in the case of the classical kinetic theory.

An additional vision, which has been applied in the derivation of crowd dynamics models within a multiscale framework [15], consists in deriving models at all three scales, independently. The derivation should be based on the same physical principles and should use analogous parameters corresponding to the same principles. Indeed, this modeling rationale provides a necessary framework to Hilbert-type derivations. In all cases, the concept of scaling and representation should be precisely referred to the specific class of systems under consideration.

5.3 Perspective ideas on agents methods

Modeling and simulations of systems, somehow of the type reviewed in Section 4, can be developed by the so-called *agent-based models* [46]. It is crucial understanding the conceptual differences between this method and KTAP and, subsequently, investigate if each method can learn skills and tools reciprocally across them.

An ABM, sometimes called MAS (Multi-Agent System) on the basis of differences that we will not explore here, is missing a definite general framework. Following Axtell and Epstein in [16], an agent-based computational model contains a population of data structures representing individual agents, acting and interacting. Systematic regularities emerge at the macro-level from the local behavior of the agents. We have no equations governing the overall social structures, thus avoiding any aggregation or misspecification bias. The only equations present–if any–are those used by individual agents for decision-making. Different agents may have different decision rules and additional information; the agents are simple, and we look for the emergence of the complexity from their interaction. Agent models are built from the bottom up, describing individual behaviors and fitting them, even heterogeneously, into the agents. We observe the individual (micro) and aggregate (macro) effects that emerge from their activities and interactions.

The main differences between ABM method and KTAP refer both modeling aspects of the individual entities constituting the overall system and on the development of simulations. In more details:

• Agent-based models (ABMs) live in computer environments as data structures, where agents are modeled by a set of variables and interaction rules stated consistently with the programming language used for the simulations. These rules are heuristically designed (invented) by the modeler with the aim of obtain realistic computer simulations of the collective behavior of each specific system under consideration.

• In the kinetic theory of active particles, a-particles are entities carrier, in probability, of mechanical and behavioral variables, their interactions are modeled accounting for their micro-state and FS as well as for the distribution functions over the micro-sate. The collective dynamics is described by differential frameworks which capture the complexity feature of living systems.

• The common feature of the two approaches is that both of them need a detailed description of interactions at the microscopic scale while the difference consists in the way of implementing it. If we look at the contents of the preceding subsection we do reach the idea that improving the modeling at the micro-scale would bring advantage both approaches, however in view of a mathematical theory suitable to unify the two methods within a unitary framework.

According to this brief description, it appears that ABMs fully relay on heuristic interpretations of real world, the KTAP theory on a rationale consistent with the frameworks and tools offered by mathematical sciences. The lack of analytic equations in ABMs is simply a technical, but not conceptual, difference as the two methods would meet if the modeling of agents would follow well defined rules such as those in the modeling of a-particles in the KTAP theory. Conversely, the kinetic theory approach would enrich its ability to describe real world phenomena by enriching the the modeling of a-particles by exploiting the flexibility of the ABMs approach. Flexibility is very useful in modeling real world situations [120] in a complexity [12] framework.

The main advantage of the ABMs, i.e., their easiness in adapting to any detail of the agent behavior, can also dangerously conflict with the need of generalization and abstraction. To avoid that kind of error we have to keep in mind the paradoxical situation that Borges pictures in [49], where

> *the Colleges of Cartographers set up a Map of the Empire which had the size of the Empire itself and coincided with it point by point.*

producing completely useless object.

These reasonings naturally lead to propose the research perspective also to the interaction between the theory of behavioral swarms and the ABMs approach. This objective pursued only when the behavioral swarms theory wll be made complete by including non-conservative interactions, corresponding to proliferative and/or destructive events, as well as interactions that lead to mutations by moving across functional subsystems, while Darwinian selection would follow.

5.4 Closure

Let us finally return to the main objective of our paper, namely, let us try to understand how far the contents of our paper has moved along the quest towards a mathematical theory of living systems. As mentioned, the theory proposed in our paper is based on the idea of referring the derivation of models to the mathematical structures that have the ability to capture a selected number of the complexity features of living systems. Mathematical models can be derived by inserting in these structures specific models of interactions at the micro-scale.

This approach justify the use of the term *mathematical models* as these refer to a well defined mathematical theory which can be further developed and improved by considering all hints given in Subsections 5.1–5.3. Hence, this paper is not exhaustive. In addition, further steps towards the derivation of models consist in improving the description of interactions consistently to the theoretical inputs which can be delivered by the science of the research field where the specific system object of modeling can be referred to. In this case, we can use terms such as *biological-mathematical theory*, *economical mathematical theory*, and so on focusing on each specific scientific field.

Finally, we stress once more that the aforementioned challenging objective needs the *interdisciplinary way of thinking* whose presence has pervaded the whole paper. We do believe that the *interdisciplinary vision* of science is not simply an approach, but a necessary way of developing research activity devoted to life. Indeed, it is a new science. This concept is precisely the message in [90]

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