Modelling Virus Pandemics in a Globally Connected World
A Challenge Towards a Mathematics for Living Systems

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This editorial paper presents the articles published in a special issue devoted to the modeling and simulation of mutating virus pandemics in a globally connected world. The presentation is proposed in three parts. Firstly, motivations and objectives are presented according to the idea that mathematical models should go beyond deterministic population dynamics by considering the multiscale, heterogeneous features of the complex system under consideration. Subsequently, the contents of the articles in this issue are presented referring to the aforementioned complexity features. Finally a critical analysis of the overall contents of the issue is proposed, with the aim of providing a forward look to research perspectives.

Keywords: Complexity, active particles, multiscale vision, virus contagion and mutations.

AMS Subject Classification

1. Motivations and plan of the special issue

The onset of the *SARS–CoV–2* virus responsible for the initial *COVID-19* outbreak and the subsequent pandemic, has brought to almost all countries across the globe huge problems affecting health, safety/security, economics, and practically all expressions of collective behaviour in our societies. The different societies throughout the world have been heavily oppressed as the pandemic has generated severe problems affecting health, but also the economies in our societies have been affected thus requiring a new vision of social organization and a greater attention to welfare problems.

Indeed, we firmly believe that mathematical sciences can effectively contribute to depicting the possible outcome of the scenarios that follow the onset of a pandemic depending on the actions that are developed at a local and international level to combat the pandemic. Specifically, mathematical models can contribute to the decision making of crisis managers within a framework where the contribution of science can reduce the space left to biased, heuristic interpretations and approaches.

Based on these concepts we identify three key problems (KP) that might guide the mathematical approach and refer to the aforementioned concepts both the scientific articles of this special issue and the search for a research perspective.

KP1: The modeling approach should go far beyond deterministic population dynamics, as individual reactions to the infection and pandemic events are heterogeneously distributed throughout the population. Different types of heterogeneity appear in addition to that corresponding to biology. For instance physical, related to age, or social including the level of education which leads to a greater or lower level of ability to reach an advanced level of awareness concerning the risk of contagion.

KP2: Modeling should be developed according to a multiscale vision. Indeed, the pathology of individuals depends on the within-host dynamics at a small scale inside the lung. The dynamics concern also to the competition between virus particles and the immune system. Interactions between individuals, either infected or susceptible, occurs at a large scale, which, however, is related to the low scale as the infection rate depends on the viral charge.

KP3: Spatial dynamics is an important feature which has to be included in the overall approach. It should account not only for the dynamics of interactions in crowds and, more in general, the aggregation of individuals, but also for interactions induced by transportation networks as we live in a globally connected world. Pursuing this objective leads to new concepts of networks being required to be considered in the complex organization of human societies referring to their transportation systems and in some way related to social interactions including the organization of the broad variety of social activities.

The list given above does not claim to be complete. However, it already identifies a number of highly challenging perspectives. The papers in this special issue tackle, at least in part, some of the key problems noted above. These have been introduced in the pioneering article [7] whose hints have been considered in some of the articles of our special issue.

All articles acknowledge that the study of the system under consideration should somehow refer to the mathematics of the so-called *behavioral systems* [17], while the collection of surveys [5] provides a phenomenological interpretation of the complexity of features of living (hence, complex) systems, from swarms to multicellular systems and networks. As observed in [2], these systems operate far from equilibrium, and require the applications of methods of kinetic theory from the Fokker-Plank equation [20], the kinetic theory for active particles that combines the kinetic theory approach, to theoretical tools of stochastic game theory as shown in crowd dynamics [3], and the mathematical theory of swarms.

The contents of our editorial paper are as follows: Section 2 presents an overview of the articles published in this issue. Section 3 is devoted to a forward-looking view of research perspectives on the study of large active particle systems and living systems in general [17].

2. Presentation of the special issue

This section provides a brief description of each of the articles published in the special issue. We focus on the innovative contents of the articles referring to the key problems proposed in Section 1 and contributing to sketching new research perspectives. In more detail, the contents of the articles are as follows:

A further refinement of SEIR models is proposed in [19] to account for social distancing, testing, contact tracing, and quarantining. This enrichment, which is consistent with KP1, leads to the identification of containment measures which minimize the economic cost of the pandemic. Then, the authors develop an approach to control problems which somehow pervade all aspects of the COVID19 dynamics treated in the papers of this issue as problems that propose a strategy to mitigate the development of pandemics can consider the application of control theory.

Methods of the kinetic theory of active particles [9] are developed in [1] to describe alternative lock-down policies and vaccination strategies. The authors integrate and refine, within the framework of KP2, the multiscale model proposed in [7] by analyzing alternative network structures and bridging two perspectives to study the complexity of living systems, specifically considering the heterogeneity over the population. Some practical indications are delivered concerning social problems. For instance, the article considers school closures and their implications on society.

The awareness that during the COVID19 pandemic, conflicting opinions on physical distancing swept across social media, affecting both human behavior and the spread of COVID19, inspired the contents of the article [21]. This paper presents a two-layer multiplex network for the coupled spread of a disease somehow conditioned by conflicting opinions. The authors model each process as a contagion thus providing a new mathematical framework that looks forward to research perspectives. For instance, towards further development of the concepts proposed in dealing with crowd dynamics [26] whose hints have subsequently guided research activity specifically focused on contagion problems in human crowds [8,15,26].

A study of spatial networks in the spread of an epidemic is developed in [10]. The approach considers a realistic data-driven model accounting for the large uncertainty in the values reported by official sources, such as the number of infectious individuals. In detail, the paper addresses the above aspects through a hyperbolic compartmental model on networks, in which nodes identify locations of interest, such as cities or regions, and arcs represent the ensemble of main mobility paths. The model is tested on real empirical data concerning the spread of an epidemic in a realistic city network, and is confirmed with a study of the outbreak of COVID-19 in Italy and its spread in the Lombardy Region.

The contribution of [27] is mainly devoted to the interpretation of real data to support a possible planning of the needs of medical infrastructures which can possibly help in reducing the fatalities and/or reducing the number of infected individuals in the population. The article specifically refers to the Pavia Province and suggests different scenarios concerning the vaccination campaign. The paper combines a new mathematical description of the spread of an infectious disease, based on mathematical tools of statistical mechanics, which takes into account both age and average daily social contacts with a detailed analysis of the data-set of all traced infected individuals in the territory.

The problem of modifying a network topology in such a way as to delay the propagation of a disease with minimal disruption of the network capacity to reroute goods/items/passengers is considered here in [6]. A strategy is developed to remove edges in a network and it is shown that this significantly delays the propagation of a disease across the network with minimal disruption of its capacity to deliver goods/items/passengers.

3. Towards research perspectives

The contents of the articles in this special issue contribute to the key problems proposed in Section 1, thus naturally leading to research perspectives. Each article shows how new frontiers of applied mathematics have been opened by the complex interaction between mathematical sciences and the time-space dynamics of pandemics driven by a mutating virus. Looking at research perspective we firstly confirm the reasonings in [7] and specifically the following statements:

> *The modeling approach should go far beyond deterministic population dynamics, since individual reactions to the infection and pandemic events are heterogeneously distributed throughout the population.*

and

> *The modeling ought to be developed within a multiscale vision, as the dynamics of individuals depend on the dynamics at smaller scales inside each individual by the competition between virus particles and the immune system.*

In more detail concerning the research perspectives, we remark that a key aspect of the modeling approach is the study of the within-host dynamics which develops, mainly in the lungs, after contagion. It consists of a dynamics of competition between the immune system and a proliferative virus. Let us indicate, referring to this topic, where and how the present state of the art can be improved.

- The modeling of the in-host competition should consider that the immune system is constituted by several interacting populations each of which can progress and proliferate. Each population has a well-defined role and some of them are messengers of different types information [16]. The literature in the field is growing rapidly, see [12,18,25], as a natural development of classical theories [13], while the immune system evolves by learning about the presence of the "unwelcome guest".
- The challenge consists in transferring the biological knowledge into a mathematical framework. A further set of dynamics to be considered is the pseudo-Darwinian mutation of the virus, from the onset to aggressive variants [14,23] by a dynamics somehow related to the lower molecular scale. The in-host dynamics is evolutionary in nature, since the virus evolves by pseudo-Darwinian mutations.
- Spatial dynamics[SMC20] develops within a multiscale framework, and medical therapies can be modeled to depict how therapeutical actions can mitigate the spatial propagation of the virus. Vaccination strategies [11,24] should be included in the modeling approach to understand, and optimize, how this action can reduce the spread through a given territory.

All above reasonings confirm the concept that applied mathematicians cannot tackle the modeling of the complex system under consideration by a stand-alone approach. Indeed, an interdisciplinary vision is necessary through mutually enriching and beneficial interactions with scientists in other fields including virology, epidemiology, immunology – namely biology in general. Not only this, but social and economic topics and knowledge should also be considered as reported in some papers of this special issue e.g. [1,21]. Indeed, the COVID19 pandemic has highlighted the fragility of our society [4], over and above that of the current climate change of our planet. This special issue aims also at supporting the fact that mathematics and mathematicians can contribute, through synergistic interactions with a whole variety of research expertise, to tackle this problem.

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