On the Complex Dialogue Between Mathematics and Virus Pandemics

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This short paper focuses on the conceptual contributions that mathematical sciences can give to modeling virus pandemics over complex interconnected environments. A critical analysis of the existing literature is proposed looking ahead to research perspectives within a multiscale vision.

1 Motivations and Plan of the Essay

The onset of *SARS–CoV–2* responsible for the initial *COVID-19* outbreak and the subsequent pandemic, has brought to almost all countries and societies across the globe huge problems *affecting health, safety/security, economics, and all collective behaviors*. Various governments, as well as a number of scientists, have used the term *black swan*. However, this event is definitely not a black swan as it might have been predicted, but what effectively appeared is that societies were not prepared to tackle this problem. Independently on arguing about the black swan, the motivation to provide a strong scientific contribution to contrast the pandemics is crucial.

Within this framework, the contribution of mathematical sciences can play an important role. As a consequence, a large number of papers have been recently appeared. We limit our citations only to a few papers simply with the aim of a concise indication of some topics that we consider important to define how and how far mathematics can contribute to the aforementioned scientific challenge.

Accordingly, we bring to the attention of the interested reader five scientific papers focused on the following key topics: 1. Development of compartmental models to model spread and dynamics of the COVID-19 epidemic in Italy focusing on the predictive ability of models to understand the role of containment measures;[1] 2. A multiscale systems approach and models of virus pandemics in a globally connected world;[2] A highly communicative description of the complex biology of the system under consideration looking ahead to research perspectives;[3] 4. Space dependent diffusion of the epidemic are treated by the

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kinetic theory approach;[4] 5. Contagion problems in crowds and agglomeration of people modeled by methods of the kinetic theory of active particles,[5] see.[6]

The overview of these selected articles allows to contribute firstly to define a modeling strategy can be developed according to the objectives that a mathematician should chase and, subsequently, to provide some ideas towards research perspectives. These two topics are treated in the next two sections.

2 Modeling Strategy

We have learned by the biological interpretation of the dynamics of virus contagion and dynamics[2,3] that *SARS–CoV–2* is mainly transmitted through the respiratory route via respiratory droplets, up to 1 millimeter in diameter, that an infected person expels. If the viral charge is high, the carrier is more infective. Subsequently to contagion, large Spike proteins form a sort of crown on the surface of the viral particles and acts as an anchor allowing the virus to bind to the Angiotensin-Converting Enzyme 2 (ACE2) receptors on the host cell. After binding, the host cell transmembrane proteases cut the Spike proteins, allowing the virus surface to approach the cell membrane, fuse with it and the viral RNA enter the cell. Subsequently, the virus hijacks the cell machinery and the cell dies releasing millions of new viruses thus generating a virus infection.

COVID-19 starts with the arrival of *SARS–CoV–2* virions to the respiratory mucosal surfaces of the nose and throat that express high levels of ACE-2 receptors on the surface. When the virus manages to overcome the barrier of the mechanisms and the mucus secreted by goblet cells from a first effective reaction, a rapid release of danger signals activates the reaction of the host's innate immunity. *Corona viruses are successful at suppressing various mechanisms, but not all of them, in an immune response.*

Bearing in the mind the above brief description, some concepts, however generated by the author's bias, can be proposed towards a possible *modeling strategy*:

- Applied mathematicians should not tackle the modeling problem by a stand-alone approach. Indeed, an interdisciplinary vision is necessary through mutually enriching and beneficial interactions with scientists in other fields as virology, epidemiology, immunology and, in general, biology. In addition, interactions should also be addressed to wider aspects of other communities in our society, e.g. economists and sociologists.
- Modeling approach should go far beyond deterministic population dynamics. Thus considering that individual reactions to the infection and pandemic are heterogeneously distributed throughout the population. Spatial dynamics is generated by nonlocal interactions and transportation devices. In addition

Darwinian mutations and selection into variants should be included in the modeling approach.

- The modeling ought to be developed within a multiscale approach, specifically the macro-scale for dynamics of contagion, while the dynamics of the health state of individuals depends on the dynamics at micro-scale by the in-host competition between virus particles and the immune system. The two scales constantly interact as the contagion at the macro scale depends of the viral load of each individuals which in turn depends on the dynamics at the micro-scale. Heterogeneity appears at both scales.

The specific complexity features to be considered in the modeling are, according to the author's bias, the following: *1. Heterogeneous ability to express a strategy* as living entities are capable to develop specific strategies and organization abilities that depend on the state of the surrounding environment; *2. Nonlinear interactions and learning ability* by nonlinearly additive and nonlocal interactions which living systems learn from past experience; *3. Darwinian mutations and selection* as birth processes can generate entities more fitted to the environment, who in turn generate new entities again more fitted to the outer environment. Hence, life is evolutionary and selective.

The key strategy of the modeling approach is as follows: *The strategy consists in replacing the field theory by a mathematical structure (say mathematical theory) suitable to capture, as far as possible, the complexity features of living systems. This structure defines the conceptual framework for the derivation of models in different fields of science of living systems.* The flow chart of Figure 1, reports the rationale and sequential steps of the approach.

Finally: *Once refined and informed by empirical data, mathematical models can produce insightful provisional simulations which can even uncover dynamics which were not previously observed (cf. emergent behavior). Hence, mathematical models can provide a broad variety of scenarios of the dynamics depending to key parameters. Indeed, this is the contribution of mathematics to crisis managers.*

3 Research Perspectives

Research perspectives can be drawn by starting from the achievements in[2] reporting that the modeling of individual based contagion is determined by short range contacts in crowds[5] and by transportation dynamics and networks,[3,4] while the modeling of the immune competition leads to a dynamics, where the outputs are (i) need of hospitalization, (ii) recovery, or (iii) death.

Research in the field is in progress by further development of[2] by including both the strategy of vaccination and Darwinian mutations and selection which lead to the presence of more aggressive variants. This development can contribute to the aforementioned dialogue between mathematics and crisis managers. In

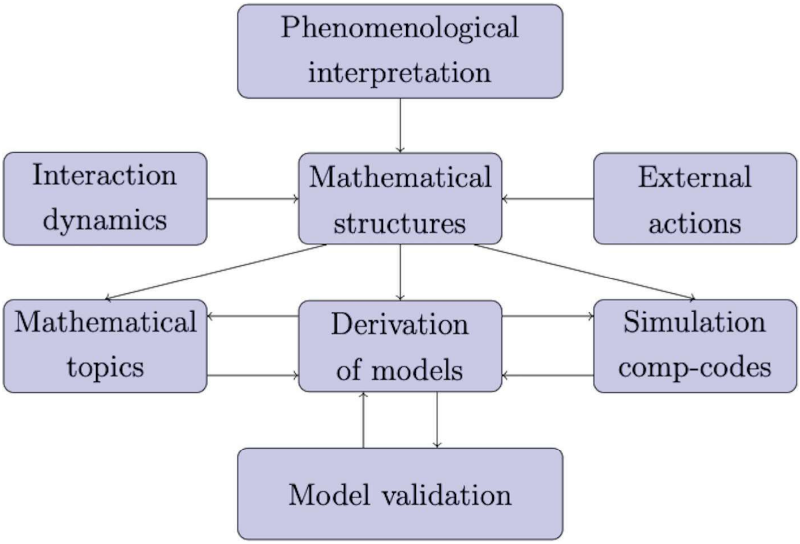

Figure 1: Rationale towards modeling.

fact, vaccination can reduce the lapse of time during which the epidemics is active, while the probability of mutations increases with the presence and local diffusion of the virus infection.

It is plain that the perspectives reported in Figure 2 do not depict the end of the story as a key development of a research strategy should focus on a deeper study, followed by modeling, of the highly complex immune competition.[7] We

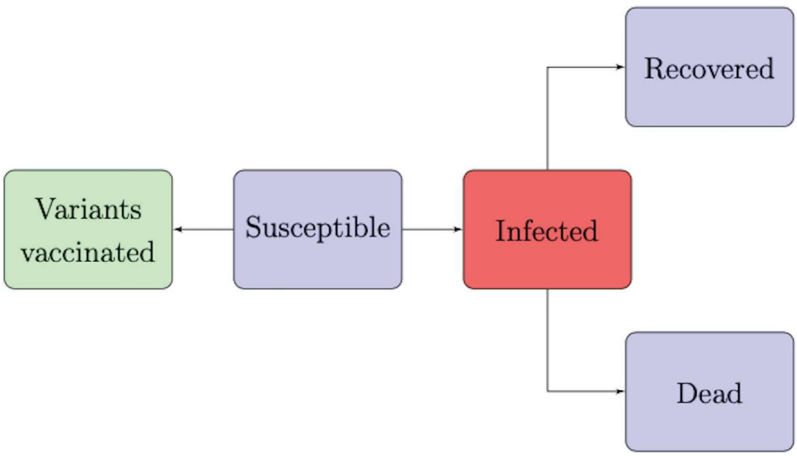

Figure 2: Flow chart of research perspectives.

do believe that further understanding of the immune competition can lead to significant improvement in the modeling approach.

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