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Editorial

New Challenges in the Mathematical Modelling and Control of COVID-19 Epidemics: Analysis of Non-Pharmaceutical Actions and Vaccination Strategies

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Following its official appearance in China in December 2019, COVID-19 (SARS-CoV-2) infection immediately reached pandemic proportions on six continents and in over 195 countries. It was the cause of a worldwide economic and health crisis inflicting USD one trillion in global economic damage in 2020 (to name just one figure) and had a very uneven impact on different age groups of society. Long-term lockdowns were not feasible, and contact-tracing procedures dramatically lost effectiveness with high case numbers. The availability of approved COVID-19 vaccines then led to mass vaccinations around the world. At the end of 2020, the US Food and Drug Administration granted emergency use authorization for COVID-19 vaccines, and several countries, including the US, began a mass vaccination campaign.

Vaccine efficacy, the duration of immunity, the escape of vaccine-induced immunity, the mechanisms of virus transmission, the effect of variants, the effects of age stratification, spatial effects, social networks, contact patterns, and the specificity of individual behaviours have provoked researchers to implement new strategies by combining innovative approaches, interpreting current epidemic scenarios and forecasting new ones.

Since the beginning of the pandemic, the entire scientific community across various fields of expertise has striven to help alleviate the associated problems. To provide just one figure, the call for papers proposed by *Nature Communications* collected more than 700 papers on the issue from 2019 to 2022. In addition to the sciences that are closely related to diseases, such as medicine, biology, and epidemiology, the mathematical modeling and control community has also endeavoured to contribute. Many journals have devoted Special Issues to the topic, mainly to give a prompt answer to the problem (see, for example, the Special Issue of *Frontiers in Physics* titled *Mathematical Modelling of the Pandemic of 2019 Novel Coronavirus (COVID-19): Patterns, Dynamics, Prediction, and Control*, composed of 34 general scope papers, or the Special Issue of *Mathematical Modelling of Natural Phenomena* titled *Coronavirus: Scientific Insights and Societal Aspects*, with 26 manuscripts). More-specialized journals also tried to share their perspectives, proposing Special Issues that helped us to better understand the impact of the pandemic from a retrospective point of view. For example, note the following instances:

- The *Bulletin of Mathematical Biology* proposed a Special Issue titled *Mathematics and Covid 19* in which they provided a general analysis of the various aspects of COVID-19, ranging from the forecasting of its evolution [1–3] to vaccination strategies [4–7] and the effectiveness of different control strategies [8–12].
- The *Journal of Theoretical Biology* proposed a Special Issue titled *Modelling COVID-19 and Preparedness for Future Pandemics* specifically focused on studying different modeling techniques to better understand which is the best model to use for each question and how efficient a model can be for disease prediction [13–22]; better understand the

cyclic phenomena observed in this pandemic [23–29]; explore the roles of different virus strains and methods with which to rapidly detect them [30–34]; and relate social problems to the pandemic [35–38].

- Even less-specialized journals decided to pay attention to COVID-19, such as the *Journal of Mathematics in Industry*, which proposed the Special Issue *Mathematical Models of the Spread and Consequences of the SARS-CoV-2 Pandemics. Effects on Health, Society, Industry, Economics and Technology*, principally devoted to the effect of the pandemic on society [39–41] and the estimation of the cost of the pandemic [42–44] and therefore particularly devoted to understanding the effects of non-pharmaceutical interventions [45–49].

Our Special Issue (SI) is part of this vibrant and dynamic context. It consists of eleven papers, namely, ten articles and one feature paper [50] (i.e., a substantial original article that covers several techniques or approaches, gives an outlook on future research directions, and describes possible research applications). Researchers from fields such as applied mathematics, data science, engineering, statistical sciences, computer science, biology, communication and information technology, economics, and management have been successfully integrated.

Indeed, this SI collects innovative results, tools for mathematical modelling and epidemic control based on a multidisciplinary approach (which is typical of complex systems), and analyses related to the following aspects:

1. The clinical characteristics and risk factors of COVID-19 related to patient survival;
2. The spread of variants;
3. The recovery of economic systems;
4. The prediction of mortality rates;
5. The impact of non-pharmaceutical interventions and their relative weight in relation to vaccination strategies in terms of deaths and infections;
6. Coordinated actions that simultaneously include non-pharmaceutical interventions and vaccination strategies.

A novel mathematical model for evaluating the effects of administering multiple constant and time-varying vaccines (including first and second doses and boosters) on the incidence and persistence of infections is presented in [51]. The authors also developed a control model to suggest the optimal strategy and thus minimize disease by introducing time-varying controls: by effectively adjusting vaccination strategies, such as the timing and frequency of doses, this model showed that the spread of disease can be significantly controlled. These time-varying controls allow for a more adaptive and responsive approach, enabling health authorities to adjust vaccination campaigns based on evolving epidemiological conditions, the emergence of new variants, and overall vaccination coverage in a population.

Regression models for competing risks can generally provide a crucial basis for precise individualized predictions. This is presented in [50], which shows how patients can be prioritized accordingly for vaccination and/or how clinical decisions can be made either for close monitoring, ICU admission, or the approval of new interventions. In addition, ref. [50] illustrates how competing risk survival analyses can be used to estimate the Cumulative Incidence Function of dying from COVID-19 and the Cumulative Incidence Function of dying from other causes for Brazilian subjects with COVID-19. In particular, exposure to asthma, diabetes, obesity, older age, male gender, being black or indigenous, lack of influenza vaccination, admission to an intensive care unit, and the presence of other risk factors, such as immuno-suppression and chronic kidney, neurological, liver, and lung diseases, significantly increase the probability of dying from COVID-19. Finally, it is noted that the highest hazard ratio was observed for people aged over 70 years (in comparison to people aged 50–60 years).

A continuous-time category model SEIRS-VB (S, susceptible; E, exposed; I, infectious; R, recovered; S, suceptible, where V stands for susceptible vaccinated individuals and B denotes individuals with vaccine-induced immunity) was used in [52] in order to model the long-term behaviour of the COVID-19 pandemic, and the basic reproduction number associated with this model in the autonomous case is defined: the single disease-free equilibrium point is locally asymptotically stable when the basic reproduction number is less than one and unstable when it is greater than one. Furthermore, a family of discrete-time models with weights is proposed that preserves the biological properties of the differential model. This study aimed to better understand why Bulgaria has the lowest COVID-19 vaccination rate in the European Union and the second highest COVID-19 mortality rate in the world.

A novel approach to simulating the spread of the Omicron variant of SARS-CoV-2 using fractional-order COVID-19 models is presented in [53]. Through the use of the Haar wavelet collocation method, the authors aimed to account for the various factors influencing virus transmission, and, using data from Pakistan, they illustrate the effectiveness of the proposed approach.

Epidemics can be modeled using both macroscopic (compartmental) and microscopic models. An example of the latter is presented in [54], where a novel agent-based simulation framework based on unique mobility patterns for agents between their home location and a point of interest and the extended SICARQD epidemic model (S, susceptible; I, incubating; C, contagious; A, aware; R, recovered; Q, quarantined; D, dead) is applied . This paper provides a qualitative assessment of the impact of quarantine policies and patient relapse rates on society in relation to the proportion of the population infected. The role of three possible quarantine policies (proactive, reactive, and no quarantine) is investigated, along with variable quarantine restriction (0–100%) and three recurrence scenarios (short, long, and no recurrence). The results show that proactive quarantine combined with a higher quarantine rate (i.e., a stricter quarantine policy) triggers a phase transition that reduces the total infected population by over 90% compared to reactive quarantine. Non-pharmaceutical guidelines are also proposed that can be directly applied by global policy-makers.

A new COVID-19 discrete-time compartmental model is presented in [55], where the number of vaccinated people is considered a new state variable. This study shows the existence of two fixed points, a disease-free fixed point (with global asymptotic stability properties) and an endemic fixed point: if a certain inequality with respect to the vaccination rate is satisfied, then the pandemic disappears. These findings can help decision-makers to better understand the epidemiological behavior of this disease over time.

The use of emergent intelligence tools to model complex network systems is the key idea proposed in [56]. This paper focuses on the possibility of analyzing the dynamics of changes in the indicators of the spread of COVID-19 during the first wave of the epidemic (when there was a lack of sufficient statistics because vaccination had not yet started). Percentage growth is therefore used as the most important parameter of the model, which has a stochastic nature. The principle of dynamic balance of epidemiological processes is also innovatively used. This principle is based on the fact that the past values of the total number of cases are close enough to the values of the total number of recovered and deceased patients at the current time. The problem of predicting the future dynamics of the exactly random values of the model parameters is then addressed to determine the future values of the total number of cases and the recovered and deceased as well as active cases. Data from Russia and European countries (Germany and Italy) collected during the first wave of the epidemic are used.

Medical shocks, such as the COVID-19 pandemic, significantly affect countries' economic systems. To understand the recovery from such shocks, ref. [57] proposes a mathematical model that accounts for the interplay between pandemic dynamics and economic development, including management considerations. This model's effectiveness was validated by applying it to five emerging economies: India, Brazil, Indonesia, South Africa, and Kazakhstan. These countries were selected to provide broad geographical coverage while representing scenarios in which developing economies may face greater challenges in allocating sufficient funds to combat the pandemic compared to developed economies. The results obtained from these applications, especially in the early stages of the pandemic's spread, underscore the crucial importance of implementing proactive corrective measures promptly to overcome the pandemic and facilitate economic recovery.

A novel statistical model for capturing the mortality rates of COVID-19 patients is proposed in [58]. The model, the New Modified Flexible Weibull Extension (NMFWE) distribution, offers a fresh perspective in the realm of data modeling. The study includes the derivation of maximum likelihood estimators for the NMFWE model and their assessment through a simulation study using specific datasets from Mexico and Canada. A comparison with other statistical models reveals that the NMFWE model outperforms them in terms of seven key statistical metrics when applied to mortality rate data.

Using a deterministic two-age-structured COVID-19 epidemic compartmental model, ref. [59] illustrates how age plays a crucial role in disease transmission dynamics. Two age classes are considered, those under 60 years old and those aged 60 and older, to align with vaccination strategies and address identifiability issues. This research examines six distinct disease transmission scenarios alongside social distancing measures and feedback interventions, including an age-stratified vaccine prioritization strategy. These interventions impact age-dependent patterns of social contact and the spread of COVID-19. Notably, this study innovatively identifies virulence parameters within these age groups during different phases. The findings from [59] contribute to our understanding of how human contact networks and behavior influence the spread of infectious diseases, without aiming for predictive applications, while also assessing the implications for public health policy planning. In real epidemics, behavioral changes not only reduce contact and intensity but also alter the structure of contact networks.

Finally, the significance of this SI cannot be overstated owing to the methodological nature of the papers contained within it. Indeed, such papers can serve as a foundational resource for continuous updates as new data become available. This concept is successfully illustrated in [60], in which the same methodology used in [59] is applied to new data, showing how the significance of the principle governs the data itself.

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