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Mathematical models for COVID-19: applications, limitations, and potentials

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The coronavirus disease 2019 (COVID-19) has led to high morbidity and mortality in China, Europe, and the United States, triggering unprecedented public health crises throughout the world. On March 11, 2020, the World Health Organization (WHO) declared COVID-19 as a global pandemic. COVID-19 is caused by a novel coronavirus which is now named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is regarded as the third zoonotic human coronavirus emerging in the current century, after SARS-CoV in 2002 and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012.

Yang *et al.* recently published an article (1) using a mathematical model to investigate the epidemic development of COVID-19 in China. Based on a modified susceptible-exposed-infectious-recovered (SEIR) compartmental framework, they predicted the magnitude and timing of the epidemic peak and the final epidemic size under various intervention strategies. This is a typical example of employing mathematical modeling techniques to study the transmission and spread of COVID-19.

Mathematical models have long been generating quantitative information in epidemiology and providing useful guidelines to outbreak management and policy development. In particular, a number of modeling studies have been performed for COVID-19. For example, Wu *et al.* (2) introduced a SEIR model to describe the transmission dynamics of COVID-19 in China and forecasted the national and global spread of the disease, based on reported data from December 31, 2019 to January 28, 2020. Read *et al.* (3) reported a value of 3.1 for the basic reproductive number of the early outbreak using an assumption of Poisson-distributed daily time increments in their data fitting. Tang *et al.* (4) incorporated the clinical progression of the disease, the individual epidemiological status and the intervention

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measures into their model, and found that intervention strategies such as intensive contact tracing followed by quarantine and isolation can effectively reduce the control reproduction number and the transmission risk. Imai *et al.* (5) conducted computational modeling of potential epidemic trajectories to estimate the outbreak size in Wuhan, China, and their results indicated that control measures need to block well over 60% of transmission to be effective in containing the outbreak. Li *et al.* (6) applied a meta-population SEIR model and Bayesian inference to infer critical epidemiological characteristics in China, and their estimates showed that about 86% of all infections were undocumented prior to January 23, 2020. Leung *et al.* (7) quantified the transmissibility and severity of COVID-19 in mainland Chinese locations outside Hubei province and simulated the potential consequences of relaxing restrictions in anticipation of a second epidemic wave in China. Additionally, there are many other modeling and simulation results published for COVID-19 but not listed in this commentary.

All these studies combined mathematical models with numerical simulation, data validation, as well as some statistical techniques. There is no doubt that their findings have covered a wide range of epidemiological characteristics associated with COVID-19 and have improved our understanding of the complex transmission mechanism of SARS-CoV-2. On the other hand, there are several limitations in the current modeling work.

Most of these studies are based on the basic SEIR framework (or, in some cases, its simple variations), exclusively focused on the direct, human-to-human transmission pathway. It has been commonly accepted that COVID-19 can be transmitted through direct contact between human hosts, and both the symptomatic and asymptomatic individuals are capable of infecting others. In contrast, the indirect transmission pathway from the environment to human hosts is also a highly possible route to spread the coronavirus but has not been sufficiently addressed in the literature. A study (8) based on the review of 22 types of coronaviruses revealed that viruses such as SARS-CoV, MERS-CoV and endemic human coronaviruses can persist on inanimate surfaces like metal, glass or plastic for up to 9 days. Another experimental study (9) published in March 2020 found that SARS-CoV-2 was detectable in aerosols for up to 3 hours, on copper for up to 4 hours, on cardboard for up to 24 hours, and on plastic and stainless steel for up to 3 days. These findings that the coronavirus can remain viable and infectious in aerosols for hours and on surfaces for days indicate a high probability and significant risk of environmental transmission, including airborne and fomite transmission, for SARS-CoV-2. Incorporating such an environment-to-human route into mathematical modeling may better characterize the transmission dynamics of COVID-19 and potentially gain deeper understanding of its epidemic patterns.

Another limitation of the current COVID-19 models is that the transmission rates are typically fixed as constants, rendering simplicity for both mathematical analysis and data fitting. In practice, however, the transmission rates may change with the epidemiological and socioeconomic status and may be impacted by the outbreak control. For example, many countries (China in particular) implemented strong disease control measures, including large-scale quarantine, intensive tracking of movement and contact, strict isolation of infected individuals, expanded medical facilities, and social distancing, which can effectively (and, in some places, rapidly) reduce the transmissibility of the virus. Meanwhile, when the reported infection level is high, people would be motivated to take voluntary action to reduce the contact with the infected individuals and contaminated environment so as to protect themselves and their family members. As a result, the actual transmission rates may decrease with an ascending outbreak, and may increase at a time of low disease prevalence. Consequently, reflecting this time and prevalence dependent feature of transmission rates could improve the accuracy in modeling and simulating COVID-19.

Thus far, epidemic models for COVID-19 typically do not consider the economic impact of the pandemic. Regarding the control of COVID-19, an intensive debate is currently on-going between the two strategies of “suppression” and “mitigation” (10). The suppression policy, implemented in China and several other countries, deploys the strongest possible measures to sharply reduce the disease transmission and rapidly contain the epidemic, at the cost of sacrificing the economic development in the period of outbreak control. The mitigation policy, adopted by the US and many European countries, employs more relaxed measures to gradually flatten the infection curve and allow herd immunity to build up, while ensuring a certain degree of economic growth. Mathematical epidemic models are well positioned to incorporate the economic impact of COVID-19, to quantify the interaction of epidemiological and economic factors, and to suggest an optimal balance between the pandemic control and economic development. In this regard, a combined epidemic-economic modeling framework would be especially useful to help governments and public health administrations with their strategy design and policy making.

At present, many details regarding the ecology, genetics, microbiology and pathology of SARS-CoV-2 remain unknown, which adds challenges to the mathematical modeling. Meanwhile, there are a number of aspects related to COVID-19, ranging from political and societal issues to cultural and ethical standards, which are difficult to be represented in a model. We should acknowledge that a mathematical model, by its nature, is a simplification and approximation of the reality. Despite these restrictions, applied mathematicians, medical researchers and public health scientists are striving to improve the epidemic models and to expand their applications for COVID-19 as well as other infectious diseases. Obviously, to better reflect the (complex) reality, a model has to incorporate more factors, at a higher level of sophistication. Although such a model could be potentially more useful in a practical sense, it is important to realize that the increased complexity of a model usually comes with increased difficulty for analysis, manipulation and implementation, thus losing part or all of the advantages of a simpler model counterpart. Meanwhile, it is essential to note that all mathematical models have underlying assumptions and conditions. Regardless of its structure and complexity, a model can never be better than its assumptions.

A promising direction to advance mathematical modeling in epidemiology is to connect the models with data-driven techniques, particularly machine learning. The work by Yang *et al.* (1) applied a machine learning approach based on a recurrent neural network that is trained by utilizing a 2003 SARS epidemic dataset as well as incorporating the COVID-19 epidemiological parameters. They found consistent patterns in the predictions from the SEIR model and from the machine learning. For another example, Gao *et al.* (11) developed a deep learning algorithm to analyze the infectivity of the novel coronavirus and predict its potential hosts, and their findings indicated that bats and minks may be two animal hosts of this virus.

These results are encouraging for wider applications of data analysis and computing approaches to study epidemics and pandemics, particularly COVID-19. Machine learning and other artificial intelligence techniques can complement and improve mathematical epidemic models by taking advantage of the large data sets currently available, including epidemic, genetic, demographic, geospatial and mobility data, the scale of which is typically far beyond the applicability of a standard mathematical model. On the other hand, mathematical modeling can provide a meaningful way to validate machine learning predictions and to guide the development of more efficient and robust algorithms in machine learning and data analytics. Thus, the development and advancement of these two different quantitative approaches could be mutually beneficial, and their integration could lead to potentially transformative progress in the study of COVID-19 and beyond.

With the on-going pandemic, we will surely see more mathematical models developed, analyzed and applied to COVID-19, and many of the modeling limitations and challenges mentioned here will hopefully be overcome soon. Although the full potential and impact of mathematical modeling for such a pandemic are still to be seen, the future looks bright. Nevertheless, in the development and application of such epidemic models, we stress the importance of validating key modeling assumptions, connecting models with realistic data, tailoring models to practical needs, and leveraging the support from other analytical and computational techniques.

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