Mathematical modeling in the age of COVID-19

August 19 2020

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Predicting the future has always been risky but never more so than at the start of 2020. COVID-19, a disease that in January barely merited a footnote in medical journals, has, in less than a year, exploded onto all

continents but Antarctica, killing over three quarters of a million people as of August 2020.

One unexpected effect of the pandemic has been an unprecedented public interest in understanding the course of the disease and, therefore, in mathematical modeling. In an opinion piece published recently in the special issue of the journal *Mathematical Modeling of Natural Phenomena*, editor-in-chief Vitaly Volpert sets out the ways in which modeling is being used to counteract the virus.

Modeling the epidemic

COVID-19 has been compared to influenza, but it differs from flu in a number of important ways. The incubation period is longer, mortality is higher (perhaps 2-4%) and the range of severity is astonishingly high—from no symptoms to severe pneumonia, multi-organ failure and death.In the case of flu, for which there are effective vaccines, the number of infected and recovered individuals plus those vaccinated will sooner or later give rise to 'collective immunity'. "Simply put, there is no one else to get infected and the disease fades," says Volpert. The lack of a COVID-19 vaccine means that collective immunity will only arise once enough people are infected: currently only about 5-10% of most populations appear to have been in contact with the virus, and allowing it to spread widely enough to create collective immunity will overwhelm any health system.

Modeling the progress of such an epidemic is relatively straightforward. The number of cases over time is governed by an ordinary differential equation with an exponential function for its solution. The key number in this function is R0, the average number of people that each new case infects: when R0 is above one, the infection grows, below one it shrinks.R0 cannot be known in advance but must be fitted to the data; it can change rapidly, as in the UK when modelers persuaded the

government to belatedly move to lockdown. "Exponential models have their limits in predicting epidemic progression, as their parameters depend on features such as seasonality, the development of immunity and—hardest of all to predict—people's behavior," says Volpert. "The epidemic has once again shown that we are not able to model and manage complex systems including collective behavior."

Modeling the lungs

"The vast majority of works devoted to the COVID-19 epidemic deal with epidemiology; some questions, including immune response to coronavirus or pathophysiology of the coronavirus disease, remain outside of these modeling efforts because of the complexity of these phenomena," explains Volpert. However, beyond epidemiology, mathematical models can also help scientists understand the disease process and how our immune systems counteract it. For example, in severe cases, COVID-19 causes inflammation of lung tissue (pneumonitis) which leads to blood clots in the lungs. Mathematical models are being used to predict clot growth and the effects of anticoagulant drugs. The main difficulties with these models arise from variation between patients. "In practice, we are having to model an 'average' patient's lungs—the ideal of personalized medicine is still some way off," says Volpert. Other groups are modeling the effect of the virus on cells that secrete mucus in the respiratory tract. Virus-infected cells secrete less mucus, and that mucus moves less efficiently through the tract, leading to further respiratory problems.

Modeling disease processes

COVID-19 can also generate an overreaction of the body's immune system—a 'cytokine storm'—which can be fatal. Mathematical models of this response are being developed but much data is still needed to

validate them. Some useful data, however, can be extrapolated from models of the very similar SARS coronavirus, which, like the COVID-19 coronavirus, enters its host cells through a receptor called ACE2. By modeling how the virus interacts with this receptor and these cells, researchers hope to learn more about disease progression. Another important point is a possible interaction between COVID-2 and influenza, which it is feared may lead to 'spikes' of serious disease in the winter months. Molecular-level modeling of the protein spike on the virus surface that binds to the receptor is another promising research direction which may provide useful insights for drug and vaccine design.

And what now? Months after the pandemic emerged, there is both good and bad news. Although case numbers continue to rise, there are fewer deaths, probably because clinicians are learning how best to treat the disease. We now know of drugs developed for other diseases that can speed recovery and calm the cytokine storm. However, specific COVID-19 drugs and vaccines are still some way off and the timetable for their development is uncertain. Nevertheless, as Volpert concludes: "Scientific research is a long and difficult process, and progress is slow, but without it there is no progress at all. We should remember this, not only during dramatic infectious outbreaks but also between them."

More information: Vitaly Volpert et al. Mathematical Modelling in the era of coronavirus (Six month in a new reality), *Mathematical Modelling of Natural Phenomena* (2020). DOI: 10.1051/mmnp/2020027

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