



# SFI TRANSMISSION

## COMPLEXITY SCIENCE FOR COVID-19

**STRATEGIC INSIGHT:** A complex systems perspective of viruses offers insight for controlling SARS-CoV-2 and future emerging viruses.

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Numerous questions emerge when considering the nature and relevance of viruses: What exactly are they? Are they even alive? How and when did viruses first evolve, and are viruses unavoidable consequences of biological replicators? Why are they so diverse in genomic architecture, yet so limited in lifestyles? Why are there so many emerging viruses, and what are the ecological and genetic drivers of that emergence? Why do they become pathogenic, and what is the nature of the complex molecular interaction they establish with their hosts?

Viruses are complex systems spanning orders of magnitude in size. The study of their behavior and structure, particularly using multidisciplinary frameworks, has revealed a number of universal patterns of organization. RNA viruses display high mutation rates that push them to the edge of disorder, where high instability, but also adaptability, occurs. As with many phenomena in virology, this edge is well described by phase transitions — where small changes in mutation rates can lead to large changes in structure — analogous to a liquid transitioning to a gas with a small shift in temperature.

Viruses have influenced evolution at all levels of biological organization, from cells and organisms to populations, ecosystems, and even the entire biosphere. Their dynamics involve nonlinear phenomena, tipping points, and self-organization. Viruses offer unique experimental and theoretical windows into the origin and evolution of complex systems.

For 30 years, I have combined experimental evolution, molecular genetics, systems biology, molecular epidemiology, mathematical modeling, and computer simulations to pursue the enigma of the virus, using different animal and plant systems. In this search for basic knowledge, we have acquired many small pieces of information that, together, delineate a picture of how viruses evolve. This picture offers insight for our current pandemic.

We now know that the mutations required for an emerging virus to adapt to a novel host come with a cost, and we know that this cost is relaxed if the virus circulates among different host types. We have also learned that high mutation rates allow RNA viruses to achieve the highest possible fitness and replication rates. And, we have identified the molecular mechanisms by which some viruses, such as influenza A, infect a wide range of hosts, whereas others, like mumps, are highly specialized to particular hosts. To generalist viruses, hosts are more or less the same on the cellular level. The range of hosts for these viruses all have common, highly conserved, elements in their genetic regulatory networks. Specialist viruses, on the other hand, interact with unique, or non-conserved, elements within their host's cells.

The emergence and pandemic spread of SARS-CoV-2 has raised many questions, hitherto of interest to fundamental, theoretical science, to the level of immediate practice. The pressure to give rapid support to authorities in our public health systems and the urgent need to find new specific antiviral treatments has moved us to rapidly repurpose the lab and to focus our research toward more urgent needs.

For example, our know-how in virus detection and purification can now be applied to diagnostics. By moving our quantitative PCR machines from the lab bench into biohazard secure rooms and adopting protective measures, our research protocols transform into medical diagnostic procedures.

Our past experimental and mathematical analyses of the interactions between viruses and so-called defective interfering particles (DIPs) — basically, the parts of a virus that are incapable of self-replication — are inspiring a research project aimed at finding new SARS-CoV-2 antivirals. Because DIPs interfere with the replication, accumulation, and transmission of the wild-type virus, we can think of them as antivirals. DIPs offer several benefits over conventional antiviral approaches: They are transmissible in the presence of the full virus and hence can spread with it to target infected cells; DIP-mediated protection is effective immediately, unlike classic vaccines that work via priming the adaptive innate immune pathways; and DIPs cannot replicate and are transcriptionally defective in the absence of the full virus, thus limiting possible side effects.

DIPs are just one example of a potential new antiviral inspired by the analysis of viruses as complex replicative systems. My colleagues and I are sure that many other biomedical applications will emerge from this multidisciplinary perspective. Basic science is not just future applied science; it is our applied reserve, available to be repurposed when society calls.

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