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Editorial: Predicting virus evolution: from genome evolution to epidemiological trends

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Editorial on the Research Topic
Predicting virus evolution: from genome evolution to epidemiological trends

1 Introduction

Evolution is central to understanding viruses, given its importance in processes such as viral emergence (1), adaptation to host immunity (2), reversion of virulence in attenuated vaccine strains (3), loss of heterologous sequences in viral expression vectors (4), and development of resistance against antivirals (5). Viruses have proved invaluable for studying evolutionary processes and identifying the underlying mechanisms of evolution, due to their potential for rapid adaptation (6). As well as evolutionary-oriented comparative analyses of clinical and environmental samples, viruses of animals, plants, bacteria, and other organisms can be experimentally evolved in the laboratory under controlled conditions. Over the last decade, evolutionary biologists have devoted great efforts to predicting the outcomes of evolutionary processes and assessing the limits of such predictability (7, 8). However, despite the importance of viruses as model systems in evolutionary biology, there are only limited examples of evolutionary predictions tested on viruses (2, 8, 9). Such a lack of studies is remarkable, given that virus evolution is (i) rapid due to short generation times, large population sizes, and high mutation rates, (ii) repeatable in the clinic and laboratory, which is an important prerequisite for high predictability, and (iii) highly relevant due to its impact on health, livelihoods, and ecosystems (6, 8). Notable predictions of virus evolution, such as of future Influenza A virus (IAV) strains (2), illustrate these various aspects, from the basic feasibility of prediction to its relevance (8).

Has evolutionary predictability been neglected in virus research, or are there insurmountable obstacles to making non-trivial predictions? Some problems, such as

host shifts and the emergence of new viruses (1), will probably remain elusive due to their extremely stochastic nature and our incomplete knowledge of the relevant ecological, demographic, and environmental variables. For known viruses, however, is it possible to develop general guiding principles and broad, meaningful frameworks? To what extent do the minutiae of each virus-host system dictate evolutionary outcomes? These largely unanswered but highly relevant questions inspired this Research Topic in *Frontiers in Virology*. Whilst the small number of submissions perhaps reflects our concern that these questions have been neglected so far, the quality and innovation of the studies makes us hopeful about the future of the field.

2 The challenge of predicting virus evolution

The emergence and global spread of SARS-CoV-2 provided a stark reality check on the predictability of virus evolution. From first principles, mutation rates for coronaviruses, and increasing knowledge of the virus, some general predictions on the future evolution of this virus could be made (8). However, our inability to make specific predictions was accentuated by the near concurrent emergence of the highly transmissible Alpha, Beta, and Gamma variants, as unexpectedly each of these variants contained a considerable number of mutations (17-21 nonsynonymous mutations) (10, 11). In this Research Topic, Ghafari et al. tackle this question using simulation models to explore the impact of different underlying fitness landscapes and the longevity of infection on the virus mutational profile. The best-supported model predicts the fitness landscape as a plateau that must be crossed to reach a steep peak. Long-lived chronic infection allows these multiple mutations to accumulate in one or a few individuals, due to the absence of narrow transmission bottlenecks. This paper exemplifies how relatively simple evolutionary models can be used to explore the plausibility of different scenarios. A key question is whether the patterns observed for SARS-CoV-2 are likely to be repeated in other viruses. We believe that long-lived viral infections require special attention in general because of their evolutionary implications. Moreover, several key requirements for the relevance of chronic infections are applicable to viruses; fitness landscapes of viruses are rugged (12), large effective population sizes enable "leapfrogging" fitness valleys, reducing repeatability of evolution (13), and the effects of infection duration on virus adaptation have been noted in other systems (4, 14). Moreover, given the small odds of leapfrogging events, these processes are not easy to study with experimental evolution due to limited replication.

One key measure adopted almost universally during the SARS-CoV-2 pandemic was social distancing, to reduce virus transmission and thereby avoid overwhelming health care systems (15). However, what are the evolutionary consequences of this intervention? In this Research Topic, Laguna-Castro and Lázaro address this question using experimental evolution of a bacteriophage Qβ in different densities of susceptible bacteria. Contrary to the expectation that more stable virus particles or prudent host exploitation would occur, higher infectivity repeatedly evolved under low host densities. This unexpected finding highlights that, even for relatively simple experiments in controlled environments that result in highly reproducible mutation patterns, it remains difficult to make global, qualitative predictions. As discussed by Laguna-Castro and Lázaro, the mechanisms that lead to adaptation to low host densities differ among viral species (16). It is plausible that other instances of evolutionary rescue in viruses facing adverse environmental conditions are also characterized by evolutionary convergence at the species level but by cross-species variability in qualitative terms. Such a possibility should be kept in mind when developing public health policies, as it implies that effective strategies for the control of viral epidemics may fail or even be counterproductive when applied to other viruses.

Virus evolution can make preventive or therapeutic interventions ineffective, but can it also be exploited? One of the most spectacular suggestions stemming from evolutionary theory is lethal mutagenesis (17). Most viruses have high intrinsic mutation rates, and mutagenic drugs could push mutation rates to catastrophic levels, resulting in the extinction of ever-smaller virus populations. However, is evolutionary escape possible and might the applications of mutagens have other undesired consequences? In this Research Topic, Bank et al. consider what kinds of mutations might rescue virus populations exposed to mutagens. Given typical distribution of mutational fitness effects (DFEs) (18), scarce beneficial mutations are unlikely to compensate for the effects of deleterious ones. Mutation-rate-modifying mutations are known to occur in some viruses (19). These mutations could protect populations in the presence of mutagens, but they must occur very early to ensure genome integrity. Otherwise, by the time mutagenesis induces an anti-mutator, the fate of the population will have been sealed by other deleterious mutations (Bank et al.). As an alternative to mutations that reduce the mutation rate, the authors explore exotic mutations that would modify the overall DFE. Changes in the DFE could rescue populations by decreasing or, in some cases, increasing the effect of other deleterious mutations (Bank et al.). Such mutations exist for cellular life forms (e.g., mutations in chaperones or transcriptional regulators), so why not for viruses? One possibility could be the disruption of coinfection exclusion when controlled by the virus (20), allowing defective genomes to complement each other at high multiplicities of cellular infection. While this would limit the role of selection and promote accumulation of more deleterious mutations (21), it could ensure short-term survival under highly mutagenic conditions.

3 Keeping a broad perspective

When it comes to predicting virus evolution, we are only scratching the surface. While the studies in this Research Topic illustrate some of the possibilities, they also highlight many of the problems and outstanding challenges. Virtually all studies on this topic are framed around human diseases. While improving human health will remain an important driver for studying the predictability of virus evolution, it is important to recognize that

the underlying questions are relevant to many fields. The evolution of viruses of livestock, crops, and microorganisms will affect the functioning of industrial and agricultural processes and natural ecosystems. On the flipside of this, these systems will typically be quite amenable to experimentation, as illustrated here by work with bacteriophages (Laguna-Castro and Lázaro). From our perspective, considering a wide range of virus systems within the virus evolution community will enrich our understanding of virus predictability. It is essential to safeguard this broad outlook that has been a hallmark for this community, to maximize the opportunities for testing, improvement, and utilization of our capacity to predict virus evolution.

Author contributions

All authors conceptualized the Research Topic and editorial. MZ drafted the editorial. JI and AK revised it. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Publisher's note

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