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Opinion

SARS-CoV-2: Cross-scale Insights from Ecology and Evolution

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Ecological and evolutionary processes govern the fitness, propagation, and interactions of organisms through space and time, and viruses are no exception. While coronavirus disease 2019 (COVID-19) research has primarily emphasized virological, clinical, and epidemiological perspectives, crucial aspects of the pandemic are fundamentally ecological or evolutionary. Here, we highlight five conceptual domains of ecology and evolution – invasion, consumer-resource interactions, spatial ecology, diversity, and adaptation – that illuminate (sometimes unexpectedly) the emergence and spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We describe the applications of these concepts across levels of biological organization and spatial scales, including within individual hosts, host populations, and multispecies communities. Together, these perspectives illustrate the integrative power of ecological and evolutionary ideas and highlight the benefits of interdisciplinary thinking for understanding emerging viruses.

Highlights

Foundational concepts from ecology and evolution can elucidate the emergence and spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and all viruses, across multiple scales.

Ecological and evolutionary methods that characterize population dynamics of organisms are potent tools to investigate viral growth and spread within individual hosts, or epidemic growth in host populations.

The field of macroevolution classically studies the diversification and adaptation of multicellular organisms, but major opportunities exist to apply macroevolutionary concepts to the evolution of viruses.

Concepts from spatial ecology, from source-sink dynamics to synchrony, can help us to understand patterns and processes in the emergence of viruses.

Interdisciplinary research across the life sciences can reveal otherwise unattainable insights into emerging infectious diseases, posing new hypotheses and refining existing knowledge in traditional disciplines.

The Integrative Power of Ecological and Evolutionary Concepts for Understanding Emerging Viruses

Zoonotic pathogens, namely those transmitted from vertebrate animals into humans, comprise a majority of the infectious diseases that plague humankind. Examples range from pathogens that infect humans exclusively via **spillover** (see Glossary) from animal **reservoir hosts** (e.g., rabies virus, *Leptospira interrogans,* West Nile virus) to those that spread among humans for decades after a successful spillover event (e.g., HIV-1, influenza A virus) [1]. Most recently, the emergence of SARS-CoV-2 triggered the COVID-19 pandemic, up-ended global society, and stimulated an unprecedented burst of research spanning multiple disciplines. Much of this research addresses the growth and change of SARS-CoV-2, which are population processes that are deeply rooted in ecology and evolutionary biology [2,3]. These disciplines have proven their utility for combating infectious diseases by informing public policy [4,5], identifying potential reservoir hosts [6], and directing vaccine research [7,8]. Yet despite their inherent power to integrate findings from other disciplines, ecological and evolutionary ideas have not been fully appreciated in the current SARS-CoV-2 literature. Vast opportunity remains to explore their fruitful applications across levels of biological organization (henceforth referred to as scales), namely within individual hosts, host populations, and multispecies communities. By recognizing parallels in the patterns and processes governing viral dynamics at these different scales, the scientific community can harness existing knowledge in ecology and evolutionary biology to drive progress in understanding, mitigating, and preventing the emergence of infectious diseases.

To advance this aim, here we illustrate how five conceptual domains of ecology and evolutionary biology can shed light on the emergence of novel viruses, including SARS-CoV-2, across the

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within-host, population, and multispecies community scales (Figure 1, Key Figure). Though these conceptual domains (hereafter, concepts) are inextricably linked, we present them separately (each partitioned into discrete paragraphs by scale) and provide graphical representation of their connections (Figure 2). In parallel, we emphasize tools and methods developed in ecology and evolutionary biology that can unlock insights for understanding this, or any, pandemic (Boxes 1 and 2). Our goal is not to provide an exhaustive review of the ballooning COVID-19 literature but instead to translate and apply relevant ideas from ecology and evolutionary biology in a manner accessible to a wide audience. In particular, we aim to: (i) demonstrate the integrative power of ecological and evolutionary ideas for scientists from different disciplines (e.g., microbiology, mathematics, public health), (ii) excite students about the broad applications of ecology and evolution across the life sciences, and (iii) prompt established ecologists

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Key Figure

Cross-scale Applications of Ecological and Evolutionary Concepts to Viruses, with Examples from Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

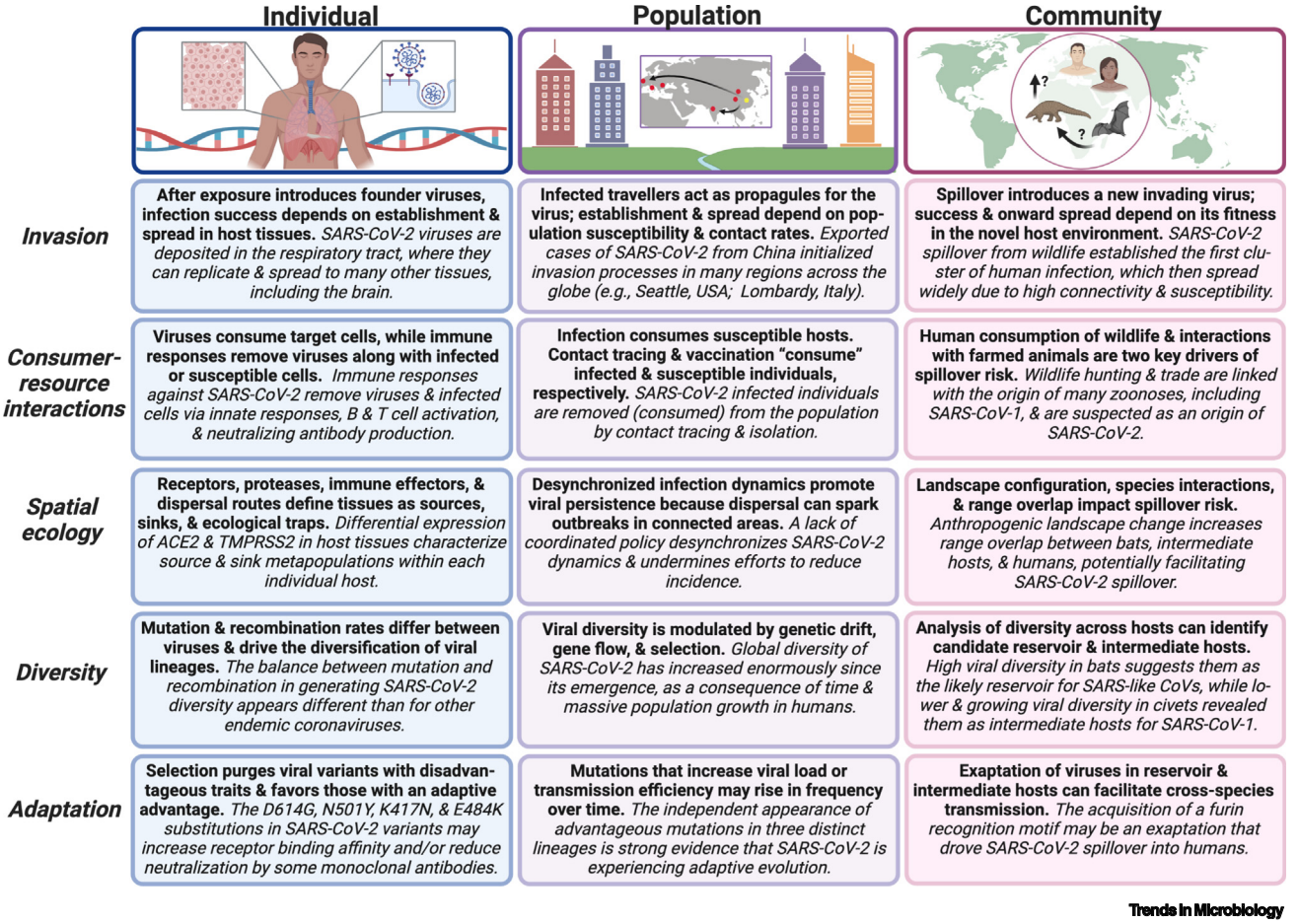

Figure 1. A series of descriptions highlighting five core ecological and evolutionary principles at multiple scales, including within host (individual; blue), within populations (population; purple), and across species (community; pink). Bolded content reflects the general applications of each concept to viruses. Italicized content reflects specific examples relevant to SARS-CoV-2 and SARS-like coronaviruses (CoVs). The references for each concept and example can be found in the corresponding paragraph of the text.

and evolutionary biologists to recognize novel opportunities to apply their expertise across disciplines and scales to fight this and future pandemics.

Ecological Dimensions of Viral Emergence

The field of ecology focuses on the distribution, abundance, and interactions of organisms across space and time, and is traditionally subdivided by levels of organization, which include the population scale (i.e., the study of one species in a given region) and the community scale (i.e., the study of multiple species). Less conventionally, an individual organism can be viewed as its own within-host ecosystem, where host cells and microorganisms interact in a landscape of host tissues. In the context of infectious diseases, ecological principles govern the **population dynamics** of many relevant entities (including viruses, cells, and host individuals), and these population processes can naturally be delineated at different scales [9]. Below, we introduce each concept at the population scale, as it provides the most intuitive platform for discussion, followed by applications at the within-host and within-community scales.

Invasion Processes and Emerging Viruses

The success of a virus in a new target population is governed by processes of ecological invasion, which manifest in phases of introduction, establishment, and spread [10–12]. For example, when the COVID-19 pandemic began, infected travelers from China transported SARS-CoV-2 to countries across the globe, including Germany, Italy, and the USA [13]. Once introduced, successful establishment of a virus requires local transmission, which depends on viral shedding, host contact patterns, and host population susceptibility [10,14]. The likelihood of establishment increases if multiple introduction events occur or if many individuals arrive simultaneously, as described by the **propagule pressure hypothesis** [15]. In the event of sustained community transmission, the virus can be considered an **invasive species** in this local host population. Subsequent **dispersal** propagates the virus further by initiating similar invasion processes in other connected regions [10]. SARS-CoV-2 showcases that these invasion waves can ultimately trigger a global pandemic.

The infection of an individual host can also be viewed as an invasion process, wherein exposure introduces a **founder population** of potentially invasive viruses (i.e., the inoculum). The route of this exposure determines the inoculation site, where receptor expression, immune activation, and other factors determine tissue susceptibility [16], just as resource availability and the presence of competitors, predators, and pathogens impact landscape suitability for introduced plant and animal species [10,17]. These host factors vary across tissues and affect the probability of establishing local infection for a given site of deposition [16,18]. Once established, onward spread is governed by tissue susceptibility, physical connectivity, and transport mechanisms. For instance, SARS-CoV-2 infection typically begins in the respiratory tract, where the cellular receptor angiotensin-converting enzyme 2 (ACE2) is highly expressed, and it has been proposed that subsequent neuroinvasion can occur via the olfactory nerve or via the bloodstream paired with damage to the blood–brain barrier [19]. While the effect of a single high-dose exposure versus multiple low-dose exposures remains largely unresolved [15,18,20], invasion theory predicts that, for a given dose, infection is more likely when viruses deposit at different sites across a heterogeneous tissue landscape [21].

At the community scale, the invasion analogy applies to viral host jumps, where a virus must overcome sequential barriers to invade a novel host species [10–12,22]. Given some type of cross-species contact, viral shedding from reservoir or **intermediate hosts** can introduce the virus to an individual from a recipient host species [11,22]. A variety of virological and evolutionary factors (dictated by the within-host invasion process) influence establishment of the virus in this

Glossary

Adaptive radiation: the rapid diversification of organisms in response to available environmental niches.
Bottleneck: a reduction in genetic variation resulting from a change in population size that occurs for at least one generation.
Convergent evolution: similarity in trait or genotype that is acquired independently in two or more lineages, often interpreted as evidence of adaptation.
Dispersal: movement of individuals across a landscape.
Ecological opportunity: the environmental potential available to a newly colonizing lineage for diversification into divergent niches.
Ecological trap: a low-quality habitat patch, where mortalities exceed births, that decreases overall population fitness because individuals settle in these habitats instead of other available high-quality habitats.
Enemy release hypothesis: this hypothesis posits that the absence of enemies (e.g., predators) within an invasive species' exotic range leads to successful invasion.
Exaptation: a trait that evolved by natural selection to perform a specific function that later performs another unrelated function.
Founder population: a group of individuals from a larger population that migrate, settle, and establish a new population in a new, uninhabited environment.
Functional response: the relationship between consumption rate of a consumer (e.g., predator) and abundance of the target resource (e.g., prey).
Gene flow: exchange of genetic material between connected populations through migration.
Genetic drift: changes in allele frequency within a population due to random chance.
Intermediate host: a host species that acts as a bridge to facilitate pathogen transmission between a reservoir species and a focal host species.
Invasive species: a species introduced to an area outside its normal range, often by human means, where it reproduces and spreads beyond the area in which it was released and negatively impacts the new ecosystem.
Landscape immunity: defined in [22] as the ecological conditions that control

host, including immune defenses and the availability of suitable cellular receptors. Even if the virus successfully infects this individual, other barriers can limit further spread within this novel host population (dictated by the population invasion process) [10,11]. For SARS-CoV-2, the path to zoonotic spillover remains unknown, though the progenitor virus likely originated in bats. The diversity of bat viruses, if paired with contact among humans and bats, potentially via intermediate hosts, can provide multiple opportunities for successful cross-species invasion to occur, as described by the propagule pressure hypothesis [15,22,23]. Several groups of bat-borne viruses, including the Henipaviruses and Ebolaviruses, are well known to have caused numerous outbreaks via independent zoonotic transmissions [23]. Given evidence of multiple spillover events of SARS-like coronaviruses [24], further investigation is warranted into whether SARS-CoV-2 could have been introduced to humans more than once. Once introduced, the contrast between the robust antiviral defenses in bats and humans, combined with the immunological naïveté of the human population, may have facilitated the successful invasion of SARS-CoV-2 as suggested by the **enemy release hypothesis** [17,25].

Consumer–Resource Interactions between Viruses, Hosts, and Intervention Strategies

The population dynamics of a virus invariably depend on consumer–resource interactions in which consumers rely on, and directly impact, resource availability. These interactions are a critical component of ecological community structure and provide the foundation for classical epidemiological models, where populations of infected hosts grow by 'consuming' susceptible individuals (i.e., the resource). In fact, the simplest epidemic models and predator–prey models are mathematically equivalent (Box 1) [26] and thus share fundamental features such as the tendency to cycle. Vaccination reduces susceptible availability and hence lowers infection prevalence [4,27], just as a loss of prey reduces predator abundance. Less obviously, nonpharmaceutical interventions can be analyzed in the consumer–resource framework where contact tracers can be viewed as hyperpredators that remove (i.e., consume) infected individuals from a population, and physical distancing alters how the infection rate depends on susceptible abundance (i.e., the **functional response**). Such epidemiological models can provide prompt insights into the population dynamics of an emerging virus under various assumptions (e.g., quarantine compliance, vaccination rates), as evidenced in the SARS-CoV-2 literature (e.g., [27]). While obtaining accurate predictions from these models requires reliable parameter estimates from high-quality datasets, strategies developed in ecology can account for and leverage imperfect data (Box 1).

The interactions between viruses and cells within an individual host can also be treated as a network of consumer–resource interactions [28]. In the simplest case, viruses (i.e., the consumer) infect susceptible cells (i.e., the resource), thus decreasing susceptible cell population size while increasing viral population size (Box 1) [29]. This conceptual framework can also incorporate the immune system, which can consume viral particles and infected cells [30] or block viral consumption of susceptible cells by stimulating an antiviral state [25]. Models that incorporate these interactions improve our understanding of the immune system and our ability to control disease progression [29]. For instance, they can explore the impacts of target cell depletion on viral load and within-host spread [28].

Consumer–resource interactions influence community-level dynamics of virus emergence by providing opportunities for spillover events and potential pandemics [2]. For instance, the hunting, handling, and consumption of livestock and wildlife can expose humans to zoonotic viruses through contact with infected tissues [11,31]. Three familiar examples include SARS-CoV, HIV-1, and 2009 H1N1 pandemic influenza virus (H1N1pdm), which are linked to palm civets in Chinese wildlife markets, hunted chimpanzees in Central Africa, and pig farms in Mexico, respectively [31,32]. Though the precise origin of SARS-CoV-2 remains unclear, the trade and consumption

pathogen populations while strengthening the immune functions of wild animals in an ecosystem.
Population dynamics: the study of how and why population size and structure change over time.
Propagule pressure hypothesis: this hypothesis posits that a greater number of individuals in a single release event or a higher frequency of release events over time increases the likelihood of invasion success.
Reassortment: a type of recombination exclusive to segmented viruses in which coinfection of a host cell results in the exchange of gene segments between similar virus strains.
Recombination: the process by which segments of genomic material are broken and exchanged during genome replication, creating new combinations of alleles.
Reservoir host: a host species in which a pathogen circulates continuously without reintroduction and which can transmit the pathogen to other hosts.
Spillover: the transmission of a pathogen from one host species to another; zoonotic spillover specifies transmission from a vertebrate animal to a human.

of exotic animals in Chinese wildlife markets have been suspected to be involved [33]. Interactions with farmed animals can also facilitate human-to-animal transmission of viruses, as most recently evidenced by SARS-CoV-2 outbreaks in mink farms [34]. Many countries have also reported human-to-pig H1N1pdm transmission, where further reassortment could generate another virus capable of infecting humans [35]. These examples highlight the inherent health risks (for both humans and animals) associated with animal products, and they emphasize the importance of developing, implementing, and managing more responsible biosecurity regulations for livestock and wildlife trade [36].

Ecological Principles Governing Virus Spatial Dynamics

Spatial ecology describes the spread, persistence, and interactions of individuals across landscapes consisting of habitat patches connected by dispersal. Individuals moving from source habitats, where birth rates exceed mortality rates, can colonize new habitats or sustain populations in sink habitats, where mortalities exceed births [37]. This source–sink framework directly applies to spatial spread of disease, where epidemiologists call sources 'supercritical' and sinks 'subcritical' for pathogen transmission. For example, during the early COVID-19 epidemic in China, infected travelers from Wuhan (i.e., the source, with positive epidemic growth) sparked outbreaks in many other Chinese cities (i.e., the new habitats). However, prompt implementation of local control measures in these cities reduced growth rates to become negative (i.e., they became sinks), so those outbreaks died out once the source outbreak was controlled [38]. In such heterogeneous landscapes, synchronous dynamics, wherein populations rise and fall concurrently, increase the likelihood of population-wide extinction. Such synchrony can arise from correlated exogenous factors (e.g., climate conditions) and/or sufficient dispersal [39]. For viruses, if prevalence declines simultaneously in connected patches, the absence of high-prevalence sources prevents dispersing hosts from recolonizing locally extinct patches [39,40]. Public health officials can leverage this principle to limit the spread of emerging infectious diseases if control policies are coordinated across cities and regions to promote synchronous declines in prevalence. Unfortunately, the lack of coordination plaguing the COVID-19 response has allowed reseeding of outbreaks in locales that had previously contained SARS-CoV-2, leading to more cases and more interventions needed [5].

These spatial ecology concepts can also illuminate viral spread within the spatially structured organs and tissues of an infected host. Because viral replication depends on many factors, including temperature, immune response, and cellular receptor and protease expression, different tissues act as sources or sinks [41]. For example, to enter a cell, the SARS-CoV-2 spike protein must bind to the ACE2 receptor and be primed by the protease TMPRSS2, although other receptors and proteases may also be involved [42]. Tissues with sufficient coexpression of ACE2 and TMPRSS2 (e.g., nasal cavity) may act as sources that seed infection of surrounding areas with lower expression levels (e.g., bronchioles) [16,43]. When ACE2 is expressed without TMPRSS2 (e.g., the heart), a tissue may function as an **ecological trap**, where virions bind target cells but cannot enter or replicate [3,41,43]. Interestingly, this concept can be leveraged to design therapeutics (e.g., [44]). Physical transport mechanisms can also create ecological traps: for instance, SARS-CoV-2 may infect the central nervous system [19], but the viral particles produced in these tissues cannot readily transmit between hosts. Additionally, SARS-CoV-2 largely infects the human upper respiratory tract, from which produced virions are readily expired, whereas Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV infections predominantly reside in the lower respiratory tract, from which viral particles cannot readily be expelled from the host [45]. This difference in tissue tropism affects the transmissibility of these coronaviruses, and likely their pandemic potential. These examples demonstrate that models designed in spatial ecology can integrate knowledge

Box 1. Ecological Methods for Modeling Viral Dynamics and Addressing Data Limitations

Classically, ecologists study population dynamics by using mechanistic models that classify entities (e.g., individuals) into compartments according to their states and quantify transition rates between them. Most models of disease transmission are based on the classification of individuals into susceptible (S), infectious (I), and recovered/immune (R) states (Figure I), though additional states are frequently included [26,27]. Other applications include within-host models of virus replication (classified by target cells, infected cells, and free-living virus) [29] and between-farm models of infected livestock (e.g., foot-and-mouth disease, classified by susceptible, noninfectious, infectious, and slaughtered farms) [83]. Various mathematical frameworks can capture these dynamics and advance a wide range of scientific aims, including estimating epidemiological parameters, assessing the effectiveness of public health strategies, and directing optimal data collection [84].

Statistical ecologists deploy another suite of tools. Bayesian joint-likelihood models are well suited to integrating multiple datasets with different units and temporal/spatial scales and can be designed to account for mechanism (e.g., [85]) or discover statistical patterns (e.g., [86]). Species distribution models classify and predict habitat suitability for a given species on the basis of environmental factors and known species occurrence [87]. These methods can be used to estimate the regional and global distribution of viruses [88], with important exceptions [89], but their application to studying tissue tropism across the within-host landscape remains largely unexplored.

Parameterizing ecological models relies on accurate quantification of state variables (e.g., prevalence) from field and laboratory data. However, data are never perfect due to factors that include sparse or irregular sampling, diagnostics with imperfect sensitivity or specificity, human error, flawed experimental design, or missing data. The possibility of false-positive and false-negative test results is particularly important for epidemiological models (Figure I). While all of these issues can introduce bias or other problems, ecologists have developed strategies and tools to account for them, including occupancy models and state-space models [90,91]. Occupancy models use repeated observations (e.g., multiple swabs per individual per day) to jointly estimate detection probability and the occupancy of a species in a landscape (or analogously, infection prevalence) (Figure I) [92]. State-space models account for imperfect observations in time series data by separating the dynamics of the biological process (e.g., infection dynamics) from noise or bias in the observation process (e.g., false negatives) [91]. Extensions of these two methods can incorporate multiple infection states [93], estimate transmission and recovery rates [86], and include multiple host or virus species [94].

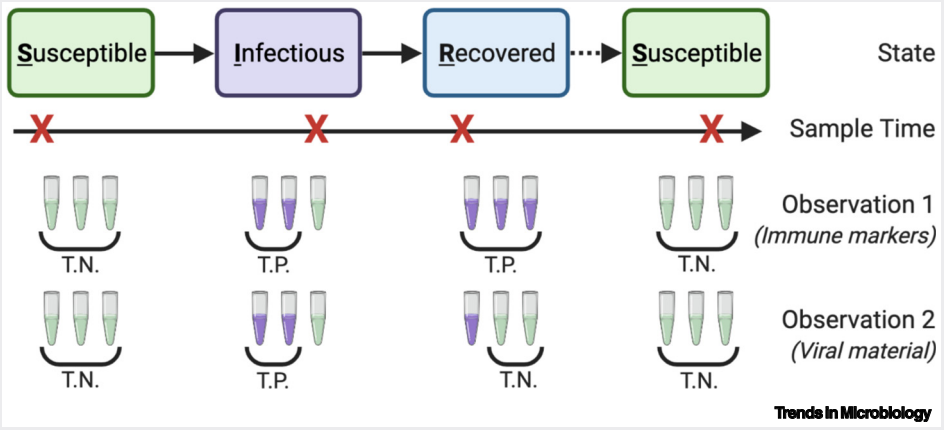

Figure I. The SIR Model of Infection Dynamics and the Occupancy Modeling Approach to Determine Infection State. The SIR model is a fundamental mechanistic model of infection dynamics. Colored boxes represent entities (e.g., cell, tissue, organ, person, or population) that are classified by their infection state: susceptible (S, green), infectious (I, purple), and recovered (R, blue). The biological system (i.e., the virus, host population, and environment) determines the transition rates between each state (represented by arrows) and whether a recovered host can become susceptible again (broken arrow). In parallel, the occupancy modeling approach uses sampling techniques to infer an entity's infection state at various time points. Here, we present two sample types (Observation 1 and 2) that are measured per sampling event (marked by a red X). In this figure, we depict measurements of immune markers (e.g., antibodies) and viral material (e.g., viral RNA), though the framework is applicable to any other observation relevant for the considered system. Three tests are conducted per sample type per sample time, and each vial represents an individual test per time point. Vial color denotes the test result (green, positive; purple, negative), which can correctly or incorrectly classify infection state [T.P. (true positive); T.N. (true negative)]. The frequency of false-negative or false-positive test results depends on the diagnostic, the sampling time, and inherent variability in infection dynamics.

from molecular biology (e.g., receptor affinity), multiomics (e.g., receptor expression), and physiology (e.g., tissue connectivity) to uncover patterns that underlie varying transmission characteristics and pathogenicity of different viruses.

Concepts and tools from spatial ecology allow us to identify and predict landscapes at high risk of experiencing cross-species spillover [46]. In particular, anthropogenic landscape changes increase spillover risk by: (i) altering the abundance and distribution of wildlife hosts, with highly modified areas potentially attracting a greater abundance of known reservoir hosts of zoonoses (e.g., rodents and some bat species), (ii) promoting stress-induced shedding and host susceptibility, and (iii) increasing contact rates among domestic animals, wildlife, and humans [1,2,11,22,47]. While interspecific contacts are difficult to quantify in the wild, advances in animal tracking [48], data sharing platforms (e.g., Movebank), and quantitative methods [49] can refine our predictions of animal encounters, so additional monitoring can be directed to high-risk locations. However, given the difficulty of identifying and tracking the multitude of potential hosts, future applications of spatial ecology to understanding and preventing cross-species transmission may focus increasingly on resilience, rather than risk, within landscapes. Scientists have called for ecological countermeasures to prevent future pandemics, including fostering **landscape immunity**. Interdisciplinary collaborations (among disease ecologists, conservation practitioners, immunologists, and many more) are necessary to understand and maintain landscape immunity across diverse ecosystems and to formulate clear guidance for policy-makers [22].

Evolutionary Dimensions of Emerging Viruses

The evolution of organisms hinges on the accumulation of heritable mutations over successive generations, which can generate phenotypic variation. When studying virus evolution, it is essential to note that virus populations can be defined simultaneously at several nested scales (within their hosts, within host populations, and across host species communities). Evolutionary forces (e.g., mutation, selection) affect viral diversity and fitness concurrently at all of these scales, always mediated by the common currency of viral genomes. Due to the inherently intertwined nature of evolutionary processes at these different scales, we explore each concept first at the within-host scale, where viral factors (e.g., mutation rates) and host pressures (e.g., immune responses) act proximately to generate viral diversity and perhaps drive adaptation [2]. Then, we discuss how processes functioning within host populations and across host species further shape the evolutionary trajectory of an emerging virus.

Evolutionary Controls of Viral Diversity

Genetic diversity accumulates over many generations through mutation and **recombination**, and the frequency of these processes varies across viral lineages. Most RNA viruses have remarkably high mutation rates due to a low-fidelity RNA polymerase that increases the frequency of spontaneous mutations [50,51]. However, SARS-CoV and SARS-CoV-2 utilize a high-fidelity, RNA-dependent RNA proofreading mechanism, which reduces the occurrence of mutations and helps the virus to maintain a functional genome [51,52]. For other coronaviruses (e.g., HCoV-OC43), recombination is essential for generating diversity, which suggests that this process may also be important for SARS-CoV-2 [52,53]. Concrete evidence of recombination seemed conspicuously absent in SARS-CoV-2 genomes sampled during early 2020, while point mutations and deletions were common [54]. However, new evidence that SARS-CoV-2 recombines readily *in vitro* [53] emphasizes that diversity may initially have been insufficient to yield detectable recombination, and further study is needed to investigate recombination in field isolates. Additionally, *in vivo* studies of within-host viral diversity could better characterize the relative frequencies of mutation and recombination. Such research has been limited so far; however, two notable case

studies of immunocompromised patients reported nonsynonymous and synonymous mutations and deletions across 15 sites arising over 150 days [55] and 30 sites over 152 days [56] but did not appear to screen for recombination.

Just as for multicellular organisms, population genetic mechanisms (e.g., **gene flow**, **genetic drift**) modulate the genetic diversity of viruses in a host population. The occurrence of **bottleneck** events eliminates viral variants, while high gene flow promotes homogeneity [57]. Despite the vast **ecological opportunity** posed by its recent zoonotic jump and the sheer number of COVID-19 cases worldwide, the global diversity of SARS-CoV-2 measured in late July 2020 was remarkably low, with 46 723 sequenced genomes from 99 countries diverging maximally by 32 SNPs, all of which were considered descendants of a single lineage [54]. However, as of January 2021, global diversity has increased enormously [58], including three novel lineages each characterized by 17 (B.1.1.7), nine (B.1.351), and 16 (P.1) nonsynonymous mutations, of which 38 are distinct [59,60]. Two explanations for this surge of diversity include sufficient time elapsed since emergence for the accumulation of viral diversity and/or transmission of diverse variants that arose in long-term COVID-19 patients [55,59]. In principle, the diversity of endemic human coronaviruses could provide a preview of the future evolutionary trajectory of SARS-CoV-2, but sparse sampling (e.g., 36 HCoV-OC43 genomes examined from four countries over 30 years [61]) makes quantitative comparisons difficult. By contrast, the massive sequencing efforts of SARS-CoV-2 provide an exciting opportunity to detect new variants in real time and, by utilizing techniques from macroevolution, investigate the controls on global coronavirus diversity (Box 2).

Phylogenetic perspectives on diversification can identify genetic relationships among viruses and provide pivotal insights into evolutionary trajectories of host jumps. Such analyses showed that **reassortment** of human, avian, and porcine influenza viruses gave rise to the 2009 H1N1 pandemic strain [35]. Early phylogenetic studies suggested that SARS-CoV-2 emergence involved recombination between bat and pangolin coronaviruses, but subsequent results showed that the lineage that gave rise to SARS-CoV-2 has been present in bats for many years [62]. However, the detection of coronaviruses in many host species (e.g., raccoon dogs, minks), coupled with their propensity to recombine, emphasizes that coinfection could facilitate recombination between various, potentially distinct, coronaviruses and thus generate novel viruses with pandemic potential [34,63,64]. Further analyses of genetic diversity can shed light on the multihost epidemiology of coronaviruses, distinguishing reservoir, intermediate, and dead-end hosts. For instance, the high and stable diversity of SARS-like coronaviruses in bats supports their role as a reservoir, while rapid growth of viral diversity in humans and civets was a hallmark of recent spillover of SARS-CoV in 2002–2004 [64]. Continuing transmission between host species can further contribute to viral diversity as evidenced by repeated transmission of SARS-CoV-2 between minks and humans, with novel variants arising in minks sometimes transmitted back to humans, which echoes observations for influenza A [34,35].

Adaptation and Viral Evolutionary Success

The evolutionary process of viral adaptation reflects selective pressures operating across multiple scales [65]. Inside an infected host, purifying selection purges viral variants with disadvantageous traits (e.g., structural instability), and positive selection favors those that confer an adaptive advantage (e.g., evasion of immune responses) [3,54,66]. Selection can act strongly on viral attachment proteins, which mediate cellular entry and are an accessible target for the immune system [67]. For SARS-CoV-2, mutations in the spike protein can alter viral fitness by enhancing ACE2 receptor binding or facilitating immune escape. Notably, the variant lineages that arose in late 2020 shared several substitutions in the spike protein, including K417N (found in the B.1.351

Box 2. Macroevolutionary Theory: An Underused Toolbox for Studying Viral Diversity

Macroevolution is the study of processes that govern the origin, persistence, and extinction of species. Despite a well-developed set of conceptual tools for understanding diversity dynamics, including models of lineage origination and extinction that vary with time, traits, and environmental conditions, macroevolutionary approaches have scarcely been applied in virological studies. Macroevolutionary ideas may apply fruitfully to viral diversity across scales, and even within a single viral species. Potential examples include:

- Macroevolution has revealed surprising ways that species persistence and diversification can be decoupled from forces governing individual fitness [e.g., selection has repeatedly favored traits associated with mammalian hypercarnivory (e.g., bone-cracking) at the individual level, but these lineages are more vulnerable to extinction than generalist clades [95]] [96,97], and may offer new perspectives on cross-scale phenomena in viruses such as the evolution of virulence.
- The concept of ecological **adaptive radiation** links ecological opportunity (e.g., absence of competitors when novel habitats are colonized) to the rapid proliferation of new species adapted to distinct niches. Host jumps leading to epidemics or pandemics could provide viruses with vast ecological opportunity to differentiate (e.g., the global population of susceptible humans for SARS-CoV-2, as well as other new host species infected by humans), yet host population movement and viral gene flow will work against differentiation. Adaptive radiation theory may help to predict evolutionary trajectories of novel viruses in humans or other hosts.
- Macroevolutionary theory around adaptive radiation and clade competition [98] may provide new insights into patterns in infectious disease emergence events, including impacts of competition with endemic viruses and the factors controlling the total diversity of viruses that can infect humans.
- Substantial challenges exist for delineating the significant evolutionary differences between variants, strains, species, and lineages. Macroevolutionary principles combined with species delimitation frameworks could help to integrate genotypic data with phenotypic data (e.g., conserved protein domains, receptor specificity) to create a rigorous system for virus species delineation which might offer insights into the properties of an emerging virus (e.g., potential host range, transmission route) [99].

Some of these questions have been approached within emerging fields such as phylodynamics [100], but macroevolution may help to develop much-needed frameworks for understanding the vastness of viral diversity, especially at deeper phylogenetic and temporal scales. Furthermore, since viruses diversify much more rapidly than plant and animal species, engagement with virology might provide macroevolutionists with heretofore nonexistent opportunities to directly observe hypothesized processes for the assembly of biodiversity.

and P.1 lineages), E484K (B.1.1.7, B.1.351, P.1), N501Y (B.1.1.7, B.1.351, P.1), and D614G (B.1.1.7, B.1.351, P.1) [60,66,68–70]. *In vitro* assays suggest that both D614G and N501Y promote an up-conformation of the spike protein subunits, which increases the likelihood of binding ACE2, exposes the cleavage site, and increases overall infectivity of a cell [69,70]. K417N exhibits diminished neutralization by monoclonal antibodies, but only moderately increases ACE2 binding affinity. E484K exhibits increased binding affinity to ACE2 and reduced neutralizing activity of monoclonal antibodies [71].

In host populations, selection favors viral variants that can transmit between hosts and propagate through the population; thus, rising frequency of particular variants suggests a selective advantage. However, similar patterns could arise due to founder effects or stochasticity [72], so cautious interpretation is warranted. For SARS-CoV-2, D614G rose to high frequency in separate global outbreaks and became dominant worldwide by March 2020 [68,73], and phylogenetic analysis in the UK suggests that D614G approached fixation after introduction into a region dominated by the wild-type [73]. These findings are consistent with an adaptive role for D614G, which is further supported by evidence that it promotes increased transmissibility compared to the wild type: (i) more efficient transmission in hamsters, (ii) increased replication in the upper respiratory tract of humans and hamsters *in vitro* and *in vivo*, and (iii) the spike conformational mechanism described above [68,69,74,75]. Similarly, B.1.1.7 became the dominant lineage in the UK within 3 months of its emergence in late September 2020, while B.1.351 and P.1 rose rapidly in frequency in South Africa and Brazil, respectively [59,76]. Although these lineages appear to have emerged independently in different countries, they share several key substitutions in the spike

protein (D614G, N501Y, E484K) associated with within-host advantages and, putatively, increased transmissibility [59,71,77]. Such **convergent evolution** is a classic sign of adaptation [58,78], and viruses may provide an unexpected opportunity to investigate the relationship between convergence in function (e.g., transmissibility) and convergence of the underlying genetic and/or structural components of the trait [79].

At the scale of cross-species emergence, the role of virus adaptation is the subject of longstanding debate: when (if ever) is adaptation required, and where does it occur [78]? Natural selection can drive the evolution of a trait that is later commandeered for a new function, and such **exaptation** of viruses in animal reservoirs can facilitate host jumps. Genetic analysis has revealed a furin-recognition motif in the SARS-CoV-2 spike protein which facilitates binding of human ACE2 and enables cleavage by the furin protease [6]. This motif is present in a coronavirus found in Malayan pangolins (*Manis javanica*) but is absent in the coronavirus (RaTG13) most genetically similar to SARS-CoV-2 (found in horseshoe bats; *Rhinolophus affinis*) [6]. The acquisition of this motif (via an unclear pathway) may have functioned as an exaptation that mediated transfer of the SARS-CoV-2 progenitor from wildlife into humans. Since cellular entry is a key determinant of viral host range, the use of highly conserved receptors (and hence a generalist life history) may function as an alternative type of exaptation that provides more opportunities for spillover events [80,81]. For example, ACE2 is highly conserved among humans, various bat species, and potential intermediate hosts [23]. Indeed, many host species have proved susceptible to SARS-CoV-2, including ferrets and cats [82]; *in silico* analysis identifies many other potentially susceptible species, providing insights into the current or future host range of the virus [80].

Concluding Remarks

Given the increasing frequency of zoonotic emergence events and their potential societal impacts, it is imperative to leverage all applicable tools to better understand, predict, and prevent the spillover and subsequent spread of novel infectious diseases. Ecological and evolutionary concepts, which have been crafted and tested for decades, provide key insights into the origin of emerging viruses, the trajectory of an outbreak or pandemic, and the risk of future spillover. These concepts, which are already inherently intertwined (Figure 2), prove even more powerful when integrated with other fields, including microbiology, epidemiology, and medicine. Such interdisciplinary approaches can uncover key insights that are otherwise unattainable, and, in particular, could answer many unresolved questions about SARS-CoV-2 (see Outstanding Questions). The insights gained, and new avenues for investigation developed from these questions, will drive progress in further refining ecological and evolutionary theory, directing future interdisciplinary research, and improving general understanding of the mechanisms that drive the emergence of infectious diseases.

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Declaration of Interests

There are no interests to declare.

Outstanding Questions

Can insights from invasion ecology be harnessed to formulate a new generation of mechanistic dose–response models? Can we leverage biomedical findings to model a viral exposure event as a population growth process on a heterogeneous landscape?

Does pre-existing immunity to SARS-CoV-2 arise from prior exposure to endemic coronaviruses? If so, do differences in these virus community interactions explain geographic variation in pandemic intensity? Can consumer–resource models be combined with patient data to investigate the impacts of pre-existing immunity on disease course?

Can animal tracking technologies reveal the interactions of potential reservoir and intermediate hosts of SARS-CoV-2? Does overlaying this information with human population data reveal regions and species that may have been involved in SARS-CoV-2 spillover? Can these techniques identify high-risk areas for future emerging viruses?

How is SARS-CoV-2 tissue tropism influenced by features of the within-host landscape (e.g., temperature, pH, protein expression)? Can species distribution models incorporate this information to clarify the apparent disparities between ACE2 expression and SARS-CoV-2 tissue tropism?

The up versus down conformation in the spike protein may favor reproduction (via better receptor binding) versus survival (via hiding epitopes from antibodies), respectively. Can the optimal balance of these states be understood using the evolutionary theory of life history trade-offs?

How will the virulence of SARS-CoV-2 in humans change over time, and will this be governed chiefly by population immunity or viral evolution, or both? Did other endemic human coronaviruses begin as catastrophic pandemics and evolve into 'common cold' viruses?

How many endemic coronaviruses can the human population sustain, and what forces govern this limit? Is there competition among coronaviruses for

susceptible human hosts? Will SARS-CoV-2 outcompete and drive another coronavirus to extinction, as seen in influenza pandemics?

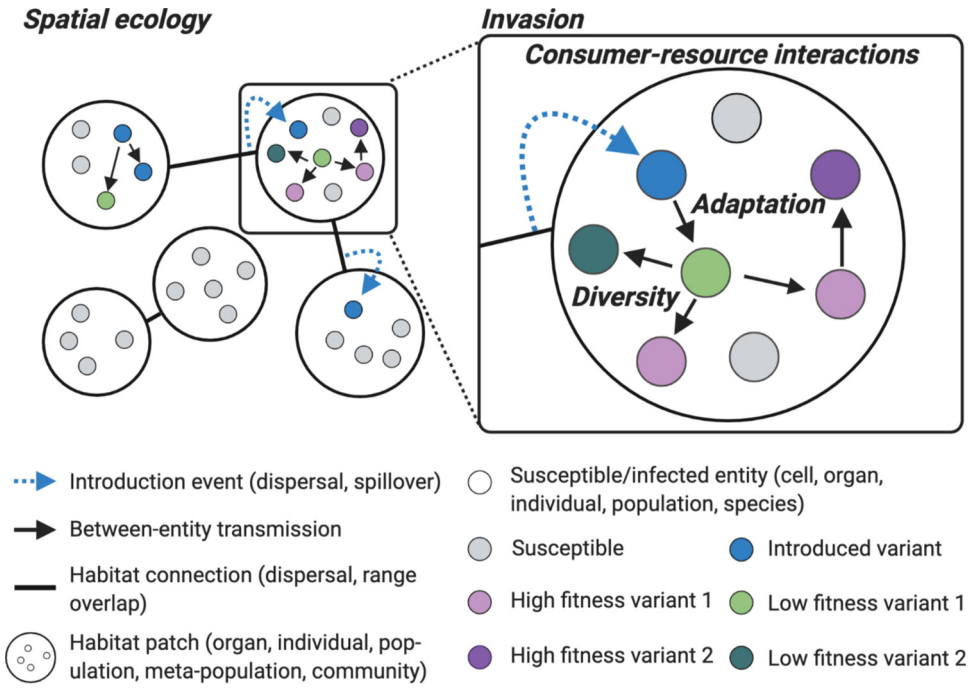

Figure 2. The Inherent Connections between Five Ecological and Evolutionary Concepts. Graphical representation of the connections between the five presented concepts. A small circle within a larger circle represents an individual entity within a higher level of biological organization, which is generalizable to: a cell within an organ, an organ within an individual host, an individual within a population, a population within a meta-population, or a species within a community. A small gray circle represents a susceptible entity, and colored circles represent infected entities, where color denotes viral strain.

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