Beyond the Mean Field in Host–Pathogen Spatial Ecology

Blake C. Stacey, Andreas Gros and Yaneer Bar-Yam

New England Complex Systems Institute

238 Main St. Suite 319 Cambridge MA 02142, USA

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Abstract

Spatial extent—the possibility that what happens at point A cannot immediately affect what happens at point B—is a complicating factor in mathematical biology, as it creates the opportunity for spatial non-uniformity. This non-uniformity must change our understanding of evolutionary dynamics, as the same organism in different places can have different expected evolutionary outcomes. Since organism origins and fates are both determined locally, we must consider heterogeneity explicitly to determine its effects. We use simulations of spatially extended host–pathogen and predator–prey ecosystems to reveal the limitations of standard mathematical treatments of spatial heterogeneity. Our model ecosystem generates heterogeneity dynamically; an adaptive network of hosts on which pathogens are transmitted arises as an emergent phenomenon. The structure and dynamics of this network differ in significant ways from those of related models studied in the adaptive-network field. We use a new technique, organism swapping, to test the efficacy of both simple approximations and more elaborate moment-closure methods, and a new measure to reveal the timescale dependence of invasive-strain behavior. Our results demonstrate the failure not only of the most straightforward ("mean field") approximation, which smooths over heterogeneity entirely, but also of the standard correction ("pair approximation") to the mean field treatment. In spatial contexts, invasive pathogen varieties can prosper initially but perish in the medium term, implying that the concepts of reproductive fitness and the Evolutionary Stable Strategy have to be modified for such systems.

I. INTRODUCTION

Mathematical modeling of biological systems involves a tradeoff between detail and tractability. Here, we consider evolutionary ecological systems with spatial extent—a complicating factor, as it implies the possibility of heterogeneity. Analytical treatments of spatial systems typically treat as equivalent all configurations with the same overall population density, the same allele frequencies, the same pairwise contact probabilities or the like. Generally, one seeks a simplified analytical model, which *coarse-grains* "microstates" (complete specification of each organism) to "macrostates" (characterized by quantities like average densities), allowing one to make useful predictions about the model's behavior [1, 2]. Corrections to simple coarse-grainings can quickly generate an overbearing quantity of algebra. Before exhausting ourselves with ever-more-elaborate refinements, it would be useful to have some understanding of when a particular series of approximations is doomed to inadequacy.

In this article, we review the context in which commonly-used coarse-grainings can be expected to fail at capturing the evolutionary dynamics of an ecosystem, and in addition we provide a novel, direct demonstration of that failure. The fundamental issue is *spatial heterogeneity,* a long-recognized concern for mathematical biology [3, 4]. When does spatial heterogeneity significantly impact the choice of appropriate mathematical treatment, and when does a chosen mathematical formalism not capture the full implications of spatial variability? We show that one can test a treatment of heterogeneity by transplanting organisms within a simulated ecosystem in such a way that, were the treatment valid, the behavior of the ecosystem over time would remain essentially unchanged. We demonstrate situations where the behavior changes dramatically and cannot be captured by a conventional treatment. The complications we explore imply that *short-term descriptions* of what is happening in an evolutionary ecological model can be insufficient and, in fact, misleading, with regard not just to quantitative details but also to qualitative characteristics of ecological dynamics.

Many modeling approaches in mathematical biology which appear distinct at first glance turn out to be describing the same phenomenon with different equations [5, 6], *e.g.,* by a different choice of coordinate system [7]. What matters for our purposes is not so much which technique is chosen, but whether the underlying assumptions do, in fact, apply.

It will be convenient to introduce a small amount of jargon: "mean-field theory" is a term from statistical physics [8, 9] which has been adopted in ecology [10–12], referring

to an approximation in which each component of a system is modeled as experiencing the same environment as any other. This implies that the probability distribution over all possible states of the system factors into a product of probability distributions for individual components. In a mean-field treatment of a magnet, for example, each atom experiences the same magnetic field. An analogue in population genetics is the assumption that a population is panmictic. That is, if a new individual in one generation has an equal chance of receiving an allele from any individual in the previous generation, then we can approximate the ecosystem dynamics using only the proportion of that allele, rather than some more complicated representation of the population's genetic makeup. Modeling evolution of that population as "change in allele frequencies over time" (per, *e.g.,* [5, 13]) is, implicitly, a mean-field approximation [14]. The mean-field approximation is also in force if one postulates that an individual organism interacts with some subset, chosen at random, of the total population, even if the form and effect of interactions within that subset are complicated (as in, *e.g.,* [15, 16]).

It is well known that real species are not necessarily panmictic. However, many treatments which acknowledge this are still mean-field models. The textbook way of incorporating geographical distance into a population-genetic model is to divide the system into N local subpopulations, "islands," connected via migration [17–19]. Within each subpopulation, distance is treated as negligible, and organisms are well mixed [4, 20]. This approach assumes a single distance scale below which panmixia prevails [21], and it relies on well-defined boundaries which persist over time [20]. Furthermore, the connections among subpopulations are frequently taken to have the topology of a complete graph, *i.e.,* an organism in one subpopulation can migrate to any other with equal ease [4, 18–20]. In this case, each of the N subpopulations do experience the same environment, to within one part in N. Thus, the mean-field approximation is in force at the island level, and the island model incorporates spatial extent without incorporating full spatial heterogeneity. For real ecosystems [21–23], or in sufficiently interesting models, one or more of these simplifying assumptions can fail. More complicated population structures require more sophisticated mathematical treatments of evolution, a fact which has real-world implications for practial issues like the evolution of drug-resistant diseases [24].

We make these issues concrete by focusing on a specific model of ecological and evolutionary interest. For definiteness, we take a model of hosts and consumers interacting on a

2D spatial lattice. Each lattice site can be empty (0), occupied by a host (H) or occupied by a consumer (C). We use the term *consumer* as a general label to encompass parasites, pathogens and predators. Hosts reproduce into adjacent empty sites with some probability g per site, taken as a constant for all hosts. Consumers reproduce into adjacent sites occupied by hosts, with probability τ per host; sometimes τ is fixed for all consumers, but we shall also consider cases in which it is a mutable parameter passed from parent to offspring. Hosts do not die of natural causes, while consumers perish with probability v per unit time (leaving empty sites behind). Because consumers can only reproduce into sites where hosts live, the effective graph topology of reproductively available sites experienced by the consumers is constantly changing due to their very presence—it is an adaptive network [25–27]. This model is a fundamentally *nonequilibrium* one: an approach to a steady state is not at all guaranteed, and even when a quasi-steady-state behavior emerges, as we shall see, it is a consequence of fluctuations over space and time.

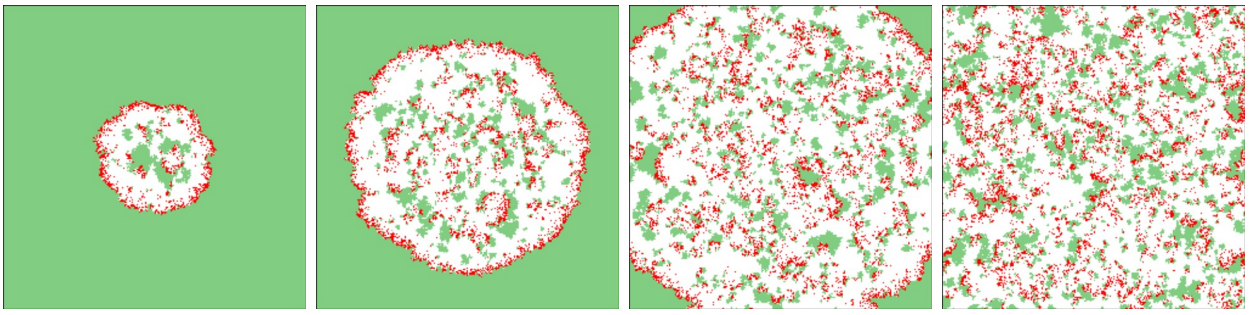

FIG. 1: Snapshots of a simulated host–consumer ecosystem on a 250×250 lattice, taken at intervals of 100 generations. Consumers are dark gray (red online), hosts are light gray (green online) and empty space is left white. The simulation began with a single consumer at the center of the lattice, which gave rise to an expanding front of consumers. The first image in this sequence shows the state of the ecosystem 100 generations into the simulation. Hosts which survive the consumer wave recolonize the empty sites, leading to pattern formation. Here, the host growth rate is $g = 0.1$, the consumer death rate is $v = 0.2$ and the consumer transmissibility is fixed at $\tau = 0.33$.

Several different types of biological interactions can be treated by this modeling framework. Hosts could represent regions inhabited by autotrophs alone, while consumers represent regions containing a mixture of autotrophs and the heterotrophs which predate upon them, for example [28]. Alternatively, host agents could represent healthy organisms, while consumers represent organisms infected with a parasite or pathogen. Thus, host–consumer models are closely related to Susceptible–Infected–Recovered (SIR) models, which are epidemiological models used to understand the spread of a disease through a population. SIR

models describe scenarios in which each individual in a network is either susceptible (S) to a pathogen, infected (I) with it, or recovered (R) from it; susceptible nodes can catch the disease from infected neighbors, becoming infected themselves, while nodes which have become infected can recover from the disease and are then resistant against further infection. Susceptible, infected and recovered individuals roughly correspond to hosts, consumers, and empty cells, respectively. An important difference between host–consumer models and epidemiological models concerns the issue of *reinfection.* To wit: in the host–consumer model, an empty site left behind by a dead consumer can be reoccupied by another consumer, but only if a host reproduces into it first. Other research has considered models where R[ecovered] individuals can also become I[nfected], with a different (typically lower) probability than S[usceptible] ones, thereby incorporating imperfect immunity into the model [29, 30]. The degree of immunity is independent of geography and the environment of the R[ecovered] individual, unlike reoccupation in the host–consumer model. Another application is illustrated by the Amazon molly, *Poecilia formosa,* which is a parthenogenetic species: *P. formosa,* all of which are female, reproduce asexually but require the presence of sperm to carry out egg development. (This kind of sperm-dependent parthenogenesis is also known as gynogenesis.) *P. formosa* are thus dependent on males of other species in the same genus—usually *P. mexicana* or *P. latipinna*—for reproduction. Because *P. formosa* do not incur the cost of sex, they can outcompete the species on which they rely, thereby possibly depleting the resource they require for survival, *i.e.,* male fish [18, 31]. Thus, hosts could be regions containing sexual organisms, with consumers standing for areas containing both sexual and asexual individuals [18].

This host–consumer model displays waves of colonization, consumption and repopulation. Hosts reproduce into empty sites, and waves of consumers follow, creating new empty regions open for host colonization. Therefore, clusters of hosts arise dynamically [32–35], a type of pattern formation which can separate regions of the resources available to pathogens into patches without the need for such separation to be inserted manually. Figure 1 illustrates a typical example of this effect. This is a specific example of the general phenomenon of pattern in nonequilibrium systems [14]. Consumers are *ecosystem engineers* [36, 37] which shape their local environment: an excessively voracious lineage of consumers can deplete the available resources in its vicinity, causing that lineage to suffer a Malthusian catastrophe [18, 32, 38–41]. Because the ecology is spatially extended, this catastrophe is a local niche

annihilation, rather than a global collapse [42]. A ravenous mutant strain can successfully invade in the short term but suffer resource depletion in the medium term, meaning that averages taken over long numbers of generations yield a relatively low virulence [10, 43]. This implies that an empirical payoff matrix or reproduction ratio will exhibit nontrivial timescale dependence [10, 44, 45].

Stochastic departures from uniformity—fluctuations—of this kind have been found to be important in the context of *phase transitions,* shifts from one "phase" or regime of behavior to another, such as the change of a substance from liquid to gas. Indeed, there exist significant and useful connections between phase transitions in physics and the present model. In certain situations, the process of pathogen propagation through the host population distributed in space can be mapped onto a *percolation* problem. A topic widely investigated in mathematics, percolation deals with movement though a matrix of randomly placed obstacles. A prototypical percolation problem is a fluid flowing downhill through a regular lattice of channels, with some of the lattice junction points blocked at random. The key parameter is the fraction of blocked junction points. If this fraction is larger than a certain threshold value, the fluid will be contained in a limited part of the system. However, if the blocking fraction is below the threshold, the fluid can percolate arbitrarily far from its starting point. This is a phase transition between a phase in which fluid flow can continue indefinitely and one in which flow always halts. Similar issues arise when a pathogen propagates by cross-infection through a set of spatially arranged hosts. Sufficiently many hosts in mutual contact are required for the pathogen to propagate successfully. Pathogen strains therefore survive or die out over time depending on whether percolation is or is not possible [12, 46–50].

The mathematical connection between pathogen–host and percolation problems can provide insight into the difficulties in analytical treatment of the biological problem. Spatial heterogeneity gives rise to failure of traditional analytic treatments of percolation and a need for new methodologies. Since the pathogen problem maps onto the percolation problem under some circumstances, the same analytic problems must arise in the biological context.

Quite generally, in systems which have spatial extent, stochastic variations close to a phase-transition point cause mean-field approximations to fail [30, 51]. Moreover, even standard types of corrections to mean-field approximations perform poorly or fail entirely [11, 52]. The question becomes whether models of interest contain such troublesome regimes,

and how likely we are to encounter them.

We will show that numerical investigation of our host-consumer model indicates that the consumer extinction transition, when the transmissibility τ becomes just large enough that the consumer population sustains itself, lies in the *directed percolation* [30, 53–56] universality class. A similar result has been reported for related models [46, 47]. The directed percolation universality class is a large set of models, all of which exhibit a phase transition between two regimes of behavior, and all of which behave in essentially the same way near their respective transition points. The scenario of fluid flow through a random medium considered above is a classic example of a directed percolation-class model, but many others exist as well [30, 53]. The *critical exponents* describe how properties of the modeled system vary over time or as a function of how far the control parameter is from the critical point. They are the same for all systems in the universality class. Other universality classes exist as well, with different classes having different quantitative values for the critical exponents. Identifying to which universality class a system belongs enables us to study a complicated phenomenon by examining a simpler representative of its class instead.

The inadequacy of the mean-field approximation implies a need for improved treatments. To include heterogeneity, as a first correction, we can include the pairwise correlations between sites. The details of the resulting calculations depend on the particular system being studied, but all these specific implementations collectively fall under the heading of *pair approximations.* This scheme is a common way of building a mathematical treatment which acknowledges spatial heterogeneity, by incorporating the idea that the local environment of an organism can have a different character and composition than the ecosystem as a whole. This is only an approximation, because it does not reflect the existence of patches (empty areas, host areas, and pathogen areas) and other population structures which involve more than two sites. We will see in §IV that pair approximations fail to capture what happens when an invasive species is introduced to a host–consumer ecosystem. We will show two reasons for this failure, *phase transitions* and *long-timescale effects.* Furthermore, these properties imply that including triple, quadruple or even higher order correlations will also be insufficient. The failure is due not to the details of any particular calculation but rather to an assumption inherent in these approximations. Thus, there exists a need for new analytical tools in spatial evolutionary ecology.

The failure of analytic approaches to address a particular problem often leads one to

consider alternative problems that can be addressed using the analytic approach. However, such a change, by its very nature, may eliminate effects that are important in the original problem, and consequently the solution does not give the correct insight into them. For example, there are host-pathogen systems defined on networks for which pair-approximation schemes can work. Prior modeling efforts have considered epidemics on adaptive networks, where the spread of the disease *through* the network changes the connections *of* the network [57–64]. In such models, if a susceptible node has an infected neighbor, it can break that connection by rewiring to another susceptible node. The key point is that the new neighbor is chosen at random from the eligible population. This choice of rewiring scheme is exactly what makes a pair approximation work, because it eliminates higher-order correlations in the system [58]. In our system, by contrast, hosts can form new connections by reproducing into empty sites, but these contacts can only connect geographically proximate individuals.

While the presence of a nonequilibrium transition point indicates that traditional analysis techniques fail, it raises the possibility that new tools from the theory of phase transitions [30, 51] will become applicable.

In §II, we start to address the issue of how mutation and natural selection operate together in a spatial host–consumer ecosystem. This leads us into the study of phase transitions and the relationship between ecological dynamics and percolation problems. In §III, we explore how to define fitness in the nonequilibrium context. In §IV, we will make direct tests of assumptions used in developing mathematical treatments for spatial evolutionary ecology. Implications for questions of wider scope are the subject of §V.

II. SUSTAINABILITY AND PHASE TRANSITIONS

A. Evolution of Transmissibility

We investigate evolution in the spatial hostconsumer ecosystem through simulation and analytic discussion. If the transmissibility τ is made a heritable trait, passed from a consumer to its offspring with some chance of mutation, what effect will natural selection have on the consumer population? Figure 2(A) shows the average, minimum and maximum values of the transmissibility τ observed in a population over time. The average τ tends to a quasi-steady-state value dependent on the host growth rate g and the consumer death rate v; if

the simulation is started with τ set to below this value, the average τ will increase, and likewise, the average τ will decrease if the consumer population is initialized with τ over the quasi-steady-state value. Even when the average τ has achieved its quasi-steady-state value, the population displays a wide spread of transmissibilities whose extremes fluctuate over time [28].

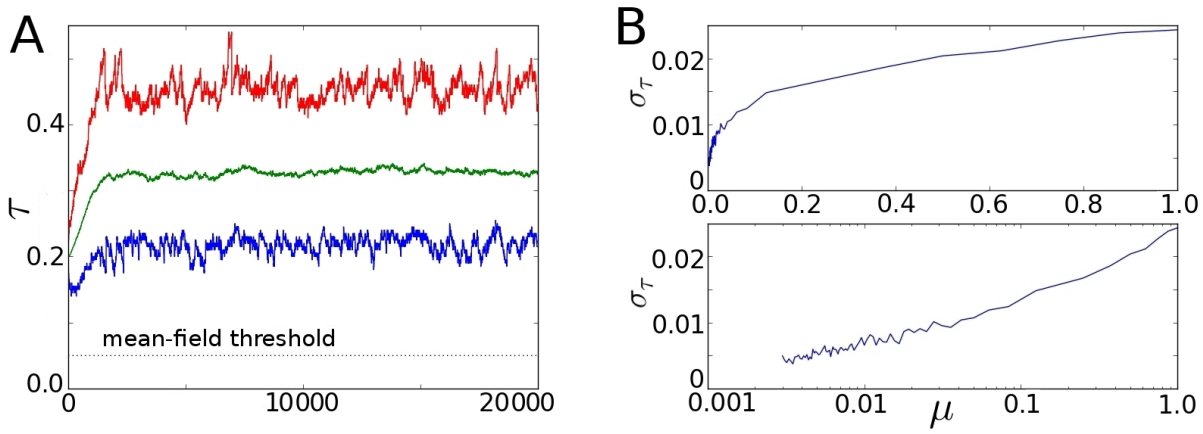

FIG. 2: **(A)** Minimum, average and maximum transmissibility τ for a consumer population over time, with $g = 0.1$ and $v = 0.2$. (The mutation rate is $\mu = 0.255$ and the step size is $\Delta\tau = 0.005$, as was used in reference [28].) The average τ tends to a quasi-steady-state value dependent on g and v; if the simulation is started with τ set to below this value, the average τ will increase, and likewise, the average τ will decrease if the consumer population is initialized with τ over the quasi-steady-state value [28]. **(B)** Standard deviation of the transmissibility, σ_τ, for a consumer population ($g = 0.1$, $v = 0.2$) measured at different mutation rates, from $\mu = 0.003$ to $\mu = 1.0$.

In a well-mixed ecosystem, the average τ of the population will tend to 1, maximizing the reproductive rate of the individual consumer. The observation of a quasi-steady-state value below 1 is an important result. This is the first breakdown of the mean-field approximation, and it indicates the inapplicability of traditional assumptions about fitness optimization, with implications for the origins of reproductive restraint, communication-based altruism and social behaviors in general [10, 28, 42, 44, 45, 65].

To gain insight into the upper and lower extremes seen in Figure 2(A), we study the simpler case of fixed τ. We fill the lattice with hosts and inject a single consumer with a selected value of τ; then, we observe how long the descendents of that consumer persist as a function of τ. The consumer population does not persist when τ is either too low or too high. Figure 3 shows the probability that a consumer strain will survive for a substantial length of time (2000 generations) after injection into a lattice filled with hosts. This probability is

hump-shaped, with an asymmetric plateau bounded above and below by cutoffs.

B. Lower Threshold: Percolation

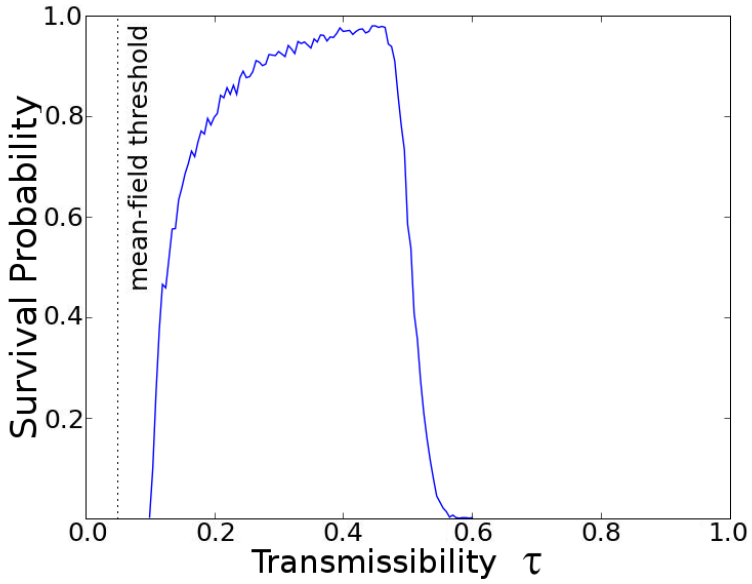

FIG. 3: Probability of a consumer strain surviving 2000 generations after injection at a single point in a 250×250 lattice filled with hosts. (Computed with 1000 runs per point. Host reproduction rate $g = 0.1$, consumer death rate $v = 0.2$.) Vertical dotted line shows the sustainability threshold found through the mean-field approximation.

The lower edge in Figure 3 is a transition between sustainable and unsustainable transmission of consumers through the lattice. We expect and will demonstrate that the system maps onto a directed percolation problem. We confirm that this is a directed percolation-class phase transition by finding the power-law growth of the population size, averaged over an ensemble of 10^3 simulation runs. As shown in Figure 4(A), the exponent of this power law is the characteristic value for directed percolation, $\approx$0.230 [30]. If the host growth rate parameter is made negligible ($g \approx 0$), then the ecosystem behavior changes. The transition instead belongs to the *dynamic percolation* universality class, examples of which have been seen in some epidemic models [30, 47]. We can construct a prototypical example of the dynamic percolation class by returning to the fluid-flow problem considered earlier and, instead of requiring that the fluid only flow downhill, allowing it to flow isotropically through the lattice.

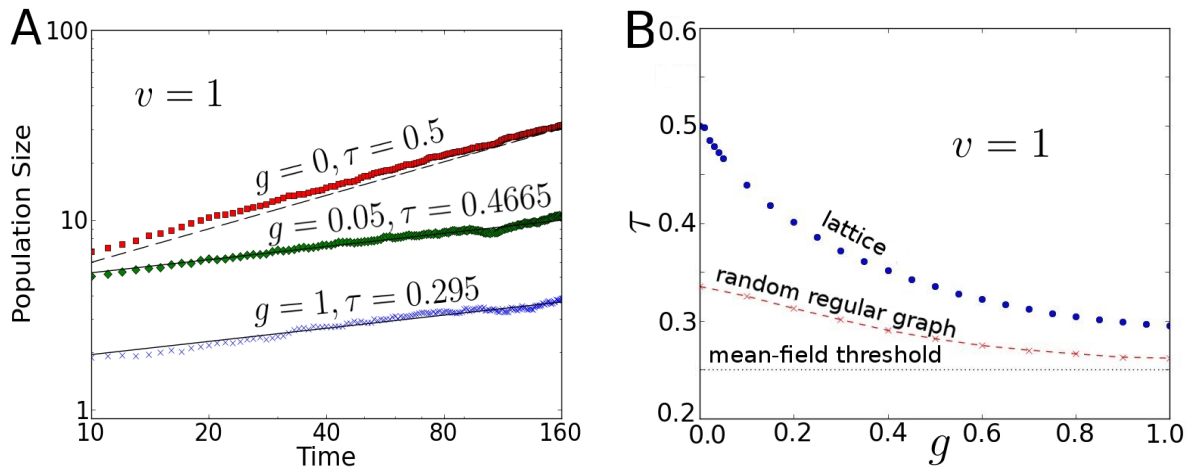

FIG. 4: **(A)** Population size as a function of time, averaged over 10^3 simulation runs, for τ values near the transition points at $g = 0$ and $g = 0.05$ on the spatial lattice, with $v = 1$. Dashed and solid lines indicate the population growth for systems at dynamic percolation and directed percolation transitions respectively, showing that these transitions have the characteristic properties of those universality classes. **(B)** Critical τ for the host–consumer ecosystem with $v = 1$. The vertical axis, where $g = 0$, maps onto the SIR epidemic process (described in [30]), while the line $g = 1$ closely resembles the SIS dynamics seen in the epidemiological lattice model of [30] when rates for initial and secondary infections are the same. The transition line crosses over from the dynamic percolation universality class at $g = 0$ to directed percolation between $g = 0.015$ and $g = 0.02$. Red Xs indicate the transition curve for the host-consumer dynamics played on a random regular graph (RRG) of uniform degree 4; the dashed line connecting them is to guide the eye. The RRG transition is neither directed percolation nor dynamic percolation.

One can calculate the minimum sustainable value of τ in the mean-field approximation [46] by balancing the birth and death rates. If the host population is small compared to the total ecosystem size, then the minimum sustainable τ is the value which satisfies $k\tau = v$, where k is the number of neighbors adjacent to a site. For the parameters used in Figure 2(A), this value would be 0.05, a factor of 4 lower than that seen in the spatial evolving ecosystem. Figure 4(B) plots the minimum sustainable τ in mean-field and spatial systems as a function of g. Both the minimum τ seen in the scenario with mutation and the minimum sustainable τ in the case without mutation are significantly larger than the mean-field threshold value. This discrepancy between the spatial and non-spatial scenarios further indicates the importance of incorporating spatial extent into epidemiological models.

It is instructive to compare the minimum sustainable transmissibilities shown in Figure 4(B), with the results of earlier investigations of spatial epidemiological models. For simplicity, we consider an SIR model in the case of rapid recovery, so that individuals which

are I[nfected] will be R[ecovered] in one simulation timestep. The infection cannot spread unless the disease transmissibility is sufficiently high [30, 66]. The minimum sustainable transmissibility is 0.5, the same as in the host–consumer model when the host growth rate $g = 0$. See Figure 4(B). Furthermore, the transition in the SIR lattice model is also in the dynamic percolation universality class, just as is the transition in the host–consumer model. If the SIR model is modified to allow reinfection, becoming an "SIRI" model, the minimum sustainable transmissibility decreases as g increases. The transition is, however, still a dynamic percolation one, up until the initial infection ($S \to I$) and reinfection ($R \to I$) probabilities are equal, in which case the transition becomes a *directed* percolation one instead. Contrast this with the host–consumer ecosystem, in which increasing the host growth rate g up from zero also decreases the critical value of the transmissibility—allowing the consumer population to sustain itself at lower τ—but the transition is a *directed* percolation, not dynamic percolation, phenomenon.

When the hosts reproduce to fill empty sites as quickly as possible ($g = 1$), then sites left open by dying consumers rapidly become available for consumer recolonization, and empty space does not play as significant a role. We expect, therefore, that for $g = 1$ the host–consumer model closely resembles the "SIS" epidemiological model, in which all non-infected individuals are intrinsically equally susceptible to infection [12, 30]. Indeed, we find that the transition points are the same for the two models: both have a directed percolation-class transition at a transmissibility of $\approx$0.295 (see Figure 4(A) and reference [30]).

Thus, in the limiting cases of $g = 0$ and $g = 1$, the host–consumer model is equivalent to the SIR and SIS epidemiological models, while over the range in between, they differ. The key difference is that reoccupying an empty site with a consumer requires prior recolonization by a host, whereas the vulnerability of a R[ecovered] individual to becoming I[nfected] is defined as an intrinsic property of the R[ecovered] type. This changes the role of ecology: both models incorporate space, but the effect of spatial extent is different.

C. Upper Threshold: Malthusian Catastrophe

The upper cutoff in Figure 3 is the value of τ above which the consumer population is unsustainable. Consider the limiting scenario where $g \approx 0$. If hosts do not reproduce into available empty sites, we have an epidemic process. In this case, the minimum τ is also a

maximum. Below $\tau = 0.5$, a consumer injected into a lattice of hosts will produce a consumer strain (which we can think of as an infection) which survives for a finite number of generations and then dies out, leaving the lattice filled with hosts (susceptibles) marred by a small patch of empty sites (recovered individuals). Above the transition point, a single consumer gives rise to an expanding wave of consumers which propagates over the lattice, leaving empty sites in its wake, until it consumes all the hosts in the ecosystem. This constitutes a process of *annular growth* [30]. No finite ecosystem can sustain annular growth indefinitely. If the host growth rate g is made non-zero, then hosts can recolonize sites left empty by the expanding consumer population, opening the possibility of host–consumer coexistence in an ecosystem of dynamically formed and re-formed patches. Figure 1 illustrates an example of this phenomenon.

We can, therefore, interpret the upper cutoff on consumer sustainability as a Malthusian catastrophe due ultimately to the limited amount of available hosts [65]. For the case of a single consumer injected into a lattice otherwise filled with hosts, the cutoff is due to the limited size of the system, a type of outcome often called a *finite-size effect*. This is the key to understanding what happens when multiple types of consumer are present on the same lattice, and in particular the case we study in the next section, where an invasive consumer variety is introduced to an ecosystem where native hosts and consumers have already formed a dynamic patch distribution. The environment experienced by the invasive variety is that formed by the native species, and the "finite size" of the resources available to the invasive variety is not the size of the whole lattice, but that of a local patch [65].

III. TIMESCALE DEPENDENCE OF INVASION SUCCESS

A key question about an ecological system is whether a new variety of organism, having a different genetic character and phenotypic trait values, can successfully invade a native population. One relevant measure is the expected relative growth rate of the number of offspring of a mutant individual within a native population, the relative growth rate of a mutant strain. This rate, known as the *invasion fitness,* is often used to investigate the stability of an evolutionary ecosystem [11, 67, 68]. If the invasion fitness is found to be positive, the native variety is judged to be vulnerable to invasion by the mutant. Conversely, if the invasion fitness is found to be negative, the native variety is deemed to be stable. We

shall see that for this host–consumer ecosystem this method gives qualitatively incorrect predictions for evolutionary dynamics.

If a mutant consumer strain with fixed transmissibility τ_m can successfully invade a population of transmissibility $\tau_0 < \tau_m$, then we expect the time-averaged value of τ seen in the evolving system to be larger than τ_0. To investigate this, we simulate $\tau = 0.45$ mutants entering an ecosystem whose native population has $\tau = 0.33$. Initially, the mutants prosper, but they ultimately fail to invade. As shown in Figure 5, the probability of a $\tau = 0.45$ strain surviving for tens of generations after injection is larger than that of a $\tau = 0.33$ strain. That is, mutants with the higher τ can out-compete the neutral case. However, after ≈ 74 generations, the survival-probability curves cross. Observed over longer timescales, the mutant strain is less successful than the native variety. This key result manifests the distinctive properties of the spatial structure of the model. The underlying reason for this result is that the mutants encounter the resource limitations imposed by the patchy native population. Over short timescales, the mutant strain enjoys the resources available within the local patch, consuming those resources more rapidly than can be sustained once it encounters the limitations of the local patch size. Short-term prosperity is not a guarantee of medium- or long-term success.

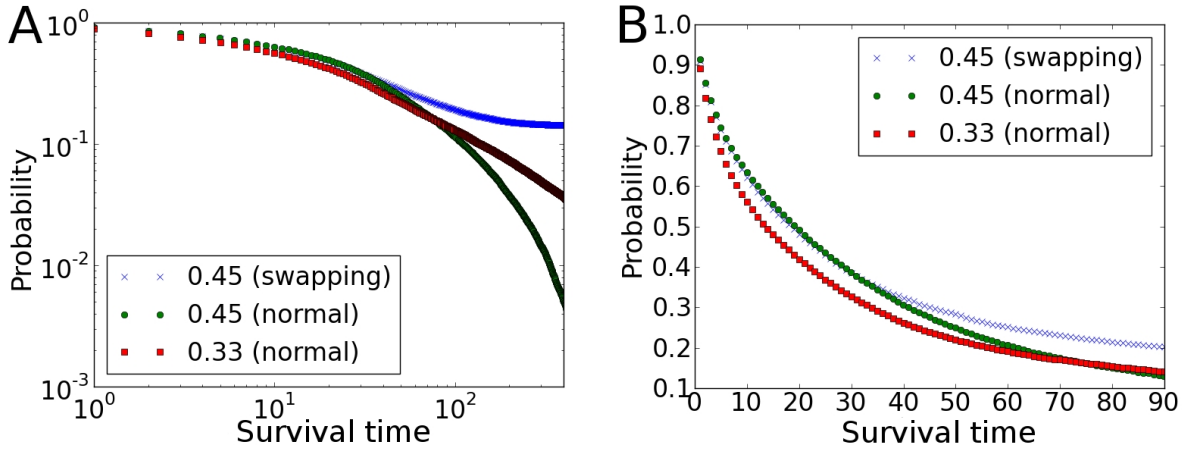

FIG. 5: **(A)** Survival probability as a function of time (logarithmic axes) for three scenarios: injecting mutants with the same transmissibility as the native consumers, injecting mutants with transmissibility $\tau = 0.45$ which is higher than the τ of the native consumers, and injecting $\tau = 0.45$ mutants with the swapping procedure described in §IV enabled. (The "background" was defined by $g = 0.1$, $v = 0.2$, $\tau = 0.33$.) Adding the swapping effect allows voracious mutants to persist long enough that they have a non-zero chance of taking over the ecosystem. **(B)** Detail of the plot showing the crossover point (linear axes).

This is to be contrasted with what happens in a well-mixed ecosystem. In the well-mixed scenario, consumer strains with higher τ successfully invade and displace the native population with a high probability. The invasion success is consistent with the dynamics of a continuously evolving ecosystem. If τ is made an evolvable trait in panmictic systems, the average τ of the population will tend to 1. There is no difference in a well-mixed scenario between short-term and long-term success. This follows from the lack of distinction between local patches and large-scale structure.

Random regular graphs (RRGs) have been used as approximations to incorporate the effects of spatial extent into population models, as they make for more tractable mathematical treatments (including the "moment closure" methods discussed in the next section), although they are typically less realistic than spatial lattices [52]. In an RRG, each node has the same number of neighbors, as they do in a lattice network, but the connections are otherwise random. The network structure is set at the beginning of a simulation and does not change over time. When we simulate our host–consumer ecosystem on an RRG, we find that an invasive consumer strain with higher transmissibility τ can out-compete and overwhelm a native consumer population with lower τ. In one simulation run, using the native and invasive τ values of 0.33 and 0.45 respectively, 2,233 out of 10,000 invasions were successful, whereas on the lattice *no* invasion succeeded using the same parameters. Thus, the RRG does not capture the essential features of the spatial scenario. In particular, our results show that the RRG case is more like the well-mixed case than the spatial lattice, as far as stability against invasion is concerned.

We have found that spatial models evolve τ values which are smaller than the maximum possible, as would be found in panmictic ecosystems. This means that consumer populations do not reproduce at the maximum rate. Whether predators can be "prudent" in their resource consumption has been a contentious issue in evolutionary biology [10]. Because the average τ does not tend to 1, it appears that consumers in the spatial ecosystem exhibit a kind of "prudence". Yet, at any time, an individual consumer is as likely to spawn an offspring with higher τ as it is one with lower τ. (Barring, of course, the boundary cases $\tau = 0$ and $\tau = 1$, beyond which the transmissibility cannot go.) Individual consumers do not judge the host resources available in their vicinity in order to adjust their reproduction rate accordingly. Instead, the apparent "prudence" arises from natural selection over the history of the population, eliminating unsustainable strains through local Malthusian catastrophies

many generations after they arise. The distribution of τ across the population is, at any moment, the product of effects at work during the past, some of which required many generations to play out.

Our investigation builds on earlier work which studied the timescale dependence of fitness indicators in spatial host–consumer ecosystems [44, 45]. In this paper we have augmented the prior work by considering the survival probability to show the effects of varying τ. In addition, we reported the case of a mutant strain invading a background population, clarifying the conceptual and quantitative results of those earlier works, which considered instead scenarios complicated by multiple ongoing mutations.

IV. PAIR APPROXIMATIONS

The inadequacy of mean-field treatments of spatial systems motivates the development of more elaborate mathematical methods. In this section, we review one such methodology, based on augmenting mean-field approximations with successively higher-order correlations, and we test its applicability to our host–consumer spatial model. The numerical variables used in this methodology are probabilities which encode the state of the ecosystem and can change over time. One such variable might be, for example, the probability p_a that an individual chosen at random is an organism of type a. Another might be p_{ab}, the probability that a randomly-chosen *pair* of neighboring individuals will have one member of type a and the other of type b. The change of these quantities over time is usually described by differential equations, for which analysis tools from nonlinear dynamics are available [11, 32, 65, 68–71].

The importance of the joint probabilities p_{ab} is that they reflect correlations which mean-field approximations neglect. To understand the relevance of the joint probabilities p_{ab}, note that if an invasive mutant variety forms a spatial cluster near its point of entry, then the average density of invasive mutants in the ecosystem, p_M, will be low, while the conditional probability that a neighbor of an invasive individual will also be of the invasive type, $q_{M|M} = p_{MM}/p_M$, will be significantly higher. A discrepancy between $q_{a|b}$ and p_a can persist when the ecosystem has settled into a quasi-steady-state behavior, and is then an indicator of spatial pattern formation. Figure 6(A) shows an example, plotting $q_{C|C}$ measured in a host–consumer ecosystem against p_C. The salient point is that in a well-mixed scenario (where

we expect the mean-field approximation to be applicable), the average consumer density p_C and the consumer–consumer pairwise correlation $q_{C|C}$ are essentially equal over time. In the spatial lattice scenario, p_C and $q_{C|C}$ are noticeably different.

Treating the correlations $q_{a|b}$ as not wholly determined by the probabilities p_a is a way of allowing spatial heterogeneity to enter an analytical model. Whether it is a *sufficient* extension in any particular circumstance is not, *a priori,* obvious. Typically, the differential equations for the pair probabilities p_{ab} depend on triplet probabilities p_{abc}, which depend upon quadruplet probabilities and so forth. To make progress, we truncate this hierarchy at some level, a technique known as *moment closure* [58, 67, 69, 72]. Moment closures constitute a series of approximations of increasing intricacy [51, 73]. The simplest moment closure is the mean field approximation; going beyond the mean field to include second-order correlations but neglecting correlations of third and higher order constitutes a *pair approximation.* These approximations destroy information about spatial structure which may be necessary to account for real-world ecological effects [67].

Pair approximations have been used to test for the existence of an *Evolutionary Stable Strategy* (ESS) in a system—that is, a strategy which, when established, cannot be successfully replaced by another [74]. In addition to the limitations of pair approximation for representing patch structure [68], as we saw in the previous section, the question of whether a mutant strain can initially grow is distinct from the question of whether that strain achieves fixation or goes extinct [37, 43, 75–79]. The former is a question about short-term behavior, and the latter concerns effects apparent at longer timescales. This distinction is often lost or obscured in analytical treatments. The reason is that one typically tests whether a new type can invade by linearizing the corresponding differential equations at a point where its density is negligible. However, this only reveals the initial growth rate (see the fixed-point eigenvalue analysis in [11, 67, 68]).

In our model, we can directly test the efficacy pair approximations in a completely general way. The key idea is to transplant individuals in such a way that the variables used in the moment-closure analytical treatment remain unchanged. At each timestep, we look through the ecosystem for isolated consumers, that is, for individual consumers surrounded only by hosts and empty sites. We can exchange these individuals without affecting the pairwise correlations. For example, if we find a native-type consumer adjacent to three hosts and one empty site, we can swap it with an invasive-type consumer also adjacent to three hosts and

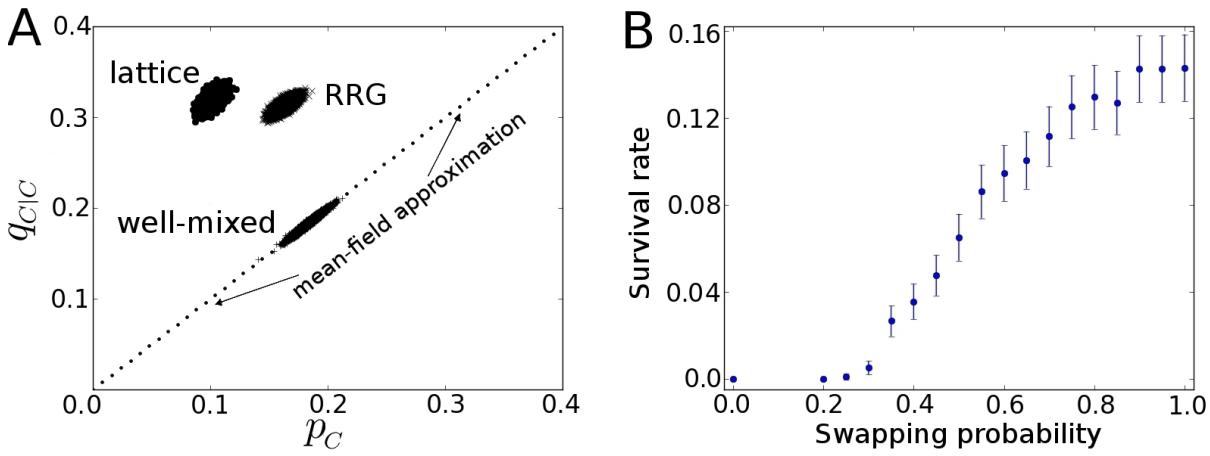

FIG. 6: **(A)** Pairwise conditional probability $q_{C|C}$ plotted against the average density of consumers, p_C, for three variations on the host–consumer model: a well-mixed case in which mean-field theory is applicable, a random regular graph (in which each site has exactly four neighbors) and a 2D square lattice. The dotted line, $p_C = q_{C|C}$, indicates the mean-field approximation. 10^4 timesteps were computed for each case. The well-mixed case is simulated by dynamically rewiring sites at each time step, precluding the generation of spatial heterogeneity; consequently, the pairwise correlation $q_{C|C}$ is essentially p_C ($R^2 = 0.953$). The random regular graph (RRG) with random but static connections does develop spatial heterogeneity so that $q_{C|C}$ is not the same as p_C ($R^2 = 0.581$). However, the discrepancy is significantly stronger in the lattice case ($R^2 = 0.304$). **(B)** Success rate of invasive mutant strains as a function of swapping probability. Voracious mutant strains with $\tau = 0.45$ are introduced into a lattice ecosystem defined by a host growth rate of $g = 0.1$, a consumer death rate $v = 0.2$ (the same for both consumer varieties), and a native consumer transmissibility of $\tau = 0.33$. Average success rates are found by simulating 2000 invasions per value of the swapping probability parameter; error bars indicate 95%-confidence intervals. Increasing the fraction of possible swaps which are actually performed makes the voracious invasive strain more likely to take over the ecosystem.

one empty site. We can also exchange isolated pairs of consumers in the same way. The variables used in the moment-closure treatment remain the same. Were the moment-closure treatment valid, we would expect to see the dynamics remain unchanged.

When we perform the simulation, however, swapping *does* affect the dynamics, and quite strongly. With this type of swapping in effect, mutants with $\tau = 0.45$ can invade a native population with $\tau = 0.33$, doing so 1,425 times out of 10,000 injections in one simulation run. Without swapping, the number of successful invasions is *zero.*

Swapping creates a new ecosystem model whose moment-closure treatment is the same as of the original. The behavior of invasive strains is different, because transplanting organisms allows invasive varieties to evade localized Malthusian catastrophies. Swapping opens the ecosystem up to invasive strains, since, in essence, it removes individuals from the "scene of

the crimes" committed by their ancestors.

This type of swapping is, to our knowledge, a new test of moment-closure validity. Randomized exchanges have been incorporated into computational ecology simulations for different purposes. For example, research on dispersal rates in an island model shuffled individuals in such a way that the population size of each island was held constant [80].

If, instead of performing every permissible swap, we transplant organisms with some probability between 0 and 1, we can interpolate between the limit of no swapping, where invasions always fail, and the case where pair approximation is most applicable and invasions succeed significantly often. The results are shown in Figure 6(B) and indicate that the impact of swapping becomes detectable at a probability of ≈ 0.25 and effectively saturates at a probability of ≈ 0.9.

It is instructive to compare the spatial lattice ecosystem with the host–consumer model defined on a random regular graph (RRG). Consider, first, the pairwise correlation $q_{C|C}$. On an RRG, the underlying network topology provides enough of a sense of locality that p_C and $q_{C|C}$ are less strongly correlated than in the well-mixed case. See Figure 6(A). We can also implement swapping on the RRG, where invasions can succeed without it; as expected, swapping does not affect the success rate on the RRG. (With 10,000 simulated invasions for each case, the 95%-confidence interval for the difference in success rates between full swapping and none is 0.004 ± 0.01.)

Other numerical investigations have also suggested the limited utility of pair approximations [52, 65, 69, 70, 74, 81, 82]. One reason cited is the problem of phase transitions. Moment closures fail when a system is near a transition such as the directed percolation and dynamic percolation ones described above [51]. However, the timescale dependence of reproductive fitness, which stems from non-equilibrium pattern formation, indicates that these problems are generic, occurring even away from the phase transition.

Our analysis implies that pair approximations are inadequate for analysis of systems with spatial inhomogeneity. One might ask whether including triple and other higher-order corrections could help. However, it is known that this series approximation is non-analytic at phase transitions [51]. Non-equilibrium pattern formation will necessarily also be poorly described, at least until the order of expansion reaches the characteristic number of elements in a patch. Given the algebraic intricacy of higher-order corrections to pair approximations [52, 65, 81], it is useful to know in advance whether such elaborations have a chance at

success. If approximation techniques based on successively refining mean-field treatments are blind to important phenomena, then we should build our analytical work on a different conceptual foundation.

V. CONCLUSIONS

Understanding the effects of spatial extent is a vital part of evolutionary ecology. Spatial extent changes the quantitative and qualitative characteristics of a model's evolutionary behavior, compared to well-mixed models. The short-term success rate of novel genetic varieties is not indicative of their long-term chance of success relative to the prevalent type. Standard stability criteria fail to reflect the actual stability achieved over time. We must instead consider extended timescales because they are determined by spatial patterns, whose ongoing formation is an intrinsic part of nonequilibrium evolutionary dynamics. Our analysis shows that there are dramatic differences between spatial models and mean-field models, which simplify away heterogenity through mixing populations, averaging over variations or mandating a globally connected patch structure. We have further shown that transplanting organisms dramatically changes the dynamics of spatial systems, even when we preserve local correlations as would be considered in a pair approximation treatment. Our results prove that any model striving to capture the effects of heterogenity that does not change its behavior with organism transplanting cannot fully capture the dynamics of spatial evolution.

In our host–consumer models, each individual either survives or it does not, and any individual can produce zero or more offspring; that is to say, an "individual fitness" (in the terminology of [83]) is a well-defined concept. To find *expected* individual fitness, or *average* individual fitness, we must define a set of individual organisms over which to take an average, which is the very concept we have established to be problematic. Consequently, derived notions of fitness, which depend on comparisons between such averages [83], become elusive, context-dependent quantities. This dependence is both temporal and spatial: Average relative fitness in one generation is not necessarily a good measure of the long-term success of a strain in one, or a combination of, the broad variety of dynamically-generated niches. This problem is not the same as the traditional concept of variation of fitness across a static set of niches, because the niche dynamics ensures that evolutionary outcomes are not reflected in any reasonable definition of the average.

One might be inclined to call the behavior of voracious invasive consumers "frequency-dependent fitness" [4, 5], as the invasive strain is successful initally when rare but fails when it becomes more common. The term "frequency-dependent fitness" is, however, a misnomer in this context. The organism type is rare and successful when it is newly introduced, but as it declines to extinction it becomes rare and unsuccessful. *Frequency,* being defined by an average over the whole ecosystem, is only a proper variable to use for describing the ecosystem in the panmictic case. One might refine the concept of global frequency to the notion of *local* frequencies, which can vary from place to place across the ecosystem. Here, though, even the extension to local frequencies fails to capture the evolutionary dynamics. Including local frequencies implies incorporating local correlations or local environmental characteristics. However, the breakdown of moment-closure techniques implies that defining fitness as a function of organism type together with average local environment [84] will, in many circumstances, not go far enough.

We find that we cannot assign a meaningful invasion fitness value to an invasive variety of organism. Consequently, we cannot assign a fitness value to a genetic characteristic which defines such an organism type. That is, defining a trait or allele fitness is likewise invalid. To restate the host–consumer model in genetic terms, we could say that an individual consumer can have one of two possible alleles of the "transmissibility gene", one coding for $\tau = 0.33$ and the other for $\tau = 0.45$. A mean-field treatment would then involve specifying the fraction of the population which carries the $\tau = 0.33$ allele versus the fraction which carries the $\tau = 0.45$ variant. Such a description, however, is too oversimplified to let us predict what will happen in the ecosystem. All of the issues we identified imply that the evolutionary dynamics cannot be characterized using the allele frequencies at a particular time.

If we can no longer summarize the genetic character of a population by an allele frequency—or a set of allele frequencies for well-defined local subpopulations—then computing the fitness of a genotype from its generation-to-generation change in frequency is a fruitless task. In a world which exhibits nonequilibrium spatial pattern formation, allele frequencies are the wrong handle for understanding the dynamics of natural selection. Formally, the conventional assumption that the allele frequencies are a sufficient set of variables to describe evolutionary dynamics is incorrect. The spatial structure itself is a necessary part of the system description at a particular time in order to determine the subsequent generation outcomes, even in an average sense.

The timescale-dependence issues which arise in spatial host–consumer ecosystems exist in a wider context. Multiple examples indicate that initial success and eventual fixation are only two extremes of a continuum which must be understood in its entirety to grasp the stability of a system. In the study of genetic drift, it has been found that neutral mutations can fixate and beneficial mutations fail to fixate due to stochasticity [4]. Likewise, in the study of clonal interference [78], one beneficial mutation can out-compete another and prevent its fixation. Furthermore, classical genetics makes much use of the Price Equation for studying the change in a population's genetic composition over time [6, 7], and it is well known that analytic models built using the Price Equation lack "dynamic sufficiency". That is, the equation requires more information about the current generation than it produces about the next [5, 6, 85], and so predictions for many-generation phenomena must be made carefully, if they can be made at all. Modeling approaches which are fundamentally grounded in the Price Equation, such as "neighbor-modulated" fitness calculations [7, 19, 41, 86] and their "multilevel" counterparts [7, 86, 87], are not likely to work well here, as the analyses in question consider only the short-timescale regime. In addition, those particular analyses which address host–consumer-like dynamics either rely on moment closures [41] or they assume a fixed, complete connection topology of local populations which are internally well-mixed [19, 87]. These simplified population structures are quite unlike the dynamical patch formation seen in the host–consumer lattice model. (Wild and Taylor [88] demonstrate an equivalence between stability criteria defined via immediate gains, or "reproductive fitness", and criteria defined using fixation probability; however, their proofs are explicitly formulated for the case of a well-mixed population of constant size, neither assumption being applicable here.)

Our results also have significance in the context of adaptive-network research. The field of adaptive networks studies scenarios in which the dynamics *of* a network and the dynamics *on* that network can occur at comparable timescales and feed back on one another. When building such a model, one chooses a rewiring rule which specifies how the states of the network nodes affect the changes of the link structure which connects them. As discussed earlier, in a spatial host–consumer system, connections can form between resource patches when hosts reproduce into intervening empty sites, whereas in adaptive-network studies of SIR models, new connections are made without regard to spatial proximity. The difference we have seen between lattice behavior on one hand and RRG or swapping-enabled behavior

on the other emphasizes the need to study the effect of spatial proximity on link rewiring. While the structure-erasing nature of unconstrained rewiring among susceptible hosts has been acknowledged [61, 62], new rewiring rules which reflect spatial and community structure have yet to be systematically investigated. "Myopic" rewiring rules, such as restricting the set of eligible new partners to the neighbors of a node's current partners, have on occasion been considered, but in contexts other than epidemiology, like evolutionary game theory [89, 90], making the endeavour of exploring such rules in epidemic models all the more worth pursuing.

Our analysis of transplanting organisms can be considered parallel to real world concerns and manifest effects of invasive species [37, 42]. These are among the well-established examples of situations in which spatial extent influences evolutionary dynamics [79, 91–94]. Identifying specific implications of the issues explored in this paper for particular biological systems [39, 43, 48, 49, 79, 93, 95] requires field and laboratory work.

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