Sources and Sinks: A Stochastic Model of Evolution in Heterogeneous Environments

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We study evolution driven by spatial heterogeneity in a stochastic model of source-sink ecologies. A sink is a habitat where mortality exceeds reproduction so that a local population persists only due to immigration from a source. Immigrants can, however, adapt to conditions in the sink by mutation. To characterize the adaptation rate, we derive expressions for the first arrival time of adapted mutants. The joint effects of migration, mutation, birth, and death result in two distinct parameter regimes. These results may pertain to the rapid evolution of drug-resistant pathogens and insects.

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Biological evolution and ecology are intimately linked, because the reproductive success or ''fitness'' of an organism depends crucially on its ecosystem. The biotic and abiotic factors defining an ecosystem often have complex time- and space-dependent dynamics [1]. Yet, most models of evolution describe homogeneous, fixed-size populations subjected to a constant selection pressure [2]. Even though such minimal descriptions have led to invaluable insights into some of the major evolutionary forces [2], their scope is clearly limited. An important challenge in evolutionary biology is therefore to understand the interaction between ecology and evolution.

In this Letter, we study how spatial heterogeneities can drive evolution in ecologies displaying so-called source-sink dynamics (SSD) [3–6]. A species' habitat is called a *sink* if the local mortality exceeds the local reproduction so that a population can persist only due to continuous immigration from a *source* habitat, where reproduction exceeds mortality. Sinks often occur at the border of a species' range: If an environmental variable such as temperature or humidity varies in space and limits a species' range, the conditions at the border are often poor. SSD results in a sustained presence of poorly adapted immigrants in the sink; this suggests that it could assist adaptation to the sink conditions. Immigrants that, due to mutations, acquire the ability to reproduce efficiently in the sink have an opportunity to establish a population there. Such a mutant can be successful even if it does not have a competitive advantage in its original habitat (the source); it is sufficient if the mutation allows it to colonize the sink. Importantly, this adaptive process driven by the opportunity to establish a new niche is qualitatively different from the conventional notion of a population climbing a fitness gradient [7,8].

Evolution in source-sink systems is not merely of theoretical interest. For instance, SSD may accelerate the evolution of drug resistance in bacteria [9]. In humans or livestock treated with antibiotics, drug levels can vary between different organs, creating sources and sinks within a host [10]. Also, SSD can emerge when bacteria migrate between treated and untreated individuals [9]. Likewise, the migration of fruit flies between plantations using different (amounts of) insecticides could assist the emergence of insecticide resistance [11,12]. The evolution of virulence has been associated with SSD as well [13–15].

Here we analyze a minimal stochastic model of adaptation driven by SSD. In particular, we study how the rate of adaptation depends on parameters such as migration and mutation rates. Earlier studies examined source-sink systems from various perspectives. Although the models proposed differ in various respects, they fall into three classes. First, several models are based on deterministic equations [16–21]. Such models are convenient but ignore the intrinsic stochasticity of the demographic processes, which, as we will see below, can be important. Second, some studies employ the formalism of quantitative genetics [22,23], which describes the response of a quantitative trait to selection in a population characterized by a distribution of phenotypes. This line of attack is appropriate only for multilocus traits and is again deterministic. Third, individual-based simulations have been used [24]. Unfortunately, such studies are necessarily limited to a narrow set of parameters. In contrast, our model is fully stochastic and yields analytical results that are valid for a wide range of parameter values.

We consider a haploid population in an environment consisting of two ''patches'' [Fig. 1(a)]. Individuals migrate between the patches at a rate ν and die at a rate δ. Each organism has one of two possible genotypes, called ''wild type'' (W) and ''mutant'' (M). Mutations turn a wild type into a mutant at a rate μ_f; the reverse occurs at a rate μ_b. The reproduction rate of genotype $g \in \{W, M\}$ in patch i obeys the logistic form $\gamma_{ig}(N_i) \equiv \max\{r_{ig}(1 - N_i/K), 0\}$, where N_i is the population size in patch i. This keeps N_i finite and introduces competition between organisms sharing a patch. K is the carrying capacity, and r_{ig} is the maximal reproduction rate. The wild type can reproduce in patch 1 only ($r_{2W} = 0$); this introduces SSD. By contrast, mutants can reproduce in *both* patches. We initially choose $r_{1W} = r_{1M} \equiv r$, so that both types are equally

"fit" in patch 1. Later we will relax this to consider the effect of a possible fitness cost conferred by the mutation.

We make a few biologically motivated assumptions. First, we limit our analysis to large populations ($K \gg 1$). Second, we assume that mutation rates are low ($\mu_b, \mu_f \ll \nu, \delta$). Third, we assume that $\nu < \delta$; i.e., organisms are unlikely to migrate multiple times within their lifetime.

The adaptation process consists of two parts. First, a mutant has to appear in the sink; next, this mutant has to establish a population. The latter process has been treated by (stochastic) models of colony growth [18,19,25]. We therefore focus on the question of how long it takes before the first mutant arrives in patch 2 starting from a wild-type population in patch 1.

Figure 1(b) shows the two pathways that can generate a mutant in patch 2. In the upper path (denoted by ↱), first a mutation occurs in patch 1 and later a mutant migrates to patch 2. In the lower path (⇁), a wild type first migrates to patch 2 and then mutates. *A priori* it is unclear which path is more likely. Below, we derive the first arrival time (FAT) distributions for both paths.

We start with path ↱. Let n_{ig} be the number of organisms with genotype g in patch i. Since $K \gg 1$, $N_1 \equiv n_{1W} + n_{1M}$ is approximately constant; it fluctuates around the value $N \equiv [1 - (\delta + \nu)/r]K$ for which the reproduction rate equals the rate at which organisms disappear from the first patch $[\gamma_{1M}(N) = \delta + \nu]$ [26]. Below, we assume that $N_1 = N$, which allows us to write a master equation for the probability $P_{↱}(n, t)$ that at time t no mutant has yet migrated to patch 2 and n_{1M} has value n:

$$\partial_t P_{↱}(n,t) = w^-(n+1)P_{↱}(n+1,t) + w^+(n-1)P_{↱}(n-1,t) - [w^-(n) + w^+(n) + u(n)]P_{↱}(n,t), \quad (1)$$

with $w^- \equiv (\delta + \mu_b)n$, $w^+(n) \equiv \gamma_{1M}(N)n + \mu_f(N - n)$, $u(n) = \nu n$, and initial condition $P_{↱}(n, 0) = \delta_{n,0}$ ($\delta_{n,m}$ is the Kronecker delta function).

We rewrite Eq. (1) in terms of the generating function $G_{↱}(z, t) \equiv \sum_n z^n P_{↱}(n, t)$ and solve the resulting partial differential equation. The probability that at time t no mutant has migrated yet, $S_{↱}(t) = G_{↱}(1, t)$, follows as

$$S_{↱}(t) = \left[\frac{c_{↱}e^{b_{↱}t}}{c_{↱}\cosh(c_{↱}t) + b_{↱}\sinh(c_{↱}t)}\right]^{a_{↱}}, \quad (2)$$

with $a_{↱} \equiv \mu_f N/(\delta + \nu - \mu_f)$, $b_{↱} \equiv (\mu_b + \mu_f)/2$, and $c_{↱} \equiv [b_{↱}^2 + \nu(\delta + \nu - \mu_f)]^{1/2}$. Now the desired FAT probability density $F_{↱}(t) \equiv -dS_{↱}(t)/dt$ can be expressed as

$$F_{↱}(t) = \nu\langle n_{1M}(t)\rangle S_{↱}(t), \quad (3)$$

where $\langle n_{1M}(t)\rangle$ is the mean value of n_{1M} at time t given that no mutant has migrated yet; it obeys

$$\langle n_{1M}(t)\rangle = \frac{\mu_f N \tanh(c_{↱}t)}{c_{↱} + b_{↱}\tanh(c_{↱}t)}. \quad (4)$$

These results show that path ↱ is governed by two time scales. First, $\langle n_{1M}(t)\rangle$ builds up in a time scale $\tau_{↱} = 1/2c_{↱}$. Second, at large times $F_{↱}(t)$ decays with time scale $\tau'_{↱} = [a_{↱}(c_{↱} - b_{↱})]^{-1}$ due to the time dependence of $S_{↱}(t)$; this time scale reflects the total migration rate after $\langle n_{1M}\rangle$ has equilibrated. We define $\kappa_{↱} \equiv \tau_{↱}/\tau'_{↱}$.

We note that $b_{↱} \ll c_{↱}$; thus $\kappa_{↱} \approx \mu_f N/[2(\delta + \nu)]$, and the mean first arrival time (MFAT) $T_{↱}$ is given by

$$c_{↱}T_{↱} \approx (\sqrt{\pi}/2)\Gamma(\kappa_{↱})/\Gamma(\kappa_{↱} + 1/2), \quad (5)$$

where $\Gamma(x)$ is the Gamma function. Interestingly, only two lumped parameters remain: $c_{↱}$ and $\kappa_{↱}$. If $\kappa_{↱} \ll 1$ (i.e., $\mu_f N \ll \delta + \nu$), the process is limited by the generation of mutants, whereas if $\kappa_{↱} \gg 1$ (i.e., $\mu_f N \gg \delta + \nu$), it is migration-limited. By expanding Eq. (5) and using Stirling's approximation, we obtain in these limits

$$T_{↱} \approx \begin{cases} \dfrac{1}{2c_{↱}\kappa_{↱}} \approx \dfrac{\sqrt{\delta/\nu + 1}}{\mu_f N} & (\text{if } \mu_f N \ll \delta + \nu), \\ \dfrac{\sqrt{\pi/\kappa_{↱}}}{2c_{↱}} \approx \sqrt{\dfrac{\pi/2\nu}{\mu_f N}} & (\text{if } \mu_f N \gg \delta + \nu). \end{cases} \quad (6)$$

The plot in Fig. 2(a) clearly reveals these two regimes.

We now turn to the lower path, ⇁. As we expect the number of mutants in patch 1 to be small, we assume that $n_{1W} \approx N$. A master equation can then be written for the probability $P_{⇁}(n, t)$ that at time t no mutation has yet occurred in patch 2 and $n_{2W} = n$. It is identical to Eq. (1) but with $w^-(n) \equiv (\delta + \nu)n$, $w^+(n) \equiv \nu N$, and $u(n) \equiv \mu_f n$. The probability $S_{⇁}(t)$ that no mutation occurs

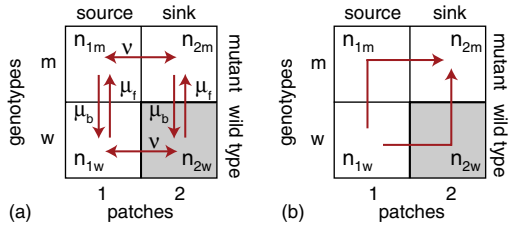

FIG. 1 (color online). Source-sink model. We consider 2 patches and 2 genotypes. The wild type can reproduce only in patch 1, while the mutant can grow in both patches. (a) Organisms mutate and migrate (indicated by arrows) and die at rate δ. (b) A wild-type population in patch 1 will in time give rise to a mutant in patch 2. Arrows indicate the two competing pathways.

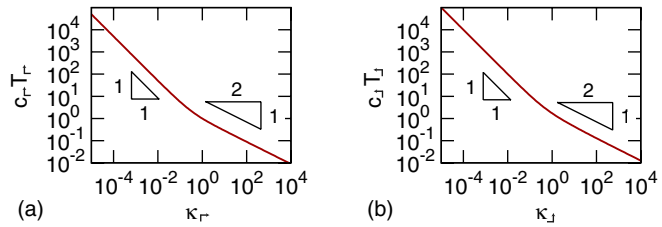

FIG. 2 (color online). MFAT vs parameters, for (a) path ↱ and (b) path ⇁. In each case the MFAT depends on only two lumped parameters: c_i and κ_i. Both plots have two regimes.

before time t and the FAT distribution $F_{\nearrow}(t)$ can now be obtained by a similar derivation as for the $\uparrow$ case.

Again the process has two time scales: $\tau_{\nearrow} = 1/c_{\nearrow}$, with $c_{\nearrow} \equiv \delta + \nu + \mu_f$, and $\tau'_{\nearrow} = c_{\nearrow}/(\mu_f N \nu)$. We define $\kappa_{\nearrow} \equiv \tau_{\nearrow}/\tau'_{\nearrow}$; the MFAT of path $\nearrow$, called $T_{\nearrow}$, then reads

$$c_{\nearrow} T_{\nearrow} = (e/\kappa_{\nearrow})^{\kappa_{\nearrow}} \gamma(\kappa_{\nearrow}, \kappa_{\nearrow}), \tag{7}$$

where $\gamma(x, y)$ is the lower incomplete Gamma function. Figure 2(b) is a plot of Eq. (7); it is again characterized by two regimes. Indeed, in the limits $\kappa_{\nearrow} \ll 1$ and $\kappa_{\nearrow} \gg 1$,

$$T_{\nearrow} \approx \begin{cases} \dfrac{1}{c_{\nearrow}\kappa_{\nearrow}} \approx \dfrac{\delta/\nu + 1}{\mu_f N} & (\mu_f N \ll (\delta+\nu)^2/\nu), \\ \dfrac{\sqrt{\pi/2\kappa_{\nearrow}}}{c_{\nearrow}} \approx \sqrt{\dfrac{\pi/2\nu}{\mu_f N}} & (\mu_f N \gg (\delta+\nu)^2/\nu). \end{cases} \tag{8}$$

We are now in the position to calculate the full FAT distribution $F(t)$ by taking into account both paths $\uparrow$ and $\nearrow$. Since both paths are nearly independent, the probability that neither path has completed at time t is $S(t) \equiv S_{\uparrow}(t) S_{\nearrow}(t)$, from which $F(t)$ and the combined MFAT T follow. However, comparing Eq. (6) to Eq. (8) we recognize that $T_{\uparrow} < T_{\nearrow}$ unless $\kappa_{\nearrow} \gg 1$, in which case $T_{\uparrow} \approx T_{\nearrow}$. Therefore we conclude that path $\uparrow$ is dominant, and we should expect $F(t) \approx F_{\uparrow}(t)$ and $T \approx T_{\uparrow}$.

We tested these results by using kinetic Monte Carlo simulations. Figure 3(a) shows T as a function of K and μ_f, and Fig. 3(b) plots T versus ν for various δ. The curves are theoretical predictions calculated by numerical integration of $S(t)$. Figure 3(c) shows all data of Figs. 3(a) and 3(b) in a single scaling plot. Since $T \approx T_{\uparrow}$, Eq. (5) predicts that all points should collapse on one curve if $c_{\uparrow} T$ is plotted against $\kappa_{\uparrow}$. This is indeed the case.

So far we have assumed that the wild type cannot reproduce at all in patch 2. One may expect that path $\nearrow$ could become more relevant if it does, albeit at a reduced rate $r_{2W} < r$. We now derive results for this extended model. In the derivations for path $\uparrow$ the rate r_{2W} plays no role, but the results for path $\nearrow$ do change. The dynamics of n_{2W} can be approximated by the rate equation

$$\frac{dn_{2W}(t)}{dt} = \nu N + r_{2W}(1 - n_{2W}/K) n_{2W} - (\delta + \nu) n_{2W}.$$

With initial condition $n_{2W}(0) = 0$ it is solved by

$$n_{2W}(t) = \frac{\nu N \tanh(c_{\nearrow} t)}{c_{\nearrow} + b_{\nearrow} \tanh(c_{\nearrow} t)}, \tag{9}$$

with $b_{\nearrow} \equiv (\delta + \nu - r_{2W})/2$ and $c_{\nearrow} \equiv (b_{\nearrow}^2 + \nu r_{2W} N/K)^{1/2}$. The expression for $S_{\nearrow}(t)$ has the same form as Eq. (2), but with $a_{\nearrow} \equiv \mu_f K/r_{2W}$, and we obtain

$$F_{\nearrow}(t) = \mu_f n_{2W}(t) S_{\nearrow}(t). \tag{10}$$

Again we find two time scales: $\tau_{\nearrow} = 1/2c_{\nearrow}$ and $\tau'_{\nearrow} = [a_{\nearrow}(c_{\nearrow} - b_{\nearrow})]^{-1}$. If $\tau_{\nearrow}/\tau'_{\nearrow} \ll 1$ (i.e., if $\mu_f K \ll r_{2W}$ or $c_{\nearrow} \approx b_{\uparrow}$), the first time scale can be ignored and $T_{\nearrow} \approx \tau_{\nearrow}$.

In Fig. 4, we test this result with simulations. Evidently, as long as $r_{2W} \ll \delta + \nu$, the MFAT is insensitive to changes in r_{2W}. Only when r_{2W} approaches $\delta + \nu$ does $T_{\nearrow}$ decrease rapidly. Indeed, if $r_{2W} = \delta + \nu$, we obtain $T_{\uparrow} \approx T_{\nearrow}$. We therefore conclude that in source-sink systems, where $r_{2W} < \delta + \nu$ (i.e., to the left of the vertical line in Fig. 4), a nonzero r_{2W} can result in at most a twofold increase in the rate of adaptation.

For $r_{2W} > \delta + \nu$, although the FAT of a mutant in patch 2 is much reduced (see the red line to the right of the vertical line in Fig. 4), it is more difficult for the mutant to conquer patch 2 because it has to compete with the wild type. To demonstrate this, Fig. 4 also shows the mean waiting time before $n_{2M} = 500$, obtained from simulations. Clearly, as $r_{2W} \to r$ the competition dramatically slows down the growth of the mutant population.

Finally, we extend the model to include a fitness cost s of adaptation; i.e., we consider $r_{1M} = (1 - s) r_{1W}$. This means that, in Eq. (1), $\gamma_{1M}(N) = (\delta + \nu)(1 - s)$. $S_{\uparrow}$ and $F_{\uparrow}$ are still given by Eqs. (2)–(4), but with modified constants $a_{\uparrow} \equiv \mu_f N/[(\delta + \nu)(1 - s) - \mu_f]$, $b_{\uparrow} \equiv [\mu_b + \mu_f + s(\delta + \nu)]/2$, and $c_{\uparrow} \equiv [b_{\uparrow}^2 + \nu(\delta + \nu)(1 - s) - \nu\mu_f]^{1/2}$. It follows that s becomes important only when $s \gtrsim \sqrt{\nu/\delta}$ (given that $\mu_b, \mu_f \ll \nu \lesssim \delta$). For example, even at a low migration rate $\nu/\delta = 10^{-2}$ (that is, 99% of the organisms

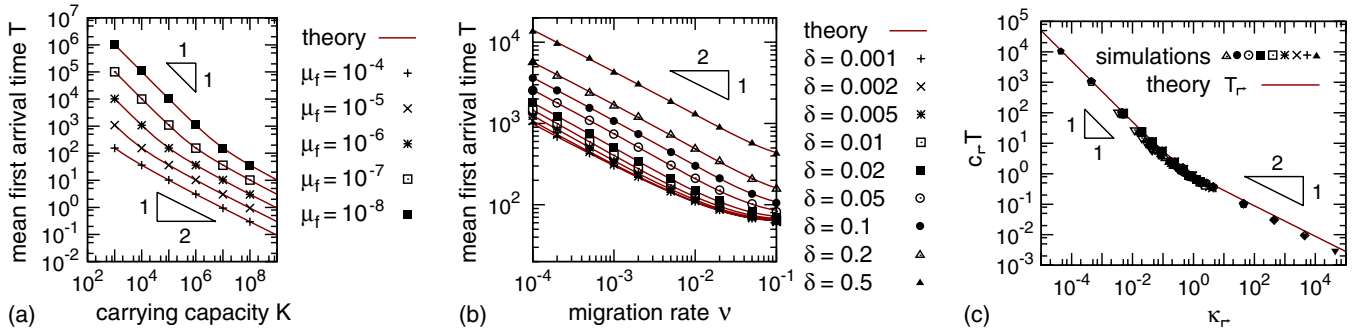

FIG. 3 (color online). MFAT T vs parameters. Unless specified, $r = 1$, $\delta = 10^{-1}$, $\nu = 10^{-3}$, $\mu_b = 10^{-4}$, $\mu_f = 10^{-7}$, and $K = 10^5$. Data points are averages over 10^4 simulations; lines are theoretical predictions. (a) T vs carrying capacity, for various mutation rates. (b) T vs migration rate, for various death rates. (c) All data points from (a) and (b) collapse on a single curve after rescaling. The plot shows two regimes, corresponding to mutation- or migration-limited dynamics.

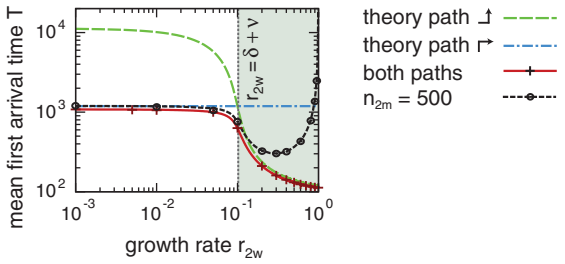

FIG. 4 (color). T vs reproduction rate of wild type in the sink, r_{2W}. As long as $r_{2W} < \delta + \nu$, T is insensitive to r_{2W} because path ↱ is dominant. When $r_{2W} \approx \delta + \nu$, $T_{↱} \approx T_{↳}$ and the process speeds up about twofold. If $r_{2W} > \delta + \nu$, patch 2 is no longer a sink. Also shown is the mean time before $n_{2M} = 500$. Clearly, the growth of the mutant colony slows down dramatically as r_{2W} approaches r. Parameters used are $r = 1$, $\delta = 10^{-1}$, $\nu = 10^{-3}$, $K = 10^5$, $\mu_f = 10^{-7}$, and $\mu_b = 10^{-4}$.

never migrate in their lifetime), the fitness cost is noticeable only if $s \gtrsim 0.1$. In population genetics, this is considered a very large fitness pressure [2]. In conclusion, the adaptation is not slowed down by a fitness cost unless the cost is very large. This apparently surprising result may be understood by noting that the mutant is initially very rare in the source so that a weak selection pressure is overwhelmed by the demographic noise [27]. This result underscores the importance of stochasticity in the process.

In summary, we formulated a stochastic model for adaptation in source-sink ecologies. In contrast with most traditional models of evolution, in which adaptation results from competition within a well-stirred population, here adaptation is driven by spatial heterogeneity. To characterize the speed of adaptation, we derived analytical results for the arrival time of the first adapted mutant in the sink. Two qualitatively distinct regimes are found, in which the system is either mutation-limited ($\mu_f N \ll \delta + \nu$) or migration-limited ($\mu_f N \gg \delta + \nu$). In the latter regime the mean FAT does not scale as $(\mu_f N)^{-1}$, as one might naively expect, but as $(\mu_f N)^{-1/2}$. Because real beneficial mutation rates and population sizes vary considerably (mutation rates in the range 10^{-5}–10^{-10} per generation and population sizes 10^4–10^{10} are reasonable), both regimes can be relevant [12]. Furthermore, the results demonstrate that the first adapted mutant found in the sink usually originates as a neutral mutation in the source which by chance migrates to the sink (the so-called "Dykhuizen-Hartl effect" [28,29]). Mutations arising in the sink contribute only if the system is migration-limited ($\kappa_{↳} \gg 1$) or if $r_{2W} \approx \delta + \nu$ (when patch 2 can hardly be called a sink). Strikingly, these results hold even if the mutation is mildly deleterious in the source habitat.

Many variations on the current model can be envisioned. For instance, we assumed that the reproduction rate in patch 2 depended on the genotype while the death rate was assumed constant. Yet, in reality both rates could vary in space. Also, the model can be extended to include more than two patches, which would presumably allow for a stepwise adaptation to an environmental gradient. In future work such variations and extensions could be explored within the formalism presented here.

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