Population structure can reduce clonal interference when sexual reproduction and dispersal are synchronized

Qihan Liu[1] and Daniel B. Weissman[1]

[1]**Dept. of Physics, Emory University, Atlanta, GA**

ABSTRACT

In populations with limited recombination, clonal interference among beneficial mutations limits the maximum rate of adaptation. Spatial structure slows the spread of beneficial alleles; in purely asexual populations, this increases the amount of clonal interference. Beyond this extreme case, however, it is unclear how spatial structure and recombination interact to determine the amount of clonal interference. This interaction is particularly interesting because dispersal and recombination are often at least partially synchronized in natural populations, both at the individual and population level, as when plants switch from vegetative growth to sexual reproduction or stress responses increase both motility and recombination in microbes. We simulate island models of populations evolving on a smooth fitness landscape and find that synchronized dispersal and sexual reproduction allow them to adapt *faster* than matched well-mixed populations. This is because the spatial structure preserves genetic diversity, while the synchronization increases the chance that recombination events occur between diverged individuals from different demes, i.e., the pairings where negative linkage disequilibrium can most effectively be reduced.

Keywords: population structure, clonal interference, synchrony, facultative sex

INTRODUCTION

On smooth fitness landscapes, adaptation is driven by the fixation of beneficial mutations. When beneficial mutations are rare, they can fix independently from each other in sequential selective sweeps. But if the beneficial mutation supply is large, multiple beneficial mutations will be simultaneously polymorphic in the population, and may compete with each other for fixation. This "clonal interference" effectively puts an upper limit on the rate of adaptation, particularly when recombination is limited [Muller, 1932, Gerrish and Lenski, 1998, Desai and Fisher, 2007, Neher et al., 2010, Weissman and Barton, 2012]. Spatial structure increases the time it takes for a selective sweep, and therefore increases the probability that multiple beneficial mutations will coexist and interfere. In asexual populations, strong spatial structure can drastically reduce the rate of adaptation [Martens and Hallatschek, 2011]. On rugged fitness landscapes, in contrast, populations must find the best combinations of mutations to adapt, and these combinations may not involve the most individually beneficial mutations. It has long been suggested that spatial structure may facilitate adaptation in this case [Wright, 1932, Kryazhimskiy et al., 2012, Nahum et al., 2015, Van Cleve and Weissman, 2015, Bitbol and Schwab, 2014, Covert III and Wilke, 2014, Cooper and Kerr, 2016, Crona, 2018], although it is controversial whether it actually does so in nature [Coyne et al., 1997].

To a certain extent, these two opposing effects of space on adaptation on smooth and rugged landscapes are caused by the same mechanism: spacial structure impedes competition and thus maintains genetic diversity. When an asexual population climbs up a smooth fitness peak, it is always advantageous to maximize the reproduction of the fittest genotype currently present in the population; thus, spatial structure necessarily increases clonal interference and slows down adaptation [Martens and Hallatschek, 2011, Kryazhimskiy et al., 2012, Nahum et al., 2015]. However, the situation is less clear when recombination is introduced. At least in some situations, adaptation is primarily driven by recombination between genotypes that are not exceptionally fit. This can certainly be the case in rugged fitness landscapes [Wright, 1932, Crona, 2018, Cooper and Kerr, 2016], but it can also be true in smooth ones [Pearce and Fisher, 2019]. Thus while maximizing the reproduction of the fittest individuals maximizes the rate of adaptation in the current generation, it also reduces the genetic diversity that would fuel future adaptation

[Robertson, 1970, Ueda et al., 2017]. This suggests that by slowing selection, spatial structure may actually be able to increase the rate of adaptation, even in smooth fitness landscapes.

Natural environments constantly fluctuate, and these fluctuations can affect dispersal and recombination. In particular, both dispersal and recombination are often increased by stressful conditions (see examples reviewed in [Gerber and Kokko, 2018]). Mobile microbes can generally gain mobility from exposure to stressful environments such as starvation, temperature shift, and exposure to toxins [Son et al., 2015, Mitchell and Kogure, 2006], in extreme cases manifesting as collective swarming behavior [Belas et al., 1998, Daniels et al., 2004]. Some microbes can also switch between asexual and sexual reproduction under stress. For example, bacteria can be induced to sexual reproduction by starvation [Foster, 2005, Kassir et al., 1988], or can become transformable in order to absorb and integrate exogenous DNA as a general response to stress [Chung et al., 1989, Redfield, 1993, Lorenz and Wackernagel, 1994, Claverys et al., 2006]. A similar response is found in yeast, which can perform meiosis and sporulate under starvation or high oxidative stress [Freese et al., 1982, Bernstein and Johns, 1989, Davey, 1998, Neiman, 2011, Kassir et al., 1988, Mai and Breeden, 2000].

The fact that dispersal and recombination are triggered by some similar environmental stimuli will tend to introduce some synchronization, both between the two processes (individual synchronization) and within processes across individuals (population synchronization, assuming that some environmental fluctuations affect many individuals in the population) [Gerber and Kokko, 2018]. In other systems, such as plants that can switch between local vegetative growth or sexual reproduction using dispersed pollen, the two processes may also be mechanistically synchronized. It has been shown that population-level synchronization of facultative recombination can affect the rate of adaptation on both smooth [Weissman and Barton, 2012, Pearce and Fisher, 2019, Kokko, 2019, Berríos-Caro et al., 2020] and rugged landscapes [Weissman, 2014, Crona, 2018]. But these results are largely from well-mixed populations, and it is still unclear how synchronization of recombination interacts with population structure and the possible additional individual-level synchronization with dispersal. Intuitively, it seems plausible that population structure could allow diversity to build up in the population in different demes, which could then be brought together to produce new genotypes in a burst of synchronized dispersal and recombination, allowing the population to balance exploration and exploitation of the fitness landscape (Fig. 1).

In this paper, we simulate evolution on smooth fitness landscapes and test the effects of population structure and fluctuating, possibly synchronized, recombination and dispersal on the rate of adaptation. We find that when the beneficial mutation supply is high, structured populations with individual- and/or population-synchronized recombination and dispersal can adapt faster than well-mixed ones. Population-level synchronization has the strongest effect, as it maximizes the probability that recombination events will occur between individuals with different beneficial mutations, the pairings that have the highest potential for generating extremely fit offspring.

MODEL

We consider a structured population distributed in D demes with N haploid individuals in each deme. We assume an island model, with bi-directional dispersal between all pairs of demes at a time-dependent rate $m(t)$ with average $\overline{m}$. As a baseline, we also simulate a well-mixed population with only one deme with the same total population size, $D \times N$ individuals. In the simulation results, $D = 100$ and $N = 10^6$ unless stated otherwise. Each individual has $L = 1000$ unlinked loci. Beneficial mutations are uniformly distributed and occur at genomic rate U. We neglect back-mutations. Each mutation has the same log-fitness advantage $s = 0.05$ and all mutations combine multiplicatively, i.e., the fitness landscape is completely smooth. Individuals are facultatively sexual, with outcrossing occurring at a time-dependent rate $f(t)$ with average $\overline{f}$. Because most reproduction is asexual, linkage disequilibrium can be large even though all loci are unlinked. We use this mating system and genetic map for simplicity, and do not believe that our results would be qualitatively different if we were to use a linear map or a model of gene conversion more similar to recombination in bacteria.

We allow for two possible ways that dispersal and recombination can be synchronized, as illustrated in Fig. 2. The first, individual-level synchronization, is a synchronization between the two processes and can be observed within a single generation. If the expected fractions of migrant and sexually produced offspring in that generation are $m(t)$ and $f(t)$ respectively, then there is individual-level synchronization if the expected fraction of offspring that are both migrants and sexually produced is $> m(t)f(t)$. If, for example, $m(t) > f(t)$, then in the most extreme case of individual-level synchronization, *all* sexually

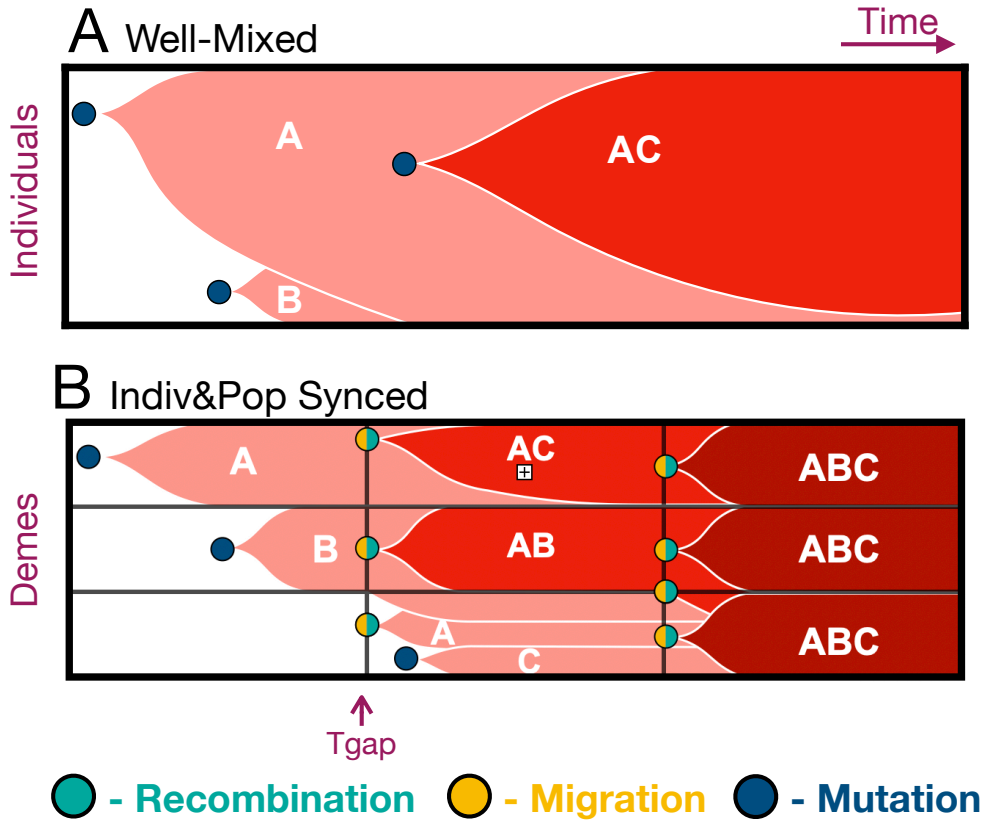

Figure 1. Schematic illustration of how population structure and synchronization can combine to accelerate adaptation. Darker red represents higher fitness, i.e., more mutations. **(A)** In a well-mixed population, mutations can rapidly spread to the whole population but drive all other diversity extinct in the process, with few opportunities for recombination between competing genotypes. **(B)** In a structured population, sweeps are slower but this preserves other beneficial mutations, which then can be brought together by synchronized dispersal and sexual reproduction, leading to faster long-term adaptation.

produced offspring would also be migrants. For simplicity, we focus on this extreme case in our simulations.

The other form of synchronization, population-level, can only be observed by comparing across multiple generations, and involves synchronizing dispersal, sexual reproduction, or both across individuals. It is automatically induced by the time dependence of $m(t)$ and $f(t)$. In generations when m is high, many individuals disperse, and in generations when it is low, few do, and similarly for f and sexual reproduction. In populations with both forms of synchronization, both dispersal and sexual reproduction are concentrated in the same generations and in the same individuals within those generations.

We consider a limiting form of population-level synchronization, in which dispersal and/or sexual reproduction occur only every t_{gap} generations, with $t_{\text{gap}} = 1$ corresponding to a steady rate, i.e., the absence of population synchronization. For $t_{\text{gap}} > 1$, then if the average probability of, e.g., dispersal is $\overline{m}$, then there will be no dispersal for $t_{\text{gap}} - 1$ generations and then dispersal with probability $\overline{m}/t_{\text{gap}}$ for a single generation. Larger values of t_{gap} therefore correspond to increased population-level synchronization. Note that since the probabilities of dispersal and sexual reproduction must both be ≤ 1 in each generation, t_{gap} must be less than $\overline{m}$ and $\overline{f}$. While this model is largely chosen for simplicity, it is also inspired by the design of microbial evolution experiments that test the effect of spatial structure [Kryazhimskiy et al., 2012, Nahum et al., 2015] or facultative outcrossing [McDonald et al., 2016] on the rate of adaptation. In these experiments, organisms have multiple generations of asexual reproduction within separate demes, interrupted by occasional generations of sexual reproduction and/or mixing among demes.

We use a form of Wright-Fisher reproduction, in which the entire population is replaced every generation. To produce an individual in deme d in generation $t+1$, we first determine whether it is a resident (with probability $1-m(t)$) or a migrant (with probability $m(t)$). We then determine if it is the offspring of uniparental or biparental reproduction. In the absence of individual-level synchronization, these have probabilities $1-f(t)$ and $f(t)$, respectively. With individual-level synchronization, all resident individuals are produced uniparentally, while migrants have a probability $f(t)/m(t)$ of being produced biparentally. (We always keep $f(t) < m(t)$ in simulations with indivual-level synchronization.) Resident individuals draw their parent or parents from the individuals living in deme d at time t with probability proportional to their fitnesses, Migrant individuals draw their parents from a migrant pool. All demes contribute equally to the migrant pool, but within each deme's contribution, individuals are weighted proportional to their fitness. In other words, selection only acts within demes. For migrants produced by biparental reproduction, the two parents' demes are chosen independently, i.e., mating is assumed to take place within the migrant pool.

The key outcome variable is the rate of adaptation v, defined as the rate of increase of mean log fitness. This is proportional to the probability of fixation of beneficial mutations, P_{fix}: $v = NDUP_{\text{fix}} \ln(1+s) \approx NDUP_{\text{fix}}s$. In the absence of clonal interference, $P_{\text{fix}} = 2s$ independent of the spatial structure [Maruyama, 1970], and the rate of adaptation is $v = v_0 \approx 2NDUs^2$ [Weissman and Barton, 2012]. To understand the dynamics underlying the observed changes in v, we also track additional statistics of the populations. We measure total genetic diversity using the heterozygosity $H = \sum_i p_i(1-p_i)$, where p_i is the frequency of the mutant allele at locus i. According to Fisher's Fundamental Theorem [Fisher, 1930], the speed of adaptation is equal to the (genetic) variance in fitness. In our simulations, the standard deviation of log fitness is always ≤ 0.15, which means that the variance in fitness is close to the variance in log fitness (see Text S1). In linkage equilibrium, this is simply $s^2 \sum_i p_i(1-p_i)$, proportional to the heterozygosity. The extent to which v/s^2 lags behind the heterozygosity therefore provides a measure of total multilocus negative linkage disequilibrium. To track the dynamics of the nose of the fitness distribution, we follow the frequency of "best genotypes", which we define as those within s of the maximum current log fitness in the population (see Text S2). Finally, to determine whether adaptation is being driven by mutations in the nose of the fitness distribution or recombinants leaping to the nose, we track the Hamming distance between the fittest individuals in the population in consecutive generations.

In our simulation, we keep $s = 0.05$ and $L = 1000$ for computational reasons. (Smaller values of s require longer run times, and larger values of L require more memory.) We choose the other parameters to probe the region in which both selection and clonal interference are strong, $1/N \ll P_{\text{fix}} \ll 2s$. This latter condition requires that mutation be frequent and recombination rare. We determined that we could achieve this with computationally feasible total population sizes with mutation rate $U = 5 \times 10^{-4}$ per generation and average frequency of sexual reproduction $\overline{f} = 1.25 \times 10^{-3}$ per generation. Unless otherwise stated, we set average dispersal probability to $\overline{m} = 2.5 \times 10^{-3}$ and the waiting time in population-synchronized

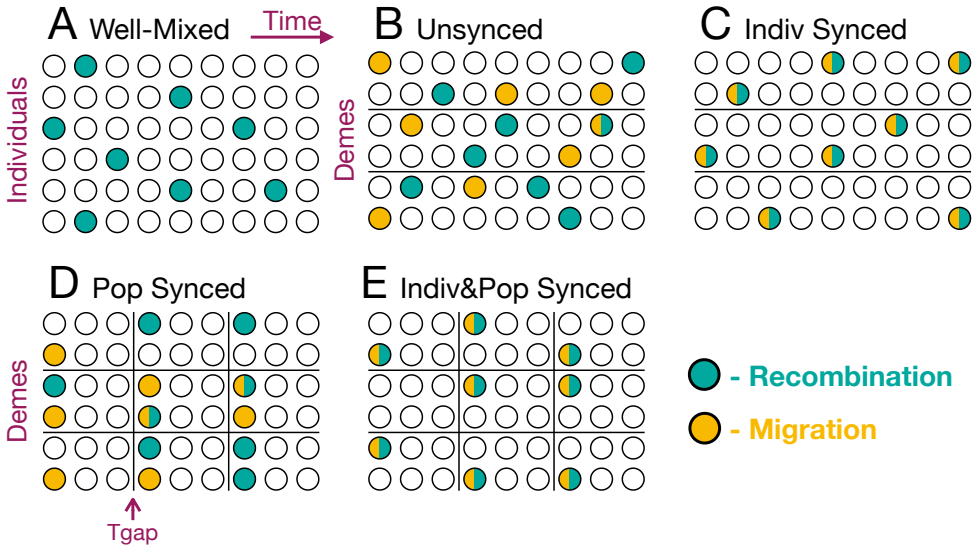

Figure 2. Illustrations of different possible forms of synchronization. **(A)** Well-mixed population with no synchronization of sexual reproduction. **(B)** Structured population with no synchronization of dispersal or sexual reproduction. **(C)** Structured population with individual-level synchronization: different dispersal events are independent from each other, and similarly for instances of sexual reproduction, but dispersal and sexual reproduction are correlated with each other. **(D)** Structured population with population-level synchronization: dispersal and sexual reproduction are concentrated in generations that occur every t_{gap} generations, but within one of these generations there is no association between the two processes. Population-level synchronization of sexual reproduction can also occur in well-mixed populations. **(E)** Structured population with both individual- and population-level synchronization: dispersal and sexual reproduction are correlated both between and within generations.

simulations to $t_{\text{gap}} = 100$.

All plots show data averaged over 100 independent simulation runs, with error bars smaller than the size of the plot markers. In plots showing the average dynamics over the course of a cycle of t_{gap} generations, the first and last data points are the beginning of two consecutive bursty cycles, i.e., $t_{\text{gap}} + 1$ generations are shown.

RESULTS

Population structure can very slightly speed adaptation even without synchronization

In asexual populations, clonal interference is stronger in spatially structured populations than it is in well-mixed ones [Martens and Hallatschek, 2011, Kryazhimskiy et al., 2012]. Sexual reproduction reduces clonal interference in both spatially structured [Martens and Hallatschek, 2011] and well-mixed populations, but how does it change their relative rates of adaptation, i.e., the effect of spatial structure? To investigate this, we first simulate populations with facultative sex and varying degrees of spatial structure but no synchronization (schematic: Fig. 2B; results: Fig. 3 and Fig. S2B, orange lines).

At small total population sizes such that the mutation supply is low ($NU \lesssim 1$), well-mixed populations experience little clonal interference and adapt at close to the maximum rate v_0, even if they are asexual. In this regime, increasing spatial structure only impedes adaptation (Fig 3A, left side), because it slows down sweeps, increasing the probability that they overlap and interfere with each other. However, for large mutation supplies ($NU \gg 1$), well-mixed populations with limited recombination experience strong clonal interference. Surprisingly, in this regime, splitting the population into demes does not slow down adaptation and even very slightly accelerates it, with the population split into 100 demes evolving 6% faster than the well-mixed population (t-test, $p = 0.035$; see Fig. 3A).

To understand this result, note that under strong clonal interference the speed of adaptation is only weakly (logarithmically) dependent on population size [Desai and Fisher, 2007, Neher et al., 2010, Weissman and Barton, 2012, Weissman and Hallatschek, 2014]. Thus, in a population large enough that each individual deme has a high mutation supply, each deme can adapt nearly as fast as a well-mixed population of the same size as the whole meta-population. So space only slightly slows down asexual evolution, and the increased genetic diversity between demes means that spatially structured populations can benefit more from recombination, pushing their overall rate of adaptation above well-mixed ones (Figs. 3A and S1).

Population synchronization of sexual reproduction and dispersal can significantly accelerate adaptation

We first examine the effects of pure population synchronization, in which both sexual reproduction and dispersal are synchronized at the population level, with no additional individual-level synchronization (schematic: Fig. 2D). This represents a scenario in which, for example, an entire experimental population is forced to go through periodic rounds of dispersal and sexual reproduction [Kryazhimskiy et al., 2012, McDonald et al., 2016]. We see that when clonal interference is strong, this life history can approximately double the speed of adaptation relative to that of a well-mixed population with no synchronization (Fig. 3A). The increase in speed relative to a well-mixed population with the same synchronization of sexual reproduction is even larger (Fig. S2A). Thus, spatial structure reduces clonal interference in this instance.

The population with synchronized sexual reproduction and dispersal achieves its higher adaptation speed via bursts of adaptation every t_{gap} generations. These bursts move both the nose and the mean of the fitness distribution. But the nose (Fig. 3B) shifts in genotype space by far more than the distribution moves toward the optimal genotype (Fig. 3C). This indicates that the leading genotype is replaced by a distantly related recombinant, unlike in the other populations. The combination of structure and synchronization apparently allows it to both maintain and exploit a large reservoir of beneficial mutations beyond those that are found in the current best genotype.

Sexual reproduction among migrants is crucial to the increase in adaptation speed

We next introduce individual-level synchronization, such as could be a response to individual-level environmental variation, as opposed to the global environmental fluctuations that lead to population synchronization. We find that it can also accelerate adaptation, although not by as much as population synchronization (Fig. 4A, yellow squares vs dark blue diamonds). Populations with both forms of synchronization adapt fastest of all (Fig. 4A, light blue triangles), although the increase in speed over pure

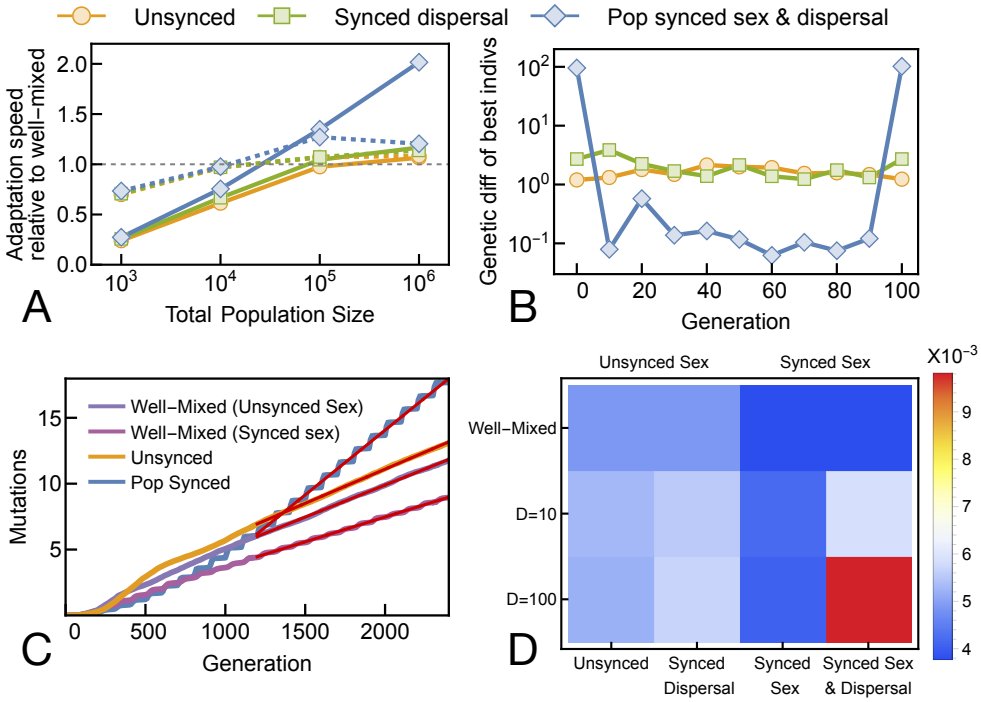

Figure 3. Population-level synchronization of dispersal and sexual reproduction accelerates adaptation by increasing the production of fit recombinants. (A) Ratios of adaptation speeds relative to a well-mixed population with unsynchronized sexual reproduction. Dashed lines show results from simulated populations comprising 10 demes, while solid lines show populations comprising 100 demes. The strongly structured (100-deme) population with synchronized sexual reproduction and dispersal adapts roughly twice as fast as other populations. Structured populations with no synchronization or synchronization of only dispersal have slight advantages over the well-mixed population (ratios=1.06 ($p = 0.035$) and 1.17 ($p < 0.001$), respectively, for populations of 100 demes). Details of the adaptation speeds are in Fig. S2. In all other simulation result, $D = 100$ and $N = 10^6$ unless stated otherwise, since they produces the fastest adaptation. **(B)** Hamming distance between the fittest individuals in successive generations, shown over the course of the $t_{\text{gap}} = 100$ generations between rounds of synchronized dispersal/sexual reproduction. All curves are averages over 10 runs, each of which consists of 2400 generations (i.e., 24 t_{gap} periods). For populations without synchronization or synchronization of only dispersal, the small (≈ 1 mutation) distances indicate that adaptation is primarily driven by the accumulation of mutations on already-fit backgrounds. Populations with synchronized sexual reproduction and dispersal, on the other hand, leap ahead suddenly by ≈ 100 mutations due to recombination between divergent parents. **(C)** Mutation accumulation trajectories of different populations. The adaptation of the synchronized population is punctuated. Red lines indicate fits used for determining adaptation speeds. **(D)** Relative adaptation speeds (rates of increase of mean fitness) of different populations. The full combination of Strong structure and synchronized sexual reproduction and dispersal is needed to substantially accelerate adaptation. Individually, these factors only have very small effects or even slow down adaptation.

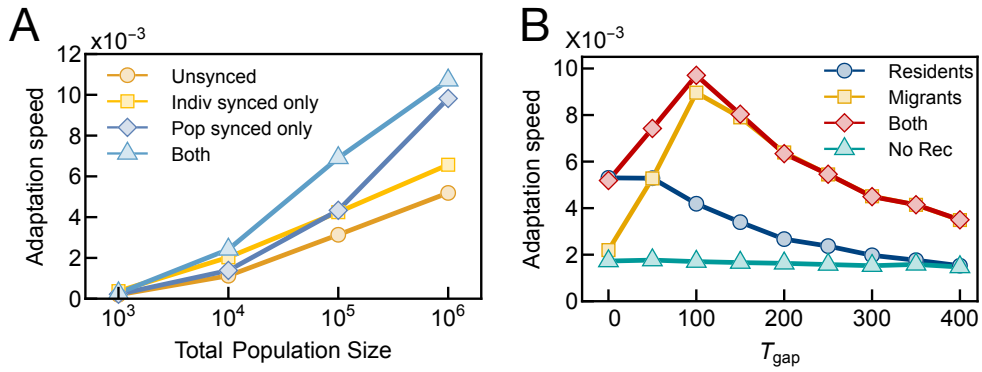

Figure 4. Sexual reproduction among migrants drives the increase in adaptation speed. (A) Adaptation speed of populations with differing synchrony between sexual reproduction and dispersal. Individual-level synchronization between sexual reproduction and dispersal accelerates adaptation, although not by as much as population-level synchronization. The two forms of synchronization act synergistically at moderate population sizes but have diminishing returns at a **(B)** Effect on adaptation speed of limiting sexual reproduction to migrant or resident individuals in populations with population-synchronized sexual reproduction and dispersal. For low values of the synchronization parameter t_{gap}, almost all individuals are residents and sexual reproduction among migrants contributes negligibly to adaptation. At higher values of $t_{\text{gap}} \approx 100$, even though migrants are still a minority, it is their offspring who are driving adaptation, with the majority residents making a negligible contribution. For even higher values $t_{\text{gap}} > 200$, migrants make up a majority of the population in the generations in which sexual reproduction takes place.

population-level synchronization is modest at the large population sizes where synchronization accelerates adaptation the most.

There are two possible explanations for why individual-level synchronization provides only a modest acceleration in large populations that already have population-level synchronization: either it is not important that sexual reproduction be happening specifically among migrants, or population-level synchronization already creates a large enough pool of sexually reproducing migrants that there are only limited benefits to increasing it further. To test these possibilities, we modify the simulations with only population-level synchronization so that either only migrants or only residents can reproduce sexually. We do not increase the rate of sexual reproduction among the group where it is allowed, so this lowers the overall rate of sexual reproduction—drastically so when sexual reproduction is limited to migrants, who are typically a minority of the population. For example, at the value $t_{\text{gap}} = 100$ where synchronization provides the greatest benefit, 25% of individuals are migrants in the high-dispersal generations. But we see that limiting sexual reproduction to these migrants hardly slows down adaptation, while limiting it to the 75% of individuals who are residents reduces the rate of adaptation by more than a factor of two (Fig. 4B). We therefore see that sexual reproduction among migrants is essential to the advantage of synchronization, suggesting that the limited benefits of individual-level synchronization are simply because population-level synchronization already creates a strong association between the two processes.

The synchronization *between* sexual reproduction and dispersal is crucial to the increase in population speed

Population-level synchronization both synchronizes dispersal with sexual reproduction and synchronizes among multiple dispersal events and among multiple instances of sexual reproduction. It seems intuitive that the former effect should be the most important for adaptation, since it focuses sexual reproduction on pairings with the greatest genetic diversity. But individual-level synchronization also produces this effect, and does not accelerate adaptation nearly as much (Fig. 4A). This raises the question of whether perhaps the synchronization between sexual reproduction and dispersal is actually unimportant, with the acceleration being driven by just the separate synchronizations among dispersal events and among instances of sexual reproduction. To test this, we introduce an offset between generations of increased dispersal and generations of increased sexual reproduction. Experimentally, this would correspond to

having separate passages in which cells were mixed across wells and in which some cells were forced to undergo sexual reproduction. In natural populations, it would correspond to different pathways triggering dispersal and sexual reproduction in response to different environmental cues.

We find that the rate of adaptation is maximized when sexual reproduction and dispersal occur in the same generation (Fig. 5A), confirming the initial intuitive expectation. The rate of adaptation decreases as the number of generations elapsing after dispersal and before sexual reproduction increases, as the genetic diversity introduced into demes by dispersal is lost. However, we find a new surprise, that the rate of adaptation partially recovers for very long delays, such that dispersal quickly *follows* sexual reproduction. Examining the statistics of the simulations further reveals that the initial decrease in the rate of adaptation can be explained by a decrease in the fitness of the fittest recombinants formed (Fig. 5B). This effect saturates for long delays, likely because within-deme genetic diversity reaches a steady state maintained by mutation. At this point, it is better for adaptation to delay sexual reproduction more so that fit recombinants can quickly be redistributed across demes in the *next* dispersal event. This is because the demes vary in fitness (Fig. 5C), so dispersal will tend to move very fit recombinants into less-fit demes, where they will compete with each other less. For these very long offsets, the absolute adaptation speed ($5.23 \pm 0.11 \times 10^{-3}$ for offset = 99) is similar to that for populations with synchronized dispersal but unsynchronized sexual reproduction ($5.68 \pm 0.15 \times 10^{-3}$, Fig. S2C) or no synchronization ($5.19 \pm 0.12 \times 10^{-3}$, Fig. S2B).

DISCUSSION

In this paper, we demonstrate that population structure, by creating the possibility for synchronized dispersal and sexual reproduction, can increase the rate of adaptive evolution. To our knowledge, this is the first demonstration that a population structure that does not affect the fixation probability of isolated alleles can accelerate adaptation on smooth fitness landscapes without epistasis by reducing clonal interference among alleles. It does this both by alternately accumulating diversity in different demes and then bringing it together and forming fit recombinants, and by tending to concentrate recombination events in pairs of migrant individuals who are likely to be genetically distinct.

While the effects found here are substantial (e.g., a two-fold increase in adaptation speed relative to a well-mixed population), they are not enormous. This is in contrast to the situation in rugged fitness landscapes, where it has been suggested that structure and synchronized dispersal and recombination can have huge effects on the rate of adaptation [Crona, 2018]. One possibility is that we have not seen very large effects simply because we have not been able to simulate large enough populations. But our simulations do not suggest that much larger effects on the horizon, as the increase in the advantage of structure with population size appears to be modest, perhaps logarithmic (Fig. 3A, blue curve). A simple combinatorial argument also suggests that the gains should be limited: if, because of strong clonal interference, each of the D demes adapts nearly as fast as a well-mixed population of size N would during the t_{gap} generations between mixing, then the best-case scenario would be that each deme acquires unique mutations and recombination is frequent enough to break down linkage disequilibrium among all of them in the mixing generation. This would create a speed-up by a factor of nearly D. But the number of genotypic combinations that need to be explored by recombination during the mixing generation grows exponentially with D, so for any reasonable population size it seems more likely that the linkage disequilibrium created by the population structure will partially persist and the realized speed-up will be much less.

Synchronization of dispersal and sexual reproduction in experiments and natural populations

Our model is meant to match the most straightforward way of implementing population structure and sexual reproduction in experimental microbial population grown in batch culture. Since dispersal is naturally done at transfers, it is automatically synchronized [Kryazhimskiy et al., 2012, Nahum et al., 2015]. Synchronized sexual reproduction (or more generally, recombination) is also natural when working with organisms such as yeast or many bacteria where it must be induced by environmental conditions [Chung et al., 1989, McDonald et al., 2016].

We believe that our model also captures important features found in natural populations. Facultative sexual reproduction is common in nature [Otto, 2009]. Sexual reproduction often carries costs, including mate-finding, performing sexual behavior, and producing males [Maynard Smith, 1978]. Facultative

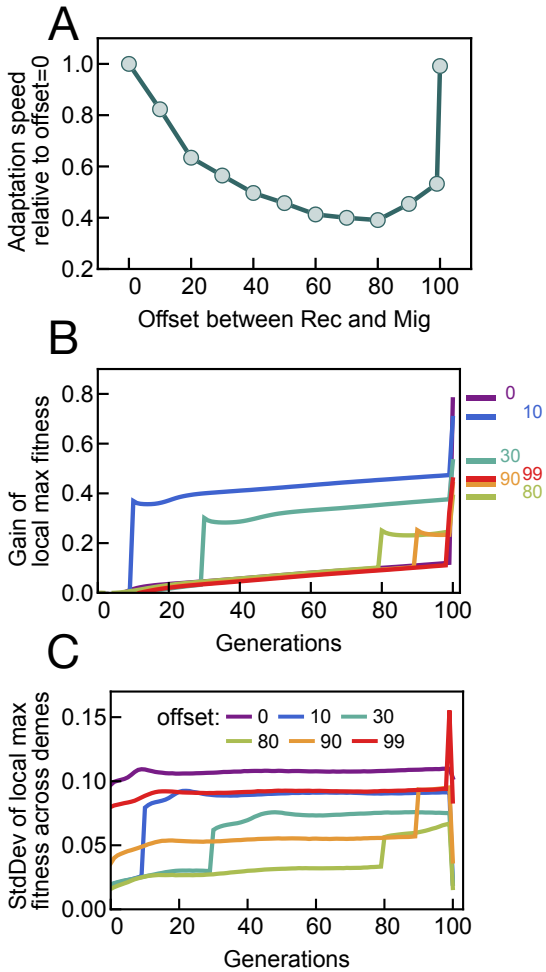

Figure 5. Simultaneous sexual reproduction and dispersal maximizes the rate of adaptation. (A) Adaptation speed as a function of the delay between high-dispersal generations and high-sexual reproduction generations. Dispersal occurs at times 0 and 100 on the horizontal axis, so an offsets of 0 or 100 are identical. Increasing the delay before sexual reproduction lowers the rate of adaptation, as the increased within-deme genetic diversity introduced by dispersal is lost. Surprisingly, there is a slight uptick in the rate of adaptation for very long delays such that dispersal follows shortly *after* sexual reproduction. **(B)** Increase in the fitness of the fittest individual in a deme over the $t_{\text{gap}} = 100$ generations between dispersal events, for different values of the delay before sexual reproduction. This local maximum fitness jumps in the sexual reproduction generation, but by less as the delay increases and the genetic diversity introduced by dispersal decays. It appears to reach a steady state at ≈ 80 generations, partially explaining the uptick in panel A. **(C)** Standard deviation of local maximum fitness across demes shows the same qualitative pattern as overall adaptation speed (A), initially decreasing as the delay increases and then rebounding for very long delays.

sexual reproduction provides most of benefits in terms of creating genetic diversity with less cost than obligate sexual reproduction [Kokko, 2019, Otto, 2009, Burke and Bonduriansky, 2017]. If sexual reproduction is rare, having it be synchronized helps reduce mate-finding costs [Kokko, 2019].

Facultatively sexual reproduction is often a response to stressful conditions [Otto, 2009]. To the extent that these stressful conditions affect multiple individuals, this provides one mechanism for synchronization. As dispersal is also often a response to stress (e.g., [Martorell and Martínez-López, 2014, Gerber and Kokko, 2018, Kokko, 2019]), it will naturally also be synchronized with sexual reproduction. While environmental fluctuations are implicitly the source of synchronization in our model, the fitness landscape is static. Presumably the primary reason that sexual reproduction and dispersal can be triggered by stress is that it is a signal that the organism is poorly adapted to its present habitat, and that it should try to improve the match by producing offspring with different haplotypes or moving to a new environment. In other words, the response most likely evolved as a way to track the fluctuating components of the fitness landscape. Our work shows that a side effect can be more rapid adaptation to the fixed components of the landscape as well.

REFERENCES

Robert Belas, Rachel Schneider, and Michael Melch. Characterization of *Proteus mirabilis* precocious swarming mutants: Identification of *rsbA*, encoding a regulator of swarming behavior. *Journal of Bacteriology*, 180(23):6126–6139, December 1998. ISSN 0021-9193.

C Bernstein and V Johns. Sexual reproduction as a response to H2O2 damage in *Schizosaccharomyces pombe*. *Journal of Bacteriology*, 171(4):1893–1897, April 1989. ISSN 0021-9193.

Ernesto Berríos-Caro, Tobias Galla, and George W. A. Constable. Switching environments, synchronous sex, and the evolution of mating types. *bioRxiv*, page 2020.07.31.230482, July 2020. doi: 10.1101/2020.07.31.230482.

Anne-Florence Bitbol and David J. Schwab. Quantifying the Role of Population Subdivision in Evolution on Rugged Fitness Landscapes. *PLOS Computational Biology*, 10(8):e1003778, August 2014. ISSN 1553-7358. doi: 10.1371/journal.pcbi.1003778.

Nathan W. Burke and Russell Bonduriansky. Sexual conflict, facultative asexuality, and the true paradox of sex. *Trends in Ecology & Evolution*, 32(9):646–652, September 2017. ISSN 0169-5347. doi: 10.1016/j.tree.2017.06.002.

C. T. Chung, S. L. Niemela, and R. H. Miller. One-step preparation of competent *Escherichia coli*: transformation and storage of bacterial cells in the same solution. *Proceedings of the National Academy of Sciences*, 86(7):2172–2175, April 1989. ISSN 0027-8424, 1091-6490. doi: 10.1073/pnas.86.7.2172.

Jean-Pierre Claverys, Marc Prudhomme, and Bernard Martin. Induction of competence regulons as a general response to stress in gram-positive bacteria. *Annual Review of Microbiology*, 60(1):451–475, 2006. doi: 10.1146/annurev.micro.60.080805.142139.

Jacob D. Cooper and Benjamin Kerr. Evolution at 'sutures' and 'centers': Recombination can aid adaptation of spatially structured populations on rugged fitness landscapes. *PLOS Computational Biology*, 12(12):e1005247, December 2016. ISSN 1553-7358. doi: 10.1371/journal.pcbi.1005247.

Arthur W. Covert III and Claus O. Wilke. Intermediate migration yields optimal adaptation in structured, asexual populations. *bioRxiv*, 2014. doi: 10.1101/003897. URL `https://www.biorxiv.org/content/early/2014/04/04/003897`.

J A Coyne, Nicholas H Barton, and Michael Turelli. Perspective: a critique of Sewall Wright's shifting balance theory of evolution. *Evolution*, 51(3):643 – 671, 1997. doi: 10.2307/2411143. URL `http://www.jstor.org/stable/2411143`.

Kristina Crona. Recombination and peak jumping. *PLOS ONE*, 13(3):e0193123, March 2018. ISSN 1932-6203. doi: 10.1371/journal.pone.0193123.

Ruth Daniels, Jos Vanderleyden, and Jan Michiels. Quorum sensing and swarming migration in bacteria. *FEMS Microbiology Reviews*, 28(3):261–289, June 2004. ISSN 1574-6976. doi: 10.1016/j.femsre.2003.09.004.

John Davey. Fusion of a fission yeast. *Yeast*, 14(16):1529–1566, 1998. ISSN 1097-0061. doi: 10.1002/(SICI)1097-0061(199812)14:16¡1529::AID-YEA357¿3.0.CO;2-0.

Michael M. Desai and Daniel S. Fisher. Beneficial mutation-selection balance and the effect of linkage on positive selection. *Genetics*, 176(3):1759–1798, July 2007. ISSN 0016-6731, 1943-2631. doi: 10.1534/genetics.106.067678.

R. A. Fisher. *The genetical theory of natural selection*. Oxford Press, 1930. ISBN 978-1-176-62502-0.

Patricia L. Foster. Stress responses and genetic variation in bacteria. *Mutation Research*, 569(1-2):3–11, January 2005. ISSN 0027-5107. doi: 10.1016/j.mrfmmm.2004.07.017.

Elisabeth Bautz Freese, Martha I. Chu, and Ernst Freese. Initiation of yeast sporulation by partial carbon, nitrogen, or phosphate deprivation. *Journal of Bacteriology*, 149(3):840–851, March 1982. ISSN 0021-9193.

Nina Gerber and Hanna Kokko. Abandoning the ship using sex, dispersal or dormancy: multiple escape routes from challenging conditions. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 373(1757):20170424, 2018. ISSN 0962-8436. doi: 10.1098/rstb.2017.0424.

Philip J. Gerrish and Richard E. Lenski. The fate of competing beneficial mutations in an asexual population. *Genetica*, 102(0):127, March 1998. ISSN 1573-6857. doi: 10.1023/A:1017067816551.

Yona Kassir, David Granot, and Giora Simchen. IME1, a positive regulator gene of meiosis in *S. cerevisiae*. *Cell*, 52(6):853–862, March 1988. ISSN 0092-8674, 1097-4172. doi: 10.1016/0092-8674(88)90427-8.

Hanna Kokko. When synchrony makes the best of both worlds even better: How well do we really understand facultative sex? *The American Naturalist*, pages 000–000, October 2019. ISSN 0003-0147.

doi: 10.1086/706812.

Sergey Kryazhimskiy, Daniel P. Rice, and Michael M. Desai. Population subdivision and adaptation in asexual populations of *Saccharomyces cerevisiae*: subdivision and adaptation in asexual populations of yeast. *Evolution*, 66(6):1931–1941, June 2012. ISSN 00143820. doi: 10.1111/j.1558-5646.2011.01569.x.

M. G. Lorenz and W. Wackernagel. Bacterial gene transfer by natural genetic transformation in the environment. *Microbiological Reviews*, 58(3):563–602, September 1994. ISSN 0146-0749.

B. Mai and L. Breeden. CLN1 and its repression by Xbp1 are important for efficient sporulation in budding yeast. *Molecular and Cellular Biology*, 20(2):478–487, January 2000. ISSN 0270-7306. doi: 10.1128/mcb.20.2.478-487.2000.

Erik A Martens and Oskar Hallatschek. Interfering waves of adaptation promote spatial mixing. *Genetics*, 189(3):1045–1060, November 2011. ISSN 1943-2631. doi: 10.1534/genetics.111.130112.

Carlos Martorell and Marcela Martínez-López. Informed dispersal in plants: *Heterosperma pinnatum* (Asteraceae) adjusts its dispersal mode to escape from competition and water stress. *Oikos*, 123(2):225–231, 2014. doi: https://doi.org/10.1111/j.1600-0706.2013.00715.x. URL `https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1600-0706.2013.00715.x`.

Takeo Maruyama. On the fixation probability of mutant genes in a subdivided population. *Genetical Research*, 15(02):221–225, 1970. doi: 10.1017/s0016672300001543.

J Maynard Smith. Optimization theory in evolution. *Annual Review of Ecology and Systematics*, 9 (1):31–56, November 1978. ISSN 0066-4162. doi: 10.1146/annurev.es.09.110178.000335. URL `http://www.annualreviews.org/doi/10.1146/annurev.es.09.110178.000335`.

Michael J. McDonald, Daniel P. Rice, and Michael M. Desai. Sex speeds adaptation by altering the dynamics of molecular evolution. *Nature*, 531(7593):233–236, March 2016. ISSN 0028-0836. doi: 10.1038/nature17143.

James G. Mitchell and Kazuhiro Kogure. Bacterial motility: links to the environment and a driving force for microbial physics. *FEMS Microbiology Ecology*, 55(1):3–16, January 2006. ISSN 0168-6496. doi: 10.1111/j.1574-6941.2005.00003.x.

H. J. Muller. Some genetic aspects of sex. *The American Naturalist*, 66(703):118–138, March 1932. ISSN 0003-0147, 1537-5323. doi: 10.1086/280418.

Joshua R. Nahum, Peter Godfrey-Smith, Brittany N. Harding, Joseph H. Marcus, Jared Carlson-Stevermer, and Benjamin Kerr. A tortoise–hare pattern seen in adapting structured and unstructured populations suggests a rugged fitness landscape in bacteria. *Proceedings of the National Academy of Sciences*, 112 (24):7530–7535, June 2015. ISSN 0027-8424, 1091-6490. doi: 10.1073/pnas.1410631112.

R. A. Neher, B. I. Shraiman, and D. S. Fisher. Rate of adaptation in large sexual populations. *Genetics*, 184(2):467–481, February 2010. ISSN 0016-6731, 1943-2631. doi: 10.1534/genetics.109.109009.

Aaron M. Neiman. Sporulation in the budding yeast *Saccharomyces cerevisiae*. *Genetics*, 189(3):737–765, November 2011. ISSN 0016-6731, 1943-2631. doi: 10.1534/genetics.111.127126.

Sarah P. Otto. The evolutionary enigma of sex. *The American Naturalist*, 174(S1):S1–S14, July 2009. ISSN 0003-0147. doi: 10.1086/599084.

Michael T. Pearce and Daniel S. Fisher. Rapid adaptation in large populations with very rare sex: Scalings and spontaneous oscillations. *Theoretical Population Biology*, 129:18–40, October 2019. ISSN 00405809. doi: 10.1016/j.tpb.2017.11.005.

R. J. Redfield. Genes for breakfast: The have-your-cake-and-eat-it-too of bacterial transformation. *Journal of Heredity*, 84(5):400–404, September 1993. ISSN 0022-1503. doi: 10.1093/oxfordjournals.jhered.a111361.

Alan Robertson. Some optimum problems in individual selection. *Theoretical Population Biology*, 1(1): 120–127, 1970. ISSN 0040-5809. doi: 10.1016/0040-5809(70)90045-6.

Kwangmin Son, Douglas R. Brumley, and Roman Stocker. Live from under the lens: exploring microbial motility with dynamic imaging and microfluidics. *Nature Reviews Microbiology*, 13(12):761–775, December 2015. ISSN 1740-1534. doi: 10.1038/nrmicro3567.

Masahiko Ueda, Nobuto Takeuchi, and Kunihiko Kaneko. Stronger selection can slow down evolution driven by recombination on a smooth fitness landscape. *PLOS ONE*, 12(8):e0183120, 03 2017. doi: 10.1371/journal.pone.0183120.

Jeremy Van Cleve and Daniel B. Weissman. Measuring ruggedness in fitness landscapes: Fig. 1. *Proceedings of the National Academy of Sciences*, 112(24):7345–7346, June 2015. ISSN 0027-8424,

1091-6490. doi: 10.1073/pnas.1507916112.

Daniel B Weissman. Stress-induced variation can cause average mutation and recombination rates to be positively correlated with fitness. *The 2019 Conference on Artificial Life*, 26:43–44, July 2014. doi: 10.1162/978-0-262-32621-6-ch008.

Daniel B. Weissman and Nicholas H. Barton. Limits to the rate of adaptive substitution in sexual populations. *PLoS Genetics*, 8(6):e1002740, June 2012. ISSN 1553-7404. doi: 10.1371/journal.pgen.1002740.

Daniel B Weissman and Oskar Hallatschek. The rate of adaptation in large sexual populations with linear chromosomes. *Genetics*, 196(4):1167 – 1183, 2014. doi: 10.1534/genetics.113.160705.

Sewall Wright. *The roles of mutation, inbreeding, crossbreeding and selection in evolution*, volume 1. Proceedings of the Sixth International Congress of Genetics, 1932.