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Selection Pressure Benefits Low-Fitness Individuals and Mitigates the Costs of Sex and Recombination

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Abstract

The maintenance of sex has long been a mystery to evolutionary biology. Though meiotic recombination helps purge deleterious mutations and has a key role in generating evolutionary innovations, it is not clear that these benefits can recoup costs of sex and recombination. By employing Wagner's genetic regulatory network (GRN) model, in this paper, we have been able to test how selection pressure affects the underlying evolutionary dynamics in sexual lineages. In the first study we find that, compared with asexual lineages, low-fitness sexual lineages can gain a higher benefit when they are subject to higher selection pressure, especially at the early stage. These indicate that selection pressure can facilitate a fast adaptation for low-fitness individuals via recombination. In the second study where we include both the recombination cost and the twofold cost (the competitive advantage of asexual lineages relative to sexual lineages) into the system, we show that though recombination is initially costly, it rapidly evolves (through rewiring gene regulation) to compensate in even a single bout for costs of sex and recombination. We further explore the parameter space and find that sexual lineages with low levels of sex and recombination can outcompete strictly asexual populations under higher selection pressure and lower mutation rates. These results have important implications for explaining the maintenance of sex and recombination in the context of genetic networks.

Keywords: Genetic regulatory networks; Maintenance of recombination; Cost of sex; *In silico* evolution

Introduction

The maintenance of sex is one of the most mysterious unsolved problems in evolutionary biology. Sexual reproduction is widespread in nature, though asexual reproduction remains ubiquitously in single-celled organisms, many plants and fungi [1]. Individuals that survive after millions of years of evolution have already proven themselves to be the fittest to the current environment. Therefore, it is hard to explain why those individuals would still favour a risky strategy where they reshuffle their genes with other individuals via recombination [2].

On the one hand, recombination has considered to be very expensive because it is associated with several costs. First, sexual reproduction is believed to disrupt favorable gene combinations, and consequently it reduces individual's fitness [1]. In addition, sexual lineages may have to pay for the substantial two fold cost of sex [3]. In anisogamy species, only half of lineages is capable of bearing babies since males cannot themselves produce offspring, whereas asexual lineages are essentially all females who are able to produce twice as many offspring as sexual lineages. Moreover, sexual reproduction is also associated with costs of mating or conjugating. For example, many plant species spend substantial resources on the size of the floral display and nectar rewards [4].

On the other hand, there is a large body of both theoretical and empirical work to explain benefits of sex and recombination [1-3,5-8]. Most of previous work can be classified into two major categories, though they are still controversial, to unravel mechanisms of the maintenance of sex and recombination [9-13]. The first major benefit of sexual recombination, in contrast to disruption of well-adapted lineages, is that recombination can facilitate adaptation by generating novel gene combinations, conferring sexual lineages a better adaptive potential to new environments, and the second major advantage is that recombination prevents the accumulation of deleterious mutations.

However, costs and benefits of sex and recombination are still equivocal. For example, the hypothesis that sex enhances the ability to purge deleterious mutations typically assumes synergistic (negative) epistasis. Keightley and Eyre-Walker [14] tested this hypothesis by estimating genomic point mutation rates for protein-coding genes in a range of animal taxa, and found that sex is not maintained by its capacity to purge the genome of deleterious mutations. Lohaus et al. [15] also argued that there is no evidence that the long and short-term advantages to sex were explained by the negative epistasis. In addition, Hörandl [16] showed that costs for maintenance of meiotic recombination are expected to be lower. Wagner [7] also broadly reviewed mechanisms underlying sexual reproduction in the context of genetic networks, and showed that the destructive role of recombination can be mild or even non-existent. There are many other explanations from previous studies to uncover the maintenance of sex and recombination, such as ecological dynamics [17], complementation [18], fluctuating epistasis [19], co-evolution [20], fluctuating environments [21] and multiple mating [22].

Selection is expected to be one of key factors that help reconcile the paradox of costs and benefits of sexual reproduction and genetic recombination under certain conditions [23]. Banner and Mc Lai [24] showed that the random nature of coronavirus RNA recombination in

the absence of selection pressure, but they found RNA recombination is highly restricted due to the selection for certain recombinants. Moutouh et al. [25] showed similarly that the genetic recombinants derived from two distinct viruses can emerge rapidly under selective conditions, and ultimately contribute to the development of HIV-1 resistance to multiple drugs. Lefébure and Stanhope [26] also emphasized the role of positive selection in the adaptation of the core-genome of different Streptococcus species to different hosts. A more recent study by Lumley et al. [27] has shown that sexual selection helps purify deleterious alleles to reduce mutation load, and consequently facilitates fixation of advantageous alleles, enhancing population survivability in the presence of genetic stress.

Although many existing studies have indicated the natural selection is critical to the maintenance of meiotic recombination, they have not explicitly considered how selection pressure affects the underlying evolution dynamics when recombination results in rewired gene regulatory networks. In this chapter, we hypothesize that selection pressure can shape the complex hierarchical representations found in the genome, and facilitate a rate of evolution sufficient to compensate both the recombination cost and the twofold cost. Here, we use a well-established computational approach to assess the costs and benefits of sex and recombination in a gene regulatory network context [28-30] since traditional genetic models are unable to investigate multiple interactions simultaneously. In the first study, we find that low-fitness sexual lineages can gain a higher benefit when they are subject to higher selection pressure, especially at the early stage. In the second study, we present a population-dynamic view of competition between asexual lineages (parthenogenesis species) and sexual lineages (anisogamy species), in which both recombination cost and twofold cost have been explicitly modeled in the system. We find that though recombination is initially costly, it rapidly evolves (through rewiring gene regulation) to compensate in even a single bout for costs of sex and recombination. We further explore the parameter space and find that sexual lineages with low levels of sex and recombination can outcompete strictly asexual populations under higher selection pressure and a lower mutation rate. These results indicate a key role of selection pressure in reducing mutation load and have important implications for explaining the maintenance of sex and recombination in the context of genetic networks.

Methods

We employed a well-established synthetic model of gene regulatory networks that was initially proposed by Wagner [28] to simulate evolution of sex. Lineages are typically cloned to reproduce offspring or allowed to recombine with each other during periodical sexual reproduction events. Here, an event of sexual reproduction refers to only having one generation of recombination in the population. Here we only provide a more detailed explanation of the computational model used in this paper.

The computational model

Formally, for each individual in a finite population of size M, an N × N matrix W can be considered as an artificial gene network that contains the regulatory interactions among N genes [31,32]. Each element $W_{i,j}$ (i,j=1, 2,……..,N) represents the regulatory effect on the expression of gene i of the product of gene j. The connectivity parameter c determines the proportion of non-zero elements in the network W. Through gene interactions the regulatory effect acts on each gene's expression pattern. This can be denoted by a state vector:

$S(t)=(s_1(t), s_2(t),……, s_N(t))$

Where $s_i(t)$ represents the expression pattern of gene i at time t.

Each value of the expression state $s_i(t)$ can be varied continuously between -1 (complete repression) and +1 (complete activation). For a given gene regulatory network W, the dynamics of S for each gene I can be modeled by the following equation [28-30].

$$s_i(t+1) = f\sum_{j=1}^{N} w_{ij}s_j(t) \quad \text{.....(1)}$$

Where f (x) is a sigmoidal function, which is normally defined [29,30].

$f(x)=2/(1+e^{-ax})-1,$

Where a is the activation constant determining the rate of change from complete repression to complete activation.

In Wagner's GRN model, it introduces the selection for phenotypic stability [28], which is defined as the progression from an arbitrary initial expression state to an equilibrium expression state (reaching a fixed pattern) by iterating Equation (1) a fixed number of times, *devT* [31]. If a given network W can achieve stability over this developmental time period, it is termed stable, otherwise it is labelled unstable. An equilibrium expression state can be reached when the following equation is met [29,30].

$$\frac{1}{\tau}\theta = t - \tau^{t} D(s(\theta), \bar{s}(t)) \le 10^{-4} \quad \text{.....(2)}$$

Where $D(S,\bar{S}) = N_{i=1}(s_i - \bar{s}_i)4N$ measures the difference between the gene expression pattern S and S and $\bar{S}$ is the average of the gene expression levels over the time interval [t-τ, t-τ +1…., t], where τ is a time-constant characteristic for the developmental process under consideration.

Fitness evaluation: The fitness is evaluated by measuring the phenotypic distance between the equilibrium state and the optimal state. For individuals that cannot achieve the developmental stability, a zero fitness will be assigned to ensure that all unstable networks cannot survive in the subsequent generation. For networks that achieve developmental stability (reaching an equilibrium state, S_{EQ}), then the fitness can be calculated as [29].

$$F(S_{EQ}) = exp - \frac{D(S_{EQ}, S_{OPT})}{\sigma} \quad \text{.....(3)}$$

Where σ is the selection pressure that we imposed on the population during evolution. S_{OPT} is usually set to be the initial state, i.e., S(0). $D(S_{EQ}, S_{OPT})$ is the phenotypic distance between the equilibrium state and the optimal state as in Equation (2).

Initialization

Each individual network in population M is generated by randomly filling W with c. N^2 non-zero elements $w_{i,j}$ drawn from the standard normal distribution, N (0,1). The associated initial expression state for each network S(0) is simply setting $s_i(0)=+1$ (i=1, 2,….., N).

Mutation: For an individual network, each non-zero entry in the W interaction matrix is replaced by $w_{/i,j}$ N (0,1) (i,j=1,2,…,N) with mutation rate μ. The expected number of mutations in W is drawn from the Poisson distribution $P(x=k)=\mu^k e^{-\mu} k!$ (k=0,1,…., c × N^2). In all simulations, we used μ=0.1, which means on average there is 0.1 non-zero entry in W that will be mutated per network per generation.

Recombination: In Wagner's GRN model, the recombination is modeled as a free recombination between circuit genes and neglect recombination within genes (promoters or enhancers) [31]. To be more specific, a recombinant is produced by picking two individuals and selecting rows of the W matrices from each parent with equal probability.

Stability and fitness selection: All individuals are subjected two layers of selection-selection for the network stability (as assessed in Equation (2)) and section for the optimal state (as assessed in Equation (3)).

Evolution: The evolutionary simulations are performed under the reproduction-mutation-selection life cycle [31]. In typical asexual evolution, an individual is chosen at random to reproduce asexually by cloning it-self, and then subject to mutation. Similarly, in typical sexual evolution, two individuals are chosen at random to reproduce sexually by recombining two individual networks, and then subject to mutation. Next, the resulting offspring network is exposed to the selection for network stability. Unless otherwise specified in certain evolutionary scenarios, if the offspring network cannot reach an equilibrium state, then it will be wiped out from the population immediately. For the stable offspring network, it is then exposed to the selection for the individual fitness, and can be selected into a new population pool for the next generation. In each generation, this process is repeated until the number of M networks is produced. The system level parameters are fixed to be a=1, $devT$=100 and τ=10 in all simulations.

Exploring effects of selection pressure on low-fitness individuals

In the first set of experiments, we investigated how different levels of selection strength benefit low-fitness individuals in both asexual and sexual lineages (Figures 1 and 2). Specifically, both asexual and sexual lineages were derived from the same population pool which contained 10,000 randomly-generated stable networks (All networks have the same initial gene expression state (all activating, i.e., $s_i(0)=+1$, i=1,…, N)). Next, the population was evolved for one generation with asexual or sexual reproduction followed by one single mutation (Here, for each network, a non-zero entry will be mutated) for each network. In the asexual population, for each individual, we recorded each individual's parental fitness at the initial generation as well as its offspring fitness in the subsequent generation.

Similarly, for sexual population, we also recorded the offspring fitness, but its parental fitness was estimated as the mean fitness of two parents at the initial generation. Next, each of two (asexual and sexual) populations was grouped into ten bins according to the parental fitness (in ascending order). Finally, the proportion of gained fitness for each individual in offspring relative to the corresponding parental fitness was measured and averaged for all individuals in each of ten bins. For both asexual and sexual populations, we also randomly selected 1000 individuals from one simulation run, and plotted each individual's parental and offspring fitness in actual phenotypic distance scale (By calculating the phenotypic distance, results obtained from different levels of selection strength can be displayed into the same scale) as shown in Figures 1-A1 and 1-A2.

In the second sets of experiments, we further investigated how different levels of selection strength benefit evolved asexual and sexual lineages (Figures A3 and 3). Specifically, similarly to the first set of experiments, the population was evolved asexually or sexually under selection pressure σ=100 and we recorded each individual's fitness at the initial, the 4th, 9th, 49th generation as well as its offspring fitness in the subsequent generation, respectively. Finally, for each of four categories for both asexual and sexual lineages, the proportion of gained fitness for each individual in offspring relative to the corresponding parental fitness was measured similarly as calculated in the first set of experiments.

Exploring effects of selection pressure on recombination cost

In this set of experiments, we tested whether sexual lineages are able to afford the recombination cost incurred by selection pressure (Figures 4 and 5). Specifically, the initial population of 10,000 randomly-generated stable networks was evolved with different recombination frequency (from recombination occurring at each generation to no recombination at all) for 1000 generations under extreme weak ($\sigma=10^9$) or strong selection pressure (σ=0.5), respectively. Individual's phenotypic distance from the optimum, i.e., $D(S_{EQ},S_{OPT})$, was measured at each generation in all evolutionary scenarios.

Modelling recombination cost and twofold cost in a competitive regime

In addition to recombination cost incurred by selection pressure, in this set of experiments, we introduced the twofold cost of sex in a competitive regime and tested if sexual lineages can out compete asexual lineages under certain conditions (Figures 6-8). Specifically, the initial population contained 10,000 randomly-generated stable networks with an equal frequency of asexual and sexual lineages (5000 individuals in each category) (Note that 5000 sexual lineages were closed from asexual lineages, forming a population of total 10,000 individuals). For asexual lineages, they can only reproduce by cloning itself. For sexual lineages, when there was no recombination event, they followed the reproduction mode of asexual lineages. But when recombination happened, sexual lineages were randomly divided by half and assigned transient 'female' and 'male' labels with an equal number. Only individuals with female labels were allowed to recombine with males to reproduce the offspring. Both asexual lineages and sexual lineages competed against each other in the population pool which can hold a fixed number of 10,000 individuals.

In a typical competition round, an individual was randomly selected from the population pool, if the selected individual was from asexual lineages, then the individual was cloned and then subject to mutation followed by selection; whereas if the selected individual was from sexual lineages, and if it was also labelled as a female, the selected individual was allowed to recombine with a randomly selected male, then similarly the recombinant was subject to mutation followed by selection. This process was repeated until 10,000 offspring were selected. The two fold cost of sex was modelled in a way where sexual lineages only had half chance to be selected to reproduce offspring than asexual lineages in the population. Note that when there was no recombination occurring in the sexual lineages, both individuals with 'female' and 'male' labels were allowed to reproduce offspring by cloning themselves. In other words, the twofold cost of sex is only considered whenever recombination occurs.

Exploring conditions for benefits of sex and recombination recouping costs of sex

In this set of experiments, we thoughtfully explored how selection pressure along with recombination frequency and mutation rate affects the winning probability of sexual lineages competing against asexual lineages in the face of both recombination cost and twofold cost (Figure 9). Specifically, in order to avoid the effects of perturbations such as drift on the competition results, instead of dividing the population into asexual and sexual lineages at the very starting generation, two categories of lineages were differentiated at the first recombination event (by randomly selecting half population is asexual and the other half is sexual). In other words, the whole population was evolved by accumulating mutations regardless sexuality before the first recombination event, and both the asexual and the sexual population had the same number of 5000 individuals when the twofold cost of sex was introduced in the model. For each competition trial, the whole population was allowed to evolve for total 500 generations. If the number of sexual lineages is greater than the number of asexual lineages at the end of evolution, the sexual population wins, and vice versa. For each parameter combination (selection pressure, recombination frequency and mutation rate), the winning probability of sexual lineages was recorded based on 100 independent competition runs. Note that we use the same population pool for all competition trials. The complete results can be found in Table A1.

Results

Strong selection pressure benefits low-fitness sexual lineages

We first investigated the effects of different levels of selection pressure on individual's fitness. We find that low-fitness sexual lineages benefit most when the population is subject to strong selection strength for the target phenotype. Specifically, we compared the gained fitness of offspring in proportion to their parental fitness for both asexual and sexual lineages evolved under different levels of selection pressure. From Figure 1, we can see that only lineages that have been classified into the group (the first bin) with the lowest fitness in the asexual population can slightly benefit when the selection pressure is sufficiently strong, whilst for the rest asexual lineages, the benefit of higher selection pressure is largely absent.

In contrast, from Figure 2, we can clearly see that the group (the first bin) of lineages with the lowest fitness in the sexual population substantially benefits under strong selection regime (σ=100). We can also see that groups of sexual lineages with lower fitness generally gain a benefit from selection in a magnitude depending on its strength. However, the magnitude of benefit for low-fitness sexual individuals generally reduces when we further studied the proportion of gained fitness in the evolved population (Figure 3).

This is because, after many generations of recombination, the sexual lineages have well adapted to the environment, approaching to the optimum. It should be also noticed that although strong selection strength slightly deteriorates high-fitness lineages at the early stage (Figure 2), it is becoming beneficial for the evolved population (Figure 3). Taken together, these results help explain why some species increase recombination rate or switch from asexual reproduction to sexual reproduction mode when they are subject to certain extreme environments such as in the face of pathogen infection.

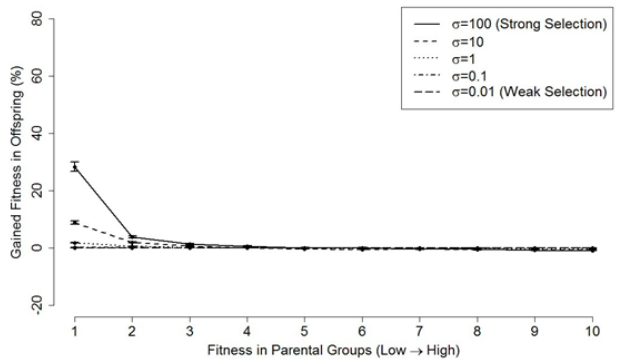

Figure 1: Comparison of effects of different levels of selection pressure on offspring fitness in asexual lineages. We first collected an initial population pool of 10,000 randomly-generated stable networks (N=10 and c=0.75). Then, we recorded each individual's initial fitness and its offspring fitness after evolving asexually for one generation under different selection pressure: σ=100 (strong), 10, 1, 0.1 and 0.01 (weak), and grouped all individuals into 10 bins based on their parental fitness in ascending order. Next, for each of ten bins, we calculated the mean gained fitness of offspring in proportion to their corresponding parental fitness. Error bars represent 95% confidence intervals based on 100 independent runs.

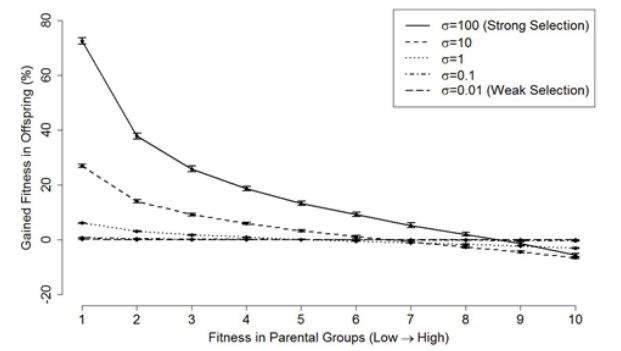

Figure 2: Comparison of effects of different levels of selection pressure on offspring fitness in sexual lineages. We first collected an initial population pool of 10,000 randomly-generated stable networks (N=10 and c=0.75). Then, under different selection pressure: σ=100 (strong), 10, 1, 0.1 and 0.01 (weak), the population was evolved sexually for one generation, and we recorded each offspring's fitness as well as the mean initial fitness of its two parents as the estimated parental fitness. All individuals were grouped into 10 bins based on their parental fitness in ascending order. Next, for each of ten bins, we calculated the mean gained fitness of offspring in proportion to their corresponding parental fitness. Error bars represent 95% confidence intervals based on 100 independent runs.

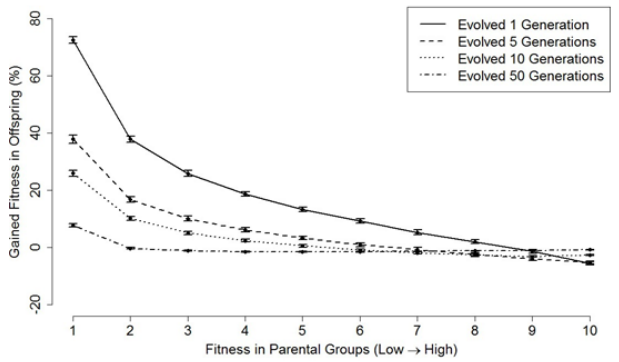

Figure 3: Comparison of gained fitness in evolved sexual lineages under strong selection pressure. We used the same population pool of 10,000 randomly-generated stable networks with size N=10 and connectivity c=0.75 as described in Figure 2. The population was evolved sexually under selection pressure σ=100. Then we recorded each individual's fitness at the initial, the 4th, 9th, 49th generation as well as its offspring fitness in the subsequent generation of the 1st, 5th, 10th, 50th, respectively. We then calculated the mean gained fitness of offspring in proportion to their corresponding parental fitness for each of four categories in which all individuals were sorted and grouped similarly as described in Figure 2. Error bars represent 95% confidence intervals based on 100 independent runs.

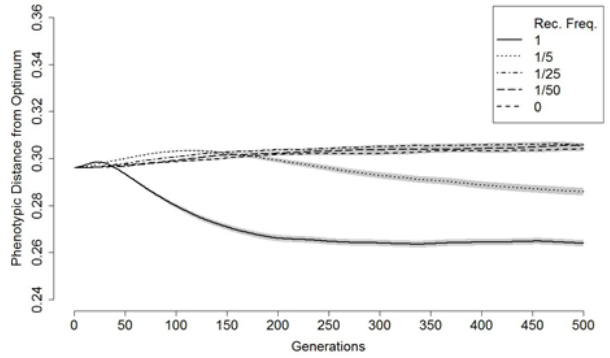

Figure 4: Phenotypic distance of the population evolved under extreme weak selection pressure. We first collected an initial population pool of 10,000 randomly-generated stable networks with size N=10 and connectivity c=0.75. Then, the population was evolved with recombination frequency at 1 (recombination occurring at each generation), 1/5, 1/25, 1/50 and 0 (no recombination at all) under extremely weak or even absent selection (σ=109) for the target phenotype. Note that, for each generation where there is no recombination happening, individuals are reproduced asexually. The mutation rate is set to be μ=0.1. Shaded areas represent 95% confidence intervals based on 10 independent runs.

Benefits of sexual reproduction can afford the recombination cost incurred by selection pressure

In our previous work [8], we have shown that sexual lineages evolve to be insensitive to mutational perturbations even when the selection for the optimal phenotype (individual's initial expression state) is largely absent. Here, we further investigated the recombination cost incurred by selection pressure. We find that selection pressure can increase benefits of sexual reproduction which are sufficient to compensate for the recombination cost. Specifically, we measured the phenotypic distance between the optimum and population that was evolved with different recombination frequency under extreme weak selection (σ=109) and strong selection (σ=0.5) regimes, respectively.

From Figure 4, we can see that when the selection pressure is extremely weak or even absent, the recombination should be sufficiently frequent (occurring at each generation or every 5 generations) to be able to drive the population towards the optimum.

Otherwise, if the recombination is less frequent or absent, then the population is unable to move towards or even slightly deviate the optimum. Note that when the population is evolved under extremely weak selection, there is no recombination cost or it can be largely neglected. This is because the differences of phenotypic distance between the individual and the optimum will not affect its fitness calculated by Equation (3) since the selection pressure is set to be σ=109. However, as shown in Figure 5, when selection strength is strong, it is expected to see that population is able to move more rapidly towards the optimum.

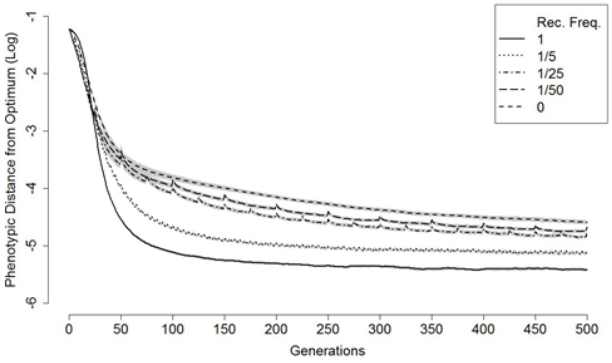

Figure 5: Phenotypic distance of the population evolved under strong selection pressure. We first collected an initial population pool of 10,000 randomly-generated stable networks with size N=10 and connectivity c=0.75. Then, the population was evolved with recombination frequency at 1 (recombination occurring at each generation), 1/5, 1/25, 1/50 and 0 (no recombination at all) under strong selection (σ=0.5) for the target phenotype. Note that, for each generation where there is no recombination happening, individuals are reproduced asexually. The mutation rate is set to be μ=0.1. Shaded areas represent 95% confidence intervals based on 10 independent runs.

We can also see that periods of recombination in sexual lineages are sufficient to drive the population evolving faster than asexual lineages (no recombination). Note that the rugged curves with recombination

frequency at 1/5, 1/25 and 1/50 appeared in Figure 5 clearly show the recombination cost, which is the disruption of well-adaptive lineages. These results suggest that periods of recombination are enough to afford its cost incurred by selection pressure.

Selection pressure can be beneficial to afford the costs of sex under certain conditions

In the previous section, we have shown that benefits of sexual reproduction are sufficient to afford the recombination cost incurred by selection pressure. Here, we first explored whether the benefits are enough to accommodate the twofold cost of sex in a competitive regime. We find that, under certain conditions, sexual lineages can outcompete asexual lineages despite the recombination cost as well as the twofold cost. Figure 6 shows the frequency of sexual lineages in the population in the first 150 generations (Note that this is a part of results presented in Figure 7 where asexual and sexual lineages compete against each other for total 500 generations).

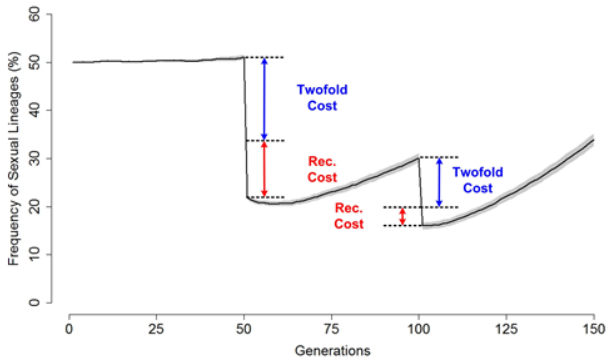

Figure 6: Visualizing recombination cost and twofold cost in a competitive regime. A total number of 10,000 individuals (5000 asexual lineages and 5000 lineages) were evolved and competed against each other for 500 generations (Figure 7 for more details). When recombination occurred at 50th and 100th generation, the reduced frequency of sexual lineages in the population is due to two costs of sex-recombination cost (in blue) and twofold cost (in red). The recombination cost is modelled in the situation where recombination disrupts well-adapted sexual lineages. The twofold cost is modelled in the situation where only half of sexual lineages, if being selected, are allowed to reproduce offspring. The selection strength σ=1, and the mutation rate is $\mu=10^{-4}$. Shaded areas represent 95% confidence intervals based on 46 sexual winning trials of total 50 independent competition runs.

From Figure 6, we can see that a single bout of recombination which occurs at the 50th and the 100th generation, the frequency of sexual lineages immediately reduces due to the recombination cost (indicated by red arrow) and the twofold cost (indicated by blue arrow). To be more specific, on the one hand, the recombination cost is caused by disrupting well-adapted sexual lineages.

On the other hand, the twofold cost has been explicitly modeled in the competition where only half of sexual lineages are able to reproduce offspring. This mimic the phenomenon in most multicellular sexual species where only females are capable of bearing babies, whilst males cannot themselves produce offspring [33,34]. However, we can also clearly see that after the first single bout of recombination, the frequency of sexual lineages increase, though there is only about 20% of sexual lineages in the population at the 51th generation. Both of recombination cost and twofold cost become smaller in the second bout of recombination happening at the 100th generation. It should be noted that the twofold cost of sex is modelled constantly associated with recombination, but it can be reduced because the reproductive output (fitness) is higher in sexual lineages than in asexual lineages (Figure 8).

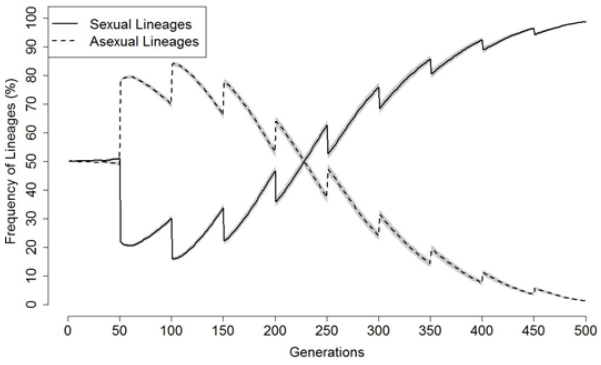

Figure 7: Frequency of asexual and sexual lineages in competition. We first collected 5000 randomly- generated stable networks with size N=10 and connectivity c=0.75 labelled as asexual lineages, then they were cloned to generate the sexual population, forming total 10,000 individuals in the initial population pool for competition. Asexual and sexual lineages competed against each other for 500 generations. When recombination occurred (in every 50 generations) in sexual lineages, only half of lineages were allowed to reproduce offspring, whereas when there was no recombination, both asexual and sexual lineages can be selected with a probability in proportion to their total amount in the population pool to reproduce offspring by cloning themselves. The resulting offspring were then subject to mutation followed by selection until the same amount of 10,000 individuals were selected for the next generation. The frequency for both asexual and sexual lineages was recorded at each generation. The selection strength σ=1, and the mutation rate is $\mu=10^{-4}$. Shaded areas represent 95% confidence intervals based on 46 sexual winning trials of total 50 independent competition runs.

In other words, although asexual lineages have a higher chance to be selected for reproduction, especially at the earlier stage, whereas only half of sexual lineages can be selected for reproduction, sexual lineages are still likely to survive in the subsequent generation if the recombinants have a higher fitness than asexual offspring. From Figure 8, we can also notice that the recombination cost in reducing the fitness indicted by the immediate drops in sexual lineages is also decreasing during the evolution. Taken together, these results suggest both of recombination cost and twofold cost can be minimized, and benefits arising from the sexual reproduction are able to facilitate a fast adaptation and ultimately help sexual lineages resist invasion by asexual lineages.

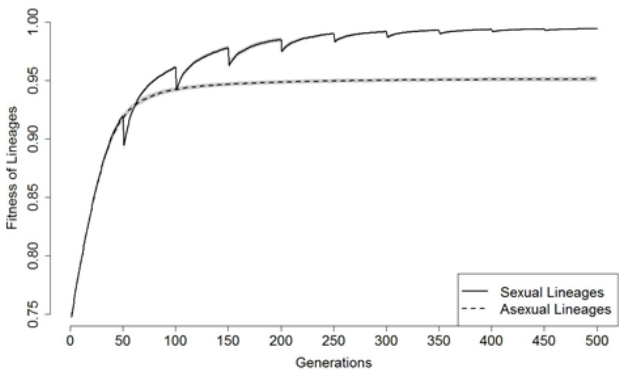

Figure 8: Fitness of asexual and sexual lineages in competition. As the results presented in Figure 7, we also measured the fitness of asexual and sexual lineages at each generation during the competition. The selection strength σ=1, and the mutation rate is $\mu=10^{-4}$. Shaded areas represent 95% confidence intervals based on 46 sexual winning trials of total 50 independent competition runs.

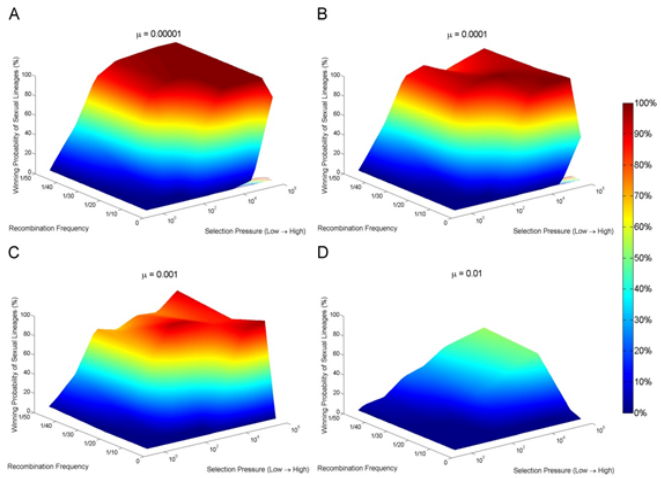

Figure 9: The influence of selection pressure and recombination frequency on competition out- comes. The asexual population contained 5000 randomly-generated stable networks (N=10 and c=0.75), and was cloned to form the same amount of sexual population, 10,000 individuals in the initial population pool. Then, asexual lineages competed against sexual lineages for total 500 generations under different se- lection pressure: σ=0.5 (weak), 1, 10, 10^2, 10^3, 10^4, 10^5 and 10^6 (strong), and different recombination frequency: $f_{Rec.}$=1/5, 1/10, 1/25 and 1/50). We also performed similar competition simulations using different mutation rate: (A) $\mu=10^{-5}$, (B) $\mu=10^{-4}$, (C) $\mu=10^{-3}$ and (D) $\mu=10^{-2}$. If the number of sexual lineages is greater than the number of asexual lineages at the end of evolution, then sexual lineages win, otherwise, asexual lineages win. The winning probability of sexual lineages was recorded based on 100 independent competition runs. The surface was generated using linear interpolation. The complete results can be found in Table A1.

Next, we explored the parameter space to investigate how recombination cost incurred by selection pressure and twofold cost incurred by recombination frequency affect competition outcomes. We also examined competition results under different mutation rate. We find that generally asexual lineages are more likely to outcompete asexual lineages when selection pressure is higher and recombination is less frequent under a lower mutation rate. Specifically, starting with an equal frequency (50%), asexual lineages and sexual lineages competed against each other in a fixed space, which can hold 10,000 individuals, for total 500 generations. Figure 9 shows competition outcomes for each combination of parameters (selection pressure, recombination frequency and mutation rate) based on 100 independent competition runs. As can be seen from Figure 9, generally recombination benefits facilitated by selection pressure are able to afford both the recombination cost caused by selection pressure itself and the twofold cost caused by recombination frequency under higher selection pressure and lower recombination frequency. It should be also noted that a lower mutation rate can also help sexual lineages outcompete asexual lineages.

Discussion

Sexual reproduction is prevailing in animals, plants and even fungi. Although a large number of theories have been proposed to explain the maintenance of sex and recombination, it remains a great puzzle in evolutionary biology [35]. Previous work has shown that recombination rate can be increased in organisms when they are subject to higher selection pressure. For example, Zhong and Priest [36]; Zhong [37] exposed Drosophila melanogaster to mating stress, heat shock and cold shock, and found that each stress treatment can increase the rate of recombination. Jackson et al. [38] also showed that the recombination rate is increased in Drosophila melanogaster in response to parasite infection. In this chapter, we have shown that low-fitness sexual lineages can greatly benefit from recombination in the presence of strong selection pressure (Figure 2), especially at the early stage. This may help explain benefits of recombination in terms of facilitating low-fitness sexual lineages to adapt to new environments under stress.

In our previous work [8], we have shown that recombination together with the selection for developmental stability can drive sexual lineages towards the optimum, even in the absence of selection for the optimal phenotype. However, it is still not clear whether these benefits can compensate for the recombination cost since the selection pressure for the target phenotype is extremely weak or even absent in the simulations presented in In our previous work [8]. When population is evolved under high selection pressure, the recombination cost cannot be neglected. If the recombinant deviates the optimum, then its fitness reduces dramatically if the individual is subject to high selection pressure. In this chapter, we have shown that benefits of recombination are able to offset the recombination cost (Figure 5). In fact, periods of recombination are sufficient to afford such a cost inured by selection pressure in sexual lineages. In the later competition study, we have explicitly modelled both the recombination cost and the twofold cost into the system to investigate whether benefits of recombination are sufficient to accommodate the two costs. Specifically, the competitive advantage of asexual lineages relative to sexual lineages (Note that here we do not consider sexual hermaphrodites), i.e., the twofold cost of sex, is associated with recombination frequency. Wherever recombination happens in sexual lineages, they have to pay for the cost such that only half of lineages is allowed to produce offspring. We have shown that sexual lineages with less frequent recombination can outcompete asexual lineages under high selection pressure (Figures 7

and 9). In addition, higher mutation rates also reduce the winning probability of sexual lineages (Figure 9). This may consistent with previous work that sexual reproduction will be favoured with a lower level of mutation rate [39,40]. This also suggests that although recombination can massively alter patterns of gene regulation, it is essentially different from hyper-mutation [8]. It should be noted that the population size, though it has not been thoroughly explored in this chapter, is expected to affect the winning probability as indicated in Le Cunff and Pakdaman [41]. The deterministic mutation hypothesis for explaining the maintenance of sexual reproduction speculates that recombination can help purge deleterious mutations more effectively [42]. This is because the theory typically assumes deleterious mutations display synergistic epistasis, causing a profound reduce in fitness via recontamination, and consequently are more likely to be eliminated by natural selection. Azevedo et al. [30] reported the supportive simulation results that synergistic epistasis can be evolved as a by-product of the selection for genetic robustness in sexual lineages in the context of genetic networks. However, many studies have challenged this deterministic mutation hypothesis. For example, MacCarthy and Bergman [43] introduced a recombination modifier to the Wagner GRN model and found that the emergent synergistic epistasis cannot explain the maintenance of sexual reproduction. Lohaus et al. [15] also examined the hypothesis, and confirmed that there is no evidence that the long and short-term advantages of sex and recombination cannot be explained by the synergistic epistasis. In fact, we also have shown that recombination can rapidly purge weaker configurations even when the selection is largely absent [8]. This pattern should be particular evident when the mutation rate is higher as indicated in Figure 9. In the competition simulations presented in this chapter, the epistasis has not explicitly measured. But it is expected that the competition results cannot be explained by synergistic epistasis since sexual lineages only have periods of recombination so that the synergistic epistasis may not exist or can be largely neglected.

If the capability of effectively reducing mutation load in sexual lineages cannot be explained by synergistic epistasis due to the lack of evidence that it can be evolved to a sufficient level, then alternative explanations for the costly sexual reproduction are needed. Becks and Agrawal [44] used experimental populations of a facultative sexual species of rotifer *Brachionus calyciflorus* to show that although recombination breaks up well-adapted gene combinations, and consequently reduces the mean fitness in offspring, but sexual reproduction can generate offspring with more variable fitness, allowing for faster adaptation. In this chapter, we also provide simulation results to support this empirical study (Figures 8 and A2). Many previous studies also have indicated that non-random mating can alter reproductive success in the face of competition or choice to help purge deleterious mutations [27,45-47]. The competition results from Figure 9 may also imply that it is non-random mating that helps sexual lineages outcompete asexual lineages. This is because one of reasons that sexual population is more likely to win under substantial selection pressure is that only certain recombinants are able to reach the threshold imposed by the selection, whereas asexual lineages are impossible to pass through the selection barrier via mutation only [21,41,48-50].

Conclusion

In this paper, we have presented two case studies to show that the selection pressure acting on rewiring gene regulation is critical to increasing benefits whilst migrating costs of sex and recombination. In the first study, we have shown that that low-fitness sexual lineage benefit most when the population is subject to strong selection pressure for the target phenotype, especially at the early stage. In contrast, the benefit of evolving under strong selection pressure is largely absent in asexual lineages. These results have important implications for explaining why some species increase recombination rate or switch from asexual reproduction to sexual reproduction mode when they are subject to certain extreme environments such as in the face of pathogen infection. In the second study, we have shown that selection pressure can increase benefits of sexual reproduction which are able to compensate for the recombination cost. In fact, periods of recombination in sexual lineages are sufficient to drive the population evolving faster than asexual lineages. In the competition study, we have shown that recombination is initially costly, but it can rapidly evolve to compensate for costs of sex and recombination. We have further explored the parameter space to investigate how recombination cost incurred by selection pressure and twofold cost incurred by recombination frequency affect competition outcomes. We have shown that that generally sexual lineage is more likely to out compete asexual lineages when selection pressure is higher and recombination is less frequent under a lower mutation rate. These results have important implications for explaining the maintenance of sex and recombination in the context of genetic networks. However, it should be noted that although we have shown that sexual lineages can outcompete asexual lineages under certain conditions, it is still not clear how sexual reproduction can still be favoured in the face of the invasion by asexual lineages that are derived from sexual lineages. In other words, if asexual lineages have gained the same benefits from the evolved sexual lineages, then how sexual reproduction can still be maintained. It is natural to envision that if both sexual and asexual lineages still compete against each other once evolved in the same environment, the asexual population is more likely to win since both asexual and sexual lineages have evolved closely to the optimum, but sexual lineages have still to pay for the twofold cost of sex. Therefore, it is interesting to explore how selection pressure, frequency of recombination and mutation rate affect the maintenance of sexual reproduction in changing environments since previously work has indicated that fluctuating environments can facilitate a fast adaptation. It is also interesting to perform simulations using different mating strategy or track the recombinant of reproductive success to thoroughly examine, for example, the role of sexual selection in maintenance of sex in the context of genetic networks.

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