Recombination Is Surprisingly Constructive for Artificial Gene Regulatory Networks in the Context of Selection for Developmental Stability

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Abstract
Recombination is ubiquitous in multicellular plants, animals and even fungi. Many studies have shown that recombination can generate a great amount of genetic innovations, but it is also believed to damage well-adapted lineages, causing debates over how organisms cope with such disruptions. Using an established model of artificial gene regulatory networks, here we show that recombination may not be as destructive as expected. Provided only that there is selection for developmental stability, recombination can establish and maintain lineages with reliably better phenotypes compared to asexual reproduction. Contrary to expectation, this does not appear to be a simple side effect of higher levels of variation. A simple model of the underlying dynamics demonstrates a surprisingly high robustness in these lineages against the disruption caused by recombination. Contrary to expectation, lineages subject to recombination are less likely to produce offspring suffering truncation selection for instability than asexual lineages subject to simple mutation. These findings indicate the fundamental differences between recombination and high mutation rates, which has important implications for understanding both biological innovation and hierarchically structured models of machine learning.

Introduction
Understanding the introduction and maintenance of innovation in evolutionary systems is of critical interest in both artificial intelligence and evolutionary biology (Hu et al., 2014; Payne et al., 2014). Yet even basic questions such as explaining the costs and benefits of sexual reproduction are still unknown to both biological and computational science. Sex implies recombination — the reshuffling of parental genetic information, which generates heritable innovations (Eshel and Feldman, 1970; Feldman et al., 1996; Otto and Feldman, 1997; West et al., 1999). However, sexual reproduction is also considered to be very costly since it may damage well-adapted lineages, and necessarily produces fewer directly reproductive offspring, since it also produces males. Evolution should favour defection to a lower-cost strategy, such as asexual reproduction. How then is sexual reproduction maintained?

For decades, researchers have been making tremendous efforts and proposing numerous theories to uncover the mystery of sex and recombination (Eshel and Feldman, 1970; Hurst and Peck, 1996; West et al., 1999; Otto and Lenormand, 2002; Meirmans and Strand, 2010; Wagner, 2011). Two classic benefits of sexual reproduction are nevertheless still controversial: 1) purging deleterious mutations more efficiently, and 2) creating novel gene combinations (Kondrashov, 1993; Otto and Feldman, 1997; Otto and Gerstein, 2006; Kouyos et al., 2007; Barton, 2009; Martin and Wagner, 2009). An important third possibility is that the process of recombination, by allowing the localization of both coherence and variation across the genomes of a population, is able to both improve robustness and facilitate evolutionary adaptation, a process known as evolvability (Wang et al., 2014). Although robustness and facilitated adaptation are observed phenomena, and are often attributed to sexual reproduction, the underlying mechanisms are still poorly understood (Wagner, 2011).

Recently, a gene regulatory network (GRN) model first proposed by Wagner (1994, 1996) has emerged as a popular computational approach to study recombination in a network context (Azevedo et al., 2006; MacCarthy and Bergman, 2007; Lohaus et al., 2010; Le Cunff and Pakdaman, 2014). One novel feature in Wagner’s GRN model is that it introduces selection for phenotypic stability, performed as a separate layer of truncation selection in addition to selection for a particular optimal phenotype. Because of this truncation selection imposed on the population, only individuals that can achieve developmental equilibrium (reaching a stable phenotypic pattern) are able to survive during evolution. The central assumption is that an individual’s phenotype should be able to buffer against genotypic variations (Wagner, 1996). In other words, stability selection provides a viable simulation for the known natural phenomenon of an individual’s phenotype being expressed relatively stably while its genotype undergoes evolution.

An interesting feature of studying evolution in artificial gene regulatory networks is that we can find clear evidence that evolution is not a simple optimisation process. The shifting genetic characteristics of the population resulting from mutation and selection optimise and innovate, but in
Nature the optima they track are also transient. Consequently, goals for an evolutionary genome always include robustness and agility, not only gradient ascent. In a previous study, Siegal and Bergman (2002) showed that even without significant selection towards an optimal phenotype, lineages are still able to move towards the optimum so long as the population is under selection for developmental stability. Although this suggests stability selection is an important evolutionary force, the role of recombination is left unclear since the earlier simulations ignored the possibility of asexual populations. In a different study, Azevedo et al. (2006) and Lohaus et al. (2010) discovered that sexually reproducing organisms evolved higher mutational and recombinational robustness than asexual lineages. But these authors did not measure the phenotypic distance of evolved asexual and sexual populations from the optimum. Therefore, it is an open question whether recombination is still able to sustain sexual reproduction as lineages near a fitness peak.

Figure 1: State transitions in an artificial gene regulatory network. There are three states in the system: C: individuals that are close to the optimum, F: individuals that are far from the optimum, and U: individuals that are unable to achieve developmental stability. U is an absorbing state in the system, since unstable genomes cannot reproduce.

To get a better intuition for the questions of evolution in a GRN presented here, we employ a simple three-state model, as shown in Figure 1. Consider the probabilities ($p_{C,F}$ and $p_{F,C}$) of a lineage’s bidirectional movements from being close to the optimum to being far from the optimum (C → F) and vice versa (F → C). We expect both to be fairly high in absence of substantial selection for the optimal phenotype. Recombination in particular is a strong force that can substantially alter gene regulation in offspring networks. Therefore, the state transition probabilities for asexual populations may differ from those of sexual populations because mutation has a weaker effect. This also indicates that one of the observations made in Siegal and Bergman (2002) (their Figure 2) may not be correct for asexual lineages since the authors only reported the results in sexual lineages. In addition, the arguments for the benefits of sex and recombination in Azevedo et al. (2006) and Lohaus et al. (2010) are also incomplete, since these only show $p_{C,U}$ becomes smaller due to a greatly increased mutational and recombinational robustness, leaving it still unclear whether or not recombination is able to retain sexual lineages in C, since $p_{C,F}$ and $p_{F,C}$ are largely unknown.

Here we report the discovery of a new possible explanation for the widespread existence of sexual rather than asexual lineages. We found this by exploring systematically the approach to optima with only negligible selection (“no selection” as per Azevedo et al. (2006)) for a particular phenotype, but only when there is selection for developmental stability. Using evolutionary simulations under the GRN model, we show that it is the evolutionary force of recombination together with developmental stability selection that drives populations towards the optimum. We further develop mathematical expressions for the conditions under which this process can be maintained. We find quite surprisingly that recombination does not frequently disrupt well-adapted lineages as conventionally expected. Rather it facilitates finding good genetic combinations robust to disruption, though it also rapidly disrupts weaker configurations. Our results indicate a fundamental difference between recombination and hyper-mutation, which has important implications for the role of gene regulation in the evolution of sex, and for the use of structured representations in machine learning.

Methods

Genotype & Phenotype

In this paper, we use the gene regulatory network (GRN) model originally proposed by Wagner (1994, 1996), and developed by Siegal and Bergman (2002). In the GRN model, the genotype is presented as a network which contains interactions among transcriptional genes. Formally, for each individual network in a finite population $M$, an $N \times N$ matrix $W$ is an artificial gene network that contains the regulatory interactions among $N$ genes (see Figure 2A). Each element $w_{ij} \ (i,j = 1,2,\ldots,N)$ represents the regulatory effect on the expression of gene $i$ of the product of gene $j$ (see Figure 2B). The network connectivity parameter $c$ determines the proportion of non-zero elements in the network $W$. A zero entry means there is no interaction between two genes. Through gene interactions, the regulatory effect acts on each gene expression pattern. The phenotype for a given network $W$ is denoted by a state vector $S(t) = (s_1(t), s_2(t), \ldots, s_N(t))$ where $s_i(t)$ represents the expression level of gene $i$ at time $t$. Each value of expression state $s_i(t)$ is within the interval $[-1, +1]$ that expresses complete repression ($-1$) and complete activation ($+1$). The basic idea is that the individual’s phenotype is controlled by the complex interactions between its genes. Formally, for a given gene regulatory network $W$, the dynamics of $S$ for
each gene $i$ is modelled by

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

where $f(x)$ is a sigmoidal function. In this paper, we define $f(x) = 2/(1 + e^{-ax}) - 1$ (Siegal and Bergman, 2002), where $a$ is a free parameter determining the rate of change from complete repression to complete activation. When $a$ is large enough, for example $a = 100$, $f(x)$ is similar as a step function where $f(x) = -1$ for $x < 0$, $f(x) = +1$ for $x > 0$ and $f(0) = 0$.

In all simulations, we define a network’s developmental stability as the progression from an initial expression state to an equilibrium expression state (reaching a fixed pattern) by iterating Eq. (1) a fixed number of times, $devT$. If a given network $W$ can achieve developmental stability, then it is termed a viable or stable network, otherwise it is labelled unviable or unstable. We consider an equilibrium state to be reached when the following equation is met:

$$\frac{1}{\tau} \sum_{\theta=\tau}^{t} D(S(\theta), S(t)) \leq 10^{-4}, \quad (2)$$

where $D(S, S') = \sum_{i=1}^{N} (s_i - s'_i)^2 / 4N$ measures the difference between the gene expression pattern $S$ and $S'$, and $S$ is the average of the gene expression levels over the time interval $[t-\tau, t-\tau+1, \ldots, t]$. We use $N = 10$, $c = 0.75$, $devT = 100$, $\tau = 10$ and $a = 100$ in all simulations.

**Fitness Evaluation**

For networks that achieve developmental stability (reaching an equilibrium state, $S_{EQ}$), we then calculate fitness as (Siegal and Bergman, 2002)

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

where $\sigma$ is the selection pressure that we imposed on the population during evolution. $S_{OPT}$ is usually set to $S(0)$. $D(S_{EQ}, S_{OPT})$ is the phenotypic distance between the equilibrium state and the optimal state. Unless otherwise specified, we assign zero fitness to individuals that cannot reach developmental equilibrium.

**Initialisation**

The initial population contains $M = 10,000$ identical clones of a founder network, which is generated by randomly filling $W$ with $c \cdot N^2$ non-zero elements $w_{i,j}$ drawn from the standard normal distribution, $N(0,1)$. The associated initial expression state $S(0)$ is setting each $s_i(0)$ to $+1$. We require that the founder network is not only able to achieve developmental stability but also able to express the optimal state, i.e., $D(S_{EQ}, S(0)) = 0$.

![Network representation of the regulatory iteration between five genes. Open and filled circles represent the genes associated initial expression state $S_{EQ}$.](image)

**Mutation**

For an individual network, each non-zero entry in the $W$ interaction matrix is replaced by $w'_{i,j} \sim N(0,1)$ with mutation rate $\mu$. The expected number of mutations in $W$ is drawn from the Poisson distribution with expectation parameter $\lambda = \mu$. In all simulations, we used $\mu = 0.1$, which means on average there is 0.1 non-zero entry in $W$ that will be mutated per network per generation. Note that mutations should be viewed as operating on the $c \cdot N^2$ cis-regulatory elements, not the coding sequences of the $N$ genes themselves (Wagner, 1996; Siegal and Bergman, 2002). In other words, the mutation operation cannot change the topology of the original network $W$.

**Recombination**

A recombinant is produced by picking two individuals and selecting rows of the $W$ matrices from each parent with equal probability. This process is similar to free recombination between units formed by each gene and its cis-regulatory elements, but with no recombination within regulatory regions.

**Stability & Fitness Selection**

If individuals are evolved under a regime of stability selection, we only allow ones that can reach developmental equilibrium to stay in the population. Otherwise, if individuals

are evolved without stability selection, then we allow both stable and unstable individuals in the population. In all simulations, we set \( \sigma = 10^0 \), which means all populations are evolved under extremely weak or absent selection for the optimal phenotypic state.

**Perturbation Test**

In order to measure the distance within the population, or the distance between the population and the optimal phenotype, we use a similar perturbation test as described in Siegal and Bergman (2002): We define a perturbation as a single mutant, i.e., exactly one non-zero entry in \( W \) is replaced by a random value drawn from \( N(0,1) \). For each individual in the population, if its perturbed network can still reach a steady state, we define it as \( S_P \), otherwise \( S_P = S(\text{dev}T) \). The distances between the perturbed individual and its unperturbed one or the optimal phenotypic state are defined as \( D(S_P,S_{EQ}) \) and \( D(S_P,S_{OPT}) \), respectively. For each individual, the distance is estimated by averaging 10 perturbations. The reported results are averaged over 10,000 individuals in the population, total 100,000 perturbations.

**State Transition Probability Measurement**

To measure all state transition probabilities \( p_{ij} \) \( (i,j \in \{ C, F \text{ and } U \}) \) as shown in Figure 1, we need to find two populations that are in state \( C \) and state \( F \) for both asexual and sexual populations, respectively. Specifically, as Figure 3 indicates, we use the below four evolved populations for further analysis purpose: For individuals that are close to the optimum, we choose the asexual and sexual populations that have been evolved 1000 generations with stability selection. For individuals that are far away from the optimum, we choose the stable individuals from the asexual and sexual populations that have been evolved 1000 generations without stability selection. Note that the chosen sexual and asexual populations are not perfect but reasonable approximations of two sets of individuals that are in state \( C \) and state \( F \), respectively.

For these four populations, each individual will experience either asexual or sexual reproduction, or be subjected to one single mutation (replacing exactly one non-zero \( w_{ij} \) with a random value drawn from \( N(0,1) \)). We can easily take the proportion of stable offspring as \( 1 - p_{C;U} \) and \( 1 - p_{F;U} \). Those stable mutants are saved to further measure the remaining four parameters in Figure 1. We take the mean and standard deviation of the phenotype distance to the optimum at the 1000th generation from sexual population (solid red line in Figure 3) as a criterion for \( C \) to test whether the mutants are closer to the optimum. Similarly, we take the mean and standard deviation of the phenotype distance away from the optimum at the 1000th generation from asexual population (dashed blue line in Figure 3) as a criterion for \( F \) to test whether the mutants are further away from the optimum.\(^1\) For each mutant that is derived from \( C \), if its phenotypic distance is smaller than 2 standard deviations, we count it as in \( p_{C;C} \), otherwise it will be counted as in \( p_{C;F} \). Similarly, for each mutant that is derived from \( F \), if its phenotypic distance is greater than 2 standard deviations, we count it as in \( p_{F;F} \), otherwise it will be counted as in \( p_{F;C} \).

**Evolution**

As in previous studies (Wagner, 1996; Siegal and Bergman, 2002; Azevedo et al., 2006; Lohaus et al., 2010), the evolutionary simulations are performed under the reproduction-mutation-selection life cycle. The population size \( M \) is fixed in every generation throughout evolution in all simulations. In typical asexual evolution, an individual is chosen at random to reproduce asexually by cloning itself, and then subject to mutation, then extremely weak selection for the optimal phenotype. Similarly, in typical sexual evolution, two individuals are chosen at random to reproduce sexually by recombining two parent networks, and then subject to mutation, then extremely weak selection for the optimal phenotype. This process is repeated until the number of \( M \) networks are produced. Depending on whether or not the population evolves under a stability selection regime, we exclude unstable networks or allow these networks to stay in the population, accordingly.

**Results**

**Evolution of Phenotypic Distance**

We design two sets of simulations to investigate how mutation and recombination influence evolutionary dynamics in asexual and sexual populations using artificial gene regulatory networks. Unlike the simulation set-ups in Siegal and Bergman (2002) and Azevedo et al. (2006), we have taken both sexuality and developmental stability into consideration. For each set of experiments, the results are presented for simulations under four different evolutionary scenarios: 1) population with asexual reproduction and stability selection, 2) population with asexual reproduction but without stability selection, 3) population with sexual reproduction and stability selection, and 4) population with sexual reproduction but without stability selection. In all four cases, the selection for the optimal phenotype is extremely weak or even absent. The reported results are the mean values averaged over 10 replicated simulations, using different randomly generated founder networks.

In the first set of experiments, we measure the phenotypic distance between the evolved populations and the optimum. We compare the results of asexual and sexual populations.

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\(^1\)Since asexual and sexual populations behave similarly (cf. two dashed lines in Figure 3) when there is no selection for developmental stability, it does not matter whether we take the mean and standard deviation of the phenotype distance from asexual population or sexual population as a criterion for \( F \).

under stability or no stability selection regimes as shown in Figure 3. When there is no stability selection, both asexual and sexual populations (dashed lines in Figure 3) rapidly move away from the optimum at a similar increasing rate. In contrast, when stability selection is imposed on the sexual population (solid red line in Figure 3), the phenotypic distance is continuously decreasing. Although under a stability selection regime the phenotypic distance of asexual population (solid blue line in Figure 3) still increases slightly, stability selection greatly helps impede deviation, compared with the situation when stability selection is absent. These results suggest that the combination of the two forces of recombination and stability selection can drive the population towards the optimum.

In the second set of experiments, we measure the phenotypic distance within the evolved populations. Similarly, we compare the results of asexual and sexual populations under stability or no stability selection regimes as shown in Figure 4. In contrast to the results where we compare phenotypic distance between the evolved populations and the optimum.
optimum, the phenotypic distance within the populations reduces when there is no stability selection in both asexual and sexual populations (dashed lines in Figure 4) with a similar modestly decreasing rate. However, there is no obvious change in phenotypic distance within the asexual population (solid blue line in Figure 4) when we include stability selection. But the phenotypic distance of the sexual population (solid red line in Figure 4) is highly reduced. This indicates that recombination and stability selection can also help sexual lineages stay close to each other. Note that this phenomenon has been similarly reported in Siegal and Bergman (2002), except it can be only observed in sexual lineages rather than asexual lineages (cf. solid red and blue lines in Figure 4).

Analysis

From Figures 3–4, we can clearly see that phenotypic distance is continuously decreasing in the sexual population as the consequence of recombination and selection for developmental stability. In order to fully understand how these two forces act together, here we further investigate the underlying evolutionary dynamics in the context of artificial gene regulatory networks.

The evolutionary dynamics in the GRN model can be regarded as a Markov process since the future of the evolution process is based solely on its present state. To simplify the analysis, we define three states in the system as per Figure 1:

- **C**: Individuals that are close to the optimal phenotype.
- **F**: Individuals that are far from the optimal phenotype.
- **U**: Individuals that are unable to achieve developmental stability, and thus will be removed from the population.

Suppose at $g^{th}$ generation, the frequency of individuals in state $C$ is $f_C(g)$, so the frequency of individuals in state $F$ is $f_F(g) = 1 - f_C(g)$. Therefore, the changing rate of frequency $f_C(g)$ between two consecutive generations can be described as $\Delta C / \Delta g = f_C(g + 1) - f_C(g)$. In order to observe a decreased phenotypic distance between the current population and the optimum, the following condition should be met: $\Delta C / \Delta g \geq 0$. More formally (see Appendix), the below quadratic equation should be satisfied:

\[
(p_{F,U} - p_{C,U}) f_C^2(g) + (2p_{F,C} + p_{F,F} - p_{C,C}) f_C(g) - p_{F,C} \leq 0.
\]

(4)

It is reasonable to assume that individuals that are far away from the optimum (F) are more likely to become unstable than individuals that are close to the optimum (C), i.e., $p_{F,U} \geq p_{C,U}$. This is because there is always a selection for developmental stability that enables population moving towards the optimum, whereas the stability selection is absent, and consequently drags the population moving away from the optimum. Given that $f_C(g) \in [0, 1]$ and $p_{F,C} \geq 0$, in order to let Eq. (4) hold, $p_{C,F} \approx 0$ should hold. This suggests that as long as the population is continuously moving towards the optimum, the evolved lineages are unlikely deviated by mutation and recombination from the area close to the optimum (C) to the area far from it (F).

From the above analysis, we can speculate that as long as $p_{C,F}$ is smaller enough, we should be able to see an increased frequency of lineages in C state. From the observation of our evolutionary simulations, we further expect that $p_{C,F}$ should be smaller in sexual lineages than in asexual lineages since sexual population is moving more quickly towards the optimum, whereas a similar pattern has not been observed in asexual population.

![Figure 5](image.png)

**Figure 5**: Mean estimated state transition probabilities in sexual populations. $p_{C,U}$: 8.95% (SD: 0.28%), $p_{C,F}$: 43.78% (SD: 0.44%), $p_{C,C}$: 47.27% (SD: 0.43%), $p_{F,U}$: 23.38% (SD: 0.36%), $p_{F,C}$: 8.92% (SD: 0.08%), $p_{F,F}$: 75.80% (SD: 0.38%). SD: Standard Deviation

![Figure 6](image.png)

**Figure 6**: Mean estimated state transition probabilities in asexual populations. $p_{C,U}$: 1.66% (SD: 0.13%), $p_{C,F}$: 3.00% (SD: 0.15%), $p_{C,C}$: 95.34% (SD: 0.18%), $p_{F,U}$: 77.19% (SD: 0.43%), $p_{F,C}$: 8.95% (SD: 0.08%), $p_{F,F}$: 21.95% (SD: 0.42%). SD: Standard Deviation

Numerical Simulations

To verify our analysis, we now treat our original simulations as numerical simulations to measure the state transition probabilities $p_{ij}$ ($i,j \in \{C, F, U\}$). We use the four evolved populations described above (see Method). The re-

ported results are based on 50 independent runs as shown in Figures 5–6 for asexual and sexual populations, respectively.

We can clearly see in Figures 5–6 that \( p_{F,U} \geq p_{C,U} \) holds for both asexual and sexual populations. But only in sexual population, \( p_{C,F} \) is a small value 0.0300, whereas \( p_{C,F} \) is a much larger value 0.4378 in asexual population. These results confirm that Eq. 4 holds only for sexual populations when there is no selection for the optimal phenotype. But please note that this does not suggest that Eq. 4 will never hold in asexual populations. When selection for the optimal phenotype is turned on, we can also observe a small value of \( p_{C,F} \) in asexual population (results not shown).

From Figures 5–6, we can further calculate the stationary probabilities of lineages with \( C \) and \( F \) states for asexual and sexual populations. For the asexual population: 2.68% in \( C \) area and 97.32% in \( F \) area. For sexual population: 96.09% in \( C \) area and 3.91% in \( F \) area. These results demonstrate that recombination substantially enables sexual lineages to sustain themselves near an optimum to a surprisingly high probability. This further indicates a fundamental difference between recombination and hyper-mutation, despite their superficial similarity in causing increased variation.

**Discussion & Conclusion**

Mutation and recombination are two important evolutionary forces that provide heritable genetic innovations that ultimately stimulate adaptation for species to survive in nature. But compared with mutation, recombination is thought to be much more mysterious because it leads to a fundamental evolutionary question: how sexual reproduction, once evolved, can be maintained in the long term. In particular, we do not clearly understand why asexual lineages do not outcompete sexual lineages, given the substantial cost of recombination (disrupting good genetic combinations) and the two-fold cost of sex (producing half as many lineages because only females reproduce). Although previous studies have posited that recombination has an important role in improving robustness and facilitating evolutionary adaptation, the underlying mechanism has been unclear.

Although Siegal and Bergman (2002) have emphasised the importance of the “phenotypic buffer” for genetic innovation provided by developmental stability selection, they did not take sexuality into consideration. In later studies (Azevedo et al., 2006; Lohaus et al., 2010), the authors have reported the observed mutational and recombinational robustness evolved from sexual lineages, but they still did not clearly explain the great benefit observed in sexual populations. Here, we have used a simple, three-state system to describe the evolutionary process in the GRN model (Figure 1). With this we have shown that even if both the mutational and recombinational robustness are greatly increased (i.e. \( p_{C,U} \) is reduced), the underlying dynamics of sexual lineages have been poorly understood. One reasonable intuition would be a high transition probability of lineages moving from area \( C \) to \( F \) since recombination is thought to greatly disrupt well-adapted lineages, and consequently it would be thought of as unlikely to sustain population \( C \), close to the optimum. Therefore \( p_{C,F} \) would be expected to be high. Instead, we find that while \( p_{F,U} \) is high as similarly predicted, individuals of sexual lineages that are close to the optimum appear to be very robust against disruption by recombination. We take this as clear evidence of evolvability.

By comparing evolutionary simulations of asexual and sexual lineages under developmental stability selection or in its absence, we have shown that the conclusion in Siegal and Bergman (2002) is not complete. It is the combination of two evolutionary forces — recombination and developmental stability selection — that drives populations towards the optimum, not just stability selection alone (Figures 3–4). We have thus clarified the benefit derived from sexual lineages. Our numerical analysis has verified our assumptions and further validated our results. We have shown that recombination is surprisingly constructive for close-to-optimum sexual lineages, and only destructive to populations far from the optimum. This indicates that recombination facilitates the evolution of evolutionary robustness — a form of evolvability in sexual lineages. In contrast, mutations are more likely to be universally mildly deleterious and thus after accumulation in an asexual population, ultimately tend to move it away from the optimum. These findings indicate a fundamental difference between recombination and hyper-mutation, which has important implications both for structuring machine learning, and for finally explaining the evolutionary stability of sex.

**References**


#### Appendix

The evolution dynamics in the GRN model can be regarded as a Markov process. As described in the main text, we simply define three states in the system: C (lineages are close to the optimum), F (lineages are far from the optimum), U (lineages are unstable, and thus unviability). Therefore, suppose at $g^{th}$ generation, the frequency of individuals with state $C$ is $f_C(g)$, the frequency of individuals with state $F$ is $f_F(g) = 1 - f_C(g)$. Then at $(g+1)^{th}$ generation, the frequency of individuals with state $C$ and $F$ are $f_C(g+1) = (f_c(g) + p_{C,C} + f_F(g) + p_{F,F})/k$ and $f_F(g+1) = (f_F(g) + p_{F,F} + f_C(g) + p_{C,F})/k$, respectively, where a normalising factor $k = (f_C(g) + p_{C,C} + f_F(g) + p_{F,F}) + (f_C(g) + p_{F,F} + f_F(g) + p_{C,F})$. Therefore, the changing rate of frequency $f_C$ between two consecutive generations can be described as in the following differential equation:

$$\frac{\Delta C}{\Delta g} = f_c(g) - f_c(g) = \frac{f_c(g) + p_{C,C} + f_F(g) + p_{F,F} - f_c(g)}{k} = \frac{f_c(g) + p_{C,C} + f_F(g) + p_{F,F} - f_c(g)}{k}.$$

As population evolves towards the optimum, we expect to see a higher frequency of $f_c$ in the population, i.e., $\Delta C/\Delta g \geq 0$. Therefore, the below equation should be satisfied:

$$f_c(g) + p_{C,C} + f_F(g) + p_{F,F} - f_c(g) \geq 0.$$

Therefore, the following condition should hold:

$$(p_{F,F} + p_{C,C}) \times f_c^2(g) + (2p_{F,C} + 2p_{C,F} - p_{C,C} - p_{F,F}) \times f_c(g) - p_{C,F} \leq 0.$$

It is reasonable to assume that $p_{F,F} \geq p_{C,C}$ since there is always a selection for developmental stability when population is moving towards C, whereas the stability selection is absent when the population is moving towards F. Therefore, the quadratic equation Eq. (4) is concave up. We know that $f_c(g) \in [0, 1]$, therefore Eq. (4) will hold as long as it holds in $[0, 1]$. Therefore, the below two conditions should be satisfied:

$$-p_{C,F} \leq 0 \quad p_{F,F} - p_{C,U} + 2p_{F,C} + 2p_{C,F} - p_{C,C} - p_{F,F} \leq 0.$$

Clearly, $p_{F,F} \geq 0$ always holds, therefore the second condition which is $p_{C,F} \leq 0$ should hold. But we know that $p_{C,F} \geq 0$. Therefore, if Eq. (4) holds, then $p_{C,F} \approx 0$ should hold.