Role of epistasis on the fixation probability of a nonmutator in an adapted asexual population

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Abstract: The mutation rate of a well adapted population is prone to reduction so as to have lower mutational load. The aim here is to understand the role of epistatic interactions in this process. Using a multitype branching process, the probability of fixation of a rare nonmutator in an asexual mutator population undergoing deleterious mutations at constant, but much higher rate than that of the nonmutator is analytically calculated here. We find that antagonistic epistasis lowers chances of mutation rate reduction, while synergistic epistasis enhances it. Below a critical value of epistasis, it can be seen that the fixation probability behaves non-monotonically with variation in mutation rate of the background population for constant selection. Also, the variation of this critical value of epistasis parameter with the strength of the mutator is discussed. For synergistic epistasis, fixation probability shows a nonmonotonic trend with respect to selection when mutation rate
is held constant.
Mutation rates being different for individuals of the same species and among species (Baer et al., 2007) points to the fact that mutation rates are subject to the action of other evolutionary forces (Raynes and Sniegowski, 2014). Laboratory experiments reveal that owing to their ability to quickly generate beneficial mutations and hitchhike with them, higher mutation rate or mutator phenotype gets positively selected in populations adapting to a new environment (Smith and Haigh, 1974; Sniegowski et al., 1997; Raynes and Sniegowski, 2014). Various theoretical studies have been done on hitchhiking in adapting populations (Taddei et al., 1997; Tenaillon et al., 1999; Johnson, 1999; Palmer and Lipsitch, 2006; Wylie et al., 2009; Desai and Fisher, 2011).

Experiment by Giraud et al. (2001) sheds light into the fact that mutators are no longer beneficial after adaptation. In fact, lower mutation rate or nonmutator phenotype gets favored in populations that are adapted to an environment (Tröbner and Piechocki, 1984; Notley-McRobb et al., 2002; McDonald et al., 2012; Turriñientes et al., 2013; Wielgoss et al., 2013), in order to have reduced load of deleterious mutations (Liberman and Feldman, 2013). Since beneficial mutations are found to be much rarer compared to deleterious mutations (Drake et al., 1998), and adapted populations are assumed to be near their fittest genotype so as not to have space for further improvement, most of the theoretical studies on adapted populations have neglected the effect of beneficial mutations (Lynch, 2011; Söderberg and Berg, 2011; Jain and Nagar, 2012). However, James and Jain (2010) studied an
asexual population at mutation - selection balance in which compensatory mutations are allowed.

Assuming selective effects to be much stronger than mutation rates, so that individuals with nonzero number of mutations will get lost from the population, Lynch (2011) addressed the problem of lowering of mutation rate in an adapted population. This is effectively a one locus model. James and Jain (2016) extended the study by relaxing the strong selection assumption, and analytically calculated the fixation probability of a nonmutator arising in a background which has very high mutation rate, using a multitype branching process (Johnson and Barton, 2002). The current study aims to have a better understanding of the process of mutation rate reduction by further extending the approach of James and Jain (2016) when epistatic interactions are present.

Except Jain and Nagar (2012), all the works listed here on adapted populations considered mutations to contribute independently to fitness, which is otherwise known as a nonepistatic fitness landscape. An epistatic landscape is more general description of the actual biological scenario, since intergenetic interactions cannot be ignored. There have been numerous experiments demonstrating the presence of epistasis (Mukai, 1969; Whitlock and Bourguet, 2000; Maisnier-Patin et al., 2005; Kryazhimskiy et al., 2009; Plucain et al., 2014). The effect of epistasis on asexual populations have been explored theoretically as well (Kondrashov, 1993; Campos, 2004; Jain and Krug, 2007; Jain, 2008, 2010; Jain and Nagar, 2012; Fumagalli et al., 2015).
While Campos (2004) studied the process of fixation of a mutant with a direct selective advantage in a population that is undergoing deleterious mutations at constant rate, and Jain and Nagar (2012) explored the fixation of mutators, the focus here is to understand the fixation of nonmutators.

In the current study, we find that, for selective effects being weaker than mutation rate of the background population, synergistic epistasis (combined effect of mutations on fitness being milder than their independent effects) rises fixation probability of a rare nonmutator, whereas, antagonistic epistasis (combined effect of mutations being greater than their independent effects) lowers it. When selection is strong compared to mutation rate, fixation probability is independent of epistasis, and increases with mutation rate, which matches with the result of James and Jain (2016) in the absence of epistasis. Below a particular value of antagonistic epistasis, we see that the fixation probability initially increases, and then decreases with mutation rate of the background. In presence of synergistic interactions, fixation probability behaves nonmonotonically with variation in selection.

Our results can be extended to argue that synergistic epistasis can save asexual populations from extinction not only by lowering the rate of accumulation of deleterious mutations (Kondrashov, 1993), but also by increasing the chances of mutation rate reduction. Antagonistic epistasis, on the other hand, pushes asexuals towards extinction due to the faster rate of accumulation of harmful mutations (Kondrashov, 1993) as well as lower probability of mutation rate decline.
MODELS AND METHODS

Details of stochastic simulations

We consider a large asexual population of haploid individuals of size $N$ on a fitness landscape (Wiehe, 1997)

$$W(k) = (1 - s)^{k^\alpha},$$ (1)

where $0 < s < 1$ is the selection coefficient and $\alpha > 0$ is the epistasis parameter. Here, $k$ is the number of deleterious mutations carried by the genome, represented using a binary sequence of length $L \rightarrow \infty$, of an individual. We also denote $k$ as the fitness class, as the fitness is decided by $k$. Antagonistic epistasis is modeled by $\alpha < 1$ and synergistic epistasis by $\alpha > 1$. $\alpha = 1$ implies no epistasis. Biologically, (1) represents a genome carrying infinite number of biallelic loci that are equivalent to each other, and the effect of a new mutation at any locus depends on the number of mutations already present in the genome. The probability that the genome of an individual accumulates $x$ number of deleterious mutations at the rate $U_d$ is Poisson distributed as given below.

$$M_{U_d}(k \rightarrow k + x) = e^{-U_d} \frac{(U_d)^x}{x!}. \quad (2)$$

The population evolves via standard Wright-Fisher dynamics (Jain, 2008), where the population size is held constant in each nonoverlapping generation,
and corresponding to each individual, we randomly assign an individual in
the previous generation as its parent, which undergoes mutation, followed by
reproduction with a probability proportional to its fitness. Asexual popula-
tions can go extinct via the accumulation of deleterious mutations, a process
known as Muller’s ratchet (Haigh, 1978; Kondrashov, 1993). But, popula-
tions of size large enough to fulfil the criterion that the number of individuals
in steady state carrying zero deleterious mutations being at least 100, will
have very slowly operating Muller’s ratchet (Kondrashov, 1993) (also, see
DISCUSSION). Here, we choose populations satisfying this condition.

Populations of large size with extremely small ratchet speed, that have
been evolving for long timescales without changes in the environment attain
steady state due to mutation-selection balance. It is assumed that the non-
mutator with mutation rate $U_d' = U_d / \lambda$, where $\lambda > 1$ is the strength of the
mutator, appears once the mutator population reaches steady state. The
nonmutator also evolves via standard Wright-Fisher process, and (1) and (2)
are applicable for it with $U_d$ being replaced by $U_d'$.

In simulations, we consider the population to be at steady state ini-
tially. This assumption is verified by ensuring that the population eventually
reaches mutation-selection balance by observing single run plots correspond-
ing to the given parameter set of $s$, $U_d$ and $\alpha$, and confirming that the
population fractions stabilize at values predicted by (A.4). Fig. 1 further
justifies it, by comparing the fixation probability of a nonmutator produced
after a time interval of $10/s$ generations in a population which initially has
no deleterious mutations, with that of a nonmutator created at time \( t = 0 \) in a population that is at steady state. In this article, each simulation point is averaged over \( 10^5 \) independent stochastic runs, and except for Fig. 1, all simulations have assumed \( N = 4,000 \). Apart from Fig. 6, only nonmutators with \( \lambda = 100 \) have been considered here.

**Analysis**

Due to lower rate of deleterious mutation accumulation and fitness decline, the nonmutator appearing in mutator background in an adapted population is effectively a beneficial allele. The fixation probability of such an allele can be studied using branching process (Patwa and Wahl, 2008). The details (Johnson and Barton, 2002) are described below.

Extinction probability \( \epsilon(k, t) \) of a nonmutator which has an effective selective advantage, arising with \( k \) deleterious mutations in generation \( t \) in a very large population of mutators of size \( N \) is given by

\[
\epsilon(k, t) = \sum_{n=0}^{\infty} \psi_n(k, t) \left[ \sum_j M_{U_d}(k \rightarrow j) \epsilon(j, t + 1) \right]^n,
\]

assuming that the extinction probabilities are independent of each other. Here, \( \psi_n(k, t) \) is the probability that the nonmutator will give rise to \( n \) offspring in generation \( t \), and \( M_{U_d}(k \rightarrow j) \) is the Poisson distributed probability of the nonmutator to mutate from class \( k \) to \( j > k \). If the probability of reproduction of the nonmutator is assumed to be Poisson distributed with mean
being the same as its absolute fitness

\[ w(k, t) = \frac{W(k)}{W(t)} , \tag{4} \]

where \( W(t) = \sum_{k=0}^{\infty} W(k) p(k, t) \) is the mean fitness of the background population with \( p(k, t) \) being the fraction of population having \( k \) deleterious mutations in generation \( t \) (see Appendix A for details on the expression \( p(k) \) for population fraction in steady state), we get

\[ \psi_n(k, t) = e^{-w(k,t)} \frac{w^n(k, t)}{n!} . \tag{5} \]

With the help of (4) and (5), we rewrite (3) as

\[ \epsilon(k, t) = e^{-\frac{W(k)}{W(t)}} \left[ 1 - \sum_{j} M_{U_d}(k \rightarrow j) \epsilon(j, t+1) \right] . \tag{6} \]

The nonmutators are considered established if they do not go extinct. Due to the selective advantage possessed by the nonmutator, establishment eventually leads to fixation, and these two are taken to be the same here. Hence, the fixation probability \( \pi(k, t) = 1 - \epsilon(k, t) \) by which, it follows from (6) that

\[ 1 - \pi(k, t) = e^{-\frac{W(k)}{W(t)}} \sum_{i} e^{-U_d^{'}(i)} \frac{(U_d^{'})^i}{i!} \pi(i+k, t+1) , \tag{7} \]

as \( \sum_{i=0}^{\infty} M_{U_d}(k \rightarrow i+k) = 1 \). For a nonmutator that arises in the background
population after the attainment of steady state, (7) becomes

\[ 1 - \pi(k) = e^{-\frac{W(k)}{W}} \sum_i e^{-U'_d(i)} \frac{U'_d(i)}{i} \pi(i+k). \]  

(8)

We get the fixation probability of a nonmutator that is produced in a genetic background having \( k \) number of deleterious mutations by solving (8). But, the mutator population is distributed across so many fitness classes, and the nonmutator can appear in any of these backgrounds. So, the total fixation probability can be calculated only by taking into account all the possible genetic backgrounds. The probability of the nonmutator to appear in fitness class \( k \) is same as the fraction \( p(k) \) of background population in that class. This is an important concept which plays a major role in understanding the results. As explained above, the total fixation probability receives contributions from both probability of appearance and probability of fixation, and therefore, can be expressed as

\[ \Pi = \sum_k p(k) \pi(k). \]  

(9)

The above expression is applicable for very large populations in which the effect of genetic drift can be neglected.

RESULTS

As considered by [James and Jain (2016)], for strong mutators which have very high mutation rates (\( \lambda \gg 1 \)) compared to the nonmutator [Sniegowski et al.,...]}
Using (A.3), the average fitness of mutators in steady state is found to be

\[ \bar{W} = (1 - s)^{k^\alpha} \approx e^{-U_d}, \]

which is otherwise the classical result obtained by Haldane (1937) for the mean fitness of an asexual population. Following the approach of James and Jain (2016), taking logarithm on both sides of (10), and neglecting terms of order greater than 2 from the expansion

\[ \ln(1 - x) = -x - x^2/2 - ... \]

we can solve the resulting quadratic equation to get

\[ \pi(k) = \begin{cases} 
2 \left( \frac{W(k)}{W} - 1 \right) = 2s \left( k^\alpha - k^\alpha \right) & \text{if } k < \left\lfloor \left( \frac{U_d}{s} \right)^{1/\alpha} \right\rfloor \\
0 & \text{otherwise},
\end{cases} \]  

(11)

where \( \left\lfloor \left( \frac{U_d}{s} \right)^{1/\alpha} \right\rfloor \) is the largest integer corresponding to \( \left( \frac{U_d}{s} \right)^{1/\alpha} \), and \( k^\alpha \) is given by (A.3). We see that with rise in background mutation rate \( U_d \), \( \pi(k) \) increases, which is rather expected. The intuitive meaning of (11) is that the effective selective advantage of a nonmutator carrying \( k \) mutations, appearing in the background having mean fitness \( e^{-sk^\alpha} \) is \( s(k^\alpha - k^\alpha) \), and its fixation probability is twice that, which follows from single locus model (Fisher, 1922; Haldane, 1927).

Plugging (A.4) and (11) in (9), and performing the resulting sum give
Table 1: Class 0 mutator frequency. These expressions are derived in Appendix B.

|                  | $\alpha \leq 1$                                                                 | $\alpha > 1$                                                                 |
|------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| $(U_d/s) > 1$    | $p(0) = (2\pi)^{\frac{\alpha-1}{2}} \sqrt{\alpha} (\frac{U_d}{s})^{\frac{\alpha-1}{2\alpha}} e^{-\alpha (\frac{U_d}{s})} \frac{1}{2}^{\frac{\alpha}{2}}$ | $p(0) = \frac{1}{1+\left(\frac{U_d}{s}\right)}$ if $\alpha > \ln\left(\frac{U_d}{s}\right)/\ln 2$ |
| $(U_d/s) < 1$    | $p(0) = (1 - \frac{U_d}{s})$ if $\alpha \ll 1$                                | $p(0) = \frac{1}{1+\left(\frac{U_d}{s}\right)}$                                |

rise to

$$
\Pi = 2U_d (U_d/s)^{\left(1-\alpha\right)U_d/s} e^{U_d\alpha/s} \frac{1}{2^{\alpha/2}} \left(\frac{2\pi U_d/s}{\pi (U_d/s)^{1/2}}\right)^{1/2} p(0) .
$$

Derivations for the frequency $p(0)$ of the background population with zero deleterious mutations are given in Appendix B and the final expressions are summarized in Table 1. Based on whether the selection is strong ($U_d/s < 1$) or weak ($U_d/s > 1$), and epistasis is antagonistic ($\alpha < 1$) or synergistic ($\alpha > 1$), there are 4 regimes for $\Pi$.

**Case I.** $U_d/s > 1$, $\alpha \leq 1$: For large $(U_d/s)^{1/\alpha}$, with the help of Stirling’s approximation $x! \approx \sqrt{2\pi x} \left(x/e\right)^x$, we obtain

$$
\Pi = \frac{2U_d (U_d/s)^{\left(1-\alpha\right)U_d/s} e^{U_d\alpha/s}}{(2\pi U_d/s)^{\alpha/2}} p(0) .
$$

Using the result from Table 1, we get

$$
\Pi = U_d \sqrt{\frac{2\alpha}{\pi}} \left(\frac{s}{U_d}\right)^{\frac{1}{2\alpha}} .
$$
Expression (14) yields the known result (James and Jain, 2016) for $\alpha = 1$. It is evident that $\Pi \propto U_d^{1-\frac{1}{2\alpha}}$, implying the total fixation probability to be an increasing function of the background mutation rate for $\alpha > 0.5$ and decreasing function for $\alpha < 0.5$, as shown in Fig. 2. The value of $\alpha$ at which this transition happens is denoted as $\alpha_c$, the critical value of epistasis parameter, corresponding to which, we have $\Pi = \frac{s}{\sqrt{\pi}}$. As the mutation rate of a population increases, we expect it to have higher probability to reduce its mutation rate. But, we see that if $\alpha < 0.5$, higher the mutation rate of a population, lower is its probability of lowering of mutation rate. The physical interpretation of this surprising trend is explained in the following paragraph.

Combining (B.2) and (B.5) enables us write

$$p(k) = \frac{e^{-\alpha(k-(U_d/s)^{1/\alpha})^2}}{\sqrt{2\pi (U_d/s)^{1/\alpha}/\alpha}},$$

which clearly states that the background population frequency $p(k)$, which is also equal to the probability of the nonmutator to appear with $k$ deleterious mutations, is a Gaussian distribution with mean $(U_d/s)^{1/\alpha}$ and variance $\alpha^{-1}(U_d/s)^{1/\alpha}$. Therefore, in the regime $\alpha < 1$ and $(U_d/s) > 1$, the mutator population will be more spread out for larger values of $U_d$ and smaller values of $\alpha$.

As $U_d$ increases, it is more likely that the nonmutator will appear with
higher number of deleterious mutations, which is disadvantageous to the invader population. But, as we saw in (11), once the nonmutator appears with a particular number of mutations, its fixation probability $\pi(k)$ increases with $U_d$, which is an advantageous factor associated with $U_d$. Competition between the advantageous and disadvantageous effects of $U_d$ on the nonmutator decides the behavior of its total fixation probability as a function of $\alpha$. As $\alpha$ falls below 0.5, the disadvantage experienced by the lower mutation rate allele due to its low fitness dominates its advantage of arising in a background that has high mutation rate.

Fig. 2 and 4 show that the trend predicted by (14) is observed in finite size populations, and (14) is a good approximation for the total fixation probability of a lower mutation rate individual in strong mutator background.

Case II. $U_d/s > 1, \alpha > 1$: We have analytical expression for $p(0)$ only for the limiting case $\alpha > \frac{\ln(U_d/s)}{\ln 2} \left( (U_d/s)^{1/\alpha} < 2 \right)$, which is given in Table I. In fact, even for $(U_d/s) = 10^6$, which is too large for actual biological populations, when $\alpha \geq 20$, we see that $[(U_d/s)^{1/\alpha}] = 1$, which physically corresponds to the population concentrated in the first two classes, and due to extremely low fitness, individuals carrying more than one mutation get eliminated. In other words, synergistic epistasis with reasonably high $\alpha$ values ensure that only first two classes contribute to $\Pi$. Therefore, from (12), it follows that

$$\Pi = \frac{2U_d U_d/s}{1 + U_d/s} \text{ if } \alpha > \frac{\ln(U_d/s)}{\ln 2}.$$  

(16)
When $\alpha > \frac{\ln(U_d/s)}{\ln 2}$, as epistasis affects neither the fixation probability $\pi(k)$ nor the appearance probability $p(k)$ of the first two fitness classes, unsurprisingly, $\Pi$ is independent of $\alpha$. From Fig. 2 we see that as $\alpha$ increases above 1, the total fixation probability of a nonmutator arising in finite size population tends to the constant value given by (16). This indicates that synergistic epistasis increases the fixation probability of a nonmutator if selection is weak relative to mutation rate of the resident population. Fig. 5 shows variation of (16) with $s$.

Note that for $(U_d/s) \gg 1$, (16) simplifies to the known result for fixation probability $\Pi = 2U_d$ (James and Jain, 2016) of a nonmutator on a nonepistatic fitness landscape, when selective effects are strong with respect to mutation rate. From (A.4) and (B.6), we see that synergistic epistasis with $\alpha > \frac{\ln(U_d/s)}{\ln 2}$ causes the background population to be concentrated around fitness class 1, and therefore, $p(1) \approx 1$ for $(U_d/s) \gg 1$. The fixation probability of a nonmutator with a single deleterious mutation is $\pi(1) \approx 2U_d$ from (11) when $(U_d/s) \gg 1$. Thus, both $p(1)$ and $\pi(1)$ give the same results as $p(0)$ and $\pi(0)$ respectively when selection is strong and epistasis is either absent (James and Jain, 2016) or synergistic (see case IV of RESULTS). Effectively, class 1 for $\alpha > \frac{\ln(U_d/s)}{\ln 2}$ and $(U_d/s) \gg 1$ “replaces” class 0 for $(U_d/s) \ll 1$ and $\alpha \geq 1$.

Case III. $U_d/s < 1$, $\alpha < 1$: As $(U_d/s) < 1$, $[(U_d/s)^{1/\alpha}] = 0$, and hence fixation probability receives contribution only from class 0. Using the result
from Table I in (12), we obtain

\[ \Pi = 2U_d (1 - U_d/s) \quad \text{if} \quad \alpha \ll 1. \quad (17) \]

Fig. 3 and 4 show the validity of (17) against finite population simulations.

Case IV. \( U_d/s < 1, \alpha > 1 \): Since \( \lfloor (U_d/s)^{1/\alpha} \rfloor = 0 \), the use of the result from Table I in (12) yields

\[ \Pi = \frac{2U_d}{1 + U_d/s} \quad \text{if} \quad \alpha > 1. \quad (18) \]

Fig. 3 and 5 show the comparison of (18) with finite population simulations. Table 2 gives the summary of results from this section.

It is obvious that, for \( (U_d/s) \ll 1 \), (17) and (18) approach the known result for fixation probability \( \Pi = 2U_d \) (James and Jain, 2016) in the absence of epistasis \( (\alpha = 1) \), which can also be obtained using single locus model, since the population consists only of class 0 individuals, and the selective advantage of nonmutators is the difference in class 0 frequencies. Because class zero individuals remain unaffected by epistasis, \( \Pi \), which receives contribution only from class zero, is independent of \( \alpha \).

When we vary \( U_d \) keeping \( s \) to be the same, for \( (U_d/s) < 1 \), only class 0 individuals decide \( \Pi \), and hence \( \alpha \) does not enter the picture. \( \Pi \) increases with rise in \( U_d \), as number of mutators in class 0 decreases. But, once we enter the regime \( (U_d/s) > 1 \), it is a multilocus problem, and as discussed in Case I, the total fixation probability depends on \( \alpha \). For antagonistic epistasis,
the nonmutator has higher chances of appearing in a lower fit background for larger values of $U_d$, and for $\alpha < 0.5$, this disadvantage cannot be compensated by its advantage of being created in higher mutation rate background due to which, $\Pi$ falls as a function of $U_d$. These two trends together give rise to a nonmonotonic behavior of $\Pi$ with respect to $U_d$ for $\alpha < 0.5$, as shown in Fig. 4. If $1 \geq \alpha > 0.5$, we see that the advantage conferred by the nonmutator owing to being produced in a high mutation rate background dominates its disadvantage and hence, $\Pi$ increases with $U_d$. Thus, $\Pi$ is a monotonically increasing function of $U_d$ for $1 \geq \alpha > 0.5$ (see Fig. 4). For synergistic epistasis, $\Pi$ rises with $U_d$ for both weak selection (see Fig. 2) and strong selection (see (18)). For $\alpha > \frac{\ln(U_d/s)}{\ln 2}$, $\Pi$ is a linearly increasing function of $U_d$ for $(U_d/s) \gg 1$ and $\ll 1$.

The selection coefficient decides the effect of a mutation. For $\alpha < 1$, when $s$ is increased, for weak selective effects, $\Pi$ increases with $s$ (refer to (14)), as the nonmutator has a higher advantage due to higher deleterious effect of a mutation, whereas for $(U_d/s) \ll 1$, $\Pi$ becomes independent of $s$ since it is determined only by class 0 individuals. For synergistic epistasis, the variation of $\Pi$ with $s$ is shown in Fig. 5. In strong selection regime, for $(U_d/s)$ not too smaller than 1, $p(0)$ falls with $s$ resulting in reduction in $\Pi$. In weak selection regime, when $\alpha > \frac{\ln(U_d/s)}{\ln 2}$, only first two classes contribute to $\Pi$. If $(U_d/s) > 1$, with reduction in $s$, class 1 individuals which are the majority in the population experience an advantage owing to lowering of the cost of mutation they carry, resulting in increment in $\pi(1)$ since $\pi(k) = 2(U_d - sk^\alpha)$
Table 2: Expressions for total fixation probability $\Pi$ of a nonmutator arising in strong mutator background.

| $\left( \frac{U_d}{s} \right)$ | $\alpha \leq 1$                                                                 | $\alpha > 1$                                                                 |
|-------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| $> 1$                         | $\Pi = U_d \sqrt{\frac{2\alpha}{\pi}} \left( \frac{s}{v_d} \right)^{\frac{1}{\alpha^2}}$ | $\Pi = \frac{2U_d}{1+U_d/s}$ if $\alpha > \frac{\ln(U_d/s)}{\ln 2}$       |
| $< 1$                         | $\Pi = 2U_d (1 - U_d/s)$ if $\alpha \ll 1$                                 | $\Pi = \frac{2U_d}{1+U_d/s}$                                                |

(refer to (11)). Even though class 0 mutator fraction (see Table 1) increases due to lower selection, the net result of these two effects - elevation in $\pi(1)$ and decline in $p(0)$ - enhances $\Pi$. As $s$ is decreased further, we have $\alpha < \frac{\ln(U_d/s)}{\ln 2}$ for which, more than the initial two classes contribute to $\Pi$. Note that for $k > 1$, $\pi(k)$ declines rapidly (refer to (11)). As a result, when $\left( \frac{U_d}{s} \right) > 1$, the classes which have significant fraction $p(k)$ of mutators have very small fixation probabilities. For lower selection, initial classes having large $\pi(k)$ values will contain smaller fraction of population. So, $\Pi$ decreases with $s$ here, which is captured by the blue triangles corresponding to $\alpha = 2$.

**DISCUSSION**

**Summary of results:** In an asexual adapted population, it is known that in presence of synergistic epistasis, higher proportion of individuals will carry less mutations, while in presence of antagonistic epistasis, fraction of individuals containing less mutations will be very low. In this article, it is found that antagonistic epistasis lowers the fixation probability of a lower mutation rate allele, thereby opposing mutation rate reduction, while synergistic epis-
tasis strengthens the reduction of mutation rate. Asexual populations can accumulate deleterious mutations quickly, and become extinct in presence of antagonistic epistasis, whereas they resist mutation accumulation, thereby preventing extinction if the interaction is synergistic (Kondrashov, 1993). The results presented here suggest that apart from being disadvantageous to the population due to fast accumulation of harmful mutations, antagonistic interactions oppose mutation rate reduction. This points to the fact that in nature, asexual populations having antagonistic epistasis may not exist. On the other hand, synergistic interactions not only stop mutation accumulation, but also favor mutation rate reduction, thereby reducing the load of deleterious mutations.

It is observed in this study that there exists a critical value $\alpha_c$ of epistasis below which probability of reduction of mutation rate in an infinite population shows negative correlation with its mutation rate. For strong mutators, $\alpha_c$ is found to be 0.5. Though mutation rate reduction happens with a nonzero probability, which is characteristic of any beneficial mutation, decline in mutation rate becomes more unlikely when $\alpha < \alpha_c$. For $\alpha < \alpha_c$, fixation probability of a nonmutator increases with $U_d$ in the strong selection regime because of the nonmutator arising in class 0 benefiting from reduction of mutational load by larger amount, whereas it decreases with $U_d$ in the weak selection regime, as the lower mutation rate allele now appears with large number of mutations, and finds it difficult to outcompete the resident population.
In presence of synergistic interactions, when selective effects are strong, because mutations are costly, individuals carrying them go extinct, and the population will be localized in class 0. In strong selection regime, fixation probability is simply proportional to class 0 mutator frequency. Higher the effects of selection, higher is the fraction of population in class 0, though for very strong selection compared to mutation rate, class 0 frequency stabilizes at its maximum value 1. Thus, as $s$ decreases, $\Pi$ initially remains constant at the value $2U_d$, and then decreases. Strong synergistic epistasis ($\alpha > \frac{\ln(U_d/s)}{\ln 2}$) is equivalent to two or more mutations interacting with each other to cause lethal effect on the genome. Hence, not more than the first two fitness classes contribute in that case. For weak selection, population will be concentrated around class 1. When $s$ decreases, nonmutators created in class 1, which contribute the most to total fixation probability, increase in their fitness. As a result, total fixation probability increases. As selection is reduced further, we go to the regime $\alpha < \frac{\ln(U_d/s)}{\ln 2}$, where more than the first two classes affect total fixation probability. In fact, the number of classes that contribute to fixation increases with reduction in $s$, and the most populated classes will have 2 or more mutations. Since the nonmutators arising in these classes will have very low fitness, the net effect of decline in $s$ is to reduce the total fixation probability. Thus, for synergistic interactions, with reduction in selective effects, total fixation probability of the nonmutator initially decreases, then increases, and finally drops again, as shown in Fig. 5.

**Limitation of the results:** To have steady state, the size of a popula-
tion needs to be of the order of 100 \( (p(0))^{-1} \) (Kondrashov, 1993). Table 3 gives \( p(0) \) values by solving (B.5) corresponding to two \( (U_d/s) \) values, changing \( \alpha \). For large \( (U_d/s) \) and small \( \alpha \), we find that, the size required to obtain steady state is too large for most of the biological populations, and populations of lower size will accumulate deleterious mutations, and go extinct. By comparing column 4 and 5, it can be seen that as \( \alpha \) decreases, (14) deviates from the exact solution of \( \Pi \) obtained using (5) because the approximation (11) does not hold good for fitness classes close to \( (U_d/s)^{1/\alpha} \), which contribute more to \( \Pi \) due to the form (15) taken by mutator frequency. Moreover, for a particular \( \alpha \), smaller the \( (U_d/s) \) value, lesser the deviation is. Since populations of size in the biological limit having larger values of \( (U_d/s) \) and smaller \( \alpha \) do not have steady state, (14) is applicable to most of the real populations except those with both \( (U_d/s) \sim 1 \) and antagonistic epistasis with very small \( \alpha \) values.

**Regarding steady state:** The argument of Kondrashov (1993) on the minimum population size necessary to ensure steady state includes only class 0 fraction. A further detailed analysis by Jain (2008) shows that the ratchet time is actually proportional to the number of individuals in the least loaded class times the selection coefficient. A very high ratchet time corresponds to very a slowly operating ratchet. For smaller values of selection coefficient, the deviation from Kondrashov (1993) becomes clearer. Nevertheless, for the parameters used in this article, there will not be any significant difference from the above theory as smaller values of selection have been used only for
Table 3: Comparison of \( (14) \) (denoted as \( \Pi \) (expression)) with the exact numerical solution for \( \Pi \) using \( (8) \) (denoted as \( \Pi \) (exact)) for small values of \( \alpha \). Note that \( p(0) \) is evaluated using \( (B.5) \). The value of \( s \) is chosen to be 0.02 for the two values of \( (U_d/s) \) used.

| \( \alpha \) | \( U_d/s \) | \( p(0) \) | \( \Pi \) (exact) | \( \Pi \) (expression) |
|-----------|----------|----------|----------------|-------------------|
| 0.5       | 5        | \( 7.44345 \times 10^{-7} \) | 0.0103135       | 0.0112838         |
| 0.45      | 5        | \( 1.56098 \times 10^{-8} \) | 0.00800162      | 0.00895185        |
| 0.4       | 5        | \( 2.11948 \times 10^{-11} \) | 0.00583467      | 0.00674928        |
| 0.3       | 5        | \( 6.23722 \times 10^{-30} \) | 0.00212538      | 0.00298917        |
| 0.2       | 1.5      | 0.02087  | 0.00380453      | 0.00388462        |
| 0.15      | 1.5      | 0.005992 | 0.0022276       | 0.0023996         |
| 0.1       | 1.5      | \( 6.983 \times 10^{-5} \)    | 0.000761517      | 0.000996793       |

synergistic epistasis.

**Critical value of epistasis for weak mutator background:** Weak mutator refers to the case when the mutation rate of the nonmutator is comparable \( (\lambda \sim 1) \) with that of the mutator. In two recent mutation reduction experiments \( (\text{McDonald et al., 2012; Wielgoss et al., 2013}) \), weak mutators with \( \lambda \) as low as 2 have been observed. By solving \( (8) \) and \( (9) \) using mathematica, we obtain \( \alpha_c \) values corresponding to different values of mutator strength. This is plotted in Fig. 6. Note that they are independent of selective effects. We see that the exact value of \( \alpha_c \) for strong mutators is 0.57, which being the lower limit, and \( \alpha_c \) saturates to 1.5 as \( \lambda \) falls towards 1. The interpretation is as follows. A significantly high deleterious mutation rate reduces fixation probability of nonmutator, since it is a disadvantageous factor. Thus, a nonmutator produced in weak mutator background that is
less spread out, corresponding to larger $\alpha$, and that created in strong mutator background which is more spread out, corresponding to smaller $\alpha$ can have the same fixation probabilities. Therefore, the critical value $\alpha_c$ of epistasis parameter rises as the strength of the mutator decreases. Of course, a quantitative analysis is needed here, which is possible if (8) can be solved for weak mutators.

**Choice of parameters and biological relevance:** Maisnier-Patin et al. (2005) experimentally confirmed that in *Salmonella typhimurium*, for various mutation rates, the fitness effect of the mutations resembles the function (1) with $\alpha = 0.46$. Synergistic epistasis has been observed in experiments (Mukai, 1969; Whitlock and Bourguet, 2000). In *Drosophila melanogaster*, the logarithm of relative productivity of genotypes was measured to be proportional to negative of the number of mutant regions carried by them (Whitlock and Bourguet, 2000), which is similar to the fitness function (1) with corresponding $\alpha$ being 2. In previous theoretical studies, the chosen values for $\alpha$ range from 0.02 (Fumagalli et al., 2015) to 5 (Campos, 2004), whereas $\alpha$ has been varied from 0.1 to 20 in the simulations in this article. The strength $\lambda$ of the mutator can be as large as 1000 (Miller, 1996) to as small as around 2 (McDonald et al., 2012; Wielgoss et al., 2013). In this study, $\lambda$ values ranging from 1.25 to 1000 are used. For real populations, $s$ and $U_d$ values are of the order of $10^{-3}$, which is up to two orders of magnitude lower than what have been assumed here. Hence, in actual biological populations, we expect $N$ to be $\sim 10^5$ so as to effectively...
Fixation time and comparison with experiments: The time required for the fixation of a nonmutator is given by the inverse of the rate at which nonmutators that are certain to get fixed are created (Weinreich and Chao, 2005). (The details of fixation time can be found in Ewens (2004).) The rate of creation of nonmutators that are expected to reach fixation is the product of their rate of production and fixation probability. Thus, for a large population, fixation time (James and Jain, 2016) $T = (Nb\Pi)^{-1}$, where $b$ is the rate at which the mutation that produces the lower mutation rate allele happens, provided $Nb \ll 1$.

Table 2 of Wielgoss et al. (2013) gives the mutation rate corresponding to 3 genotypes and their respective times of origin. Assuming the time of origin corresponds to the time when a genotype was significantly high in proportion in order to get detected, we see that time for reduction of mutation rate is inversely proportional to magnitude of the reduction. But, the experiment of McDonald et al. (2012) indicates that this reduction time is higher for higher magnitude of decline in mutation rate. The opposite trends observed in the above two experiments can be explained with epistasis, as fixation probability can be either increasing or decreasing function of mutation rate, depending on epistasis parameter.

Comparison with previous theoretical works: It is known that the fixation probability of an allele with effective selective advantage $S$ in a finite population of size $N$ is $\Pi(N) = (1 - e^{-2S})/(1 - e^{-2SN})$ (Kimura, 1962). As
$N \to \infty, \Pi = 2S$. That is, the fixation probability of a beneficial allele in an infinite population is twice its net selective advantage. For a harmful allele, $S$ is negative, and hence, fixation probability falls exponentially with $N$ (Kimura, 1980; Assaf and Mobilia, 2011). Excluding beneficial mutations, Jain and Nagar (2012) studied the fixation time of mutators in an asexual population of nonmutators, and the time was found to increase exponentially with $N$. Thus, when selection is weak, we extract the effective selective disadvantage conferred by the mutator in this case to be 

$$\sqrt{\frac{2\alpha \lambda}{\pi}} \cdot s^{\frac{1}{2\alpha}} \cdot (U_d)^{1-\frac{1}{2\alpha}},$$

which has similar dependence on $U_d$ as (14), though the mutator strength does not enter our expression. For $\alpha = 1$, these two solutions differ only by a factor 2. Nevertheless, when selection is strong, the net selective disadvantage of the mutator is simply $(U_d - U'_d)$, which exactly matches with our result. In the case of the work of Jain and Nagar (2012), there is a continuous production of mutators from nonmutators owing to which, mutators sweep to fixation in a finite population, and for a large population, the corresponding steady state fitness is $e^{-U_d}$. In the present article, we analyze a mutator population that is initially at steady state with mean fitness $e^{-U_d}$, where the nonmutator allele can appear in a background carrying $k$ mutations, and reach fixation to form a distribution of nonmutators with mean fitness $(1 - s)^k e^{-U'_d}$. Though the initial state of the problem addressed in this article is the same as the final state of the problem considered by Jain and Nagar (2012), the reverse is not true.

**Future goals:** The analysis here is incomplete for weak mutators, and
requires a detailed analysis. Actual biological populations may not have all mutations having the same selective effects. There are models in which selection coefficient is chosen from a distribution. However, the robustness of the results presented here could be tested using other fitness functions. Real biological populations will have beneficial mutations acting on them, which we excluded in our study. There have been works taking in to account the possible physiological costs associated with lowering mutation rates (Kimura, 1967; Kondrashov, 1995; Dawson, 1998; Johnson, 1999; Baer et al., 2007). The effect of this factor could be explored.

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Figure 1: Plot showing the variation of fixation probability with population size. A nonmutator is allowed to appear at time $t = 10/s$ in a population that is initially at its fittest genotype. For large $N$ ($= 4,000$), result in this case (shown using the red squares) is in good agreement with fixation probability of a nonmutator arising in a population which is initially at steady state (blue circle). The parameters are $s = 0.1$, $\alpha = 0.5$, $U_d = 0.15$ and $\lambda = 100$. 
Figure 2: Plot showing variation of total fixation probability with epistasis parameter, for a lower mutation rate individual with mutation rate 100 times smaller than that of the background when selective effects are weaker than background mutation rate. The symbols represent simulation data (red circles for $s = 0.1$, $U_d = 0.1$ and blue squares for $s = 0.1$, $U_d = 0.15$). The corresponding solid curves indicate (14), and the dashed lines represent (16). The green vertical broken line is drawn at $\alpha = 0.5$. 
Figure 3: Plot showing the variation of total fixation probability with $\alpha$, for a lower mutation rate individual with $\lambda = 100$ when selective effects are stronger than background mutation rate. The symbols represent simulation data (red circles for $s = 0.1$, $U_d = 0.05$ and blue squares for $s = 0.1$, $U_d = 0.01$). The solid curves correspond to (17), and the broken lines represent (18).
Figure 4: Plot showing the variation of total fixation probability with $U_d$ for constant selection $s = 0.1$ in presence of antagonistic epistasis, for a lower mutation rate individual with $\lambda = 100$. The symbols represent simulation data (red circles for $\alpha = 1$ and green triangles for $\alpha = 0.2$). The solid curves correspond to (14), and the broken curve represents (17). Clearly, (17) deviates from simulation results as $(U_d/s) \to 1$. 
Figure 5: Plot showing the variation of total fixation probability of a nonmutator with \((1/s)\) when \(U_d\) remains constant at 0.01, and synergistic epistasis is present. The parameters are \(\alpha = 16\) (black circles), \(\alpha = 2\) (blue triangles), and \(\lambda = 100\). The broken curve corresponds to (18), and the solid curve stands for (16). The blue asterisks represent the numerical solution of (8) and (9) for the case \(\alpha = 2\), as we do not have analytical expression for those points.
Figure 6: Main figure shows the variation of $\alpha_c$ with the strength of the mu-tator. These points (red filled circles) are obtained using numerical solution of (8) and (9). Corresponding to $\lambda = 2, 4$ and 100, we have compared data from simulations for $N = 4000$, and the points are represented using blue open squares.
A Frequency of mutator population

When $s$ and $U_d$ are small, the steady state fraction of mutators can be expressed using the equation

$$U_d [\bar{p}(k - 1) - \bar{p}(k)] - s[k^\alpha - \overline{k^\alpha}]p(k) = 0 , \quad (A.1)$$

where

$$\overline{k^\alpha} = \sum_{k=0}^\infty (k^\alpha)p(k) . \quad (A.2)$$

Solving (A.1) for $k = 0$ yields expression for negative of the mean Wrightian fitness (logarithm of Malthusian fitness given by (1)) of the population per selection coefficient

$$\overline{k^\alpha} = U_d/s , \quad (A.3)$$

which can be substituted back in (A.1) and iterated to get (JAIN, 2008)

$$p(k) = \frac{(U_d/s)^k}{(k!)^\alpha}p(0) . \quad (A.4)$$

The normalization condition $\sum_{k=0}^\infty p(k) = 1$ gives (JAIN, 2008)

$$p(0) = \left[ \sum_{k=0}^\infty (U_d/s)^k (k!)^{-\alpha} \right]^{-1} . \quad (A.5)$$
B Approximate expressions for class zero mutator frequency

By taking the ratio $p(k)/p(k-1)$ in (A.4), we can see that the maximum of $p(k)$ is at $k_m = (U_d/s)^{1/\alpha}$.

Case I: $U_d/s > 1$, $\alpha \leq 1$

When selection is weaker than mutation rate, for $\alpha \leq 1$, $(U_d/s)^{1/\alpha} > 1$, and hence the distribution of mutators can be approximated by a Gaussian. As a first step, upon using Stirling’s approximation $k! \approx \sqrt{2\pi k} \ (k/e)^k$ in (A.4), we obtain

$$p(k) = \frac{(U_d/s)^k e^{k\alpha}}{\left(\sqrt{2\pi k} \ k^k\right)^{\alpha}} p(0). \quad (B.1)$$

Now, converting (B.1) to an exponential and, and then expanding around its maximum $(U_d/s)^{1/\alpha}$ using Taylor series gives

$$p(k) = \frac{e^{\alpha(U_d/s)^{1/\alpha}}}{(2\pi(U_d/s)^{1/\alpha})^{1/2}} e^{-\frac{\alpha(k-(U_d/s)^{1/\alpha})^2}{2(U_d/s)^{1/\alpha}}} p(0). \quad (B.2)$$

By replacing the sum in (A.5) by an integral and using (B.2), we get

$$p(0) = \left(\frac{e^{\alpha(U_d/s)^{1/\alpha}}}{\sqrt{2\pi(U_d/s)^{1/\alpha}}} \int_{x=0}^{(U_d/s)^{1/\alpha}} e^{-\frac{\alpha x^2}{2(U_d/s)^{1/\alpha}}} dx + \int_{x=(U_d/s)^{1/\alpha}}^{\infty} e^{-\frac{\alpha x^2}{2(U_d/s)^{1/\alpha}}} dx\right)^{-1}. \quad (B.3)$$
Performing the integral in (B.3) yields

\[
p(0) = \left( \frac{e^{\alpha(U_d/s)^{1/\alpha}}}{\left(\sqrt{2\pi(U_d/s)^{1/\alpha}}\right)^\alpha} \sqrt{\frac{\pi(U_d/s)^{1/\alpha}}{2\alpha}} \left[ 1 + erf\left(\frac{\sqrt{\alpha(U_d/s)^{1/\alpha}}}{2}\right) \right] \right)^{-1}.
\]  

(B.4)

For large values of \( x \), we have the expansion \( erf(x) \approx 1 - \frac{e^{-x^2}}{x\sqrt{\pi}} \approx 1 \), using which we can simplify (B.4) to write

\[
p(0) = (2\pi)^{\frac{\alpha-1}{2}} e^{-\alpha(U_d/s)^{1/\alpha}} \alpha^{1/2}(U_d/s)^{\frac{\alpha-1}{2\alpha}}.
\]  

(B.5)

Note that (B.5) reproduces the known result \( p(0) = e^{-U_d/s} \) for \( \alpha = 1 \). Fig. 7 shows a comparison of (B.5) with (A.5). The inset at the left top clearly indicates that (B.5) very well captures the exact sum even for negligibly small values of \( p(0) \).

Case II: \( U_d/s > 1, \alpha > 1 \)

In this case, Gaussian approximation does not hold good. When \((U_d/s)^{1/\alpha} < 2\), mutator frequency peaks around 1 (also, see RESULTS), and contributions to \( p(k) \) from classes with \( k > 1 \) can be neglected. Effectively, we get

\[
p(0) \approx \frac{1}{1 + U_d/s} \text{ if } \alpha > \frac{\ln(U_d/s)}{\ln 2}
\]  

(B.6)
as the upperbound of \( p(0) \). For values of \( \alpha \) that are not very large, other classes also contribute, and as a result, \( p(0) \) will be smaller than what is predicted by (B.6). Fig. 7 shows that (B.6) matches well with (A.5) for large
values of $\alpha$.

**Case III: $U_d/s < 1$, $\alpha < 1$**

In the limiting case $\alpha \to 0$, (A.5) becomes

$$p(0) \approx \left[ \sum_{k=0}^{\infty} (U_d/s)^k \right]^{-1} = (1 - U_d/s), \quad \text{if} \quad \alpha \ll 1 . \quad (B.7)$$

Note that when $\alpha = 0$, it follows from (1) that all individuals carrying nonzero mutations have the same fitness $(1 - s)$. Thus, in practice, the population has only two classes differing in fitness by $s$, with mutation rate from class 0 to 1 being $U_d$. For this, the steady state solution for population fraction in class 0 yields (B.7). The right bottom inset of Fig. 7 shows that $p(0)$ predicted by (A.5) decreases to (B.7) for very small values of $\alpha$.

**Case IV: $U_d/s < 1$, $\alpha > 1$**

Like Case II studied here, class zero mutator fraction increases with $\alpha$ and saturates to the limiting value

$$p(0) \approx \frac{1}{1 + U_d/s} \quad \text{if} \quad \alpha > 1 . \quad (B.8)$$

From the right bottom inset of Fig. 7 we can see that $p(0)$ predicted by (A.5) increases to (B.8) for large values of $\alpha$. When $(U_d/s) \ll 1$, (B.8) and (B.7) give almost the same result close to 1 for $p(0)$, indicating the fact that fraction of individuals with zero deleterious mutations in the population is unaffected by epistasis when selective effects are strong. Since the population
is localized around class zero, frequency of individuals in other fitness classes will be insignificant.

Results of this section are summarized in Table 1.
Figure 7: Plot showing the validity of the expressions (B.5) (solid curves) and (B.6) (broken lines) for $p(0)$ when selective effects are weaker than mutation rates, $(U_d/s) = 1$ (blue squares). The symbols represent the numerically evaluated values of the full sum in expression (A.5). The inset at the top left shows comparison of equation (B.5) in log scale with numerical data using (A.5) for extremely small values of $p(0)$ for $(U_d/s) = 5$ (red circles). Inset at the right bottom shows the validity of the expressions (B.7) (solid lines) and (B.8) (broken lines) for $p(0)$ when selective effects are stronger than mutation rates, for $(U_d/s) = 0.05$ (black triangles) and $(U_d/s) = 0.5$ (green diamonds). The symbols represent the numerically evaluated values of the full sum in expression (A.5).
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