RECOMBINATION AND PEAK JUMPING

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ABSTRACT. We find an advantage of recombination for a category of complex fitness landscapes. Recent studies of empirical fitness landscapes reveal complex gene interactions and multiple peaks, and recombination can be a powerful mechanism for escaping suboptimal peaks. However classical work on recombination largely ignores the effect of complex gene interactions. The advantage we find has no correspondence for 2-locus systems or for smooth landscapes. The effect is sometimes extreme, in the sense that shutting off recombination could result in that the organism fails to adapt. A standard question about recombination is if the mechanism tends to accelerate or decelerate adaptation. However, we argue that extreme effects may be more important than how the majority falls.

1. INTRODUCTION

Throughout the paper, we will consider haploid biallelic $L$-loci populations. Let $\Sigma = \{0, 1\}$ and let $\Sigma^L$ denote bit strings of length $L$. $\Sigma^L$ represents the genotype space. In particular,

$$\Sigma^2 = \{00, 10, 01, 11\} \quad \text{and} \quad \Sigma^3 = \{000, 100, 010, 001, 110, 101, 011, 111\}.$$

We define a fitness landscape as a function $w : \Sigma^L \rightarrow \mathbb{R}$, which assigns a fitness value to each genotype (Wright, 1931). The fitness of the genotype $g$ is denoted $w_g$. The metric we consider is the Hamming distance, meaning that the distance between two genotypes equals the number of positions where the genotypes differ. In particular, two genotypes are adjacent, or mutational neighbors, if they differ at exactly one position. We will use fitness graphs (Crona et al., 2013), as a representation of coarse aspects of fitness landscapes. Roughly, the nodes represent genotypes and each arrow points toward the more fit genotype. A fitness landscapes is smooth if it can be represented by a fitness graphs where all arrows point up.

We are interested in the effect of recombination for complex fitness landscapes with multiple peaks. For general background on recombination, see e.g. Otto and Lenormand (2002). As conventional, recombination is modeled so that for a resulting genotype, each locus is equally likely to agree with either parent’s allele.

In general, recombination has no effect for monomorphic populations. Large population, or subdivided population, are likely to be polymorphic, so that recombination
can produce new genotypes. One potential advantage of recombination is the Fisher-Muller effect. The effect has been discussed in recent work on complex fitness landscapes (Nowak et al., 2014). Briefly, in the absence of recombination, beneficial mutations may get lost due to clonal interference. For instance, if two single mutants of high fitness co-exist in a population, then one of them may outcompete the other. However, recombination can incorporate beneficial mutations in the same genome, and thereby prevent loss of genetic variation due to clonal interference.

2. RESULTS

We will study the effect of recombination for an adapting organism. After a recent change in the environment, the wild-type, denoted $0 = 0 \ldots 0$ does no longer have maximal fitness. We restrict to landscapes where there is no path to the global maximum in the fitness graph, so that an adapting organism could be trapped at suboptimal peaks. At the same time the global maximum should be within reach, in the sense that gene shuffling of [suboptimal] peaks can generate the global maximum. Specifically, the fitness landscapes should satisfy the following conditions.

**Main assumptions.** Let $g_{\text{max}}$ denote the genotype of maximal fitness in $\Sigma^L$. There exist genotypes $g^1, \ldots, g^L \in \Sigma^L$, not necessarily different such that:

(A1) There is no path from 0 to the $g_{\text{max}}$ in the fitness graph.

(A2) $g_{\text{max}} = g^1 \ldots g^L$, where $g^k_i$ is the $i$:th bit of $g^k$.

(A3) For each $k$, there exists a path in the fitness graph from 0 to $g^k$.

(A4) Each $g^k$ is at a local peak.

Note that Conditions A1-A3 are important for our conclusions, whereas A4 could be relaxed under some circumstances. From a biological perspective, A1 means that an adapting population could be trapped at a suboptimal peak, A2 that the global maximum ($g_{\text{max}}$) can be obtained by a sequence of recombination events using genotypes in $\{g^k\}$. Conditions A3 and A4 imply that the genotypes $g^k$ have a reasonable chance to encounter each other in large populations.

Landscapes satisfying A1-A4 are of interest, because of the potential advantage of recombination. Our first observation is that no landscape satisfies A1-A4 in the 2-loci case. Indeed, if A1 holds then the genotype 11 is at a global maximum. In addition, the single mutants 10, 01 are deleterious. In summary

$$w_{10}, w_{01} < w_{00} \quad w_{10}, w_{01} < w_{11}.$$  

Figure 1 shows the fitness graph determined by these conditions, and clearly A2-A4 are not satisfied. However, A1-A4 are satisfied for Examples 1 and 2 (see Figures 2 and 3).

**Example 1.** Consider a system of genotypes

$$000, 100, 010, 001, 110, 101, 011, 111$$
The genotypes 100, 010, 001 have higher fitness than the wild-type 000. The double mutants 110, 101, 011 have lower fitness than the wild-type. The genotype 111 is at the global maximum.

Example 2. For \( L = 4 \), consider the following case. The genotypes 1000, 0100, 0010, 0001 have higher fitness than the wild-type 0000. The double mutants 1100, 0011 have higher fitness than the single mutants. The remaining double mutants 1010, 0101, and the triple mutants 1110, 1101, 1011, 0111 have low fitness. In summary,

\[
\begin{align*}
\omega_{1000}, \omega_{0100}, \omega_{0010}, \omega_{0001} &> \omega_{0000} \\
\omega_{1100} &> \omega_{1000}, \omega_{0100}, \\
\omega_{0011} &> \omega_{0010}, \omega_{0001}, \\
\omega_{1111} &> \omega_{1100}, \omega_{0011}, \\
\omega_{1001}, \omega_{1010}, \omega_{0110}, \omega_{0101}, \omega_{1110}, \omega_{1101}, \omega_{0111} &< \omega_{0000}.
\end{align*}
\]

The double peaked 2-loci case (Figure 1) and Example 2 (Figure 3) have some similarities. Indeed, in both cases there are obstacles for adaption from the wild-type to the global maximum. In the 2-loci case, the frequency of 10 and 01 are expected to be very low, so that recombination is not a powerful generator of the optimal genotype 11. In contrast, in Example 2 both 1100 and 0011 are peak genotypes, and recombination may be a powerful generator of the optimal genotype 1111. Informally, one needs to combine "rare and rare" in the 2 loci case, and "abundant and abundant" in Example 2. The potential advantage of recombination for an Example 2 population should not be underestimated. For instance, consider a relatively small subdivided population.
Then each subpopulation would be likely to end up at 1100 or 0011. Recombination could generate 1111, as soon as there is some migration between the subpopulations. However, in absence of recombination the expected time before 1111 appears would be very long. Indeed, a double mutation or some other rare scenario would be necessary. A relatively small population, may fail to produce 1111 genotypes all together.

One can ask how frequent fitness landscapes of the type described in Example 2 are. The TEM-family of $\beta$-lactamases provide an interesting example. TEM-1 is the wild-type in the system, and approximately 200 mutants have been found clinically, for a record see http://www.lahey.org/Studies/temtable.asp.

Consider TEM-1, the 4-tuple mutant TEM-50 and intermediates. The clinically found subset of these 16 genotypes are compatible with the Example 2 fitness graph. More precisely, the clinically found alleles can be represented as:

$$0000, 1000, 0100, 0010, 0001, 1100, 0011, 1111.$$  

In particular, none of the triple mutants have been found clinically. It seems reasonable to interpret the absence of mutants as an indication of low fitness in a natural setting. If that interpretation is correct, the set of clinically found mutant is compatible with the Example 2 fitness graph.

Recombination will generate the optimal genotype for Example 2 landscapes in many cases. Other fitness landscapes satisfying A1-A4, may not be quite as favorable. However, the basic mechanism is similar.

For instance, consider Example 1. From the three peak genotypes 100, 010, 001 recombination could produce some of the intermediates 110, 101, 011, and in the next step 111.
Figure 3. A fitness graph for 4 loci. The fitness landscapes satisfies A1-A4.

For instance, 100 and 010 could produce 110, and then 110 and 001 could produce 111. Notice that this scenario requires that $w_{110} > 0$. In addition, the population structure would have to allow for different genotypes to recombine.

In summary, recombination has the potential to generate the optimal genotypes for A1-A4 landscapes. As we have seen, some restrictions on intermediate genotypes, and population structure and size may be necessary. In particular, suboptimal peak genotypes should have a chance to recombine. Notice also, that non-recombining populations will get trapped only if genetic diversity is somewhat restricted, so that double mutations are rare. We restrict to A1-A4 landscapes satisfying the following conditions. **Additional conditions:**

- $w_g \neq 0$ for critical intermediate genotypes,
- the potential generic diversity is not extreme (double mutations should still be rare).
• The $g^k$ elements are likely to co-exist, encounter each other and recombine during some stage of adaptation.

The last condition imposes constrains on the fitness landscape as well as the population structure. For Examples 1 and 2, as well as closely related examples, the requirement on the population structure is modest. (Strictly speaking we do not need A4, if the last condition is satisfied in any case.)

We have so far discussed how recombination can generate optimal genotypes. However, even if the optimal genotype appears in a population, it is far from obvious that the genotype will go to fixation. If optimal genotypes recombine poorly, they may stay rare in the population.

**Main result.** Consider populations which satisfy A1–A4, as well as the three additional assumptions summarized above. We argue that recombination $r > 0$ will speed up adaptation provided that $r$ is sufficiently small.

Indeed, in the absence of recombination a population will be trapped at a suboptimal peak for a very long time. Rare events, such as double mutations, will be necessary for escapes. However, recombination will generate the optimal genotype within a relatively short time interval under our assumptions. As soon as the optimal genotype appears, Theorem 1 [below] shows that the proportion is expected to grow provided that $r$ is sufficiently small.

**Theorem 1.** For a fitness landscape $w : \Sigma^L \mapsto \mathbb{R}$, let $g_{\text{max}}$ be the genotype of maximal fitness $w_{\text{max}}$ and let $w_{\text{max}}'$ denote the second to highest fitness. Consider a population with genotypes in $\Sigma^L$ and recombination rate $r$. If $g_{\text{max}}$ is present in a population, then its proportion is expected to increase provided that

$$r < \frac{w_{\text{max}} - w_{\text{max}}'}{w_{\text{max}} + w_{\text{max}}'}$$

The proof of Theorem 1 depends on the following lemma.

**Lemma 1.** For a fitness landscape $w : \Sigma^L \mapsto \mathbb{R}$, let $g_{\text{max}}$ be the genotype of maximal and, and let $r$ denote the recombination rate. Then $|\Sigma^L \setminus \{g_{\text{max}}\}|$ will not increase more than by a factor $(1 + r)$ as a result of recombination.

**Proof.** Recombining pairs of genotypes are of three types:

$$\{g_{\text{max}}, g_{\text{max}}\}, \ {g_{\text{max}}, g : g \neq g_{\text{max}}}, \ {g, g' : g, g' \neq g_{\text{max}}}.$$

In the first case, recombination has no effect. In the third case, the number of elements in $|\Sigma^L \setminus \{g_{\text{max}}\}|$ will not increase. In the second case, recombination will result in at most 2 elements in $\Sigma^L \setminus \{g_{\text{max}}\}$. In summary, only the second case may lead to an increase of $|\Sigma^L \setminus \{g_{\text{max}}\}|$, and the maximal net effect is one more element in $\Sigma^L \setminus \{g_{\text{max}}\}$.

An increase of $|\Sigma^L \setminus \{g_{\text{max}}\}|$ cannot exceed the case where all recombining pairs are of the second type, which translates to an increase by a factor $(1 + r)$. \qed

**Proof of Theorem 1.**
Proof. The proportions \( p_1 \) of \( g_{\text{max}} \) genotypes, and \( p_2 \) of remaining genotypes after reproduction can be expressed as

\[
\begin{align*}
p_1 &= \frac{C_1 \tilde{p}_1}{C_1 \tilde{p}_1 + C_2 \tilde{p}_2}, \\
p_2 &= \frac{C_2 \tilde{p}_2}{C_1 \tilde{p}_1 + C_2 \tilde{p}_2},
\end{align*}
\]

where \( \tilde{p}_1, \tilde{p}_2 \) are the former proportions. From considering \( g_{\text{max}} \) individuals which do not recombine, one concludes that

\[
C_1 \geq w_{\text{max}} (1 - r)
\]

Consider \( \Sigma^L \setminus \{g_{\text{max}}\} \). In order to obtain an upper bound of \( C_2 \) we need to consider fitness as well as the effect of recombination. In total,

\[
C_2 \leq w'_{\text{max}} (1 + r),
\]

by Lemma 1. It follows that the \( g_{\text{max}} \) proportion increases if

\[
w_{\text{max}} (1 - r) > w'_{\text{max}} (1 + r),
\]

or if

\[
r < \frac{w_{\text{max}} - w'_{\text{max}}}{w_{\text{max}} + w'_{\text{max}}}.
\]

One can ask how important it is that \( r \) is small. We performed simulation of Example 1 fitness landscapes and large populations, using the programming language R. According to our simulations, the population quickly goes to fixation at the optimal genotype for a wide range of values \( r \). However, the optimal genotype does not go to fixation if \( r \) is close to 1. Intuitively, this should make sense, since 111 recombines poorly with all mutational neighbors 110, 101, 011. The exact threshold for \( r \) depends on the choice of parameters. However, the general pattern is clear. Recombination is a powerful mechanism for escaping peaks, as long as \( r \) is sufficiently small.

One of the most favorable situations for A1-A4 populations is probably subdivided populations with regular mixing of subpopulations. For subdivided populations, chances are good that all the necessary peak genotypes are available in the global population. The fact that recombination sometimes is especially advantageous for subdivided populations is well known (e.g. Otto and Lenormand 2002). One favorable case is the puddle and flood model (Crona 2013), where long periods of isolated adaptation for the subpopulations are alternated by brief periods of population mixture.

3. DISCUSSION.

We have demonstrated an extreme advantage of recombination for a category of complex fitness landscapes. We refer to the mechanism as "peak jumping", since shuffling of peak genotypes generate a new peak (the jump is from peaks to peak, rather than from valleys to peak).

The peak jumping effect should not be confused by the Fisher-Muller effect mentioned in the introduction. The Fisher-Muller effect, depends on clonal interference, but
the advantage of peak jumping is different. For instance, suppose that some peak genotypes (such as 1100 and 0011 in Example 2) have equal fitness, and co-exist in similar proportions in the population. Then clonal interference is not an issue. Indeed, the genetic variation would be maintained in the population also in the absence of recombination. However, because of potential peak jumps, (such as the move from 1100 and 0011 to 1111 in Example 2) recombination may be advantageous.

The peak jumping effect typically require that the recombination rate is relatively small, and we have provided a sufficient condition on the rate. Our observation that rare recombination works better than frequent recombination, agrees to some extent with other studies of complex fitness landscapes (Nowak et al., 2014; Morivagaravandi and Engelstadter, 2012; De Visser et al., 2009). Infrequent recombination can be a powerful mechanism for escaping peaks also in cases when frequent recombination is not advantageous.

Whether the peak jumping effect is important or not is an empirical question. As mentioned, the TEM-family of $\beta$-lactamases provides some empirical support. In general, empirical fitness landscapes are many times complex with multiple peaks (e.g. Hartl, 2014; De Visser and Krug, 2014; Kondrashov and Kondrashov, 2014; Szendro et al., 2012). Notice also that there are theoretical arguments why an adapting organism would tend to show more complex gene interactions over time (Greene and Crona, 2014; Draghi and Plotkin, 2013).

A few recent studies analyze the effect of recombination on complex fitness landscapes, (e.g. Nowak et al., 2014; Morivagaravardi and Engelstadter, 2012; Misevic et al., 2009; De Visser et al., 2009). The results point in slightly different directions, depending on assumptions and how the problem is phrased. Recombination is sometimes described as a disadvantage. However, we argue that extreme effects of recombination, such as peak jumping, may be more important than how the majority falls, i.e. if recombination more frequently accelerate or decelerate adaptation. The peak jumping effect observed has no correspondence in the two-loci case, or for smooth landscapes. It would be interesting to further explore effects of recombination specific for complex fitness landscapes.

Along with results on higher order epistasis (Beerenwinkel et al., 2007a,b), see also Weinreich et al. (2013), our results suggest that fitness landscapes need to be studied in their full complexity. Arguments based on pairwise gene interactions or average curvature may be misleading.

Recombination is wide spread in nature, but remains poorly understood. One of the most important challenges in the field in our view, is to better understand the relation between higher order epistasis and the effect of recombination.
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