

Part I

Systems

1

On the Role of Stress in Evolution

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1.1

Introduction

Most of the work on stress considers its mechanisms and effects during the lifetime of the stressed individual. In this chapter, we concentrate on the possible effects of stress on genes and populations. In particular, we consider the effects of the information contained in the stress response, especially in chronic stress: namely, that the stressed individual is maladapted to its current environment.

In addition to the physiological responses induced by stress, it can also have genomic responses. One type of response which is of particular interest is an increase in genetic variation, especially the mixing of different genotypes through recombination, sex and outcrossing. Here, we consider the evolution of such a genomic response and its possible implications for the long-term success of the population and for the evolution of complex traits.

When considering the evolution of a genomic response to stress, we can take one of two approaches: we can either consider what would be the “best” response at the level of the population (i.e., the response that would, on average, maximize the average fitness of the population), or consider the fate of a selectively neutral modifier allele [1] inducing the genetic response—would such an allele increase in frequency within the population, due to the forces of natural selection?

1.2

Stress Through the Gene's Eye: the Evolution of Stress-Induced Genetic Mixing

Let us consider the point of view of a gene that regulates genetic mixing—for example, recombining with a different genotype—in response to stress. This gene affects its own probability of moving to a different genetic background in the next generation. When would it be advantageous (at the level of the gene) to move to a different background? The answer depends on the quality of the current genetic background. If the current background is maladapted to the current environment

(e.g., includes multiple deleterious alleles), there is a much greater advantage in “taking the risk” of moving to a different, unknown, background. But how can the gene “know” the quality of the whole genome? One crucial source of information can be stress responses, which relay information about the well-being of the whole organism down to the molecular level. An individual carrying an unfit genome is more likely to be stressed, and the stress responses it experiences can affect the gene regulating genetic mixing. As a result, an increase in mixing is more likely to occur in the presence of stress.

An increase in genetic mixing can occur through various mechanisms, acting at different levels. Each of these mechanisms carries its own costs and benefits. Below we specifically discuss four of these mechanisms—recombination, sex, outcrossing and dispersal.

1.2.1

Stress-Induced Recombination

1.2.1.1 Classic Models of the Evolution of Recombination

The evolution of recombination has been the subject of scientific debate for over 70 years, see [2–7] for reviews. One major problem is that uniform recombination not only generates new advantageous combinations, but also breaks down existing good ones that were generated by selection [8, 9].

Models concentrating on population-level effects show that recombination might be advantageous only under limited conditions [10, 11]. Specifically, recombination can only be advantageous when associations between different loci in the genome result in decreased variation within the population (a situation termed negative linkage disequilibrium). Such associations can be generated by drift [12], synergistic epistasis [13, 14], or environmental changes [15–17]. In these cases recombination reduces linkage disequilibrium and leads to increased average fitness, resulting in a long-term advantage for the population as a whole.

The same question was also studied using modifier models, concentrating on the short-term dynamics of an allele affecting the rate of recombination. These models found that, in the absence of deleterious mutations or environmental changes, a recombination modifier tends to increase from rarity only if it *reduces* the recombination rate between selected loci [18], a result known as “the reduction principle”. However, negative epistasis between deleterious mutations [19, 20], drift [21], or adaptation [22, 23], including inter-species interactions [24, 25], can explain the evolution of recombination modifiers under some circumstances. Nevertheless, none of these models fully accounts for the wide abundance of sex and recombination among higher eukaryotes.

1.2.1.2 The Evolution of Stress-Induced Recombination

When introducing the possibility of stress-induced recombination, radically different results are obtained. Let us first consider the modifier approach: a modifier regulating the level of recombination in a haploid organism according to the state

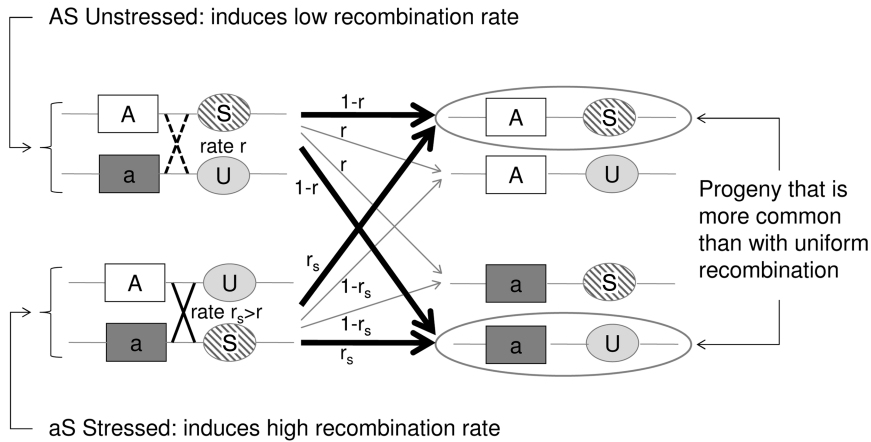


Figure 1.1 The “abandon ship” principle: intuition for fitness-associated mixing. An illustration of the short-term advantage of stress-induced recombination in a two-locus haploid model. The alleles: A—high fitness, a—low fitness, S—stress induced recombination, U—uniform recombination. The recombination products of the two double heterozygotes are shown, where the likelier-than-random changes are shown in bold arrows and the less-likely than random ones in gray arrows. We can see that if the

allele S (for stress-induced recombination) induces a higher recombination rate than random when it is linked to the low fitness allele a and/or a lower recombination rate than random when it is linked to the high fitness allele A, then an association is generated between A and S, resulting in a short-term evolutionary advantage for S. A similar argument holds for mechanisms of genetic mixing other than recombination. (Adapted with permission from [2]).

of the individual—with stressed individuals recombining at a higher rate—can evolve under a very wide parameter range from any population where the rate of recombination is uniform and independent of stress [28]. This result was obtained for an analytical model with two loci (see Figure 1.1 for intuition), generalized using stochastic models with long genomes and finite populations and further confirmed using a QLE approach [26]. It means that increased recombination as a result of stress is expected to be a common pattern in the world. Empirical evidence strongly supports this prediction (see below).

What would be the effects of such a pattern of recombination on the population as a whole? Let us consider the effect of recombination in general and of stress-induced recombination in particular on the distribution of different allele combinations. In the absence of epistatic interactions and drift, uniform recombination does not alter the distribution of allele combinations from the one expected had alleles at different loci been entirely independent of each other. This situation is called linkage equilibrium, and the ineffectiveness of uniform recombination in that situation led many researchers to argue that recombination is advantageous only when the population is at linkage disequilibrium due to other forces acting on it [27]. However, this result changes when we consider recombination that is stress-induced. Such plasticity of the recombination

response can allow it to generate good genetic combinations between alleles at other loci more than to break them down, thus generating “extreme” genotypes more often than random (a situation called positive linkage disequilibrium) and increasing variation in fitness within the population. Variation in fitness is the substrate on which selection can work—resulting in increased average fitness in the population. As a result, even under the conditions which are least favorable for the evolution of uniform recombination (i.e., an infinite population, no epistasis, linkage equilibrium), stress-induced recombination can still result in an increased average fitness [28].

1.2.1.3 Evidence for Stress-Induced Recombination

Evidence for stress-induced recombination has been found in a wide range of organisms and stressors. This includes elevated levels of recombination in response to DNA damage [29–33], starvation [34–41], temperature stress [42–46] and behavioral competition [47]. Further supportive evidence comes from studies which found an association between low fitness and recombination within the same population [48, 49]. See Refs. [5, 50] for reviews.

1.2.2

Stress and Sex

For recombination to be effective in the sense of mixing genetic material from different individuals, sexual reproduction needs to take place. However, sexual reproduction is one of the greatest puzzles in evolutionary theory: in addition to the difficulties associated with explaining recombination itself (mentioned above), sex is a very *costly* mechanism. First, it requires the generation of male offspring, thus resulting in the “twofold cost of males”: An asexual mutant female would have only female offspring, identical to herself, producing twice as many copies of its genes in comparison with a similar sexual female. This advantage would be doubled in the next generation and—everything else being equal—would lead to a fast takeover of the sexual population by asexual mutants [51]. Furthermore, a sexual organism has to invest time and energy in courtship and mating and risks transmission of pathogens and conflicts between the sexes. Altogether, the wide abundance of sexual reproduction in the world strongly suggests that sexual organisms have significant advantages over asexual ones in both the short term and the long term, but these advantages are not yet fully understood.

We can study the evolution of sexual reproduction by considering the case of facultative sexuals—organisms that can reproduce either sexually or asexually—and the evolution of a gene that alters the investment in sex in such a system. When can a gene that results in increased investment in costly sexual reproduction spread in the population? What would be the long-term effects for the survival of such a population when it has to compete with asexual populations? This is a harder question than the question of recombination alone, as the cost of sex favors decreased investment in sexual reproduction.

If we consider facultative sexuals that have the same tendency to reproduce sexually at all times, then the evolution of sex is rather hard to explain. Indeed, classic models require rather extreme parameters in order to account for the evolution of sex [3]. Such extreme conditions do exist in certain systems, but do not seem to explain the ubiquity of sexual reproduction. As in the case of stress-induced recombination, the solution may lie in the fact that facultative sexuals, including viruses, protists, fungi and plants, are more likely to have sex when their own condition is poor—when they are stressed [31, 36, 37, 52–62]; see [63] for a review.

When we take stress into account, the picture is rather different. Reproducing sexually more often when the individual is stressed allows the allele regulating sexual reproduction to “abandon ship” and move to a different genetic background. But at what cost? Interestingly, even in the face of high cost, an allele promoting sexual reproduction under stress can evolve [64]. An intuition for that can be gained by considering the fate of this allele if it stays in a maladapted genome. It is almost surely doomed, together with its “neighbor genes”, unless a mutation or a change of the environment happens first. Thus, from the allele’s viewpoint, it is worth “paying” a significant cost to break away.

At first sight, it might seem that regardless of its association with stress the costs involved in sexual reproduction should be harmful for the population as a whole. However, taking stress into account alters the population-level effects as well. If the stressed individuals—the ones that are, on average, less fit in the current environment—are the ones most likely to reproduce sexually *and pay the cost of sex*, then they are less likely to transmit their genes to the next generation. As a result, the maladapted alleles they carry are more likely to be eliminated. In such a case the cost of sex becomes a component of natural selection and can actually be beneficial in the long term [64].

1.2.3

Stress and Outcrossing

It might seem that obligatory sexual organisms are much more limited in their ability to regulate genetic mixing. However, any mechanism that affects the probability of mating with a genetically dissimilar individual is in fact a mechanism that regulates the likelihood of genetic mixing. This includes many mate-preference mechanisms that are sensitive to familial relatedness (e.g., inbreeding avoidance) or physical similarity (e.g., opposites attract) and indirect mechanisms that increase the probability of meeting unrelated individuals—and thus also the probability of mating with them. In other words, all sorts of outcrossing are potential mechanisms for regulating genetic mixing.

The evolution of outcrossing is a riddle resembling the evolution of sex: in populations of self-compatible hermaphrodites, alleles for self-fertilization have an inherent advantage over alleles for outcrossing, as they help the spread of alleles that are identical by descent [65–67]. However, the effect of inbreeding is not identical to that of asexual reproduction—selfed offspring, in contrast with asexual

ones, are not genetically identical to their parents. In particular, they might suffer from inbreeding depression: reduced fitness due to homozygotization of deleterious mutations.

However, the level of inbreeding depression is unlikely to be the same for all the individuals within the population. The selfed offspring of individuals carrying many deleterious mutations are expected to experience stronger inbreeding depression in comparison with the offspring of individuals carrying fewer deleterious mutations. As a result, we would expect stressed individuals to have a higher tendency for outcrossing. The effects of such plasticity on the entire population are less obvious: parallel to fitness-associated recombination [28] it could increase the average fitness of the population by generating positive linkage disequilibrium. Additionally, the costs of outcrossing would become part of natural selection, further benefitting the population as a whole. In contrast, outcrossing of individuals that carry more deleterious mutations would also result in increased heterozygosity in the population. This would lead to decreased selection on recessive deleterious alleles, resulting in a short-term disadvantage but also in increased potential for adaptation when the environment changes.

1.2.4

Stress and Dispersal

Dispersal combines several different effects. First, the dispersing individual increases its probability to mate with individuals that are unrelated to it. As a result, a gene regulating the probability of dispersal regulates its chance to change its genetic background. Second, dispersal increases the probability of the disperser to change its biotic and abiotic environment, including intra-species competition. Last, dispersal often carries costs of its own (e.g., the probability to die on the way, not to find a new territory, to lose time and energy) in addition to the inherent cost of outcrossing mentioned above.

The evolution of dispersal has classically been explained by inbreeding avoidance [68–70], kin competition [71, 72], habitat variability [73–75], or competition for resources [76, 77], including potential mates [78].

In most cases, the potential benefits for the dispersing individual are not the same for all individuals. As in previous examples, less-fit individuals have more to gain from changing their environment, the genes of their offspring, or both. In many species, there is evidence that less-fit individuals indeed disperse further than fitter ones [79–87]. We propose (L. Hadany *et al.*, in prep.) that fitness-associated dispersal could have evolved due to the advantages of stress-induced mixing, even in the absence of direct competition or environmental heterogeneity. We further suggest that the advantage of stress-induced dispersal may increase in a heterogeneous environment, where dispersal has a chance to change both the environment of the dispersing individual and the genetic background of the modifier allele affecting dispersal.

Dispersal has many ecological implications and is a particularly important factor for the survival of metapopulations. The effects of dispersal act in two opposite

directions: on one hand, dispersal is necessary for colonization in empty patches [88] and can “rescue” sink populations from extinction [89–91]; on the other hand, dispersal can impede the stability of already colonized subpopulations [92–94]. The regulation of dispersal by stress could change the balance between these opposing effects and therefore may have important ecological implications that have not yet been explored.

1.3

The Effect of Stress-Induced Variation on the Evolvability of Complex Traits

The principle of stress-induced variation also offers a novel solution to the classic “peak shift” problem in population genetics [95]: For traits that are affected by multiple loci, there might exist allelic combinations that represent “local peaks” in the adaptive landscape (the plot of the fitness as a function of the underlying genotype, see Figure 1.2). When starting from such a combination, any single mutation would result in decreased fitness, but multiple mutations can lead to increased fitness. How can organisms evolve from one such co-adapted gene complex to a better one if the intermediate genotypes are less fit?

This question has been studied extensively, and most of the models that try to answer it assume that the population is divided into groups (“demes”), with a limited rate of migration between these groups. Under such conditions, rare

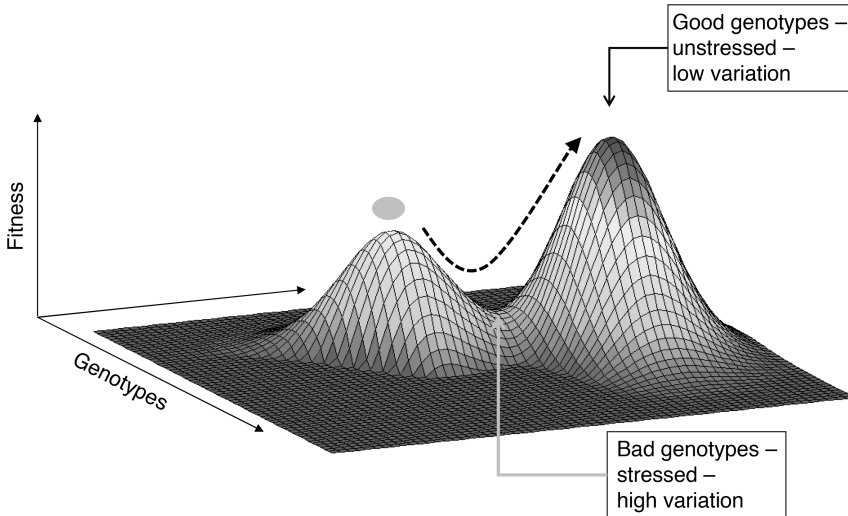


Figure 1.2 The problem of complex adaptation. The adaptive landscape is the plot of the fitness as a function of the genotype. The problem, first described by Wright [96] is how a species can evolve from one “adaptive peak” to a higher one, crossing a less-fit

“valley”. Increased variation under stress (when fitness is low) and/or decreased variation when not stressed (when fitness is high) can facilitate adaptation in such genetic systems.

advantageous combinations can appear and fix in one deme with the aid of random genetic drift and can later expand to other demes [95, 96]. However, these models typically require specific parameter settings, particularly a limited range of dispersal rates [97–100]. This has to do with the double-sided effect of genetic mixing on adaptive peak shifts: on one hand, mixing facilitates the appearance of rare advantageous combinations; on the other hand, recombination with different genotypes acts to break down these very combinations when rare, resulting in offspring within the “adaptive valley”.

Stress-induced variation largely relieves that limitation. The effect has two aspects: more mixing when fitness is low increases the generation of new advantageous gene combinations by maladapted individuals in the “adaptive valley”, whereas decreased mixing when fitness is high protects rare advantageous combinations when they appear. This basic principle works both for recombination [28] and for dispersal [101]. Stress-induced variation can thus facilitate the ability of a population to move between adaptive peaks, potentially allowing evolutionary breakthroughs and significant advantages in the very long term.

1.4

Stress-Induced Variation and Pathogen Evolution

Stress-induced variation has some ominous implications when it comes to the evolution of pathogens. One of these is its effect on the evolution of pathogens. Pathogens are constantly evolving to overcome their hosts’ defenses, including medications. Parallel to other organisms, evidence suggests that the tendency of pathogens to produce genetic variation is affected by the stress they experience [102, 103]. Whenever man-made drugs become a major source of pathogen stress, our use of such drugs should be much more carefully considered. In particular, recent results suggest that massive use of drugs (including prophylactic and veterinarian use) can facilitate pathogen adaptation to these drugs not only through direct selection, but also through induction of increased generation of variation, resulting in a much more dramatic effect than previously thought [104]. This is particularly problematic when complex pathogen evolution (including multiple mutations, possibly with epistatic interactions between them) is required for drug resistance (V. Leontiev and L. Hadany, submitted).

1.5

Stress-Induced Mortality

This section discusses the most counter-intuitive effect of stress on evolution: the evolution of death. Normally, we do not consider early death as an evolved feature, but rather as an “accident”, or an undesirable by-product of a trait with selective advantages in other contexts. A classic example is the increase in blood pressure associated with the “flight or fight” response—a response with obvious

selective advantages in the short term, but disadvantages in the long term [105]. While some of the harmful effects of long-term exposure to stress can be easily explained in that way, others—such as the down-regulation of the immune response and the apoptosis of lymphocytes [106, 107]—are less so. Here, we suggest an alternative explanation for these harmful effects, without requiring a short-term benefit.

Let us start by assuming a structured population, where neighbors are likely to be more genetically related than randomly chosen individuals and where resources like space or food limit the number of individuals inhabiting a given area. Consider a gene that affects mortality in such a population. Under what circumstances would an allele whose only effect is to increase mortality (without any benefit to the individual) spread in the population? Stress can have a dramatic effect on the answer. An allele that occurs in a chronically stressed individual has very poor prospects: it is unlikely to be passed to the next generation, and in the rare case that it does, it would often still be linked to the deleterious genetic background that caused the stress to begin with. However, if the individual carrying this allele dies, then another individual—with a higher probability to carry the allele than a random individual—would take its place and would have better chances of passing its genes to the next generation. By that, other copies of the allele (possibly having a better genetic background) would have better chances of passing. Thus, if the condition of the first individual is poor enough, the increased mortality allele can do better by inducing the death of the individual carrying it than by helping it to survive. Indeed, such an allele can increase from rarity and fix in the population under the conditions described above [108].

We can regard the individual dying from stress under such circumstances as the ultimate altruist—it gives its life for the benefit of its neighbors and kin. This is advantageous only when the self-sacrificing individual has some information (in the form of stress) that it is not doing as well as others in this environment. This argument gives us some intuition about which kinds of stress are more likely to induce a harmful effect: social stress (e.g., losing a fight) is more indicative about the relative fitness of the individual than, for example, abiotic stress (e.g., heat). The former is thus more likely to result in evolved harmful effects.

What would be the effects of such an allele for stress-induced mortality at the level of the population as a whole? If such an allele takes over the population, it would lead to more effective natural selection. Deleterious mutations would be eliminated more efficiently (as their carriers would more often tend to die prematurely) and beneficial alleles would have a greater relative advantage (as their carriers do not tend to die prematurely). Altogether it would result in an increase in the average fitness of the population in the long term.

Of course, we can think of less drastic ways to help others which carry a cost for the helping individual. One way would be to decrease the use of the common resource of potential mates: indeed, stress-induced reduction in fertility is a well-documented phenomenon [109–111], which could have evolved along very similar lines. The results described above [108] suggest that many other kinds of altruistic behaviors are also likely to evolve to increase in times of stress.

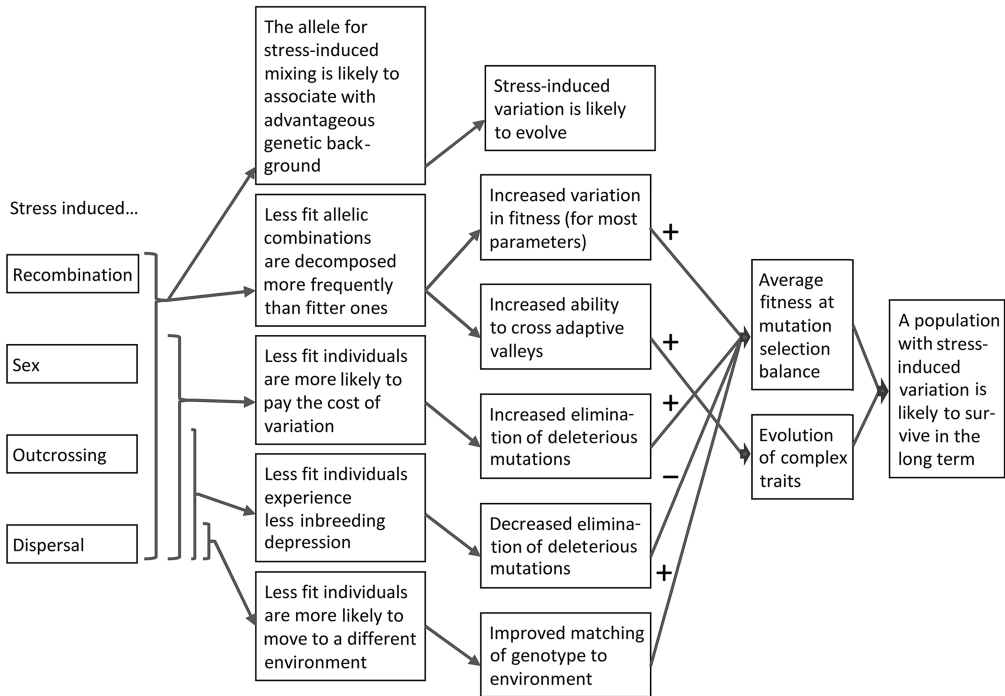


Figure 1.3 Key evolutionary implications of stress through four mechanisms of stress-induced variation: recombination, sex, outcrossing and dispersal.

Summary

In this chapter we reviewed some of the evolutionary implications of stress responses. We have seen that stress might have played an important role in the evolution of mechanisms of genetic mixing, shedding new light on the evolution of recombination, sex, outcrossing and dispersal. Stress-induced genetic variation can alter the evolution of species, both in the short term and in the long term—by allowing them to better adapt to their environments, especially when complex adaptation is required. Figure 1.3 summarizes some of the implications of stress-induced variation.

The evolutionary effects of stress can have significant ecological implications: from improved survival of metapopulations to more effective evolution of pathogens exposed to drugs. Evolutionary considerations might also suggest a new perspective on other possible responses to stress, including early death, reduced fertility, or altruistic behavior.

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