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PhD thesis

­­­­­The Evolution of Stress-Induced Hypermutation: Causes and Consequences

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I dedicate this thesis to my grandfather, Eng. Herbert Zvi Littman.

He submitted his own PhD thesis in the Winter of 1938 at TU Wien, but got it back, including his fees, before leaving for Palestine the following Summer.

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Acces this thesis online at <https://github.com/yoavram/thesis>.

# Abstract

Empirical studies show that in bacteria and eukaryotes, stress can induce a state of mutagenesis – a temporary increase in mutation rates. However, theoretical treatment of this phenomenon is lacking.

Using mathematical models and computer simulations, I have developed a theoretical basis to explain the evolution of stress-induced mutagenesis. My results show that (i) stress-induced mutagenesis is favored by selection under both changing and constant environments due to the beneficial mutations it generates; (ii) this is also true in the presence of rare recombination; (iii) stress-induced mutagenesis increases the ability of populations to adapt to new conditions without jeopardizing their ability to remain adapted to stable environments.

In addition, I developed a new probabilistic approach to analyze the probability that a random mutation leads to an improved phenotype in Fisher's geometric model, a widely used model of adaptive evolution.

Because mutation is a fundamental evolutionary force, my PhD research has important significance to various aspects of biology. Most importantly, my research makes an important theoretical contribution to our understanding that mutation is more likely to occur in individuals who are mal-adapted to their environments and therefore are more likely to benefit from it.

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Nothing in Evolution Makes Sense Except in Light of Population Genetics

– Lynch, M, PNAS 2007

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# Introduction

## The evolution of the mutation rate

The evolution of the mutation rate is a long-standing problem in evolutionary biology, dating back to an article by Sturtevant (1937) that suggested there are *“genes that affect general mutation rate”* (mutator alleles) and that *“in wild populations, such genes must be subject to selection”*. But how does selection affect mutator alleles? And how will the other evolutionary forces – mutation, recombination, and genetic drift – change the evolutionary fate of mutator alleles? The answers to these questions depend on a number of evolutionary and ecological factors.

An optimal mutation rate balances between *adaptedness*, the ability to retain existing adaptations, and *adaptability*, the ability to produce new adaptations (Leigh 1973). The distribution of mutational effects (Eyre-Walker and Keightley 2007) is therefore an important factor for the evolution of the mutation rate. Briefly, in well-adapted populations beneficial mutations might be very rare and therefore selection will favor the reduction of the mutation rate (Liberman and Feldman 1986). In mal-adapted populations, on the other hand, beneficial mutations could be much more common. Mutator alleles can then “hitch-hike” (Maynard Smith and Haigh 1974) with the beneficial mutations they generate and reach high frequencies (Taddei et al. 1997; Sniegowski, Gerrish, and Lenski 1997; Tenaillon et al. 1999).

Kimura (1967) suggested two hypotheses for the evolutionary adjustment of the mutation rate: (i) the mutation rate is optimized by intra-group selection to minimize the genetic and substitutional loads (respectively, the fitness cost due to the accumulation of deleterious mutations and due to the elimination of mal-adapted individual during the fixation of a well-adapted genotype), and (ii) most mutations are deleterious, and therefore the mutation rate is at the lowest level permitted by physical and physiological constraints. Leigh (1970; 1973) used an analytical model to demonstrate that in asexual populations evolving in a periodically changing environment, inter-group selection may favor mutator alleles due to the increased standing variation they generate, which allows rapid adaptation to environmental changes. Also, Leigh found that the optimal mutation rate in asexual populations is equal to the frequency of environmental change (Lachmann and Jablonka 1996). In sexual populations, however, selection will act against alleles that increase the mutation rate.

More recently, Lynch (2010; 2011) framed the *drift barrier hypothesis*. This hypothesis suggests that the reduction of the mutation rate is limited by random genetic drift rather than by physical constraints: when the mutation rate is low enough, selection towards further decreases is too weak to overcome random sampling in small populations. Other authors explored a model in which any reduction of the mutation rate entails a reduction in fitness owing to a *cost of DNA replication fidelity* (Dawson 1998; Sloan and Panjeti 2010). This cost may be due to a shortage in resources and energy required to proof and repair replication errors, or due to the reduced replication rate of higher fidelity DNA polymerases. Under this model, the mutation rate has an optimal value which, in asexual populations, depends only on the relationship between the mutation rate and the *cost of fidelity*. In sexual populations this optimal value also depends on the magnitude of selection (Dawson 1998).

To summarize, the evolution of the mutation rate depends on a variety of population and environmental factors [reviewed by (Sniegowski et al. 2000; de Visser 2002; Denamur and Matic 2006)] (**Figure 1**). First, mutator alleles are subject to indirect negative and positive selection due to the deleterious and beneficial mutations they generate. The overall direction and magnitude of selection varies for different populations, environmental conditions, and molecular constraints. Second, mutator alleles are also under direct selection due to the *cost of fidelity*. Third, genetic drift affects the fate of mutator alleles by limiting the influence of direct and indirect selection and by driving the accumulation of deleterious mutations in small populations, which can lead to the extinction of mutator alleles (Lynch et al. 1993). Fourth, *clonal interference* reduces the adaptation rate of asexual populations and reduces the indirect selection for mutator alleles due to the beneficial mutations they generate (de Visser et al. 1999).Lastly

Recombination influences the mutation rate in several ways (**Figure 1**): i) it alters the direction and magnitude of indirect selection on mutator alleles by breaking the association between mutator alleles and the mutations they generate, ii) it increases the effective population size by reducing *clonal interference* (Martens and Hallatschek 2011), thereby changing the balance between drift and selection, and iii) it combines different beneficial mutations in the same genotype, thereby accelerating the rate of adaptation and reducing the need for mutations – this is known as the *Fisher-Muller effect* (Christiansen et al. 1998).



Figure 1. Evolutionary forces involved in the evolution of mutator alleles. Recombination weakens the effect of mutations (of all kinds) and genetic drift on the evolution of mutation rates (noted by Rec-). If we consider the optimal mutation rate rather than *adaptability*, drift is not considered and recombination can increase the impact of beneficial mutations rather than decrease it.

## Stress-induced mutagenesis

During the beginning of the 21st century it became increasingly clear that *"various types of stresses induce responses that have mutagenic consequences"* (Foster 2007) and that *"the same cellular stress responses long appreciated to shore-up damaged cellular hardware (other than DNA) can, surprisingly and importantly, also remodel genomic software (DNA) by increasing rates of random mutagenesis"* (Galhardo, Hastings, and Rosenberg 2007) . Research with laboratory strains of *Escherichia coli* has uncovered some of the mechanisms which underlie stress-induced mutagenesis (Gonzalez et al. 2008; Galhardo et al. 2009; Gibson et al. 2010; Shee et al. 2011). This phenomenon is common in many bacterial species (Cirz et al. 2007; Galhardo, Hastings, and Rosenberg 2007; Kivisaar 2010; van der Veen et al. 2010; Debora et al. 2010), and evidence suggests that mutations are more common in stressed yeast (Heidenreich 2007), algae (Goho and Bell 2000), flies (Sharp and Agrawal 2012), and even human cancer cells experiencing hypoxia stress (Bristow and Hill 2008; Ruan, Song, and Ouyang 2009).

Several explanations for the evolutionary origin of stress-induced mutagenesis were proposed, and they can be roughly divided to adaptive hypotheses and non-adaptive hypotheses (Sniegowski and Lenski 1995; Sniegowski et al. 2000; Tenaillon, Denamur, and Matic 2004; Saint-Ruf and Matic 2006; Denamur and Matic 2006; Lynch 2011): (i) the *adaptive hypothesis*, or *second-order selection hypothesis*, suggests that mutagenesis in times of stress is favored by natural selection because it increases variation and allows faster adaptation; (ii) non-adaptive hypotheses suggest that mutagenesis is an inevitable by-product of stress that is caused by lack of energy and resources needed to maintain replication fidelity or by some other causes, such as random genetic drift (Sung et al. 2012). Non-adaptive hypotheses have received theoretical treatment (Heo and Shakhnovich 2010; Hilbert 2011; Lynch 2011) but, until now, the adaptive hypothesis has not been studied using population genetics models. Such models can determine if a mutator allele that induces elevated mutation rates in response to mal-adaptation can increase in frequency by indirect selection on the mutations it generates.

The consequences of stress-induced mutagenesis are largely unknown. Agrawal (2002) studied a model of fitness-dependent mutation rates (FDMR) in an infinite population and showed that FDMR increases the two-fold cost of sex. His model was later extended for finite populations (Shaw and Baer 2011), in which the correlation between the mutation rate and fitness was shown to slow or stop *Muller's Ratchet* (Haigh 1978), thus helping to explain how asexual populations cope with deleterious mutations to avoid mutational meltdown. Other outcomes of a plastic mutation rate could span a variety of evolutionary, epidemiological, and ecological scenarios: the evolution of drug-resistance in bacteria (Cirz and Romesberg 2006; Obolski and Hadany 2012), the evolution of cancer cells and the emergence of chemotherapeutic-resistance (Huang et al. 2007; Bristow and Hill 2008; Ruan, Song, and Ouyang 2009), the evolution of pesticide resistance in commercial crops (Gressel 2011), industrial applications using bacteria in stressful environments (Machielsen et al. 2010), host-parasite co-evolution (Pal et al. 2007; Racey et al. 2010; Morgan, Bonsall, and Buckling 2010), and the evolution of pathogen virulence (Oliver et al. 2000; Merino et al. 2002; Boshoff et al. 2003). More importantly, because the mutation rate is a fundamental element of population genetics models and theories (Loewe and Hill 2010), the basic notion that it is plastic rather than constant has a huge importance to our understanding of evolution and biology.

## Research objectives

Since the famous work of Luria and Delbrück (1943), evolutionary and ecological models assume that the mutation rate is constant and uniform. However, an alternative assumption, that the mutation rate is plastic and that stress induces elevated mutation rates, can lead to remarkably different results and conclusions, at least in some cases. Furthermore, the lack of theory and applicable models contributes to the slow adoption of these ideas by evolutionary biologists and geneticists, as well as researchers in the medical sciences.

In light of this, the objectives of my PhD thesis are:

1. Develop a theoretical basis to explain the evolution of stress-induced mutagenesis:
   1. In constant and changing environments
   2. In asexual populations
   3. In the presence of recombination
   4. On rugged fitness landscapes
2. Explore the evolutionary consequences of stress-induced mutagenesis on:
   1. Adaptation
   2. Evolution of the recombination rate
   3. Evolution of complex traits

## Thesis overview

During my PhD I have authored three peer-reviewed manuscripts on stress-induced mutagenesis and the evolution of the mutation rate; a fourth manuscript is in preparation.

### The evolution of stress-induced hypermutation in asexual populations

In the first peer-reviewed manuscript (Ram and Hadany 2012) I have provided the first theoretical support for the *adaptive hypothesis* by showing that stress-induced mutagenesis is favored by natural selection due to the beneficial mutations it generates specifically in individuals that need them the most. The manuscript focused on asexual populations. Using a deterministic model, I analysed evolution in a constant environment in which mutations are either deleterious or compensatory (compensating for existing deleterious mutations). I have shown that increasing the mutation rate in individuals with below average fitness increases the mean fitness of the population, but only if compensatory mutations are possible. This is a new and surprising result; selection is usually predicted to reduce the mutation rate rather than increases it (Liberman and Feldman 1986). Using stochastic computer simulations, I analysed evolution in a changing environment and considered models in which alleles for different mutational strategies compete against each other. Stress-induced mutator alleles, which induce increased mutation rates in mal-adapted individuals, were highly successful in competitions with non-mutator alleles and constitutive mutator alleles that induce a constant low and high mutation rate, respectively. Populations with stress-induced mutator alleles also had a higher mean fitness than populations with non-mutator or constitutive mutator alleles. Therefore, I concluded that stress-induced mutagenesis is likely to evolve in asexual populations because it is favored by natural selection, both in constant and changing environments. This is in contrast to constitutive mutagenesis, which can only be favored in rapidly changing environments, and is always selected against in a constant environment (Giraud, Radman, et al. 2001).

### The evolution of stress-induced mutagenesis in the presence of recombination

In a manuscript that is still in preparation, I have extended my previous model (Ram and Hadany 2012) to include recombination in the form of horizontal gene transfer (Avery 1944; Milkman and Bridges 1990).

Recombination has a complex effect on the evolution of mutator alleles, involving several mechanisms that operate in different times and directions. During adaptive evolution(Christiansen et al. 1998).T (Tenaillon et al. 2000)prevents In a constant environment, recombination can prevent the accelerated accumulation of deleterious mutations that lead to an increased mutational load and the loss of the fittest genotype in a process called *Muller's Ratchet* (Haigh 1978), thus allowing mutator alleles to survive despite the excess deleterious mutations they generate.

I have used stochastic models of evolution in changing environments to study the evolution of stress-induced mutator alleles in the presence of recombination. My results suggest that stress-induced mutator alleles are favored by natural selection as long as the recombination rate is not too high (not much higher than the mutation rate). In addition, I found that selection favors alleles that increase both the mutation rate and the recombination rate in response to stress; this integrates previous results on the evolution of stress-induced recombination (Hadany and Beker 2003) into a unified framework, suggesting that stress-induced variation can operate via several parallel genetic mechanisms.

### Stress-induced mutagenesis and complex adaptation

In the above, I developed a framework to explain the evolution of stress-induced mutagenesis; in contrast, in my second peer-reviewed manuscript (Ram and Hadany 2014b) I studied the consequences of stress-induced mutagenesis on the evolution of complex traits. Complex traits require two or more mutations that are beneficial together but deleterious separately. The evolution of complex traits is an open question in evolutionary biology for over 80 years (Wright 1931; Wright 1988), as it is not clear how individuals can accumulate the required mutations if each of them is deleterious on its own.

I have used mathematical analysis and computer simulations to estimate how stress-induced mutagenesis increases the rate of complex adaptation in comparison to normal mutagenesis and constitutive mutagenesis. Combining these estimates with estimates of population mean fitness in a constant environment, I have demonstrated that stress-induced mutagenesis is the most efficient mutational strategy, as it breaks the classical trade-off between *adaptability*, the ability to adapt to new conditions, and *adaptedness*, the ability to remain adapted to current conditions (Leigh 1970). These results provide the first estimates of the effect of stress-induced mutagenesis on adaptation.

### The probability of improvement in Fisher's geometric model: a probabilistic approach

Fisher's geometric model is a widely used model of adaptive evolution (Fisher 1930). In my third published manuscript (Ram and Hadany 2015), I developed a new probabilistic approach for determining the probability that a random mutation leads to an improved phenotype in Fisher's geometric model. This new approach opens new opportunities for understanding and analysing Fisher's model because it provides an alternative interpretation of the relationship between the probability for a beneficial mutation and the model parameters: the effect size of the mutation, the number of traits affected by the mutation, and the distance from the current phenotype to the optimal one.

My previous research suggests that stress-induced mutagenesis is very sensitive to the probability that a mutation is beneficial; indeed, the advantage of stress-induced mutator alleles in a constant environment disappears if compensatory (beneficial) mutations are not possible (Ram and Hadany 2012), and the rate of adaptive evolution is, of course, an increasing function of the probability that a mutation is beneficial (Ram and Hadany 2014b). My new approach for determining the probability that a mutation is beneficial is therefore an important step towards understanding the evolutionary origin of stress-induced mutagenesis.

## Methods overview

Next, I will discuss several theory-oriented methods which I used during my PhD research.

### Individual-based simulations

Individual-based simulations (also called *agent-based simulations*) are composed of populations of individuals and a set of rules for the individuals' life cycle and interactions. These rules are often defined using parameters and include stochastic elements. Emerging population dynamics are then studied using repeated runs of the simulations for different sets of parameters and by applying statistical analysis to determine the significance of the results.

To study competitions between different mutator alleles (Ram and Hadany 2012), I developed a Java open source framework for individual-based simulations (Ram 2011, https://github.com/yoavram/proevolutionsimulation). This software was later reused in a separate research project (Gueijman et al. 2013). The software allows the definition of life cycle rules necessary to model natural and sexual selection, mutation, recombination, sexual reproduction, migration, and random genetic drift. I performed over 100,000 simulations on the Hadany computer cluster.

### Wright-Fisher models

The *Wright-Fisher model* is a standard population genetic model (Otto and Day 2007). It is used to describe the change in allele frequency from generation to generation (with non-overlapping generations) and can include the effects of natural selection, mutation, random genetic drift, recombination, and migration. In its simplest form, the Wright-Fisher model follows the frequency *p* of an allele of interest that has an adaptive advantage *s* over the rest of the alleles:

,

where *p'* is the frequency of the allele of interest in the next generation. This example only includes natural selection. If the model includes more genotypes of interest, then it is described by a system of similar equations.

The Wright-Fisher model can be studied using mathematical or computational analysis. With mathematical analysis, one attempts to find or approximate a solution to the set of equations defined by the Wright-Fisher model. In computational analysis, one attempts to approximate or estimate a solution by calculating the set of equations for specific parameter values. It is common to include random fluctuations to model the effect of random genetic drift; in such cases, the analysis produces estimates of the required quantities, which then require further statistical analysis to test for their significance.

At the mutation-selection balance, the equilibrium of a model that only includes natural selection and mutation, the expected allele frequencies do not change from generation to generation. I studied the mean fitness of populations with different mutational strategies at the mutation selection balance (Ram and Hadany 2012; Ram and Hadany 2014b) using eigenvalue analysis and found an analytical expression for the relation between the population mean fitness and the rate of mutation of individuals with *x* deleterious mutations (Ram and Hadany 2012). I have also developed software for calculating the expected mean fitness of a population with a given mutator allele, given the basal mutation rate, the selection coefficient against deleterious mutations, and the rate of compensatory mutations (Ram and Hadany 2014b; see supplementry material at <https://github.com/yoavram/ruggedsim/blob/master/manuscript/supplementry.ipynb>).

Focusing on competitions between mutator alleles, I have developed a software implementation of the Wright-Fisher model with multiple loci, fluctuating selection, stress-induced mutagenesis, random genetic drift, and stress-induced recombination (in the form of gene conversion). These simulations (so called because of the stochastic element of random genetic drift) were used to run competitions between different mutator alleles in the presence of different levels of recombination. The software was written in order to accommodate different kinds of evolutionary simulations so that it could be reused in other research projects and by other researchers.

Focusing on adaptive evolution, I have used a Wright-Fisher model in combination with a Branching process (see below) for estimating the adaptation rate with different mutational strategies. The model was used to estimate the waiting time for the appearance of an adaptive genotype that goes to fixation (Ram and Hadany 2014b).

To validate the results of this mathematical analysis, I developed a software implementation of a Wright-Fisher model with selection, mutation, and random genetic drift (<https://github.com/yoavram/ruggedsim/tree/master/stochastic>). Over 100,000 simulations were performed on the Hadany computer cluster and all data relevant to the publication (Ram and Hadany 2014b) was deposited on dryad (Ram and Hadany 2014a).

### Branching processes

Branching processes are stochastic models that study the random extinction and fixation of different types in a population (Harris 1969). I used branching processes to calculate the fixation probability of beneficial mutations (Eshel 1981; Patwa and Wahl 2008), a crucial step in calculating the rate of adaptation.

### Probability theory

For my third peer-reviewed manuscript (Ram and Hadany 2015) I developed a probabilistic approach to study the probability of improvement in Fisher's geometric model. A geometric approach has been published previously by several authors (Rice 1990; Waxman and Welch 2005), albeit not by Fisher himself (Fisher 1930). However, using probability theoretical arguments I reached the same solution without applying any geometric arguments. The analysis was implemented in Python and can be viewed and interacted with at <https://mybinder.org/repo/yoavram/FGMProb> by opening the file *Expected improvement.ipynb*.

# Discussion

I studied the evolution of stress-induced mutagenesis – the increase of mutation rate in response to stress and mal-adaptation. First, I have used population genetics models to show, for the first time, that stress-induced mutagenesis can be favored by natural selection in asexual populations due to the beneficial mutations it generates (Ram and Hadany 2012; Ram and Hadany 2014b). Second, I have extended these models to include recombination; my results show that stress-induced mutagenesis is still favored if the recombination rate is not too high (Ram and Hadany, in preparation). Third, I have shown that stress-induced mutagenesis increases the rate of adaptation and the mean fitness of adapting populations without jeopardizing the fitness of well-adapted populations in a stable environment (Ram and Hadany 2012; Ram and Hadany 2014b). Fourth, I have developed a new method for determining the probability that a mutation is beneficial: a crucial constraint on the evolution of stress-induced mutagenesis (Ram and Hadany 2015).

Despite evidence that stress-induced mutagenesis is a common mechanism in many species of bacteria (Foster 2007; Rosenberg et al. 2012; Galhardo, Hastings, and Rosenberg 2007) as well as in yeast (Heidenreich 2007), many authors doubted if stress-induced mutagenesis can have a significant adaptive advantage, if such an advantage can lead to its evolution and maintenance in natural populations, and if it stress-induced mutagenesis has an important role in evolution (Tenaillon et al. 2001; Tenaillon, Denamur, and Matic 2004; Saint-Ruf and Matic 2006; Lenski and Sniegowski 1995; Roth et al. 2006).

My results show, for the first time, that stress-induced mutagenesis can have an evolutionary advantage over constant mutation rates, low or high. Moreover, my results show that this evolutionary advantage is due to stress-induced mutagenesis breaking the trade-off between *adaptability* (the ability to adapt) and *adaptedness* (the ability to remain adapted), allowing rapid adaptation to environmental challenges without compromising the population mean fitness in a stable environment. Furthermore, this evolutionary advantage persists even in the presence of rare recombination, suggesting that stress-induced mutagenesis can evolve in microbial species that experience limited recombination.

Classical theory predicts that in asexual populations with constant mutation rates the mean fitness can be estimated by *e-U*, which is a decreasing function of the mutation rate *U*, and that selection acts to reduce the mutation rate (Kimura and Maruyama 1966). This effect has been referred to as the *Reduction Principle* (Liberman and Feldman 1986; Altenberg 2011). My results show that this is not necessarily true: natural selection only acts to reduce the mutation rates of individuals with above average fitness. In contrast, selection acts to increase the mutation rate of individuals with below average fitness, even in a constant environment (Ram and Hadany 2012).

Several non-adaptive hypotheses exist for the evolution of stress-induced mutagenesis. It has been suggested that decreasing the mutation rate carries a cost, called *the cost of DNA replication fidelity*. Such a cost may arise from extra energy, time, and resources required for operating the DNA replication proofing and error correction systems (Sniegowski et al. 2000; Johnson 1999). Increasing the mutation rate during stress can therefore directly increase the fitness of the individual, regardless of beneficial mutations and adaptation. My models do not include a direct cost or benefit for increasing or decreasing the mutation rate. Although the *cost of fidelity* might increase the advantage of stress-induced mutator alleles over non-mutator alleles, it might also increase the success of constitutive mutator alleles in competitions, as these alleles will constitutively benefit from not paying the *cost of fidelity*. However, recent empirical studies suggest that the *cost of fidelity* does not play an important role in the evolution of constitutive mutator alleles in bacteria (Giraud, Matic, et al. 2001; Mérino et al. 2002; Gentile et al. 2011; Shee et al. 2011). Future studies can integrate the *cost of fidelity* (Johnson 1999) to my models to try and find how the *cost of fidelity* affects the evolutionary advantage of stress-induced mutagenesis.

Another cost might be associated with the regulation of the mutation rate: to determine their condition, cells must invest in costly sensory and signaling mechanisms. However, such mechanisms already exist for various unrelated purposes, such as the maintenance of cell cycle and homeostasis. Therefore, I consider these mechanisms as "free", in terms of fitness costs. Indeed, in *E. coli* mutagenesis is induced by several stress responses that serve other cellular functions (Foster 2007; Al Mamun et al. 2012);

The *drift barrier hypothesis* (Sung et al. 2012) offers another explanation for the origin of stress-induced mutagenesis: enzymes involved in DNA replication and proofing induced during stress did not become error-prone because natural selection favored the beneficial mutations generated during stress, but rather because they were only rarely expressed and therefore experienced less natural selection on their normal function: maintaining high fidelity during DNA replication. This reduced selection allowed deleterious mutations to accumulate in the genes encoding these enzymes (*e.g.*, DNA polymerases), making them error-prone. Future research could test this hypothesis by estimating the effective population size and the frequency of stress that allow stress-induced mutagenesis to evolve without generation of beneficial mutations.

My models assume that individuals have perfect information regarding their condition or fitness, so that the mutagenesis response is only induced in mal-adapted or stressed individuals. However, it is more reasonable to assume that such information is only an estimate and that sometimes fit individuals induce mutagenesis, and stressed individuals fail to do so, by mistake. In such cases, an error correction mechanism, based on the population mean fitness or the parent fitness, can be used to mitigate errors in fitness estimation.

## Conclusions

Mutation is a fundamental evolutionary force and therefore affects diverse areas in biology. Pathogens experience stress during drug treatment and when interacting with host immune systems. Neglecting the effect of these stresses on pathogen mutation rates can lead to incorrect conclusions on the ability of the pathogens to evolve virulence (Oliver et al. 2000; Mérino et al. 2002) and drug resistance: Obolski and Hadany (2012) demonstrated that stress-induced mutagenesis changes the recommended drug administration policy in hospital departments, whereas Cirz an co-workers (2007) showed that inhibiting mutagenesis reduces the ability of *Staphylococcus aureus* to evolve drug resistance.

Similar effects of stress, caused by pesticides, are expected to occur in agricultural settings, allowing plant and livestock pathogens to develop resistance and virulence more rapidly than expected (Gressel 2011). Likewise, microbes are commonly used in industrial applications, from cheese, yogurt, beer, and wine to antibiotics and biofuel production. However, the genetic integrity of industrial strains may be at a larger risk than previously thought, as in most cases microbes are kept in stressful conditions in order to produce the desired products (Machielsen et al. 2010).

An important corollary to microbial evolution is the development of cancer by the clonal proliferation of cancer cells (Sprouffske et al. 2012). Cancer cells are exposed to different stresses, due to therapy - chemotherapeutic drugs and radiation – as well as the abnormal growth of the tumor. It has been shown that mutagenesis is induced in cancer cells under hypoxia stress (Huang et al. 2007; Ruan, Song, and Ouyang 2009), which can lead to mutations that cause durg resistance, tumor progression, and metastasis (Jackson and Loeb 1998; Tomlinson and Bodmer 1999).

Most importantly, my work contributes and supports the ongoing shift in our understanding of mutation as a regulated response to mal-adaptation and stress, rather than an inevitable result of biophysical and biochemical processes. My results provide theoretical support to the observation that mutations are more likely to occur in mal-adapted individuals and in stressful environments.

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אוניברסיטת תל-אביב

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המדרשה לתארים מתקדמים ע"ש משפת סמולרש

המחלקה לביולוגיה מולקולרית ואקולוגיה של צמחים

עבודת דוקטור

האבולוציה של מוטציה מושרית-עקה: גורמים ותוצאות

מאת יואב רם



מנחה: פרופ' לילך הדני

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