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PhD thesis

­­­­­The Evolution of Stress-Induced Hypermutation: Causes and Consequences

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January 2016

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

# Abstract

# Acknowledgements

I thank my partner, Tal Simon, for her love, support, and friendship.

I thank my advisor Prof. Lilach Hadany for more than seven years of guidance, teaching, and collaboration. It has been a daily privilege to study and work in the supportive and challenging environment provided by Lilach.

I thank A. F. Agrawal, T. Beker, I. Ben-Zion, T. F. Cooper, D. Gilat, N. Goldenfeld, A. Gueijman, J. Hermisson, U. Obolski, P. Reuven, N. Rosenberg, S. M. Rosenberg, N. Roseth for insightful discussions, comments, and suggestions.

I thank the members of my PhD committees, A. Eldar, A. Lotem, I. Mayrose, and T. Pupko, for their advice and feedback.

This research has been supported in part by the Israel Science Foundation 840/08 (L.H.), the Israeli Science Foundation 1568/13 (L.H.), by Marie Curie reintegration grant 2007–224866 (L.H.), the Manna Program in Food Safety and Security (Y.R.), the Israeli Ministry for Science and Technology (Y.R.), the Morris and Helen Mauerberger Scholarship Fund, South Africa (Y.R.).

It's tough to make predictions, especially about the future.

– Yogi Berra

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# Introduction

## The evolution 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 these mutator alleles? And how will other forces – mutation, recombination, and genetic drift – change their evolutionary fate? 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 a most 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. In maladapted 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). Also, populations with low mutation rates may suffer a greater substitutional load than populations with high mutation rates, due to the elimination of unfit individuals from the population during the longer adaptation time (Kimura 1967; Kimura and Maruyama 1969).

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, and (ii) because most mutations are deleterious, the mutation rate is at the lowest level permitted by physical and physiological constraints. Leigh (1970; 1973) used a simple analytical model to demonstrate that in asexual populations inter-group selection may favor mutator alleles due to the increased variation they generate, which allows rapid adaptation to environmental changes. Also, he found that the optimal mutation rate in asexuals is equal to the frequency of environmental change. 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 genetic drift rather than by physical constraints, because when the mutation rate is low enough, selection towards further decreases is too weak to overcome random sampling in small populations. Moreover, Lynch suggested his hypothesis is also relevant to microbial species experiencing "clonal interference" (referring to the process in which several clones with different beneficial mutations interfere with each other, reducing their effective population sizes (Gerrish and Lenski 1998)). Alternatively, Dawson (Dawson 1998; Sloan and Panjeti 2010) explored a model in which any reduction of the mutation rate entails a reduction in fitness owing to a "cost of DNA replication fidelity" (Sniegowski et al. 2000). This cost may be due to a shortage in resources and energy required to repair mutations, or due to the reduced replication rate of higher fidelity 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.

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)). 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, which can lead to the extinction of these alleles due to mutational meltdown (Lynch et al. 1993). Fourth, "clonal interference" reduces the adaptation rate of asexual populations and reduces the advantage to mutator alleles due to indirect selection on the beneficial mutations they generate (de Visser et al. 1999). Fifth, recombination influences the mutation rate in several ways: i) it alters the direction and magnitude of indirect selection on mutator alleles by breaking the association between these alleles and the mutations they generate, ii) it affects 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 individual, thereby accelerating the rate of adaptation and reducing the need for mutations in a process called the "Fisher-Muller effect" (Christiansen et al. 1998). Sixth, complex fitness landscape (Loewe 2009; Papp, Notebaart, and Pal 2011) and co-evolution of different species (Pal et al. 2007) may have an important role in determining the evolutionary fate of mutator alleles.

## Stress-induced mutagenesis

In an influential paper, Cairns and colleagues (Cairns, Overbaugh, and Miller 1988) suggested that *"cells may have mechanisms for choosing which mutations will occur"*. This idea was controversial in the genetics and evolutionary biology communities (Lenski, Slatkin, and Ayala 1989; Lenski and Sniegowski 1995b; Roth et al. 2006), and for the next 10 years the *adaptive mutation hypothesis* was a major controversy and the subject of numerous publications (Hall 1990; Hall 1994; Foster 1992; Foster 1993; Foster 1999; Mittler and Lenski 1992; Rosche and Foster 2000; Rosenberg, Thulin, and Harris 1998; Lenski 1989; Sniegowski and Lenski 1995). During the beginning of the 20th century it became increasingly clear that *"various types of stresses induce responses that have mutagenic consequences, and that sometimes this essentially random process can appear to be directed"* (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) . Recent research on laboratory strains of *Escherichia coli* have uncovered some of the mechanisms which underlie stress-induced hypermutation (Gonzalez et al. 2008; Galhardo et al. 2009; Gibson et al. 2010; Shee et al. 2011). This phenomenon is not restricted to the lab (Bjedov et al. 2003), nor to a single bacterial species (Cirz et al. 2007; Galhardo, Hastings, and Rosenberg 2007; Kivisaar 2010; van der Veen et al. 2010; Debora et al. 2010), nor is it restricted to the bacterial domain: evidence suggests that mutations are more common in stressed yeast (Heidenreich 2007), algae (Goho and Bell 2000), flies (Agrawal and Wang 2008; 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 hypermutation were proposed, and they can be roughly divided into adaptive hypotheses and the 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 hypermutation in times of stress is favored by selection because it increases variation and allows faster adaptation to stress. (ii) Non-adaptive hypotheses suggest that mutagenesis is an inevitable by-product of stress that is caused by lack of energy and resources that are 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 the adaptive hypothesis has not been studied using population genetics models. Such models are necessary to examine if a mutator allele that induces elevated mutation rates in response to maladaptation can increase in frequency by indirect selection on the mutations it generates.

Furthermore, the consequences of stress-induced hypermutation are largely unknown. Agrawal (2002) studied a model of fitness-dependent mutation rates (FDMR) in an infinite population, and showed that FDMR increases the twofold 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 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 et al. 2005; Cirz and Romesberg 2006), 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). Even more importantly, because the mutation rate is a corner stone in 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 the mutation rate is constant. However, the 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 in 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 were:

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

## Thesis overview

During my PhD I have authored three published 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 published manuscript (Ram and Hadany 2012) I have provided the first theoretical support for the *adaptive hypothesis*: I have shown, using deterministic and stochastic models, that stress-induced mutagenesis is favored by natural due to the beneficial mutations it generates specifically in individuals that need them. The manuscript focused on asexual populations. First, I studied 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 (beneficial) mutations are possible. This is a new and surprising result; selection usually reduces the mutation rate rather than increases it (Liberman and Feldman 1986). Second, I studied 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 rate 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 higher mean fitness than populations of 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 is only sometimes favored in changing environments (Giraud, Radman, et al. 2001).

### The evolution of stress-induced hypermutation 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.

For example, in a constant environment recombination can prevent the accelerated accumulation of deleterious mutations that can lead to the loss of the fittest genotype in a process called Muller's Ratchet (Gordo and Charlesworth 2000), thus allowing mutator alleles to survive despite the excess deleterious mutations they generate. By reducing the mutational load in the population, recombination also increases the chance that a beneficial mutation appears on a good genetic background, thereby increasing the probability that the beneficial mutation goes to fixation, sweeping the mutator allele along (Johnson and Barton 2002).

In contrast, recombination provides an alternative adaptive strategy to mutation, at least when more than a single mutation is required for adaptation (Tenaillon et al. 2000); therefore, recombination prevents mutator alleles from fixing in populations during adaptive evolution. Recombination also separates mutator alleles from hitch-hiking with the beneficial mutations they generate (Maynard Smith and Haigh 1974).

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 is 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 in parallel using different genetic mechanisms.

### Stress-induced mutagenesis and complex adaptation

In the above manuscripts I developed a framework to explain the evolution of stress-induced mutagenesis; in contrast, in my second published manuscript (Ram and Hadany 2014b) I have 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 has been a long time open question in evolutionary biology (Wright 1931; Wright 1988), as it is not clear how individuals can accumulate the required mutations if each of them is deleterious when not together with the other mutations.

I have used mathematical analysis and computer simulations to estimate how stress-induced mutagenesis increases the rate of complex adaption in comparison to normal mutagenesis and constitutive mutagenesis. Combining these estimates with estimates of population mean fitness in a constant environment, I have shown that stress-induced mutagenesis is the most efficient mutational strategies, 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 adaption.

### 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 to analyze 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 analyzing Fisher's model because it provides an alternative interpretation of 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 – and their effect on the probability of improvement.

My other manuscripts suggest 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, and the rate of adaptive evolution is, of course, also a decreasing function of the probability that a mutation is beneficial. My new method for determining the probability that a mutation is beneficial in Fisher's geometric model, therefore, is an important step towards understanding the evolutionary origin of stress-induced mutagenesis, as it facilitates the analysis of the most important constraint, the rate of beneficial mutations.

## Methods overview

During my PhD research I used several theory-oriented methods.

### Individual-based simulations

In individual-based simulations (also called *agent-based simulations*), the simulations defines a population of individuals and a set of rules for their life cycle and interactions (Conway 1970) which often include some stochastic element. The 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 used by another student for his PhD research (Gueijman et al. 2013). The software allows the definition of life cycle rules for modeling selection, mutation, recombination, sexual reproduction, migration, and random genetic drift. I ran over 100,000 simulations on the Hadany computer cluster.

### Wright-Fisher models

The *Wright-Fisher model* is one of the standard population genetic models (Otto and Day 2007). It is used to describe the change in allele frequency from generation to generation (with non-overlapping generation) and can include the effects of natural selection, mutation, random genetic drift, recombination, and migration.

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.

When focusing on the mutation-selection balance, one focuses on the equilibrium of the model, in which the expected allele frequencies do not change from generation to generation, under the influence of mutation and selection. I used such analysis to find the mean fitness of populations with different mutational strategies (Ram and Hadany 2012; Ram and Hadany 2014b). I 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 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 at <https://github.com/yoavram/ruggedsim/blob/master/manuscript/supplementry.ipynb>).

When focusing on competitions between mutator alleles, I have developed a software implementation of the Wright-Fisher model with selection, mutation, random genetic drift, and 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.

When focusing on adaptive evolution, I have used a Wright-Fisher model 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 (Ram and Hadany 2014b); the fixation probability of the adaptive genotype was then estimated using Branching processes (see below).

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), the first step in calculating the rate of adaptation.

### Probability theory

For my third published 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. Frist, 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've developed a new method for analyzing 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), there were serious questions if stress-induced mutagenesis can have an adaptive advantage and if such an advantage can lead to its evolution and maintenance in natural populations (Tenaillon et al. 2001; Tenaillon, Denamur, and Matic 2004; Saint-Ruf and Matic 2006; Lenski and Sniegowski 1995a; Roth et al. 2006).

My results show, for the first time, that stress-induced mutagenesis can have an evolutionary advantage over constant mutation rates. Moreover, my results show that this 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 (as is the case in many microbes), 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 (Kimura and Maruyama 1966), and that selection acts to reduce the mutation rate. 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: 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 error correction and DNA proofing machinery (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 for increasing or decreasing the mutation rate. While a cost of fidelity might increase the advantage of stress-induced mutators over non-mutators, it might also increase the success of constitutive mutators in competitions versus stress-induced mutators and non-mutator alleles, as constitutive mutators 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 mutators in bacteria (Giraud, Matic, et al. 2001; Mérino et al. 2002; Gentile et al. 2011; Shee et al. 2011). Future studies can integrate a cost of fidelity (Johnson 1999) to my models to find how such a cost affects the evolutionary advantage of stress-induced mutagenesis.

Another cost might be associated with the *regulation* of the mutation rate: for individuals to determine their condition, they must invest in costly sensory 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. Moreover, in *E. coli* mutagenesis is induced by several stress responses that serve other cellular functions (Foster 2007; Al Mamun et al. 2012); this is probably the case in other organisms, too.

The *drift barrier hypothesis* (Sung et al. 2012) offers another explanation for the origin of stress-induced mutagenesis: cell machinery that is induced during stress didn't became error-prone because selection favored the beneficial mutations generated during stress, but rather because it was only rarely expressed and therefore experienced less selection. This reduced selection allowed deleterious mutations to accumulate in the genes coding for stress-induced DNA polymerases and error proofing proteins, making them error-prone. Future research could test this hypothesis by estimating the effective population size and frequency of stress that allows stress-induced mutagenesis to evolve without generation of beneficial alleles.

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's fitness, can be used to mitigate errors in fitness estimation.

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 the pathogen mutation rate can lead to incorrect conclusions on the ability of the pathogen to evolve virulence (Oliver et al. 2000; Mérino et al. 2002) and drug resistance: Obolski and Hadany demonstrated that stress-induced mutagenesis changes that recommended drug administration policy in hospital departments (Obolski and Hadany 2012); Cirz et al. (Cirz et al. 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 to produce products, from cheese, yogurt, beer and wine to antibiotics and biofuel. However, the genetic integrity of the industrial strains may be at a larger risk that previously thought, as in most cases microbes are grown in stressful conditions to produce the required 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 growth of the tumor. It has been shown that mutagenesis in 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 crucial theoretical support to the observation that mutations are more likely to occur in stressed individuals.

# References

Agrawal, Aneil F. 2002. “Genetic Loads under Fitness-Dependent Mutation Rates.” *Journal of Evolutionary Biology* 15 (6) (October 25): 1004–1010. doi:10.1046/j.1420-9101.2002.00464.x.

Agrawal, Aneil F., and Alethea D. Wang. 2008. “Increased Transmission of Mutations by Low-Condition Females: Evidence for Condition-Dependent DNA Repair.” Edited by Mohamed A. F Noor. *PLoS Biology* 6 (2) (February): e30. doi:10.1371/journal.pbio.0060030.

Al Mamun, Abu Amar M., Mary-Jane Lombardo, Chandan Shee, Andreas M. Lisewski, Caleb Gonzalez, Dongxu Lin, Ralf B. Nehring, et al. 2012. “Identity and Function of a Large Gene Network Underlying Mutagenic Repair of DNA Breaks.” *Science* 338 (6112) (December 7): 1344–8. doi:10.1126/science.1226683.

Altenberg, Lee. 2011. “An Evolutionary Reduction Principle for Mutation Rates at Multiple Loci.” *Bulletin of Mathematical Biology* 73 (6) (June): 1227–70. doi:10.1007/s11538-010-9557-9.

Avery, Oswald T. 1944. “STUDIES ON THE CHEMICAL NATURE OF THE SUBSTANCE INDUCING TRANSFORMATION OF PNEUMOCOCCAL TYPES: INDUCTION OF TRANSFORMATION BY A DESOXYRIBONUCLEIC ACID FRACTION ISOLATED FROM PNEUMOCOCCUS TYPE III.” *Journal of Experimental Medicine* 79 (2) (February 1): 137–158. doi:10.1084/jem.79.2.137.

Bjedov, Ivana, Olivier Tenaillon, Bénédicte Gérard, Valeria Souza, Erick Denamur, Miroslav Radman, François Taddei, and Ivan Matic. 2003. “Stress-Induced Mutagenesis in Bacteria.” *Science* 300 (5624) (May 30): 1404–9. doi:10.1126/science.1082240.

Boshoff, Helena I.M., Michael B Reed, Clifton E. Barry III, and Valerie Mizrahi. 2003. “DnaE2 Polymerase Contributes to In Vivo Survival and the Emergence of Drug Resistance in Mycobacterium Tuberculosis.” *Cell* 113 (2) (April): 183–193. doi:10.1016/S0092-8674(03)00270-8.

Bristow, Robert G., and Richard P. Hill. 2008. “Hypoxia and Metabolism: Hypoxia, DNA Repair and Genetic Instability.” *Nature Reviews. Cancer* 8 (3) (March): 180–92. doi:10.1038/nrc2344.

Cairns, John, Julie Overbaugh, and Stephan Miller. 1988. “The Origin of Mutants.” *Nature* 335 (6186) (September 8): 142–5. doi:10.1038/335142a0.

Christiansen, Freddy B., Sarah P. Otto, Aviv Bergman, and Marcus W. Feldman. 1998. “Waiting with and without Recombination: The Time to Production of a Double Mutant.” *Theoretical Population Biology* 53 (3) (June): 199–215. doi:10.1006/tpbi.1997.1358.

Cirz, Ryan T., Jodie K. Chin, David R. Andes, Valérie de Crécy-Lagard, William A. Craig, and Floyd E. Romesberg. 2005. “Inhibition of Mutation and Combating the Evolution of Antibiotic Resistance.” *PLoS Biology* 3 (6) (June): e176. doi:10.1371/journal.pbio.0030176.

Cirz, Ryan T., Marcus B. Jones, Neill A. Gingles, Timothy D. Minogue, Behnam Jarrahi, Scott N. Peterson, and Floyd E. Romesberg. 2007. “Complete and SOS-Mediated Response of Staphylococcus Aureus to the Antibiotic Ciprofloxacin.” *Journal of Bacteriology* 189 (2) (January): 531–9. doi:10.1128/JB.01464-06.

Cirz, Ryan T., and Floyd E. Romesberg. 2006. “Induction and Inhibition of Ciprofloxacin Resistance-Conferring Mutations in Hypermutator Bacteria.” *Antimicrobial Agents and Chemotherapy* 50 (1) (January): 220–5. doi:10.1128/AAC.50.1.220-225.2006.

Conway, John. 1970. “The Game of Life.” *Scientific American* 223 (4): 4.

Dawson, Kevin J. 1998. “Evolutionarily Stable Mutation Rates.” *Journal of Theoretical Biology* 194 (1) (September 7): 143–57. doi:10.1006/jtbi.1998.0752.

De Visser, J.Arjan G.M. 2002. “The Fate of Microbial Mutators.” *Microbiology (Reading, England)* 148 (Pt 5) (May): 1247–52.

De Visser, J.Arjan G.M., Clifford Zeyl, Philip J. Gerrish, Jeffrey L. Blanchard, and Richard E. Lenski. 1999. “Diminishing Returns from Mutation Supply Rate in Asexual Populations.” *Science* 283 (5400) (January 15): 404–6. doi:10.1126/science.283.5400.404.

Debora, Bernardo N., Luz E. Vidales, Rosario Ramírez, Mariana Ramírez, Eduardo A. Robleto, Ronald E. Yasbin, and Mario Pedraza-Reyes. 2010. “Mismatch Repair Modulation of MutY Activity Drives *Bacillus Subtilis* Stationary-Phase Mutagenesis.” *Journal of Bacteriology* 193 (1) (October): 236–45. doi:10.1128/JB.00940-10.

Denamur, Erick, and Ivan Matic. 2006. “Evolution of Mutation Rates in Bacteria.” *Molecular Microbiology* 60 (4) (May): 820–7. doi:10.1111/j.1365-2958.2006.05150.x.

Eshel, Ilan. 1981. “On the Survival Probability of a Slightly Advantageous Mutant Gene with a General Distribution of Progeny Size - a Branching Process Model.” *Journal of Mathematical Biology* 12 (3) (August): 355–362. doi:10.1007/BF00276922.

Eyre-Walker, Adam, and Peter D. Keightley. 2007. “The Distribution of Fitness Effects of New Mutations.” *Nature Reviews. Genetics* 8 (8) (August): 610–8. doi:10.1038/nrg2146.

Fisher, R.A. 1930. *The Genetical Theory of Natural Selection*. Oxford: Clarendon Press.

Foster, Patricia L. 1992. “Directed Mutation: Between Unicorns and Goats.” *Journal of Bacteriology* 174 (6) (March): 1711–6.

———. 1993. “Adaptive Mutation: The Uses of Adversity.” *Annual Review of Microbiology* 47 (January): 467–504. doi:10.1146/annurev.mi.47.100193.002343.

———. 1999. “Mechanisms of Stationary Phase Mutation: A Decade of Adaptive Mutation.” *Annual Review of Genetics* 33: 57. doi:10.1146/annurev.genet.33.1.57.MECHANISMS.

———. 2007. “Stress-Induced Mutagenesis in Bacteria.” *Critical Reviews in Biochemistry and Molecular Biology* 42 (5): 373–97. doi:10.1080/10409230701648494.

Galhardo, Rodrigo S., Robert Do, Masami Yamada, Errol C. Friedberg, P. J. Hastings, Takehiko Nohmi, and Susan M. Rosenberg. 2009. “DinB Upregulation Is the Sole Role of the SOS Response in Stress-Induced Mutagenesis in *Escherichia Coli*.” *Genetics* 182 (1) (May): 55–68. doi:10.1534/genetics.109.100735.

Galhardo, Rodrigo S., P. J. Hastings, and Susan M. Rosenberg. 2007. “Mutation as a Stress Response and the Regulation of Evolvability.” *Critical Reviews in Biochemistry and Molecular Biology* 42 (5): 399–435. doi:10.1080/10409230701648502.

Gentile, Christopher F, Szi-Chieh Yu, Sebastian Akle Serrano, Philip J. Gerrish, and Paul D. Sniegowski. 2011. “Competition between High- and Higher-Mutating Strains of *Escherichia Coli*.” *Biology Letters* 7 (3) (June 23): 422–4. doi:10.1098/rsbl.2010.1036.

Gerrish, Philip J., and Richard E. Lenski. 1998. “The Fate of Competing Beneficial Mutations in an Asexual Population.” *Genetica* 102-103 (0): 127–144–144. doi:10.1023/A:1017067816551.

Gibson, Janet L., Mary-Jane Lombardo, Philip C. Thornton, Kenneth H. Hu, Rodrigo S. Galhardo, Bernadette Beadle, Anand Habib, et al. 2010. “The sigma(E) Stress Response Is Required for Stress-Induced Mutation and Amplification in Escherichia Coli.” *Molecular Microbiology* 77 (2) (July): 415–30. doi:10.1111/j.1365-2958.2010.07213.x.

Giraud, Antoine, Ivan Matic, Olivier Tenaillon, Antonio Clara, Miroslav Radman, Michel Fons, and François Taddei. 2001. “Costs and Benefits of High Mutation Rates: Adaptive Evolution of Bacteria in the Mouse Gut.” *Science* 291 (5513) (March 30): 2606–8. doi:10.1126/science.1056421.

Giraud, Antoine, Miroslav Radman, Ivan Matic, and François Taddei. 2001. “The Rise and Fall of Mutator Bacteria.” *Current Opinion in Microbiology* 4 (5) (October): 582–585. doi:10.1016/S1369-5274(00)00254-X.

Goho, Shaun, and Graham Bell. 2000. “Mild Environmental Stress Elicits Mutations Affecting Fitness in Chlamydomonas.” *Proceedings of the Royal Society B: Biological Sciences* 267 (1439) (January 22): 123–9. doi:10.1098/rspb.2000.0976.

Gonzalez, Caleb, Lilach Hadany, Rebecca G. Ponder, Mellanie Price, P. J. Hastings, and Susan M. Rosenberg. 2008. “Mutability and Importance of a Hypermutable Cell Subpopulation That Produces Stress-Induced Mutants in *Escherichia Coli*.” *PLoS Genetics* 4 (10) (January): e1000208. doi:10.1371/journal.pgen.1000208.

Gordo, Isabel, and Brian Charlesworth. 2000. “The Degeneration of Asexual Haploid Populations and the Speed of Muller’s Ratchet.” *Genetics* 154 (3) (March): 1379–87.

Gressel, Jonathan. 2011. “Low Pesticide Rates May Hasten the Evolution of Resistance by Increasing Mutation Frequencies.” *Pest Management Science* 67 (3) (March 14): 253–7. doi:10.1002/ps.2071.

Gueijman, Ariel, Amir Ayali, Yoav Ram, and Lilach Hadany. 2013. “Dispersing Away from Bad Genotypes: The Evolution of Fitness-Associated Dispersal (FAD) in Homogeneous Environments.” *BMC Evolutionary Biology* 13 (1) (June 19): 125. doi:10.1186/1471-2148-13-125.

Hadany, Lilach, and Tuvik Beker. 2003. “On the Evolutionary Advantage of Fitness-Associated Recombination.” *Genetics* 165 (4) (December): 2167–79.

Haigh, John. 1978. “The Accumulation of Deleterious Genes in a Population - Muller’s Ratchet.” *Theoretical Population Biology* 14 (2) (October): 251–267. doi:10.1016/0040-5809(78)90027-8.

Hall, Barry G. 1990. “Spontaneous Point Mutations That Occur More Often When Advantageous than When Neutral.” *Genetics* 126 (1) (September): 5–16.

———. 1994. “On Alternatives to Selection-Induced Mutation in the Bgl Operon of Escherichia Coli.” *Molecular Biology and Evolution* 11 (2) (March): 159–68.

Harris, Theodore E. 1969. *The Theory of Branching Processes*. Berlin: Springer.

Heidenreich, Erich. 2007. “Adaptive Mutation in *Saccharomyces Cerevisiae*.” *Critical Reviews in Biochemistry and Molecular Biology* 42 (4): 285–311. doi:10.1080/10409230701507773.

Heo, Muyoung, and Eugene I. Shakhnovich. 2010. “Interplay between Pleiotropy and Secondary Selection Determines Rise and Fall of Mutators in Stress Response.” *PLoS Computational Biology* 6 (3) (March): e1000710. doi:10.1371/journal.pcbi.1000710.

Hilbert, Lennart. 2011. “Shifting Gears: Thermodynamics of Genetic Information Storage Suggest Stress-Dependence of Mutation Rate, Which Can Accelerate Adaptation.” *arXiv* (April 11): 15.

Huang, L. Eric, Ranjit S. Bindra, Peter M. Glazer, and Adrian L. Harris. 2007. “Hypoxia-Induced Genetic Instability--a Calculated Mechanism Underlying Tumor Progression.” *Journal of Molecular Medicine (Berlin, Germany)* 85 (2) (February): 139–48. doi:10.1007/s00109-006-0133-6.

Jackson, a L, and Lawrence A Loeb. 1998. “The Mutation Rate and Cancer.” *Genetics* 148 (4) (April): 1483–90.

Johnson, Toby. 1999. “The Approach to Mutation-Selection Balance in an Infinite Asexual Population, and the Evolution of Mutation Rates.” *Proceedings of the Royal Society B: Biological Sciences* 266 (1436) (December 7): 2389–97. doi:10.1098/rspb.1999.0936.

Johnson, Toby, and Nicholas H. Barton. 2002. “The Effect of Deleterious Alleles on Adaptation in Asexual Populations.” *Genetics* 162 (1) (September 1): 395–411.

Kimura, Motoo. 1967. “On the Evolutionary Adjustment of Spontaneous Mutation Rates.” *Genetical Research* 9 (01) (April 14): 23–34. doi:10.1017/S0016672300010284.

Kimura, Motoo, and Takeo Maruyama. 1966. “The Mutational Load with Epistatic Gene Interactions in Fitness.” *Genetics* 54 (6) (December 22): 1337–51.

———. 1969. “The Substitutional Load in a Finite Population.” *Heredity* 24 (1) (February): 101–114. doi:10.1038/hdy.1969.10.

Kivisaar, Maia. 2010. “Mechanisms of Stationary-Phase Mutagenesis in Bacteria: Mutational Processes in Pseudomonads.” *FEMS Microbiology Letters* 312 (1) (November): 1–14. doi:10.1111/j.1574-6968.2010.02027.x.

Leigh, Egbert Giles Jr. 1970. “Natural Selection and Mutability.” *The American Naturalist* 104 (937): 301–305.

———. 1973. “The Evolution of Mutation Rates.” *Genetics* 73 (April): Suppl 73:1–18.

Lenski, Richard E. 1989. “Mutation and Selection in Bacterial Populations: Alternatives to the Hypothesis of Directed Mutation.” *Proceedings of the National Academy of Sciences* 86 (8) (April): 2775–2778. doi:10.1073/pnas.86.8.2775.

Lenski, Richard E., Montgomery Slatkin, and Fransisco J. Ayala. 1989. “Another Alternative to Directed Mutation.” *Nature* 337 (6203) (January 12): 123–4. doi:10.1038/337123b0.

Lenski, Richard E., and Paul D. Sniegowski. 1995a. “Directed Mutations Slip-Sliding Away?” *Current Biology* 5 (2) (February): 97–9. doi:10.1016/S0960-9822(95)00023-6.

———. 1995b. “‘Adaptive Mutation’: The Debate Goes on.” *Science* 269 (5222) (July): 285–288. doi:10.1126/science.7618089.

Liberman, Uri, and Marcus W. Feldman. 1986. “Modifiers of Mutation Rate: A General Reduction Principle.” *Theoretical Population Biology* 30 (1) (August): 125–42.

Loewe, Laurence. 2009. “A Framework for Evolutionary Systems Biology.” *BMC Systems Biology* 3 (27) (January). doi:10.1186/1752-0509-3-27.

Loewe, Laurence, and William G. Hill. 2010. “The Population Genetics of Mutations: Good, Bad and Indifferent.” *Philosophical Transactions of the Royal Society B: Biological Sciences* 365 (1544) (April 27): 1153–67. doi:10.1098/rstb.2009.0317.

Luria, Salvador E., and Max Delbrück. 1943. “Mutations of Bacteria from Virus Sensitivity to Virus Resistance.” *Genetics* 28 (6) (November): 491–511.

Lynch, Michael. 2010. “Evolution of the Mutation Rate.” *Trends in Genetics* 26 (8) (June 29): 345–352. doi:10.1016/j.tig.2010.05.003.

———. 2011. “The Lower Bound to the Evolution of Mutation Rates.” *Genome Biology and Evolution* 3 (0) (August 4): 1107–1118. doi:10.1093/gbe/evr066.

Lynch, Michael, Reinhard Bürger, D Butcher, and Wilfried Gabriel. 1993. “The Mutational Meltdown in Asexual Populations.” *The Journal of Heredity* 84 (5): 339–44.

Machielsen, Ronnie, Ingrid J. van Alen-Boerrigter, Lucy A. Koole, Roger S. Bongers, Michiel Kleerebezem, and Johan E. T. Van Hylckama Vlieg. 2010. “Indigenous and Environmental Modulation of Frequencies of Mutation in Lactobacillus Plantarum.” *Applied and Environmental Microbiology* 76 (5) (March): 1587–95. doi:10.1128/AEM.02595-09.

Martens, Erik A., and Oskar Hallatschek. 2011. “Interfering Waves of Adaptation Promote Spatial Mixing.” *Genetics* 189 (3) (September 6): 1045–1060. doi:10.1534/genetics.111.130112.

Maynard Smith, John, and John Haigh. 1974. “The Hitch-Hiking Effect of a Favourable Gene.” *Genetical Research* 23 (1) (April 14): 23–35. doi:10.1017/S0016672300014634.

Mérino, Delphine, Hélène Réglier-Poupet, Patrick Berche, and Alain Charbit. 2002. “A Hypermutator Phenotype Attenuates the Virulence of Listeria Monocytogenes in a Mouse Model.” *Molecular Microbiology* 44 (3) (May): 877–87.

Milkman, Roger, and Mellissa McKane Bridges. 1990. “Molecular Evolution of the *Escherichia Coli* Chromosome. III. Clonal Frames.” *Genetics* 126 (3) (November): 505–17.

Mittler, John E., and Richard E. Lenski. 1992. “Experimental Evidence for an Alternative to Directed Mutation in the Bgl Operon.” *Nature* 356 (6368) (April): 446–8. doi:10.1038/356446a0.

Morgan, Andrew D., Michael B. Bonsall, and Angus Buckling. 2010. “Impact of Bacterial Mutation Rate on Coevolutionary Dynamics between Bacteria and Phages.” *Evolution* 64 (10) (October): 2980–7. doi:10.1111/j.1558-5646.2010.01037.x.

Obolski, Uri, and Lilach Hadany. 2012. “Implications of Stress-Induced Genetic Variation for Minimizing Multidrug Resistance in Bacteria.” *BMC Medicine* 10 (89) (January): 1–30. doi:10.1186/1741-7015-10-89.

Oliver, Antonio, Rafael Cantón, Pilar Campo, Fernando Baquero, and Jesus Blazquez. 2000. “High Frequency of Hypermutable *Pseudomonas Aeruginosa* in Cystic Fibrosis Lung Infection.” *Science* 288 (5469) (May 19): 1251–1253. doi:10.1126/science.288.5469.1251.

Otto, Sarah P., and Troy Day. 2007. *A Biologist’s Guide to Mathematical Modeling in Ecology and Evolution*. Princeton University Press.

Pal, Csaba, María D. Maciá, Antonio Oliver, Ira Schachar, and Angus Buckling. 2007. “Coevolution with Viruses Drives the Evolution of Bacterial Mutation Rates.” *Nature* 450 (7172) (December): 1079–81. doi:10.1038/nature06350.

Papp, Balázs, Richard A. Notebaart, and Csaba Pal. 2011. “Systems-Biology Approaches for Predicting Genomic Evolution.” *Nature Reviews. Genetics* 12 (9) (August 2): 591–602. doi:10.1038/nrg3033.

Patwa, Z, and Lindi M Wahl. 2008. “The Fixation Probability of Beneficial Mutations.” *Journal of the Royal Society, Interface / the Royal Society* 5 (28) (November 6): 1279–89. doi:10.1098/rsif.2008.0248.

Racey, Daniel, Robert Fredrik Inglis, Freya Harrison, Antonio Oliver, and Angus Buckling. 2010. “The Effect of Elevated Mutation Rates on the Evolution of Cooperation and Virulence of Pseudomonas Aeruginosa.” *Evolution* 64 (2) (February): 515–21. doi:10.1111/j.1558-5646.2009.00821.x.

Ram, Yoav. 2011. “Proevolution Simulation.” Tel-Aviv, Israel: Google Code.

Ram, Yoav, and Lilach Hadany. 2012. “THE EVOLUTION OF STRESS-INDUCED HYPERMUTATION IN ASEXUAL POPULATIONS.” *Evolution* 66 (7) (July 28): 2315–2328. doi:10.1111/j.1558-5646.2012.01576.x.

———. 2014a. “Data from: Stress-Induced Mutagenesis and Complex Adaptation.” *Dryad Digital Repository*. doi:10.5061/dryad.3066j.

———. 2014b. “Stress-Induced Mutagenesis and Complex Adaptation.” Populations and Evolution. *Proceedings of the Royal Society B: Biological Sciences* 281 (1792) (October 7): 20141025–20141025. doi:10.1098/rspb.2014.1025.

———. 2015. “The Probability of Improvement in Fisher’s Geometric Model: A Probabilistic Approach.” *Theoretical Population Biology* 99 (February): 1–6. doi:10.1016/j.tpb.2014.10.004.

Rice, Sean H. 1990. “A Geometric Model for the Evolution of Development.” *Journal of Theoretical Biology* 143 (3) (April): 319–342. doi:fisher.

Rosche, William A., and Patricia L. Foster. 2000. “Determining Mutation Rates in Bacterial Populations.” *Methods (San Diego, Calif.)* 20 (1) (January): 4–17. doi:10.1006/meth.1999.0901.

Rosenberg, Susan M., Chandan Shee, Ryan L. Frisch, and P. J. Hastings. 2012. “Stress-Induced Mutation via DNA Breaks in *Escherichia Coli*: A Molecular Mechanism with Implications for Evolution and Medicine.” *BioEssays* (August 22): 1–8. doi:10.1002/bies.201200050.

Rosenberg, Susan M., Carl Thulin, and Reuben S. Harris. 1998. “Transient and Heritable Mutators in Adaptive Evolution in the Lab and in Nature.” *Genetics* 148 (4) (April): 1559–66.

Roth, John R., Elisabeth Kugelberg, Andrew B. Reams, Eric Kofoid, and Dan I. Andersson. 2006. “Origin of Mutations under Selection: The Adaptive Mutation Controversy.” *Annual Review of Microbiology* 60 (January): 477–501. doi:10.1146/annurev.micro.60.080805.142045.

Ruan, Kai, Gang Song, and Gaoliang Ouyang. 2009. “Role of Hypoxia in the Hallmarks of Human Cancer.” *Journal of Cellular Biochemistry* 107 (6) (August): 1053–62. doi:10.1002/jcb.22214.

Saint-Ruf, Claude, and Ivan Matic. 2006. “Environmental Tuning of Mutation Rates.” *Environmental Microbiology* 8 (2) (February): 193–9. doi:10.1111/j.1462-2920.2005.00968.x.

Sharp, Nathaniel P., and Aneil F. Agrawal. 2012. “Evidence for Elevated Mutation Rates in Low-Quality Genotypes.” *Proceedings of the National Academy of Sciences* 109 (16) (April 17): 6142–6. doi:10.1073/pnas.1118918109.

Shaw, Frank H., and Charles F. Baer. 2011. “Fitness-Dependent Mutation Rates in Finite Populations.” *Journal of Evolutionary Biology* 24 (8) (August 3): 1677–84. doi:10.1111/j.1420-9101.2011.02320.x.

Shee, Chandan, Janet L. Gibson, Michele C. Darrow, Caleb Gonzalez, and Susan M. Rosenberg. 2011. “Impact of a Stress-Inducible Switch to Mutagenic Repair of DNA Breaks on Mutation in *Escherichia Coli*.” *Proceedings of the National Academy of Sciences* 108 (33) (August 1): 13659–13664. doi:10.1073/pnas.1104681108.

Sloan, Daniel B., and Vijay G. Panjeti. 2010. “Evolutionary Feedbacks between Reproductive Mode and Mutation Rate Exacerbate the Paradox of Sex.” *Evolution* 64 (4) (April 1): 1129–35. doi:10.1111/j.1558-5646.2009.00869.x.

Sniegowski, Paul D., Philip J. Gerrish, Toby Johnson, and Aaron Shaver. 2000. “The Evolution of Mutation Rates: Separating Causes from Consequences.” *BioEssays : News and Reviews in Molecular, Cellular and Developmental Biology* 22 (12) (December): 1057–66. doi:10.1002/1521-1878(200012)22:12<1057::AID-BIES3>3.0.CO;2-W.

Sniegowski, Paul D., Philip J. Gerrish, and Richard E. Lenski. 1997. “Evolution of High Mutation Rates in Experimental Populations of E. Coli.” *Nature* 387 (6634) (June): 703–5. doi:10.1038/42701.

Sniegowski, Paul D., and Richard E. Lenski. 1995. “Mutation and Adaptation: The Directed Mutation Controversy in Evolutionary Perspective.” *Annual Review of Ecology and Systematics* 26 (1) (November): 553–578. doi:10.1146/annurev.es.26.110195.003005.

Sprouffske, Kathleen, Lauren M F Merlo, Philip J. Gerrish, Carlo C Maley, and Paul D. Sniegowski. 2012. “Cancer in Light of Experimental Evolution.” *Current Biology* 22 (17) (September 11): R762–71. doi:10.1016/j.cub.2012.06.065.

Sturtevant, A. H. 1937. “Essays on Evolution. I. On the Effects of Selection on Mutation Rate.” *The Quarterly Review of Biology* 12 (4) (December): 464–467. doi:10.1086/394543.

Sung, Way, Matthew S. Ackerman, Samuel F. Miller, Thomas G. Doak, and Michael Lynch. 2012. “Drift-Barrier Hypothesis and Mutation-Rate Evolution.” *Proceedings of the National Academy of Sciences of the United States of America* 109 (45) (November 6): 18488–92. doi:10.1073/pnas.1216223109.

Taddei, François, Miroslav Radman, John Maynard Smith, Bruno Toupance, Pierre-Henri Gouyon, and Bernard Godelle. 1997. “Role of Mutator Alleles in Adaptive Evolution.” *Nature* 387 (6634) (June): 700–2. doi:10.1038/42696.

Tenaillon, Olivier, Erick Denamur, and Ivan Matic. 2004. “Evolutionary Significance of Stress-Induced Mutagenesis in Bacteria.” *Trends in Microbiology* 12 (6) (June): 264–70. doi:10.1016/j.tim.2004.04.002.

Tenaillon, Olivier, Herve Le Nagard, Bernard Godelle, and François Taddei. 2000. “Mutators and Sex in Bacteria: Conflict between Adaptive Strategies.” *Proceedings of the National Academy of Sciences* 97 (19) (September): 10465–70. doi:10.1073/pnas.180063397.

Tenaillon, Olivier, François Taddei, Miroslav Radman, and Ivan Matic. 2001. “Second-Order Selection in Bacterial Evolution: Selection Acting on Mutation and Recombination Rates in the Course of Adaptation.” *Research in Microbiology* 152 (1): 11–6.

Tenaillon, Olivier, Bruno Toupance, Herve Le Nagard, François Taddei, and Bernard Godelle. 1999. “Mutators, Population Size, Adaptive Landscape and the Adaptation of Asexual Populations of Bacteria.” *Genetics* 152 (2) (June): 485–93.

Tomlinson, Ian, and Walter F Bodmer. 1999. “Selection, the Mutation Rate and Cancer: Ensuring That the Tail Does Not Wag the Dog.” *Nature Medicine* 5 (1) (January): 11–2. doi:10.1038/4687.

Van der Veen, Stijn, Saskia van Schalkwijk, Douwe Molenaar, Willem M. de Vos, Tjakko Abee, and Marjon H. J. Wells-Bennik. 2010. “The SOS Response of *Listeria Monocytogenes* Is Involved in Stress Resistance and Mutagenesis.” *Microbiology (Reading, England)* 156 (Pt 2) (February): 374–84. doi:10.1099/mic.0.035196-0.

Waxman, David, and John J Welch. 2005. “Fisher’s Microscope and Haldane's Ellipse.” *The American Naturalist* 166 (4) (October): 447–57. doi:10.1086/444404.

Wright, Sewall. 1931. “Evolution in Mendelian Populations.” *Genetics* 16 (2) (March): 97–159.

———. 1988. “Surfaces of Selective Value Revisited.” *American Naturalist* 131 (1): 115–123. doi:10.1086/284777.

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

ינואר 2016