An Examination of the Effects of Age-Structure on Mutation Rate Evolution in a Changing Environment by Computer Simulation

Christian P. Landy

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ABSTRACT

AN EXAMINATION OF THE EFFECTS OF AGE-STRUCTURE ON MUTATION RATE EVOLUTION IN A CHANGING ENVIRONMENT BY COMPUTER SIMULATION

Christian P. Landy
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Advisor:
Dr. Cortland Griswold

A life-history involves the scheduling of events in an individual's life, such as growth, reproduction, and survivorship. This thesis seeks to focus on the possibility than an individual could also schedule its rate of mutation, such that different mutation rates may occur as an organism ages. These different mutation rates may be adaptive and evolve by natural selection. In a simulated population with iteroparity, genotypes that encoded age-structured mutation outcompeted genotypes that did not encode age-structured mutation provided that the rate of environmental change was sufficiently high. My finding that age-structured mutation rates can be adaptive may lead to a new understanding of the adaptive role of aging.

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CHAPTER ONE

INTRODUCTION AND LITERATURE REVIEW

Introduction

Purpose

This thesis examines the connection between age-structure and mutation rates, within the context of evolutionary adaptation.

Specific Focus

In this thesis, I derive a model for a haploid asexual population with age-structure. Age-structure occurs because individuals can potentially live and reproduce for two time steps. In the model, generations are overlapping. Two types of individuals occur in the model. First, there are those with potentially two age-structured mutation rates (Double Mutation Rate Individuals, DMRI), with one evolvable mutation rate at the first age of reproduction and a second evolvable mutation rate at the second age of reproduction. Second, there are those with only a single evolvable mutation rate at both reproductive ages (Single Mutation Rate Individuals, SMRI). DMRI and SMRI compete in a single population to determine which of these two strategies has higher fitness in environments undergoing environmental change. In the model, SMRI are akin to control subjects whereas DMRI are the experimental treatment. If DMRI outcompete SMRI in a statistically significant proportion of simulations then their evolutionary fitness is greater. This would support the conclusion that there is adaptive benefit to evolving different mutation rates for each age of reproduction.

Hypothesis

The hypothesis of my thesis is that, in age-structured organisms, the ability to express different mutation rates at different reproductive periods is evolutionarily adaptive in a changing environment. In a changing environment, there are times when an individual's phenotype matches its environment and it is advantageous for this

individual to produce phenotypically similar offspring relative to itself. In contrast, there are other times when an individual's phenotype may mismatch the environment and it is advantageous for this individual to produce phenotypically different offspring relative to itself. In each of these cases, age-structured organisms with different mutation rates at each reproductive period may provide an adaptive solution. The added flexibility of having even somewhat independent mutation rates may be evolutionarily advantageous.

In organisms that have evolved the ability to produce different mutation rates, this ability is likely most adaptive in high stress environments. A higher proportion of mutations are beneficial in high stress environments. This makes mutation rates more important to survival in these environments. DMRI have the ability to have more finely tuned mutation rates than SMRI. In this way, high stress environments may make more finely tuned mutation rates adaptive.

Model Outcome Prediction

Under high rates of environmental change it is expected that DMRI will outcompete SMRI.

Literature Review

In order to give context to my thesis, it is necessary to outline several topics in evolution. Each of the following subsections builds on the material of the previous section(s). I start with a general introduction to evolution. This is followed by an introduction to mutation, one of the components necessary for biological evolution. After these introductions, I discuss relevant research findings about the evolution of mutation rates. This naturally leads into a discussion of the connections between mutation rate evolution and aging. I will discuss one proximal theory, the free radical theory of aging. I will finish this section with a discussion of the more controversial adaptive theories of aging.

The Process of Evolution by Natural Selection

Evolution is change in gene frequencies over time resulting in changing proportions of the traits of living organisms within a population (Futuyma 2013). Evolution by natural selection has led to tremendous complexity and diversity in living things, despite its apparent procedural simplicity. In this section, I will provide a brief synopsis of the five major elements required for biological evolution by natural selection to take place. First, it requires individuals that together form a population. Second, these individuals must contain some variation in their traits, across the population. Third, some of this variation needs to be heritable reproductively. This happens mainly through the molecules of DNA and RNA, but can also be the result of epigenetic effects. Fourth, a process of mutation leads to changes in genetic material and hence heritable differences among individuals through time. Fifth, a process of natural selection, whereby the environment acts to limit the survival and reproduction of individuals, also needs to occur. It is widely accepted that these few elements together result in biological evolution by natural selection.

Mutation

Mutations are genetic changes. They can be caused by several factors: imperfect copying of genetic material, faulty DNA repair mechanisms, high-energy electromagnetic radiation (e.g. UV and X-rays), mutagenic chemicals, and highly reactive molecules (including free radicals).

While the outcomes of mutations are random, mutation rates are not. There is evidence for heritable variation in mutation rates across organisms (Johnson 1999b). Furthermore there is evidence that natural selection can act on mutation rates such that they can evolve (Sniegowski et al. 2000; Metzgar and Wills 2000; Johnson 1999b). Many organisms have evolved specific mutation rates as well as mechanisms that can adjust these rates, based on environmental and organismal conditions. Further, according to the research findings of Drake et al. (1998), the spontaneous mutation rates of many organismal taxa are conserved, while simultaneously varying between less closely related taxa. For example, two closely related species may have similar

mutation rates, while two significantly different species may more readily have dissimilar mutation rates. These two observations, between and within taxa, suggest that mutation rates are at equilibrium values (Drake et al. 1998). However, this does not mean that mutation rates are adaptive.

Mutations can be beneficial, deleterious, or neutral to the fitness of organisms. A beneficial mutation is one that increases the relative fitness of an organism to its wildtype progenitor. A deleterious mutation decreases the relative fitness of an organism to its wildtype progenitor. Neutral mutations have little or no effect on relative fitness. Nearly neutral mutations have weak selective effects relative to the rate of drift. It is well documented that the average effect of mutations is deleterious (Agrawal and Wang 2008; Stich, Manrubia, and Lazaro 2010; Drake et al. 1998), despite the knowledge that most mutations are nearly neutral (Kimura and Ohta 1971). Due to the typical harmful nature of mutations, non-zero mutation rates tend to cause a reduction in mean population fitness. This reduction in fitness due to mutation is called mutation load (Kimura, Maruyama, and Crow 1963). It is also important to note that the effect of a mutation is contingent on the environment in which an organism is found.

Significant Findings in the Area of Mutation

1. Current Methods of Studying Mutation

The evolution of mutation rates can be studied empirically, through the use of living organisms. Two commonly used organisms in the study of mutation are *Drosophila* and bacteria, including *Escherichia coli*. Mutation rates can also be studied theoretically. Researchers use both deterministic and stochastic models to study the evolution of mutation rates.

2. Three Factors Influencing Mutation Rates

Both mutation rate evolution and the trade-offs between selection and harmful mutation have received much attention from theoretical population geneticists (Johnson 1999a). Johnson (1999b) suggests that three major factors impact the evolution of

mutation rates. The first factor is the probability of deleterious mutations. The second is the probability of beneficial mutations. The third factor is the cost of DNA replication fidelity; repair and error proofing mechanisms have metabolic costs. Adding to this third factor, mutations typically lead to deterioration of DNA copying and proofing mechanisms and hence less faithful replication of DNA; error begets more error. It is important to note that all three of these factors can be influenced by environmental conditions.

The average effect of a mutation is to increase the mutation rate; individuals are thought to naturally tend toward increasing mutation rates (Johnson 1999a). In past, some researchers considered living organisms analogous to machines like cars and so thought that their parts would wear out over time (Charlesworth 2000). Also, inferring from the second law of thermodynamics, that entropy will increase in closed physical systems naturally, it appears that organisms should deteriorate with age. However, living organisms are not closed systems and can counter increasing entropy within themselves to some extent by the input of energy.

The three mutation-impacting factors have different condition-based relative importance in the evolution of organisms. Sniegowski (1997) identifies two possible tradeoffs between mutation-impacting factors. First is the tradeoff between the cost of DNA replication fidelity and that of minimizing mutation rates. Second is the tradeoff between the harmful and beneficial effects of mutations on overall fitness. He suggests that these two explanations operate under different circumstances, including whether or not the minimum attainable mutation rate is lower than the optimal mutation rate. In this case, selection would act to increase mutation rates. An optimal mutation rate is one that maximizes the individual fitness of a given organism in its current environment; factors impacting optimal mutation rates will be discussed in a later section. Sniegowski (1997) notes that mutation rates do not evolve to zero. This is likely due to the physical limits on the replication and repair of DNA, although this is clearly only a partial explanation. If mutation rates were solely determined by the physical limits of DNA one would expect mutation rates to be the same in all DNA based species with similar

genome structure. This likely has not been tested due to complications in determining similar genome structure but is nevertheless an interesting thought experiment. Johnson (1999b) adds to the theoretical understanding of trade-offs by suggesting that in models where the cost of genetic fidelity is increased, it can be expected that mutators will increase and hence there will be more mutations, both beneficial and deleterious. Organisms with elevated mutation rates are referred to as mutators.

Sniegowski (1997) points to research that shows there can be fitness costs to reducing mutation rates below certain levels. In *Drosophila melanogaster*, after temporary (up to 600 generations) X-ray exposure, mutation rates were found to be reduced (*cf.* Sniegowski et al. 2000). Some populations returned to wild-type levels of mutation (they evolved increases in their mutation rate) in the generations after the treatment was removed. This finding suggests that mutation rates were able to compensate when additional mutation causing factors were introduced or removed. It also suggests that low mutation rates have increased fitness costs when very low. To continue, Sniegowski et al. (2000) also refer to a study showing the existence of anti-mutator *E. coli* which suggests that mutation rates can decrease below equilibrium values. They mention that one anti-mutator *E. coli* type has a genomic mutation rate that is two-fold lower than is found in wildtype individuals.

3. Linkage, Mutator Alleles, and Adaptation

Adaptive fixation of genes is the process whereby a single version of a gene, through selection, becomes the only form of that gene left in a population. Alleles, or forms of genes, tend to become fixed within populations provided the force of selection on them is greater than the forces of drift and mutation. When beneficial alleles become fixed, typically, alleles for other genes linked with the beneficial allele also reach fixation. This phenomenon is called genetic “hitchhiking” and is due to the small physical distance between beneficial genes and other genes on a strand of DNA. Through linkage, genes that increase mutation rates may reach fixation provided they are associated with the production of beneficial genotypes (Sniegowski et al. 2000). When mutator genes reach fixation, it may appear that mutators must serve an adaptive

purpose. However, Sniegowski et al. (2000) make an important distinction:

> "A mutator phenotype that has hitchhiked to fixation is properly regarded as a consequence of adaptation, however, not an adaptation itself. The adaptive value of a mutator phenotype depends on whether it increases the rate of subsequent adaptation in an asexual population, and the circumstances under which this is likely are limited."

Natural selection is not considered a process with foresight (Stich, Manrubia, and Lazaro 2010; Metzgar and Wills 2000); selection does not act on the potential for future adaptive benefits of a change, but instead on the current fitness effects of mutations. Out of this understanding, traits that appear adaptive may not have evolved for their current function; it is only by serendipity that they provide one. Increased mutation rates may be an example of serendipity, whereby alleles that raise the mutation rate are fixed by an indirect process, not direct selection, and are later found beneficial. Despite this understanding, environmental change can take the form of consistent cyclical or directional changes, and can also have predictable magnitude changes. Without evolution requiring foresight, organisms can arrive at phenotypes that benefit future survival. An example of this is the development of phenotypic plasticity in an environment with predictable variance in its changes. Starving *E. coli* can lead to the production of mutator-types, organisms with elevated mutation rates that are likely due to adaptive plasticity (Metzgar and Wills 2000). Drake et al. (1998) suggest that elevated mutation rates may be adaptive in populations under, "strong directional selection." This is thought the case because higher rates of mutation will mean a faster increase in allelic variation. In turn, this would increase the rate beneficial alleles being introduced into the population, fostering adaptation. However this explanation assumes that the production of beneficial mutations will overcome the cost of harmful mutations. Drake et al. (1998) also, in passing, mention that life-history is a core determinant of an organism's mutation rate.

Mutation rates are determined, in part, by the external and internal environments of organisms. It has been shown, theoretically, that in some high stress environments organisms will evolve higher mutation rates (Stich, Manrubia, and Lazaro 2010). Also,

individual organisms with low relative fitness may experience increased mutation rates (Agrawal and Wang 2008). Both of these findings may be the result of a reduction in the effectiveness of mutation repair processes, caused by stress. However, according to Stich, Manrubia, and Lazaro (2010), mutation and selection act in tandem to improve the adaptation of organisms within changing environments. They mention that, in theory, individuals and populations closer to an optimal level of fitness are more likely to have deleterious mutations. In contrast, the further organisms are from the environmental optimum, the more likely they are to have beneficial mutations. Since optimal mutation rates are, to a large extent, dependent on the rate of environmental change and environments change constantly, mutation rates are continually under selection. Low mutation rates, and hence anti-mutator types, are more optimal under low environmental change and higher mutation rates, and mutator types, are optimal under high environmental change (Stich, Manrubia, and Lazaro 2010). Theoretically, populations that produce large amounts of phenotypic variance in constant environments would not be favoured over the long term.

Mutator are known to outcompete wildtype *E. coli* in long term empirical competition studies due to their, “strong selective advantage” (*cf.* Chao and Cox 1983). In their own study, Chao and Cox (1983) compared different strains of *E. coli*, mutators and wildtype, in direct competition experiments. They found that mutator *E. coli* outcompete their wildtype counterparts in resource limited environments. They also determined that this effect was contingent on the mutator population having an initial frequency that was sufficient to statistically provide adaptive mutations.

4. Condition Dependent Mutation

Agrawal and Wang (2008) performed an empirical study of the effects an individual’s condition has on mutation repair and hence mutation rate. They were careful not to refer to an individual’s evolutionary fitness but to their “condition” (Agrawal and Wang 2008). Fitness can be very difficult to measure; fitness is related to the probability of survival and reproduction of an organism over a pre-determined interval. They expected that the mutation rate is dependent, in part, on the condition of

individuals because of the potential adaptive benefits to increasing mutation rates under stress. To continue, it is known that *Drosophila* females can repair damaged male sperm DNA after their eggs have been fertilized (Agrawal and Wang 2008). Females were categorized as high or low-condition. The researchers looked at mutation repair in paternally inherited X chromosomes. It was found that offspring of low-condition females had a 30% greater incidence of lethal alleles in this chromosome. They also found that the sperm that they had exposed to a mutagen before impregnation was just as competitive in forming a zygote in low as compared with high-condition females. This check was done to ensure that their treatments were not differing due to an unknown mechanism in high-condition females to limit the number of damaged sperm reaching eggs. The overall results of their study suggest that the condition of *Drosophila* contributes to their mutation rate. Individuals' characteristics are an important factor governing mutation. Agrawal and Wang (2008) note that little work has been done to examine these relationships.

5. Sexual Versus Asexual Reproduction, and Mutation Rates

There are significant evolutionary differences between sexual and asexual populations. Asexual populations lack significant recombination, leading to stronger effects of linkage than can be found in sexual populations (Sniegowski et al. 2000; Johnson 1999b). This is because recombination can undermine the effects of linkage; recombination breaks the linkage between genes in the genome. Since recombination can minimize the linkage between mutator genes and the beneficial alleles that they help to produce, it can do the same thing to non-mutator genes and beneficial alleles as well. In my readings, this has not been mentioned because it is commonly understood that mutations will almost always be deleterious and that non-mutator types form an evolutionary stable strategy. However, this is not always the case; Sniegowski et al. (2000) note that asexual populations evolve higher mutation rates more readily in high stress environments. It has also been shown that organisms may alter their mutation rates in response to stress.

A Gap in the Literature

The preceding review provides two questions that my study will examine. First, can life-history affect mutation rates? Second, can age-structured mutation rates be adaptive? In my thesis, I will add to our understanding in both of these areas. I do this by examining the effects of a simple life-history trait on mutation rates. In organisms that can reproduce twice in their lifetime, can having different mutation rates at these time points be adaptive?

Aging Defined

Johnson, Sinclair, and Guarente (1999) indicate that an organism must meet two criteria in order to be considered aging: it must have an increasing probability of death, and a similar pattern of phenotypic change relative to others in its species with advancing chronological age. They point out that the second criterion in their definition ensures that diseases caused by aging are not considered aging (e.g. cancer). There are thought to be hundreds of mechanistic theories of aging (Hughes & Reynolds 2005). These theories often support a definition of aging in which there is the progressive loss of function over time of cellular components, tissues, organs, and the body of an organism. For example, Harman's (1956) seminal paper on the free radical theory of aging posits that, with age, there is an increase in damage in cells due to free radicals. Free radicals are damaging towards many of the functional building blocks of cells, including proteins and DNA (Hughes & Reynolds 2005; Harman 1956).

In many organisms, the probability of death increases exponentially with increasing chronological age throughout life (Johnson 1990). However, mortality can also decrease or remain constant over the lifetimes of some species (Baudisch and Vaupel 2012). As such, aging is not limited to the post-reproductive period but also can occur during the pre-reproductive period; traits harmful to the fitness of organisms can be expressed in early life. Rose and Burke (2011) suggest that aging is a polygenic trait, controlled by many genes.

Connection with Aging

My thesis likely has implications for our understanding of the evolution of aging. It examines the evolution of mutation rates contingent on age-structure, and whether this structure can lead to adaptation in a changing environment. My model satisfies the second criteria of aging, that there is a pattern of phenotypic change with increasing age. However, it does not meet the first criteria that the probability of death increases with increasing age. A logical next step in modeling would be to include a direct fitness cost for increased mutation rates over the lifetime of individuals. This may tie the age-structured mutation rates that evolve in my model to the understanding of aging, as discussed in Chapter 3. My model of age-structured mutation rates is consistent with many of the mechanistic descriptions of aging involving elevated cellular damage with increased age. This is because I restrict treatment individuals to have mutation rates, in later life, that are greater than or equal to their earlier life mutation rates. There is empirical evidence from research into humans and other organisms that free radical concentrations, that can cause mutation, increase over an organism's lifetime (Nussey et al. 2009; Beckman and Ames 1998; Sohal et al. 1994). However, Nussey et al. (2009) point out that this finding is not always the case.

Free Radical Theory of Aging

Because my study focuses on the evolution of mutations rates contingent on age-structure, it is necessary to describe a major proximal theory of aging that is highly linked with the evolution of mutation rates. The free radical theory of aging states that aging follows from an organism's increasing probability of disease and death over their lifetime due to chemical changes that result from cell constituent molecules' reactions with free radicals (Harman 1988). Free radicals can be produced by the organism itself (e.g. through metabolism) or by external forces (e.g. ionizing radiation leads to increased free radical concentrations within the cell) (Harman 1956). Free radicals cause mutations (Beckman and Ames 1998). Evolutionarily, DNA repair/fidelity of replication, ROS production (e.g. through metabolism), and reactive oxygen species (ROS) mediation (though the production of antioxidants) have been fine-tuned (Beckman and Ames 1998; Sniegowski et al. 2000; Yu and Chung 2006). Organisms

both prevent and mediate the effects of internal and external causes of aging. This ability is controlled by genetic factors and thus organisms have heritable variation in the degree to which they age and rate at which they age.

Free radical production is known to increase in many mammals with increasing chronological age (Johnson et al. 1999). Free radical concentrations can also increase in other organisms; Back et al. (2012) found that the hydrogen peroxide free radical concentration increases in *C. elegans* with advancing age. They also found that when aging was slowed due to restrictive diets, the increase in hydrogen peroxide was also slowed. Increasing ROS damage leads to senescence in many organisms, both prokaryotic and eukaryotic (Nystrom 2003).

Free radicals can accumulate or decline in concentration through an individual's life. For example, free radical damage has been compared in young lambs and adult sheep; oxidative damage is higher in lambs (Nussey et al. 2009). This is contrary to what is often found; in general, the older the organism is, the higher the free radical concentrations (Back et al. 2012; Hekimi, Lapointe, and Wen 2011; Nussey et al. 2009; Yu and Chung 2006; Sohal et al. 1994). Though this is a common finding, it is largely unknown why this is the case evolutionarily.

Due to changes in free radical concentrations and variation in the expression of free radical mediating systems, mutation rates may differ significantly between life stages. Little research has been done on variable mutation rates throughout the lifespan and how this affects organism fitness. When an organism has successive reproductive periods, I believe that the relationship between the mutation rates for each stage is dependent on previous stages, as well as population and environmental dynamics.

It has been predicted that in a static environment, mutation rates would ideally evolve to be zero since there is no need for adaptation and most mutations are harmful or neutral (Sniegowski et al. 2000). In a changing environment, mutation rates will differ

between life-stages in order to balance the need for adaptation with mutation's harmful effects (Sniegowski et al. 2000). The rate of change of environment, along with organism life-history, will affect the relationship between ROS concentrations and mutation.

Background Material for Mathematical Model Design

In the next sections I will provide background information relating to the construction of my mathematical model. First, I discuss why a stochastic model is used to model age-contingent mutation rate evolution. Second, I explain why *E. coli* were chosen as a model organism. Third, I outline theoretical supports for my model's basic functionality; this includes modeling mutation rates and their associated costs, environmental change, selection, reproduction, and heritability. Finally, I provide justification of the parameters used in the model. It is my aim that by the end of this section the reader will have a clear understanding of the background material that factored into the model's creation.

Stochastic models provide a way of simulating biological evolution. Through the use of pseudo-random number generators, they mimic many of the partially random elements comprising the evolution of populations. These random elements include mutation, mutational effects, environmental changes, and survival outcomes. Champagnat, Ferriere and Meleard (2006) suggest that models must contain individuals with one or more traits under selection. They outline a stochastic model where traits can affect the probability of mutation, birth rate and death rate. Stochastic models can be used to facilitate experiments where different genotypes are directly competed. By competing individuals with differing genotypes, within the same population and under the same environmental changes, an understanding of the relative evolutionary fitness of each genotype or strategy can be found. This often requires a large number of replicate populations to be simulated, each with variability due to the random elements in the model. It is suggested that stochastic models are much harder to analyze and combine than deterministic ones (Champagnat, Ferriere and Meleard 2006; Page and Nowak 2002). Also, Champagnat, Ferrier, and Meleard (2006) mention that

deterministic and stochastic models can have different behaviors and outcomes. A stochastic model is suitable for my study because it takes into consideration the random elements that contribute, in natural populations, to many processes influencing evolution.

1. Model Organism

In my thesis, I utilize a simplified version of the bacteria *E. coli* as a model organism. *E. coli* prove to be a useful model for several reasons. First, there is a wide breadth of scientific literature on *E. coli*; we have a good understanding of these organisms and many empirical results for some of their basic traits. Second, *E. coli* are highly amenable to experimentation. As such, my research findings could be readily tested empirically. Third, *E. coli* are single celled and largely asexual. The removal of a germ-soma distinction simplifies my task in theoretically examining mutation rates. Also, mutator genes in asexual organisms will more readily fix due to the lack of significant recombination (Sniegowski et al. 2000; Johnson 1999b; Drake et al. 1998). Fourth, *E. coli* have large population sizes and short generation times; *E. coli* populations can have more than 10^6 individuals and can reproduce rapidly (Chao and Cox 1983). *E. coli* studies can examine results over 10000 generations of evolution (Sniegowski, Gerrish, and Lenski 1997). I anticipated that if there is an adaptive component to mutation, the effect would be very small because, on average, mutational effects are harmful. As such, the large populations and rapid generation times of *E. coli* would help to make this effect visible; larger populations have a higher chance of adaptation due to their increased rates of beneficial mutations (Chao and Cox 1983). Rapid reproduction, with mutation occurring during DNA replication, means faster potential adaptation. In the absence of selection, it would also lead to an even greater accumulation within the population of deleterious mutations. Fifth, it has been recently found that *E. coli* age, through the partitioning of damaged cellular contents when dividing (Chao 2010). Lastly, I wanted my findings on evolutionary theory to be conclusive, with few confounding factors. The relative simplicity of *E. coli* caters to this outcome.

Sniegowski et al. (1997) performed an empirical study of *E. coli* where mutator and wildtype populations were found to have no significant differences in fitness when they were measured over approximately 10000 generations in an environment where glucose was restricted. In contrast, Chao and Cox (1983) found that mutator can have an advantage over wildtype *E. coli* when competed in a resource limited environment because of their ability to evolve faster. However, their results were found over far fewer generations (approximately 120) than Sniegowski et al. (1997).

2. Modeling Mutation

In my model, I chose to use a Poisson distribution to determine the expected number of mutations affecting a given trait per reproductive event. A Poisson distribution can be used to model the number of occurrences of an event, over a fixed time frame. The Poisson distribution is the limiting case of the binomial distribution, where there are a large number of trials and the success of any given event is of low probability. This is similar to an organism's probability of having one or more mutations given its mutation rate. Hence, a Poisson distribution can be used to determine the expected number of mutations. Johnson (1999a) used the Poisson distribution in modeling mutation rates of evolving asexual populations. Also, he notes that the scientific literature on asexual microbes contains no estimate of the distribution of mutational effects in these organisms. Mutational effects are the results of mutation and not related to the probability of mutation.

Mutations have associated costs. First, in individuals, reducing mutation has physiological and energetic costs. Selection acts, mainly to reduce mutation rates (Sniegowski 1997); it acts against the natural tendency toward entropy. Second, mutation leads to the production of, on average, less fit offspring due to mutation load. As has been stated, more mutations are harmful than beneficial, and so the tendency is for mutation to reduce individual fitness.

The genomic mutation rate per generation in *E. coli* is approximately 0.0025 (Drake et al. 1998). Although it is known that these organisms can survive for, at a

minimum, ten generations with a genomic mutation rate per generation of 10. Microbes have the ability to briefly increase their mutation rates based on internal and external conditions. According to Drake et al. (1998) around ten genes are currently linked to long-term elevated mutation rates in *E. coli*.

I assume that the effects of mutation follow a continuum-of-alleles model. The continuum-of-alleles model is a standard model in theoretical biology dating to the work of Kimura and Crow (1964) and allows for direct comparison between my work and other theoretical work such as Johnson (1999a) and Burger and Lande (1994). In the model, a mutation's effect is randomly drawn and added to an individual's genotypic value.

3. Modeling the Environment

According to Wilbur and Rudolph (2006), environmental change can be of several types: directional, cyclic, or stochastic. Directional environmental changes are those tending to move only in one direction (e.g. global warming). Cyclic changes can be things like seasonal changes, the periodic fluctuations of the tide, or alternation of night and day. Stochastic changes are random. They offer little ability of prediction and accommodation by adaptation. In my thesis, the environment changes stochastically under a diffusion model. At each time step, the random deviate from a Gaussian with a mean of 0 and a variance, σ^2, is added to the current environment Gaussian's mean. The diffusion model offers some predictability in that the deviates added to the environmental mean are drawn from the same distribution, such that "unexpected" changes do not occur. However, overall, the effects are largely stochastic.

4. Modeling Selection

In a model with a changing environment, it is standard to model the fitness of an individual using the Gaussian function (Burger and Lynch 1995). For a given environment there is an optimal phenotype. As an individual's phenotype deviates from this optimum its fitness declines in a Gaussian-like manner, such that the fitness of an individual with phenotype *z* in an environment with optimal phenotype *t* is,

$$w = exp^{-\frac{(z-t)^2}{2}}.$$

In this model, fitness varies from 0 < *w* <= 1. In my thesis there is a one-to-one relationship between fitness and survivorship, such that the probability of survival is equal to an individual's fitness. Once the probability of survivorship is determined for an individual, a random number between, 0 and 1, is drawn to determine if the individual, in fact, survives. If the deviate is below its probability of survival, then it survives. If it is not, then the individual dies.

5. Modeling Reproduction

There are two central ideas to consider when looking at reproduction in my model. First, iteroparity is the ability of an organism to reproduce multiple times, and is important in my model. Wilbur and Rudolf (2006) suggest that living organisms mature at different chronological ages and have different numbers of potential reproductive periods as an adaptation to life in variable environments; an organism's specific life-history can be an adaptation. Second, fecundity remains constant in my model because, provided an individual survives, it can have only a single offspring by binary fission.

6. Model Parameters and Constraints

The model contains several important constraints. While bacteria can often attain population sizes of 10^6 individuals (Chao and Cox 1983), computer models are limited by computing power, time and memory. As such, it was necessary to limit population sizes in my model to approximately 1500-15000 individuals. Therefore, my model can only detect adaptive processes which increase fitness by a factor of about 1/15000-1/1500 based on the principle that mutations with relative selective benefits less than about 1/Ne are nearly neutral (Kimura and Ohta 1971).

There can also potentially be interactions between individuals, and between individuals and the environment (Champagnat, Ferriere, and Meleard 2006). Models often do not take into account that the traits of individuals within a population can

change the environment in which they live. Nevertheless, in my model, individuals don't affect the environment or each other's phenotype.

Importance of Study

Mutation and aging are important areas of study to evolutionary biologists. Much research has been done on these two interconnected topics. Despite this abundance of research, it appears that no work has been done to examine how age-structure can affect mutation rates.

This study could provide an adaptive explanation for the observation that free radicals increase in many organisms as they increase in chronological age (Back et al. 2012; Hekimi, Lapointe, and Wen 2011; Nussey et al. 2009; Yu and Chung 2006; Sohal et al. 1994). My thesis also provides future directions for research into the evolution of aging. Empirical studies in living organisms could be done to test my findings.

The closest work I have found to my thesis topic is a study examining how organism "condition" can affect mutation repair capability (Agrawal and Wang 2008). As such, it appears that my research is relevant, novel, and important to the field of evolutionary biology.

Lastly, my study of the evolution of mutation rates contingent on life-history may lead to improvements in the genetic algorithms used by computer scientists, engineers, and mathematicians. Many important applied problems require finding an optimal solution in situations where there are a large number of variables contributing to the properties of a system. Evolutionary approaches can be used to solve many of these problems. Furthermore, developing methods that can improve the efficiency of genetic algorithms in finding optimal solutions can be useful.

Introductory Chapter Summary

This chapter has provided a context to my thesis. In it, my research question is outlined. It provided background material on the evolutionary process, the evolution of

mutation rates, the evolution of aging, and the free radical theory of aging. It also provided theoretical precedence for methods used in the construction of my mathematical model. It is my hope that the reader is now sufficiently apprised of the field to understand chapter two of this thesis.

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CHAPTER TWO

AGE-STRUCTURED MUTATION RATES CAN BE ADAPTIVE IN A CHANGING ENVIRONMENT

Introduction

1.1 Mutation

This paper focuses on whether mutation rates can be optimized to life-history, and whether this can be adaptive relative to control individuals. It examines the effects of life-history on mutation rates in low, medium, and high change environments. *E. coli*-like model organisms were constructed for use in a stochastic-based theoretical model. The organisms had either one or two evolvable mutation rates for successive reproductions and were competed in various environments.

Mutations are random genetic changes. Mutation rates, however, are not random. They have heritable components and as such can be adjusted through selection (Johnson 1999; Sniegowski et al. 2000; Metzgar and Wills 2000). Mechanisms that affect an organism's mutation rates are likely highly regulated; this is why mutation rates are often highly conserved within species, and vary across species and levels of environmental disturbance (Drake et al. 1998). Mutation and selection are responsible, in part, for species adaptation to changing environments. Mutation is also responsible for a vast array of maladaptive outcomes; more often than not, it leads to a reduction in fitness (Agrawal and Wang 2008; Drake et al. 1998; Stich, Manrubia, and Lazaro 2010). Mutations are more likely to move optimized traits away from their optimum values (Stich, Manrubia and Lazaro 2010). Organisms face a trade-off between mutation's necessity in adaptation and its harmful phenotypic effects, on average. Agrawal and Wang (2008) looked at the effects an organism's fitness has on its ability to repair mutations. They found that lower fitness individuals passed on more lethal mutations. It has also been shown that organisms may alter their mutation rates in response to stress; stress-induced mutation has been modeled and shown to be

adaptive (Bjedov et al. 2003). No studies have examined the effects of life-history on mutation rates.

1.2 Mutation's connection to the evolution of aging

My model, as mentioned in chapter 1, does not directly test whether age-structured mutation can lead to adaptive aging. This is because, within the model, fitness is not necessarily reduced in later life-stages except where environmental changes can lead to reductions in fitness over the lifetime of an individual. However, my model provides a potential connection between some proximate causes of aging and the potential for aging to be adaptive.

For example, the accumulation of free radicals provides a proximate mechanism for aging. Furthermore, elevated mutation rates may result from increasing free radical concentrations as an organism ages (Back et al. 2012; Hekimi, Lapointe, and Wen 2011; Nussey et al. 2009; Yu and Chung 2006; Sohal et al. 1994). DNA repair/fidelity of replication, reactive oxygen species (ROS) production (e.g. through metabolism), and ROS mediation (though the production of antioxidants) affect mutation rates and serve as mechanisms to fine-tune mutation rates as an organism ages (Beckman and Ames 1998; Sniegowski et al. 2000; Yu and Chung 2006). The free radical theory of aging suggests that free radicals will damage many organisms as they get chronologically older (Harman 1956). Due to free radical's harmful consequences, organisms have mechanisms that mitigate their effects in early life. However, these mechanisms may deteriorate with increasing age (Yu and Chung 2006).

Elevated mutation rates can be adaptive (Chao and Cox 1983; Drake et al. 1998; Bjedov et al. 2003). Similarly, there is also theoretical support that suggests aging can be an adaptive trait, despite reducing immediate survival and reproduction (criteria 1, Johnson et al. 1999; Williams 1957). While aging leads only towards a reduction in fitness for the individual, it may improve the survival of an individual's direct descendants through the adaptive effects of mutation. Although mutational effects are harmful on average, mutation is necessary for adaptation in changing environments.

Organisms may trade-off the harmful effects of aging for its provision of beneficial adaptive potential to offspring. This suggests that age-structured mutation rates, which may result in phenotypic changes harmful to the survival of individuals, could also be linked to an adaptive explanation of aging.

Mitteldorf and Pepper (2009) give several supported reasons that, in combination, suggest senescence appears adaptive: it is determined by genes that have been, "highly conserved over vast evolutionary distances", when genes causing aging are disabled animals can live longer, and lifespans are plastic. These reasons suggest that there must be more to understand about the phenomenon of aging. Recent papers are starting to examine the issue from an adaptive perspective.

Mitteldorf and Pepper's (2009) theoretical study found aging adaptive in that it limited the spread of disease, by reducing population density. It also increased genetic diversity, through more rapid population turnover, thereby increasing a population's chances of surviving epidemics. In their model, older organisms that were more susceptible to illness, by removing themselves from the population reduced the spread of pathogens. Advantages were more readily passed on to kin due to increased proximity.

Martins' (2011) theoretical work also found aging to be adaptive in some changing environments because it increased the rate of adaptation of species. In his model there was direct competition between aging and non-aging individuals, where aging individuals had a limited lifespan. He suggests that group selection is a force that helps aging to be adaptive. Older individuals are likely to have accumulated deleterious mutations and hence, are more likely to have lower individual fitness than younger individuals. The death of older individuals increases the proportion of better adapted kin surviving when resources are limited. This is because kin are more likely to share resources in the model, due to proximity.

1.3 Modeling evolution

This paper is the result of the development and analysis of series of computer simulations constructed to mimic the evolution of mutation rates in age-structured populations. In the simulations, two distinct genotypes compete in a population. One genotype has a single evolvable mutation rate that impacts offspring produced during its life. The other genotype has two evolvable mutation rates impacting the production of successive offspring and, as such, can evolve age-structured mutation rates. Single celled, *E. coli* like organisms are modeled because of their small size, short generation times, asymmetrical division (Chao 2010), and amenity to experimentation. Key parameters regarding single celled organisms, like *E. coli*, can be estimated based on a wide breadth of literature. For example, rates of mutation in *E. coli* are low, and were measured to be around 0.0025 mutations per genome per replication (Drake et al. 1998). A benefit of modeling using a system such as this is that it may potentially be replicated empirically using *E. coli*. Empirical experiments using *E. coli* have examined populations over 10000 generations (Sniegowski et al. 1997).

Methods

2.1 Model construction, implementation, and analysis tools

The model was designed to mimic the evolution of a population of simplified *E. coli*-like organisms. It assumes that individuals are haploid, single celled, asexual, and non-recombining. The model assumes that time is discrete, and that an individual can potentially live a maximum of two units of time. At the end of each unit of time, an individual that survives the interval reproduces by mitosis. During mitosis, mutations may occur as a result of copy error. Generations are overlapping (see Appendix D for a diagram of the model organism's life-history).

The model studies two life-histories. Single mutation rate individuals (SMRI) have a single evolvable mutation rate throughout their entire life. Double mutation rate individuals (DMRI) have two evolvable mutation rates. In DMRI, there is one mutation rate for the first unit of time in an individual's life and, potentially, a second mutation rate

for its second unit of time. These mutation rates are genetically encoded and do not change during the individual's life as a result of, for instance, differences in environmental conditions including the fitness of an individual.

SMRI only produce SMRI offspring. DMRI only produce DMRI offspring. The relative frequency of DMRI to SMRI changes as the model is run as a result of drift and selection.

In SMRI the rate of mutation at both potential periods of reproduction is μ_S. In DMRI the rate of mutation at the first reproduction is μ_1 and at the second is μ_2. The values μ_S, μ_1, and μ_2 are all affected by mutation, such that these values can change and potentially evolve by natural selection. In DMRI individuals, μ_2 is restricted to be greater than or equal to μ_1. This is because, as organisms age, there is often a reduction in the ability of cells to maintain themselves. Cellular deterioration is a hallmark of aging. Mutation rates are also likely to be greater in many organisms as they age since mutation causing and cell damaging free radicals have been observed to increase in organisms as they age (Back et al. 2012; Hekimi, Lapointe, and Wen 2011; Nussey et al. 2009; Yu and Chung 2006; Sohal et al. 1994).

While one component of each organism's genotype affects mutation rate, a second component encodes a phenotype that affects its ability to survive. The difference between an individual's phenotype and the optimal phenotype at a particular point in time determines the individual's probability of survival. The phenotype for survival of an individual is also affected by mutation.

The simulated population experiences a changing environment. The environment changes by a diffusion process, such that the optimal phenotype changes at each unit of time with diffusion coefficient, σ_E. The initial optimal phenotype is zero and all individuals start with this optimal phenotype.

Appendices A through D provide a detailed description of the model.

Results

Simulation parameters are provided in the legend below. In my results, mutation rates (μ_S, μ_1, and μ_2) are evolvable parameters and a property of genotype. The population size is potentially variable depending on the average fitness of the population, such that a population can go extinct. Population size is limited by a carrying capacity (K) that is constant.

Legend for simulation parameters:

μ_S, Mean final mutation rate for SMRI

μ_1, Mean final mutation rate for life-stage 1 in DMRI

μ_2, Mean final mutation rate for life-stage 2 in DMRI

R, Number of simulation replicates

G, Maximum number of generations

K, Maximum carrying capacity

N, Initial population size

P, Initial percentage DMRI

Q, Initial percentage SMRI

σ_E, Standard deviation for environmental change

M, Initial mutation rate

σ_M, Standard deviation for mutation rate change

σ_S, Standard deviation for survival genotype change

α, Cost of mutation function parameter

β, Cost of mutation function parameter

m_{min}, Minimum mutation rate

3.1 Model tests under neutrality

Initially the model was run under selectively neutral conditions, to test that it meets the expectations of neutral evolution. Since the model contained two types of individuals, DMRI and SMRI, the expectation is that their respective final frequency should equal their initial frequency over a large number of replicates. Therefore the hypothesis for these simulations is that there is no significant difference between initial

and final frequencies of SMRI and DMRI. The initial and final frequencies of SMRI and DMRI did not differ significantly after 10000 generations (Table 1). In these results, the mean final individual frequencies for each run were approximately normally distributed. This justified the use of a random sampling test to find the confidence intervals. For σ_E=0.35 (R=960), the results were marginally, but significantly different from the null expectation [with a final ratio of DMRI to SMRI of 0.91822 (0.90120, 0.93498)] so an addition independent run was conducted (R=960) and the results of the two runs were combined (R=1920). Then it was found that there was no significant difference from the null expectation.

3.2 Calculation of optimal mutation rates for SMRI in low, medium, and high change environments

In order to give SMRI the best opportunity to outcompete DMRI, optimal mutation rates were calculated for SMRI individuals in low, medium, and high change environments. These rates were found by evolving populations solely comprised of SMRI with low, medium, and high environmental change until the average mutation rate reached equilibrium. This took two iterations for each rate of environmental change, updating the starting mutation rate based on previous findings. Equilibrium was determined visually (Figure 1, 2, and 3). Since all individuals were SMRI, the mutation rate was identical for both life-steps. The mean mutation rate was calculated for the last 500 generations on each population that survived the total 10000 generations (Table 2). Confidence intervals were found by use of the random sampling method since the mean mutation rates were approximately normally distributed.

3.3 Direct Competition of DMRI and SMRI in low, medium, and high change environments

SMRI and DMRI strategies were directly competed. Simulations are grouped based on the rate of environmental change. The initial proportions of DMRI to SMRI were varied. By varying the initial frequencies of DMRI to SMRI the model could test whether there were frequency-dependent effects on mutation rates. When the frequency of individuals is varied, this can allow phenotypes to potentially evolve

towards different fitness peaks provided the individuals' fitnesses are frequency-dependent (Lande 1976). Table 3, 4, and 5 show the results for low, medium, and high change environments respectively. In all of these simulations, the initial mutation rate used for every DMRI and SMRI was the optimal value computed for SMRI in each of the different environments (found in Section 2). In principle, SMRI had an advantageous start since their mutation rate was at its optimal level whereas DMRI were not at their optimum.

SMRI's mean final mutation rate statistic was calculated by finding the mean mutation rate over the last 500 generations of each population that survived all 10000 generations. The DMRI mean final mutation rate statistics for life-step 1 and 2 were separately calculated using the same method as used with SMRI. The 95% confidence intervals were calculated for these three values in each simulation by using the random sampling method, since the data appeared normally distributed.

The proportion of replicates where DMRI outcompeted SMRI was calculated. For a low rate of environmental change (Table 3), it was necessary to determine whether DMRI had outcompeted SMRI by looking at the final genotype frequencies and determining which genotype was proportionally the largest. If a particular genotype was proportionally larger, then it was the winner and the proportion of wins was recorded for the DMRI genotype. For higher rates of environmental change (Tables 4, 5, 6, and 7) only DMRI or SMRI survived in each replicate that didn't go extinct, such that the proportion of DMRI was either 1 or 0. Significance of the proportion of wins was measured using a Wilson 95% confidence interval for each binomial proportion (Fagerland, Lydersen, and Laake 2014). For the final simulation (Table 8), a carrying capacity of 15000 individuals was used. As such, there were numerous simulations where both DMRI and SMRI survived the interval. This made it necessary to calculate the final genotype frequency confidence intervals using the same method as was used for the low rate of environmental change (Table 3).

For an initial set of simulations, each involving 960 replicates, the DMRI genotype never significantly outcompeted the SMRI genotype relative to its initial frequency (Tables 3, 4, and 5). The frequencies at which the DMRI genotype outcompeted the SMRI genotypes were either below or not significantly different from the initial DMRI frequency. Nevertheless, there was an indication that as the rate of environmental change increased, the frequency at which DMRI outcompeted SMRI increased. Furthermore, some mean competition values were close to being significant and in favour of DMRI. Consequently, a new set of replicate simulations was run in which the number of replicates increased from 960 to 7680. Confidence intervals decrease in magnitude with increased sample size. At this level of replication, the DMRI genotype outcompeted the SMRI genotype for the highest rate of environmental change (Table 7), but not for the moderate level of environmental change (Table 6).

A final simulation was run (Table 8) using identical conditions to those of Table 7 with the exception of an increased carrying capacity (K=15000), an increased initial number of individuals (N=15000), and fewer replicates (R=960). The expectation was that the increased population size would reduce the effects of drift, leading to more efficient selection for the beneficial DMRI genotype. This outcome was confirmed when the final DMRI frequency significantly increased from 0.52396 (Table 7) to 0.59031 (Table 8).

Discussion

Several observations suggest that the model was operating correctly. First, the model performed as would be expected under the conditions of neutral evolution (Table 1). Second, equilibrium mutation rates increased with elevated environmental change rates, as would also be expected (Table 2). Third, the SMRI equilibrium mutation rate (μ_S) was intermediate to μ_1 and μ_2 in moderate and high change environments (Tables 4-8). It is interesting that μ_1 and μ_2 are greater than μ_S in Table 3, low change environments. This is likely due to the overall mutation rate being low and, hence, the populations not having enough time for μ_1 and μ_2 to evolve to their equilibrium values. Fourth, aging appeared adaptive when environmental change was elevated. This likely

moved the population further from the optimal phenotype and hence increased the proportion of beneficial mutations. Since the optimal phenotype was modeled by a Gaussian distribution, the further an individual is from the maximum value at the center of the distribution the more likely mutation becomes 50:50 beneficial to deleterious. About half of the mutations will take an individual closer, while the other half will move individuals away from the optimal value. Similarly, as an individual nears the optimal phenotype the proportion of beneficial mutations will decrease. If an individual is at the optimum a mutation can only keep it at the optimum value, or more likely, move it farther from the fitness peak. Fifth, the adaptive benefit of age-structured mutation became more apparent with increased carrying capacity of populations because selection becomes a stronger force relative to drift (Table 8).

In DMRI-SMRI competition runs with moderate and high environmental changes (σ_E=0.35 and σ_E=0.4), DMRI had average μ_1 values that were significantly lower than respective SMRI's μ_S and significantly greater average μ_2 values than the SMRI's average μ_S. Since the simulation experiment controlled for other factors that could affect fitness of a genotype, it appears that the ability to generate these different mutation rates gave the DMRI a fitness advantage relative to SMRI in the high change environment. In nature, the mutation rates of organisms are achieved in a variety of ways. For example, they can be increased through free radical production and potentially decreased through free radical mediation. Mutation rates are also controlled through DNA repair and error checking mechanisms. There is heritable variation in many mechanisms that affect mutation rates (Johnson 1999; Sniegowski et al. 2000; Metzgar and Wills 2000). Based on my results, it is possible that in single celled organisms there is selection for an increase in mutation with chronological age. A potential experiment could be to experimentally evolve a population in a changing environment and measure early and late-life mutation rates.

In low change environments (Table 3), the average final mutation rates for DMRI and SMRI were approximately 0.005. Drake et al. (1998) found the genomic mutation rate of *E. coli* to be 0.0025. This suggests that the model is on the right track toward

being comparable with studies of *E. coli*. To continue, as the rate of environmental change increased in the model, the final average mutation rates for both DMRI and SMRI also increased. This is also to be expected based on studies of *E. coli*: in high stress environments *E. coli* tend to evolve higher mutation rates (Metzgar and Wills 2000). In my model, a high rate of environmental change was required to observe an adaptive effect of age-structured mutation rates. This is likely the case because my simulations had maximum effective population sizes of approximately 10^4 individuals. While this is the restriction in my model, bacteria can often have population sizes that are one to two orders of magnitude greater than those which I used (Chao and Cox 1983). The increase in effective population sizes of natural bacterial populations could allow for more efficient selection on traits with even smaller fitness effects. In turn, this could allow age-structured mutation rates to be adaptive in less rapidly changing environments.

In the simulations, it appeared that there were no DMRI-SMRI frequency-dependent effects. In the low, medium, and high change environments that measured frequency-dependent effects there were no significant differences in the average final mutation rates between DMRI or SMRI based on their different starting frequencies.

Agrawal and Wang (2008) found that mutation rates increased in individuals with poor condition. My results differ from their findings since DMRI individuals are actively increasing their mutation rates in later life and mutation rates are otherwise independent of the condition of an individual. My results also differ from those found in the study of Bjedov et al. (2003), which determined that stressful environments increased mutation rates in bacteria. In my study mutation rates are not affected by poor environmental conditions that induce stress. Mutation rates adapt in an age-structured manner to changing environmental conditions.

Johnson, Sinclair, and Guarente (1999) define aging as a trait that meets two criteria: the probability of death must increase with increased chronological age and there must be a phenotypic change that is similar among chronologically aging

individuals. While the DMRI individuals found in my model do not meet the first criterion in the strong sense, they do meet the second criterion. DMRI evolved a higher mutation rate at an older reproductive age; this means that they had different phenotypes as they got chronologically older. Furthermore, my results suggest that aging could be adaptive if the reduction in survival of individuals at the later reproductive step does not overwhelm the adaptive effects of age-structured mutation rates on individuals' direct descendants.

Conclusions

This research provides a new insight into the evolution of mutation rates in individuals that can reproduce more than once. It supports the idea that aging can be adaptive. Future directions for work could include empirical studies on microbes, and theoretical work comparing the number of potential reproductive periods to fitness potential.

Appendix A

Simulation overview

A computer simulation was constructed in c++. Message passing interface (MPI) code was utilized to ensure efficient simulation run times. A small local computer cluster and Sharcnet consortium (www.sharcnet.ca) were used to run simulations.

The model was stochastic based. The Mersenne Twister was used in the generation of pseudo-random numbers within simulations. Seeds for the Mersenne Twister were initialized using similar code to Katzgraber (2010). The GNU Scientific Library v. 1.13 (http://www.gnu.org/software/gsl/) was used to generate random deviates from the Poisson and Gaussian distributions.

Appendix B

Order of simulation procedures

In each replicate the following procedures take place:

A. The population is initialized. Each individual gets its starting values.
B. The following 5 steps are repeated until the maximum number of generations (10000) has been reached, or the population is extinct.

1. Reproduction and Mutation (both occur at this step)
2. Environmental change
3. Remove any old individuals (life-step 3 individuals)
4. Selection
5. Culling to carrying capacity

Appendix C

Description of simulation procedures

Below is an outline of what is done during each procedure, the overview of which is given in Appendix B.

Initialize population

A specified number of individuals are created (n=1500 for most simulations). The specified proportion (10:90, 50:50, or 90:10) of DMRI to SMRI is created within the single population. All individuals start with a survival genotype of zero and are at life-step zero. The values of μ_S, μ_1, and μ_2 are all set to an identical initial mutation rate. In DMRI-SMRI competition runs μ_S, μ_1, and μ_2 are all initialized to the pre-determined optimal mutation rate for SMRI given the specific level of environmental change used for the simulation.

Reproduction/mutation

Reproduction is asexual. When an individual reproduces, a daughter cell buds off of the parent cell. SMRI produce SMRI daughter cells and DMRI produce DMRI daughter cells. Daughter cells inherit their parent's survival genotype (see below) and mutation rate(s). The daughter's survival genotype and mutation rates may then change because of mutation. To determine the number of mutations that occur affecting the survival genotype, a random deviate, *T*, is drawn from a Poisson distribution. To determine the number of mutations that occur affecting the mutation rate, a random deviate, *P*, is drawn from a Poisson distribution. Both of these deviates have a mean of μ_S (SMRI), or μ_1 and μ_2 (DMRI).

Mutations affecting μ_S, μ_1, or μ_2

A set of *P* mutation causes μ_S, μ_1, or μ_2 to deviate from its previous state by a value, *C*, which is drawn from a Gaussian distribution with a mean of zero and a standard deviation ($\sqrt{P}\sigma_M$).

In DMRI, μ_2 is only allowed to be equal to or greater than μ_1; this restriction is based on the assumption that mutation rates typically increase with age.

Mutations affecting the survival genotype (S)

A set of *T* mutations causes the phenotype of an individual, affecting survivorship, to deviate from its previous state by a value drawn from a Gaussian distribution with mean zero and standard deviation ($\sqrt{T}\sigma_S$).

The Environment

The optimal phenotype follows a diffusion model due to corresponding changes in the environment. The optimal phenotype changes with each generation following a random walk: each generation a random deviate, *D*, from a Gaussian distribution with a mean effect of zero and standard deviation σ_E is added to the current optimal phenotype to mimic changes in the environment.

Remove All Old Individuals

Any individuals that have reached life-stage 3 are removed from the population. This is akin to reaching the maximum lifespan of an individual.

Selection

The probability that an individual survives selection is modeled by equation (1). *S* is the survival phenotype of the organism and *E* is the optimal phenotype for the given environment.

$$\text{Probability}(\text{survival}) = \exp^{-\frac{(S-E)^2}{2}} \qquad (1)$$

After the probability an individual survives has been calculated, a further process takes place. The probability of survival is multiplied by, *C* ($0 < C <= 1$), the cost of maintaining low mutation rates. The cost of a low mutation rate for a given life-step is determined by equation (2), where $\alpha = 0.05$, $\beta = 800$, and *x* is the current mutation rate.

$$C = 1 - (\alpha * (e^{-(\beta * x)}) \quad (2)$$

Culling

Should the population exceed the carrying capacity of the environment, individuals are randomly removed until the population reaches the carrying capacity. Culling is independent of the fitness of individuals.

Appendix D

Model organism life-history

Life-step	Description
0	Individual created
1	First potential reproduction
2	Second potential reproduction
3	Death

Below is a diagram showing the life-history of an individual. The numbers below each circle indicate the current life-step of an individual. Individuals at life-step zero are newly born. Should the individual survive life-step zero it will become a life-step one individual and automatically reproduce. Should it survive life-step one, it will be become a life-step two individual and automatically reproduce again. Individuals can only reproduce a maximum of two times in their lifetime. Should an individual survive and reproduce twice, following this it will immediately die within the model. The arrows on the diagram indicate that an individual has survived to the next life-step. When an individual reproduces, a daughter cell buds off of the parent cell and starts life at life-step zero. Mutation can only occur in the genotype of an individual when it is born. Both SMRI and DMRI each have a genotypic value that helps determine their viability in the current environment. In SMRI, there is a single evolvable mutation rate in each individual that can affect the genotype of offspring when produced at both life-step one and two. SMRI are the control group. In DMRI individuals, there are two separate evolvable mutation rates, one for life-step one and one for life-step two in each

individual. DMRI are the treatment group. The viability genotype in DMRI and SMRI can evolve, as can their mutation rates.

Diagram of life-history

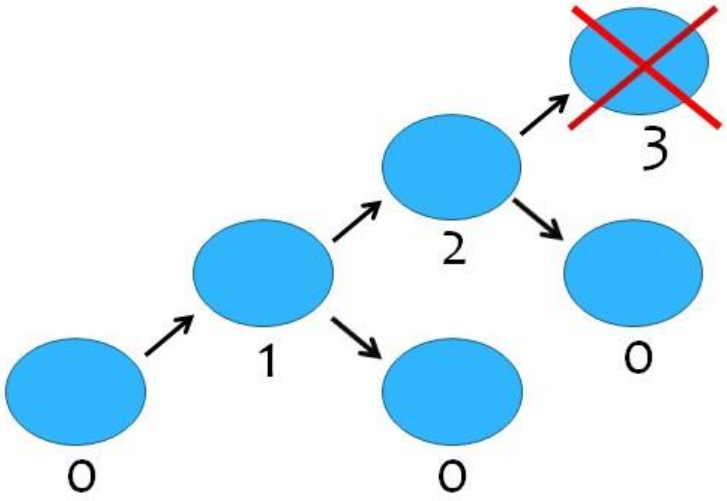

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Table 1 Results after 10000 generations with no selection*

P:Q	Mean final individual frequency DMRI/(DMRI+SMRI)
10:90	0.10623 (0.08795, 0.12524)
50:50	0.49822 (0.46779, 0.52864)
90:10	0.90141 (0.89729, 0.92218)

*For all runs initial parameters were: σ_E=0.35, R=960 (except for run 90:10, where R=1920), G=10000, K=1500, N=1500, M=0.135331818, σ_M=0.001, σ_S=1, α=0.05, β=800, m_{min}=0.00000001

Table 2 Results for the calculation of optimal mutation rates for SMRI*

σ_E	M	μ_S	Replicates surviving interval
0.0001	0.002	0.0055787961 (0.00554, 0.00562)	960
0.35	0.1335	0.1353318176 (0.13426, 0.13641)	894
0.4	0.169	0.1682640155 (0.16679, 0.16971)	695

*For all runs R=960, G=10000, K=1500, N=1500, P=0, Q=100, σ_M=0.001, σ_S=1, α=0.05, β=800, m_{min}=0.00000001

Table 3 Low change environments ($\sigma_E = 0.0001$), mean final mutation rate(s) for SMRI and DMRI, and proportion of populations where DMRI outcompeted SMRI*

P:Q	μ_S	μ_1	μ_2	Final Proportion** of DMRI/(DMRI+SMRI)
10:90	0.00554 (0.00551, 0.00558)	0.00573 (0.00556, 0.00591)	0.00790 (0.00758, 0.00824)	0.05313 (0.04064, 0.06918)
50:50	0.00555 (0.00550, 0.00560)	0.00558 (0.00551, 0.00565)	0.00769 (0.00757, 0.00781)	0.34792 (0.31845, 0.37860)
90:10	0.00555 (0.00545, 0.00565)	0.00564 (0.00560, 0.00569)	0.00773 (0.00766, 0.00781)	0.83333 (0.80844, 0.85557)

*For all runs R=960, G=10000, K=1500, N=1500, σ_E=0.0001, M=0.005578796, σ_M=0.001, σ_S=1, α=0.05, β=800, m_{min}=0.00000001

**Did not use mean final proportion of DMRI since the distribution is largely flat, instead used binomial with the results for which had the larger population at the end of the interval (DMRI or SMRI)

Table 4 Medium change environments (σ_E = 0.35), mean final mutation rate(s) for SMRI and DMRI, and proportion of populations where DMRI outcompeted SMRI*

P:Q	μ_S	μ_1	μ_2	DMRI/(DMRI+SMRI) where only one group survived
10:90	0.13544 (0.13436, 0.13653)	0.12504 (0.12121, 0.12879)	0.16337 (0.15996, 0.16685)	0.10567 (0.08723, 0.12747)
50:50	0.13498 (0.13347, 0.13648)	0.12636 (0.12460, 0.12809)	0.16554 (0.16375, 0.16732)	0.52413 (0.49130, 0.55675)
90:10	0.13575 (0.13154, 0.13986)	0.12669 (0.12537, 0.12803)	0.16433 (0.16302, 0.16564)	0.91859 (0.89900, 0.93466)

*For all runs R=960, G=10000, K=1500, N=1500, M=0.135331818, σ_M=0.001, σ_S=1, α=0.05, β=800, m_{min}=0.00000001

Table 5 High change environments (σ_E = 0.4), mean final mutation rate(s) for SMRI and DMRI, and proportion of populations where DMRI outcompeted SMRI*

P:Q	μ_S	μ_1	μ_2	DMRI/(DMRI+SMRI) where only one group survived
10:90	0.16986 (0.16838, 0.17138)	0.15853 (0.15332, 0.16366)	0.20096 (0.19565, 0.20653)	0.09770 (0.07780, 0.12202)
50:50	0.16843 (0.16648, 0.17045)	0.15941 (0.15686, 0.16199)	0.20167 (0.19937, 0.20395)	0.52482 (0.48793, 0.56145)
90:10	0.16906 (0.16445, 0.17362)	0.16099 (0.15921, 0.16275)	0.20255 (0.20085, 0.20427)	0.90267 (0.87936, 0.92187)

*For all runs R=960, G=10000, K=1500, N=1500, M=0.168264016, σ_M=0.001, σ_S=1, α=0.05, β=800, m_{min}=0.00000001

Table 6 Moderate change environment (σ_E=0.35), increased replicates (R=7680), mean final mutation rate(s) for SMRI and DMRI, proportion of populations where DMRI outcompeted SMRI*

P:Q	μ_S	μ_1	μ_2	DMRI/(DMRI+SMRI) where only one group survived
50:50	0.13520 (0.13469, 0.13571)	0.12667 (0.12603, 0.12732)	0.16443 (0.16381, 0.16504)	0.50685 (0.49526, 0.51842)

*For all runs R=7680, G=10000, K=1500, N=1500, M=0.135331818, σ_M=0.001, σ_S=1, α=0.05, β=800, m_{min}=0.00000001

Table 7 High change environment (σ_E=0.4), increased replicates (R=7680), mean final mutation rate(s) for SMRI and DMRI, proportion of populations where DMRI outcompeted SMRI*

P:Q	μ_S	μ_1	μ_2	DMRI/(DMRI+SMRI) where only one group survived
50:50	0.16976 (0.16902, 0.17046)	0.15991 (0.15909, 0.16072)	0.20148 (0.20071, 0.20224)	0.52396 (0.51119, 0.53669)

*For all runs R=7680, G=10000, K=1500, N=1500, M=0.168264016, σ_M=0.001, σ_S=1, α=0.05, β=800, m_{min}=0.00000001

Table 8 High change environment (σ_E=0.4), increased carrying capacity (K=15000), mean final mutation rate(s) for SMRI and DMRI, proportion of populations where DMRI outcompeted SMRI*

P:Q	μ_S	μ_1	μ_2	Final Proportion** of DMRI/(DMRI+SMRI)
50:50	0.16805 (0.16703, 0.16905)	0.15308 (0.15199, 0.15419)	0.19780 (0.19661, 0.19895)	0.59031 (0.56707, 0.61315)

*For all runs R=960, G=10000, K=15000, N=15000, M=0.168264016, σ_M=0.001, σ_S=1, α=0.05, β=800, m_{min}=0.00000001

**Did not use mean final proportion of DMRI since the distribution is largely flat, instead used binomial with the results for which had the larger population at the end of the interval (DMRI or SMRI)

Figure 1: A plot of the average SMRI mutation rate (μ_S) versus time (in generations) for a low rate of environmental change (σ_E=0.0001)

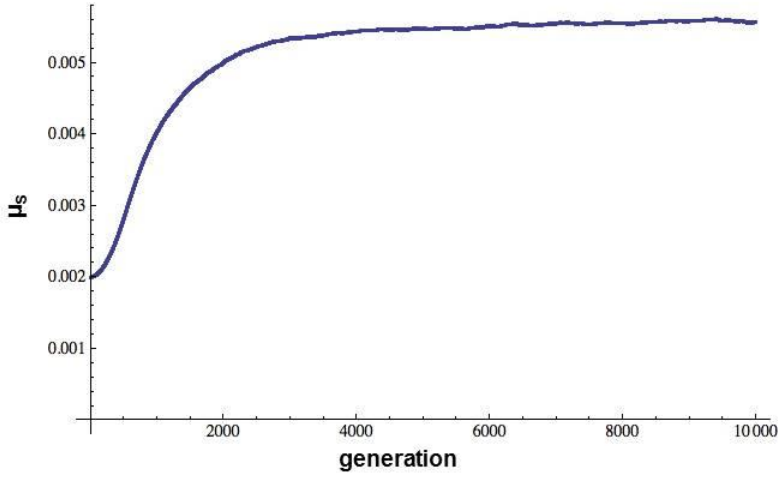


Figure 2: A plot of the average SMRI mutation rate (μ_S) versus time (in generations) for a medium rate of environmental change (σ_E=0.35)

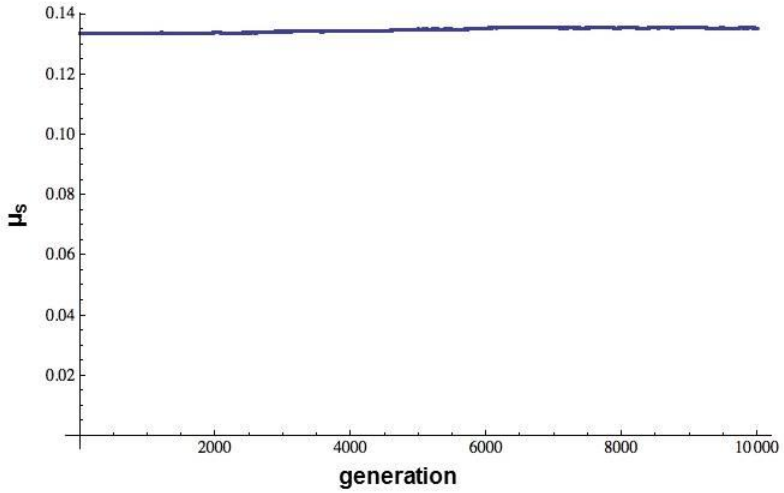
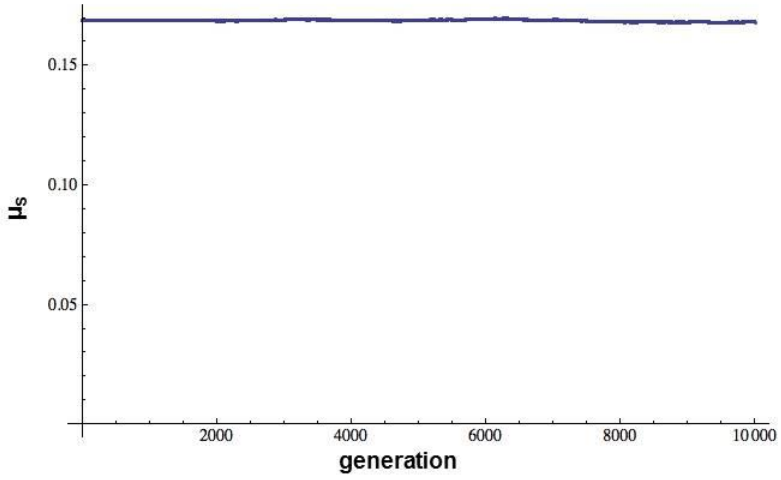


Figure 3: A plot of the average SMRI mutation rate (μ_S) versus time (in generations) for a high rate of environmental change (σ_E=0.4)



CHAPTER THREE

CONCLUDING REMARKS

My research has uncovered a novel evolutionary principle, that iteroparous individuals can improve adaptation above controls by evolving age-structured mutation rates. While my findings of adaptation are exclusive to environments that experience relatively high rates of environmental change, my simulation study was limited to detecting adaptive effects with selective coefficients of approximately 0.0001-0.001. The effective population size of bacteria can be higher than 10^5 and, in principle, respond to processes with selection coefficients of approximately 10^{-5}, which may allow for the adaptive evolution of age-structured mutation rates in more slowly changing environments. In addition, my research may provide the basis for an adaptive theory of aging. Although individuals in my model did not experience reduced survivorship with increased age, this could be added to future models. The adaptive effect was strong enough that, with an added cost to survival with increasing age, there would likely still be cases where age-structured mutation rates are adaptive. This is significant because the theory that aging serves an adaptive purpose is highly contentious (Mitteldorf 2004). Below I will outline the three major current evolutionary theories of aging and some observations that they don't explain. Following this I will describe two adaptive theories of aging.

Mutation Accumulation Theory of Aging

First, in the mutation accumulation theory of aging, aging occurs after organisms have reached reproductive maturity. Alleles that negatively affect organisms later in life, after they have had their offspring, are not removed by selection because they have little direct effect on fitness. Evolutionarily, once an organism has passed reproductive age, there is less selective pressure to keep it healthy. However older individuals in some species may, through kin selection, continue to aid the survival of their genes in descendants and hence will still be under mild selection. In the mutation accumulation theory of aging, deleterious mutations (which cause aging) are introduced into a

population and not removed due to the timing of their expression in life (Turke 2008; Ljubuncic and Reznick 2009; Gavrilov and Gavrilova 2002). Hence, they passively accumulate.

Antagonistic Pleiotropy Theory of Aging

Second, in the antagonistic pleiotropy theory of aging, genes have two opposing effects during early survival and reproduction (early life) versus post reproduction (late life). The early life effect is beneficial and the late life effect is deleterious. Since the early life effect is beneficial, it will not be removed from the population (Williams 1957; Charlesworth 2000; Turke 2008; Ljubuncic and Reznick 2009; Gavrilov and Gavrilova 2002). Aging, according to both mutation accumulation and antagonistic pleiotropy, is something that should not negatively affect individuals until they reach and exceed reproductive maturity. However, in nature aging is a lifelong process. My research may address this issue.

Trade-off Theory of Aging

Third, in the trade-off theory of aging organisms face two opposing pressures. Evolution and the environment contribute to whether it is better to put energy and resources towards survival, including somatic maintenance and growth, or towards reproduction. Organisms have limited energy and resources and so they cannot do both jobs perfectly. It is thought that what an organism puts into reproduction limits its ability to maintain itself and so it ages (Baudisch and Vaupel 2012; Abrams and Ludwig 1995; Ljubuncic and Reznick 2009).

Problems with the Current Understanding of Aging

The current theories of aging fail to explain some empirical findings. First, it has been found that aging leads to deterioration and reduced repair capabilities of organism systems that have the ability to be maintained. The harmful effects of aging are not universal to all living organisms; some animals do not appear to age (Mitteldorf and Pepper 2009; Martins 2011). Ljubuncic and Reznick (2009) provide the example of female turtles that produce more offspring the older they get and also have a

decreasing probability of death with increased age. Second, many study organisms live longer lives when genes for aging are disabled, without experiencing a cost to reproduction. Mitteldorf (2004) mentions that when increased lifespans are selected in *Drosophila* these longer-lived individuals have increased, not decreased, fertility. He also refers to a study in *C. elegans* that found many aging genes don't have connections with fertility. These finding contradict the antagonistic pleiotropy theory of aging.

Adaptive Theories of Aging

Mitteldorf and Pepper (2009) give several supported reasons that senescence appears adaptive: it is determined by genes that have been, "highly conserved over vast evolutionary distances", when genes causing aging are disabled animals can live longer, and lifespans are plastic. These reasons suggest that there must be more to understand about the phenomenon of aging. Recent papers are starting to examine the issue from an adaptive perspective.

Mitteldorf and Pepper's (2009) theoretical study found aging to be adaptive in that it limited the spread of disease, by reducing population density. It also increased genetic diversity, through more rapid population turnover, thereby increasing a population's chances of surviving epidemics. In their model, older organisms that were more susceptible to illness, by removing themselves from the population, reduced the spread of pathogens. On average, kin gained more benefit from aging individuals due to proximity.

Martins' (2011) theoretical work also found aging to be adaptive in some changing environments. It increased the rate of adaptation of species. In his model there was direct competition between aging and non-aging individuals, where aging individuals had a limited lifespan. He suggests that group selection is a force that helps aging to be adaptive. In this model, kin also gained benefit from related individuals' aging due to proximity and the reduction in competition for limited resources. Lastly,

when the effect size of mutation was increased senescent species went extinct less quickly.

A New Adaptive Theory of Aging

My model could provide the basis for a new adaptive theory of aging. The theory would be based on age-structured mutation rates leading to an adaptive advantage in a changing environment. It may also provide some explanation for the observation that mutation causing free radicals tend to increase as organisms increase in chronological age.

Potential Applications of Findings

There are several applications for my research findings. First, they may be used to support an empirical study into the adaptive nature of age-structured mutation rates. This type of experiment would likely be most feasible in the bacteria *E. coli* and a first step would be to determine whether there are age-structured rates of mutation in this species. The second application links my biologically-motivated study to computer science and engineering. An effective approach to problem solving in computer science and engineering is the use of genetic algorithms. Genetic algorithms use the principles of random mutation and recombination, inheritance, and selection to find solutions to practical problems like the design of airplane wings and the organization of computer chips. A feature of research in genetic algorithms is the development of approaches that find solutions more efficiently. My research indicates that incorporating age-structured mutation processes may lead to better genetic algorithms.

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