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# Evolution of the rate of biological aging using a phenotype based computational model

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## Abstract

In this work I introduce a simple model to study how natural selection acts upon aging, which focuses on the viability of each individual. It is able to reproduce the Gompertz law of mortality and can make predictions about the relation between the level of mutation rates (beneficial/deleterious/neutral), age at reproductive maturity and the degree of biological aging. With no mutations, a population with low age at reproductive maturity  $R$  stabilizes at higher density values, while with mutations it reaches its maximum density, because even for large pre-reproductive periods each individual evolves to survive to maturity. Species with very short pre-reproductive periods can only tolerate a small number of detrimental mutations. The probabilities of detrimental ( $P_d$ ) or beneficial ( $P_b$ ) mutations are demonstrated to greatly affect the process. High absolute values produce peaks in the viability of the population over time. Mutations combined with low selection pressure move the system towards weaker phenotypes. For low values in the ratio  $P_d/P_b$ , the speed at which aging occurs is almost independent of  $R$ , while higher values favor significantly species with high  $R$ . The value of  $R$  is critical to whether the population survives or dies out. The aging rate is controlled by  $P_d$  and  $P_b$  and the amount the viability of each individual is modified, with neutral mutations allowing the system more "room" to evolve. The process of aging in this simple model is revealed to be fairly complex, yielding a rich variety of results.

*Keywords:* evolution, aging, computer simulations, age-structured populations, modelling

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## 1. Introduction

Aging is probably one of the most familiar, yet least understood aspects in biology (Kirkwood, 2005). It can be defined, from an evolutionary point of view, as a progressive decline in fitness (the ability to survive and reproduce) with increasing age (Partridge, 2001). It has been used interchangeably with the term senescence, which is the lowering of survival rates as time goes by. Cellular senescence is the phenomenon by which normal diploid cells lose the ability to divide, while organismal senescence refers to the aging of organisms. Senescence is a complex process, which may derive from a variety of mechanisms, such as the shortening of telomeres with each cell cycle, oxidative stress (i.e. the imbalance between the production of reactive oxygen and ability to readily detoxify the reactive intermediates) and others, and its role in organismal aging is at present an active area of investigation.

Senescence of the organism can give rise to the Gompertz law of mortality. This law, observed by Gompertz (1825), was proved to be valid for the populations of most industrialised countries, describing the age dynamics of human mortality rather accurately in the age window from about 30 to 80 years of age (Thatcher, 1999). The Gompertz law of exponential increase in mortality rates with age is observed in many biological species (Strehler, 1978; Finch, 1990), including humans, rats, mice, fruit flies, flour beetles, and human lice (Gavrilov and Gavrilova, 1991). Let  $S(\alpha)$  be the probability of surviving from birth to age  $\alpha$ , which can be obtained by the cumulative distribution of the stable age distribution. Then, the mortality function  $\mu(\alpha)$  is:

$$\mu(\alpha) = -\frac{d(\ln S(\alpha))}{d\alpha} \quad (1)$$

Because data normally is given in yearly intervals, equation (1) can be approximated by:

$$\mu(\alpha) = \ln\left(\frac{S(\alpha)}{S(\alpha+1)}\right) \quad (2)$$

The Gompertz law states that the mortality rate of certain organisms increases exponentially with age  $\alpha$ :

$$\mu(\alpha) \propto c \cdot e^{b\alpha} \quad (3)$$

This law, however, is not without exceptions. Some animals, including many reptiles and fish, age extremely slowly and exhibit very long life spans

(negligible senescence) (Finch, 1990). Some produce even more offspring as they get older, while their mortality rate actually drops, in disagreement with the Gompertz "law", a phenomenon called negative senescence (Vaupel et al., 2004). Another notable exception are Hydras, which do not undergo senescence and are therefore biologically immortal (ageless) (Martinez, 1998).

## 2. Aging theories

"There is no shortage of theories of aging" (Partridge, 2007). Almost every aspect of an organism's phenotype undergoes modification with aging, and this phenomenological complexity has led, over the years, to a bewildering proliferation of ideas about specific cellular and molecular causes (Kirkwood, 2005). An attempt by Medvedev (Medvedev, 1990) to rationalise the multiplicity of hypotheses resulted in a listing of more than 300 mechanistic "theories" of aging, that describe how aging occurs. However, there are only a few evolutionary theories about why aging evolved.

Evolutionary biology is concerned with the reasons behind the aging process and the challenge of why aging occurs, in spite of its obvious drawbacks (Kirkwood, 2005). Aging results in significant loss of Darwinian fitness, giving rise to the question why it has not been eliminated by natural selection. It was proposed (Hamilton, 1966; Templeton, 2006) that if mutations can occur that kill their bearers at a sufficiently advanced age, such mutations are effectively neutral and some will go to fixation, thereby destroying the agelessness of the initial population.

The "mutation accumulation" theory (Medawar, 1952) claims that aging results from the non-adaptive process of mutation accumulation. If a deleterious mutation manifests itself at a young age, there will be strong selection pressure to eliminate it because it will affect the fitness of a large majority of the population. However, if that same mutation does not manifest itself until later in life, many of the individuals carrying it will have died before it is expressed. Therefore, mutations killing an individual before it reaches reproductive maturity vanish from the population, while those acting later in life allow it to reproduce and are selected with a much weaker force (Charlesworth, 1997).

Williams in 1957 proposed a similar theory, in which the existence of pleiotropic genes of special sort have opposite effects on fitness at different ages. Their effects are beneficial in early life, when natural selection is strong, but harmful at later ages, when selection is weak. If these genes

confer increased reproductive success early in life they would be selected for, despite the fact that they may later cause senescence. This is now known as "antagonistic pleiotropy" theory (Williams, 1957), which claims that aging results from an adaptive process of selection favoring certain genes with net-positive effects. The p53 gene is perhaps one of the clearest examples of an antagonistically pleiotropic gene (Leroi et al., 2005).

Another major theory is the "disposable soma" theory (Kirkwood, 1977; Kirkwood and Holliday, 1979; Kirkwood and Rose, 1991), which focuses on the idea that cell maintenance (e.g. DNA repair, protein turnover etc) is costly. It suggests that longevity is controlled primarily through genes that regulate the levels of somatic maintenance and repair (Kirkwood, 2005). The organism should optimally allocate its metabolic resources, chiefly energy, between the maintenance and repair of its soma and its other functions in order to maximise its Darwinian fitness. The necessity for trade-off arises because resources allocated to one function are unavailable for another. Therefore, the allocation of resources to maintenance and repair is determined by evolutionary optimization.

Mutation accumulation and antagonistic pleiotropy provide the backbone for much of the thinking about the evolutionary genetics of aging. However, evidence for mutation accumulation remains limited and controversial (Kirkwood, 2005; Shaw et al., 1999), while evidence for antagonistic pleiotropy, although stronger, is as yet lacking in detail. There have been suggestions (Kirkwood, 2005) that these theories may all provide a partial explanation for the phenomenon of aging but no single theory has been explicitly proven to explain the aging process.

### 3. Computational modelling for biological aging

While there is an abundance of aging theories, the same cannot be said about computer simulations of biological aging (Stauffer, 2007). T. J. P. Penna implemented the mutation accumulation theory (Penna, 1995) by dividing individual lifetime into  $B$  time intervals, representing the genome with a string of  $B$  bits (chronological genome). An analytic solution is also available (Coe and Mao, 2003). The model has been successful in reproducing the senescence of the pacific salmon (Penna et al., 1995), and has been modified to account for the antagonistic pleiotropy mechanism (Sousa and de Oliveira, 2001; Cebrat and Stauffer, 2005) and spatial distributions on a lattice (Makowiec, 2000). Speciation in age structured populations has

also been of interest, and in specific sympatric speciation (Sousa, 2000; Luz-Burgoa et al., 2003) and parapatric speciation (Schwammle et al., 2006), in some cases including sexual reproduction, diploid and even triploid organisms (de Oliveira, 2004; Sousa et al., 2003).

A rather obscure model for the evolution of aging is the Heumann-Hotzel model (Heumann and Hotzel, 1995), which is a generalization of the Dasgupta model (Dasgupta, 1994). In this model, each individual carries a "chronological genome" of size  $x_{max}$ , with a survival probability per time step  $G(x)$  at age  $x$ , which can be modified according to some mutations. The model has been modified to account for its weaknesses, namely its incapacity to treat populations with many age intervals and its ability to handle mutations exclusively deleterious (de Medeiros and Onody, 2001), where the catastrophic senescence and the Gompertz law have been demonstrated. Optimization models of the disposable soma theory have been developed by several groups (Cichon and Kozłowski, 2000; Mangel and Munch, 2005; Abrams and Ludwig, 1995; Vaupel et al., 2004; Baudisch, 2008; Drenos and Kirkwood, 2005), which describe how the optimal investment in maintenance is affected by varying the parameters that specify the schedules of reproduction and mortality.

#### 4. The model

A computational model was constructed to study the evolution of the rate of biological aging. This is a phenotype (in contrast to genotype) centered model and does not focus on a specific genetic procedure that affects the aging process. It does not assume any genetic mechanism of aging at work, just the idea that each individual's ability to survive is age dependent. It focuses on the phenotypic results of the genome i.e. the viability of each individual. The model uses asexual reproduction and assumes a well mixed population (i.e. no spatial effects) and no interaction between the individuals.

The motivation behind this work is to provide a simple model to understand how various parameters, such as the age at maturity or different kinds of mutations affect the evolution of the rate of aging. In this model I assume that the viability of each individual is age dependent and diminishes with age. Given this hypothesis, mutations can produce offspring with increased or decreased viability. Consequently, natural selection acts on these mutations, affecting the overall viability of the population. The model can make predictions about how the mutation probabilities, mutation strength, and

age at reproductive maturity shape aging patterns and affect the aging rate and the final state of the system.

I focus in the simplicity of the model rather than how it would be more realistic. As a result, a small number of parameters have been used and a number of simplifying assumptions have been made. It assumes asexual reproduction only, a fixed age at reproductive maturity (which is known to differ from the strategy many organisms use in the face of limited resources), a constant number of offspring and a very specific function which is used to calculate each individual's viability. Consequently the model has its limitations and favors simplicity over realism. The intention behind it is to give a qualitative understanding and some initial predictions on the influence of each individual's viability and how its change affects the aging process and thus and instigate future work on the subject.

Let  $N_0$  be the initial number of individuals. Each individual is characterized by a parameter  $f$  that is responsible for the individual's viability  $F(\alpha)$ , which is age dependent and stays in range from 0 to 1. Parameter  $f$  is the measure of aging and the change of its value over time shows the evolution of biological aging. The value of  $f$  indicates how an individual's viability changes over its life course; high values of  $f$  imply fast aging and low  $f$  slow aging (see also Eq. (4)). Parameter  $f$  can be related to Darwinian fitness under the assumption that individuals with higher survival potential will be able to maintain or increase their numbers in succeeding generations, leading to a better representation of their genome.

The threshold parameter  $T$ , which controls the number of hits an individual can withstand is typically set to 2. Simulations have been also performed with  $T = 1$ ,  $T = 4$ ,  $T = 8$ , and  $T = 16$ . The Gompertz pattern arises typically for small  $T$  values (e.g.  $T \leq 4$ ), because for higher values stochastic effects are more pronounced and the mortality pattern is more scattered due to noise, deviating significantly from the exponential function. Therefore, a small constant value of  $T$  is used to minimize this effect and to reduce the complexity in the study of the model's behavior.

An aging function, which is a logistic function, is used to calculate the individual's viability at age  $\alpha$  in the form of:

$$F(\alpha) = \frac{1}{1 + \left(\frac{1}{B} - 1\right) \cdot e^{f\alpha}} \quad (4)$$

where:  $B$  is a constant (typically equal to 0.99),  $f$  is each individual's characteristic parameter for its viability, which can be modified due to mutations,

and  $F(\alpha)$  each individual's viability at age  $\alpha$ . A time step is completed when all the individuals at the specific time are selected. The simulation begins with  $N_0$  individuals. The algorithm at each time step is as follows:

1. An individual is selected.
2. Its age is increased by 1.
3.  $F(\alpha)$  is calculated for the individual's current age  $\alpha$ . It then receives a "hit" with probability  $1 - F(\alpha)$ . Let  $H$  be the number of total hits an individual can withstand.
4.  $T$  is the parameter which represents the threshold of hits. If  $H = T$  ( $T$  typically equal to 2), the individual dies and the next individual is selected.
5. If the individual survives and its age  $\alpha$  is  $\alpha \geq R$  (where  $R$  is the age at reproductive maturity), it generates 1 offspring.
6. The offspring survives with probability:  $1 - \frac{N(t)}{N_{max}}$ . This is the Verhulst Factor, which accounts for the limited carrying capacity of the environment.
7. If the offspring survives, they receive their parents' genome with mutations that affect their viability (parameter  $f$ ). These mutations can have a beneficial effect ( $f$  is reduced with probability  $P_b$ ), detrimental effect ( $f$  is increased with probability  $P_d$ ), or neutral ( $f$  remains constant).

As a result of the aging function (Eq. (4)), low values of  $f$  correspond to high viability of each individual (and vice versa). The amount that the  $f$  is modified in the newborn is parameter  $M$  of the simulation (mutation step). To keep the exponent in Eq. (4) above zero, the minimum value of  $f$  is restricted to be equal to  $M$  in each simulation. In this model, the maximum age of each individual does not depend on an external parameter, but emerges naturally from the aging function.

The Verhulst factor is applied here in a different fashion than the Penna or the Heumann-Hotzel model. Instead of acting as a random death probability for all the population, it acts here only on the individuals whose genomes have not been tested by the environment yet, the newborn. From the economics of the population, this is clearly a better choice, since little investment is wasted (Lee, 2003). From the biological perspective, although it is not yet the most faithful representation of the real natural processes, it has an advantage since the genome of the newborn is on the average less well-fitted, because of the

overwhelming majority of bad over good mutations and random deaths will only occur for a fraction of the population that has more bad mutations than the average (Martins and Cebrat, 2000; Niewczas et al., 2000).

The quantities I monitor in the simulation are the total population  $N(t)$ , the mortality function  $\mu(\alpha)$  when the population reaches a stable age distribution, and the average value  $\langle f \rangle(t)$  of the population over time, which is a measure of the evolution of aging in the population. Typical values used for the population dynamics in our model are  $N_0=100$  and  $N_{max} = 10^4$ . All results are an average of 100 independent runs in each case.

## 5. Results and Discussion

Firstly, we would like to observe the population dynamics of the model with no mutations present, i.e the parameter  $f$  of each lineage remains constant during the simulation. In Fig. 1,  $N(t)$  is shown with no mutations for different values of reproduction age  $R$ . It is clear that populations with low  $R$  become fixed at higher values than the ones where  $R$  is high (see also inset of fig. 3). This can be attributed to the fact that as  $R$  increases, the average number of individuals that will be given the opportunity to reproduce is decreased. For  $R = 8$  the limiting factor is the carrying capacity of the environment (Verhulst factor) and  $N(t)$  quickly approaches  $N_{max}$  and settles a little below it, while for  $R = 30$  the reproduction age is principal factor for limiting population growth.

The time it takes for the population to stabilize is also higher for high values of  $R$ . Because not everyone has the chance to reproduce,  $N(t)$  increases much slower compared to lower values of  $R$ . The fluctuations in the population density become more pronounced for high  $R$ . For  $R = 30$ , when a new generation is born, it will take 30 time intervals for its individuals to reproduce. The effect is obviously less pronounced for lower values of  $R$  and disappears when the population density becomes stable. If  $R$  is sufficiently high, the population will perish, because very few individuals will reach the age of reproduction and the rate of deaths will surpass the birth rate.

Fig. 2 shows the mortality function  $\mu(\alpha)$  for different initial values of  $f_0$ , for a stable age distribution. It is clear that the main factor that affects the mortality function is the viability of the individuals, with lower values of  $f$  allowing them to survive longer. The model is able to reproduce the Gompertz-law of mortality (eq. 3), and  $\mu(\alpha)$  is shown to depend exponentially on age  $a$ , with the exponent having a linear dependence on the value

on  $f_0$  (fig. 2, inset). Simulations were also performed for different values of  $R$ , where it is evident that it does not have a dependence on the mortality function (although it can affect the stable state of the system when mutations are present, as is later shown).

Population density  $N(t)$  in the presence of mutations is shown in fig. 3. For  $R = 30$ ,  $N(t)$  increases significantly slower than  $R = 8$ , just as in the case without mutations. With mutations however, it takes more time to reach a stable population density. There is a significant difference in this case; the population will reach  $N_{max}$  regardless of  $R$  in contrast to the case with no mutations, where the final population density is greatly affected by  $R$  (see inset of fig. 3). While the population has a tendency to die out due to mutations, it is obvious that it stabilizes at a value close to the carrying capacity of the environment. This happens since beneficial mutations increase survival chances, and so even for large  $R$  the population evolves to survive to maturity and thus eventually is able to reach its size limit.

Mutations change the viability of the individuals and give the opportunity to the system to reach a different stable state. In fig. 4 I plot  $\langle f \rangle(t)$  of the population during the course of the simulation. A high value for deleterious mutations is used; 90% of the newborn will not survive as long as their parents (same values of simulation parameters as in fig. 3). A high probability of detrimental mutations tends to reduce significantly the overall viability of the population. This is evident by the initial increase of  $\langle f \rangle(t)$  and the peak in fig. 4. However, natural selection is at work and the small percentage of individuals with increased viability will reproduce more and carry their healthy genes to their offspring.

Consequently, in the system there are two forces at work: mutations which tend to decrease the viability of the population (increase  $\langle f \rangle$ ) and natural selection, which allows individuals with low  $f$  to generate more offspring and so contributes to a decrease of  $\langle f \rangle$ , namely an increase in the average viability of the population. Therefore, mutations combined with low selection pressure start to move the system towards a low viability with weaker phenotypes and after the time delay selection pressure is tightened and only the small percentage of the healthier phenotypes survive and reproduce, thus increasing the viability of the population. The constant reproductive potential, which the model assumes, favors simplicity over realism. Real organisms produce different number of offspring and this can affect greatly the dynamics of the system.

The effect of  $R$  on the final state of the system is evident in fig. 4. High

values of  $R$  will have as a result a stable state with low  $\langle f \rangle$ . This happens because for low  $R$  individuals with reduced viability will still have a high probability to reproduce, because they reach the reproduction age early in their lives. In this case the selection force on them is very relaxed and  $\langle f \rangle$  tends to increase and stabilize at higher values. Consequently, the force of natural selection is tightened for higher reproduction ages, e.g. in the case of  $R=30$ . Individuals with reduced viability are strongly selected against, because they will not have a chance to reproduce. As a result, the value of  $\langle f \rangle$  will not have a high tendency to increase compared to lower  $R$  values. This explains the lower peak in the case of  $R = 30$  compared to  $R = 8$  in fig. 4 and the lower value of  $\langle f \rangle$  where the system reaches equilibrium. If, however, the reproduction age is very high the individuals will not have a chance to reproduce,  $\langle f \rangle$  increases and does not stabilize and the population dies out, as shown below.

In fig. 5-9 I relax the probability of mutations, allowing a large room for neutral mutations, which do not change the viability of individuals. The population density still reaches the environment's carrying capacity regardless of  $R$ , as long as the  $R$  remains within the limits that allow the individuals to reach reproductive maturity (fig. 5). The mortality function obeys the Gompertz law and does not depend on  $R$  (inset of fig.5). Detrimental mutations still happen much more frequently than beneficial ones. As a direct result  $\langle f \rangle$  decreases slower and the selection pressure is less evident for different  $R$  (compare fig. 4 to fig. 6).

If  $P_d$  is increased even more (fig. 7-8) an interesting thing happens, namely the population dies out for low  $R$  values. In this case, the relaxed selection pressure at low  $R$  can be fatal to the population as  $f$  keeps increasing (fig. 8) at a rapid rate at  $R = 8$ . Here, detrimental mutations decrease the population's viability because they are not selected against and the population perishes. For high  $R$  values, however,  $\langle f \rangle$  decreases and the system reaches equilibrium, because the strong selection pressure eliminates deleterious mutations and weaker phenotypes. There seems to be a critical value close to  $R = 16$ , below which the population dies out and above which it survives and reaches a stable state. Therefore, the system's final state is shown to be very sensitive to the age at reproductive maturity. It should be noted that these dynamics assume a constant age at reproductive maturity in order to keep the model simple, while the age at reproductive maturity changes dynamically for many organisms (e.g. given the strategy that they use in the face of limited resources), and this change could have a great effect

on the evolution of the system.

The probability of beneficial or detrimental mutations is therefore shown to affect how the population evolves, as well as  $R$ , which plays a critical role in the final state of system. For lower values in the ratio of the probability of detrimental/beneficial mutations ( $P_d/P_b$ ), aging evolves almost as fast regardless of  $R$  (fig. 6). Higher values favor significantly species with late age of maturity, in which case there seems to be a critical value in the age at reproductive maturity, below which the population dies out and above which it survives and evolves to a stable state (fig. 8). High absolute values of these probabilities produce peaks in viability of the population  $\langle f \rangle(t)$ , because strong selection pressure takes over after a significant number of weaker phenotypes have appeared due to the high mutation rate (fig. 4). In species with high age at reproductive maturity, natural selection is stronger and quickly eliminates the weaker phenotypes, while in species with low  $R$  it is more relaxed and the peaks in  $\langle f \rangle(t)$  are more pronounced.

The role of mutation step  $M$  is examined in fig. 9, which shows  $\langle f \rangle(t)$  for various  $M$  values. The system is again shown to evolve towards a low  $\langle f \rangle$  of its individuals. However in this case, it will take considerably more time ( $\langle f \rangle(t)$  decreases very slow) to reach the final state for  $M = 0.001$ , with  $M$  controlling the speed with which evolution takes place. The process, however is also controlled by  $P_d$  and  $P_b$ . If the mutations are relaxed, the system will evolve to a steady state of individuals with higher potential for survival. If we use  $P_d = 0.9$  and  $P_b = 0.1$  (same values as fig. 3-4), the population will die out for  $M = 0.001$ . This happens because the small difference in fitness in the newborn is not significant enough to be selected by natural selection and compete with the high tendency of mutations to reduce the population's viability. The carrying capacity of the environment however, is also to be taken into account in conjunction with the value of  $M$ . Simulations have been performed with larger populations ( $N_{max} = 100000$ ), where the population reaches a stable state because a larger number for individuals allow natural selection more "room" to act.

The effect of different mutation probabilities  $P_d$  and  $P_b$  is studied in fig. 10. The frequency of beneficial and deleterious mutations and their ratio is again revealed to play a crucial role in the system, controlling not only the evolution rate, but also whether the population survives or perishes. When the probability of beneficial mutations is sufficiently small the population will die out, otherwise the system will evolve to a stable state with better overall viability (see also inset of fig. 10, where the effect is apparent in the final

population density). The higher the absolute values of these probabilities, the more pronounced the peaks are for  $\langle f(\cdot) t \rangle$ . Not only that, but lower values allow the system to stabilize at lower  $\langle f(\cdot) t \rangle$ , namely evolving towards a more viable population (compare  $P_d = 0.9, P_b = 0.1$  with  $P_d = 0.5, P_b = 0.05$  and  $P_d = 0.1, P_b = 0.01$  in fig. 10). High relative values of  $P_d/P_b$  slow down evolution, while for even higher values the overall viability decreases rapidly ( $\langle f(\cdot) t \rangle$  increases) and the population dies out (compare  $P_d = 0.9, P_b = 0.1$  with  $P_d = 0.9, P_b = 0.05$  and  $P_d = 0.9, P_b = 0.01$  in fig. 10).

## 6. Conclusions

A simple model, based on physical viability, was constructed to study the evolution of biological aging. The mortality rates are shown to obey the Gompertz law. It's clear that given sufficient "room", i.e. number of individuals and amount their viability is modified, natural selection drives the system towards better phenotypes, reducing aging effects. Mutations appearing at later ages may be acted weakly upon by natural selection as suggested by the mutation accumulation theory, but beneficial mutations which extend the survival of the species will always have a tendency to increase in the population, as shown by the model.

Life exists far from thermodynamic equilibrium. Maintaining its stability could be regulated by optimally allocating the organism resources, however this does not exclude the existence of an ageless phenotype in an optimal environment. Entropy must inevitably increase within a closed system, but living beings are not closed systems. A single theory that fully describes all aging phenomena and why aging has evolved, is still lacking. This model is not concerned with why aging evolved, but can make predictions about how various parameters, such as the age at reproductive maturity or mutation probabilities, affect the aging patterns.

More specific, in the absence of mutations lower ages at reproductive maturity  $R$  tend to reach higher values of final population density. With mutations present, the population stabilizes near the maximum density, except for species with short pre-reproductive periods, which can only tolerate low rates of deleterious mutations and thus the populations dies out. For lower values in the ratio of the probability of detrimental/beneficial mutations ( $P_d/P_b$ ), aging evolves almost as fast regardless of  $R$ . Higher values favor significantly species with late age of maturity, in which case there seems to be a critical

value in the age at reproductive maturity, below which the population dies out and above which it survives and evolves to a stable state.

High absolute values of these probabilities produce peaks in  $\langle f \rangle(t)$  and low values allow the system to stabilize at lower  $\langle f \rangle(t)$ . In species with low  $R$  selection pressure is more relaxed and the peaks are more pronounced. High relative values of  $P_d/P_b$  decrease the evolution rate, and if this ratio is further increased,  $\langle f \rangle(t)$  increases rapidly and the population dies out. The rate of aging is controlled by the mutation probabilities in conjunction with the amount they modify each individual's phenotype, with neutral mutations allowing the system more "room" to evolve. Therefore, even in this simple model, the process of evolution of biological aging is shown to be fairly complex and very sensitive to the parameters that control it.

## References

- Abrams, P. A., Ludwig, D., 1995. Optimality theory, gompertz' law, and the disposable soma theory of senescence. *Evolution* 49, 1055–1066.
- Baudisch, A., 2008. Inevitable aging? Contributions to evolutionary-demographic theory. Springer, Berlin [et al.].
- Cebat, S., Stauffer, D., 2005. Altruism and antagonistic pleiotropy in penna ageing model. *Theory Biosci.* 123, 235–241.
- Charlesworth, B., 1997. Aging: Questions and prospects. *Science* 278, 5337.
- Cichon, M., Kozłowski, J., 2000. Ageing and typical survivorship curves result from optimal resource allocation. *evolutionary ecology research* 2, 857-870. *Evol. Ecol. Res.* 2, 857–870.
- Coe, J. B., Mao, Y., 2003. Analytical solution of a generalized penna model. *Phys. Rev. E* 67, 061909.
- Dasgupta, S., 1994. A computer simulation for biological ageing. *J. Phys. I* 10, 1593.
- de Medeiros, N. G. F., Onody, R. N., 2001. The heumann-hotzel model for aging revisited. *Phys. Rev. E* 64, 041915.
- de Oliveira, S. M., 2004. Evolution, ageing and speciation: Monte carlo simulations of biological systems. *Braz. J. of Phys.* 34, 1066–1076.

- Drenos, F., Kirkwood, T. B. L., 2005. Modelling the disposable soma theory of ageing. *Mech. Ageing Dev.* 126, 99–103.
- Finch, C. E., 1990. *Longevity, Senescence, and the Genome*, 1st Edition. The University of Chicago Press Ltd, Chicago.
- Gavrilov, L. A., Gavrilova, N. S., 1991. *The Biology of Life Span: A Quantitative Approach*. Academic Publisher, New York: Harwood.
- Hamilton, W. D., 1966. The moulding of senescence by natural selection. *J. Theor. Biol.* 12, 12–45.
- Heumann, M., Hotzel, M., 1995. Generalization of an aging model. *J. Stat. Phys.* 79, 483.
- Kirkwood, T. B. L., Holliday, R., 1979. The evolution of ageing and longevity. *Proc. R. Soc. Lond. B. Biol. Sci.* 205, 531–546.
- Kirkwood, T. B. L., Rose, M. R., 1991. Evolution of senescence: late survival sacrificed for reproduction. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 332, 15–24.
- Kirkwood, T. B. L., 1977. Evolution of ageing. *Nature* 270, 301–304.
- Kirkwood, T. B. L., 2005. Understanding the odd science of aging. *Cell* 120, 437–447.
- Lee, R., 2003. Rethinking the evolutionary theory of aging: Transfers, not births, shape senescence in social species. *Proc. Natl. Acad. Sci.* 100-16, 9637–9642.
- Leroi, A. M., Bartke, A., Benedictis, G. D., Franceschi, C., Gartner, A., Gonos, E., Feder, M. E., Kivisild, T., Lee, S., Kartal-Ozer, N., Schumacher, M., Sikora, E., Slagboom, E., Tatar, M., Yashin, A. I., Vijg, J., Zwaan, B., 2005. What evidence is there for the existence of individual genes with antagonistic pleiotropic effects? *Mech. Ageing Dev.* 126, 421–449.
- Luz-Burgoa, K., de Oliveira, S. M., Martins, J. S. S., Stauffer, D., Sousa, A. O., 2003. Computer simulation of sympatric speciation with penna ageing model. *Braz. J. of Phys.* 33, 623.

- Makowiec, D., 2000. Penna model of biological aging on a lattice. *Acta Phys. Pol. B* 31, 1036.
- Mangel, M., Munch, S. B., 2005. A life-history perspective on short and long-term consequences of compensatory growth. *The American Naturalist* 166-6, E155–E176.
- Martinez, D. E., 1998. Mortality patterns suggest lack of senescence in hydra. *Exp. Gerontol.* 33, 217–225.
- Martins, J. S. S., Cebrat, S., 2000. Random deaths in a computational model for age-structured populations. *Theory Biosci.* 119, 156–165.
- Medawar, P. B., 1952. *An Unsolved Problem of Biology*. Lewis, London.
- Mevdevev, Z. A., 1990. An attempt at a rational classification of theories of ageing. *Biol. Rev. Camb. Philos. Soc.* 65, 375–398.
- Niewczas, E., Cebrat, S., Stauffer, D., 2000. The influence of the medical care on the human life expectancy in 20th century and the penna ageing model. *Theory Biosci.* 119, 122.
- Partridge, L., 2001. Evolutionary theories of ageing applied to long-lived organisms. *Exp. Gerontol.* 36, 641–650.
- Partridge, L., 2007. A singular view of ageing. *Nature* 447, 262–263.
- Penna, T. J. P., de Oliveira, S. M., Stauffer, D., 1995. Mutation accumulation and the catastrophic senescence of the pacific salmon. *Phys. Rev. E* 52, 3309.
- Penna, T. J. P., 1995. A bit string model for biological aging. *J. Stat. Phys.* 78, 1629.
- Schwammle, V., Sousa, A. O., de Oliveira, S. M., 2006. Monte carlo simulations of parapatric speciation. *Eur. Phys. J. B* 51, 563–570.
- Shaw, F. H., Promislow, D. E. L., Tatar, M., Hughesa, A. K., Geyes, C. J., 1999. Toward reconciling inferences concerning genetic variation in *drosophila melanogaster*. *Genetics* 152, 553–566.

- Sousa, A. O., de Oliveira, S. M., Martins, J. S. S., 2003. Evolutionary advantage of diploidal over polyploidal sexual reproduction. *Phys. Rev. E* 67, 032903.
- Sousa, A. O., de Oliveira, S. M., 2001. An unusual antagonistic pleiotropy in the penna model for biological ageing. *Physica A* 294, 431–438.
- Sousa, A. O., 2000. Sympatric speciation in an age-structured population living on a lattice. *Eur. Phys. J. B* 39, 521–525.
- Stauffer, D., 2007. The penna model of biological aging. *Bioinf. and Biol. Ins.* 1, 91–100.
- Strehler, B. L., 1978. *Time, Cells and Aging*, 2nd Edition. Academic Press, New York and London.
- Templeton, A. R., 2006. *Population Genetics and Microevolutionary Theory*, 1st Edition. Wiley, New Jersey.
- Thatcher, A. R., 1999. The long-term pattern of adult mortality and the highest attained age. *J. R. Statist. Soc. A* 162-1, 5–43.
- Vaupel, J. W., Baudisch, A., Dolling, M., Roach, D. A., Gampe, J., 2004. The case for negative senescence. *Theor. Pop. Biol.* 65, 339–351.
- Williams, G. C., 1957. Pleiotropy, natural selection, and the evolution of senescence. *Evolution* 11, 398–411.

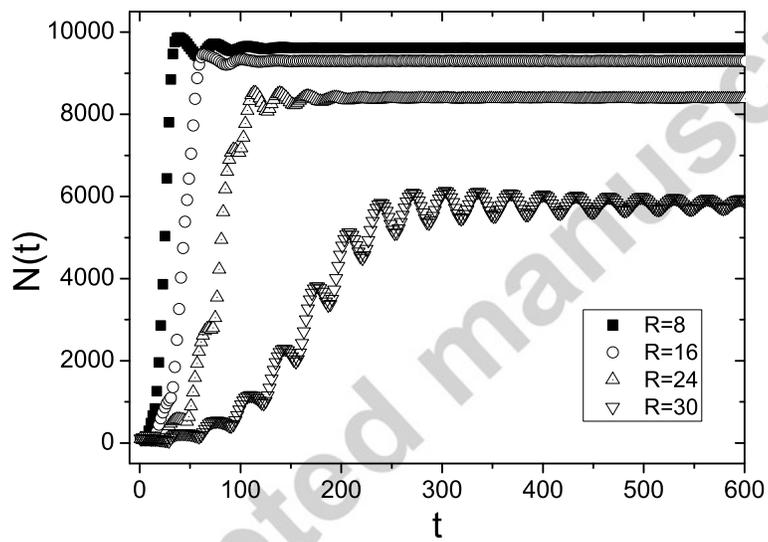


Figure 1:  $N(t)$  vs  $t$  for different values of reproduction age  $R$ .  $t = 10^4$ ,  $f_0 = 0.1$ , no mutations.

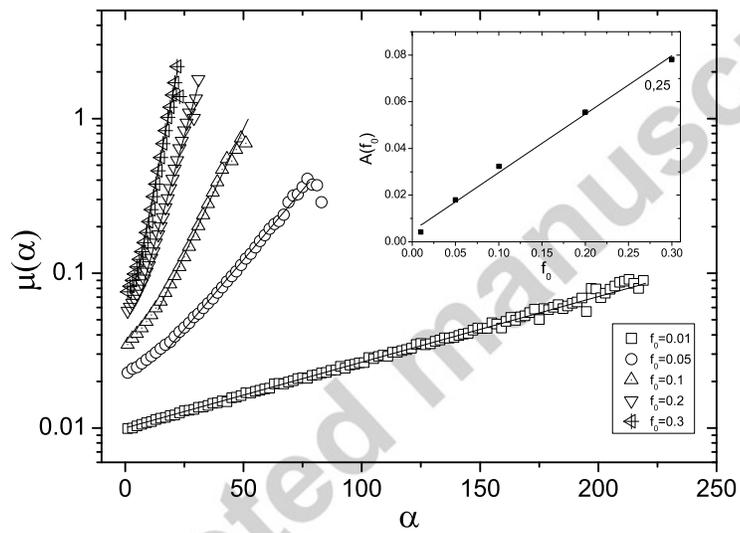


Figure 2:  $\mu(\alpha)$  vs age  $\alpha$  for the population at  $t = 10^4$  for various values of initial fitness  $f_0$ .  $R = 8$ , no mutations. Inset: Slope  $A$  of  $\mu(\alpha)$  vs  $f_0$ .

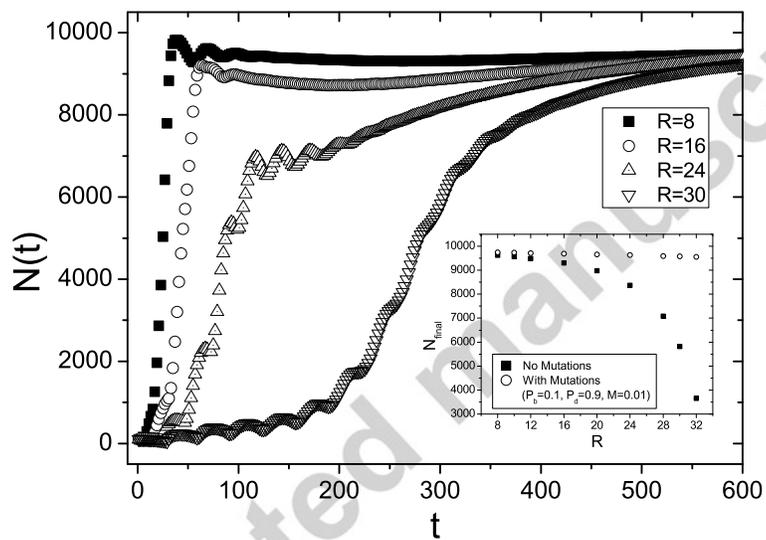


Figure 3:  $N(t)$  vs  $t$  for different values of reproduction age  $R$ .  $t = 10^4$ ,  $f_0 = 0.1$ , Mutations are allowed,  $P_b = 0.1$ ,  $P_d = 0.9$ ,  $M = 0.01$ . Inset: Final population  $N$  for the stable state vs  $R$  and comparison with the case with same simulation parameters, but no mutations

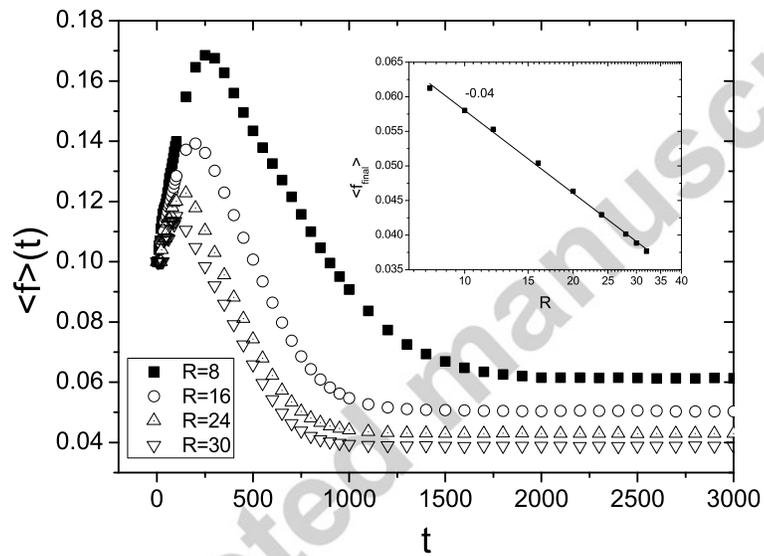


Figure 4:  $\langle f \rangle(t)$  vs  $t$  for different values of reproduction age  $R$ .  $t = 10^4$ ,  $f_0 = 0.1$ , mutations are allowed,  $P_b = 0.1$ ,  $P_d = 0.9$ ,  $M = 0.01$ . Inset: Final  $\langle f \rangle$  for the stable state vs  $R$ .

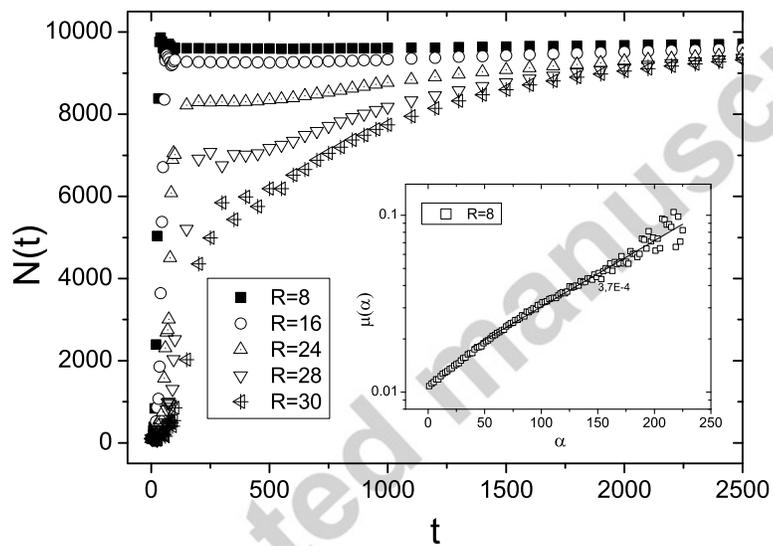


Figure 5:  $N(t)$  vs  $t$  for different values of reproduction age  $R$ .  $t = 10^4$ ,  $f_0 = 0.1$ , mutations are allowed,  $P_b = 0.01$ ,  $P_d = 0.1$ ,  $M = 0.005$ . Inset: Mortality function  $\mu(\alpha)$  vs  $\alpha$  for  $t = 10^4$  ( $R = 8$  only shown for clarity).

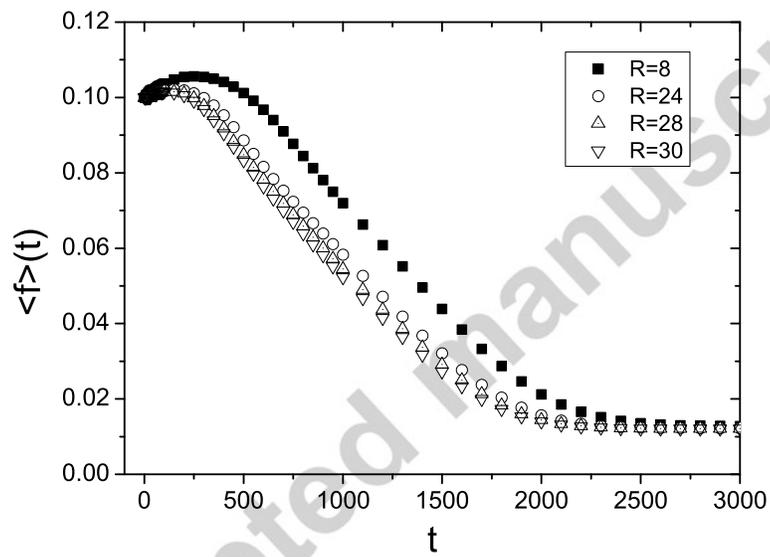


Figure 6:  $\langle f \rangle(t)$  vs  $t$  for different values of reproduction age  $R$ .  $t = 10^4$ ,  $f_0 = 0.1$ , mutations are allowed,  $P_b = 0.01$ ,  $P_d = 0.1$ ,  $M = 0.01$ .

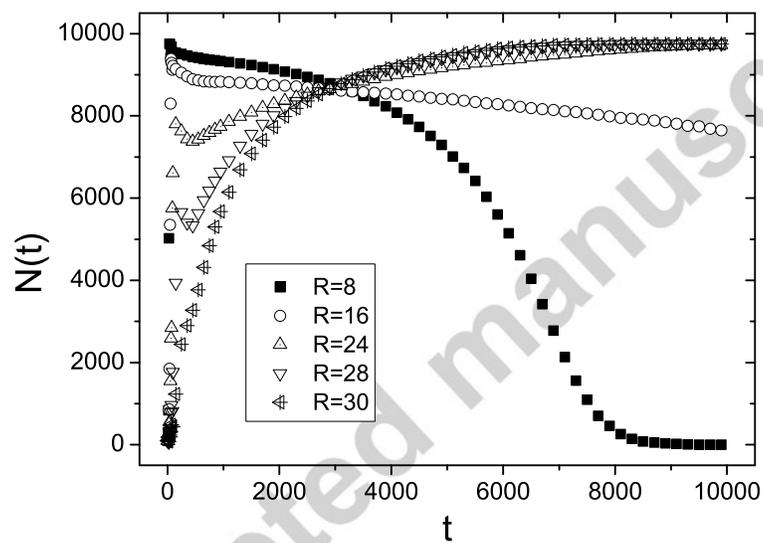


Figure 7:  $N(t)$  vs  $t$  for different values of reproduction age  $R$ .  $t = 10^4$ ,  $f_0 = 0.1$ , mutations are allowed,  $P_b = 0.01$ ,  $P_d = 0.5$ ,  $M = 0.005$ .

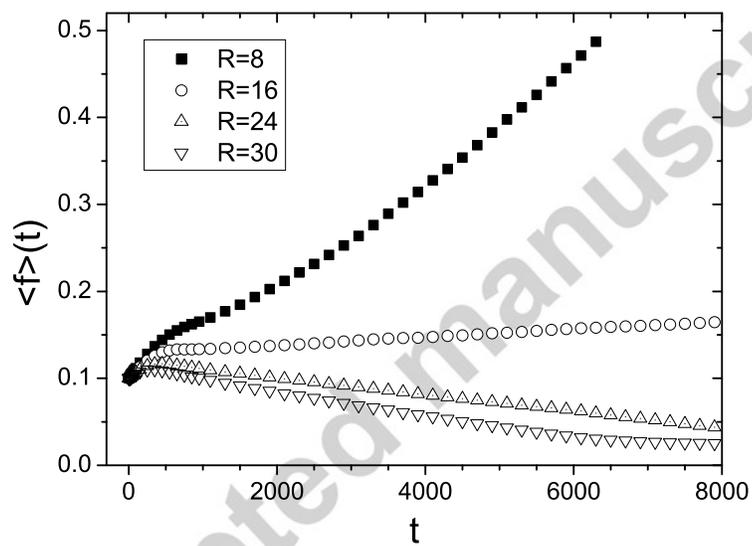


Figure 8:  $\langle f \rangle(t)$  vs  $t$  for different values of reproduction age  $R$ .  $t = 10^4$ ,  $f_0 = 0.1$ , mutations are allowed,  $P_b = 0.01$ ,  $P_d = 0.5$ ,  $M = 0.005$ .

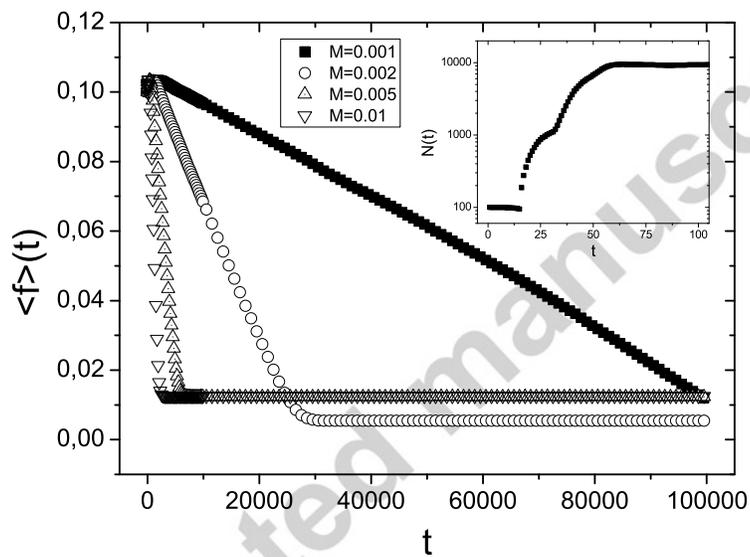


Figure 9:  $\langle f \rangle(t)$  vs  $t$  for different values of mutation step  $M$ .  $t = 10^5$ ,  $f_0 = 0.1$ , mutations are allowed,  $P_b = 0.01$ ,  $P_d = 0.1$ ,  $R = 16$ . Inset: Population  $N(t)$  vs  $t$  ( $M = 0.001$  only shown for clarity).

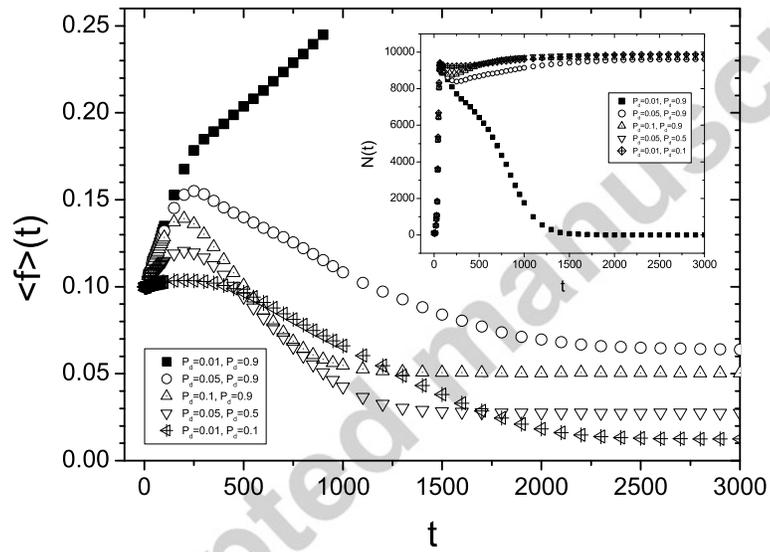


Figure 10:  $\langle f \rangle(t)$  vs  $t$  for different values of mutation probabilities  $P_b$  and  $P_d$ .  $t = 10^4$ ,  $f_0 = 0.1$ ,  $M = 0.01$ ,  $R = 16$ . Inset: Population  $N(t)$  vs  $t$ .