An Unusual Antagonistic Pleiotropy in the Penna Model for Biological Ageing

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Abstract

We combine the Penna Model for biological aging, which is based on the mutation-accumulation theory, with a sort of antagonistic pleiotropy. We show that depending on how the pleiotropy is introduced, it is possible to reproduce both the humans mortality, which increases exponentially with age, and fruitfly mortality, which decelerates at old ages, allowing the appearance of arbitrarily old Methuselah’s.

Key words: Ageing. Penna model. Monte Carlo Simulations.

1 Introduction

According to the evolutionary theory of aging the ultimate cause of senescence is the declining force of natural selection with age \cite{Charlesworth1998}. From 1950s to 1980s, this idea has been formulated in a progressively more explicit and formal way, culminating in the mathematical treatment of Charlesworth \cite{Charlesworth1998}. Several different genetic mechanisms may be involved in this lack of selection pressure at old ages, but the two major alternative population genetic mechanisms are the antagonistic pleiotropy and the mutation-accumulation mechanism.

Pleiotropic genes are those that have different effects on fitness at different ages. The antagonistic pleiotropy mechanism \cite{Sulkin1993, Christakis1993, Violin1993, Violin1995} proposes that ageing is caused by pleiotropic genes that have opposite effects at young and old ages, that is, genes that confer some advantage during the period of maximum reproductive probability, at the expenses of some disadvantage or declining vigor late in life. An example is the accumulation of calcium to build up bones first,

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and the appearance of arteriosclerosis later. The mutation-accumulation mechanism [2,4,7] proposes that ageing is caused by the accumulation of deleterious alleles having effects that appear only at old ages, when selection pressure is already weak, and in this way may remain in the population, being transmitted from parents to offspring.

After the analytically treated mathematical model of Partridge and Barton in 1993 [8], a continuous flow of Monte Carlo simulations of ageing started (for a review see [9]). The bit-string Penna model of life history was published in 1995 [10] and is now by far the most widely used Monte Carlo simulation technique to predict many of the features related to ageing (for a review see [11]). It is based on the mutation-accumulation theory and gives that the probability to die within the next year increases exponentially with age, in agreement with the 19th century empirical Gompertz law for human mortality.

In this paper we combine the Penna model with an antagonistic pleiotropy mechanism. However, this antagonistic pleiotropy does not work in the usual way explained above, since it does not give any advantage at young ages. On the contrary, it gives a disadvantage before reproduction age and some advantage at old ages. Our biological motivation is the existence of a rather curious gene involved in the cholesterol transportation by the bloodstream [12]. This gene can be found in three different forms, $\epsilon_2$, $\epsilon_3$ and $\epsilon_4$. The allele $\epsilon_4$ seems to be the most dangerous one: those who carry it have a high cholesterol level and a high probability of suffering from heart diseases and also Alzheimer. In contrast, the allele $\epsilon_2$ seems to be relatively beneficial: it is associated to low levels of cholesterol and a low incidence of Alzheimer. The allele $\epsilon_3$ has an intermediate influence concerning these diseases. Surprisingly, studies in different populations have shown that the form $\epsilon_3$ is by far the most common one, followed by the dangerous form $\epsilon_4$. The less common form is the beneficial one, $\epsilon_2$. Since deleterious mutations that may affect the individuals at young ages are generally eliminated from the population, the persistence of the allelic form $\epsilon_4$ may be related to some antagonistic effect.

Combinations of the usual antagonistic pleiotropy mechanism with the Penna model can be found in [13,14]; simple pleiotropy, understood as a two-fold effect of a harmfully mutated gene, has also been recently introduced into the model in order to show the advantages of sexual reproduction [15].

This paper is organized as follows: in section 2 we review the traditional sexual version of the Penna Model; the readers already familiar with the model can skip this section. In section 3 we present our pleiotropy mechanism and results, and in section 4, our conclusions.
2 The Penna Model for Sexual Populations

In the sexual version of the model, each individual of a population is represented by a “chronological genome” that consists of two bit-strings (diploid) of 32 bits (zeroes and ones). These two strings are read in parallel, which means that each position is associated to two bits (alleles). One time step corresponds to reading a new bit position in all genomes. The first position contains the information about the individual’s first period of life, the second one about the second period and so on. Each individual can live at most for 32 periods, each period corresponding to one day, week or year depending on the species. Genetic defects (harmful mutations) are represented by bits 1 and healthy genes by bits 0. Homozygous loci (positions) are those with two equal alleles (bits). Heterozygous loci are those corresponding to different alleles, meaning that the individual inherited opposite informations, 0 and 1, from each parent. If an individual has two bits 1 (homozygous) at the third position, for instance, it starts to suffer the effects of a genetic defect at its third period of life. If it is an homozygous position with two bits zero, no disease appears at that age. If the individual is heterozygous in some position, it will become sick only if the mutation at this position has a dominant effect. Six of the 32 bits positions are randomly chosen, at the beginning of the simulation, where the alleles 1 are dominant; in the remaining 26 positions this allele is recessive. These dominant positions are the same for all individuals and kept fix during the whole process. When the number of accumulated diseases of any individual reaches a threshold value $T$, the individual dies.

If a female succeeds in surviving until the minimum reproduction age $R$, it generates, with probability 0.5, one offspring every period until death. The female randomly chooses a male to mate, with age also greater or equal to $R$. The offspring genome is constructed from the parents’ ones; first the strings of the mother are randomly crossed, and a female gamete (one string of 32 bits) is produced. $M_f$ deleterious mutations are then randomly introduced. The same process occurs with the father’s genome (with $M_m$ mutations), and the union of the two remaining gametes form the new genome. The sex of the baby is randomly chosen, each one with probability 50%.

Deleterious mutation means that if the randomly chosen bit of the parent’s gamete is equal to 1, it remains 1 in the offspring genome, but if it is equal to zero in the parent’s gamete, it is set to 1 in the baby genome. The most important characteristic of this dynamics is that the bits 1 accumulate, after many generations, at the end part of the genomes, that is, after the minimum reproduction age $R$. For this reason ageing appears: the survival probabilities per period decrease with age, in agreement with the mutation accumulation hypothesis and reality [16].
Although only harmful mutations are considered, a population that increases exponentially in time is obtained. In order to avoid this exponential increase, each individual has also a probability to die due to a lack of food or space. This probability is given by the Verhulst factor

\[ V = \frac{N(t)}{N_{\text{max}}} , \]

where \( N(t) \) is the number of individuals at time \( t \) and \( N_{\text{max}} \) is the maximum carrying capacity of the environment, which is defined at the beginning of the simulation. At every time step, for each individual, a random number between 0 and 1 is generated and compared to \( V \): if this number is smaller than \( V \) the individual dies, independently of its age and genome.

### 3 Pleiotropy and Results

Two different strategies of the antagonistic pleiotropy mechanism are now introduced into the Penna model. In both cases we chose a priori two different positions among the 32 possible ones, to be considered as special positions. Let us call them \textit{markage}1 and \textit{markage}2. If, and only if, an individual has two bits 1 (homozygous) at \textit{markage}1, or if only one bit is equal to 1 but \textit{markage}1 happens to be a dominant position, and the individual succeeds in surviving until the age \textit{markage}2, then:

- Case 1: There is a probability \( P_{\text{clean}} \) that the current number of accumulated mutations is decreased by one. When the individual reaches \textit{markage}2, a random number between 0 and 1 is generated. If it is greater or equal to \( P_{\text{clean}} \), the number of accumulated diseases is decreased. If it fails, in the next time step another random number is generated, and the process is repeated until it works. So in this case the number of accumulated mutations is decreased by one only once, at an age that can be equal or greater than \textit{markage}2.

- Case 2: Every year, from \textit{age} = \textit{markage}2 until death, there is a probability \( P_{\text{clean}} \) that the current number of accumulated mutations is decreased by one. So in this second case there is a cumulative probability of decreasing the current number of accumulated mutations.

It is important to notice that in both cases the genomes of the individuals are not changed: only the counter of the number of mutations is decreased by one.

We measure the survival rates and the mortalities of the populations as a function of age. For an already stable population the survival rate is defined as the ratio between the number of individuals with age \( a + 1 \) and the number
of individuals with age $a$:

$$S(a) = \frac{N_{a+1}(t)}{N_a(t)}.$$  \hspace{1cm} (1)

The mortality is defined as [17]:

$$q(a) = -\ln \left[ 1 - \frac{D_a(t)}{N_a(t)} \right],$$ \hspace{1cm} (2)

where $D_a$ is the number of deaths, due to genetic diseases, at age $a$.

The figures below were obtained using the following parameters:

- Initial population = $10^5$ individuals (half males and half females) and maximum population size = $10^6$ individuals;
- Minimum reproduction age $R = 10$;
- Limit number of accumulated diseases $T = 3$;
- Mutation rates $M_m = M_f = 1$;
- Pleiotropic positions $markage_1 = 9$ and $markage_2 = 16$;
- Results averaged from 100 independent runs of $10^5$ steps each. For each run measurements are averaged from the last 5000 steps.

In figure 1 we show the mortalities versus age in a linear-log scale, for the traditional Penna model (circles) and for our case 1. Squares correspond to $P_{\text{clean}} = 0.4$ and diamonds to $P_{\text{clean}} = 0.5$. As can be seen this strategy gives the same results as the traditional model, with the curves presenting an “s” shape, as already obtained before [11]. (In fact, a much better agreement with the Gompertz law is obtained for asexual populations [17], where the traditional Penna model gives a straight line for the linear-log plot of the mortality as a function of age, for ages above the minimum reproduction age $R$).

In figure 2 we show the results for our case 2, where a strong difference between the standard result (circles) and the cases where the cumulative probability $P_{\text{clean}}$ is adopted can be noticed. Now the mortalities decelerate at older ages, as observed for drosophiles [18,19], and may even present a peak (triangles), as observed for medflies [20]. (For a review on experimental results see [21]). The small sharp peaks at age 9 (squares and diamonds), which corresponds to our $markage_1$, shows that the population prefers to have the 9-th bit set to 1, in order to profit from a decrease of the probability to die at older ages.

In figure 3, we show the survival rates for the same cases presented in figure 2. Again it can be seen a decrease of the survival probabilities at age 9, for $P_{\text{clean}}$.
equal to $0.4$ and $0.5$, showing that after many generations there is a fixation of the 9-th bit inside the population.

4 Conclusions

We introduce an unusual form of antagonistic pleiotropy into the bit-string Penna model for biological ageing. We show that it is possible to simulate the drosophila mortality, which decelerates at old ages, as well as the medfly mortality, which presents a peak around a given age (Fig. 2), even considering only homogeneous stable populations. Depending on how the pleiotropy is introduced, the exponential increase of human mortality with age is also obtained (Fig. 1).

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References

[1] M.R. Rose, *Evolutionary Biology of Aging*, Oxford University Press, Oxford (1991).

[2] B. Charlesworth, *Evolution in Age-Structured Populations*, Cambridge University Press, Cambridge (1980).

[3] P.B. Medawar, *Mod. Quart.* 1 (1946) 30.

[4] P.B. Medawar, *An Unsolved Problem of Biology*, H. K. Lewis, London (1952).

[5] G.C. Williams, *Evolution* 11 (1957) 398.

[6] G.C. Williams, in *The Biology of Aging*, B. L. Streheld, Washington DC (1960) pp 332-37.

[7] E.B. Edney and R.W. Gill, *Nature* 220 (1968) 281.

[8] L. Partridge and N.H. Barton, *Nature* 362 305.

[9] D. Stauffer, *Braz. J. Phys.* 24 (1994) 900.

[10] T.J.P. Penna, *J. Stat. Phys.* 78 (1995) 1629.
[11] S. Moss de Oliveira, P.M.C. de Oliveira and D. Stauffer, *Evolution, Money, War and Computers*, Teubner, Stuttgart-Leipzig (1999).

[12] Steven N. Austad, *La Recherche* **322** (1999) 26.

[13] A.T. Bernardes, *Annalen der Physik* **5** (1996) 539.

[14] G. Medeiros, M.A. Idiart and R.M.C. de Almeida, *Int. J. Mod. Phys* **C** **11** (2000) number 7.

[15] J.S. Sá Martins and D. Stauffer, e-print cond-mat/0102176, submitted for publication.

[16] T.J.P. Penna, S. Moss de Oliveira and D. Stauffer, *Phys. Rev. E* **R52** (1995) 3309.

[17] A. Racco, M. Argollo de Menezes and T.J.P. Penna, *Theory Bioscien.* **117** (1998) 101.

[18] J.W. Curtsinger, H.H. Fukui, D.R. Townsend and J.W. Vaupel, *Science* **258** (1992) 461.

[19] D.E.L. Promislow, M. Tatar, A.A. Khazaeli and J.W. Curtsinger, *Genetics* **143**(2) (1996) 839.

[20] J.R. Carey, P. Liedo, D. Orozoco and J.W. Vaupel, *Science* **258** (1992) 457.

[21] James W. Vaupel in *Between Zeus and the Salmon. The Biodemography of Longevity*, ed. K.W. Watcher and C.E. Finch, National Academy Press, Washington D.C. (1997).
Figure Captions

Figure 1 - Mortalities as a function of age in a linear-log scale. Circles correspond to the traditional Penna model; squares and diamonds correspond to our case 1, for $P_{\text{clean}} = 0.4$ and $P_{\text{clean}} = 0.5$, respectively. Other parameters are mentioned in section 3.

Figure 2 - Mortalities as a function of age, now for the cumulative probabilities of case 2. Circles: traditional Penna model; Triangles: $P_{\text{clean}} = 0.2$; Squares: $P_{\text{clean}} = 0.4$; Diamonds: $P_{\text{clean}} = 0.5$.

Figure 3 - The survival rates as a function of age for the traditional model and for our case 2. The symbols are the same of Fig. 2.
