Heumann-Hötzel model for aging revisited

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Since its proposition in 1995, the Heumann-Hötzel model has remained as an obscure model of biological aging. The main arguments used against it were its apparent inability to describe populations with many age intervals and its failure to prevent a population extinction when only deleterious mutations are present. We find that with a simple and minor change in the model these difficulties can be surmounted. Our numerical simulations show a plethora of interesting features: the catastrophic senescence, the Gompertz law and that postponing the reproduction increases the survival probability, as has already been experimentally confirmed for the drosophila fly.

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I. INTRODUCTION

Death is inevitable. It is usually preceded by a progressive deterioration of our bodies. This phenomenon is called aging or senescence and it is characterized by a decline in the physical capabilities of the individuals. Although rare, some old people gaze at senescence with fine humor: ''Old age is not so bad when you consider the alternative'' said M. Chevalier (French singer and actor); ''It is good to be here. At 98, it is good to be anywhere'' taught us G. Burns (U.S. comedian and actor).

The new millennium, which is just beginning, will certainly be witness of a holy crusade against aging. The principal battle will be fought in the biochemical and medicine fields. Can the physicist help in any way? If we look at the progress made in the last decade, we believe that the answer is yes. Indeed, physicists have brought new perpectives on the subject — the Occam's razor principle. William of Occam, a Franciscan monk, philosopher, and political writer who was born in England in the thirteenth century, believed that for every phenomenon occurring in the universe we need to look at the simplest explanation first — complexity should not be assumed without necessity. This is the way physicists like to think of nature but this may not be followed by biologists. They love to see differences and complexity where physicists love to see similarities and simplicity. A good model in physics means one with a small number of parameters. With the Occam's razor principle in mind, what kind of aging model can we propose?

There are two kinds of aging theories: biochemical and evolutionary. The first invokes damages in cells, tissues, and organs, the existence of free radicals or the telomeric shortening, that is, it sees senescence as a natural consequence of biochemical processes [1,2]. The second is the evolutionary theory [3,4], which explains the senescence as a competitive result of the reproductive rate, mutation, heredity, and natural selection.

Evolutionary theories of aging are hypotheticodeductive in character, not inductive. They do not contain any specific genetic parameter, but only physiological factors and constraints imposed by the environment. There are two types: the optimality theory and the mutational theory. In the optimality theory [5], senescence is a result of searching an optimal life history where survival late in life is sacrificed for the sake of early reproduction. A typical representative of such theories is the Partridge-Barton model [6,7]. For the mutational theory [4,8], on the other hand, aging is a process that comes from a balance between Darwinian selection and accumulation of mutations. The natural selection efficiency to remove harmful alleles in a population depends on when in the life span they come to express. Alleles responsible for lethal diseases that express late in life, escape from the natural selection and accumulate in the population, provoking senescence. However, if the natural selection is too strong then deleterious mutations might not accumulate [9]. The most successful aging theory of the mutational type is the Penna model [10,11]. By the way, throughout this paper, aging simply means that the average survival probability of the population decreases with the age.

Here, in this paper, we analyze the Heumann-Hötzel model [12]. Although released at the same year as the Penna model it has remained in limbo. The Achilles' heel of the Heumann-Hötzel model was its incapacity to treat populations with many age intervals (which we all expect to be a free parameter in a reasonable model). Last but not least, in its original formulation the model could not handle mutations exclusively deleterious (harmful mutations are 100 times more frequent than the beneficial ones) leading to population meltdown. With minor modifications we were able not only to repair those points but also to find some nice characteristics of the model: it is Gompertzian, it exhibits catastrophic senescence, and the effect ''later is better'' (explained in the paper) is present.

II. THE HEUMANN-HÖTZEL MODEL

In 1994, Dasgupta [13] proposed an aging model very similar to the Partridge-Barton [6] model, but without the antagonistic pleiotropy. The antagonistic pleiotropy [14] arises when the same gene is responsible for multiple effects.

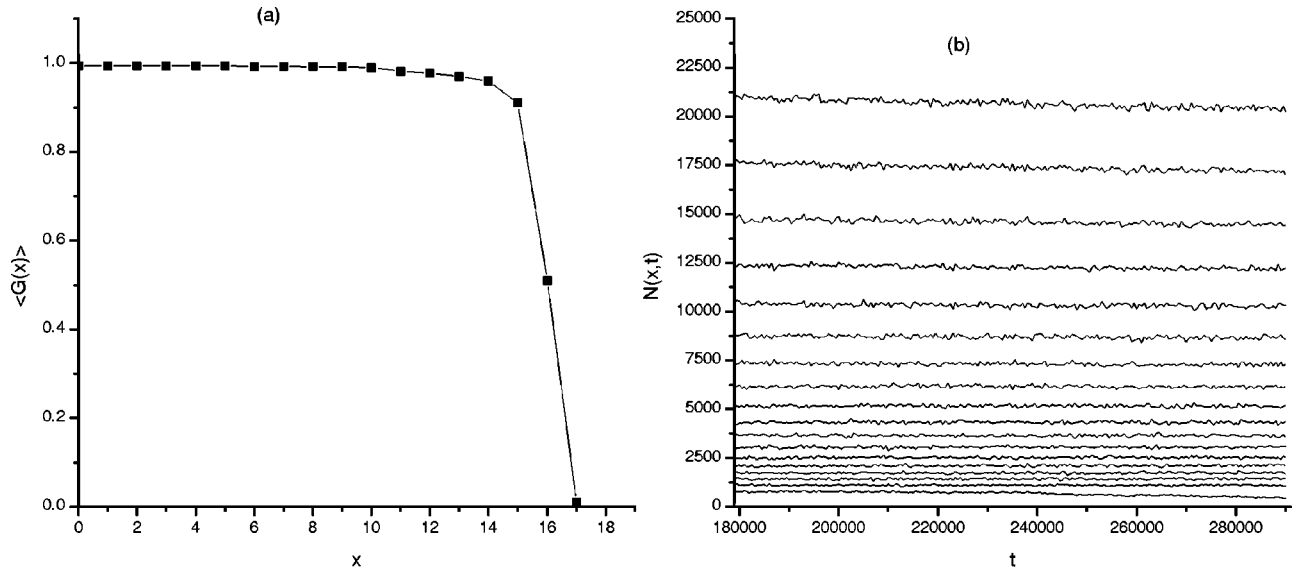*Electronic address: ngfm@ ifsc.sc.usp.br

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FIG. 1. The Heumann-Hötzel model with 18 ages. The parameters used were: $F=0.1$, $m=1$, $|a|=0.2$, $|b|=0$, $R_{min}=8$, and $R_{max}=17$. (a) Plot of the survival probability versus the age; (b) time evolution of the number of individuals with age x, $N(x,t)$. From top to bottom $x=0,\ldots,17$.

For example, genes enhancing early survival by promotion of bone hardening might reduce later survival by promoting arterial hardening. Reproduction is asexual. As in the Partridge-Barton model, every individual in the Dasgupta model can have only three ages.

Heumann and Hötzel [12] generalized the Dasgupta model to support an arbitrary number of ages. However, when they simulated a population with 11 ages, they found that (in the final stationary state) there is again only three ages, recovering the Partridge-Barton results. This fact put the Heumann-Hötzel model in limbo. We will show later how some simple modifications can change drastically this scenario.

Let us now briefly describe the Heumann-Hötzel model. At time t, there is a population composed by $N(x,t)$ individuals with age x, $x=0(babies),1,2,\ldots,x_{max}$. Each individual carries a ''chronological genome'' of size x_{max} with a survival probability per time step $G(x)$ at age x. There will be senescence if this genome, averaged over the whole population, has $G(x)$ diminishing with x. At each time step t, *every* individual passes through the following stages.

The Verhulst factor V(t). The Verhulst factor plays the role of the environment (e.g., food restrictions). It is given by

$$V(t)=1-\frac{N(t)}{N_{max}}, \qquad (1)$$

where $N(t)$ is the total population at time t and N_{max} is a chosen parameter. If an individual at age x has $G(x)>1-V(t)$ then he survives to the next step, otherwise he is eliminated. Actually, it is the Verhulst factor that prevents the population to blow up.

The natural selection. A random number $r\in[0,1]$ is drawn. If an individual has $G(x)>r$ then he survives.

The asexual reproduction. In the interval $R_{min}\leq x \leq R_{max}$ an individual has m offspring, every one carrying a genome inherited from his father.

The mutations. At a randomly chosen position x, each individual has his survival probability $G(x)$ mutated to $G'(x)$ by a random number u ($-|a|\leq u\leq|b|$, i. e., the mutations can be deleterious or beneficial)

$$G'(x)=G(x)e^{u}. \qquad (2)$$

All individuals die after x_{max}.

As we said before, such a dynamics has two bad consequences: $x_{max}=2$ and there is population meltdown when only deleterious mutations are allowed.

To overcome these difficulties, we made two simple but essential modifications: mutations are allowed only on a fraction F ($0\leq F\leq 1$) of the *babies* ($x=0$). By restricting the mutations only to the babies we brought the model more close to reality, since it is well known that hereditary mutations mostly take place during the reproduction process acting on the babies not in their fathers. Mutations affecting the adults are predominantly of the somatic kind. The original formulation — mutations happening for every individual at any age — not only imposes a colossal rhythm of mutations but also it seems to be unnatural. Furthermore, as there is a chance that some babies could escape from mutations, we introduced the parameter F that represents the fraction of the mutated babies. In the presence of one parameter $F<1$ there will be no population meltdown. We point out that such a parameter also exists in the Penna model, but in an underground way.

Taking into account such modifications, we have performed some numerical simulations and found a lot of interesting results.
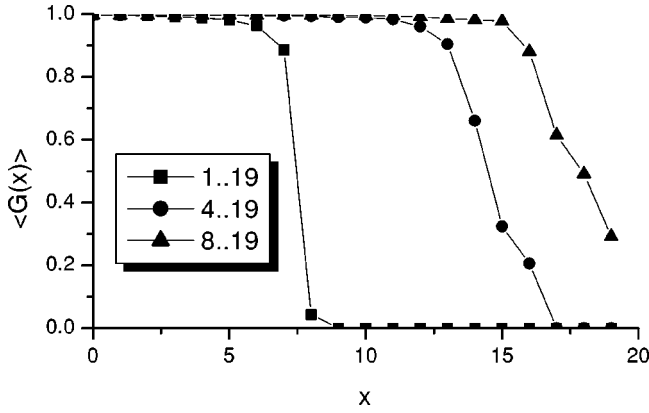
FIG. 2. The effect "later is better" in the modified Heumann-Hötzel model. The parameter's values are: $F=0.1$, $m=1$, $|a|=0.04$, and $|b|=0.02$. The interval ages of reproduction $R_{min}\ldots R_{max}$ corresponding to the curves are shown in the inset.

III. OUR RESULTS

We simulated the modified Heumann-Hötzel model with the starting condition $N(x,t=0)=N_0\delta_{x,0}$. The initial number of babies, N_0, varied from 10 to 20 000 and the genome distribution was chosen to be random or "pure," which means that all babies have the genome $G(x)=1\ \forall\ x$. For $N_0=20\,000$, we did not find any qualitative difference between the two distributions. Of course, for very small initial population only the pure distribution can reach the stationary regime. In general, we run 300 000 time steps and average all quantities over the last 10 000 steps (when the stationary regime had already been achieved). We fixed $N_{max}=800\,000$. The measured quantities were: $N(x,t)$, $\langle N(x)\rangle$ — the time average over $N(x,t)$, $\langle G(x,t)\rangle$ — the average genome of the individuals with age x at the instant t, $\langle G(x)\rangle$ — the survival probability — i. e., the time average over $\langle G(x,t)\rangle$.

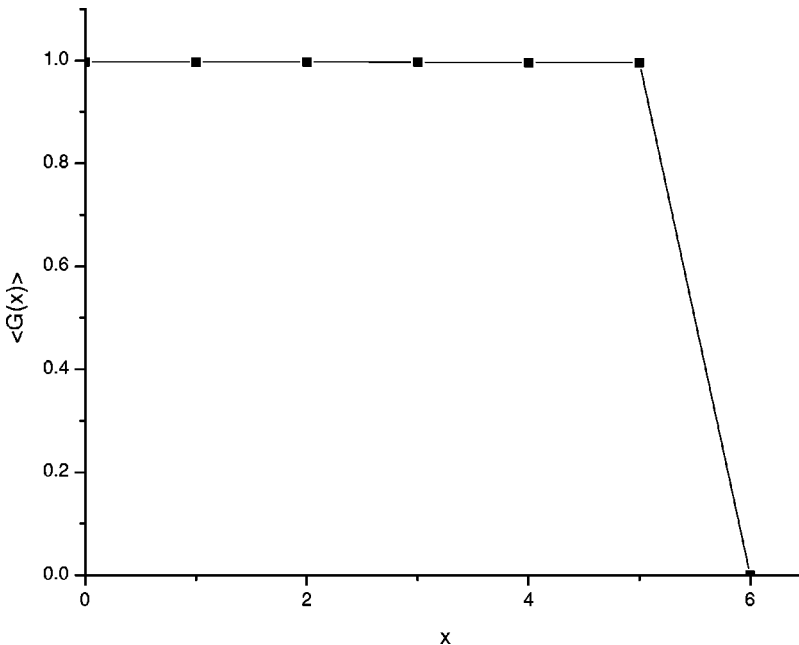Figure 1(a) shows that the modified Heumann-Hötzel model does not lead to a population meltdown even when the mutations are exclusively deleterious. Figure 1(b) indicates that the stationary regime has been achieved after $t=180\,000$.

Some recent experiments [15], done with the fruit fly drosophila melanogaster, unequivocally demonstrate that postponing reproduction favors the population. In the experiments, the male and female flies were put together some time later than they have reached their sexual maturity. The result was an improvement of the population characteristics — both male and female flies have increased their survival probabilities at old ages. Okay, the Heumann-Hötzel model treated here is asexual, but we can think of this effect — later is better — by studying what happens if we delay the initial reproduction age R_{min}. Figure 2 shows that the effect "later is better" is in fact present.

While iteroparous individuals can breed repeatedly, semelparous individuals breed only once. The Pacific salmon is a good example of the latter. This fish has a dramatic manifestation of aging, the so called catastrophic senescence. It dies just after its sexual maturity. The Heumann-Hötzel model exhibits the catastrophic senescence if we make $R_{min}=R_{max}$ (see Fig. 3).

As a final study, we verified that the Heumann-Hötzel model obeys nicely the Gompertz law. Based on actuarial observations, Gompertz [16] found in 1825 that the human mortality function

$$q(x)=-\frac{d\ln\langle N(x)\rangle}{dx} \qquad (3)$$

grows exponentially with age x for some interval age. Removing the Verhulst factor, i.e., considering only deaths by natural causes, it is easy to show that $q(x)=1-\langle G(x)\rangle$.

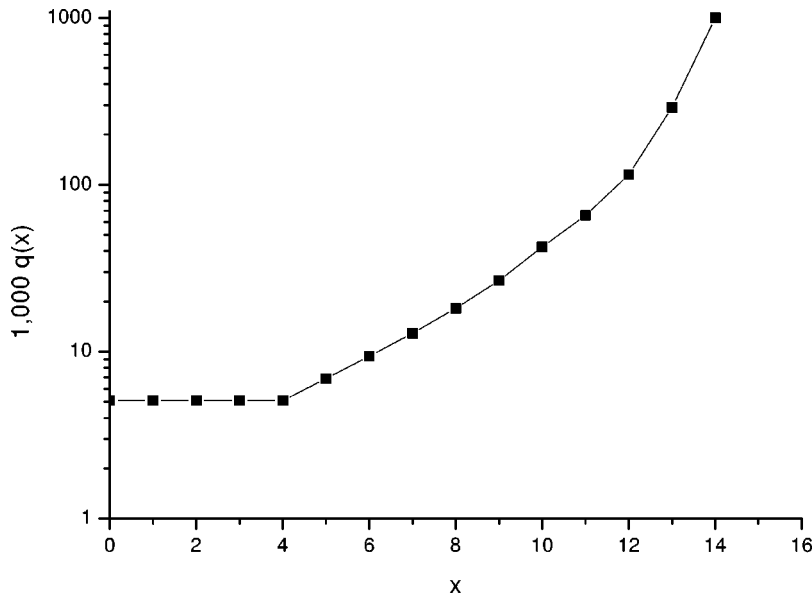FIG. 3. The catastrophic senescence in the modified Heumann-Hötzel model. The parameter's values are: $F=0.1$, $m=4$, $|a|=0.04$, $|b|=0.02$, and $R_{min}=R_{max}=5$.

FIG. 4. The Gompertz law holds in the age interval $x \in$ [4,9]. The parameters are: $F=0.1$, $m=1$, $|a|=2$, $|b|=0$, $R_{min}=4$, $R_{max}=15$.

Figure 4 shows our result. The Gompertz law is satisfied only in an age interval (see discussion below).

IV. DISCUSSION

In this paper, we have modified the Heumann-Hötzel model in order to fix its main deficiency — to be a senescence model with only three possible ages. The crucial point was to change the huge amount of mutations. This was done by permitting only mutations in a fraction F of the babies. The consequences were surprisingly very good.

The first achievement was to get an arbitrary (and stable) number of ages. Without this it would be impossible to obtain all the other results. Our numerical data show that the modified Heumann-Hötzel model has some sensitive and also robust parameters. From a qualitative point of view, it does not matter what type of initial condition we use: random or ''pure.'' The two parameters: N_{max} (of the Verhulst factor) and m (fertility) only determine the size of the final

stationary population. We tried to implement the Verhulst factor $V(t)$ in two different ways: (i) for each individual (with any age x) a random number r is drawn and if $r < 1 - V(t)$ he dies (aleatory decimation); (ii) each individual at age x with $G(x) < 1 - V(t)$ dies (discriminatory decimation). We did not detect any important differences between these two cases. On the other hand, the three parameters: F (fraction of mutated babies), a (deleterious mutation intensity), and b (beneficial mutation intensity) are very sensitive: a bad choice may lead to a population meltdown. This is what happens, for example, for $b=0$, $F=1$, and arbitrary a. Finally, the other two parameters, R_{min} and R_{max} (corresponding to the reproductive age interval) may also conduct to a population meltdown if not wisely chosen. Postponing the sexual maturity, i.e., increasing R_{min} (up to a maximum value over which there will be again extinction of the population) clearly favors aging, in the sense that now the individuals live longer. Although, as far as we know, such a phenomenon has only been detected in organisms with
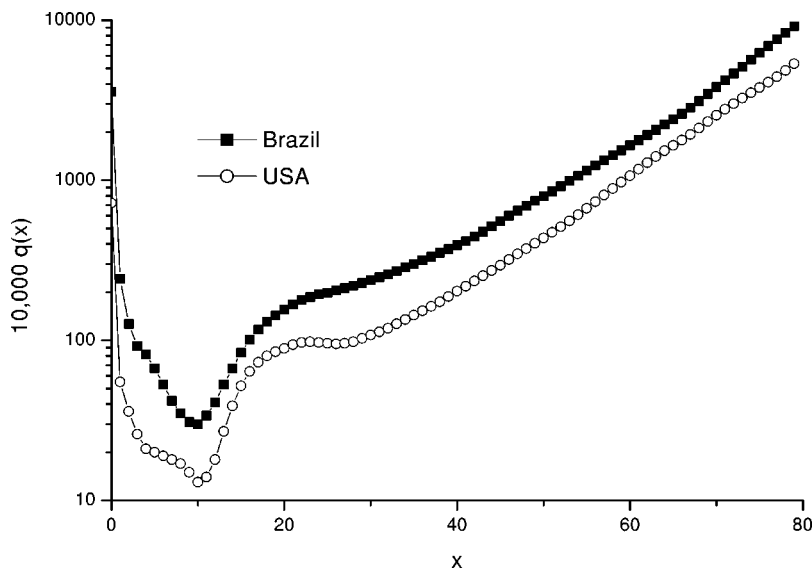

FIG. 5. Mortality in Brazil and the U.S.A. in the year 1998. Searches: Instituto Brasileiro de Geografia e Estatística and U.S. Department of Health and Human Services. The Gompertz law holds in the age interval $x(\text{years}) \in$ [35,60].

sexual reproduction, it was amazing to find it also here. If $R_{min} = R_{max}$, i.e., if an individual reproduces only once in his entire life, there will be a catastrophic senescence.

In Figure 5 we show the mortality function in the year 1998 for Brazil and U.S. The Gompertz law holds only in an age interval, something between the ages 35–60. It is only in this region that the mortality function grows up exponentially. Our simulation (Fig. 4) exhibits the same behavior in the interval 4–9. Here again, sex does not seem to play any relevant role. Comparing the two plots one can see that the modified Heumann-Hötzel model reproduces correctly neither the high infantile mortality (Fig. 5, for $x < 10$) nor the mortality decay for $x > 80$ (not shown in Fig. 5). For the fruit fly Drosophila such a late-life decay forms a plateau [17]. On the other hand, the modified Heumann-Hötzel model predicts (see Fig. 4) that the mortality is almost constant for $x < 4$ and it grows faster than an exponential for $x > 10$. These discrepancies are almost certainly connected to the fact that, independently of their ages, the Verhulst factor (which plays the role of the environment) is the same for all individuals. So a Verhulst factor varying with the age x would be very nice. Recently [18], a kind of infantile mortality was found by defining the Penna model in a lattice.

To conclude, let us compare the Heumann-Hötzel model with the Penna model. There are some pros and cons. One difference is how the natural selection is implemented in each model. In the Penna model there is a parameter (fixed and equal for all individuals) — the threshold — which is a kind of destiny. Any individual having a number of mutations greater than the threshold dies. The Heumann-Hötzel model on the other hand gives to any individual a chance to escape from natural selection even when his survival probability is very small. This aleatory aspect is closer to the Darwinian ideas of natural selection. In the Penna model a deleterious mutation cannot occur twice in the same position of the genome. This means that some babies will not mutate. Through the parameter F this feature is also present in the modified Heumann-Hötzel model, but here the number of deleterious mutations in the same position of the genome is not restricted or limited. Finally, due to its bit-string characteristics, the Penna model is easier to simulate and is more suited to treat large populations. The Heumann-Hötzel model, on the other hand, can start with a very small population ($N_0 \sim 10$ of ''pure'' babies) and still reach the stationary regime. In a conversation with Professor Stauffer he recommended including sex in the Heumann-Hötzel model. This is now under way.

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