Monte Carlo Simulation for Biological Aging

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Various models are simulated which try to explain senescence for living beings. Severa1 types of mutation are combined with Darwirnistic selection of the fittest and optimization constraints. The balance or mutation and selection leads to a lower survival rate for old than for young people, i.e. to senescence. A simple formula, neglecting interactions between different individual, describes well some of the aging results even when the growth of the population depends crucially on these interactions.

I. Introduction

When men get old, they usually run slower than as twenty year old, acquire a beer belly, are less sexy and physically less strong, become less creative in theoretical physics, start to discuss philosophy of physics, and show other signs of senescence. Even Pelé no longer wins soccer world championships (not to mention other experimental evidence from July 10, 1994). Of course, there are always exceptions, like this writer. More quantitatively, the probability to die within the next year drastically increases at old age. Can we understand these effects from a simple model, which finally might help increasing the quality of life for old people and the average life expectancy?

Many theories of aging (ageing in British spelling) were suggested[1]; at the beginning of Genesis, Adam blames Eve for the event leading to their expulsion from the garden of Eden, and we will mention below more recent evidence in this direction. Insects may have their wings damaged in the course of time, and athletes break their bones or strain their ankles. Perhaps cells have a preprogrammed death[2] by allowing only a limited number of cell divisions. Chemicals like oxygen radical have also been blamed[2]. None of these approaches seem to be suited for the methods of theoretical physics and computer simulations, and thus they are ignored here; that does not mean that these approaches are wrong.

Rose[1], on the other hand, voiced the opinion that methods of mathematical physics more than traditional biochemical knowledge may contain clues for aging. He and others[3] combine evolution theories (Darwinistic selection of the fittest) with population dynamics; the latter is known e.g. from prey-predator relations like the Lotka-Volterra equation, where big fish eat small fish. Basically, a random mutation diminishing our survival probability is more dangerous to the species as a whole if it affects young age than if it affects old age. For young people produce more offspring than old people and thus are more valuable for population growth. Thus bad mutations affecting the young are weeded out stronger by selection pressure[4] than bad mutations affecting only old age. Statistical Physicists know that mean field theories neglecting fluctuation effects are unreliable. Thus Ref.[3] triggered some Monte Carlo simulations of these genetic population dynamics, which are summarized here.

II. Model

To see senescence we need at least two age intervals[3], and thus three points in time: Babies at time = 0, juveniles at time - 1, and adults at time = 2. Thus time is measured in generations; its translation into years depends on the species studied. Each individuum can give birth at times 1 and 2, but not at time 0. The probability of one individuum to survive from t=O to t=l is the juvenile survival rate J, whereas that from t=l to t=2 is the adult survival rate A. If J = A, there would be no senescence: old people are

as healthy as young ones. Normally one has moderate senescence: $0 < A < J$, whereas the limit $A \to 0$ means catastrophic senescence, as observed in Pacific salmon[3]. Sex is difficult for this writer and thus ignored here; the reason why people are interested in sex is another controversial field of research[5].

The Euler-Lotkal[1,3] equation now relates these two survival rates J and A with the growth factor r, if the population increases as $\exp(rt)$, and with the number of offspring given by juveniles, m_1, and adults, m_2:

$$m_1 J e(t^{-1})r + m_2 A J e(t^{-2})r = \mathrm{e}tr \qquad (1)$$

since the number of babies at time t (basically the LHS of this equation) is produced by the surviving juveniles born one generation before and by the surviving adults born two generations earlier. Of course, the factor $\exp(tr)$ cancels out. For a stationary state, $r = 0$, this means $m_1 J + m_2 A J = 1$, i.e. a stable population needs on average one child per parent. In this way the fitness, as expressed through r, is determined by the two survival rates A and J, for given fertilities m.

Mutations now can change these survival rates. A deleterious mutation reduces them by some factor, and a helpful mutation increases them.. We call this factor $\exp(\epsilon)$ and thus allow ϵ to be both positive and negative, but always small. Therefore it does not matter much whether we have two mutations of strength ϵ or one with strength 2ϵ, and thus we take into account the possible difference in the effect of mutations on A and J by a ratio v: Mutations affect old age $(A)v$ times stronger or more often than young age (J). Experts[3] call a mutation affecting both young and old age "pleiotropic"; thus v measures this pleiotropy. In this way, if u mutations per generation affect the juvenile survival, then J is changed by a factor $\exp(u\epsilon)$ and A by a factor $\exp(uv\epsilon)$.

Mutations can be somatic or hereditary. Somatic mutations, like skin cancer acquired by having too much sunshine on the beach, happen during the lifetime of an individuum and are not transmitted to the offspring. (Also the errors of the Kowald-Kirkwood simulations[2] behave like somatic mutations.) Hereditary mutations are given on to the offspring, like hemophilia. For hereditary mutations we have to distinguish between "old" and "new": old ones are transmitted unchanged from one generation to the other and determine the characteristics of that family through time-independent values of J and A; new ones happen first to the individuum we investigate, and are then transmitted to the offspring. Thus the new hereditary mutations accumulate in the family line and make J and A depending on time. If all new hereditary mutations are negative (= deleterious), their bad effects accumulate so much that after a sufficiently long time J and A are no longer large enough to sustain the population. This vanishing of the species was called "mutational meltdown"[5,6] and means that the model is unrealistic as far as a description of stable or growing species is concerned. Monte Carlo simulations have been made for hereditary mutations alone, for somatic mutations alone, and for both together.

If boys chase girls all the time instead of studying, they may reduce their own survivability on the job market. Ref. [7] found that males not allowed to mate live significantly longer than mating males. Other recent research[8] confirmed this anti-feministic *cherchez la femme* result not at all or only under certain conditions. A simple way to include this antagonistic balance between producing many offspring in the youth and surviving healthily in old age is the assumption of Partridge and Barton[3]

$$J + A^x = 1\,, \quad (x \geq 1) \qquad (2)$$

where x = 4 was taken in ref.[3]. Combining Eqs. (1,2) we get a quadratic equation[3] for the conditions of maximal growth, with the solution

$$J_0 = 0.935,\ A_0 = 0.505 \to r = 0.26 \qquad (3)$$

for $m_1 = m_2 = 1$.

Thus after exactly u bad somatic mutations with $\epsilon < 0$ the survival rates are reduced to

$$J = J_0 \exp(\epsilon u),\quad A = A_0 \exp(\epsilon u v) \qquad (4a)$$

The same is true for "old" hereditary mutations (in the above sense) since they are the same for all generations. Fluctuations can be introduced by a Poisson[9] distribution of the number of mutations. Then a mathematical exercise shows that the fluctuations cancel out: Eq.(4a) remains valid with u now meaning the average number of mutations[10]. More interesting is therefore an exponential distribution of events, where the probability

for exactly U mutations varies as $(u/(1+u))^{-U}$ where again u is now the average value. Then[10]

$$J = J_0/(1 - EU), \quad A = A_0/(1 - \epsilon uv) \qquad (4b)$$

(Of course, positive mutations are allowed only as long as they do not increase the survival probabilities beyond unity.)

Similarly, the birth rate has been assumed to be exactly m_1 and m_2, or to fluctuate with an exponential distribution. Thus one child per generation means in the case of fluctuations: no child in half of the cases, one in one quarter of the cases, two in an eighth of the cases, etc. In addition, one may put the living beings onto a square lattice and allow childbirth only if there is an empty neighbor site[10]. It is numerically much easier to take into account limitations of food and space by reducing the juvenile survival probability by a factor $1 - N/L$, where N is the total number (e.g. of babies) and L, some limiting parameter, so that N cannot increase beyond L. This reduction in juvenile survival corresponds to the fact that budget cuts at universities first affect the employment of junior staff, not the tenured faculty; however, years later an age gap will develop in the tenured faculty.

III. Computational techniques

The juvenile and adult survival rates are floating point numbers, stored as usual. If instead the total number of mutations in the family history is stored, that number can be quite large. Thus traditional programming methods have to be employed, no storage in bits is possible. Vectorization also has not been attempted. The discrete nature of generations, $t = 0, 1,$ and 2 only, avoids the difficulties of differential equations. Thus one has discrete iterations, calculating from one time step to the next how many babies become juveniles, how many juveniles become adults, and how many children are born, all that with or without fluctuations, and with the effect of the mutations. Darwinistic selection then simply means that in the total population, the fraction of fitter individuals increases with time due to the above iteration.

So one time step for Partridge-Barton-type models may look like that: first, for each baby (age=0) we get the number u of mutations from the assumed exponential distribution; these mutations reduce J by a factor $\exp(-\epsilon u)$, and only if some random number is smaller than the reduced J does this individuum reach age 1. Then the same procedure is repeated for the juveniles (age=1) and their probability A to reach old age (=2); only now the average number of mutations is v times larger. Thereafter, the surviving juveniles and adults each produce a randomly determined number of children (such that this number again follows an exponential distribution). Now the number of adults is compared with the number of juveniles at the previous time step to give the average A, and the number of present juveniles divided by the number of babies after the previous iteration is the average J, and both averages are printed out. Finally, A and J are set back to their optimal values like A = 0.505, J = 0.935, and a new iteration may start.

If heredity is taken into account either by new hereditary mutations or by starting from A and J values which are different for different individual, then these genes (as represented by the values of A and J and/or by the numbers of mutations) have to be transmitted properly to the offspring, which is the most difficult part of the program. Without heredity only one value of J and A, not a whole array, has to be stored.

The problem seems ideally suited for parallel computers, where many processors with distributed memory work simultaneously on one problem. Each processor gets initially an equal share of the whole population to work with. After each iteration we sum up the resulting numbers of babies, juveniles, and adults from the different processors, calculate the survival rates by comparing the number of adults with the number of juveniles at the previous time step, and the number of juveniles with the number of babies at the previous time step. (This summation over all processors is needed if we want the ratio of the averages and are not satisfied with the average of the ratios; the latter one also would give difficulties if the population has died out on one processor but not yet on all.)

In this way, up to 280 million initial babies with a distribution of different survival probabilities could be observed over several hundred generations. Fig. 1 shows the survival rates in a simulation on 140 processors of an Intel Paragon, which took six minutes only on these i860 chips. We distributed initially the J values

homogeneously between 0 and 1, calculated the initial A values through Eq.(2) with x = 4, then took into account fluctuations in the somatic mutations at $u \to 30$, v = 2, $\varepsilon = 0.01$ and also fluctuations in the number of births about the averages $m_1 = n_2 = 1$. We see that the two survival rates move rapidly from an initial equality to stationary values J > A (i.e. with senescence), before the population dies out due to the high mutation rate u. Numbers of this order of magnitude correspond e.g. to the number of cod fish around Newfoundland before these stocks nearly vanished. Modern computers thus give us the technology to simulate about the same number of organisms as in nature, in contrast to simulations of a glass of cachaça. What we need here are better models, not necessarily better computers.

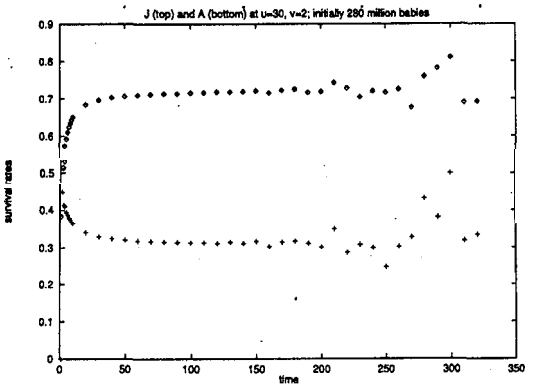

Figure 1: Variation with time of the juvenile (upper data) and adult (lower data) survival rates. The very high rate $u = 30$ of deleterious mutations leads to a decay of the initial population of 280 million down to zero; nevertheless during this time the average survival rates relax towards some equilibrium value before finally fluctuations take over. With u = 25 the population decay is much slower; with u = 23 the population reaches a minimum and increases afterwards. These simulations are made in a Partridge-Barton type model with hereditary survival rates and somatic deleterious mutations.

IV. Results

Dasgupta[1] studied a particularly simple model to show how the balance of new hereditary mutations with the pressure from selection of the fittest leads to senescence. Starting from identical juvenile and adult survival probabilities J = A = 1, taking into account only new hereditary mutations, ignoring fluctuations in the births and mutations ($m_1 = m_2 = 1$), selecting randomly half of the mutations to be positive and the other half as negative, and avoiding both Eq.(2) and any input value for the mutation ratio *v*, he found that the reduction of A due lo mutations is about twice as large as that for J. If the mutation strength is taken such after some initial time the popuiation neither grows nor decays, then J and A approach values near 0.7 and 0.5, respectively. (Since no ratio v was predetermined, each new mutation selected randomly with equal probability whether it affects young or old age.)

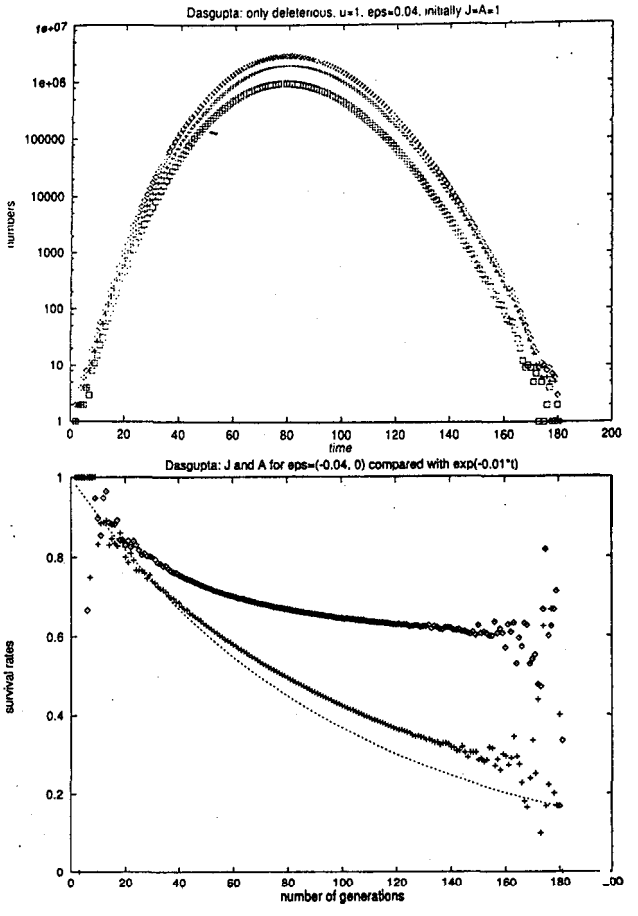

Figure 2: Growth and decay from a single individuum in Dasgupta's model[11]. Part a shows the numbers of babies, juveniles and adults (from top), part b the decrease with time of the survival rates J (diamonds, squares) and *A* (+, x). Here all mutations are inheritable, and there are no fluctuations in the number of mutations and births, nor is eq(2) needed.

Fig. 2 shows results from Dasgupta's model with only negative mutations: a single individuum with J = A = 1 and its children and grand children first create a new species with millions of animals (Fig.2a), but then the mutations reduce the two survival probabilities unsymmetrically (Fig.2b) until the whole species dies out ("mutational meltdown"[6]). We thus see that without *assuming* any asymmetry like Eq.(2) between juvenile and adult survival rates, senescence in the sense

of J > A and pleiotropy v > 1 is found, merely through the fact that juveniles can give birth also later in life and adults no longer have this chance. Selection pressure against bad mutations acts less on adults. The continued occurrence of new mutations prevents selection to yield the ideal choices J = A = 1.

Hötzel[17] generalized Dasgupta's model to more than just two age intervals J and *A*. He found in one case that the populations in the higher age groups then die out after some time, reducing the model to its original two-age version. In another "diffusion" model of Dasgupta, he simulated four ages and found all of them being stable, with the survival rate decreasing first slowly and then rapidly with increasing age, like the "Gompertz" curves of real life.

Many aging intervals were also simulated by Penna[18] in a particularly efficient bit-string algorithm; again the survival rate decreases with age as it should.

Heumann[17] found in some region of the parameter space of Dasupta's model[11] that a species has a better chance to survive catastrophic weather etc. if in case of trouble the babies can move into a "dauer" state[15] instead of becoming normal juveniles. In this state, similar to hibernation, they don't have offspring, don't eat and drink much, and thus behave very decently. You may not call it life, but when conditions improve these dauer individuals return to adult life and contribute to the survival and recovery of the species. Unfortunately, homo sapiens has not developed this ability to survive its own wars.

Some work was also, done on more complicated models based on the Partridge-Barton Eq. (2). For $m_1 = m_2 = 1$, Stauffer and Jan[10] took into account fluctuations in the somatic mutations ($\epsilon = 0.01$) and the births ($m_1 = m_2 = 1$), started with J = 0.935 and A = 0.505 (the values which optimize growth under the constraint (2)) for all individual, and found the Monte Carlo results to agree with the simple prediction (4b). Changing the birth rates changed the growth factor r but not the survival rates J and *A*. Even for simulations on a square lattice, A and J remained the same. This has to be expected since survival and mutations in this model are not collective phenomena: once the individuum is born it ages all by itself. In short, this "lone ranger" model is more appropriate for Clint Eastwood in Unforgiven than for ant colonies; we have not yet found complexity in it. (Partridge and Barton[3] claimed that A jumps to zero at some finite mutation rate for v → ∞, thus explaining the catastrophic senescence of Pacific salmon; but that effect was an artifact of their complicated mathematics.)

More interesting is the case of heredity[10], already used for Fig. 1, when initially the J values are distributed homogeneously between 0 and 1, with A coupled through (2) and x = 4. (The mutations are still somatic.) Then automatically selection drives the population towards the optimal values J = 0.935, A = 0.505, and the creationist model above (how does the computer know that 0.935, 0.505 is optimal?) is replaced by an evolutionary model: *Selforganization* towards the optimum as the outcome, not the aim, of a random process. Less philosophically, one sees that the system moves to a fixed point for J and A, independent of their initial distribution. The final values are very close to Eq.(4b), as Fig. 3 shows for one million initial babies.

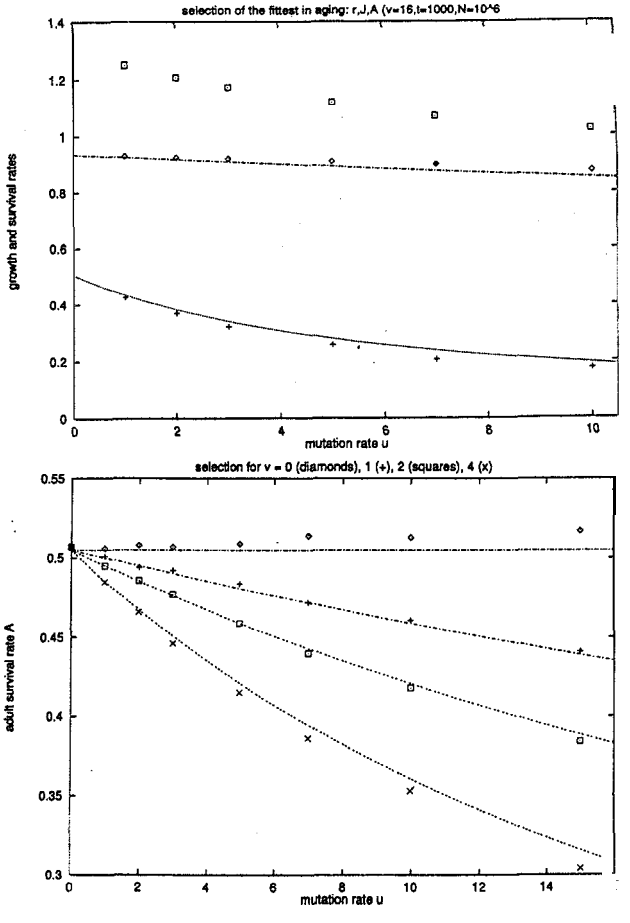

Figure 3: Variation of growth rate r, juvenile survival rate J and adult survival rate A (from top in part a) with mutation rate u, for v = 16 ï10å in the same model as for Fig.1. Part b gives only A for lower values of the ratio v. The curves denote approximation (4b).

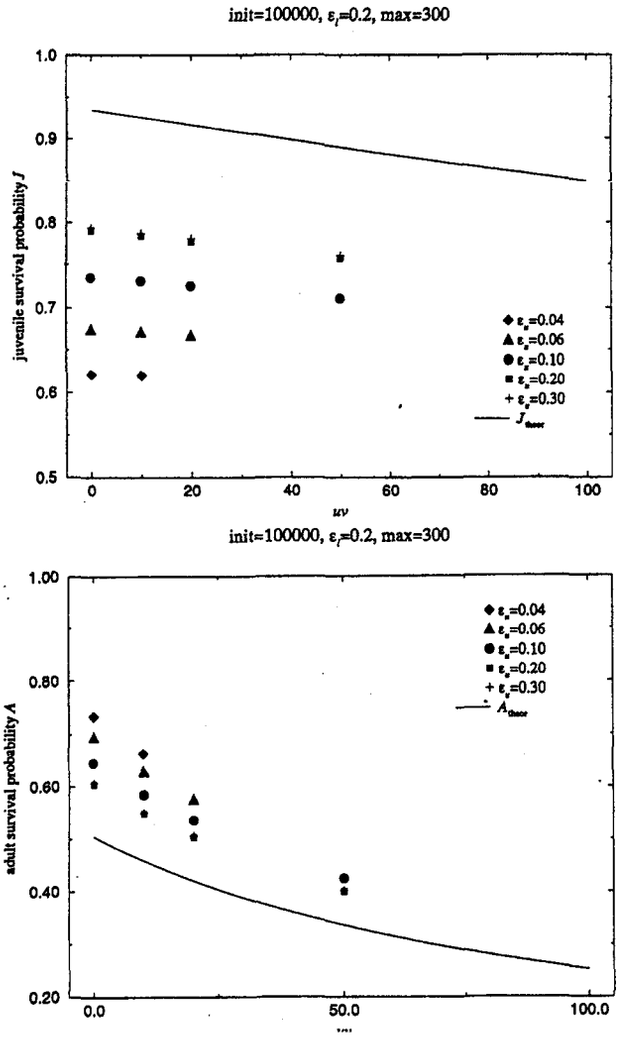

Figure 4: The Partridge-Barton model is now enlarged by hereditary mutations. We show the juvenile (part a) and adult (part b) survival rate as a function of somatic mutation rate for a balance of positive and negative hereditary mutations of strength ϵ_u and -0.1, respectively. The data sets end where the population decays to zero. From Vollmar[11]. The curves give approximation (4b).

In this case of heredity[10], Ray looked at the time dependence of the approach towards the stationary state[12]. With both a mean field theory and Monte Carlo simulations, he showed the approach to be proportional to the reciproca1 number of generations, i.e. to $1/t$. (The dominating effect during this relaxation is the narrowing in the distribution of survival rates, i.e. in the approach to the above-mentioned fixed point.) It is not clear at present if this lack of an exponential relaxation means self-organized criticality (i.e. adaption to the edge of chaos[13]). Ray's time-dependent theory thus can predict how our survival rates change after the escape of dinosaurs from Jurassic Park.

Inheritable mutations cannot be all bad if a species is to survive. Vollmar[11] thus studied a balance of positive mutations, distributed randomly in the interval $0 < \epsilon < \epsilon_U$, and negative mutations with $O > E > \epsilon_L$. Half of these new hereditary mutations are good, the others are bad for survival. The other aspects are taken over from refs. [10,12]: somatic mutations, fluctuations, and (2). Now the deviations from Eq.(4b) are much stronger, Fig. 4, and the effects of the hereditary mutations on A and J often have different signs.

Married men[14] are anxious, at least since Lorena Bobbitt, about Pacific salmon and death after sex. Already the Euler-Lotka equation, coupled with assumption (2), gives this effect: The adult survival rate A goes to zero if the exponent x goes to unity (Fig. 5). A mathematical exercise shows that for birth rates m equal to one, this Partridge-Barton model with Eqs.(1,2) and without fluctuations gives $A \propto x - 1$ apart from a logarithmic factor; for m > 1 it predicts $A \propto m^{1(x-1)}$. The fluctuation effects taken into account by Jan[14] then smooth out this sharp phase transition at x = 1; but still a survival rate of only five percent, as seen in Fig. 5, is very close to zero: catastrophic senescence[3].

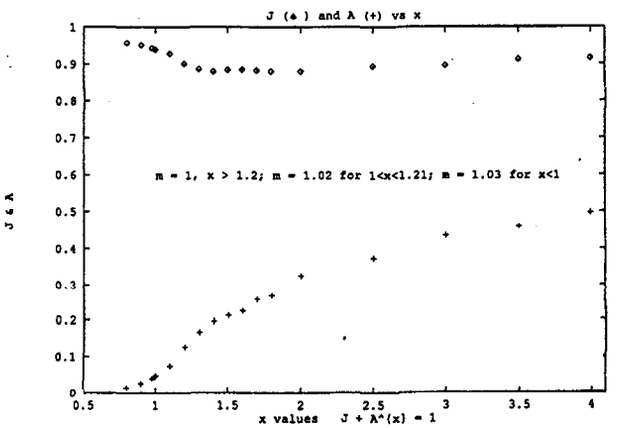

Figure 5: Catastrophic senescence for x near 1; reprinted from Jan[14] without permission. These simulations use the model of Fig.1 and decrease the exponent x of Eq.(2) below the Partridge-Barton value of 4.

V. Discussion

The first publication of Monte Carlo results for biological aging, as reviewed here, came out[12] only in 1994. Thus the whole field is still in its infancy. Computational techniques have been developed but at present computer power seems less than a problem than the choice of a correct model. If after years of discussion, experimental biology has not yet determined[7,8]

whether or not sex is dangerous to your health, simulations of complex aging models necessarily are much more speculative than in traditional physics. (Real life seems to be more complicated than a two-dimensional Ising model.)

Presently, techniques have been developed which made possible the simulation of systems as large as typical biological systems, a satisfactory solution compared with the frustrations of Statistical physics. Even the primitive models used here, with and without the antagonism of Eq.(2) between youth and old age, resulted in the expected senescence: Selforganization to an adult survival rate below the juvenile survival rate, due to mutations. No explanation yet has been given by these simulations why some species have catastrophic senescence ($A \to 0$) like Pacific salmon[3], whereas others, e.g. trees, can give offspring for numerous generations.

Even speculations like those presented here are not without dangers. Decades ago, eugenicists advocated forced sterilizations of humans with genes judged inferior. Typically, "inferior" were people outside the scientist's group; normally the scientist was a white male with European heritage. After Hitler came to power in Germany, such policies were implemented. Muller-Hill[16] has warned that such applications of genetic knowledge, not accidental creation of monsters out of flowers with genetically changed colors, are the real danger of genetics. Genetic computer simulations, with their easy and versatility, could in the future be misused to justify other forms of discriminations.

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