International Journal of Modern Physics C
Vol. 17, No. 6 (2006) 923–931

World Scientific
www.worldscientific.com

FLUCTUATIONS, ENVIRONMENT, MUTATIONS ACCUMULATION AND AGEING

PRZEMYSŁAW BIECEK and STANISŁAW CEBRAT

Department of Genomics, Institute of Genetics and Microbiology
Wrocław University, ul. Przybyszewskiego 63/77, 51-148 Wroclaw, Poland

Received 18 January 2006
Revised 27 January 2006

We present a model of evolution of the age structured population based on the Monte Carlo method. We have assumed that the health status of an individual is described by variance of its fluctuations. Each expressed deleterious mutation increases the fluctuations. Additionally, the fluctuations of the environment are superimposed on the fluctuations of individuals in the population. An individual dies if the combination of both stochastic processes trespass the limit (level of homeostasis) set as the model parameter.

The genes are switched on chronologically, what leads to accumulating defective genes expressed during the late periods of life in the genetic pool of the population. That results in the specific age structured population, in accordance with the predictions of Medawar's hypothesis of ageing and the results of the Penna model simulations. A decrease of the variation of the environmental noise increases the average expected lifespan of individuals.

Keywords: Ageing; mutation accumulation; fluctuations; environment.

1. Introduction

The best way to imagine how complex life systems are, is to look at the complexity of the simplest systems which are supposed to be even "nonliving" according to the definition of life. Bacteriophage lambda — a bacterial virus is an example of such a simple "nonliving creature". There are only a few genes and a few control sequences in the genome of this bacteriophage which are involved in one simple decision of a yes/no kind — to multiply in the bacterial cell or to integrate with its chromosome. If genetically identical bacterial cells from one clone are infected in one experimental tube (practically the same environment) by genetically identical bacteriophages, the fate of a bacteriophage in a particular cell seems to be totally random — in some cells bacteriophages enter the cycle of multiplication, in other cells they integrate with the chromosome and stay there for many cell generations (for review see Ref. 1). Some extremely subtle differences in the cell interior induce the different developmental decisions of the bacteriophages. It is like in Lorenz's butterfly and tornado.[2]

In the human organism there are thousands of genes and probably millions of their different products which interplay with each other, with a huge number of shorter or longer feedback regulatory loops and additionally all this is immersed in the very variable and unpredictable environment, including butterflies and tornados. Nevertheless, we are still alive. Most of biologists claim that it is possible due to a very peculiar property of living systems — homeostasis, a capability for staying in equilibrium or steady state. Physicists claim that living systems are rather far from equilibrium and the fluctuations of many physiological parameters describing the state of organisms are not regular, they are rather highly nonlinear, chaotic. Instead of homeostasis physicists prefer to use the term homeodynamics[3] or homeokinetics.[4] Moreover, transition from the nonlinearity and the loss of long range correlations in the fluctuation of the physiological parameters could be a diagnostic signal of a disorder or even a life threatening disease.[5,6] Such a shift from nonlinear behaviors to the regular ones is observed also in the case of genetically determined disorders, like the Huntington disease or ageing.[7]

On the other hand, one of the most widely accepted hypotheses of ageing assumes that ageing is caused by accumulation of defective genes in the genetic pool of populations.[14] Information coded by these genes would be indispensable for performing the life functions in the late periods of life of individuals. It is also possible that some genes could have pleiotropic effects and their functions could be important and correct during the earlier stages of life but deleterious in the old age. The Penna model using the Monte Carlo method predicts such an accumulation of defective genes in the genetic pool.[9] The main assumption of the model is chronological switching on of at least a fraction of genes of the individual's genome. The details of the Penna model and its achievements even in demographic studies were described in many reviews.[18,10,13] The other important parameter of the model is the number of genetic defects which an individual could survive. This parameter corresponds also to the relationships between the individual and the environment.[12,11] Under very opportune conditions, with a very good medical care, more genetic defects could be complemented and an individual could survive more expressed defects. Nevertheless, in the standard Penna model the environment stays invariable.

In our model we have implemented the idea of chronological switching on of some genes, but the effects of genetic defects are different. Individuals are characterized by their fluctuations which are superimposed on the fluctuation of the environment. Each expressed defect increases the variance of the individual's noise. As a result, we have obtained age structured populations, with corresponding structures of the genetic pool.

2. Model

The state of an organism is determined by the value of its fluctuation (described as stochastic process). Fluctuations of the individual (I) are sum of fluctuations of the environment (E) and the individual (P). We use Gaussian processes with discrete

time to describe fluctuations for individual i

$$I_i(t) = E(t) + P_i(t)\,, \tag{1}$$

$$E(t) \sim \mathcal{N}(0, \sigma_e^2)\,, \tag{2}$$

$$P_i(t) \sim \mathcal{N}(0, \sigma_i^2(t))\,. \tag{3}$$

Note that the environmental component of fluctuations is the same for all individuals, while personal components are different. If the sum of fluctuations of noises in a given individual trespasses the value of parameter $P_i(t) + E(t) \geq F$ the individual dies (F — like Fluctuation limit).

The genetic background of each organism is represented by a vector of genes $g_i = (g_{i,1} \cdots g_{i,L})$ (called bitstring) L bits long ($L = 32$), representing a haploid genome (in case of diploids — two bitstrings). There are two possible states for a gene j

$$g_{i,j} = \begin{cases} 0\,, & \text{denote that individual } i \text{ has a correct allele of gene } j\,, \\ 1\,, & \text{denote that individual } i \text{ has a defective allele of gene } j\,. \end{cases} \tag{4}$$

The number of consecutively switched on genes situated on the genome corresponds to the age of the organism. One gene is switched on every D time points (we interpret realizations of both process as states in consecutive months, we set $D = 12$ so one gene is switched on every one year). In case of the diploid, sexual model two alleles at the corresponding loci are switched on simultaneously.

The variation of the personal component $\sigma_i^2(t)$ depends on the genetic background of the organism. Each switched on defective gene (in the diploid model a locus with both defective alleles) increases the variation in following way

$$\sigma_i^2(t) = \sigma_0^2 + \sum_{j=1}^{\mathrm{age}(i,t)} g_{i,j}\sigma_d^2\,. \tag{5}$$

Thus, personal fluctuations can be composed of two components — the basic one and genetically determined.

When an individual survives R years it turns into the reproduction stage (minimum reproduction age $R = 8$). Then, in every year its genome replicates and produces B copies. Into each new copy mutations are introduced into the each bit with probability $p_{\mathrm{mut}} = M/L$. The mutation turns state of the gene $g_{i,j} = 0$ to $g_{i,j} = 1$, and state $g_{i,j} = 1$ is left $g_{i,j} = 1$ (in genetics it means that there are only harmful mutations, no reversions). These new genomes represent genetic backgrounds of new organisms. In diploid model, haplotypes recombine after mutations and one recombined haplotype of one organism play a role of gamete which form a complete genome by joining the second gamete produced by another organism at reproduction age.

As was mentioned before, the individual dies when the sum $E(t) + P_i(t) \geq F$. There are two other causes of death of an organism. The first one, if the organism

reaches the maximum lifespan which equals L years, and the second one is connected with the maximum capacity of the environment declared as $N_{\max}$. The surviving probability is described by the Verhulst factor $V = 1 - N_t/N_{\max}$.[21] This factor is set for the newborns only and in fact it additionally regulates the birth rate.

Thus, parameters describing states of individual E and P_i are

- L — the length (number of genes) of the genome (bitstring);
- F — the level of homeostasis;
- σ_d — the increase of variation caused by one defective gene;
- σ_0 — the base variation of the individual state;
- σ_e — the variation of the environmental state;
- D — the period of time needed to switch on next gene;

and genetic parameters describing the strategy of reproduction

- R — minimum reproduction age;
- M — mutational rate (the average number of mutations introduced in the new haplotype during replication or gamete production in the diploid model);
- B — number of offsprings produced in one year by an organism at the reproduction age (or female at the reproduction age);
- $N_{\max}$ — the maximal capacity of the environment;

In the diploid model another parameter is introduced — C corresponding to the frequency of recombination between the parental genomes. In the diploid model we have assumed that all defects are recessive which means that in one locus both genes have to be defective to determine deleterious phenotype.

In the Penna model there is an additional parameter T determining the minimum number of defects which kills the individuals. In our model this parameter corresponds to F.

3. Results and Discussion

We discuss the results of our simulations in the context of the standard Penna model which supports Medawar's mutation accumulation hypothesis of ageing.

Medawar's hypothesis assumes that organisms, like tubes in chemical laboratories, are eliminated randomly during their live. If they are replaced in the population by younger organisms, the fraction of older ones in the whole population diminishes with their age exponentially. Thus, their role in the reproduction potential of the whole population also diminishes to eventually become negligible — and, as a result, selection does not care about older examples in the populations and allows to accumulate deleterious mutations in the genes which could be indispensable for surviving the later periods of life. The Penna model, which assumes that genes are switched on chronologically, supports this hypothesis.[9] Nevertheless, it is not necessary to assume that organisms are eliminated randomly during their life, if there are some genes switched on chronologically after they reach the reproduction age,

the defects of the genes expressed in the later periods of life accumulate in their genomes even if there is no random death during lifespan.[16] In the Penna model the individual is represented only by its genome (bitstring (s)). If the number of expressed defective genes reaches the threshold T, set in the model as a parameter — the individual dies. If the Verhulst factor decides about the survival of newborns only, there is no random death during the rest of the whole lifespan in the Penna model. Thus, the fate of each individual is determined genetically only and can be anticipated at its birth. Instead of the threshold T parameter, in the presented model we have introduced the increase of energy of fluctuations caused by each switched on defective gene — individuals dies when the amplitude of the fluctuations trespasses the limit of their "homeostasis" set as parameter F. But such a death could happen randomly even for ideal genomes. That is why the life spans of the individuals can not be deterministically predicted at birth. The probability of random death depends on the energy of fluctuations which is composed of two components: the inner one and the fluctuation of the environment. Thus for a large time scale and large populations, the number of individuals even with ideal genomes would decrease exponentially with their age. But, the inner (personal) noise depends on the genetic status of the individual. If there are no expressed defective loci, the fluctuations are at the basic level — in this version of the model the same for all individuals in the population. Each switched on defective locus increases the energy of fluctuations and increase the probability of trespassing the limit of homeostasis.

In Fig. 1 an example of fluctuations during three consecutive years is shown. In this example, the individual would die at the 12th "month" of the second "year" if there was no environmental noise which saved it. The sum of personal and environmental noises kills the individual at the end of the third year.

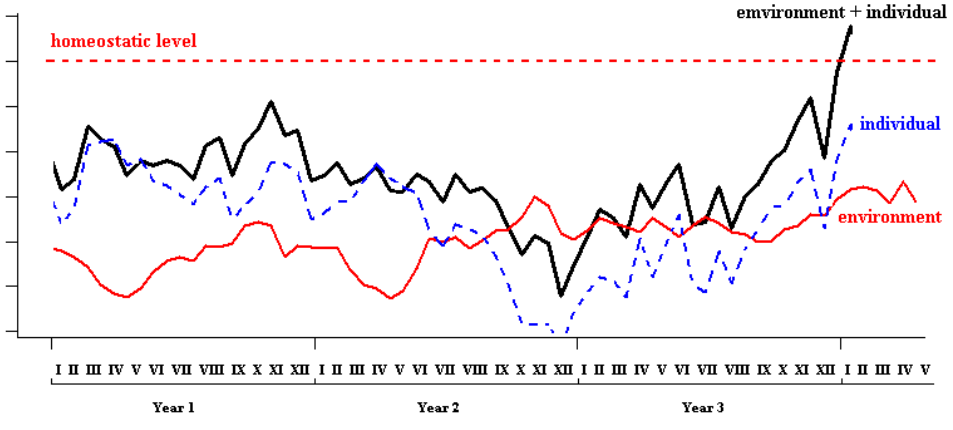

Fig. 1. Thin line presents the environmental fluctuations, dotted line presents the individual fluctuations and the sum of both fluctuations is presented as the bold line. When the bold line trespasses level F the individual dies.

Next three figures show the results of simulations with the standard Penna model and our model with three different sets of parameters describing the noise and mutation rate:

scenario 1: $\sigma_d^2 = 1$, $M = 0.33$;
scenario 2: $\sigma_d^2 = 1$, $M = 1$;
scenario 3: $\sigma_d^2 = 0.7$, $M = 1$.

In Fig. 2 the age distributions of populations evolved under the parameters described in the figure's footnote are shown. The distribution resembles both, the age distribution of human populations (not shown) and the results of simulations in the standard Penna model. Nevertheless, there are some differences between the standard Penna model and a new one. It is better seen in the Fig. 3, where the mortality is shown. According to the Gompertz law,[17] the mortality in natural populations grows exponentially with age. Thus, if y-axis, showing the fraction of individuals dying in a given age is in the logarithmic scale, the curve describing the mortality with age is linear. In the standard Penna model, if Verhulst factor regulates the size of the population only at the level of birth, there are no random

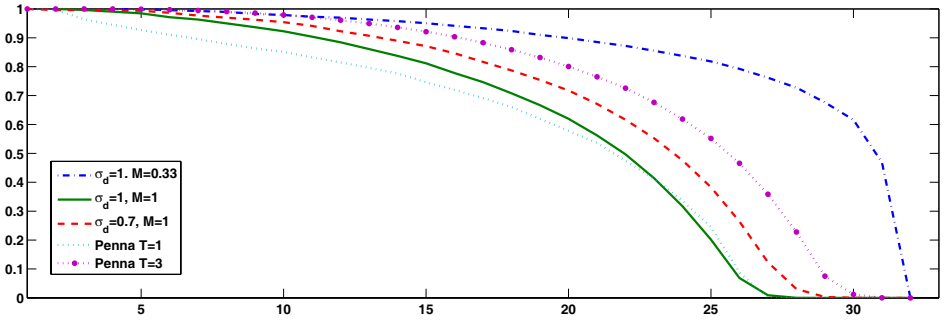

Fig. 2. The age distribution for three simulated scenarios and Penna model with $T = 1$ and $T = 3$).

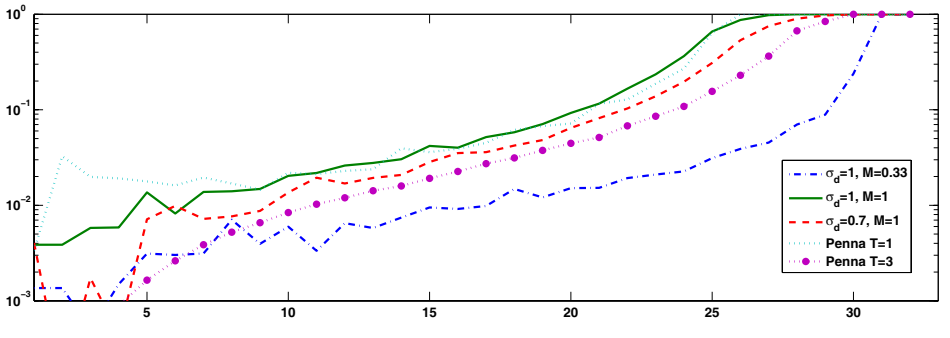

Fig. 3. The Gompertz (mortality) curve for three simulated scenarios and Penna model with $T = 1$ and $T = 3$).

deaths later, the mortality curve is in fact of s-shape with very low death rate for the youngest (in fact no death of individuals younger than T) and the mortality rate above the Gompertz law prediction for the last parts of the lifespan. In our model the shape of the mortality curve changes. Even the youngest organism may die, and the results of simulations better fit to the real mortality curve of human populations, even for the oldest part of populations some downward deviation of mortality in comparison with the Gompertz law is observed. This deviation, called plateau, is controversial and according to Stauffer[18] it is a result of imperfect demographic data available for the oldest parts of the human populations (nowadays it concerns data from the end of nineteenth century).[24]

Nevertheless, if the heterogeneity of populations is generated by introducing specific parameters into the Penna model, the downward deviation from the Gompertz law prediction for the oldest could be obtained in the computer simulated populations.[22,23] There is another important difference in results between the standard Penna model and our model. One of the critics of the Penna model was that this model predicts simultaneous death (or exactly the same lifespan) of individuals in clones, in inbreaded populations or twins, which obviously is not true.[25] In our model such determinism disappears. The moment of death is a result of random fluctuations of individuals, the environmental ones and interplay of the two.

In Fig. 4 the distribution of defective genes in the genetic pool of the population is shown. It is in agreement with both Medawar's hypothesis and the standard Penna model predictions. The fraction of defective genes expressed before the reproduction age is low, these genes are under strong selection and individuals with defects in these genes are mostly eliminated — they do not reach the reproduction age and these defects cannot be passed to the offspring. Defects expressed later, after the carrier organisms reached their reproduction age can be transferred to the offspring and inherited. That is why we observe the growing fraction of defective genes with age at which they are expressed. It is also observed in the standard Penna model. But in the standard Penna model the first gene which in the genetic pool is set for one in all genomes determines the maximum lifespan in this

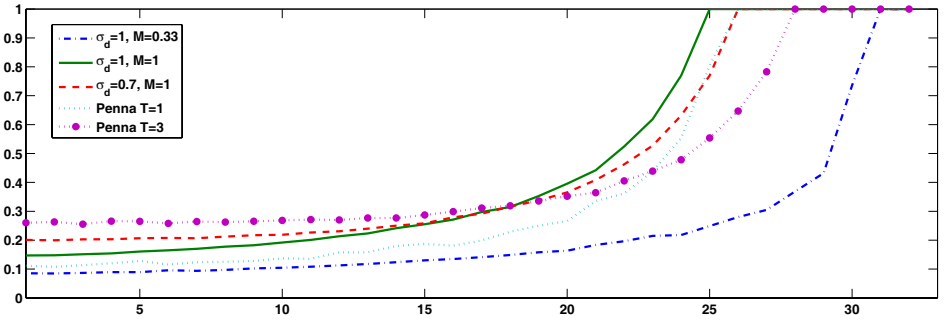

Fig. 4. The frequency of defective allels three simulated scenarios and Penna model with $T = 1$ and $T = 3$).

population. All loci switched on later in all genomes are also defective and they determine the reaching the threshold T in the next few steps. In our model the first locus in which all genes in the populations are defective does not deterministically indicate the maximum lifespan.

The main difference between the Penna model and the model presented here is the role of the environment. In the Penna model the environment is invariant. There have been only a few attempts to introduce the changing environment by declaring the probability of switching the demands for single loci. In our model, the environment is characterized by its own noise. The noise of the environment is superimposed on the noise of each individual in the population but it doesn't mean that individuals react in the same way. For some this noise could be death threatening while other individuals could be even saved by the environment fluctuations (the example presented in Fig. 1). In the standard Penna model, the differences between independent simulations are statistically negligible and sometimes such differences could be discovered only if the populations were forced to compete in one environment.[19] Fluctuations of the environment influence the age structure of populations causing significant differences even in the size of populations (try simulations at `http://neuron.im.pwr.wroc.pl/Aging/` (you need java to run this applet)).

A dozen years ago, Lipsitz and Goldberger Ref. 8 suggested that ageing is associated with a loss of complexity in a variety of physiological processes. In the presented model, we have used only a substitute of noise — a randomly distributed amplitude of fluctuations with a constant frequency. It is like summing up the amplitudes of white noise for a constant periods (here for 1/12 of MCS). The basic energy of fluctuations of each organism in the population is the same and constant for its whole life — the effects of the environment and effects of genetic defects are superimposed on this basic individual noise but there are still no factors introducing long range correlations into this fluctuations. In fact there is no inheritance of any parameter of the individual's basic noise. We plan to introduce some memory into the system, which will allow it to adapt (i.e., immunological system during the history of one individual's life) and to evolve (in evolutionary scale of populations or species), respecting the changes of the environment. Another prospect is to replace the total individual noise by the sum of noises generated by individual functions of living organisms, determined genetically. Thus, synchronization of the noise of individual function would increase the probability of trespassing the limit of "homeostasis".

References

1. H. Echols, *Trends in Genetics* **2**, 26 (1986).
2. J. Gleick, *Chaos* (Viking Press, New York, 1987).
3. F. E. Yates, *J. Cyber. Info. Sci.* **2**, 57 (1979).
4. H. Sodak and A. S. Iberall, *Science* **201**, 579 (1987).

5. C.-K. Peng, J. Mietus, J. M. Hausdorff, S. Havlin, H. E. Stanley and A. L. Goldberger, *Phys. Rev. Lett.* **70**, 1343 (1993).
6. A. L. Goldberger, L. Findley, M. J. Blackburn and A. J. Mandell, *Am Heart J.* **107**, 612 (1984).
7. L. A. Lipsitz, *J. Gerentol.* **57A**, B115 (2002).
8. L. A. Lipsitz and A. L. Goldberger, *JAMA* **267**, 1806 (1992).
9. T. J. P. Penna, *J. Stat. Phys.* **78**, 1629 (1995).
10. A. Łaszkiewicz and S. Cebrat, *J. Insurance Medicine* **37**, 3 (2005).
11. P. M. C. de Oliveira, S. M. de Oliveira, D. Stauffer and S. Cebrat, *Physica A* **273**, 145 (1999).
12. E. Niewczas, S. Cebrat and D. Stauffer, *Theory in Biosciences* **119**, 122 (2000).
13. M. Kowalczuk, A. Łaszkiewicz, M. Dudkiewicz, P. Mackiewicz, D. Mackiewicz, N. Polak, K. Smolarczyk, J. Banaszak, M. R. Dudek and S. Cebrat, *Trends in Stat. Phys.* **4**, 29 (2004).
14. P. B. Medawar, *An Unsolved Problem of Biology, an Inaugural Lecture Delivered at University College London* (H. K. Lewis & Co. Ltd., London, 1952).
15. A. Sousa and S. M. de Oliveira, *Physica A* **294**, 431 (2001).
16. J. S. SaMartins and S. Cebrat, *Theory in Biosciences* **119**, 156 (2000).
17. B. Gompertz, *Philosophical Trans. Royal Soc. London* **115**, 513 (1825).
18. D. Stauffer, S. M. de Oliveira, P. M. C. de Oliveira and J. S. Sa Martins, *Biology, Sociology, Geology by Computational Physicists* (Elsevier, Amsterdam, 2006).
19. A. Łaszkiewicz, E. Niewczas, Sz. Szymczak, A. Kurdziel and S. Cebrat, *Int. J. Mod. Phys. C* **13**, 967 (2002).
20. S. Cebrat and D. Stauffer, *Theory in Biosciences* **123**, 235 (2005).
21. P.-F. Verhulst, *Mem. Acad. Royale Belg.* **20**, 1 (1845).
22. J. Coe, Y. Mao and M. Cates, *Phys. Rev. Lett.* **89**, 2881041 (2002).
23. A. Łaszkiewicz, Sz. Szymczak and S. Cebrat, *Int. J. Mod. Phys. C* **14**, 1355 (2003).
24. L. A. Gavrilov and N. S. Gavrilova, *Newsletter of American Aging Association* **4**, 6 (2005).
25. S. D. Pletcher and C. Neuhauser, *Int. J. Mod. Phys. C* **11**, 525 (2000).