ELSEVIER

Physica A 258 (1998) 493–498

PHYSICA A

Penna model from the perspective of one geneticist

Stanisław Cebrat *

Department of Genetics, Institute of Microbiology, Wrocław University, ul. Przybyszewskiego 63 50-204 Wrocław, Poland

Received 23 October 1997

Abstract

Penna model of ageing predicts many phenomena in population dynamics. Since the model assumes that all genes in genomes are switched on chronologically and that there are no structural differences between male and female genomes, it cannot explain genetic death before birth and differences in mortality rates of men and women. I suggest adding the set of housekeeping genes, which are switched on during the embryo development, to the "death genes" of Penna model. Taking into account the large fraction of genes located on X chromosome whose deleterious mutations exert dominant effect on the male phenotype and recessive on the female phenotype would make it possible to avoid introducing somatic mutations as a cause of higher mortality of men. The modelling of linkage disequilibrium and its implications on eugenics have also been suggested. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Ageing; Death genes; Linkage disequilibrium; Penna model

1. Introduction

People have always been interested in the problem of ageing. Probably not only because of this slim figure of a young man which has a tendency to be deformed by the belly of the older one as Stauffer has noted [1] but because of death which inevitably strikes each human being. There are extremely rare examples of getting immortality – always for extraordinary merits, like Frodo, who was allowed to go to Valinor – a country of immortal beings, as documented by Tolkien [2]. What is worse, I am not sure if the example of Frodo could apply to man because Frodo was a hobbit. It seems then, that people should join their efforts to understand ageing to cope with this malicious natural phenomenon. Unfortunately, it is not the case. Physicists have been working on the Penna model of ageing [3,4] for a few years and not a single

* Tel.: +48.71 324 7303; fax: +48.71 325 2151; e-mail: cebrat@angband.microb.uni.wroc.pl.

0378-4371/98/$19.00 Copyright © 1998 Elsevier Science B.V. All rights reserved.
PII: S0378-4371(98)00246-5

biologist has tried to understand it and to publish criticism. I have decided to be a traitor and to read the papers on the Penna model and even to try to understand them. Since I am a geneticist, I have looked at the model from the very narrow perspective of genetics. I would like to encourage other biologists, especially evolutionists, to devote some time to compare the assumptions and the predictions of the model with real life.

The assumptions of the model are very simple. Each individual in the population is described by a bit string of length n. Each bit represents a gene which has a value 0 if it is a functional allele or can be set for 1, if it is a bad allele. A good (wild) allele can mutate with mutation rate m becoming the bad allele but there are no reverse mutations – an allele already set for 1, if mutated – stays mutated. When an organism reaches the fertility age of F years it gives b offspring each year. The offspring inherits the bits set in parental genome and gets a new mutation in a random position. An individual at the age of a feels each bad mutation (set for 1) in bit positions $\leqslant a$. If it feels at least T bad mutations it dies. Since the length of the bit string also determines the maximal life span of individuals, an individual must die at the age of n anyway. Any individual can also die with probability $Nt/N\,max$ where Nt is the current number of individuals in the population and $N\,max$ is the maximal capacity of the environment. In other words, in this model each individual possesses a genome with as many loci as the maximal life span and genes are switched on chronologically, one gene per time unit in the preestablished order (as they are ordered in the bit string).

An organism can be haploid, and then it possesses a single bit string and can reproduce asexually. But the model can easily predict the results of sexual or asexual reproduction of diploid organisms. The simulation of sexual reproduction according to the Penna model proves that Nature invented the sexual reproduction because of its higher efficiency [5]. The previous model of Redfield [6] was not able to find the advantage of the sexual reproduction.

The Penna model has a lot of modifications which allow, according to the authors, simulations of different populations (for review see Moss de Oliveira, de Oliveira and Stauffer [7]). I want to criticise some of the assumptions of the original model and its modifications with the hope that physicists will immediately find the appropriate solution to the problem – if I am right. I hope that I will not be the only traitor from the biology discipline who will help to build the ageing model on the foundation set by physicists.

2. The genes get switched on chronologically

One of the main assumptions of the model is that all genes in the genome are switched on chronologically. That means that if the maximum life span of an organism is 64 years, then only 1/64 part of the genome is switched on in the first year and then each year a fraction of the genome of the same size is switched on. It is not explicitly said that all the genes switched on during life stay active and are indispensable until the end of life, but in fact there is such an assumption in the model. In one modification of

the model for the explanation of the "oldest old effect" it was assumed that organisms feel bad mutations expressed only in the last K years.

The authors claim that the model predicts the mortality rate or age distribution of people in the German population very well [8]. In my opinion, it could be true only for the part of population which has already reached the reproduction age. This model does not predict the genetic death during the first period of embryo development. It has been estimated that at least 60% of human embryos die before birth [9]. Even if we assume that a fraction of embryos dies in peri-implantational period because of some "non-genetic causes", we have to accept that about 50% of embryos have to die because of genetic defects. Defects in the small fraction of genes switched on chronologically cannot explain the phenomenon of zygotic death and actually contradict this effect – the frequency of bad mutations in the genes switched on early is the lowest in the population, according to the model. Many genes, perhaps even most genes of the genome are necessary during the first periods of embryo development and during the tissue differentiation. Many genes are switched on temporarily during a specific period of development and some are adaptive, switched on only under specific environmental conditions. Geneticists call some genes the housekeeping genes to stress that these genes are necessary to run all indispensable functions of each living cell to keep it alive. Many mutations causing the death of embryos occur in this class of genes controlling the basic cellular functions (see Copp for review [9]). For our purpose we can call all the genes which are necessary during the whole life of man, even if switched on only in some tissues, the *housekeeping genes*. The genes which are taken into consideration by the Penna model could be called *death genes*. These genes can kill a human being when their bad alleles are switched on, but contrary to the housekeeping genes, the death genes are switched on only at specific age. If we assume that death genes form only a small fraction of the genome and that the rest of genes are necessary to run the developing programme from the very beginning of a living organism, we can get the prediction of the genetic death as the result. We should assume such a mutation rate for housekeeping genes which would be balanced by the frequency of genetic death eliminating these mutations. Muller [10] estimated the frequency of deleterious mutations in the human population for 0.1–0.2 per haploid genome per generation, corresponding to the genetic death nearly 0.2–0.4. Assuming that about 60% of human beings are eliminated by genetic death, this mutation rate should be even higher.

3. Why women live longer than men or somatic mutation story

Men are anxious about the fact that women live longer than they do and that they cannot take care of their wives for as long as they would like to. It seems that the best way to solve the problem is to understand it. Moss de Oliveira, de Oliveira and Stauffer [11] and Penna and Stauffer [8] have tried to solve the problem by introducing somatic mutations into the model. Somatic mutations affect only genes in the genomes

of somatic cells. Heritable mutations affect genes located in the genomes of gametes. But gametes are produced only by very specific, small cell lines! All the rest of the huge number of cells of a living man – somatic cells (of the order of 10^{12}) are not able to contribute to the status of germ cells genomes. If anything happens to the genomes of somatic cells, it cannot be transferred to germ cells, at least with a reasonable probability. But sometimes, even one somatic mutation in one somatic cell can kill the whole organism. Moss de Oliveira, de Oliveira and Stauffer [11] and Penna and Stauffer [8] assumed that higher frequency of those somatic mutations is responsible for the higher mortality rate of men than women. Heritable mutation in the germ cell is transferred to the embryo and could affect each cell of the new organism because it will be present in each cell of this organism.

The effect of somatic mutations is quite different. Usually it affects only the somatic cell whose genome had been mutated. If the mutation has affected a housekeeping gene – the cell will be killed, probably by apoptosis and replaced by a new cell. These mutations will not be seen by the organism as long as the regeneration processes can replace the dead cells or the rest of cells in the tissue can fulfill their functions. Genetic programmes for killing mutated cells or cells which are not well prepared for their role in the organism (for example in the immunological system) are very sophisticated. Nevertheless, there is a very important class of mutations which fit to the model assumptions: mutations in oncogenes. Those mutations are of the "gain of the function" type. They do not kill the cell, instead, they can give the cell a selective advantage which can lead to cancer development and death of the whole organism. Even recessive mutations of the class "loss of the function" in anti-oncogenes (suppressors) can kill the organism if followed by "loss of heterozygosity". It is also possible that some prior diseases are caused by spontaneous somatic mutations. If we assume that all the diseases caused by the mutations mentioned above are responsible for the observed differences in man versus woman mortality, then the assumptions about the role of somatic mutations could be correct. If not, then we have to modify the model to cope with the accumulation of somatic mutations in cells or accumulation of cells with somatic mutations and something like genetic meltdown of the soma. But this would not be the Penna model. Probably, we can avoid the problem of the different rate of somatic mutations if we consider the influence of X chromosome in man and woman genomes on their phenotypes. Women possess two copies of X chromosome and men only one copy. The X chromosome is quite big and there are a lot of genes localised on it. To simplify our estimations let us assume that:

- X chromosome represents 10% of all genetic information of our genome;
- 10% of all mutated genes are dominant and the rest are recessive;

then: if we assume that there are about 100 000 genes in our genomes (probably much less) – the woman in her genome possesses 10 000 loci which, when mutated, could be dominant. Man possesses in his autosomes (chromosome other than X and Y) 90 000 genes. Ten percent of these genes (9000) could be dominant when mutated. Additionally, 10 000 loci in X chromosome would affect the male phenotype like dominant because they could not be balanced by alleles in the homologous chromosome – any

mutation in these loci could be deleterious for man phenotype. This explanation needs less unproved assumptions than the one with somatic mutations. The effect of single X chromosome in man's genome could explain the Penna model's prediction that the ratio of male to female mortality is going down towards unity for old age as observed in reality. The Penna model predicts that the mutations accumulate in the genes expressed after the reproduction period. If there are 100% of bad alleles (set for 1) at the end of the bit string, the differences between the effect of recessive and dominant defects disappear.

4. The effect of the environment

As I have already mentioned, the authors of the Penna model claim that the model predicts very well the mortality rate or age distribution of German population [8]. But the plots of the mortality rate for the same population a few generations back show that the distribution of age was different [12]. Both plots obey the Gompertz's law but grand-grand-parents of contemporary living people lived shorter. Genetic difference between populations separated by only a few generations is not big enough to explain this phenomenon. It is necessary to introduce the influence of environment into the model. There is a hidden influence of environment on the individual surviving in the Penna model – bad mutations are killing the individual. What is a bad mutation? It is the mutation which diminishes the fitness of the organism – the organism does not fit in its environment any more. If the model does not predict any change of the environment – after many generations the populations will get to the steady state. The role of mutation rate is not the same as the role of changes in the environment. Mutation changes only the fitness of the organism in whose genome it has happened. Change in the environment conditions touches all organisms living in that environment. These changes can shift populations far from the equilibrium state and, in fact, the populations simulated by the model have to pursue the environment. The results of modelling of the environmental influence on the genome structure and genetic pools of populations could explain the linkage disequilibrium or even address some eugenic problems.

5. Penna model and eugenics

Let us assume that there are three different linked loci A, B and C in a haplotype and the environmental conditions have been eliminating bad mutations (set for 1) in all these loci for long time (linkage is a measure of the degree to which alleles of two genes assort independently after recombination). Thus, most of these loci in the population are set for 0. Let us assume that the environment changes in such a way that locus A set for 0 is now a deleterious recessive allele and it will be eliminated from the genetic pool by the genetic death of diploids. But we are living in a better world now and geneticists could help the Nature and diminish reproduction of not only

homozygotes but of heterozygotes, too – by the genetic counselling, by some economical pressure via insurance companies or just by using the presymptomatic diagnosis performed on the embryo in the tube followed by a "good embryo implantation". What will be the result? Probably the elimination of the heterozygotes with deleterious *A* gene would eliminate good alleles in loci *B* and *C* with much higher frequency than expected. It seems, that after some time, the recombination processes would separate wild genes *B* and *C* from deleterious loci *A*. Modelling this effect would be possible after introducing the housekeeping genes to the Penna model. In the recent model, genetic linkage is predetermined by the order of genes in the bit string, which has no biological explanation. The conclusion could be: if we have no idea how far from the equilibrium the population is, we have to be very careful in using any eugenic methods.

Do we know where we are?

Acknowledgements

I would like to thank Dietrich Stauffer for long discussions which have helped me to understand not only the Penna model but the physicist's language, too.

This work was supported by a Wrocław University grant number 2027/W/97.

References

[1] D. Stauffer, Comput. Phys. 10 (1996) 341.
[2] J.R.R. Tolkien, The Silmarillion, George Allen and Unwin, London 1997.
[3] T.J.P. Penna, J. Stat. Phys. 78 (1995) 1629.
[4] T.J.P. Penna, D. Stauffer, Int. J. Mod. Phys. C 6 (1995) 233.
[5] D. Stauffer, P.M.C. de Oliveira, S.M. Moss de Oliveira, R.M. Zorzennon dos Santos, Physica A 231 (1996) 504.
[6] R.J. Redfield, Nature 369 (1994) 145.
[7] S. Moss de Oliveira, P.M.C. de Oliveira, D. Stauffer, Sex, Money, War and Computers, Springer Lecture Notes in Computational Science and Engineering, Springer, Berlin, 1998.
[8] T.J.P. Penna, D. Stauffer, Zeits. Phys. B 101 (1996) 469.
[9] A.J. Copp, Trends Genet. 11 (1995) 87.
[10] H.J. Muller, Acta Genetica et Statistica Medica 6 (1956) 157.
[11] S. Moss de Oliveira, P.M.C. de Oliveira, D. Stauffer, Braz. J. Phys. 26 (1996) 626.
[12] M.Ya. Azbel, Proc. Roy. Soc. London B 263 (1996) 1449.