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The Influence of the Medical Care on the Human Life Expectancy in 20th Century and the Penna Ageing Model

E. Niewczas[1], S. Cebrat[1] and D. Stauffer[2]

[1]Institute of Microbiology, University of Wrocław, Wrocław, Poland
[2]Institute for Theoretical Physics, Cologne University, Köln, Euroland

Address for correspondence: E. Niewczas, Institute of Microbiology, University of Wrocław, ul. Przybyszewskiego 63/77, PL-54148 Wrocław, Poland

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Summary: The expression of many genetic defects may be suppressed by proper medical care or even by changing the environmental conditions. We have used the Penna model of ageing to show that such efFects may be responsible for increasing the human life expectancy during the 20th century. This effect is equivalent to the shift of the threshold (T) in the Penna model, which determines how many deleterious, expressed mutations kill an organism. For long genomes, the shift of T changes the age distribution significantly with negligible relative changes in the maximum life span, while for short genomes, the shift of T changes both, the age distribution as well as the maximum age. Unfortunately the same simulations show that the strategy of enhancing the medical care requires more and more effort to keep the mortality rate of our populations at the same lower level and that some new defects could be exposed to selection.

1. Introduction

The Penna model of ageing, invented in 1994 by Penna [1], has been used for simulating many phenomena relevant to population dynamics. It may be used for simulating the evolution of populations of haploid organisms as well as diploids, exploiting asexual or sexual strategies of reproduction [2, 3]. It also predicts the differences between male and female mortality caused by the genes located on X chromosome [4]. The main assumption of the Penna model is that genes are switched on chronologically and, in the classical version of this model, the number of genes switched on grows linearly with the age of an individual. Furthermore, the sequence of genes switched on corresponds strictly to the linkage map of the genome, the

first gene in the genome is switched on in the first step (first year of life), the second in the next and so on. Many studies of populations using Penna model have been done with short genomes of 32 or 64 bits (read genes) because simulations on such genomes are fast and do not need fast computers. Results of these studies describe the phenomena of natural populations quite well, especially the age structure of populations. To fit the results of simulations to the statistics of real populations, for example the human one, it is necessary to assume some input parameters, like mutation rate, minimum reproduction age and/or menopause and birth rate, and next to rescale the results for fitting the maximum age of simulated population to the demographic data. Usually these methods give satisfying results [5].

To avoid the exponential growth of the population, the Verhulst factor is introduced. In the classical version of the model the Verhulst factor $N_t/N_{\max}$ kills individuals independently of their genetic structures with the same probability (N_t – is the size of population in the t – step and $N_{\max}$ is the carrying capacity of the environment). Thus, the Penna model is a strictly genetic one – after subtracting individuals killed because of Verhulst factor, all other individuals are killed by genetic diseases. Usually, the bad genes accumulated at the end of the genomes are not even tested by natural selection in the individuals living in the populations in equilibrium because of their earlier death. People die at different times because their genomes are not identical; the model does not work well for a population of clones etc [6]. Similar ideas, but without a bit-string representing the genome, were implemented in other Monte Carlo simulations [7].

In the Penna model, the non-random distribution of damaged genes along the genomes of individuals determines the age distribution of the population. The structure of the human genetic pool could not change during the last two hundred years significantly enough to justify the observed prolongation of the average life span. Thus, the Penna model, being based on genetics, should be able to explain which factors have been responsible for the changes in human life expectancy during that time. This problem has been already addressed by de Oliveira et al. [8]. In the standard Penna model an individual dies when T damaged genes are switched on. Ref. [8] had assumed that this is true only in the optimal condition – (read: our beautiful times). In worse conditions, the number of damaged genes killing individuals could be reduced with an assumed probability. That seems to be a reasonable approach. There are examples of the influence of medical care on the survival of people touched with a genetic disorder. Children with cystic fibrosis can live longer due to antibiotic therapy and the life expectancy of people with Down Syndrome has increased significantly during the last 50 years. In this approach, the position of damaged genes in the bit string determines the maximal age at which they are switched on, assuming that the population lives in the optimal environmental condi-

tions including medical care. Worse conditions cause higher probability of earlier switching on the damaged genes.
In some instances, proper medical care may significantly prolong the life span of patients or even produce a phenocopy – a person with a phenotype of a healthy one as in the case of curing the phenylketonuria or hemophilia. There are a lot of examples of diseases which are caused by genetic defects which do not kill inevitably but enhance the probability of the onset of the disorder, for example cancers which may be promoted by inherited defects in suppressors of oncogenes (antioncogenes). In some instances these defects will never kill their carriers and these people will die because of other ageing processes, also genetically determined.
Demographic studies [9] of the human population of the last two centuries have shown that life expectancy has grown significantly while the maximum observed age has changed less spectacularly. The mutational load of the human genetic pool could not have changed so significantly during the last few generations as to explain the observed growth in our life expectancy. In this paper we have assumed that the proper medical care, diet and more hygienic life style may produce phenocopies mimicking that some defects connected with our susceptibilities to some diseases or infections are just eliminated from the genetic pool. In the Penna model language that means, that the threshold of bad mutations killing the individual should be shifted to higher numbers. The prolonged life span is caused mainly but not exclusively by the lower mortality of children and people at the reproduction age.

2. Model

The equilibrium has been reached for three diploid, sexually reproducing populations:

1. Length of the bit string – 32, mutation rate – 1 per genome replication, one recombination per replication, minimum reproduction age – 10, 15 or 20, maximum reproduction age not set, $T = 3$ or as stated in the results section. Each female of reproductive age gives birth to one offspring per time step.
2. Length of the bit string 640, mutation rate – 1 per genome replication, three recombination events per replication, minimum reproduction age – 460, maximum reproduction age not set, women at the reproduction age can produce one offspring every eighth time unit with a randomly chosen man, T = 3. (The first 400 bits correspond to "housekeeping" genes activated before birth.)
3. The same as population 2 but every tenth gene on the genome is supposed to lie on the X chromosome which means that any of these genes, if defect, is deleterious (dominant like) for men and recessive for women.

There were no dominant loci in these genomes. To avoid the exponential growth of the population, we have introduced the Verhulst factor limiting the birth rate (killing zygotes at the conception) with the probability N_t/N_{max}. N_t is the number of people at step t. N_{max} has been set for 20 000. After the populations have reached the equilibrium with the parameter $T = 3$, their age structure is counted by averaging over 1 000 steps. Then, the T parameter for the same population was changed to 5 and the populations have been allowed to evolve for different number of steps as described in the results section.

3. Results and discussion

After 10^5 steps, populations of individuals with 32-bit genome have been already at equilibrium. Populations with 640 bit strings reached the equilibrium after $1.5 \cdot 10^7$ steps. Fig. 1 shows good agreement between simulated and real survival probabilities. In Fig. 2 the distributions of the damaged genes in all the populations are shown. Note that the fraction of damaged genes in the part of genomes switched on before the reproduction age in case of the long genomes is much lower than in the short ones. That is ob-

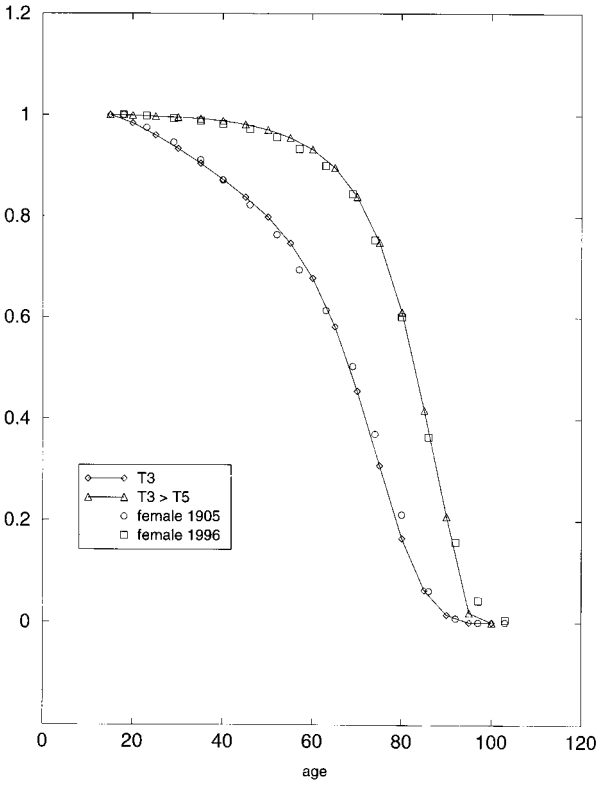

Fig. 1. Comparison of computer simulations with real survival probabilities from German life tables. The end of the 20th century was simulated by shifting the threshold T upwards, as indicated in the figure. We fitted the time scale such that at the minimum age of reproduction and at the maximum age of 100 years the probabilities agreed.

vious, since more loci are tested by selection before the reproduction age is reached by individuals with long genomes. With the fraction of damaged genes as in the case of 32-bit genome and the same threshold T, the probability of reaching the reproduction age by individuals with long genomes

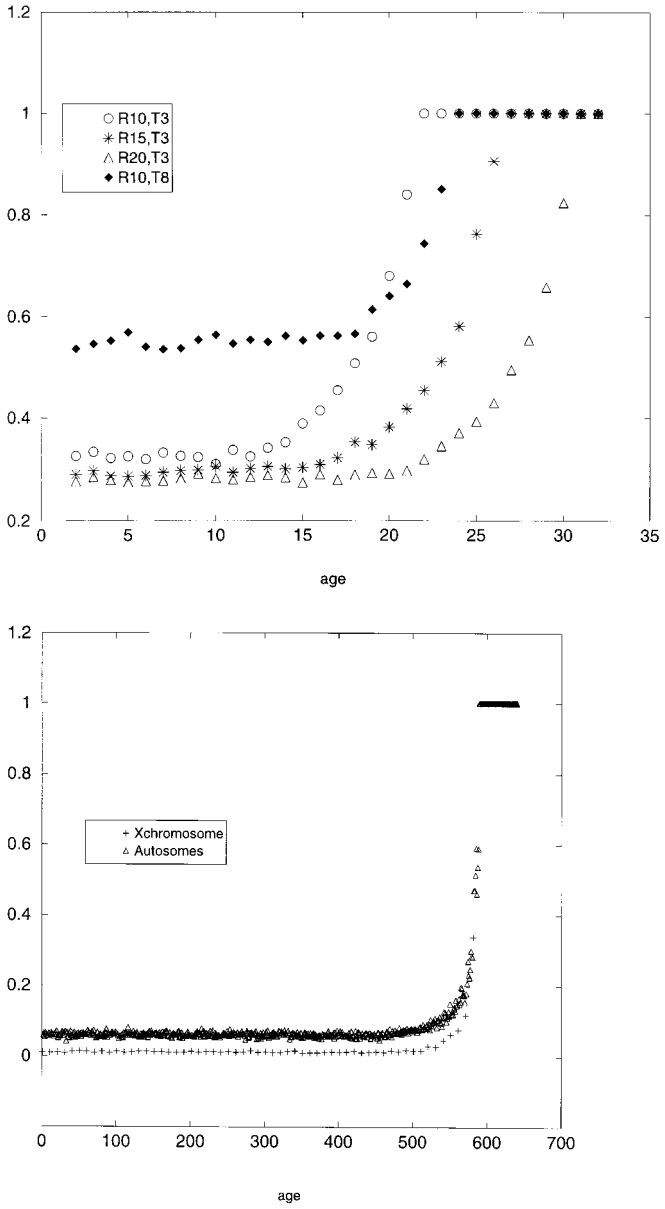

Fig. 2. Fractions of damaged genes in relation to the number of genes switched on before the reproduction age. Upper plots: genomes 32 bits long with different minimum reproduction age R, $T = 3$, one simulation for $T = 8$. Lower plots for simulations the populations with 640 bits long genome, minimum reproduction age at step 460; genomes with X chromosomes.

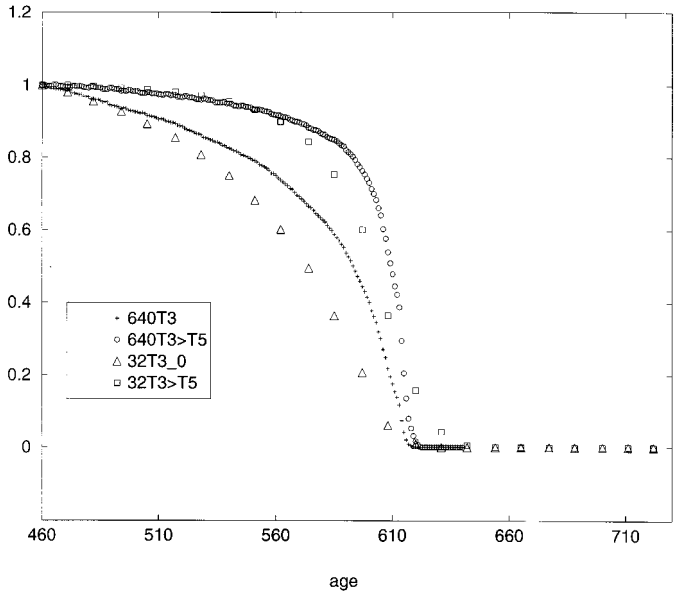

Fig. 3. Curves of survivors for simulations with 32 bit strings, $R = 10$ and for 640 bit strings (model 2). The results were re-scaled to fit the length of the period of life between the minimum reproduction age and the maximum age for the simulations with $T = 3$.

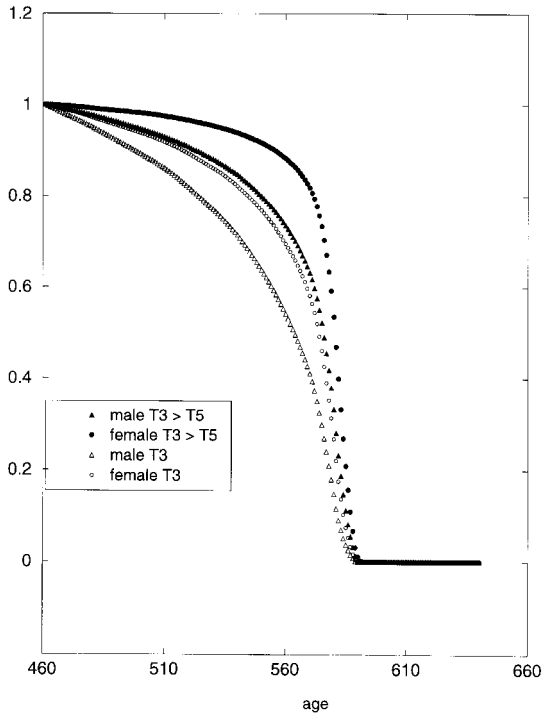

Fig. 4. The effect of the shift of the threshold from 3 to 5 in the model with X chromosomes.

would be negligible and the population would die. This effect is already visible with the 32 bit string model with different minimum reproduction age.

In Fig. 3 we have shown the effect of T shift from 3 to 5 in populations in equilibrium. In this figure we have rescaled the results of simulations for the long genomes and for the short ones, fitting the survivor curves according to the minimum reproduction age and the maximum age for populations in the equilibrium at $T = 3$. When increasing the threshold T in the populations with short genomes, the effect of increasing the maximum age is distinct. Nevertheless, the change in the shape of the survivor curve is also visible. In the case of the populations with long genomes the effect of the relative shift of the maximum age is negligible, but the curve describing the age distribution changes significantly.

We have also simulated this effect with sex determined by X and Y chromosomes (model 3, Fig. 4). In this model, every tenth gene has been declared to be situated on the X chromosome. With the set of parameters used for modelling, the curve of age distribution for women living in worse conditions fits very well the curve of men living in better conditions, suggesting that the effect of T shift, mimicking the

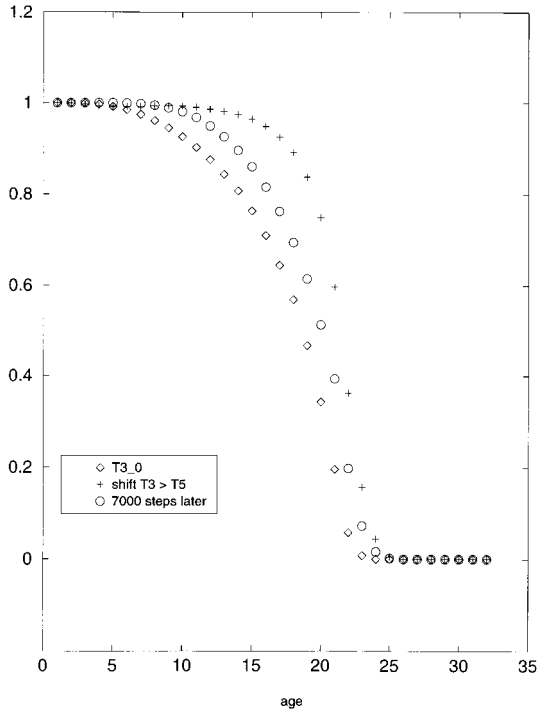

Fig. 5. The effect of prolonged evolution of population after the shift of the threshold from 3 to 5.

better medical care, is equivalent to the suppression of dominant genes [3].

The lower density of damaged genes switched on before the reproduction age in populations with long genomes prevents the exact scaling of the *T* shift effect [10]. During the reproduction period, the fraction of the damaged genes grows from the minimum characteristic for the loci switched on before reproduction to 1. Since the minimum depends on the length of the string before the reproduction age, the shape of curves changes. Furthermore, since the organisms are diploid, the probability of phenotypic onset of the disorder is the square of the frequency of its damaged allele in the population.

The effect of *T* shift was more pronounced than earlier [8] because the present longer genomes lead to two phenomena:

– one step in the simulation corresponds to a smaller fraction of life, causing a smaller *relative* shift in the maximum age;
– during the reproduction age, the fraction of damaged genes grows from a very low level up to 1, while the fraction of damaged genes at the start of reproduction age in short genomes is much higher.

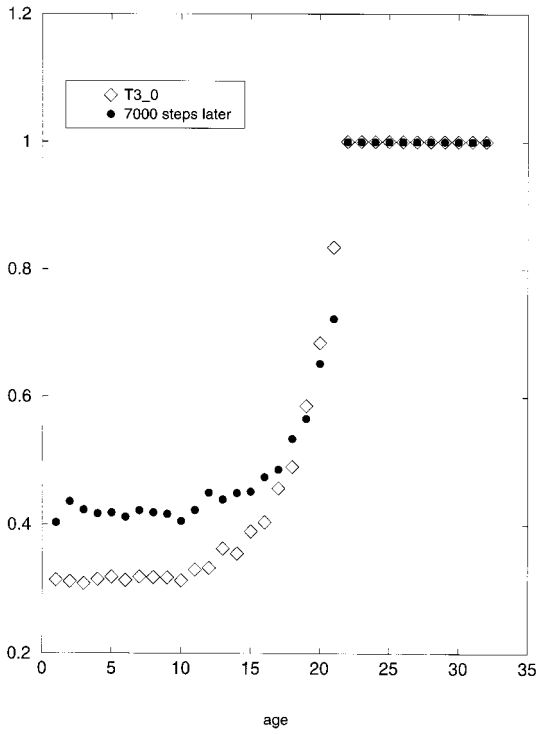

Fig. 6. The distribution of the damaged genes in the population in equilibrium with the threshold $T = 3$ and in the same population evolved for 7 000 steps with $T = 5$. Note the crossing point at locus 19.

In fact, with the parameters we have used in our model, the mortality of people before reaching the reproduction age is still too low (about 0.25) while the prenatal mortality in the human species is estimated at 0.60 [11]. To reach the proper mortality rate, the proportion of genes switched on before the reproduction age should be still higher.

We have got another interesting effect. When the populations after the T shift from 3 to 5 evolved for another 7 000 steps in case of short genomes (and much more for longer genomes), the age distributions move back towards the initial ones, characteristic for the time before the T shift, Fig. 5. It means that by improving medical care, we move the population away from the equilibrium, and if nothing changes, the population will come back to the equilibrium with the mortality rate very close to that from before the shift but just with a higher level of damaged genes in the genetic pool, Fig. 6. To keep the same mortality as now, the costs of medical care should grow in the future. This is not very optimistic! The other conclusion is even more pessimistic – if the medical care efforts in the future will come back to that of nowadays, the mortality rate will increase dramatically and life expectancy will decrease compared to present situation. This

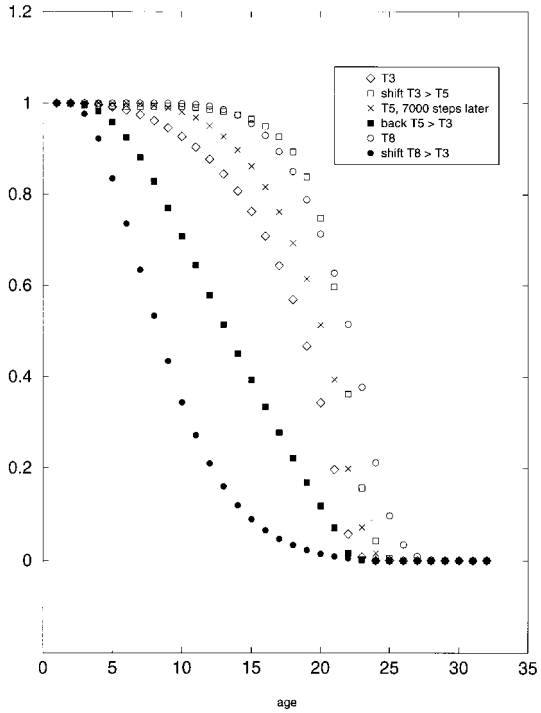

Fig. 7. The "reverse" effect. The popuiations in equilibrium with $T = 3$ (T3) was allowed to evolve for 7 000 steps (shift T3 > T5) and then the T was shifted back to T3 (back T5 > T3). Another population reached equilibrium with $T = 8$ (T8) and then it was shifted to $T = 3$ (shift T8 > T3).

effect is very well visible when we have changed T from 8 to 3, Fig. 7. Such a T shift caused immediate death of a large fraction of the population.
Our pessimistic findings could lead someone to the conclusion that the best solution for the demographic strategy is eugenics. It would be a very false conclusion. As it has been already shown in earlier studies, eugenics leads to homogeneous populations and next, to their extinction [12].
Another effect of the T shift has been observed. The curves describing the defect-gene distributions in the genomes evolving with different T cross, which means that some genes expressed in the older ages in populations with a higher T have selection values while the same genes in populations evolving with a lower T have no selection values (see bits 22 and 23 in Fig. 2) and all are set for 1. When the population in equilibrium with $T = 3$ is shifted to a higher T, these genes are exposed for selection. In such a situation we could expect genetically determined disorders with the onset at older age which were not known before introducing intensive medical care. Furthermore, the determining genes could not be replaced by correct ones, because there are no correct alleles of these genes in our genetic pool. The results are thus history-dependent.

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