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INFLUENCE OF A SMALL FRACTION OF INDIVIDUALS WITH ENHANCED MUTATIONS ON A POPULATION GENETIC POOL

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It has been observed that a higher mutation load could be introduced into the genomes of children conceived by assisted reproduction technology (fertilization *in-vitro*). This generates two effects — slightly higher mutational pressure on the whole genetic pool of population and inhomogeneity of mutation distributions in the genetic pool. Computer simulations of the Penna ageing model suggest that already a small fraction of births with enhanced number of new mutations can negatively influence the whole population.

Keywords: Population genetics; ageing; Penna model; *in-vitro* fertilization.

1. Introduction

Medical progress has prolonged enormously the life expectation in the industrialized world, compared with two centuries ago. But the case of antibiotics has told us also that there are disadvantages: While many human lives were saved, many bacteria became resistant, and new antibiotics have to be developed. In normal biological evolution, this balance of effort and countermeasures is called the "Red Queen" effect. In all such cases, advantages and disadvantages have to be balanced if they are known; the present simulation adds knowledge for the disadvantages of assisted reproduction technology (ART).

In particular for humans, computer simulations of the Penna ageing model[1,2] suggested that after many centuries, the human genetic pool may have acquired so many new inherited mutations, which due to medical intervention are not removed from the population, that life expectancy and health at old age no longer improve.[2]

An example which is only a few decades old is *in-vitro* fertilization.[3] Nevertheless, in the so-called developed countries, more than 1% of babies are born following ART. It could be critical to assess if ART is associated with birth defects and/or genetic defects. According to data from the National Birth Defects Prevention Study

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published by Center for Disease Control and Prevention in Atlanta[4,5] the incidence of birth defects among singletons born after ART is significantly higher, i.e. septal heart defects (adjusted odds ratio) 2.1, cleft lip with or without cleft palate 2.4, esophageal atresia 4.5, and anorectal atresia 3.7. Those birth defects could be genetically determined or not. Nevertheless, in other studies it has been found that genetic defects, causing retinoblastoma occurs also 5–7 times more frequently in newborns after ART.[3] Since retinoblastoma is caused by a genetic defect which could be seen in the first generation while most of other mutations are recessive and can be expressed only when they occur in a homozygous state (both alleles in one genome are defective), it is reasonable to check if the increased frequency of mutations in a small fraction of individuals can affect the reproduction potential of the whole population.

Normally, a preselection of sperm cells happens since only an extremely small fraction of sperm cells out of hundreds of millions reaches the ovum surface and only one of these groups is allowed to enter the cytoplasm. There are some suggestions that an egg can actively chose this winner.[6] Sperm cells which are slower or less viable due to some genetic defects are losers in this competition. This preselection is abolished by *in-vitro* fertilization and thus may deteriorate the genetic pool.

All these medical interventions are rare: Not everybody takes antibiotics each day, and most pregnancies start traditionally and not by *in-vitro* fertilization. Nevertheless, it is also possible that technology of *in-vitro* fertilization increases the incidence of mutations in the newborns genomes. Moll *et al.*[3] have estimated that the incidence of retinoblastoma in children born after *in-vitro* fertilization increased 5–7 times comparing with the children born after natural conception. Since retinoblastoma is caused by inherited or somatic mutation followed by loss of heterozygosity, it is legitimate to ask the question if such a small fraction of population with increased mutation load can significantly affect the genetic pool and reproduction potential of a population. Thus, we simulate here that with 2% probability only the number of mutations at birth are enhanced from one to four, and we check how this affects the *overall* population. Can there be detrimental effects far exceeding the level of a few percent?

For the simulations we use the Penna model[1] since it includes ageing and is widely used.[7,2] Thus, we do not repeat here all the details of that model. We believe that similar results could be found also in other ageing models.[8–10]

2. Results

2.1. *Parameters*

Each individual of the sexual Penna model has two bit-strings of length L each, representing the genome. All mutations are inheritable; a mutation changes a bit from zero to one, or leaves it at one, and is never reversed; at birth one mutation happens for each bit-string. Age is increased by one bit position at each timestep t. Starting from age R, each female at each timestep selects randomly a male of age

$\geq R$ and gives birth to B offspring; the offspring dies immediately with a Verhulst probability $N(t)/K$, where N is the current population (male plus female) and K is often called the carrying capacity, varying here from 1000 up to 30 million. An individual is killed if the number of mutations expressed at that age reaches a threshold T; a mutation is expressed if in the same positions from one up to the current age both bit-strings have a bit set to one. Thus all mutations are recessive, deleterious, and inheritable. Before at birth one bit-string from the mother is given on to the child and mutated, with a crossover probability C the two maternal bit-strings are crossed-over at a randomly selected position; the same happens for the father.

Further details on the Penna model are given in many articles and a few books[7]; the influence of a recombination probability between 0.001 and 1 is given in Ref. 11. We now add new to it that with probability of 2% the mutation rate increases from one to four for each bit-string at every birth. We call this case *inhomogeneous* and compare with the standard homogeneous case of always one mutation. (Our inhomogeneity is not inherited; if instead we let males give on the property of enhanced mutation to their male offspring, then the fraction of males with that genetic property dies out after about 10^3 timesteps from initially 2%. Also, if both the homogeneous and the inhomogeneous population are simulated together, with one shared carrying capacity, mostly the inhomogeneous population dies out for large K and large C.)

Normally, we take $R = L/4$, $B = 2$, $T = 3$ in agreement with numerous previous studies of the Penna model, but for the transition to complementing bit-strings we use[11] $R = 5L/8$, $B = 6$, $T = 1$ (for $B = 5$ in the latter case populations became extinct). Throughout we made 20 000 timesteps and averaged over the second half of the simulation. (Selected simulations up to 1 million timesteps did not change Fig. 1 beyond the large scattering, but increased the probability of population extinction.) Except for large K we averaged over 10–1000 samples.

2.2. *Normal case*

Figure 1 shows the three ratios of the "homogeneous" to the "inhomogeneous" numbers, for: the total population, the lifespan (more precisely, the life expectancy at birth), and the reproductive fraction of the population (having at least the age R). We see that these ratios are of the same order as the 2% inhomogeneity, i.e. the additional mutations reduce the overall fitness (as measured by these three quantities). The longer the bit-strings are, the smaller is the influence of the inhomogeneity, i.e. the closer are the ratios to unity; this effect is seen even stronger, not shown, for $L > 64$. The reason is that the longer the bit-strings are, the larger is the total number of births over the lifetime and thus the closer are the populations N to the carrying capacity K, not shown, making other influences less important. Actually, the L loci of the Penna model refer to the small fraction[13] of life-threatening diseases, not to tens of thousands of less important genes. Figure 2 shows an inbreeding depression for small K.

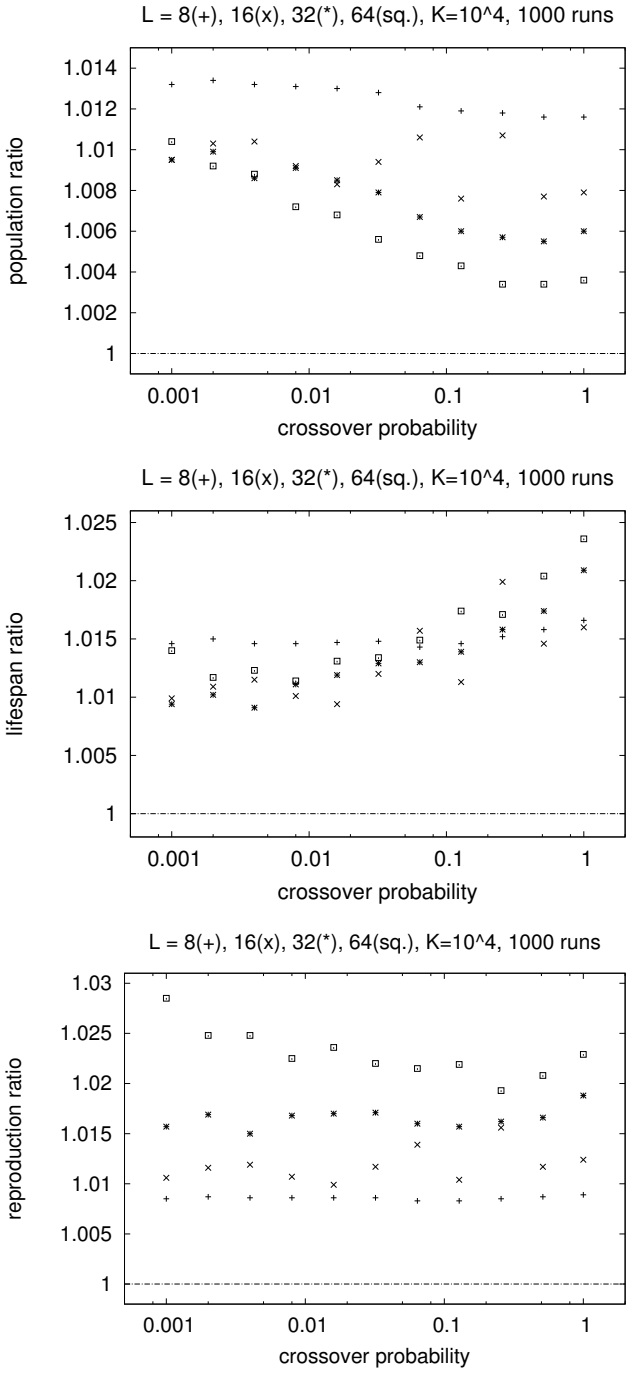

Fig. 1. Normal case: The three fitness ratios for a carrying capacity of 10^4. Similar results were obtained for $K = 10^3$, 10^5, and 10^6.

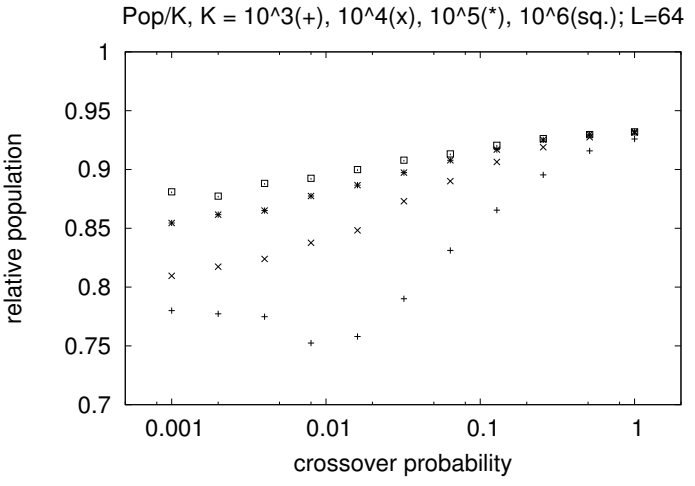

Fig. 2. Normal case: Variation of population (normalized by carrying capacity) with C.

(The error bars in Fig. 1 increase with increasing L and decreasing C and are at most about 1/4%, from 1000 samples. Later in Fig. 6(b), based on only 100 samples, they can reach 6%.)

While it is plausible that a probability of 2% for an enhanced mutation rate reduces the fitness also by a few percent, it is less obvious that this reduced population is still higher by a few tenths of a percent, Fig. 3, than the one obtained by a mutation rate of 1.06 for all, corresponding to the weighted average of 1 and 4 mutations used before. (We always make one mutation, and then with probability 0.06 another one.)

Another alternative for the homogeneous case is to have always one mutation, but to assume infertility in 2%, randomly selected. Even then the homogeneous case is fitter than the inhomogeneous one, Fig. 4.

2.3. *Transition to complementing bit-strings*

In the above normal case, Darwinian selection of the fittest tries to reduce the fraction of mutated bits; we call the fraction of bits set to one the mutation load and the fraction of bit pairs where the two bit-strings differ (at the same position) the heterozygosity. The mutation load is low, and the heterozygosity about twice as high.

Instead, for low recombination probabilities C and high minimal reproduction ages R, and only recessive loci, selection of the fittest leads to complementary bit-strings: At many loci, one bit is set to one and the other to zero. Thus the load is nearly half, and the heterozygosity nearly 100%. Figure 5 shows this effect[11]; the higher the population is the lower C must be to allow for complementarity.

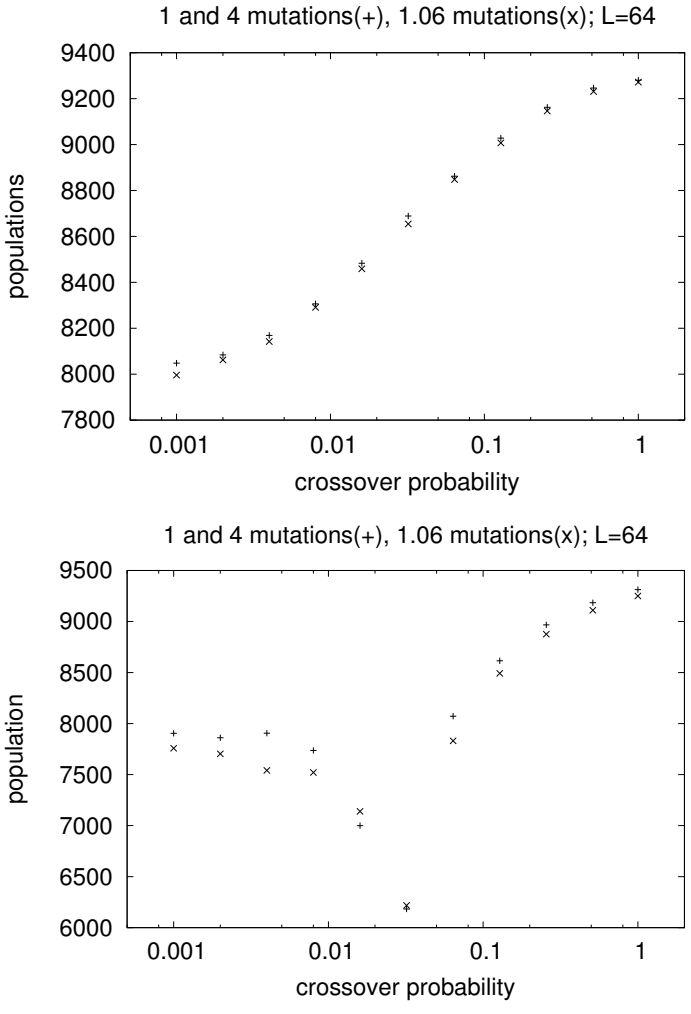

Fig. 3. Comparison of inhomogeneous case (higher values) with homogeneous mutation rate of 1.06 (lower values). The upper figure shows the normal case, the lower figure the transition case, $K = 10^4$ everywhere.

The above ratios between the homogeneous and inhomogeneous cases, Fig. 6, now deviate much stronger from unity at low crossover rates.

3. Discussion

From published data on retinoblastoma and other diseases we concluded that artificial reproduction technology can enhance the probability of new mutations for the zygote. We put in a 2% effect, and in most cases got out results also of the order of 2%, Fig. 2; this is good. Only at the transition from purification to complementarity was the danger enhanced appreciably, Fig. 6. Nevertheless, even 1% reduction in

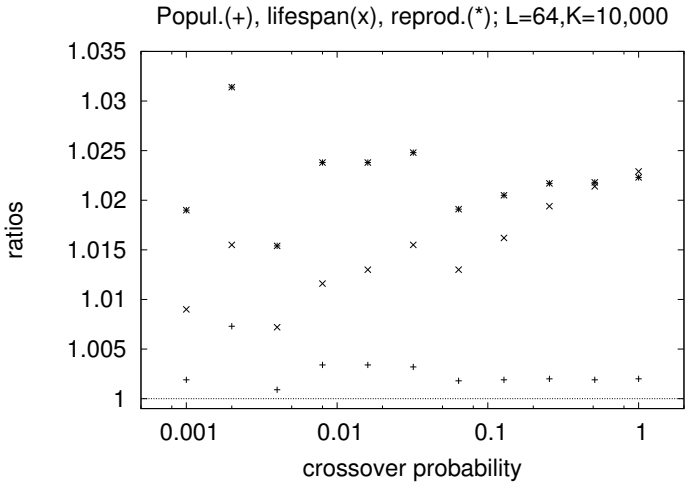

Fig. 4. Normal case with 2% infertility in the homogeneous population: Variation with C of the three fitness ratios, homogeneous to inhomogeneous.

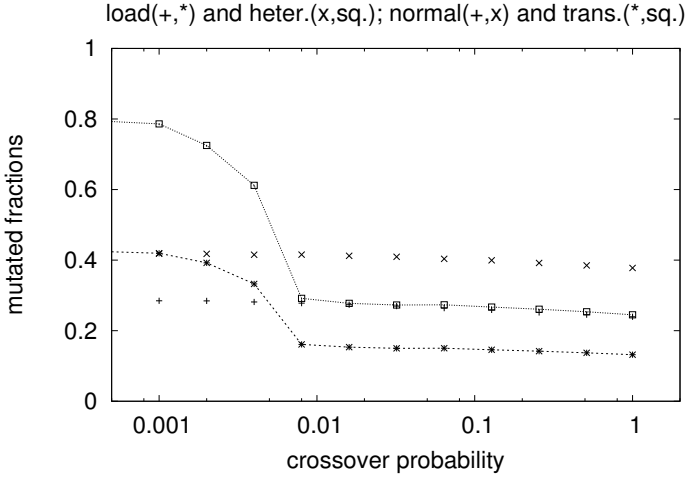

Fig. 5. Normal $(+, \times)$ and transition (stars, squares) case: Mutation load and heterozygosity vs C; small C give complementarity only for the transition case (stars and squares), not the normal case ($+$ and $\times$). $K = 10^5$ in both cases.

fitness could be problematic; perhaps *Homo neanderthalensis* was only a few percent less fit than *Homo sapiens*, and nevertheless lost out in the competition after thousands of years.[14]

As an alternative to modern medicine, we do *not* advocate eugenics.[12] Instead medical research should be aware of the long-term dangers and look for better methods reducing these dangers. Only when both dangers and advantages are known can they be compared for a rational decision.

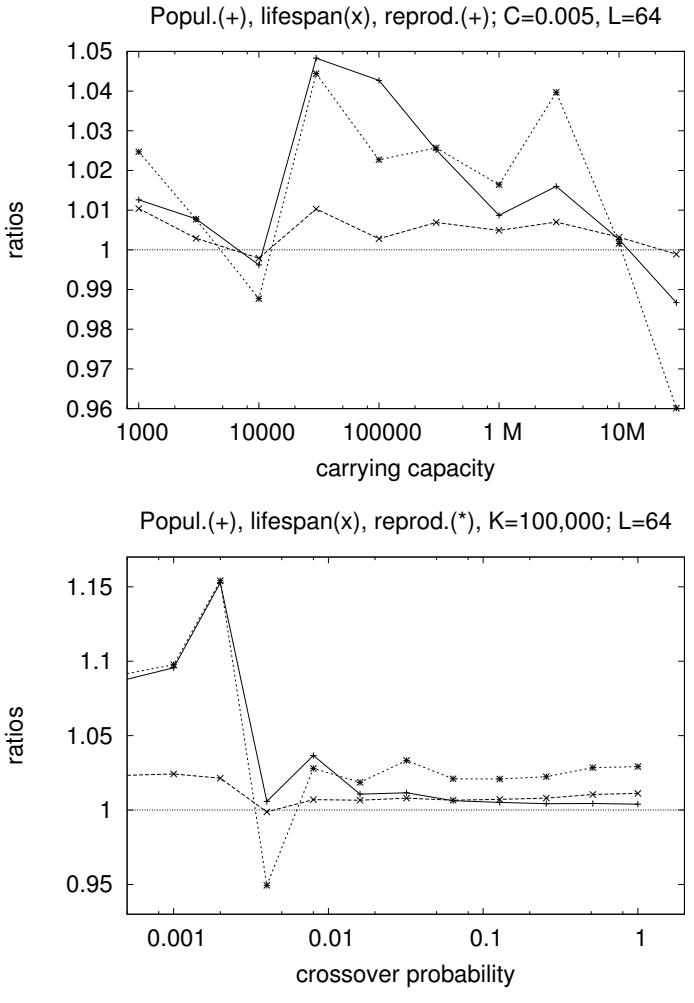

Fig. 6. Transition case: Fitness ratios vs K and vs C (ratio of homogeneous case with one mutation, to inhomogeneous case with one and four mutations).

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