Love kills: Simulations in Penna Ageing Model

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The standard Penna ageing model with sexual reproduction is enlarged by adding additional bit-strings for love: Marriage happens only if the male love strings are sufficiently different from the female ones. We simulate at what level of required difference the population dies out.

Love may have been a female invention long ago, when the brain of genus Homo became large and required more food. Thus the father was needed to help feed mother and baby. We try to check here if the restriction in the number of suitable mates caused by love can drive the whole population to extinction. First we describe the biology, then our model, and finally our results.

For sexual reproduction of diploid organisms, usually two individuals of different gender are necessary (hermaphrodites are the exception). In theoretical concepts, considering a random assortment of genes, any preferences in the selection of partners for reproduction usually are ignored. In fact, it is known that such a selection can be a very important factor for the evolution of the genetic pool of a species. However, the selection of potential mates is only the first step influencing the assortment of genes. Generally, the assortment of genes can be affected at the pre-zygotic stages, like mating preferences or gamete pre-selection, or at post-zygotic stages, like miscarriage, or any other differential selection of individuals before and during their reproduction period. Sometimes it is difficult to find out at which stage the random assortment is disturbed.

The first step generating non-random distribution of genes is the mating preference. There are more and more informations suggesting that there are not only the obvious phenotypic traits like size or strength of the male (or his bank account) which are preferred by females but that there are some other genetic characters which influence the mating decisions or even tune the genetic relations between mating pairs. Odour of individuals is such a trait determined by its genetic configuration. In the generation and recognition of an individual’s odour at least two groups of genes are involved. One group is the Major
Histocompatibility Complex (MHC) and the second one is a family of Olfactory Receptor (OR) genes (the largest gene family in the mammal genomes).

MHC is a large cluster of genes located on the 6th human chromosome composed of more than 200 loci involved in different immunological functions [2]. The main function of MHC gene products is presenting the foreign antigens on the surface of cells. Products of MHC class I are present on all nucleated cells of organisms and their role is to present in their context a foreign antigen (i.e. peptide of a virus infecting the cell). Such a stigmatised cell is recognized and killed by T lymphocyte. Products of genes of MHC class II are present on the special group of immunological competent cells - “antigen presenting cells” involved in stimulation the immunological response against the presented antigen.

There are several characteristic genetic properties of the MHC gene cluster: Compared with the rest of the genome, the recombination rate is lower, the mutation rate may be lower for some loci and higher for others, and other properties less relevant for the present simulations.

It is assumed that those specific properties of the cluster are connected with its functions - individuals which possess more different MHC alleles can present more different foreign antigens. This is one reason for being highly heterozygous in the MHC region. Nevertheless, to keep the high level of heterozygosity in the MHC regions other specific properties of this region have developed. The most intriguing is the possibility of recognizing the configuration of MHC complex of the potential mating partner. It was already in 1976 when Yamazaki et al., found out that mice heterozygous in MHC loci are more preferred as mating partners than homozygous mice. Next, it was found that the fraction of born homozygous mice is lower than expected under assumption of random mating [3]. It was an effect of both, the non-random mating and biased miscarriage.

Other experiments indicated that mice and rats can recognize partners differing in MHC loci [4, 5] and sometimes even in one locus (i.e. H-2K locus [6]). This ability of MHC recognition and non-random mating seems to be a more general property of many species. It has been found in fish [7, 8] that they can choose a partner such that the probability of producing heterozygous offspring is higher or that the two mating partners differ in MHC loci.

The most spectacular finding was that humans also have the ability of recognizing the MHC of the partner. It has been found that women prefer the odour of men which differ in their HLA-A, HLA-B and HLA-DR alleles [9]. Next, experiments performed on humans have shown that selection prefers combination of partners which have the least number of common alleles which renders the highest heterozygosity of the offspring [10]. (That is why it would help to put at least four-alleles loci into MHC bitstrings. In such a case two mating partners can have different all alleles which ensures that the mother and her foetus are also different). There are at least two non-excluding hypotheses explaining the trend for non-random mating and higher heterozygosity in the MHC loci. The first one assumes that heterozygous individuals can present more foreign antigens what could be especially important during multifactor infections [11, 12, 13, 14]. The second hypothesis assumes that it is a Red Queen effect...
There is a continuous arms race between parasites and hosts. If a high fraction of hosts can present the parasite’s antigen to their immunological system, the parasite has to change its antigen to broaden its effective host range. That induces further diversification of MHC alleles.

This mechanism could be also important in avoiding the mating between too closely related individuals - the cheapest way for generating a higher biodiversity.

The partner’s MHC recognition is a kind of pre-zygotic selection but there is also an early post-zygotic selection connected with MHC. It has been observed that if couples share more common alleles in the MHC region, women are more prone for early spontaneous abortion [Hedrick 1998]. Probably this is connected with an expression of a specific progesterone-induced blocking factor (PIBF) which prevents the immunological attack of mother against the foetus. If MHC antigens inherited from father differ negligibly from those inherited from mother, the PIBF genes are under-expressed which allows the mother to develop effective immunological response against her foetus [16] and leads to the recurrent spontaneous abortion.

This mechanism could be also important in avoiding to give birth to relatively highly homozygous offspring, if avoiding the mating between too closely related individuals has failed - the next cheapest way for generation a higher biodiversity.

If we assume that there are mechanisms providing the non-random assortment of MHC alleles, then these phenomena should affect the assortment of other genes, at least those linked to the MHC region. What is also interesting, the other cluster of genes, the Olfactory Receptor (OR) genes, is closely linked to MHC and it could be a cooperation between MHC and OR genes which renders this MHC recognition by smell.

Pełalski [17] assumed mate selection to be governed by MHC. In the same spirit now the sexual Penna ageing model [18] is modified to include mate selection by two additional strings of 16 bits each, for each individual, unrelated to the two usual bit-strings of length $L$ containing the age-relevant genome. Initially, the additional love bit-strings are chosen randomly, different for each individual. This model is therefore more complicated than the gamete recognition of Cebrat and Stauffer [19] based on one bit. It has some similarity with the peacock tail or bird song simulations in [20].

During the at most 20 attempts per iteration of a female to find a suitable unmarried male partner, the new “love” bit-strings of the male (A and B) and the female (C and D), which should be dissimilar, are compared. If the difference (as defined below) is smaller than a universal love limit, the male is rejected. Thus with too stringent requirements for love, the female will often not find a suitable partner within the allowed 20 attempts, stay single during this iteration, thus reduce the total number of new babies, and finally lead the population to extinction, as indicated for Germany by present trends. (With two love strings A and B, and gametes a and b for the usual parental genome, love string A is transmitted if haplotype a was selected for the gamete, and love string B if haplotype b was selected.) Except when stated otherwise, no crossover and no
mutation happens in the love strings.

The difference $d$ between the female and the male she selects should be large and is defined as follows: For the male (strings A and B) we determine for each of the 16 bit positions the sum $m_i$, $i = 1, 2, \ldots, 16$ of the two love bits: zero, one or two. The analogous sums $f_i$ are calculated for the female. Then

$$d = \sum_{i=1}^{16} |m_i - f_i|$$

is the difference used in our simulations and varies between 0 and 32. The extremum $d = 32$ is reached if the two mates are fully complementary to each other in the love strings, and the two love strings within one individual agree (no heterozygous positions).

We assume the couple to stay together until death does them part [21], with the widow or never married woman demanding a $d$ not smaller than the love limit.

We start with the standard Penna model [18] with usually $L = 64$, a minimum reproduction age $R = 5L/8$, $T = 3$ active mutations kill, $B = 2$ births are attempted per female and iteration, all mutations are recessive, both males and females suffer from one (deleterious irreversible) mutation per bitstring and iteration, Verhulst deaths are applied to births only with a carrying capacity $K$ up to 10 million. After 10,000 iterations, when a rough age equilibrium has been established, love is switched on, and the population may die out (Fig.1). Time, up to $10^7$, is measured by the number of iterations after love has been switched on. We look at the average $<d>$ as well as the squared width $W2 = <d^2> - <d>^2$.

Fig.1 shows extinction or recovery, depending on parameters like the love limit which could vary between zero and 32. The top part shows examples of long-time behaviour at $L = 32$ (symbols) and 64 (line) indicating partial or full recovery after a decay within the first few hundred time steps after love selection was switched on. The middle part shows survival tests when our love limits for the difference increase from top to bottom. Extinction occurs first at a love limit of 18 (from 32 maximal), $K = 3 \times 10^6$. (Curves for $K = 10^5$, $3 \times 10^5$, $10^6$ look similar.) The bottom part shows for these and other simulations how with increasing love limit and thus decreasing population the average difference (+) increases while the squared width ($\times$) goes to zero. (Averages in the bottom part are taken from 201 to 400 iterations after switching on love at time 10,000.) Thus, as expected, when the love limit is higher (more demanding), then the average difference is higher and the scattering of the distances is lower.

For longer times the differences for all couples may collapse to one value, as seen in Fig.2 for $K = 10^6$ and love limit = 16. After 2000 iterations, all couples have $d = 16$, but most females have no partner which is counted as $d = 0$ in the left upper corner of Fig.2b.

Thus far only the genome was mutated with one mutation per bit-string, iteration and individual. When the same mutation rate is applied also to the love
strings then no final fixed point as in Fig.2a is reached; the average difference always fluctuates slightly and the width of the distribution does not become zero. (In the case of $10^7$ iterations and love limit 16 close to extinction, only after $10^5$ iterations was a roughly stationary equilibrium found.) These love mutations are reversible.

If we add to these mutations the option of a recombination (or crossing) rate $C$ smaller than one (until now $C = 1$), then complementarity [22] of the genome is seen for small $C$ and small populations. Fig.3 shows in its top part the number of bits set to one as a function of bit position: Youth to the left, old age to the right. At the right, the maximum number (seen as a plateau) is twice the population since each individual has two genomic bit-strings. At the left we see for $C = 0$ (+ and ×) about half that value as needed if at each bit position the two bits are complementary to each other and thus without damage to the phenotype. For $C = 0.512$, in contrast, the curves increase much steeper from left to right, meaning that most youth bits are set to zero. This picture is confirmed by a bit-by-bit comparison of the genomic bit-strings within each individual (bottom part). Thus, love reduces the population but does not change the complementarity. (Here, $K = 1000$; for larger $K$ complementarity is more difficult [22].) As in Fig.1b, Fig.4 shows the average difference for couples to increase with increasing love limit; the width again decreases (not shown); the recombination rate $C$ has less influence on this average.

Finally, as mentioned at the beginning, instead of only two choices (one bit) for the love alleles, we now use 8 bits (one byte) for each of the 16 elements of the two love strings (two times 128 bits in total). Thus it is easily possible that at one locus all four alleles on the love strings (two in the father, two in the mother) are different. The activity $M$ of a male allele is the number of bits set to one and varies between 0 and 8; the same holds for the female activity $F$. A superscript (1 or 2) denotes the two love strings.

The difference is now

$$d = \sum_{i=1}^{16} |M_i^1 + M_i^2 - F_i^1 - F_i^2|$$

and can vary between 0 and 256. Actually already at a love limit near $d = 64$ the population dies out, Fig.5. Fig.6 shows a slow increase with time of the average difference; again the recombination rate has little influence on $<d>$. Complementarity in the genome bit-strings is again observed for $C = 0$ even at a population of 400,000, Fig.7.

Returning to our earlier love strings with 16 bits (instead of 16 bytes), recombination rate $C = 1$, and no mutations for love strings, we now assume a birth rate increasing linearly with increasing difference $<d>$ of the couple, somewhat similar to [23]. Fig.8 shows that now the populations are higher than for a constant $B = 2$; those for the standard Penna model without love are in between near 0.9 million (not shown). In this way love can be justified by evolution if it leads to a higher effective birth rate through paternal child care [21] or the above-mentioned postzygotic selection.
For this version we also introduced crossover for the love strings, in addition to the crossover for the genomic bit-strings (one recombination per time step). Fig. 9 shows that after 400 love steps this does not matter: With or without crossing, with or without love mutations, the results are about the same and look like Fig. 1 centre. (For much longer times and love limit zero, \( W^2 \) fluctuates a lot and after millions of time steps, a true equilibrium with only one bit-configuration in all the love strings may arise: \( <d> = W^2 = 0 \).)

In summary, high requirements for love endanger the survival of the population. That love nevertheless has evolved in humans proves beyond reasonable doubt how important the father’s contribution in raising the children was. We restricted ourselves here to love strings (corresponding to MHC and OR) rather decoupled from genomic bit-strings; in reality both are stored in the DNA of the chromosomes, and are linked to each other.

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References

[1] M. Kohn and S. Mithan, Antiquity 73, 518 (1999).
[2] G. Weisbuch and A.S. Perelson, Rev. Mod. Physics 69, 1219 (1997).
[3] W.K. Potts, C.J. Manning and E.K. Wakeland, Nature 352, 619 (1991).
[4] K. Yamazaki, M. Yamaguchi, L. Baranoski, J. Bard, E.A. Boyse, L. Thomas, J. Exp. Med. 150, 755 (1979).
[5] R.E. Brown, P.B. Singh and B. Roser, Physiology and Behavior 40, 65 (1987).
[6] K. Yamazaki, G.K. Beauchamp, I.K. Egorov, J. Bard, L. Thomas and E.A. Boyse, Proc. Natl. Acad. Sci. USA, 80, 5685 (1983).
[7] C. Landry, D. Garant, P. Duchesne and L. Bernatchez, Proc. R. Soc. Lond. B, 268, 1279 (2001).
[8] P.B. Aeschlimann, M.A. Haberli, T.B.H. Reusch, T. Boehm and M. Milinski, Behav. Ecol. Sociobiol 54, 119 (2003).
[9] C. Wedekind, T. Seebeck, F. Bettens and A.J. Paepke, Proc. R. Soc. Lond. B, 260, 245 (1995).
[10] C. Wedekind and S. Furi, Proc. R. Soc. Lond. B., 264 1471 (1997).
[11] P.C. Doherty and R. Zinkernagel, Nature 256, 50 (1975).
[12] A.L. Hughes and M. Nei, Genetics 132, 863 (1992).
[13] D.J. Penn, K. Damjanovich and W.K. Potts, Proc. Natl. Acad. Sci. USA 99, 11260 (2002).
[14] E.E. McClelland, D.J. Penn. and W.K. Potts, Immunity 71, 2079 (2003).

[15] A. Langefor, J. Lohn, M. Grahn, O. Andersen and T. von Schant, Proc Biol Sci. 268, 479 (2001).

[16] R. Druckmann and M.A. Druckmann, J. Steroid Biochem. Mol. Biol. 97, 389 (2005).

[17] A. Pękalski, Int. J. Mod. Phys. C 18, 1619 (2007); for real humans see S. Jacob, M.K. McClintock, B. Zelano and C. Ober, Nat. Genet. 30, 175 (2002); J.N.Lundström et al., Science 320, 1160 (2008).

[18] T.J.P. Penna: J. Stat. Phys. 78, 1629 (1995), D. Stauffer, S. Moss de Oliveira, P.M.C. de Oliveira, J.S. Sá Martins, Biology, Sociology, Geology by Computational Physicists (Elsevier, Amsterdam 2006), D. Stauffer, Bioinformatics and Biology Insights. 1, 91 (2007): http://www.la-press.com/article.php?article_id=520.

[19] S. Cebrat and D. Stauffer, Int. J. Mod. Phys. C 19, 259 (2008).

[20] A. Ticona and T.J.P. Penna, Braz. J. Phys. 33, 619 (2003); S.G.F. Martins and T.J.P. Penna, Int. J. Mod. Phys. C 9, 491 (1998).

[21] A.O. Sousa and S. Moss de Oliveira, Eur. J. Phys. B 10, 781 (1999).

[22] M. Zawierta, P. Biecek, W. Waga, S. Cebrat, Theory in Biosciences 125, 123 (2007); D. Stauffer and S. Cebrat, Frontiers in Bioscience, in press, arXiv:1003.1896.

[23] K.N. Bertnse, Int. J. Mod. Phys. C7, 731 (1996).
Figure 1: Long-time examples (top), search for extinction limit (centre) and trends with increasing love limit (bottom).
Figure 2: For love limit = 16, the top part shows the time development of the population (normalised by the carrying capacity $K$, central solid line), the average difference between couples (line increasing to top), and the squared width (line going to zero after 5300 iterations). The bottom part shows the histograms for the differences after one, nine and 20000 iterations.
Figure 3: Complementarity is seen for small but not for large recombination rate $C$. $K = 1000$, love limit 0 and 15, measured after 400 love iterations (10400 iterations in total). The vertical scale is scaled by the population in the lower part and by twice the population in the upper part.
Figure 4: $\langle d \rangle$ versus time for love limit 0, 13, 14, ..., 19 bottom to top, and for recombination rate $C = 0, 0.001, 0.002, 0.004, \ldots, 0.512$ and 1.
Figure 5: 8-bit version: Variation of the love limit at which first an extinction within 400 iterations was observed, versus recombination rate $C$. Top part: $K = 10^3 (+), 10^4 (\times, \text{average over 2 samples}), 10^5 (\text{stars, average over 4 samples}), 3 \times 10^5 (\text{open squares}), 10^6 (\text{full squares})$. Bottom part: Genome length $L = 16, 32, 64, 128$ and 256 from bottom to top, at $K = 10^5$. We see that $< d >$ increases with increasing population and increasing $L$, and is nearly independent of the recombination rate $C$. 
Love limits = 50, 56, 61, C=0.001 (+), 0.512 (x), K=10^5

Figure 6: 8-bit version: < d > versus time for love limit and crossing rate = (50, 0.512) and (50, 0.001) (two lowest curves), (56, 0.001: central curve), (60, 0.512: top curve); the higher love limit is one unit below extinction. Not much changes for longer times (not shown).

Figure 7: 8-bit version: Complementarity versus purification for K = 10^6 and love limit 50: At C = 0 (+) about half the bits are set to one at younger ages; for C = 0.001 (x) this fraction is much lower. The plateaus to the right give twice the total population. The two lines connect the data for the heterozygous loci at C = 0 (x) and 0.001 (squares). 400 love iterations.
Figure 8: One-bit version with fertility increasing with increasing difference: $B = 2 + \Delta$. The love limits = $<d> - \Delta$ (which defines the relative difference \Delta) are 13 and 15. Similar results were obtained in the 8-bit version using $B = 2 + \Delta/10$.

Figure 9: Lack of influence from crossing of love strings.