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Sex versus non-sex versus parasite

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Pressure of parasites that are short-lived and rapid-evolving compared to the hosts they attack could be an evolutionary factor sufficiently general to account for sex wherever it exists. To be such a factor, parasites must show virulences specific to differing genotypes. Models are set up on this basis (one-locus diploid-selection and two-locus haploid-selection) in which the rapid demographic reactivity of parasite strains to abundance of susceptible hosts becomes represented in a single frequency-dependent fitness function which applies to every host genotype. It is shown that with frequency dependence sufficiently intense such models generate cycles, and that in certain states of cycling sexual species easily obtain higher long-term geometric mean fitness than any competing monotypic asexual species or mixture of such. In the successful cycle of the two-locus model, it is seen that both population size and gene frequencies may be steady while only oscillating linkage disequilibrium reflects the intense selection by parasites. High levels of recombination work best. Fecundity in the models can be low and no incidence of competition of siblings or other relatives is required.

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Пресс паразитов с коротким циклом и быстро распространяющихся в сравнении с их хозяевами, может оказаться эволюционным фактором, достаточно важным для определения соотношения полов в случае разнополых животных. Будучи таким фактором, паразиты могут проявлять видулентную специфичность в отношении разных генотипов хозяина. На этой основе созданы модели (1-локусная диплоидная селекция и 2-локусная гаплоидная селекция), в которых быстрая демографическая реактивность популяций паразита на обилие доступных особей хозяина описывается единственной функцией, частоты встречаемости, что имеет значение для любого генотипа хозяина. Показано, что если частотная зависимость достаточно интенсивна, такие модели дают законченные циклы, и на определенной стадии цикла у разнополых видов легко получаются более высокие долговременные геометрические средние, чем у конкурирующих монотипических асексуальных видов или у комплексов таких видов.
На законченном цикле в 2-локусной модели видно, что размеры популяции и частота генов могут быть стабильны, и лишь колебания отдельных связей при нарушенном равновесии отражают интенсивную селекцию паразита. Лучше всего работают высокие уровни рекомбинации. Плодовитость в моделях можеь быть низкой, и случай конкуренции между особями одного помета или другими родственными особями необязателны.

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Introduction

Given acellular simple organisms in the early history of life it is not difficult to imagine selection that would favor multicellularity. Provided cell aggregates were clonal, so that they would cooperate well, differentiation of somatic cells could give several advantages. There are parallels with the trends to eusociality currently occurring in some insects. Here *defense* against predators and parasites – including conspecific parasites – and increasing ability of a colony to *buffer* local changes of the physical environment seem to be very important. Similar factors most probably applied to simple multicellular organisms. Achievements with regard to the second factor permit occupation of new habitats.

Specialized somatic cells can increase the sophistication of defense but also introduce new vulnerability. One new weakness is in the inevitable slowing of the intrinsic growth rate due to physico-chemical logistics. Thus all parasites that remain much smaller than a host (these parasites might be called, in a broad sense, pathogens) have an advantage in rate of evolution which will help them to keep abreast.

A second weakness, brought in by multicellularity and crucial to the theme of this essay, is that body-building in itself requires that cells adhere to cells: the difficulty then may be to recognize as non-self, and to deny attachment, all other cells that present themselves at a cell surface. Non-self cells are potential parasites. Attached without having alerted any defense system in the host, an alien parasite cell is strongly placed with regard to further exploitation. Somewhat similar considerations can apply rather more weakly to unicellular organisms as hosts under attack by smaller and still shorter-lived parasites, notably viruses: here the argument would be cast in terms of chemical systems and organelles.

Thus an ongoing antagonistic co-evolution is to be expected over the matter of recognition. The parasite evolves towards a presentation which is either so bland that to the victim it seems like being touched by an inert body or by nothing at all or else involves some positive mimicry of attributes of host cells. The host on its side would evolve ever keener methods for discriminating what are truly the cells of its own clone. Provided each individual host is able to know its own idiosyncracy, mimicry by the pathogen is an incentive to variation by the host, for a host which has a new mutation in a recognition substance is able to react to the existing mimetic race of pathogen. But the pathogens by virtue of short generation time can be expected to evolve an appropriate mimetic presentation soon after the new type's advantage has made it common. Obviously a frequency dependent polymorphic equilibrium is likely. Thus in somewhat vague outline we can imagine this coevolution becoming more complex and diversified, with arbitrary password-like identification substances (histo-compatibility antigens?) and facultative responses (current pathogen strains matched by clone proliferation of specific defense cells, as in immune system?) being brought in by the host, and special difficulties for the host (such as mimicking common small particles like pollen grains or self-enwrapping in the membranes of the previous host) being invented by the parasite.

To elaborate on this coevolution in terms of immunology and microbiology is beyond my present competence and beyond the scope of this paper. Instead I intend to consider very simple model systems involving the general kind of frequency dependence just outlined and consider what "steps" the host might take (to adopt for the moment a loose teleology) to make a password system as effective as possible – effective, I will assume, not through facultative adjustment, as with an immune system, but through continual random recreation of "passwords" by sex and recombination.

Historically my theme makes up a thread concerning the role of parasitism in evolution recently followed by Clarke (1976) in pursuit of reason for the abundance of protein polymorphism. Before Clarke the thread started perhaps (as so often) with Haldane (1949); after Clarke it was traced in my present direction – decisively towards sex although not very far – by Jaenike (1978). Besides the stimulus of Jaenike's paper, a similar suggestion from William Irons (pers. comm.), emphasizing pathogen mimicry of host self-recognition antigens, contributes direction to the present paper.

Randomness per se in recreation of passwords will not be a particular focus in this account. However, it seems worth noting here in passing that randomness of that kind first identified in the rules of Mendel and subsequently proven so universal in sexual processes, already suggests a theme of escape from enemies. Such randomness, in other words, might be a parallel to that entering the solution of the game of "matching pennies" and others of similar conflictual coevolutionary slant (Fisher 1934). Thus randomness in cellular events, which it is as easy to imagine following fixed courses as random ones, seems a further hint that in this area of antagonistic coevolution may lie the answer to why sex arose and how it is maintained (Hamilton 1975).

Specifically, in the models that follow, a cell is supposed able to make antibodies to a certain class of substances and actually to make them to those variants within the class that it itself possesses. Detection, by use of these antibodies, of self-antigens in another cell results in a *pacification* of the defense system and facilitation of attachment. Any exterior living object in which the self-antigens are not detected is not allowed attachment and is treated as potentially dangerous.

One-locus model

In the case of a diploid there are imagined to be two

quasi-independent genomes checking for their own passwords: hostility results if either genome fails to find its password. A pattern of genetical partial resistance that is interpretable roughly on these lines is that shown by mice to three strains of a leukemogenic virus (Lilly 1972). This particular virus, however, seems unlikely to be a major selection factor in the wild.

In general the heterozygote might be expected to have an advantage over homozygotes since it imposes a harder test on a mimetic parasite cell and will be harder to fool. However, where the parasites are abundant and short-lived, heterozygote-mimetic strains can be expected to appear all the same. This is especially true because in the balanced polymorphism earlier outlined heterozygotes tend to be the commonest genotype. Once the heterozygote mimic is present and itself common the tendency of the heterozygote to be common is to its disadvantage, so that it is likely, over a series of generations, to become the least fit class. But because of the frequency dependence neither homozygote will fix; we see the possibility of an interesting interaction of stabilizing and destabilizing influences.

Before proceeding to examine this interaction in a specific case it may be noted, by way of introduction to the later model of this paper, that for a host to make its password depend on two syllables coded at independently segregating loci increases the range of passwords. So also, of course, does adding new alleles at a single locus. But eventually adding alleles distributed between two loci makes the number of types rise as a fourth power instead of as a square. For this among other reasons multi-locus password systems certainly merit attention.

Here it also seems appropriate to note that while the story has been told so far in terms that imply microbial parasites, it is by no means only these that practice highly specific wiles against their hosts, or that are short-lived enough to show the very reactive frequency dependence that the models will be found to require. Special resistance in particular genotypes of host, special virulence in particular genotypes of parasite, and matched polymorphic systems for attributes of these kinds, are being found ever more widely. In the case of wheat and hessian fly (Hatchett and Gallun 1970), for example, it is seen that the parasite in such a system does not have to be a microbe. The models that follow are much too simple to fit any such known cases but hopefully their very simplicity may serve to bring out basic principles that might apply in a wide set of more complex realistic interactions.

Consider a population with three mutant genotypes of an asexual host species (A, B, C). To each genotype a parasite species has produced a virulent pathotype. The presence of these pathotypes affects the fitness of each host genotype in the same frequency-dependent fashion: let $w_i(f_i)$ be the fitness where i is the genotype symbol, f_i is the frequency of type i in the population and w is a fitness function that monotonically declines with increasing f and is such that always $w(\frac{1}{3}) = 1$. Thus the system has a fixed point at $(\frac{1}{3}, \frac{1}{3}, \frac{1}{3})$ in the frequency space, and the decline of w with frequency means that at least for some functions this point represents a stable equilibrium. If, however, the decline of w is steep in the neighborhood of the fixed point it can happen that the equilibrium becomes unstable. Then any disturbance gives rise to an oscillating departure.

For example, suppose the fitness function is

$$w_i = r^{1-3f_i}$$

If $r = e^g$ and $f_i = \frac{1}{3} + d_i$ then this may also be written

$$w_i = \exp(-3gd_i)$$

In the neighborhood of the fixed point ($gd = 0$), this is approximately

$$w_i = 1 - 3gd_i$$

Multiplying by the frequency, $\frac{1}{3} + d_i$, summing for all three types, normalizing (actually unnecessary here because mean fitness approximates to 1 near the fixed point), and neglecting terms in d^2, the approximate frequency in the next generation is $\frac{1}{3} + d_i(1-g)$. Hence the recurrence relations near the fixed point are of the simple form

$$d_i' = d_i(1-g)$$

This shows that for $0<g<1$ there is monotonic approach to the fixed point; for $1<g<2$ there is oscillatory approach; and for $g>2$ there is an oscillatory departure from which a permanent oscillatory state can be predicted to result.

A more general analysis using a Taylor Theorem expansion of w gives the recurrence equation

$$d' = d\{1 + \tfrac{1}{3}\dot{w}(\tfrac{1}{3})\}$$

where w is the first derived function of w with respect to f.

Now consider a sexual host population with two alleles at a single locus such that antigenically, relative to the asexuals just considered, we have equivalences AA≡A, AB≡C and BB≡B. Suppose the fitness function is the same. This sexual system in the presence of the parasite species does not have a fixed point for the three phenotypes at $(\frac{1}{3}, \frac{1}{3}, \frac{1}{3})$; for if A and B are equally frequent genotype AB occurs with frequency $\frac{1}{2}$ and hence has lower fitness than the homozygotes.

It is clear, however, that equal frequencies of alleles corresponds to a fixed point. Stability at this point can be examined. It is now convenient to cast the argument in terms of gene frequencies. Thus d will now be used

differently, as the measure of the departure of a gene frequency from $\frac{1}{2}$.

Using the Hardy Weinberg ratio and working with objective as before we obtain

$$d' = 2\ \frac{w(\frac{1}{4}) + \frac{1}{4}\dot{w}(\frac{1}{4})}{w(\frac{1}{4}) + w(\frac{1}{2})}\ d$$

which can be abbreviated to $d' = \lambda_s d$.

With the fitness function as before, $w(f) = r^{1-3f} = \exp\{g^{(1-3f)}\}$, it is found that

$$\dot{w}(f) = -3g.\ \exp\{g(1-3f)\}$$

So

$w(\frac{1}{2}) = \exp(\frac{1}{2}g)$, $w(\frac{1}{4}) = \exp(\frac{1}{4}g)$ and $\dot{w}(\frac{1}{4}) = -3g.\exp(\frac{1}{4}g)$

$$\text{Hence } \lambda_s = 2\ \frac{\exp(\frac{1}{4}g) - \frac{3}{4}g.\exp(\frac{1}{4}g)}{\exp(\frac{1}{4}g) + \exp(-\frac{1}{2}g)}$$

$$= 2\ \frac{1 - \frac{3}{4}g}{1 + \exp(\frac{3}{4}g)}$$

When $g = 2$ we find $\lambda_s = -0.82$, but for $g = 2^1/_6$, $\lambda_s = -1.04$ so as g increases stability gives place to oscillations at a value a little higher than was found for the asexual population.

Location of the break points where permanent oscillation appear as frequency dependence becomes more sensitive is not, however, the main point of the model: it is enough to have shown that when once the fitness function enters a certain range of steepness oscillations of some kind are almost certain to occur in any mixed population. It is assumed for a mixed population that fitness depends on the joint frequency of the sexual genotype and its asexual counterpart. Regarding a possible advantage to the asexual population in a mixture, interest centers on the separate *long-term geometric mean fitness* (LGMF) of the sexual strain versus the best such mean achieved by an asexual when all asexuals are given a two-fold fitness advantage, corresponding to the worst case of wastage due to unproductiveness of males (Williams 1975, Maynard Smith 1978). I have not attempted formal analysis of the dynamics of mixtures but instead have studied the situation by computer simulation. Results indicate that analysis would certainly have to be complex: various oscillatory patterns were observed including 6-point cycles and also seemingly chaotic fluctuations. Often both sexuals and asexuals persisted together indefinitely. Sometimes just one asexual strain went extinct, sometimes two did so while one persisted. But in general the advantage which the sexual strain gets from having, each generation, the arithmetic mean of a concave fitness set (Hamilton et al. 1980) insures that if g is made large enough all asexual strains go extinct, or are at least kept at such low frequencies that, in nature, extinction would be probable. For example, if $g = 4.67$ (fitness function illustrated in Fig. 1a), total frequency of the persisting asexuals was kept below 0.0001. Polymorphism here was apparently chaotic. With this value of g the maximum fitness possible in the model (given by $r = e^g$) is 106.3 and the minimum is 0.00009. The maximum fitness proves less important for predominance of the sexual strain than the form of the lower part of the

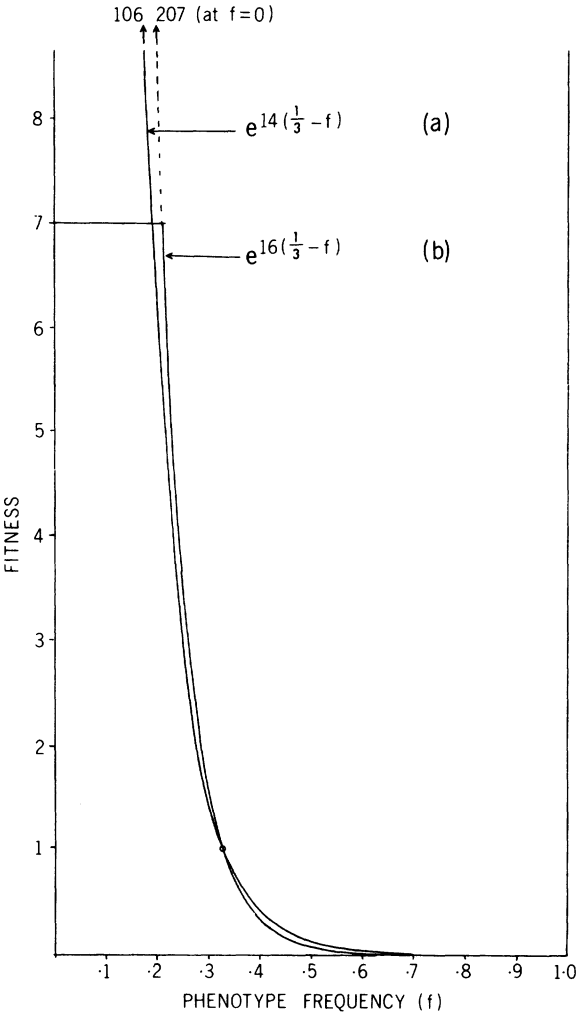

Fig. 1. Two examples of frequency-dependent fitness functions that permit a sexual species to preponderate against its set of asexual emergent strains despite effectively doubled fecundity in the latter.

In case (a) the limiting fitness of a very rare phenotype is 106. This case gives rise to chaotically changing polymorphism in which asexual strains go to very low frequencies (below 10^{-20} for homozygous strains; below 10^{-3} for heterozygous strain). Maximum and minimum fitnesses observed are about 3.0 and 1.7, and the overall LGMF is 2.6.

In case (b) a maximum fitness of 7 is imposed on a function otherwise going to 207 at f = 0. This case gives rise to a 6-point cycle with highest mean fitness at 2.03, lowest at 0.88, and LGMF at 1.41. Here asexual genotypes reduce to very low frequencies and may be going to zero: in the simulation cycle preceding generation 200 none is above 10^{-5} and the heterozygotes are below 10^{-33}.

curve; it was found that with g slightly higher than the minimum needed to give predominance of the sexuals a "plateau fitness" could be imposed which was much less than the natural maximum and yet still high enough to enable the sexual strain to drive out the asexual. For example, this happens when g is 5.33 (giving r = 207.1) and a plateau fitness is imposed at w = 7 (Fig. 1b). In this case a steady 6-point cycle occurred. Using a different fitness function, $w_i = \{\frac{3}{2}(1 - f_i)\}^g$ success with an even lower plateau was shown: with g=10 asexuals could be kept below one per thousand when maximum fitness is only 4.

Such low maximum fitnesses are of interest because of the difficulty previous authors have noted of finding any models where the two-fold effective fecundity advantage of an asexual can be overcome unless the maximum fecundity is set rather high, roughly in hundreds or thousands (Williams 1975, Maynard Smith 1978). However, the "plateau" models just mentioned have not really evaded this difficulty as regards *origin* of sex, although they may possibly reveal an aspect of the strength of sex to defend itself once it is well established. This is because in the plateau models the asexuals on their own cannot even constitute a viable population. In the last mentioned model if the sexual strain is absent the asexuals fluctuate wildly and go effectively to extinction in a few generations. In the preceding exponential model the three strains enter a stable three-point cycle. When without plateau, the fitness function dictates that the LGMF of each strain must be at two (twofold fecundity advantage of asexuality being already entered); but imposing the plateau causes this mean fitness to drop. In the case where g = 5.33 and the plateau is at 7, the LGMF is 0.228. Obviously such a population is inviable. But the model does show that once sex is established it can evolve into regions of stable coevolved fluctuation with its parasites that are uninhabitable by any mixtures of parthenogenetic lines that the sexual could give rise to. The sexual species in the last case is viable, with LGMF at 1.407. In summary, artificial as it is this simple one-locus model may be claimed to be a little more realistic and relevant to sex than that model which appears to be its only one-locus predecessor in the literature so far (Hamilton et al. 1980).

Two-locus haploid selection model

Close to a model already outlined, without formal analysis, by Jaenike (1978), I next consider a system with two loci each with two alleles. For simplicity selection will be supposed to operate only in the haploid phase. This is an unwished for assumption from the present point of view because elaborate multicelled sexual organisms that we aim to explain are mostly diploid. But if viable haploid-selection models can be found, it is to be expected that diploid-selection versions can likewise be devised (Hamilton et al. 1980), although so far, it has to be admitted, it has been easier to make haploid ones realistic).

There are now four haplotypes, AB, Ab, aB, ab, and each is supposed to confront a corresponding pathotype in the parasite species. We assume that asexual variants of each haplotype exists, each as before of twice the effective fecundity of its sexual counterpart.

The following picture of the life cycle can be suggested. After gamete fusion diploids persist only briefly and undergo no selection in this stage (they might be resting eggs, say). Then after meiosis haploid unicells are formed which multiply by division and then initiate the multicellular bodies to whose parasitism and selective elimination our previous story applies. Once past a certain stage of development parasite infection no longer kills them but the infected survivors can still harbor and multiply parasites. Thus each haplotype breeds up the clone to which it is susceptible. From among these clones, that corresponding to the most numerous genotype among current adults decimates the young of the same genotype next season. So a high fitness one season tends to be followed by low fitness next season and so on. Alternatively, with probably little difference to the behaviour of the model, it could be supposed that the young haploid hosts support infectious epidemics such that each host genotype suffers as a function of its density which is directly dependent on frequency. However strictly it is only the first of the above alternatives that has been investigated so far.

Fitness in the model is assumed to be frequency-dependent as before but a frequency of $\frac{1}{4}$ instead of $\frac{1}{3}$ now plays the crucial role. Corresponding as closely as possible to the last model although more general (see also Hamilton et al. 1980 for the rationale) the following fitness function is chosen

$$w_{11} = \exp\left[-\delta\left\{\begin{matrix}(1-z)P_{11}+zP_{12}\\ +\ zP_{21} + (-1-z)P_{22}\end{matrix}\right\}\right]$$

$$= \exp\left[-\delta\ \{v_{11} - v_{22} - 2z(v_{11} + v_{22})\}\right]$$

where P_{ij} are frequencies of haplotypes, and $v_{ij} = P_{ij} - \frac{1}{4}$ Likewise $w_{12} = \exp[-\delta\ \{v_{12} - v_{21} - 2z(v_{12} + v_{21})\}]$, and likewise for the others.

These functions have the property that when all four are present and persist and a sexual strain is absent the LGMF of every strain is 1 (or 2 after two-fold fecundity advantage of asexuals has been applied). However, if a sexual strain is present with asexuals or is present alone then the situation is more complicated. Whatever the case a haplotype, whether sexual or asexual, is to have its fitness formulated from the above expressions using the *total* frequency of the haplotype (i.e. sexual-type frequency + asexual-type frequency). We consider a pure sexual population; analysis of this case covers that

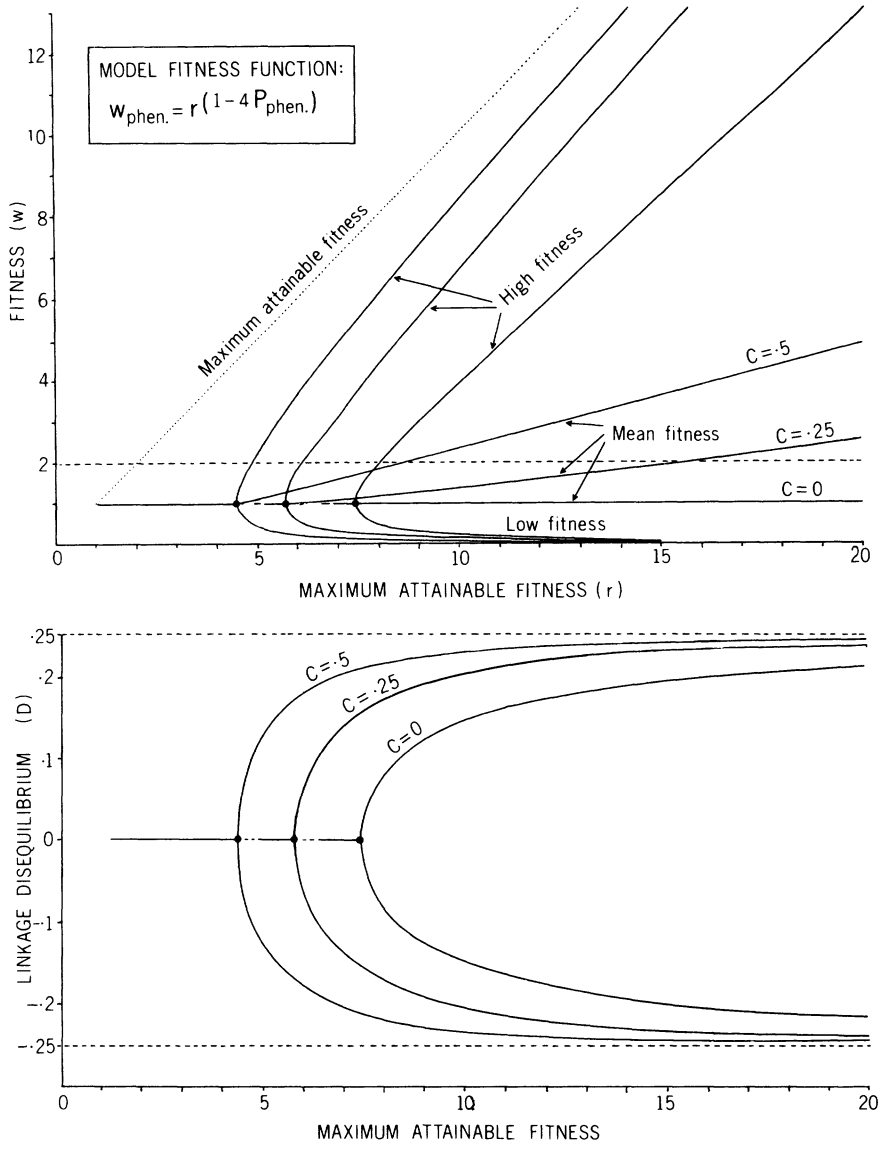

Fig. 2. Linkage disequilibrium and fitness performance displayed as functions of maximum attainable fitness (r) for a model of haploid selection on two alleles at each of two loci. At a bifurcation point depending on the linkage parameter (c), increasing r renders a stable equilibrium for four constant equi-frequent genotypes unstable and a two-point cycle supervenes. Unless there is no recombination (c = 0), almost linearly rising geometric mean fitness in the cycles indicates that from some r upwards the sexual species will out-compete the set of its emergent asexual strains. The critical r occurs where the mean fitness rises through w = 2 (dashed line; 2 represents effectively doubled fecundity of the asexual strains). High and low fitness of a particular genotype in the cycle are also shown.

of a pure mixture of asexuals if the parameter for linkage, c, is set to zero.

Let P_{11}, P_{12}, P_{21}, P_{22} be frequencies of adult haplotypes just after a round of selection. Then after meiosis and fertilization corresponding frequencies among offspring are P_{11}–cD, P_{12}+cD, P_{21}+cD, P_{22}–cD where c is linkage and D is initial linkage disequilibrium, $D = P_{11}P_{22} - P_{12}P_{22}$.

The transformation of the system from one generation of adults to the next is given by a system of four equations of which the following is typical

$$P'_{11} = (P_{11} - cD)w_{11}/\bar{w}$$

where $\bar{w}$, the mean fitness, is the sum of the four products of frequency and fitness like the product shown.

When all the v are small all w approach to 1. Thus $\bar{w}$ can be ignored and using the linear approximation to the exponential function, the above equation becomes approximately

$$\tfrac{1}{4} + v'_{11} = (\tfrac{1}{4} + v_{11} - cD) \times [1 - \delta\{v_{11} - v_{22} - 2z(v_{11} + v_{22})\}]$$

Again ignoring terms in v^2, this is

$$v'_{11} = v_{11} - cD - \tfrac{1}{4}\delta\{v_{11} - v_{22} - 2z(v_{11} + v_{22})\}$$

D can be approximated by $\frac{1}{2}(v_{11} + v_{22})$; hence we obtain the system of four linear transition equations of which the above is the first. This linear system can be analyzed

for stability, and its eigenvalues prove to be $1 - \frac{1}{2}\delta$ and $1 - c + \delta z$.

We are interested only in the positive range of the parameter δ, which roughly specifies the severity of selection. The first eigenvalue shows that $\delta>4$ is a sufficient condition for instability at the fixed point, tending to specify an oscillatory departure. Independence of this eigenvalue of c indicates that both pure sexual and pure asexual populations will show cycles in this range of δ. However, instability due to the second eigenvalue can occur at lower values: assuming z to be in the range $-\frac{1}{2}$, $\frac{1}{2}$ instability can start as low as $\delta>3$ if $c = \frac{1}{2}$ and $z = -\frac{1}{2}$ (oscillatory departure), and occurs at every positive value of δ if $c = 0$ and $z>0$ (non-oscillatory departure).

Non-oscillatory departure does not imply extinction or that, once far from the fixed point, cyclical patterns cannot occur. In fact $z>0$ can give cycles and these in turn can lead to stability of sex if δ is high enough. But much easier conditions for stability of sex are obtained in the cases where $z<0$. Since in this range $z = -\frac{1}{2}$ (assuming this to be the lower limit) is both best for sex and gives the simplest equations and closest similarity to the previous one-locus model (giving $w_{11} = \exp\{2\delta(\frac{1}{4} - P_{11})\}$, etc.), I will now confine attention to this case.

Numerical simulation of the system in this case for $3 < \delta < 4$ shows that a stable 2-point cycle develops.

In this cycle allele frequency does not vary at all at either locus; instead each locus has frequencies constant at $\frac{1}{2}$. As to absolute values, all v's are also identical and constant but cycle in the following way: in one generation v_{11} and v_{22} are positive while v_{12} and v_{21} are negative, then v_{11} and v_{22} are negative while v_{12} and v_{21} are positive, and so on.

Knowing that this cycle existed, it was possible to locate the equilibrium absolute value of D analytically. In the briefest form I could obtain, the equilibrium equation is

$$\cosh\{\ln(4\sqrt{bD})\} - \cosh(\ln\sqrt{b})\coth 2\delta D = 0$$

where $b = 1 - c$.

Treating the LHS expression as f(D) we obtain, in preparation for a Newton method approximation to the solution for D,

$$f'(D) = 1/D \sinh\{\ln(4\sqrt{bD})\} + 2\delta\cosh(\ln\sqrt{b})\,\mathrm{cosech}^2(2\delta D)$$

Using this I obtained the results graphed in Fig. 2. As can be seen, the 2-point cycle described above potentially occurs at all $\delta>3$. But when δ rises through 4 a further pair of stable cycles is potentiated. These are actually homologous to the case already implied in the figure where $c = 0$: if loci are completely linked the system becomes equivalent to one of four independent asexual strains. The figure shows that there is a stable cycle where $c = 0$ and D alternates. D is $P_{11}P_{22} - P_{12}P_{21}$: thus considering the other ways of pairing among four independent asexual strains there must also exist stable cycles for $D' = P_{11}P_{12} - P_{22}P_{21}$ and for $D'' = P_{11}P_{21} - P_{12}P_{22}$. As is implied in the graph and easily confirmed by simulation experiments, cycles for D' and D'' exist as attractors for all $\delta>4$, whether or not $c = 0$. A little thought based on what has been said about the cycle already analyzed shows that these two new cycles, respectively, must arrange that $P_{11} = P_{12}$ and $P_{21} = P_{22}$, or else that $P_{11} = P_{21}$, and $P_{12} = P_{22}$; in other words, either gene frequency of A goes to 0.5 while that of B alternatives, or vice versa. As apparent from the $c = 0$ case in Fig. 1 (and as designed for in construction of the fitness function) cycles of this kind give no advantage to sexual reproduction for any magnitude of δ. Thus when $c>0$ and there is some hope for sex from the cycle and circumstances mentioned previously, the possibility that the system enters the domain of the alternative type of cycle must be considered a danger for sex, for as soon as the alternative cycle occurs the system is likely to be invadable by asexual mutants. Unfortunately, there is little that can be reported here on the sizes of the domains of "good" and "bad" cycles. When $c = 0$ and $\delta>4$ it is obvious from symmetry that all three cycles have equal domains; but then all three are equally bad. Since the inception of the cycle favorable to sex "grows" back to $\delta = 3$ as c increases to 0.5, it seems conjecturable that this cycle will have the largest domain at all $\delta>3$ for all $c>0$. But one finding suggesting this may not be true is that in one set of simulation runs a certain fixed starting point was observed to pass out of the attractance of the good cycle into that of the bad as δ increased from 6 to 7.

Having given cautionary outline concerning the existence of cycles unsatisfactory for sex, I now resume consideration of the hopeful two-point cycle.

For the purpose of displaying results Fig. 2 does not use δ itself as abscissa but instead that highest fitness which a given δ makes possible. This highest fitness occurs when the frequency of a type is zero and is given by $r = \exp(\frac{1}{2}\delta)$. Here r is equivalent to what Williams (1975) called the ZZI ("zygote-to-zygote increase") of a species. Its interest for the theory of sexuality, arising from the difficulty of devising successful models when r is low, has already been mentioned.

In the case of the present model values of r capable of making sex succeed against parthenogenesis are satisfyingly low. It can be seen from the figure that the changes accompanying the onset of instability as r increases are quite dramatic. Most relevant here, in best case, $c = \frac{1}{2}$, the mean fitness of the sexual begins a very nearly linear ascent at the bifurcation and passes 2 when $r \simeq 8.6$. The fecundity of a sexual species with a 1:1 sex ratio corresponding to this is 17.2. The actual highest fitness expressed in the cycle at this point is about 6.8, corresponding to fecundity 13.6.

There are hardly any sexual species – if any at all –

whose normal potential fecundity is less than this. Even for man, for example, an expressed birth fecundity of 14 would not be extreme. Of course a severe caution has to accompany such an example, for even foetal selection in man is on diploids: for man and most other sexual species only wastage of gametes could be strictly relevant to the model. A previous model (Hamilton et al. 1980), however, gave some ground for expectation that similar models with diploid selection can be produced. Work on this is in progress.

Another cause for caution in applying the above results lies in the fact that the model studied so far covers a sexual species alone, or the set of four parthenogenetic strains alone (the case c = 0) but does not cover the behavior of a mixed sexual-asexual population. Thus it is not clear that as soon as the LGMF of a pure sexual species rises above 2, the same species in a mixed population will be able to shed its asexual competitors. However, it is clear that the sexual population with LGMF>2 is an ess with regard to low frequency invasion by asexuals, and it will be surprising if results suggested in Fig. 2 are not also robust against high frequency invasions.

As Fig. 2 shows and as all the foregoing discussion has led to expect, the best result for sex comes when c is maximal (i.e., there is independent assortment of loci). For the benefit of sex as in these models, different syllables of a password are best coded in different chromosomes. While I am not aware that contributions to self-identifying antigens can come from unlinked loci, there is evidence, again for mice, that such loci may contribute to competence of antibodies against complex artificial antigens (Caldwell 1976: 135). This and other recent evidence that recognition of foreign substances is not wholly dependent on a single short region of chromosome (Rosenstreich 1980) perhaps adds plausibility to the recombinant password idea.

Again we have not strictly shown that a high recombination population beats a low recombination one, still less that a linkage modifying locus is selected to cause high values of c, but these outcomes seem probable. The demand for high recombination values in models like these which assume fluctuating environments is in contrast to the requirements on linkage found in other broad classes of models concerned with sex, where usually the puzzle is to see why selection for closer linkage doesn't make the genotype "congeal" (Turner 1967, Maynard Smith 1978).

Attempting to resolve this puzzle, Charlesworth (1976) has shown that alleles causing higher rates of recombination can be selected when linkage disequilibrium is made to fluctuate; and very recently Graham Bell (pers. comm.) has shown this also in a model where the changes in linkage disequilibrium result from spontaneous cycling. Bell's model is frequency dependent and coevolutionary like the present one but uses different fitness functions. His analysis is focussed on length of time lag rather than selection intensity in the induction of cycling, and on the selection for degree of linkage rather than ability of sexuals to beat a doubled effective fecundity of asexuals.

In the present model lowest possible fitnesses are very low [$\exp(-\frac{3}{2}\delta)$]. Low fitnesses in the stable cycles are less low – in fact merely reciprocals of the high fitnesses – but their contrast to the high fitnesses still implies an intensity of selection that may seem very implausible. However, bearing in mind another feature, that all this selective elimination goes on with both mean fitness and gene frequencies remaining *constant,* it seems that the occurrence of such intense selection might easily escape notice. Ideally, to reveal the kind of process envisioned, mortality statistics are needed classified both for genotype and for major biotic causes. Lacking such data the most hopeful simple sign would be linkage disequilibrium observed to fluctuate radically from one generation to another. Hitherto there have been too few genetic surveys of natural populations that both cover enough loci to make likely the detection of polymorphism loci that are at least close to "password syllable" loci, and at the same time cover enough generations. Data for the same natural population over many generations are particularly lacking.

Conclusions

Of course the above model is bound to be an extreme oversimplification of any real situation. However this model, plus some simple modifications and extensions which cannot be detailed here, plus also the even more artificial one-locus system described earlier, can be summarized as having made certain possibly useful points about what might be expected in nature if biotic interactions (Glesener and Tilman 1978), and especially interactions with short-lived parasites, are responsible for maintenance of sexuality. The points emerging from the model are:

(1) Frequency dependent selection acting hardest against the most common genotype easily sets up cyclical processes (Jaenike 1978).

(2) In such processes population size may remain relatively constant and so fail to suggest intensity of selection.

(3) When more than one locus is involved gene frequencies also may remain relatively constant; but intense fluctuating selection then remains reflected by fluctuating linkage disequilibria.

(4) In a two-locus model cyclical or fluctuating processes tend to onset at lower intensities of selection for sexuals than for asexuals.

(5) As selection intensity increases there comes a point, usually achievable at moderate levels of fecundity, where a sexual species has an advantage over any asexual strain even when the latter are given a two-fold advantage in effective fecundity. Asexuals then die out or are maintained only at very low frequency.

(6) High levels of recombination facilitate such exclusion of asexuals by sexuals.

(7) Pressures on a host species by a set of varieties, or of species, of parasites seems particularly likely to engender the cycling discussed. In particular, shortness of life-cycle of parasites relative to hosts gives their populations the kind of overreactive frequency dependence that is particularly favourable to sex.

(8) Success of sex due to the frequency-dependent selection processes described does not require competition between sibs or other relatives.

References

Caldwell, J. L. 1976. Genetic regulation of immune responses. – In: Fudenberg, H. H. et al. (ed.), Basic and clinical immunology. Lange, Los Altos, pp. 130–139.

Charlesworth, B. 1976. Recombination modification in a fluctuating environment. – Genetics 83: 181–195.

Clarke, B. 1976. The ecological genetics of host-parasite relationships. – In: Taylor, A. E. R. and Muller, R. (ed.). Genetic aspects of host-parasite relationships. Blackwell, London, pp. 87–103.

Fisher, R. A. 1934. Randomisation and an old enigma of card play. – Math. Gazette 18: 294–297.

Glesener, R. R. and Tilman, D. 1978. Sexuality and the components of environmental uncertainty: Clues from geographical parthenogenesis in terrestrial animals. – Am. Nat. 112: 659–673.

Haldane, J. B. S. 1949. Disease and evolution. – La Ricerca Sci. Suppl. 19: 68–76.

Hamilton, W. D. 1975. Gamblers since life began: barnacles, aphids, elms. – Quart. Rev. Biol. 50: 175–180.

– , Henderson, P. A. and Moran, N. 1980. Fluctuation of environment and coevolved antagonist polymorphism as factors in the maintenance of sex. – In: Alexander, R. D. and Tinkle, D. W. (ed.), Natural Selection and Social Behavior: recent research and theory. Chiron Press, New York.

Hatchett, J. H. and Gallun, R. L. 1970. Genetics of the ability of the Hessian fly, *Mayetiola destructor,* to survive on wheats having different genes for resistance. – Ann. ent. Soc. Am. 63: 1400–1407.

Jaenike, J. 1978. An hypothesis to account for the maintenance of sex within populations. – Evol. Theory 3: 191–194.

Lilly, F. 1972. – In: McDevitt, H. O. and Landy, M. (ed.), Genetic control of immune responsiveness: relationship to disease susceptibility. Academic Press, NY.

Maynard Smith, J. 1978. The evolution of sex. – Cambridge Univ. Press, Cambridge.

Rosenstreich, D. L. 1980. Genetics of resistance to infection. – Nature, Lond. 285: 436–437.

Turner, J. R. G. 1967. Why does the genome not congeal? – Evolution 21: 645–656.

Williams, G. C. 1975. Sex and evolution. – Princeton Univ. Press, Princeton, New Jersey.