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Origin of Sex

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The competitive advantage of sex consists in being able to use redundancy to recover lost genetic information while minimizing the cost of redundancy. We show that the major selective forces acting early in evolution lead to RNA protocells in which each protocell contains one genome, since this maximizes the growth rate. However, damages to the RNA which block replication and failure of segregation make it advantageous to fuse periodically with another protocell to restore reproductive ability. This early, simple form of genetic recovery is similar to that occurring in extant segmented single stranded RNA viruses. As duplex DNA became the predominant form of the genetic material, the mechanism of genetic recovery evolved into the more complex process of recombinational repair, found today in a range of species. We thus conclude that sexual reproduction arose early in the evolution of life and has had a continuous evolutionary history. We cite reasons to reject arguments for gaps in the evolutionary sequence of sexual reproduction based on the presumed absence of sex in the cyanobacteria. Concerning the maintenance of the sexual cycle among current organisms, we take care to distinguish between the recombinational and outbreeding aspects of the sexual cycle. We argue that recombination, whether it be in outbreeding organisms, self-fertilizing organisms or automictic parthenogens, is maintained by the advantages of recombinational repair. We also discuss the role of DNA repair in maintaining the outbreeding aspects of the sexual cycle.

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1. Introduction

In this paper we propose an explanation for the origin of sexual reproduction based on an immediate selective advantage to individuals. We argue that sex evolved at a very early stage in the history of life as a means of overcoming genetic damage. In broad outline, our argument is similar to that of Dougherty (1955), who was the first, to our knowledge, to argue that the origin of sex is based on overcoming genetic damage. However, a much better understanding of sex in simple microorganisms (see Section 6 and 7) and a firmer picture of early evolutionary events (Eigen, 1971; Eigen *et al.*, 1981; Bernstein *et al.*, 1983) has been achieved since the time of Dougherty's paper. Consequently, we are able to offer a clearer and more detailed argument about both the events leading up to the origin of sex and the selective advantages of sex itself. In particular, we offer a novel explanation as to why it is the complete sexual cycle, involving both the coming together of the genomes from two separate individuals in a common cell and their subsequent separation into daughter cells, that is the most advantageous strategy to overcome genetic damage.

A number of authors have suggested that sex originated very early in the history of life (e.g. Dougherty 1955; Haldane 1954; Hunter 1955; Maynard smith 1978, pp. 6–7; Mayr 1963, p. 411–412; Muller 1955, Stebbins 1960), while several others have maintained that sex originated relatively late, with the evolution of primitive cellular organisms being entirely asexual (Boyden 1953, Darlington 1958). In order to pose precisely the question of whether sex arose early or late in evolution and what selective mechanisms were involved, it is necessary to begin with some general assumptions concerning the origin of life. Eigen and co-workers have studied the properties of single-stranded RNA replicators in detail (for recent review, see Eigen *et al.*, 1981), and have proposed that such a system provides a plausible and testable model for understanding early evolutionary events. In a previous paper (Bernstein *et al.*, 1983), we argued that the features of Eigen and coworker's scenario for the origin of life are generic.

For the reasons given in the previous paragraph, we begin in section 3 with the evolution of simple single-stranded RNA replicators and discuss the stages leading to encapsulation of these replicators in a protocell. The problems faced by encapsulated genes are discussed in section 4. These problems primarily involve damage to the genes and segregation of the genes into progeny. In the absence of sophisticated repair enzymes and mitotic apparatus (the small genome could not yet encode for such functions), we argue that these problems were initially overcome by maintaining redundant copies of the genes within the protocell. All of our models of

redundancy contain the alternative of rapid proliferation to maintain a pool of viable (undamaged) protocells against loss of information. As discussed in sections 4–6, and as modeled in the appendix, redundancy has costs. It is less costly, and hence more adaptive, first to partition the redundant copies between cells which periodically fuse, allowing recovery of the damaged or lost genes, and subsequently to split into daughter cells. We consider this cycle of fusion and splitting to be the sexual cycle in its most primitive form.

In our discussion of the origin of sex we are concerned only with identifying the major evolutionary forces acting on the replicators, along with the likely effects of these forces, rather than the exact sequence of molecular events, which is still highly speculative. We do, however, base our account of the origin of sex on our understanding of sex in current microorganisms, which we discuss in section 7. We then comment on the evolutionary history of sexual reproduction (section 8) and on the role of DNA repair in the maintenance of recombination (section 9) and outbreeding sex (section 10). We conclude by discussing the general effects that sex has on the dynamics of evolution, a topic which will be pursued in more detail in a later paper.

2. Terminology

It is important to distinguish the problem of genetic damage from that of deleterious mutations. The term genetic damage, as conventionally used in molecular biology, denotes chemical alterations of the genetic material which disrupt the regularity of the DNA or RNA molecule and interfere with replication or gene expression. Mutations, which consist of changes in the nucleotide sequence, alter the information content but not the integrity of the physical structure of the DNA or RNA molecules. Genetic damage is distinct from mutation in that damaged genes are not copied during replication. Known examples of damage are: thymine dimers caused by UV light; apurinic sites caused by spontaneous hydrolysis; and alkyl additions caused by a wide variety of organic compounds.

We use the term sex to refer to a process in which the genomes of two parents are brought together in a common cytoplasm to produce progeny which may then contain reassorted portions of the parental genomes.

We propose that sex initially arose as a means for genetic recovery, which refers to any process leading to the reconstitution of an intact, functional genome that has been in some way damaged. There are a variety of well-studied specific mechanisms for genetic recovery in current organisms, such as DNA excision repair, and multiciplicity reactivation in viruses. In sections 4 and 5, we propose a mechanism of genetic recovery operating in primitive

protocells, which acts similarly to multiplicity reactivation of single-stranded segmented RNA viruses.

3. Primitive RNA Replicators

As discussed by Eigen (1971) and Bernstein *et al.* (1983), natural selection began to operate on simple RNA replicators at a very early stage, when RNA sequences were less than 50 nucleotides long. It is assumed that these RNA molecules replicated by a primitive mechanism involving complementary base pairing. Errors of replication would lead to occasional mutational variants with a nucleotide sequence that enabled more rapid replication, greater stability to decay, or enhanced ability to utilize resources. Such variants would tend to increase at a greater rate than competitors and thus, in time, to predominate. Our earlier paper (Bernstein *et al.* 1983) ended with the replicator at the stage of non-enzymatic, template-mediated replication. The present paper develops the consequences of the subsequent evolutionary stages, in which protein replication and encapsulation in a protocell have been attained (see also Michod, 1983, for discussion of these issues). We first summarize the selective factors responsible for the evolution of enzyme catalyzed replication and encapsulation.

Present enzymes catalytically increase by orders of magnitude the rates of RNA replication. Even small influences of primitive proteins on replication would be strongly selected for. We assume at this stage that the primitive RNA replicator was not encapsulated so that its proteins were simply released into the surrounding medium, and were thus available to the RNA molecules which specified them, as well as to competitors. Such protein-producing replicators are "hypercycles", the dynamical properties of which have been extensively studied (Eigen & Schuster, 1979; Bernstein *et al.*, 1983, and references therein). Hypercycles may be simple, involving only a single RNA molecule and its encoded protein, or complex, containing several interacting RNA molecules and their encoded proteins. The reader interested in the technical aspects of selection among hypercycles is referred to the works just cited. We now simply summarize some of the properties of hypercycle dynamics.

The fitness (per capita rate of increase; Fisher, 1958) of a hypercycle is proportional to the concentration of the proteins that it makes, but this concentration is, in turn, proportional to the concentration of the hypercycle RNA. Thus the fitness of the hypercycle is very small when it is rare, since a rare hypercycle produces few proteins and has problems encountering them. Consequently, the first hypercycle (RNA and their encoded proteins) has difficulty expanding when rare even in competition with replicators that

do not use proteins (Michod, 1983). This is so because the benefits of making a protein are density-dependent and are not realized until the hypercycle is common. However, the costs of making the protein are density (numbers of molecules per unit volume) independent and are paid even when the hypercycle is rare. Consequently, the first hypercycle needs some favorable accident to get started, but once started it replicates under favorable circumstances and easily out-competes the comparatively ineffective replicators which do not produce proteins. Subsequent hypercycles have a much more difficult time competing with a hypercycle already present. They have the same difficulty of expanding when rare as the first, but now must do so in an environment occupied by the first hypercycle, which has substantially used up the resources in maintaining its own population. Thus the new hypercycle has a more difficult problem in expanding than the first. This difficulty is quite independent of whether it might be better adapted than the first if both were equally common (Michod, 1983, 1984).

As proposed by Eigen and coworkers, hypercycles can have a number of RNA segments, or genes, which interact in a mutually dependent fashion. The most likely hypercycle has only one gene and its encoded protein. We use this case to illustrate the point that a hypercycle is doomed to extinction unless it becomes encapsulated. Consider a hypercyclic replicator which produces a protein that it uses to replicate itself, (e.g. a primitive polymerase). Such a replicator is vulnerable to the occurrence of a "selfish" mutant that also uses the protein, but does not make one. Since the mutant spends no time encoding proteins, it can replicate more frequently and will expand in the population. This expansion drives the original hypercycle, as well as the mutant, to extinction. This lethal mutant acts just like a "cheater" in sociobiology; indeed hypercyclic and social dynamics have important similarities (Eigen, 1971; Michod, 1983). For these reasons, we believe that encapsulation is necessary at this point for evolution to continue. We do not propose a specific hypothesis concerning the mechanisms by which this was accomplished. However, we should note that passive localization of a hypercycle and its proteins through the population structure created by coacervates (Oparin, 1965, 1968), rock crevices, or water droplets (Woese, 1980; van Holde, 1980; Kuhn & Wasser, 1983), may have preceeded active encapsulation by a cell membrane, and may have played an important role in getting a hypercycle started (Michod, 1983).

4. Encapsulated Replicators

The transition to encapsulation could, in practice, involve many details which are peripheral to our argument. The important evolutionary step

occurs when a hypercycle codes for a protein which promotes the encapsulation process, thereby increasing the likelihood that its progeny will have capsules of their own. The simplest processes to imagine, which are similar to processes observed in cells today, are promotion by the genome of accretion of material into a capsule envelope and/or promotion of splitting when the genome has replicated enough copies of itself (the accretion process can occur spontaneously). It seems to us improbable that a single protein can carry out both this function and the function of replication. Therefore the essential question is whether a sufficiently complex hypercycle can arise to carry out the several functions implied by this step.

To study this question, we have simulated populations of single-gene hypercycles, each of which produces a protein which has random effects on the other hypercycles in the population. The hypercycles in this population are assumed to be competing for a common resource. Approximately one per cent of the time, we find that this competition results in the formation of a hypercycle containing four or more genes. Given the vast number of trials implied by repeated extinctions due to selfish mutants, it seems certain that, by chance alone, a hypercycle would arise which has enough genes to simultaneously promote encapsulation and replication.

We now envision an encapsulated hypercycle which exploits the available compounds in the primitive soup to form a simple surrounding membrane (possibly a lipid bilayer) of the protocell. Since the proteins encoded by the genome are kept in the protocell, their density is higher than the density of encoded proteins in the case of the free hypercycle. Since, as discussed in the last section, fitness is proportional to protein density, the encapsulated hypercycle is more fit than the free hypercycle. Finally, the encapsulated hypercycle is no longer at the mercy of selfish mutants, since if they arise in one protocell they kill off only that one protocell instead of parasitizing the whole population of protein-producing replicators.

We thus see evolution inexorably leading to a stage in which it functions as it largely does today, where the individual organism, i.e. the protocell, becomes the basic unit of selection, rather than the naked gene itself. A number of evolutionary processes such as perfection of the protocell structure will be going on at this stage, but we do not discuss these except to note that the genome will have to expand in size to accommodate the additional information needed. The three problems faced by these primitive protocells which are most important for the evolution of sex are: (i) the effect of damage to the gene; (ii) the cost of redundant genomes; (iii) the problem of gene segregation during protocell division.

For hypercycles containing more than one gene, the problem of segregating a complete complement of genes into progeny protocells arises immedi-

ately, once the primitive RNA hypercycle becomes encapsulated in a protocell. Failure of segregation would result in protocells missing one or more genes of the complete hypercycle. Such protocells would be metabolically inert and hence incapable of replication. Multiple copies of each gene within a parent protocell would help insure that progeny cells receive a full complement of the hypercycle genes.

A more crucial problem for the primitive RNA protocells, and indeed all living systems, is to maintain the transmission of information upon replication. The protocells must deal with damage to the RNA that would be expected to result from spontaneous hydrolysis or from the effect of extrinsic agents such as UV light or reactive chemicals. On the basis of studies on existing RNA viruses, such damage prevents replication unless repaired (McClain & Spendlove, 1966, and references therein). To overcome such damage, redundant copies of the genes must be available, from which the protocell containing a damaged genome can recover the lost information.

Three stages in the evolutionary response to the problems created by genetic damage or gene loss can be distinguished, all of which rely on redundancy in one form or another. In addition to overcoming the problems posed by genetic damage, the first two stages counteract the problems posed by failure of segregation. In the first stage, the redundant information is carried within a protocell in the form of multiple copies of the genome (i.e. a K-ploid protocell). In the two subsequent stages, the redundancy is partitioned between protocells which periodically fuse to allow recovery of the lost information. This genetic recovery is accomplished in the second stage through replacement of the damaged or lost gene through fusion and then "hypercyclic cooperation" (discussed below) which restores the correct proportion of the gene (see Fig. 2 below). In the third stage, genetic recovery is accomplished through more sophisticated means of repair such as those found in current organisms (for review see Bernstein, 1983). The second stage, in which the redundancy is partitioned between different protocells which fuse and then split, represents the sexual cycle in its most primitive form.

5. Hypercyclic Cooperation

The primitive genome consisted of a cooperative set of genes, each of which encodes a function necessary for the reproduction of the whole genome. Consequently, if genes $A, B, C, \ldots$ encode for protein products $a, b, c, \ldots$, respectively, then all of the protein products are necessary for reproduction of each gene in the genome. This is an example of a totally connected hypercycle or "compound hypercycle" of the sort studied by

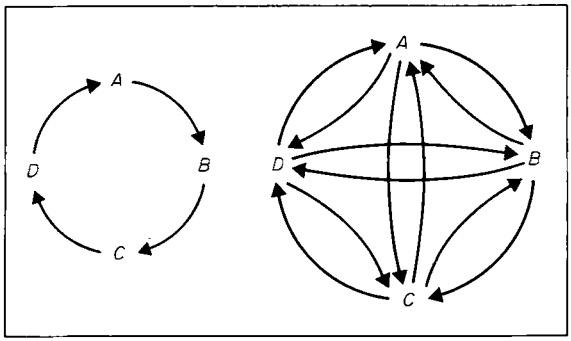

FIG. 1. Elementary and compound hypercycle. See text for explanation.

Eigen & Schuster (1979, pp. 43–44; see Fig. 1(b)). A simpler form of the hypercycle occurs if each gene product aids the replication of only one other gene (Fig. 1(a), also see below). Eigen & Schuster (1979, pp. 44–49) term such a hypercycle an "elementary hypercycle". Since the elementary hypercycle is more amenable to discussion and interpretation, it will be used in the discussion which follows. However, the points made concerning it also hold for the compound hypercycle. (The illustration in Fig. 1(b) is insufficient to specify the dynamics of the compound hypercycle. For example, one arrives at different equations depending on whether one assumes that the proteins act sequentially, i.e. one at a time, or simultaneously in replicating an RNA segment. Eigen & Schuster assume the latter, whereas our calculations mentioned above (but not reported here) concerning the likelihood of hypercycles with four or more genes assume the former. Empirical data on present day viruses (Bernstein *et al.*, 1983) indicates that reality lies somewhere between these extremes. Since the results in either case are similar, this is a detail that is relatively unimportant for the present discussion.)

We now summarize the qualitative properties of hypercycles as developed by Eigen & Schuster (1979). We view the hypercycle as the precursor of the genome. The most important property of the hypercycle for our argument is that its component genes cooperate in each other's replication. If this were not the case, it would be unstable. It would either not grow at all and eventually go extinct, or it would evolve into a cooperative cycle by discarding the non-cooperative components. Consequently, all hypercycles, whether elementary or compound, act as a single coherent entity, and not as a sum of independently functioning parts. If we denote by $A, B, C, \ldots$ the genes of an elementary hypercycle, and by $a, b, c, \ldots$ the proteins they

encode, then *a* must assist the replication of *B*, *b* must assist the replication of *C*, and so on until the loop is closed by the last gene that assists the replication of *A*. A crucial consequence of the mutual cooperation is that it maintains a fixed proportion among the genes. If one gene is damaged, the correct proportionality is rapidly restored. (In multi-gene hypercycles, the proportions can coherently oscillate in time, but on the average over time the proportionality is maintained.) Thus, so long as there is more than one copy of each gene for an encapsulated hypercycle, the abundance (i.e. ploidy) of a damaged gene segment will be rebuilt through hypercyclic cooperation.

6. The Competitive Advantages of Sexual Reproduction

This section summarizes the results of our analyses of the model presented in the Appendix. We feel that our argument can be understood on a qualitative level without going into details of the model here. High ploidy initially guaranteed the redundancy needed to allow replication of the protocell in the presence of gene damage and failure of segregation. However, there are costs to having the redundancy within a protocell. First, mononucleotide resources must be committed to producing this redundancy. For such simple organisms, the resources actually tied up in the genetic material would be a large fraction of the total resource budget. Consequently, under conditions of limiting resources, a higher ploidy will lower the protocell birth rate. Second, protocells with higher ploidy will tend to be larger and therefore more vulnerable to external agents which disrupt the protocell membrane. Consequently, although a higher ploidy decreases the vulnerability to gene damage because of redundancy, there is a cost for creating and maintaining this redundancy. Although a lower ploidy lowers the cost of redundancy, it does so by vastly increasing the rate at which organisms become metabolically inert because of genetic damage and hence incapable of replicating.

The advantage of sex for these early unicellular organisms is that it minimizes the costs of redundancy by partitioning the genomes among protocells, while allowing protocells to reap the benefits of genetic recovery through fusion and hypercyclic cooperation (Fig. 2). This cost-benefit pressure operated throughout the phase of evolution being discussed. Failure of segregation, which high intracellular redundancy initially counteracted, has the same consequences as damage, since the protocell with missing genes is also incapable of replication. Such protocells which lack one or more genes will recover by hypercyclic cooperation once they fuse with a protocell which contains the missing genes.

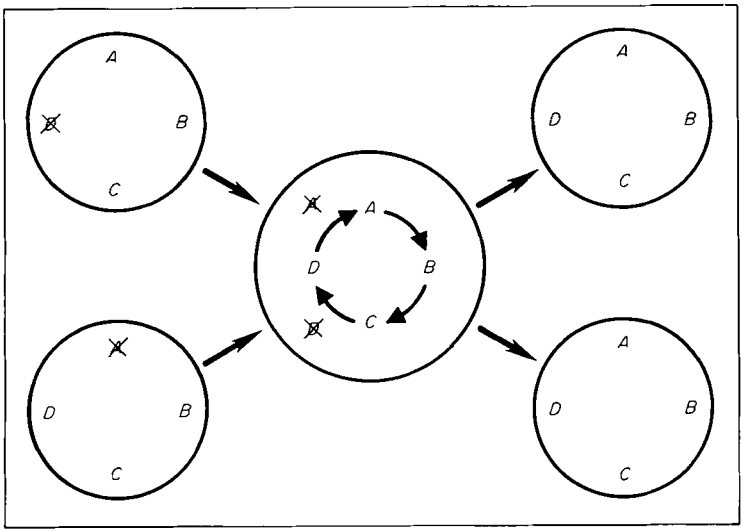

FIG. 2. Primitive sexual cycle. Fusion of two protocells with different damaged genes to undergo genetic recovery. Hypercyclic cooperation in the fused protocell restores the level of each of the genes. The fused protocell then splits into daughter protocells which now have a complete set of non-damaged genes. This figure also depicts multiplicity reactivation of two damaged influenza viruses. In this case the damaged viruses invade a bacterium instead of fusing with one another.

We therefore conclude that selective forces lead to the recovery of genetic information through the union of two protocells with homologous genomes. This fusion followed by splitting depicted in Fig. 2 constitutes the sexual cycle in its most primitive form. The recovery of genetic information lost by damage is thus the essential adaptive reason for the origin of sexual reproduction. Another major advantage of sex is that it allows protocells with low intracellular redundancy (i.e. low ploidy) to out compete protocells with high intracellular redundancy because of the cost of this redundancy. A typical situation in our models is to find that haploidy, which minimizes the cost of redundancy, is nonviable without sex because the haploid protocell is sensitive to damage and the problems posed by segregation. With the introduction of sex as a mechanism of genetic recovery, haploidy is not only viable but becomes the strategy with the highest fitness. Conversely, without sex there are cases in which diploidy is less fit than triploidy.

It is not clear whether there was a precise evolutionary moment at which sex evolved. We regard the "ploidies" that we have been discussing, as statistical norms of a highly imperfect process. The advantages to the protocell of splitting (to decrease the cost of redundancy) and fusion (to reap the benefit of redundancy) exerted a continuous and increasing pressure

on the evolution of the life-cycle of the primitive protocell, with the sexual cycle as the end product.

7. Sex in Current Microorganisms

In constructing the above argument for the origin of sex, we were guided by information on recombinational mechanisms for overcoming damage in extant organisms. Since we assume that life started as simple single stranded RNA replicators and that sex emerged at this early stage, we turned to the single stranded RNA viruses for clues to the primitive origins of sex. Thus Eigen's model of the hypercycle and our argument on the origin of sex are both based explicitly on single-stranded RNA viruses. As evolution proceeded, more complex genomes arose, each needing mechanisms for overcoming damage. We give examples of the following: (i) single-stranded segmented RNA, (ii) double stranded segmented RNA in which each segment corresponds to a separate gene, (iii) double-stranded segmented RNA in which each segment corresponds to several genes, and (iv) double-stranded unsegmented DNA. Organisms with each of these kinds of genome are discussed with respect to our proposal for the origin of sex.

Influenza virus contains a segmented single-stranded RNA genome composed of eight physically separate segments, corresponding approximately to genes (see, for example, the review by Kilbourne, 1981). The reactivation by fusion of two protocells having different damaged genes discussed in sections 4–6 and represented in Fig. 2, is directly analogous to the known phenomenon of multiplicity reactivation of UV light inactivated influenza virus (Barry, 1961). Multiplicity reactivation is a process common to many viruses in which two viral genomes with potentially lethal damages undergo recombination to form undamaged progeny.

In our detailed models of the origin of sex (see appendix), we have implicitly assumed that the genome (i.e. the hypercycle) was initially segmented, as in the influenza virus. The rationale for this is clear if one considers the opposite case of a comparable unsegmented genome in which all the genes are physically linked. In the case of unsegmented genomes, a single damage can prevent replication of the entire genome rather than just one gene. Thus in an unsegmented genome, recovery by means of a sexual cycle as outlined above would simply not occur (at this stage enzyme mediated recombination has not yet evolved). Consequently, the unsegmented case is competitively disadvantageous in comparison to the segmented one.

In the early protocell, as for the influenza virus, some assortment mechanism must have evolved to maximize the chances that a copy of, say, gene

A and a copy of gene *B* are segregated to each daughter protocell rather than having two copies of *A* pass to one daughter and two copies of *B* to the other. A simple solution would be for the *A* and *B* genes to evolve terminal complementary base sequences. This would allow temporary non-covalent joining of the two genes to promote appropriate segregation. Such appropriate segregation does occur in influenza virus, though the segregation is sloppy, with defective particles frequent. However, the molecular details of segregation in this case are not yet known.

We assume that the primitive single-stranded RNA replicators evolved into double-stranded RNA replicators, because an RNA duplex is more stable than an RNA single strand. These still existed in a segmented form with each gene on a separate segment. They underwent sexual union and recombination, as did the single-stranded RNA replicators, but continued to suffer from the segregation problem. Reovirus is an example of a segmented double-stranded RNA virus that undergoes multiplicity reactivation of damaged genomes (McClain & Spendlove, 1966). At the next stage, the segregation problem was partially solved by clustering genes with related functions on one duplex RNA segment. The bacteriophage $\phi 6$ has three duplex RNA segments which contain respectively at least four, three and three genes (Cuppels *et al.*, 1980). At a later stage of evolution, duplex RNA was replaced by duplex DNA because of the greater stability of DNA. To cope with the segregation problem while still permitting recombination, all genes became covalently linked end to end, but special enzymatic mechanisms evolved to allow reassortment of undamaged segments of DNA. This situation is illustrated by bacteriophage T4. The genome of this organism is in the form of a continuous DNA duplex. Bacteriophage T4 is able to overcome effectively various types of DNA damage by multiplicity reactivation. This phenomenon has been extensively studied, and has been shown to be a recombinational process carried out by particular enzymes specified by genes of the bacteriophage (for review, see Bernstein, 1981).

8. Does Sex Have a Continuous Evolutionary History?

It has been argued that sexual reproduction in microorganisms and multicellular organisms have separate evolutionary origins (Boyden, 1953; Darlington, 1958; Bell, 1982, pp. 84–87). This argument is based in large part on the presumed absence of sexual reproduction in cyanobacteria. Cyanobacteria are considered by Bell (1982, pp. 86–87) to be direct descendants of a species that was the ancestor of green plants. However, the more common interpretation is that the cyanobacteria are ancestors of only the chloroplast organelle of higher plants (Margulis, 1981). Nevertheless, in

recent years convincing evidence has been presented for sexual reproduction even among the cyanobacteria (Stevens & Porter, 1980; Shestakov & Khyen, 1970; Singh & Sinha, 1965), implying that the inferred major gap (e.g. Bell, 1982, pp. 84–87) in the evolutionary sequence of sexual reproduction does not actually exist. Considering the similarities in recombinational repair between organisms as different as phage T4, *E. coli.*, yeast and *Drosophila* (see Bernstein, 1983, for review), it seems likely to us that recombinational repair, and hence sexual reproduction, has a common origin and continuous evolutionary history.

9. The Maintenance of Recombination

In this section, we argue that genetic repair is an important factor in maintaining the recombination aspects of the sexual cycle (see, also, Bernstein, Byers & Michod 1981). In the next section, we deal with the selective factors that maintain the *outbreeding* aspects of sex. Here we deal only with the maintenance of recombination, whether in outbreeding organisms, self-fertilizing organisms, or in automictic parthenogens. All the above forms of reproduction include a step in which chromosomes synapse in pairs. We argue that this pairing serves the key function of allowing recombinational repair of germ line DNA. In outbreeding sexual forms, pairing is between homologous chromosomes of different parental origin. In self-fertilizing forms and most automicts, pairing is between homologous chromosomes, although from the same parent. In animals, some of the most conspicuous parthenogens undergo premeiotic, endomitotic doubling in chromosome number; formation of bivalents presumably between identical sister chromosomes; and then two successive meiotic divisions (Cuellar, 1971).

Bernstein (1983) has reviewed evidence that recombinational repair is highly efficient in overcoming certain types of lethal DNA lesions such as double strand breaks and crosslinks. It seems likely that recombination provides a powerful selective advantage at each generation by eliminating lethal genome damages. This leads us to suggest the hypothesis that in general recombination is maintained by the selective advantage of germ line repair. We will refer to this as the Repair Hypothesis for the maintenance of recombination.

For the repair hypothesis to be proven correct, it would have to be shown that accumulation of DNA damage is a serious problem in germ line DNA, and also that the types of damage accumulating naturally are efficiently removed by recombinational repair. There is substantial evidence that DNA lesions do accumulate naturally in somatic cells, but germ line cells have

not been studied from this point of view (see review by Gensler & Bernstein, 1981). It has been shown that recombinational repair efficiently removes artificially induced lesions but naturally occurring lesions have not been studied from the point of view of removal by recombinational repair (see review by Bernstein, 1983).

An alternative to the repair hypothesis for the maintenance of recombination is the Variation Hypothesis, which regards the production of variation the primary advantage of recombination. The Variation Hypothesis has been the subject of three recent reviews (Williams, 1975; Maynard Smith, 1978; Bell, 1982, especially Chapter 5.2). Despite a great deal of effort devoted to the task, it has not been possible to show that selection for variation is a powerful enough evolutionary force to account for the ubiquity of recombination in nature. This hypothesis has the status of dogma in evolutionary biology and it is not our purpose to discuss it here. We only want to present an alternative hypothesis as clearly as possible.

10. The Maintenance of Outbreeding Sex in Diploids

If unicellular haploid organisms are to use redundancy to repair damage which occurs prior to replication, it can only be done through outbreeding sex since only other individuals can be the source of the redundant genome. In contrast, diploid organisms can find the redundant information either within themselves or from another individual (i.e. outbreeding sex). Bernstein, Byers & Michod (1981) have proposed that diploidy in sexual organisms emerged in evolution as a strategy for dealing with the inaccuracy of the DNA replicative machinery. Such inaccuracy causes mutation. As early haploid organisms evolved genomes with increasing information content, they became more vulnerable to deleterious mutation. Initially their adaptive response to this vulnerability was to improve the fidelity of the replicative machinery. However, at some point (e.g. when the genome size exceeded about 5000 genes) an alternative strategy for dealing with this problem evolved. The diploid stage of the life cycle became the dominant stage, since diploidy allows deleterious mutations in one genome to be masked by complementary information in the other genome. In sections 4–6, we argued that the diploid stage was transient for a long period of evolution due to the costs of redundancy. However, as organisms became more complex, the direct costs of replicating and maintaining an extra genome in a cell decreased relative to the costs of maintaining the cellular machinery itself (e.g., ribosomes, enzymes, etc.). At some point, the benefits of complementation outweighed the decreasing costs of redundancy.

Using diploidy for masking mutation, however, makes it difficult to abandon outbreeding sexual reproduction in favor of self-fertilization or automixis, since these forms of reproduction inevitably entail increased homozygosity and hence expression of the previously masked recessive deleterious alleles. Certain types of automixis (e.g. where meiosis is followed by fusion of second-division non-sister nuclei) tend to maintain heterozygosity. However even in these cases, homozygosity will be introduced due to recombination between the heterozygous alleles and the centromere (see White, 1973, pages 705–709, for a more detailed discussion). Such recombination events, we think, are largely a reflection of recombinational repair of DNA damage. Thus the need to deal with germ line damage appears to be in conflict with parthenogenetic strategies for maintaining heterozygosity. We consider that all automictic and self-fertilizing forms are handicapped because of the inevitable expression among their progeny of deleterious recessive mutations which were previously masked in the outbreeding sexual forms from which they arose. Maintenance of outbreeding, of course, avoids these problems.

It is often argued that parthenogenetic populations lack the potential for producing the high level of genetic variation that is characteristic of sexual populations. This lack of genetic flexibility is commonly regarded as an evolutionary handicap (e.g. White, 1973, pp. 763–764). The advantage of sexual reproduction in producing genetically varied progeny has been the subject of much thoughtful work (see e.g. Williams, 1975; Maynard Smith, 1978). Despite this, it remains unclear what, if any, are the main general advantages of genetic diversity.

It is generally assumed that parthenogens have a two-fold advantage over sexual females because of the cost of producing males (see Maynard Smith, 1978, for a discussion of this issue). We should point out that the repair hypothesis predicts reduced fecundity of parthenogenetic females. This is the case because, in apomictic parthenogenesis, recombinational repair is reduced and, in automictic parthenogenesis, strategies to repair damage run afoul of the effects of inbreeding depression. The inference that recombinational repair is probably drastically reduced in apomixis comes from data in yeast showing that the spontaneous mitotic recombination frequency for a given genetic region can be as much as 1000 times less than the meiotic recombination frequency (Kunz & Haynes, 1981). This suggests greater efficiency of recombinational repair during the sexual process.

The data on the distribution of parthenogenesis as recently reviewed by Bell (1982; see also Trivers, 1983) shows that the primary ecological correlates of parthenogenesis are marginal and open habitats in which finding a mate is difficult. Thus, one finds parthenogenesis where the benefits of

not having to find a mate outweigh the costs implied by the repair hypothesis. See Vepsalainen & Jarvinen (1979) for similar arguments in which the benefits of parthenogenesis are associated with polyploidy instead of mating.

11. Discussion

A number of the most fundamental features of life have their origin in properties of RNA or DNA molecules that were the likely precursors of all life (Eigen *et al.*, 1981). One example is cell duplication, and biological reproduction in general, which probably evolved from the capacity of RNA or DNA to undergo template mediated replication. Another example is inheritable variation, which arises from errors in this replication. In a previous paper (Bernstein *et al.*, 1983) we showed that the concept of adaptation can be clarified by considering the origin of adaptation in simple RNA replicators.

In the present paper we deal with another fundamental aspect of life, sexual reproduction. We argue that this process arose from the necessity of early replicators to cope with genetic damage. In accord with a large body of evidence, we assume that damage to the genetic material is an ubiquitous problem that needed to be dealt with very early in the evolution of life. A general strategy for dealing with loss of information in a strand of RNA or DNA is to obtain the correct information elsewhere, from another strand. Thus, we argue that the key to coping with informational damage is informational redundancy. We have tried to show by cost-benefit analysis, in which the costs of maintaining redundancy were balanced against the costs of damage, that the optimum solution is the sexual cycle. In the sexual cycle, haploid cells (with minimum redundancy) periodically fuse to reap the benefit of redundancy through exchange of genetic material (recombination). The cycle is completed by splitting to again form haploid cells and thereby avoid the continued costs of redundancy. We further argue that this primitive form of sexual reproduction is connected by continuous evolution to sexual reproduction in extant organisms. Currently, a good deal of effort is being devoted to understanding how sexual reproduction is maintained in extant organisms, but the issues remain largely unresolved. We have tried to show that considerable clarification of the underlying generalities is achievable by analyzing sexual reproduction in primitive replicators and in simple extant organisms such as segmented RNA viruses. We have argued that sexual reproduction provides the immediate selective advantage of allowing RNA or DNA that is passed on to progeny to be freed of damage. This occurs during meiosis or equivalent processes in viruses and bacteria.

In diploid organisms, other factors also contribute to the maintenance of outbreeding sexuality. One major factor is the need to mask deleterious recessive mutations through complementation. Also, population variation, which is a byproduct of recombination between parental genomes, may help to maintain outbreeding by protecting against epidemic spread of parasites or more generally against environmental unpredictability.

When sexual reproduction is viewed as a fundamental attribute of life arising from the inherent vulnerability of information bearing molecules to damage, one's perspective on another fundamental problem relating to sexual reproduction also changes. The concept of species is tied intimately to sexual reproduction since individual organisms are, by definition, allocated to species on the basis of sexual compatibility. We argue elsewhere (Bernstein *et al.*, submitted) that the dynamic of natural selection is altered in a fundamental way by sexual reproduction since this imposes a requirement for union of separate individuals, and thus generates an intrinsic cost to rarity. We propose that the distribution of organisms in discrete species rather than in a continuum of microspecies reflects constraints imposed by the cost of rarity. We have already illustrated the cost of rarity, and the consequent difficulty of expanding when rare, for the case of hypercycles. The same difficulty of expanding when rare is present in the models of sexual strategies given in the Appendix. Thus, we contend that species are a consequence of sex, and sex is a consequence of genetic damage.

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APPENDIX

Models of Competition and Selection between Sexual and Asexual Replicators

In this appendix we present the models used to study the selective factors responsible for the origin of sex. Three models are studied which contain the same underlying ideas, but serve different purposes in the argument. The first two computer models are similar and study competing species of protocells, where each species is defined by a precise life cycle. By allowing

these species to compute for common resources, we are able to determine the competitively superior life cycle. We find that under a very wide range of circumstances the competitively superior life cycle is sexual, involving fusion of two protocells for genetic recovery followed by splitting of the fused protocell into four daughter protocells. To more explicitly pose the question of the origin of sex, we then study a simplified model for the spread of a mutation for sex within an asexual population. The mutation model maintains the basic ideas of the computer models but can be studied analytically.

As noted in the text, we do not regard the sexual cycle as having a distinct origin in time. We believed, instead, that the cycle gradually emerged as a solution to the problems posed by gene damage and failure of assortment. For simplicity in presentation, failure of assortment is neglected in the following models, since, as discussed in the text, it has the same basic effect as gene damage. We will show that, under most conditions, a sexual life cycle is competitively superior to the options available without sex, which involve either letting inert protocells die, or maintaining high levels of redundancy to prevent the inactivating effects of damage.

In these investigations, we are not interested in the refinement of the sexual cycle *per se.* As discussed below, if we were to model the details of the primitive sexual cycle after present day microorganisms, we would build a cost-free model of sex. We do not, however, want to make the model vulnerable to assumptions of cost-free benefits. Hence we deliberately choose relatively inefficient models of the sexual process as a means of assessing a cost.

State-Matrix Model

We illustrate the basic model in Figure 3 for the case of haploid protocells. The definitions of the terms used in the model are given in Table 1.

In Fig. 3(a), we show the asexual cycle, in which a protocell goes from haploid to diploid at which point it splits into two haploids. The splitting is taken to occur instantaneously as soon as the dipoloid stage is reached, which is itself represented by a dotted circle. In addition to reproduction, the protocell can either "die", by which we mean that the protocell physically disintegrates and the component parts revert to resources, or it can become inert because of gene damage. Protocells which are inert but not yet dead are labeled with an X across them. In Table 1 and in the computer simulations, the rates of these various processes depend on the number of genomes per protocell. However, in Fig. 3, these dependencies are left out for ease of representation.

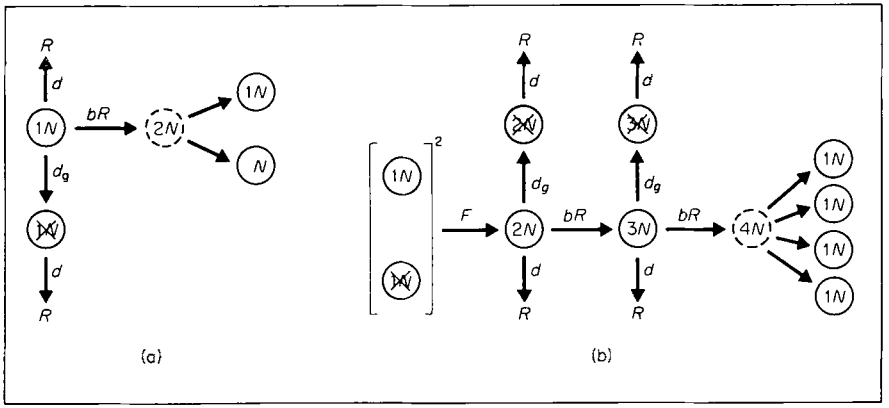

FIG. 3. Schematic of state matrix model for haploids (a) asexual phase, (b) sexual phase. See text for further explanation.

In Fig. 3(b) we illustrate the sexual phase of a haploid sexual species. The haploid protocells fuse with a rate F that depends on the density of the populations involved. The fusion is assumed to be at random between haploid protocells in a binomial ratio. Hypercyclic cooperation (see text) is assumed to restore metabolic activity of damaged protocells immediately upon fusion. There are basically two options available at this point, either of which could be assumed. The first is to let the fused protocell immediately split into two metabolically active protocells, which then go on to reproduce

TABLE 1

Definitions of terms for state-matrix and streamlined model

n	Density of protocells.
L	Number of genomes per protocell.
N	Number of gene segments per genome.
A	Cross-sectional area of the protocell, taken to be proportional to $L^{2/3}$.
K	Ploidy of the cycle (minimum L), used as a species label (minimum L of the asexual part of a sexual life cycle).
d	Cell disruption rate; proportional to area A.
d_g	Rate of inactivation by DNA damage, proportional to $1/N^{(L-1)}$
b	Rate coefficient for accreting resources sufficient to build one genome; proportional to area A.
R	Amount of free resources (monomers).
f	Rate coefficient for fusion, proportional to the product of the two areas.
F	Overall rate of fusion (a function of f and appropriate population densities).
r	Rate of splitting of the sexual phase into the asexual phase (used only in second computer model discussed later)

asexually at some future point. This is the optimum sexual life strategy and approximates the sexual cycle in many present day microorganisms. However, we are concerned that by assuming such a cost-free sexual strategy, our results would be vulnerable to criticism. Consequently, we assess a cost, due to redundancy (see also assumption (3) below), by requiring the fused protocell to grow to the $4K$ state at which point they split into four K protocells.

In summary, the various species are denoted as sexual or asexual according to whether they do or do not have a sexual phase. The "ploidy" of the species, labeled K, refers to the minimum number of genomes found in the protocell during the cycle. The K ploid asexual protocell has a $K \rightarrow 2K$ cycle only. The K-ploid sexual protocell has a $K \rightarrow 2K$ asexual cycle and a $2K \rightarrow 4K$ sexual cycle. Our model assumes the following.

(1) The species compete for limiting resources.

(2) The competitions of interest are among species with the same N.

(3) If a protocell in a fused state becomes gene damaged, it cannot be recovered.

(4) Materials used in making the membrane are not limiting. Resources refer to free mononucleotides.

(5) In the case of a fused protocell, once the $4K$ stage is reached, the protocell immediately divides into $4K$-ploid protocells.

(6) As discussed in the text, the inactivating effects of gene damage fall off rapidly with large redundancy (L).

(7) As in other models of competition among primitive replicating systems (Eigen & Schuster, 1978; Bernstein *et al.*, 1983, and references therein), we introduce limiting resources by the constraint that the total "biomass" of genomes plus resources (i.e. free monomers) is constant.

Assumptions (1) to (7) underly the verbal arguments used in the main text. However, to construct the computer models, we need to be specific about the rate processes. These specific aspects of the model are given in Table 1.

In the numerical simulations, several species were taken to be involved; usually four asexual species and two sexual ones. Each species is described by a time dependent state matrix containing all active and all inert protocells of the various ploidy levels. A fine time grid was chosen, and the rates of the various processes were computed according to the assumptions in Table 1. These rates are the probabilities that a process will occur over a small time interval, and a Monte-Carlo technique was employed at each step to ascertain whether it did or did not happen. The process was continued until all but one species was extinct. Several cases were explored using this technique, but it turns out to take a substantial amount of computer time

to reach the final state. Hence we were able to obtain only five cases using this model.

For this reason we studied a simplified population model which is motivated by the previous model, but is not, strictly-speaking, derived from it. This simpler model was checked against all points computed with the full state matrix calculation, and was found to give the same answers. Since the model described below is not strictly derived, it should be regarded as a means of fitting a curve to the data derived from the state-matrix procedure.

Streamlined Model

In the new model, we lump the number of protocells in each species into four categories (two if the species is asexual). These four categories are the number of active and inert protocells in the asexual and sexual phases. We denote these populations as n_K (asexual phase, active), n'_K (sexual phase, active), n''_K (asexual phase, inert), n'''_K (sexual phase, inert). The subscript K identifies these populations as belonging to the K-ploid sexual species (for simplicity, we leave out the subscripts distinguishing the sexual from asexual species). Equations of this form are senseless unless one neglects the differences between the rate coefficients within any one lumped group of protocells. We thus specify the calculation of the rate coefficients in this streamlined model with a further assumption.

(8) In calculating the area A, we replace L, the number of genomes per protocell, by the smallest number of genomes found in the cycle, i.e. by K in the asexual cycle and $2K$ in the sexual cycle.

The sexual cycle in this streamlined model is illustrated in Fig. 4.

Assumption (8) suggests writing the following equations for a sexually-reproducing species:

$$\frac{dn_K}{dt} = \left(\frac{bR}{K} - d - d_g\right) n_K + r n'_K - f n_K (n_K + n''_K) \tag{A1}$$

$$\frac{dn'_K}{dt} = \left(\frac{bR}{2K} - d - d_g\right) n'_K - r n'_K + f (n_K + n''_K)^2 \tag{A2}$$

$$\frac{dn''_K}{dt} = -d n''_K + d_g n_K - f n''_K (n_K + n''_K) \tag{A3}$$

$$\frac{dn'''_K}{dt} = -d n'''_K + d_g n'_K. \tag{A4}$$

All of the terms in these equations have a one-to-one correspondance to those in the previous model except for two. The quantity r is a splitting

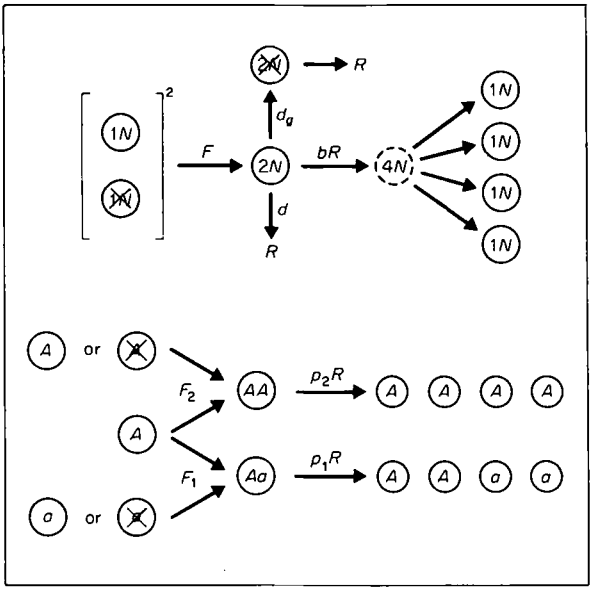

FIG. 4. (a) Schematic of sexual phases for the streamlined population model. (b) Schematic of sexual phases for the mutation model. See Table 2 for definitions of terms. See text for further explanation.

rate out of the sexual phase which is discussed below. The more interesting term is the factor $1/K$ in equation (A1) (the factor $1/2K$ in equation (A2) is a similar sort of term). This term is needed to take into account the fact that b, in the state-matrix model governs the rate by which the number of genomes is increased by one ($L \rightarrow L+1$). In the streamlined model, protocell replication describes the entire cycle ($K \rightarrow 2K$). Previously, one resource was accreted to make one genome, now K resources are accreted to make one protocell. For that reason the time needed to replicate a K-ploid protocell is proportional to K, so that the rate goes inversely as time, scaling as $1/K$.

The term $1/K$ is the cost of redundancy, which gives an advantage to species with low K, and it appears explicitly for the first time in this streamlined model. Note that this term does not stem from any further assumptions. In the state-matrix model there is no term at all of this type, and the notion of a cost of redundancy is, in that case, a way of understanting the mathematical results. In equations (A1)–(A4) this cost is not arbitrarily introduced. It is inferred explicitly in the process of streamlining. If it is left out, these equations do not give the same answers as the state-matrix model, and if it is included the two answers are the same. (It is interesting

to note that, in animals, there is a strong correlation between polyploidy and parthenogenesis (Bell, 1982). This data is consistent with the beneficial effects of redundancy as modeled here, since polyploidy protects the organism against the deleterious effects of DNA damage through the redundant copies present in a polyploid. In plants, the relationship between polyploidy and parthenogenesis is less clear. Nevertheless, completely apomictic (ameiotic) plants are almost always polyploid (Stebbins, personal communication). While it is unlikely that the cost of redundancy would work in the same way in present organisms as we have modeled here for primitive protocells, it is also interesting to note that polyploid plants often grow more slowly than closely related diploids (Stebbins, 1950, p. 304)).

In this discussion, we have emphasized that we know of no logical necessity for finding that equations (A1)–(A4) give results which agree with those derived using the full state matrix. We believe that the reason this works is that all absolute rates are treated uniformly, so that the relative rates, which are the key to determining who wins the competition, are largely uneffected by the approximation. We use these equations in the same way as the state matrix. All populations (usually a mix of two or three sexual species with four or five asexual species) are started out in a condition of equal biomass, and the calculation is run until all but one are extinct.

There are a large number of parameters in this study. The crucial parameter in assessing the role of sex is the relative magnitude of the rates of death and gene damage, which in turn is a function of N and K. We have found it convenient to adopt a scaling procedure that is mathematically awkward, but translates all these parameters into a biologically comprehensible form. We consider, at first, only asexual species. For any combination of parameters (note that r and f are not involved here), there is a ploidy that is competitively superior in that it is large enough to overcome the effects of damage and small enough to avoid being overly redundant. This ploidy increases monotonically with the amount of gene damage. It can be determined analytically, and this analysis is important in checking the numerical calculation. We use the ploidy of the winner of the asexual competition as the independent variable in the study of conditions where sex is competitively advantageous. The advantage of using this scaling is that it reduces all parameters to one. The disadvantage is that ploidy is a discrete variable, so the reverse translation from ploidy back to parameters is not simple.

When the sexual species are introduced, new parameters r and f are involved. The numerical values of both parameters only affect the results in an obvious way. Clearly if $f=0$ or $r=0$ (no fusion or no splitting) the sexual cycle is prevented, and sex is either neutral (if it doesn't take place)

or it loses. We have found no other sensitivity of the final outcome of competition to these parameters. Sex is also eliminated in competition if the total populations are kept very low by choosing a very low value for the total resources, so that all species are rare. In these cases, sex is disadvantageous because fusion becomes impossible by virtue of the unlikelihood of a collision between two sexual protocells. These parametric effects are limiting cases of the model, and except for these, we find that the winning species does not depend upon the choice of these parameters.

The results of this study which are of main interest are summarized in Fig. 5. The independent variable (horizontal axis) is the ploidy of the asexual

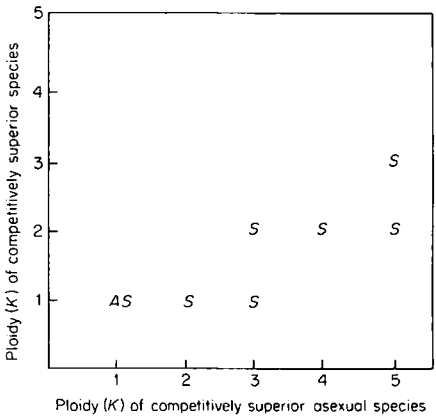

FIG. 5. Summary of results of population models. Horizontal axis is ploidy of competitively superior asexual life cycle when in competition with only other asexual species. Gene damage increases along the horizontal axis. Vertical axis is ploidy of competitively superior life cycle when in competition with both asexual and sexual species. The letters *A* and *S* indicate that an asexual or sexual species, respectively, is competitively superior. For further explanation see text.

species which wins in competition with other asexual species as discussed above. This ploidy, or redundancy, level increases as gene damage increases. The vertical axis is the ploidy of the competitively superior species when in competition with both asexual and sexual species. If the competitively superior species is asexual, it is indicated in the figure by *A*, if it is sexual it is denoted by *S*. In some cases the independent variable does not uniquely specify a winner. In that case two letters are shown. If the letters refer to different ploidies of the winner, then the upper letter applies to higher levels of gene damage. If the letters refer to the same ploidy, then the letter on the right is appropriate for higher levels of gene damage. Note that with

only one exception, the sexual life cycle is competitively superior. The only exception is at extremely low levels of damage, in which case the asexual life cycle is best.

Mutation Model

The previous models of interspecific competition serve to clarify those aspects of the sexual life cycle which are most important in maintaining a sexual species once it has arisen. To study explicitly the problem of the expansion of a genetic factor which encodes the sexual cycle, we consider a population of asexually reproducing protocells, in which a sexual mutant protocell arises. This is the subject of the third and final model. Consider an asexual species, a, in which a mutant protocell, A, arises that can fuse with A or a protocells to undergo genetic recovery. The mates of the mutant A will primarily be metabolically active or inactive asexual a protocells, since the mutant sexual protocell is by definition rare. Consequently, a rare sexual mutant will tend to primarily benefit damaged a protocells. Can such a sexual mutant increase when rare? The following discrete time model addresses this problem. The definitions of all variables and parameters for this model are given in Table 2. We maintain to the degree possible the

TABLE 2
Definitions of terms for mutation model

d_g	Probability of gene damage for an a haploid protocell
$d_{g'}$	Probability of gene damage for an A haploid protocell
n_t	Density of asexual haploid a's at time t
n'_t	Density of sexual haploid A's at time t
n''_t	Density of gene damaged a's at time t
$n'_t{}''$	Density of gene damaged A's at time t
R_t	Density of resources at time t
b'	Constant asexual birth parameter for the sexual protocell
b	Constant asexual birth parameter for the asexual protocell
f_1	Fusion constant for $A \times a$ matings
f_2	Fusion constant for $A \times A$ matings
M	Total density of mononucleotide building blocks, assumed constant
p_1	Parameter describing the transition from $2N$ to $4N$ in the sexual cycle of Aa diploid protocells
p_2	Parameter describing the transition from $2N$ to $4N$ in the sexual cycle of AA diploid protocells

notation of the previous models. For simplicity, we will only present the case in which $K = 1$. Accordingly, the K subscript is suppressed in what follows.

In addition to assumptions (1)–(7) of the computer models above, we assume the following in the discrete time mutation model:

(9) The diploid protocells at time t produce four haploid daughter cells at time $t+1$ with probabilities p_1R_t and p_2R_t for Aa and AA respectively. With probabilities of one minus these probabilities, the respective diploid cells revert to resources.

(10) For the haploid protocell, the life history events (if they occur) occur in the following order: asexual reproduction, gene death, fusion.

(11) Haploid protocells whose genomes are damaged in any interval of time are stable until the end of the next interval of time when they revert to resources.

(12) Daughter protocells produced at the beginning of an interval of time are not able to fuse or be recovered until the beginning of the next time interval.

(13) Gene-damaged, haploid protocells are immediately able to fuse and to be recovered. That is, they can become recovered in the same interval of time in which they became damaged.

(14) Of the offspring produced from a mating between a sexual haploid and an asexual haploid, two are sexual and two are asexual: $A \times a \to 2A, 2a$.

(15) The probability that a sexual protocell becomes damaged at the same site of the mutation that made the protocell sexual in the first place is small and can be ignored. Note that an a protocell would not be able to convert an A protocell which is damaged at the site of the mutation causing sex to an a protocell.

(16) A gene damaged, haploid sexual protocell cannot fuse with another such protocell.

(17) The number of diploid Aa protocells at time t is equal to the number of $A \times a$ fusions at time $t-1$ or $F_1 = f_1(1-d_{g'})n'_{t-1}(n_{t-1}+n''_{t-1})$.

(18) The number of diploid AA protocells at time t is equal to the number of $A \times A$ fusions at time $t-1$ or $F_2 = f_2(1-d_{g'})n'_{t-1}(n'_{t-1}+n'''_{t-1})$.

The issues raised in assumptions (9)–(18) are unique to the mutation model and result from (i) our assuming that time is discrete and (ii) the fact that there are two different types of matings possible for a sexual protocell: $A \times a$ (mating type 1) and $A \times A$ (mating type 2).

These assumptions result in the following system of second-order difference equations:

$$n_{t+1} = n_t b R_t + 2p_1 R_t f_1(1-d_{g'})n'_{t-1}(n_{t-1}+n''_{t-1}) \tag{A5}$$

$$n'_{t+1} = n'_t b' R_t + 2p_1 R_t f_1(1-d_{g'})n'_{t-1}(n_{t-1}+n''_{t-1}) + 4p'_2 R_t f_2(1-d_{g'})n'_{t-1}(n'_{t-1}+n'''_{t-1}) \tag{A6}$$

$$n''_{t+1} = n_t d_g \tag{A7}$$

$$n'''_{t+1} = n_t d_{g'}, \tag{A8}$$

with

$$R_t = M - n_t - n_t' - n_t'' - n_t''' - 2f_1(1-d_{g'})n_{t-1}'(n_{t-1}+n_{t-1}'') - 2f_2(1-d_{g'})n_{t-1}'(n_{t-1}'+n_{t-1}'''). \tag{A9}$$

Consider the following equilibrium of this system of equations in which only asexuals are present,

$$n'' = d_g n, \qquad n = \frac{bM-1}{b(1+d_g)}, \qquad n' = 0, \qquad n''' = 0. \tag{A10}$$

This is the equilibrium of interest concerning the increase of a rare mutant sexual protocell in an asexual population. We want this equilibrium to be unstable in which case the sexual individual will increase when rare. The eigenvalues determining the stability of the system at this equilibrium are given by the roots of the following equation in λ

$$\lambda^2[\lambda^2(1+d_g) - \lambda(2+d_g-bM) + d_g(bM-1)] \times [\lambda^2 b^2 - \lambda bb' - 2f(1-d_{g'})(bM-1)p_1] = 0. \tag{A11}$$

The roots of the first bracketed quadratic in the above equation describe the stability of the asexual species before the mutation occurred. Of course, we assume that the asexual population was stable before the mutation occurred so that the roots of this quadratic are less than one in absolute value. The roots of the second bracketed quadratic in the above equation are greater than one in absolute value (i.e. A mutation will increase when rare) if

$$2p_1 f_1(1-d_{g'})\left(M - \frac{1}{b}\right) > b - b'. \tag{A12}$$

We assume that $b > b'$, otherwise the sexual mutant will increase no matter what. Consequently, $b-b'$ is the cost in terms of the asexual birth rate of a protocell becoming sexual. It is easy to see that $1/b$ is the equilibrium level of resources R, so $M-1/b$ is the equilibrium level of metabolically active or inactive asexual haploid a's, with which the newly arisen A mutant can mate. Furthermore, using the definitions above it is easy to see that the left hand side of the last equation is the expected number of sexually produced A offspring for a rare A mutant. Thus the condition for increase of a sexual mutant by conventional means is simply that the benefit, in terms of the number of sexually produced offspring that are genetically like the mutant, exceed the cost, in terms of the asexual birth rate.

There are other mechanisms by which a genetic factor encoding sex can expand in a population. These are dynamically similar to the chance

processes by which hypercycles originate in general, which have been qualitatively discussed in the text. These mechanisms are not amenable to traditional analysis, since to first order, hypercycles cannot expand when rare. They need favorable historical accidents to get started, but once started they expand rapidly, and, when common, can be very stable.