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A Centrosomal Theory of the Short Term Evolutionary Maintenance of Sexual Reproduction

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A new mode of inheritance is postulated in which a sexual offspring receives a contribution from each parent and selects the better to pass on to its own offspring. This could provide a simple advantage to sex over asex whose magnitude is shown to be of the order of a doubling of fitness in each generation, large enough to cancel the twofold cost of sex. This possible advantage to sex can be realized only if a cell component is in fact inherited in this selectively ambiguous way. No such component is known of, but the eukaryotic centrosome is a possible candidate. The possibility is discussed that the centrosome contains an obligatorily non-digital replicator which has an essential function in the initiation of microtubules. If this theory is true, it has the capacity to apply as widely as sex is found, and it would rescue theories of the long-term maintenance of sex from the necessity to provide a twofold advantage in each generation. If false, the theory will soon be disproved.

Introduction

Recently the problem of sex has received much attention from evolutionary biologists. Most previous theorists (Felsenstein, 1974; Williams, 1975; Maynard Smith, 1978; Hamilton, 1982; Bell, 1982) have worked on the assumption that the point of sex is the ecological advantage derived from recombination of genes. Others consider the possibility that sex allows selection for advantageous biassed conversion (Bengtsson 1985), or maintains diploidy which is important for masking deleterious mutations (Bernstein 1977, further developed by Bernstein *et al.*, 1985), or is advantageous because of non-multiplicative fitness interactions between deleterious mutations (Kondrashov 1982). This paper suggests a radically different theory as to why sex is maintained in the short term, a theory in which genes play no direct part.

The difficulty faced when considering the ecological theories of sex is that, accepting the fairness of meiosis as a general rule, offspring have, on average, the same gene frequencies as their parents. Hence, the advantage to sex must come about because certain *combinations* of genes are favoured by selection, and that the favoured combinations change through the generations. In order to overcome the "two fold cost of sex" (Maynard Smith 1971), these fluctuations in selection pressure must be rather violent.

The new theory introduced below begins with the postulation of a different mode of inheritance, in which the offspring is not on average the same as its parents. The idea is that an offspring receives a contribution from each parent and that as a result of competition, the offspring passes on in its own gametes the better of the two

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parental contributions. There is clearly some advantage to sex in a system where the offspring are better than the average of their parents. An asexual individual cannot make a choice of the best of two. In section two below, mathematical arguments show what magnitude of advantage can accrue to sex from ambiguous inheritance.

The reasons for hypothesizing this ambiguous mode of inheritance are purely formal: if it existed, then it would supply a simple advantage to sex. But if it is the true explanation for the occurrence of sexual reproduction, then a cell component must exist which in fact is inherited ambiguously. The plausibility of the theory as a candidate explanation of sex therefore depends on the plausibility that such a cell component exists. Section three below presents the case that the centrosome may be inherited in this way.

The ubiquity of sexual reproduction is curious, from the viewpoint of current evolutionary biology. Maynard Smith (1976) has expressed this by saying that "one is left with the feeling that some essential feature of the situation is being overlooked". The present theory places that essential feature in the cell, a location with two advantages. First, a theory about cell components is likely to be faced soon with decisive evidence, as knowledge of the workings of the cell continues to expand. Second, cells are far more similar than the different organisms they comprise. A cellular explanation for sex is likely to apply to a very wide class of organisms, and it is the ubiquity of sexual reproduction among eukaryotes that is its main puzzle. In respect of both testability and scope of theories, cell biology has much more to offer than ecology.

The Advantage of Selectively Ambiguous Inheritance

In this section, two very simple mathematical arguments will show that the advantage gained from selectively ambiguous inheritance can be as great as twofold, and will be very close to twofold in a wide range of circumstances. Comparison with a twofold advantage is important because of the twofold cost of sex (Maynard Smith 1971). I shall conclude that, in combination with other inevitable consequences of the models, selectively ambiguous inheritance effectively cancels the twofold cost of sex.

The basic model has an infinite population with discrete generations. Each individual has a certain number of errors associated with its inherited factor. The fraction of the population with exactly i errors is x_i, where i can be 0, 1, 2 etc.. The quantity of interest is the mean fitness of the population under a mutation-selection balance, relative to a population consisting of only the type with no errors. It is therefore necessary to specify how selection and mutation operate. We assume that the viability of an individual of type i is w^i, where w is less than one. The viability of an individual with no errors is therefore one, and individuals with more errors have poorer viability. The form of mutation is that each individual suffers no mutation with probability π_0, and suffers a mutation adding i errors to its total with probability π_i. The population undergoes mutation, then selection and then forms the next generation.

In the asexual model, the next generation has the same frequency distribution of number of errors as the old generation after mutation and selection. Let us represent the frequencies of types in the next generation by x_i' and let the mean fitness be λ. Then we can write the following series of equations:

$$\lambda = \sum_{i=0}^{\infty} x_i w^i$$

$$x_i' = \left(\sum_{j=0}^{i} \pi_j x_{i-j} \right) \Big/ \lambda.$$

For $i = 0$, this reduces to $x_0' = x_0 \pi_0 / \lambda$.

Mutation-selection balance brings about an equilibrium distribution of errors in which $x_i' = x_i$. It then follows easily from the equation for $i = 0$ that $\lambda = \pi_0$, i.e., the mean fitness of the population equals the probability that an individual suffers no mutation. The asexual model is the same as the Muller's ratchet model discussed by Muller (1964), Felsenstein (1974) and Maynard Smith (1978), who gives the result above in a slightly less general form. The result that $\lambda = \pi_0$ implies that the mean fitness of the population is unaffected by the selective disadvantage of a mutation, an implication familiar from Haldane's (1937) closely parallel genetic load argument. The argument given here also shows that if the mutation rates depend on the number of mutations already possessed, then it is only the chance of non-mutation from the optimal extant class which determines λ. This applies even if the optimal extant class contains only 1% of the population.

The sexual case is slightly more complicated. After selection and mutation, a process of choice of best of two takes place. This means that each offspring receives a pair of inherited factors, chosen at random from the distribution of errors after selection and mutation. Each offspring is assumed to adopt the factor with fewer errors. The distribution of offspring is therefore the distribution of the better of a sample of two from the distribution of adults after selection and mutation. Let the distribution after selection and mutation be y_i. Then we can write

$$\lambda = \sum_{i=0}^{\infty} x_i w^i$$

$$y_i = \left(\sum_{j=0}^{i} \pi_j x_{i-j} \right) \Big/ \lambda$$

$$x_i' = 2 y_i \left[\tfrac{1}{2} y_i + \sum_{j=i+1}^{\infty} y_j \right].$$

Again we can concentrate on the equation for x_0', which turns out to be

$$x_0' = 2 x_0 \pi_0 [1 - \tfrac{1}{2}(x_0 \pi_0)] / \lambda.$$

When $x_0' = x_0$, it follows that

$$\lambda = 2\pi_0 - x_0 \pi_0^2.$$

The mean fitness for a sexual population relative to the mean fitness of an asexual population, neglecting the twofold cost of sex, is therefore

$$2 - x_0 \pi_0 \tag{1}$$

In this expression for the ratio, x_0 is the fraction of the sexual population which have no errors. If either x_0 or π_0 is small, then the sexual population's fitness is very close to twice that of the asexual population. x_0 is small when w is close to one, that is, when each individual error makes only a small difference to the fitness of its bearer. For sex to have a twofold advantage over asex, it must be that the asexual fitness is less than a half. This in turn has the important implication that π_0, the probability of suffering no mutation, must be less than a half.

It is important that the choice of two should be between two randomly selected factors. A choice between similar factors would correspond to close inbreeding, or to the selection from factors present in the different cells of an asexual individual which would all share a recent common ancestor. A choice of two perfectly correlated factors is of course no choice at all. The advantageousness of a choice depends on the difference between the successful and unsuccessful factors, and this is greater in the case of less correlated factors.

The analytical result is therefore summarized in expression (1), and we now turn to consider what part this result could play in the maintenance of sexual reproduction. First it will affect the fate of an asexual mutant in a sexual population. The loss of the "choice of best of two" in the heritable factor will reduce the fitness of the asexual clone by a factor of nearly two, according to expression (1). This may take a number of generations to build up, but it will eventually nearly cancel a twofold cost of sex. In species with paternal care, or where the cost of sex is less than two for other reasons, the loss of choice of two will provide a clear advantage to sex over the asexual mutant. In the early stages of its spread, the mutant will also be vulnerable to Muller's ratchet. A click of the ratchet occurs when all members of the optimal class die out or mutate, so that there is a new and less fit optimal class, with one more error than the old one. This occurs when the number of individuals in the optimal class is small, and this is bound to be the case when the number of individuals in the whole clone is small. The choice of best of two may therefore effectively cancel the twofold cost of sex felt by sexual populations facing asexual mutants.

The second role is in interspecific competition. The twofold cost of sex is felt here as the cost of making sons. A species which abandons sex has twice as many females, and so twice as many young. If there is a stage of juvenile competition between members of different species, then an asexual species has an advantage in providing more competitors. However, the loss of choice of two suffered by the asexual species will affect its fitness in interspecific competition as well, and nearly cancel out any twofold cost to sex. This interspecific result contrasts with the theory of Bernstein *et al.* (1985) that the advantage of sex is the maintenance of diploidy, which masks deleterious recessives. As they point out, the mean fitness under mutation selection balance is the same for their haploid and diploid models, with diploidy providing only a transient advantage.

The loss of choice of two cannot be the only force maintaining sex, however. It effectively cancels out a twofold cost, but can do no more than this. A taxon without sex would therefore be more or less neutral in competition against an otherwise similar taxon with sex. The observation is that asexual taxa are less successful than sexual taxa. Many explanations for this depend on genetic diversity and temporal or spatial fluctuations in selection pressures. The necessity to overcome a twofold cost gives many of the theories an air of implausibility, and some theorists an understandable attitude of despair (Williams, 1975, p. 14). If the choice of best of two theory is true, then other explanations start from a position of near neutrality in finding an advantage to sex.

The Centrosome as a Candidate for Selectively Ambiguous Inheritance

In the previous section, the advantage to selectively ambiguous inheritance was calculated. But if the theory is true, then some cell component must satisfy the postulates of the theory. The nuclear genes are inherited, by and large, in a proper Mendelian manner. The exceptions include segregation distorters in *Drosophila melanogaster*, and the *t*-alleles in mice (reviewed by White, 1973). In both cases, the circumvention of Mendelian inheritance acts to the detriment of the organism, while benefitting the gene. The choice of two theory requires that the choice should benefit the organism and so nuclear genes may be tentatively rejected.

Before moving on to other cell components, it is worthwhile considering what kind of mechanism could operate to make genes candidates. It would be necessary that by matching up the haplotypes received from each parent, some class of mutations might be recognized. An essential additional point is that when the two haplotypes differ, it must be clear which one is in error, otherwise there is a danger that the correction mechanism will propagate the error instead of correcting it. This essential point is made by Bengtsson (1985) in contrasting his models with those of Bernstein *et al.* (1985). Mutations which can be recognized as errors may be compared to a scratch on a gramophone record—a disturbance of form. Those which cannot may be compared to a record with a different tune; it is different, but it is not possible to say which of two tunes is the mutant. Only if a significant class of mutations are of the first sort could the choice of best of two theory apply to genes.

The initial candidates besides genes are the replicators in the cell, and mitochondria are the only other known replicators that are near universal among eukaryotes. The evidence is quite strong, however, that mitochondria are strictly uniparentally inherited in many species (e.g. Lansman *et al.*, 1983), though not in yeast (Birky *et al.*, 1978). I will now make the case that a plausible candidate is the centrosome, a cell component not yet known to be a replicator.

The centrosome, *sensu* Mazia (1984), is the body that organizes mitotic spindles. Immediately after cell division, a cell has one centrosome. Two centrosomes then appear where one was before and these move to opposite sides of the nucleus, each forming half a mitotic spindle. Each centrosome passes into the daughter cell with the chromosomes which migrate towards its pole during mitosis. Mazia believes that the centrosome is the sole microtubule organizing centre in the cell, and that

it also organizes membranes. He speculated on the flexible nature of the centrosome and on how its shape changed in conformation with the sites of microtubule initiation. Many of these speculations have since been fully confirmed by Schatten *et al.* (1986). The centrosome is seen as a cloud of osmiophilic granules which are physically associated with the centriole in cells which contain centrioles.

The theory relies heavily on the assumption that the centrosome is a replicator. This is suggested by the fact that during the cell cycle two centrosomes gradually appear in the same place as one was before, and by the ability of centrosomes to continue behaving normally during a series of ghostly mitoses in which there are no chromosomes inside the spindles (Wilson, 1928). The only satisfactory evidence would be the discovery of differences between centrosomes that were inherited independently of the genome. For the remainder of the paper I shall simply assume that centrosomes are replicators.

Centrosomes have a number of attractive features as candidates for the choice of two theory. No eukaryotes are known to lack mitosis or microtubules, and so, presumably, none are known without centrosomes. A theory of sex based on centrosomes could have a wide scope. In the following paragraphs, I shall discuss their mode of inheritance, how selection of the best of two could be done, and what kind of replicator a centrosome might be. This will not amount to a convincing case that the centrosomal best of two theory is true, but I hope to persuade the reader that the theory is worth considering for two reasons: first in attempts to understand the evolutionary maintenance of sex, and second in scrutinizing evidence on centrosomes as it becomes available for conformity to the theory, and possibly even in collecting evidence on centrosomes specifically to test the theory.

The mode of inheritance of centrosomes was thought to be understood many years ago. Boveri's theory of fertilization (Wilson, 1928) was that while the egg contributed the nutritive centre of the zygote, the sperm supplied the dynamic centre, namely the centrosome. Using recently developed techniques Schatten *et al.* (1986) have shown that in sea urchins the sperm supplies the centrosome to the zygote, but that in mice the oocyte supplies the centrosome. They suggest that mammals have maternal inheritance while all other animals obey the paternal rule.

These two different uniparental modes of inheritance may seem to deal a double blow to the centrosome's candidature for the choice of best of two theory. Sea urchins and mice have a common ancestor, however, and even if we accept that sea urchins and mice have opposite forms of uniparental inheritance we are forced to admit that ambiguous inheritance must have existed at some point in evolutionary history. Only one view can avoid the conclusion that ambiguous inheritance has existed, and it is that contrary to appearances sea urchins and mice inherit the centrosome from the same parent.

The evidence adduced by Schatten *et al.* (1986) is that the centrosome which organizes the apposition of the two pronuclei can be seen to have physical continuity with the centrosome provided by the donor sex, and that only the donor sex has centrosomes in its gametes. This observation could be consistent with the discovery of ambiguous inheritance only if centrosomes have a dormant state in the sense that they are not recognized by the technique and do not initiate microtubules. One

possible scheme would then be as follows. One gamete provides an active centrosome whose task it is to appose the gametic pronuclei, while the other provides a dormant centrosome. At some stage during the development of the organism the dormant centrosome becomes active in a cell. Competition between two centrosomes could then occur within that cell, with one centrosome succeeding in forming both halves of the mitotic spindle. Alternatively, the centrosomes could each form one mitotic half spindle. The developing organism would then become a mosaic. One clone of cells would have copies of the paternal centrosome and another clone copies of the maternal centrosome. Competition between the two clones would then be competition between the paternal and maternal centrosomes.

It seems likely that dormant centrosomes exist, as cytoplasm which contains no centriole or centrosome can give rise to fully formed centrioles and a spindle (Wilson, 1928). Germ plasm in *Xenopus laevis* eggs is a granular material present in the part of the egg which will normally become the germ line. Wylie *et al.* (1985) show that it does not commit the cells containing it to become germ cells, and describe it as "maternally synthesized cytoskeletal material". According to the view proposed here, this could be a cloud of dormant centrosomes, ready in the right place to compete with the active (presumably paternally derived) centrosomes in the germ line of the developing embryo.

As well as having the correct mode of inheritance, centrosomes must compete with each other for presence in the germ line in a way that benefits the organism. One function of the centrosome is to initiate polymerization of tubulin, and to do so in conditions less favourable than those which would allow spontaneous polymerization throughout the cell. Mitchison & Kirschner (1984) show that centrosomes initiate microtubules at concentrations of about 3 to 4μM of tubulin, while microtubules form spontaneously by polymerization of tubulin in the cell only at 14μM. This suggests a possible mechanism of selection between centrosomes. The purpose of pursuing this suggestion is to provide a concrete example of how the ideas of the theory could be implemented.

Suppose that the most important inherited property of a centrosome is the concentration of tubulin at which it can polymerize microtubules, and that copying errors tend to increase this critical concentration. A centrosome whose critical concentration is 14μM is useless, as control of the microtubules in the cell is lost. As 14μM is approached, the cell would need more tubulin to function properly. Thus, mutation unbalanced by selection would lead to cells which had lost all abilities that depend on microtubules, such as mitosis, meiosis, and locomotion. A test between the critical concentrations of two centrosomes which are present in the same cell is easy to imagine. The cell begins with a very low concentration of tubulin, and slowly increases it. The better centrosome will be able to act first in dividing, and working the next mitosis. Only a centrosome with the power of movement could ensure that a copy was inherited by each daughter cell.

Two general points may be made on the basis of this rather specific speculation. The test between the centrosomes is imagined to be arranged by the nuclear genes. This is because the nuclear genes are the dominant replicators in the cell. The conflict between levels of selection is thought of as being resolved by the low

information content and poor fidelity of replication of the centrosome. The centrosomes are being "farmed" by the nuclear genes, and it must be supposed that if the heritable information in the centrosomes could have been incorporated into the nucleus, it would have been. The second point is that if there is heritable information in the centrosome, then it is almost inevitable that a mutation selection balance will operate. The random alterations that take place in copying are bound to be deleterious on average, and so lead, eventually, to centrosomes which cannot play their proper part in mitosis, meiosis, and in the many other essential cellular functions which involve microtubules (for some details of these see Alberts *et al.*, 1983). The "mutational load" of the centrosome must be greater than a half under the present theory. One possibility is that centrosomal degradation plays a part in cell senescence.

The essential microtubular functions suggest other possible tests that could be made between centrosomes. Cells with a more rapid mitotic cycle will come to predominate in a tissue, which could favour cells with fast-acting centrosomes. Alternatively, the migration of germ line cells in vertebrates (Alberts *et al.*, 1983) could act as a test of microtubular function: cells which have better powers of locomotion, and by inference a better centrosome, might have a better chance of completing the journey, or of reaching favoured locations within the developing gonads.

Finally, I consider the nature of the replicator. So far as I am aware the chemical composition of the centrosome is not yet known. The centrosome need not be a nucleic acid replicator. One possibility is that a crystal of some kind acts as a seed for microtubule initiation and that this crystal is the replicator, and another is that the precise physical configuration of microtubules is achieved by means of a buckled plate which replicates by some process of moulding of new onto old. If the centrosomal theory of sex is true, then it must be that the centrosome has to be a replicator for robust biochemical reasons—otherwise it would have been replaced with a non-replicating body which could be created new and in perfect condition each generation. The only conclusion I draw here is that a non-digital replicator would be likely to have very high mutation rates, and this would be consistent with the theoretical requirement noted in the previous section that the probability of mutation must be greater than a half.

Discussion

The theory of choice of two, and the case for the candidature of the centrosome, have now been set out. The first points I would make concern theories of sex that rely on recombination of genes. There may be other effects of sexual reproduction and so it is not safe to assume that the existence of sexual reproduction implies an advantage to recombination. At the moment, the only reason recombination is suspected to be ecologically advantageous is because some advantage must be found for sex (and probably because of the historical accident that those initially interested in the evolutionary side of sex were ecologically minded). It would be encouraging to have independent reasons for believing that recombination has beneficial effects

in a wide variety of species, or indeed in any one species. These cautionary points about ecological theories hold whether the centrosomal theory is true or not. An encouraging consequence of the truth of the centrosomal theory would be that recombinational theories would need to find only a small advantage, not a twofold advantage, to recombination.

The centrosome theory may also be compared with the other non-ecological theories. Kondrashov's (1982) theory involves the population mean fitness under mutation–selection balance, and the advantage to sex depends on non-multiplicative fitness interactions between mutations at different loci. It is not a full theory of sex because no explanation is given of why the epistatic interactions should be of the required type, and would become an ecological theory if that explanation was ecological. Bengtsson's (1985) ingenious theory has two disadvantages: the extent of advantage to sex is conjectural, even its order of magnitude is unknown, and a procedural difficulty is that it is hard to see what evidence would favour or contradict the theory. Bernstein *et al*'s (1985) theory, as has already been noted, implies only a transient advantage for sex, and so the twofold cost of sex between species remains unaccounted for.

A second conclusion from the theory concerns the nature of the centrosome. There is little reason from within cell biology to expect the centrosome to have the properties required by the centrosomal theory of sex. However, if the puzzle of sex is accepted, then some unlikely set of facts must be true, and these facts may be located in cell biology. The consequences of the truth of the theory are set out in the previous section. They may be worth bearing in mind as new facts become available about centrosomes. Decisive facts about centrosomes should soon settle the question of the candidature of the centrosome for the starring role in the choice of two theory of sex.

Finally, suppose all the required facts were true, and that the centrosomal theory of sex was established. What picture would sexual reproduction then present? The technology of mitosis and microtubules has committed eukaryotic cells to the possession of a replicator with a high mutation rate. Cell fusion and subsequent division, which may have arisen as precursors of fertilization and meiosis through the parasitism of large by small cells, would have the consequence that two of these unfaithful replicators were present in the cell at once. Competition between them then could have favoured cell fusion, if all daughter cells retained descendants of the better one. As sex evolved, the mechanism of competition could be refined and organized in the interests of the dominant replicators in the cell—the nuclear genes. Sex is then a technique used by the cell to circumvent the undesirable properties of an indispensable cell component. The larger size of eukaryotic compared to prokaryotic genomes is probably made possible by microtubular technology, and the complexity of eukaryotic cells and the organisms they comprise probably relies on large genomes.

The association (discussed for example by Bell, 1982) between organismal size of eukaryote species and their participation in sexual reproduction, could be explained by the role mutation rate plays in the model. If the centrosomal copy error rate is constant per cell generation, then species with more mitotic divisions per generation

would have a higher centrosomal error rate per generation. This makes sex more advantageous in larger species.

Sex can only double the fitness of a species, and so is not necessary for controlling the unfaithful replicator. The long-term success of sexual reproduction, particularly where the twofold cost of sex is present in full, or where the cost of sex is more than twofold (e.g. Bierzychudek 1987), must be caused by other factors, for example by an advantage to the recombination of genes. One major concern of recent evolutionary theory has been how long-term forces could explain sex, in view of the apparent short-term advantage to asex. The centrosomal theory may provide the answer.

The main attractive feature of the centrosomal theory of sex is its wide scope of application. The universality of cell structure has been employed to find a candidate explanation for sex. No ecological theory can hope to apply so widely, nor to be so susceptible to empirical test.

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