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Evolutionary dynamics of extranuclear genes

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SUMMARY

We studied the evolutionary dynamics of extranuclear genes taking into account simple kinds of selection, two modes of inheritance and the multiplicity of genomes within a cell. Particular attention was paid to the accumulation of advantageous or deleterious mutations in an extranuclear genome. Within-generation drift due to multiplicity of genome and non-Mendelian segregation promotes the fixation of advantageous mutations and prevents deleterious mutations from accumulating. We show also that the extent of paternal contribution makes little difference in the rate, but, in contrast, the configuration of the genome and the mode of transmission both makes a large difference. These results are compatible with what is known about extranuclear genomes.

INTRODUCTION

The genes of mitochondria in multicellular animals and the genes of mitochondria and chloroplasts in multicellular plants differ from nuclear genes in their modes of inheritance and in their potential exposure to selection. Mitochondria and chloroplasts are almost completely maternally inherited (Lansman *et al.* 1983, and references therein). The mitochondrial and chloroplast genomes contain numerous copies of each linkage group (Gillham, 1978; Birky, 1978; Beale & Knowles, 1978). There can be genetic drift (Thrailkill *et al.* 1980) and possibly selection occurring within each generation through mitotic cell divisions occurring before gamete formation.

There are also regularities in mitochondrial and chloroplast DNA in multicellular plants and animals (Wallace, 1982, Grivell, 1983). The genomes of mitochondria in different species and of chloroplasts tend to be similar in size and function, and within individuals there is little or no heterogeneity among different cells or among gametes. But there is considerable variability among individuals in a single population, more so than for nuclear genes (Avise *et al.* 1979*a*, *b*). Furthermore mitochondrial genes, particularly tRNA and rRNA genes, have a much higher rate of gene substitution (Brown *et al.* 1979; 1982).

To understand the evolution of extranuclear genes and to understand the evolutionary forces that might account for regularities that have already been found, mathematical models of extranuclear genes are needed. Some models have

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already been developed (Takahata & Maruyama, 1981; Chapman *et al.* 1982; Birky *et al.* 1983) to investigate the dynamics of neutral extranuclear genes. We will extend those models here to account for simple kinds of selection. We will be concerned particularly with the rates of accumulation of advantageous and deleterious mutations in extranuclear genomes in a population and in the effects of genetic drift occurring within each generation and of any paternal inheritance on those rates.

Our motivation for this study is the recognition that if the inheritance of extranuclear genomes is strictly maternal and if there is no genetic drift within each generation then extranuclear genomes are equivalent to asexual genomes. Felsenstein (1974), developing an idea of Muller (1932; 1964), used a simulation model to show that in asexual genomes deleterious mutations will tend to accumulate. In an asexual population in which there is no opportunity for recombination, there is no genetic mechanism to reduce the number of deleterious mutations carried by descendants of an individual. Felsenstein (1974) showed that in an asexual species, genetic drift will tend to cause a steady increase in the number of deleterious mutations carried despite selection acting against those mutations. He called this mechanism 'Muller's ratchet', and Haigh (1978) and Maynard Smith (1978) have further explored its workings. Charlesworth (1978) used the similarity of the nonrecombining portions of *Y* chromosomes in mammals to asexual genomes to argue that both the loss of function of the nonrecombining portions of *Y* chromosomes and dosage compensation in *X* chromosomes were due to the action of Muller's ratchet. Using our simulation model, we will show that Muller's ratchet will also be at work in extranuclear genomes unless, as seems to be the case, mechanisms of transmission of extranuclear genomes during mitosis allow for genetic drift within generations. This within-generation genetic drift acts like recombination in stopping Muller's ratchet.

1. SIMULATION MODEL

Our simulation model is of the same type as those developed by Takahata & Maruyama (1981) and Chapman *et al.* (1982), with the difference that we allow for the possibility of selection acting on zygotes based on the total number of advantageous or deleterious mutations they carry. We will not model selection within generations.

We modeled a population with N_f females and N_m males. Each individual was assumed to carry n copies of the extranuclear genome each of which codes for k completely linked loci. A generation of $N = N_f + N_m$) zygotes was formed by choosing pairs of gametes from the male and female gamete pools (with replacement) and then assigning sex at random but preserving the sex ratio. For each zygote, a fraction $1-\beta$ of the extranuclear genomes were chosen from the female and a fraction β from the male gametes (both with replacement). The value $\beta = 0$ represents completely maternal inheritance and $\beta = 0{\cdot}5$ represents equal contributions from the two sexes. At the present time, it appears that β is small for the inheritance of mitochondria in animals but with values as large as 0·05 not being excluded empirically (Avise *et al.* 1979*b*; Reilly & Thomas, 1980; Dawid & Blacker,

1972; Giles *et al.* 1980). In a study of the tobacco budworm, Lansman *et al.* (1983) showed paternal leakage (β) to be less than 0·004 %.

We assume mutation occurs irreversibly at a rate v per locus per cell division with λ mitotic cell divisions per generation. Selection takes place among the zygotes with the likelihood that a zygote contributes gametes to the gamete pool being proportional to its relative fitness. We assume at each locus, each mutation has a fitness of 1-s relative to the allele present before the mutation and that fitnesses are multiplicative, so the relative fitness of a zygote is $(1\text{-}s)^i$ where i is the total number of mutations carried.

We used two different assumptions about the transmission of the extranuclear genome during mitosis. We will follow the terminology of Chapman *et al.* (1982) in distinguishing the two possibilities. The first assumption (Model I), 'perfect transmission', assumes that each daughter cell receives an exact copy of the extranuclear genome. With this assumption, there is no genetic drift within each generation: each cell in the adult will have the same number of mutations as the zygote, except for any new mutations that have occured. There is no mechanism for reducing the number of mutations carried. We agree with Ohta (1980) and Chapman *et al.* (1982) that this assumption is biologically unrealistic, at least in the absence of a known mechanism for achieving perfect transmission (see also Birky, 1978 and Gillham, 1978).

The second assumption (Model II), 'imperfect transmission', assumes that at each mitotic cell division extranuclear genomes were sampled randomly from the extranuclear genome of the parent cell. We assumed both sampling with replacement and, after a doubling of the extranuclear genome, sampling without replacement, but we found only a slight difference between those two choices. Both kinds of sampling cause genetic drift within a generation and allow the possibility that extranuclear genomes in gametes carry fewer or more mutations than the zygote that produced those gametes. The only difference between sampling with and without replacement was a slightly stronger effect of genetic drift for the case of sampling with replacement. Model II of Chapman *et al.* (1982) assumes sampling with replacement.

The imperfect transmission of extranuclear genomes during mitosis causes what we will call within-generation genetic drift. This is the key feature of our model and we will show that it has two consequences for the evolution of extranuclear genes. First, within-generation drift can act like recombination because gametes derived from a zygote can carry more or fewer mutations than the zygote. It is this effect that will slow or stop the accumulation of deleterious mutations and prevent Muller's ratchet from acting. Second, within-generation drift can increase the genetic variability in the population thereby making selection more effective. It is this effect that causes advantageous mutations to accumulate more rapidly than if there were no within-generation drift.

To summarize, the parameters of our model are: N_f and N_m, the numbers of male and female zygotes; v, the mutation rate per cell division; λ, the number of mitotic cell divisions per generation; n, the number of chromosomes in the extranuclear genome; k, the number of loci per chromosome; and β, the fraction of the extranuclear genome contributed by males. In addition, the model of

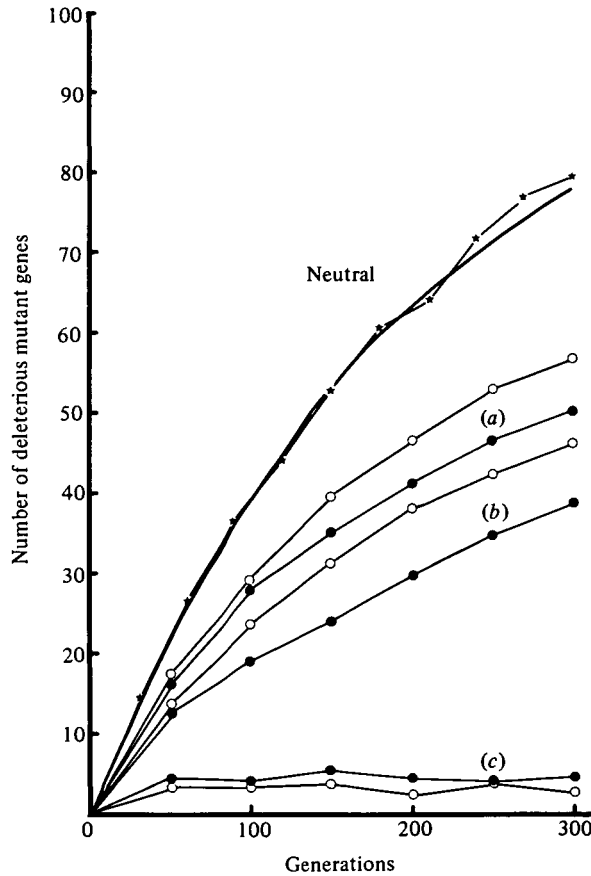

Fig. 1. Accumulation of deleterious mutant genes with time. Here and in Fig. 2 the ordinate represents the average number of mutants within a cell that is given by $kn(1-\exp(-\lambda vt)$ if selection is absent, and the abscissa represents time, t, measured in unit of generation. The solid stars are the result of a control simulation when $s = 0$, $n = 10$, $\lambda = 5$, $k = 10$, and $\beta = 0{\cdot}5$. Genome configuration is specified by three letters (a), (b), and (c), and for each genome configuration the open circles represent the case of $\beta = 0$ while the solid circles represent the case of $\beta = 0{\cdot}5$. Within-generation drift was simulated by sampling with replacement. The simulation results of 'perfect transmission' are almost the same as (a) irrespective of genome configuration.

transmission during mitosis and the initial conditions were specified. We assume n is a constant; we will discuss later the possible effects of changes in n during embryogenesis. In all cases, we assumed the initial population was homogeneous and contained no mutations.

2. RESULTS

To obtain an adequate number of replicates for a variety of parameter values, we restricted the population sizes and genome sizes to relatively small values. In all cases, we assumed $|s| = 0{\cdot}01$, $\lambda = 5$, $N_m = N_f = 25$, $v = 0{\cdot}001$ for deleterious mutations and 0·0001 for advantageous mutations and that the total number of loci in the extranuclear genome was restricted to 100 ($= nk$). The three cases we

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simulated were: (*a*) $n = 1$, $k = 100$; (*b*) $n = 2$, $k = 50$; (*c*) $n = 10$, $k = 10$. We will use those letters to label the figures. Note that for case (*a*), there is no difference between Models I and II because there can be only perfect transmission of the genome. For all sets of parameter values, the results are for the average behaviour of 10 independent replicates.

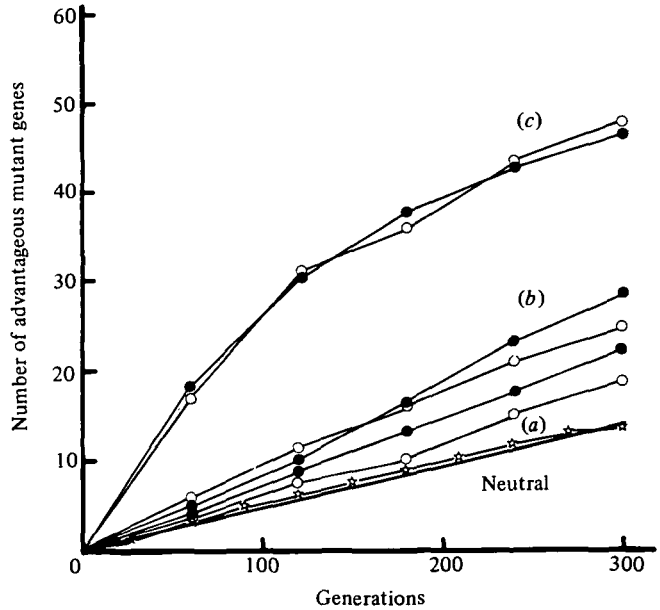

Fig. 2. Accumulation of advantageous mutant genes with time. The open stars are the results of a control simulation when $s = 0$, $n = 1$, $\lambda = 5$, $k = 100$, and $\beta = 0$. See the legend of Fig. 1 and the text for details.

Deleterious mutations ($s > 0$)

Under our assumptions, deleterious mutations do accumulate with the rate strongly dependent on the parameter values. The results for Model II are shown in Fig. 1, which also has the analytic and simulation results for neutral alleles. The analytic values for neutral alleles were obtained as follows. Let $x(t)$ be the expected number of mutations carried in a cell, in the tth generation. Within-generation drift and random sampling of gametes do not change the expectation. If we assume mutation is irreversible, then approximately

$$\frac{dx}{dt} = (kn - x)\,\lambda v,$$

which implies

$$x(t) = kn(1 - exp\,(-\lambda vt)),$$

under the initial condition $x(0) = 0$.

From the figure, we can draw three conclusions. First, the extent of paternal contribution makes little difference in the rate. There are relatively small differences between the pairs of curves for $\beta = 0$ and $\beta = 0{\cdot}5$. Second and in contrast, the configuration of the genome makes a very large difference. Under the assumptions

of Model II, case (*c*) leads to a mutation-selection balance with relatively few mutations per genome. Third, the mode of transmission also makes a large difference. If there is perfect transmission (Model I) Muller's ratchet is not slowed by much through any paternal contribution. We found the simulation results of (*c*) under Model I to be very similar to those of (*a*) under Model II. If there is a substantial opportunity for genetic drift within each generation – Model II, case (*c*) – then Muller's ratchet is effectively stopped.

Advantageous mutations ($s < 0$)

We can also use our model to investigate the rate of accumulation of advantageous mutations. We simulated the same sets of parameter values with the only difference being the sign of the selection coefficient and the mutation rate $v = 0{\cdot}0001$. The results for Model II are shown in Fig. 2. The results of Model I are similar to (*a*) under Model II.

Fig. 2 shows that both the mode of transmission and the configuration of the genome affect the rate of accumulation of advantageous mutations, with the opportunity for genetic drift within each generation being more important than the possibility of a paternal contribution. Within-generation drift promotes the fixation of advantageous mutations by increasing the genetic variation on which selection can act.

3. DISCUSSION AND CONCLUSIONS

The results from our simulation study show the potential evolutionary importance of two, as yet poorly understood processes affecting the evolutionary dynamics of extranuclear genes: the mode of transmission during mitosis and the configuration of the genome in the germ cell line. As we show, the mode of transmission strongly affects the extent of genetic drift occurring within generations, and within-generation drift retards the accumulation of deleterious mutations and accelerates the accumulation of advantageous mutations. Both of these results are because within-generation drift increases the genetic variability of the extranuclear genome in the population and provides greater opportunity for selection to act. The model of perfect transmission (Model I), which allows for no within-generation drift, leads to predictions that are incompatible with what is known about extranuclear genomes. Our theory predicts that deleterious mutations would accumulate and lead to a loss of function of extranuclear genes, yet mitochondrial and chloroplast genes have clearly established functions and little indication of nonfunctional DNA. The importance of within-generation genetic drift has been pointed out in the evolution of selfish DNA and multigene families by Ohta (1983 and references therein).

We also found that the configuration of the genome affects the action of within-generation drift. In general, the more copies of the genome (larger n) the more effective within-generation drift is in preventing the accumulation of deleterious mutations and accelerating the accumulation of advantageous mutations. This may seem paradoxical because, by analogy with genetic drift in conventional population genetics theory, within-generation drift would be expected

to be strongest when there are fewer copies of the genome (as long as there were more than one). While within-generation drift is indeed stronger for smaller values of n, its effect on the genetic variability in the population as a whole is weaker. Larger values of n lead to larger genetic variation on which selection can act. If n varies during a generation, then the effective value of n would, by analogy with conventional genetic drift, be smaller than its average value. This could lead to a bottleneck caused by small values of n in one state of the life cycle.

Another way to understand the effect of within generation drift is to note that it increases the selection experienced by each mutation. Consider the fate of a single mutation of relative fitness 1-s. It appears initially in a single copy but, because of within generation drift that occurs before it is exposed to selection, it is either lost or it increases in copy number, probably to n for the parameter values we have used. Therefore, when it is first exposed to selection, the individual carrying the mutation has a relative fitness not of 1-s but $(1\text{-}s)^n$. The selection is, therefore, much stronger than experienced by a comparable nuclear mutation. For deleterious alleles, it is this stronger selection that stops the action of Muller's ratchet.

In saying that within-generation drift is potentially a strong force affecting the dynamics of extranuclear genes, we have assumed that the appropriate cases to compare are those in which mutations with the same effect of each copy. If instead, we assume that mutations have the same effect per genome, regardless of the number of copies per genome, we would reach a different conclusion. If we assume for example that the relative fitness of an individual fixed for a mutation at all n copies of the genome is 1-s, so the relative fitness of each allele is much less than s if n is at all large, then the results from our simulations do not depend on n. The multiplicity of extranuclear genomes will strongly affect the evolution of individual mutations only if the multiplicity does not result in the dilution of the selection experienced by each copy of the mutation.

The parameter values were chosen to illustrate how the various mechanisms interact. As yet, there is insufficient information to provide good estimates of the parameters. From what is known, it seems that for mitochondria in higher animals, case (c), in which there are several copies of the genome with relatively few genes on each is the most appropriate. On the other hand, for chloroplasts of higher plants, there are fewer copies of the genome and more genes on each, so cases (a) or (b) are more appropriate.

We did not simulate the process of recombination among extranuclear genomes but we can anticipate its effect. If there is more than one copy of the genome and if there is some recombination, then the effect would be to increase the variation in the number of mutations carried by gametes produced by a single zygote. That is the same as increasing n. Therefore, our conclusion about the role of within-generation drift is strengthened if there is some recombination, because recombination would augment the effect of within-generation drift.

For our purposes, the paternal contribution to extranuclear genomes is less important. A paternal contribution can be viewed as increasing the extent of genetic drift within generations. While there is definitely some effect of a small paternal contribution, it is less important than the overall effect of genetic drift within generations. This feature of our results is due to our assumption of relatively

large values of λ and small values of n. Takahata & Maruyama (1981) showed paternal inheritance becomes important when β exceeds λ/n.

More realistic models will be needed to investigate the generality of our results, but we see nothing in our model that produces any bias for the importance of genetic drift occurring within each generation.

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