

## ON FACTORS AFFECTING THE FIXATION OF CHROMOSOMAL REARRANGEMENTS AND NEUTRAL GENES: COMPUTER SIMULATIONS

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*Abstract.*—Computer simulation models were developed to determine which conditions are favorable for the stochastic fixation of chromosomal mutations within small isolated demes. The models incorporated biological parameters of litter size, age-dependent mortality, overlapping generations, potentially varying sex ratios, and fertility reduction due to meiotic problems when the mutation was present in a heterozygous condition. Results of the models indicated that random processes alone may adequately explain the frequency of fixation of chromosomal mutations under the conditions of a) the number of initial founders is small (5 or 10); b) there is relatively little fecundity reduction due to meiotic problems; c) the number of offspring per mating is high. Furthermore, results of our models imply that fixation of a mutation is unlikely when the number of karyotypic rearrangements is low and when there is high survivorship of individuals from one breeding period to the next. However, if bottlenecks involve larger numbers of individuals (20 or more), few offspring per mating, or substantial reductions in fecundity, then it is unlikely that fixation by random processes will be adequate to explain the situations observed in nature. A significant conclusion of these simulations is that when population size is reduced to five or ten individuals, the extinction rate may exceed 40% or 30%, respectively.

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Identification of the primary factors responsible for the rate, magnitude and direction of chromosomal evolution has been an area of considerable debate in recent years (Atchley and Woodruff, 1981). Theoretically, chromosomal change has been implicated as an isolating mechanism during speciation (White, 1968, 1978; Templeton, 1979), and as being an accurate long-term indicator of effective population size (Lande, 1979, 1984). Certain models of chromosomal evolution imply that the primary circumstances under which chromosomal rearrangements become fixed are population bottlenecks which cause sampling error to override negative heterosis due to meiotic problems (Wright, 1941; Bengtsson and Bodmer, 1976; Lande, 1979). Lande's model reinforced the idea that chromosomal evolution was facilitated by social structuring and inbreeding within populations (Wilson et al., 1975; Bush et al., 1977).

There appears to be little accord regarding the circumstances governing chromosomal evolution (Atchley and Woodruff, 1981). Studies of the relative fitnesses of organisms possessing different chromosomal rearrangements (John and Lewis, 1957, 1958, 1959; Lewis and John, 1957; Dobzhansky, 1970; Vosselman and Van Heemert, 1980; Baker et al., 1983) strongly emphasize the possible adaptive nature of the karyotypic

rearrangements and indicate that selection, either for or against a novel arrangement, must remain a viable alternative in chromosomal evolution (Bickham and Baker, 1979; Bush, 1981; John, 1981). However, John (1981) concludes that there are insufficient data to distinguish among alternative hypotheses regarding the causes and consequences of chromosomal change.

It was our purpose to implement computer simulations to determine which conditions are favorable for the stochastic fixation of chromosomal mutations within small isolated demes. We have incorporated biological parameters, such as litter size, age-dependent mortality, overlapping generations, and potentially varying sex ratios, that have not been included in previous mathematical models of chromosomal evolution (Lande, 1979, 1984). Ultimately, we wished to determine from these simulations whether the fixation rate of chromosomal rearrangements due to drift was adequate to explain the magnitude of chromosomal evolution observed in lineages of bats and rodents (Baker and Bickham, 1980; Baverstock et al., 1983). We realize that additional models of stochastic fixation of chromosomal arrangements other than those presented here are possible (e.g., Hedrick, 1981). Hedrick invoked inbreeding among close relatives, an assumption not used in

our model. However, our purpose was to investigate the conditions of feasibility of the most widely referenced model of chromosomal evolution (Lande, 1979).

### *The Model*

Results from two computerized stochastic models were analyzed to document the probability of fixation of chromosomal rearrangements which appear in small founding populations. Both models assume that no migration occurs, that survivorship is a function only of age, and that all individuals have an equal opportunity to produce offspring. In the first model, founding populations consisting of 5, 10, 20, or 50 individuals were established. The sex of each individual was arbitrary, and the chromosomal mutation was randomly assigned to a single heterozygous individual. A maximum age of 10 breeding periods was possible, but the probabilities of survival from one breeding period to the next were as follows: 0-1 = 0.4; 1-2 through 8-9 = 0.70; 9-10 = 0.50; 10-11 = 0. Age-specific survival patterns for this model were derived from Humphrey and Cope (1976) for the bat species *Myotis lucifugus*. All founders were of age five. Mates were selected randomly, and inbreeding was not avoided. The number of offspring was set as either one, two, or five. Reduction in the number of offspring was possible only by way of fertility reductions for individuals heterozygous for the chromosomal rearrangement. In such cases, the probability of birth for each offspring was one minus the fertility reduction due to meiotic problems. These values (0, 0.1, 0.25, and 0.5) encompass the range of fertility reduction usually associated with chromosomal rearrangements (White, 1978).

Extinction of a deme was possible if either one sex or all individuals were eliminated. Although fixations may have occurred at any time during the execution of the model, a population size of at least ten individuals must have been attained before the simulation ceased for the fixation to be accepted. This procedure was invoked to omit transient fixations in populations that quickly became extinct subsequent to fixation. If fixation occurred when population size was less than ten but the population subsequent-

ly grew to a deme size of ten or greater, then the fixation was accepted. All trials were run for 1,000 breeding periods or until an accepted fixation was achieved. Simulations for model one were repeated 1,000 times for each set of conditions.

The second simulation model was similar to the first except that the survivorship and mating periods were set to approximate that for the Yanomama Indian tribe (Neel, 1978). Population characteristics were varied between the two models to include disparate survivorship patterns. Offspring survivorship in humans is high relative to bat populations (Type IV vs. Type II survivorship curves). The maximum number of breeding periods was seven. The probabilities of survivorship from one breeding period to the next were: 0-1 = 0.44; 1-2 and 2-3 = 0.87; 3-4 and 4-5 = 0.86; 5-6 and 6-7 = 0.85. All founders were of age three (in the third breeding period). The number of offspring in this model was set at one. Reductions in fertility by the probabilities of 0.0, 0.1, 0.25, and 0.5 were possible for individuals heterozygous for the chromosomal rearrangement as in the previous model. Fixation for a chromosomal rearrangement was not accepted until a subsequent deme size of 50 individuals was obtained. All trials were repeated for 500 replicates.

### RESULTS AND DISCUSSION

The results of the simulations are given in Tables 1 and 2. If the trends observed in the simulations are accurate, then the following observations should apply to biological situations.

When the number of founders is five, the most important factor regarding the number of fixations and the frequency of extinction is the number of offspring per breeding period (Table 1). Growth of the population out of such a severe bottleneck is enhanced by the number of progeny per mating. At low reproductive rates the population expansion is not sufficient to avoid a large number of extinctions. However, in the first model, the mutation was most frequently fixed when the founding population consisted of five individuals (a total of 61 of 12,000 trials; 0.51%; Table 1). The relatively high rate of fixation with fertility reductions indicates that, with small pop-

TABLE 1. The numbers of fixations for mutant chromosomal rearrangements, extinctions, fixations for the common chromosomal morph, and polymorphic conditions after 1,000 breeding periods for simulations based on survivorship probabilities for *Myotis lucifugus*. Females had one, two, or five offspring per breeding period unless the fertility reduction prevented the production of viable offspring. Numbers in parentheses indicate the average number of breeding periods necessary to fix the mutant morph. All simulations were repeated 1,000 times.

Initial population	Number of offspring	Fecundity reduction	Alternate fixations	Extinctions prior to fixation	Common fixations	Polymorphisms maintained
5	1	0.00	0	354	646	0
		0.10	1 (7)	328	641	0
		0.25	0	354	646	0
		0.50	0	325	675	0
	2	0.00	7 (11)	274	729	0
		0.10	5 (14)	282	713	0
		0.25	6 (17)	236	758	0
		0.50	4 (19)	237	759	0
	5	0.00	14 (46)	50	936	0
		0.10	11 (54)	58	931	0
		0.25	8 (69)	61	931	0
		0.50	5 (81)	67	931	0
10	1	0.00	1 (9)	156	843	0
		0.10	0	132	868	0
		0.25	1 (14)	140	859	0
		0.50	0	94	906	0
	2	0.00	10 (25)	61	929	0
		0.10	8 (32)	63	929	0
		0.25	0	56	944	0
		0.50	1 (31)	47	952	0
	5	0.00	18 (57)	22	960	0
		0.10	12 (68)	20	968	0
		0.25	2 (80)	28	970	0
		0.50	0	28	972	0
20	1	0.00	0	60	940	0
		0.10	0	53	947	0
		0.25	0	46	954	0
		0.50	0	26	974	0
	2	0.00	2 (48)	12	968	18
		0.10	4 (47)	9	987	0
		0.25	0	7	993	0
		0.50	0	3	997	0
	5	0.00	5 (71)	4	971	20
		0.10	3 (94)	5	990	2
		0.25	0	5	995	0
		0.50	0	6	994	0
50	1	0.00	0	0	998	2
		0.10	0	0	1,000	0
		0.25	0	0	1,000	0
		0.50	0	0	1,000	0
	2	0.00	0	0	976	24
		0.10	0	0	995	5
		0.25	0	0	1,000	0
		0.50	0	0	1,000	0

TABLE 1. Continued.

Initial population	Number of offspring	Fecundity reduction	Alternate fixations	Extinctions prior to fixation	Common fixations	Polymorphisms maintained
5	1	0.00	0	0	968	32
		0.10	1 (91)	0	987	12
		0.25	0	0	999	1
		0.50	0	0	1,000	0

ulation sizes, stochastic processes may indeed overcome negative heterosis as predicted (e.g., Wright, 1941; Lande, 1979).

The numbers of extinctions in the second model (Table 2) were proportionally greater than those in the first model even though the probabilities of survival from one breeding period to the next were relaxed. In the initial model a fixation was accepted with a population size of ten. After the magnitude of the extinction problem became apparent, we concluded that a population of ten individuals was not adequate to eliminate the possibility of subsequent extinction. Therefore, for the second model, fixation of a genetic type was not accepted until the population size reached 50. The fact that there were no extinctions in the 4,000 trials starting with an initial population size of 50 (Table 1) justified this conclusion. In both models, fixation of the mutation occurred early, when population sizes were still small.

Meiotic problems, which may reduce fecundity, are relatively unimportant to either the fixation or extinction rates when the number of founders is small but become increasingly important with higher numbers of founders. No fixations of the mutations were observed with fecundity reductions of 0.25 or greater when founding population sizes were 20 or 50 for either model.

Meiotic problems, however, appear to be relatively unimportant to the rate of extinction, regardless of the number of founders. Hence, the stochastic processes associated with age-specific survivorship and sex ratios are more important to extinction than to reduced fecundity of heterozygous individuals. In fact, in both models, fewer extinctions were observed when the fecundity reduction was high. The reduced frequency of extinctions was due to the rapid fixation of the common chromosomal type. For this reason, the number of extinctions observed

TABLE 2. The numbers of fixations for mutant chromosomal rearrangements, extinctions, fixations for the common chromosomal morph, and polymorphic conditions after 1,000 breeding periods for simulations based on the survivorship possibilities for Yanomama Indian Tribes. All simulations were repeated 500 times, and females had only one offspring per breeding period unless fecundity reduction prevented the production of a viable offspring. Numbers in parentheses indicate the average number of breeding periods to arrive at each chromosomal condition.

Initial population size	Fecundity reduction	Alternate fixations	Extinctions prior to fixation	Common fixations	Polymorphisms maintained
5	0.0	7 (81)	410 (14)	80 (52)	3
	0.1	7 (93)	420 (15)	73 (31)	0
	0.25	2 (46)	430 (13)	68 (29)	0
	0.5	1 (20)	415 (12)	84 (26)	0
10	0.0	4 (49)	289 (25)	201 (25)	6
	0.1	2 (106)	286 (22)	212 (25)	0
	0.25	2 (64)	324 (20)	174 (22)	0
	0.5	0	310 (21)	190 (21)	0
20	0.0	3 (92)	114 (32)	378 (16)	5
	0.1	1 (157)	160 (31)	339 (16)	0
	0.25	0	125 (28)	375 (13)	0
	0.5	0	132 (28)	368 (11)	0
50	0.0	1 (182)	69 (38)	426 (15)	4
	0.1	0	71 (36)	428 (14)	1
	0.25	0	80 (32)	420 (12)	0
	0.5	0	88 (30)	412 (10)	0

is probably an underestimate, especially when fertility reductions are high.

Fixation of a mutant chromosomal type is unlikely when the number of offspring per mating is one and survival probabilities are low, as in the first model (Table 1). Bengtsson (1980) hypothesized that fixation of mutant forms is more difficult for animals with low intrinsic rates of increase. It is important to note that, in this model, the mutant is present in only a single, heterozygous founder. Hence, the probability of loss of the rearrangement in the first breeding period is one-half the probability of mortality for the possessor of the mutation. In our two simulations, the mutation would be expected to be lost subsequent to the first breeding period in 12.5% (model one) and 7.0% (model two) of the trials. Fecundity problems further reduce the probabilities of establishment and, as before, factors that increased the frequency of the mutant type would also be driving the population toward extinction.

Fixation of the mutant chromosomal type is a rare event when the size of the founding population is 20 or greater (15 of 24,000 trials; 0.0625% [model one]; and 5 of 4,000 trials; 0.125% [model two]). A population size greater than 20 decreases the probability that random events will fix the mutation. In addition, the enhanced effect of high reproductive rates on the fixation frequency is greatly reduced when the founding population consists of 20 or more individuals.

The magnitude of the fecundity reduction had a profound effect on the frequency with which both chromosomal morphs were maintained in a polymorphic condition for a duration of 1,000 breeding periods. Selection against heterozygotes strongly affects the probability of establishment of the mutation. Survivorship probabilities also had an effect on the maintenance of polymorphisms. In the second model which simulated primitive human tribes, polymorphisms were maintained when initial population sizes were low (e.g., 5 and 10) whereas the first simulation established polymorphisms only when population sizes were 20 or greater. It should be noted that some polymorphisms observed after 1,000 breeding periods would disappear after a greater number of generations.

The simulations usually allowed the maximal opportunities for fixation of the chromosomal mutation. Additional factors such as dispersal and inbreeding avoidance, which are usually characteristics of mammalian species but which are not included in the models, would work to inhibit fixation further. Lande (1979) and others have noted that dispersal (gene flow) greatly reduces the chance of fixation of chromosomal mutations. When dispersal rate exceeds one-fourth of the effective population size, then even temporary fixations are unlikely (cf. Lande, 1979). The high rates of extinction of isolated demes (Tables 1 and 2), particularly with low numbers of founders, imply that immigration would be necessary for continued existence of the deme. Lande (1979 p. 238) in fact stated that "for continued existence, a population must normally consist of multiple demes with dispersal from them at a rate exceeding the local extinction rate." Our data indicate that the dispersal rates would necessarily be great

(sometimes greater than 40%) to avoid local extinction, particularly when the number of founders and the number of progeny are low.

Our results do not support Lande's (1979) assumption that any deme, regardless of effective population size, has an equal probability of becoming the progenitor of the species and that the probability of fixation within a deme is equal to the probability of fixation within the species. We think that, within a species, all demes will encounter population bottlenecks at one time or another, but at any one time demes within a species will vary in numbers of individuals. Results of our models suggest that the larger demes are the ones that have the greatest probability of survival. These are therefore more likely to recolonize areas where demes become extinct. High rates of extinction within small demes make it unlikely that chromosomal mutations in small demes will become fixed in the species. Therefore, the likelihood of chromosomal evolution by way of random processes is even less probable than the maximum rate of fixation in small demes (Tables 1 and 2) (cf. Lande, 1979).

Other models simulating the fate of neutral mutations in human populations based on the Yanomama Indian tribe (Li et al., 1978) found that the mutation seldom escaped the native village even when gene flow among villages was high (Li et al., 1978 p. 92). This implies that the frequency of a fixation of a mutant neutral gene or a chromosomal rearrangement is lower in nature than the values in Tables 1 and 2 would imply. Furthermore, the probability that any single deme will be the progenitor of an entire species appears to be very low for species with the populational characteristics of the Yanomama Indians or those used in the simulations in Table 1.

The results of the simulations presented in this paper are independent of the mutation rate, because the mutation was introduced into each population. In reality, the probability of inclusion of a mutant in a population is dependent on the mutation rate and the number of founding individuals. In the most favorable conditions for fixation in the first model (ten individuals, no fecundity reduction, and five offspring

per mating), a fixation occurred in one in every 55.56 trials. Assuming the highest mutation rate given by Lande (1979) of  $10^{-3}$ , then on the average 5,556 such bottlenecks would be necessary to fix a chromosomal mutation or neutral gene. Empirical data from cladistical analysis of congeneric species for some mice (Hood et al., 1984; Baverstock et al., 1983) and bats (Baker and Bickham, 1980; Capanna, 1982; Capanna et al., 1977; Haiduk and Baker, 1982) indicate that some species have undergone as many as 20 or more euchromatic rearrangements since separating from congeners. Assuming optimal conditions of Table 1 and sequential fixations, as many as 111,120 bottlenecks may be necessary for random events to fix the neutral rearrangements. It is not realistic to hypothesize such a large number of bottlenecks in such cases as *Reithrodontomys megalotus* and *R. zacatecae*, which are distinguished by over 20 euchromatic rearrangements (Hood et al., 1984) which have not been accompanied by any detectable genic differentiation (Nelson et al., 1984).

Many species have numerous fixed chromosomal rearrangements which have resulted in radically reorganized genomes (karyotypic megaevolution; Baker and Bickham, 1980, 1984; Baverstock et al., 1983), yet the magnitude of the evolution would not be predicted by random processes alone. Of the 38 species of phyllostomid bats examined, 22 species have 15 or more fixed chromosomal rearrangements that are different from those of the karyotype proposed as the primitive for the family (Baker and Bickham, 1980). However, bats usually have only one offspring per breeding period, and several of the rearrangements identified in these bats would be expected to impose severe meiotic difficulties (Baker and Bickham, 1980). According to the results of our simulations, the probabilities of fixation of chromosomal mutations under these conditions by random chance alone would be small, even in very small populations. It is our conclusion that, in examples like these, factors other than stochastic processes and populational bottlenecks are probably important to the fixation of chromosomal mutations.

Other factors not included in our models

could enhance the fixation of chromosomal mutations. We assumed that the mutation was either neutral or was detrimental to the reproductive success of heterozygous individuals. However, translocation heterozygotes have been shown to be selectively favored in *Periplaneta americana* and *Blaberus discoidalis* (John and Lewis, 1957, 1958, 1959; Lewis and John, 1957) as a result of inbreeding depression. Positive heterotic effects of chromosomal rearrangements have been documented in *Drosophila*, the onion fly *Hylemya antiqua* (Vosselman and Van Heemert, 1980), and the plains pocket gopher (Patton et al., 1978; Baker et al., 1983). In these cases, heterosis was apparently of sufficient magnitude to prevent the fixation of alternative chromosomal morphs. These studies emphasize the possible adaptive nature of some chromosomal rearrangements (Bickham and Baker, 1979) and provide alternative mechanisms for the increase of frequency of a chromosomal mutation in populations, regardless of the deme size. However, heterosis alone will not promote the fixation of chromosomal rearrangements.

It is possible that species with greater age-specific probabilities of survival than those used in this study may have higher rates of fixation because of a lower frequency of extinction. However, for any given mutation, the probability of fixation is still like that shown in Tables 1 and 2. The second model does demonstrate that higher survivorship may increase the probabilities of fixation somewhat, but fixations remain relatively rare. Furthermore, the life-histories of many organisms probably involve lower survivorships than those simulated here, and species which have high survivorship (such as those in our models) usually have low fecundity.

Higher mutation rates would increase the opportunities for chromosomal evolution. The possibility of a mutation rate much higher than  $10^{-3}$  is suggested by the data presented by Capanna (1982), Koop et al. (1983), and McClintock (1978). Our models assumed that mutations resulted in unique chromosomal rearrangements. However, there is evidence (e.g., Shaw et al., 1983) that recurrent mutations may be feasible. Multiple origins of a given rearrangement

and/or presence of many different mutations (Koop et al., 1983) would certainly increase the probabilities of inclusion of a mutation within a small deme and of fixation due to genetic drift.

Random processes may adequately explain the frequency of fixation of chromosomal mutations under the following conditions: a) the number of initial founders is small (5 or 10); b) there is relatively little fecundity-reduction due to meiotic problems; and c) the number of offspring per mating is high. Our models imply that fixation of a mutation is unlikely if the total number of karyotypic rearrangements is small and the survivorship of the individuals from one mating period to the next is great. However, if bottlenecks involve larger numbers of individuals, few offspring per mating, or high fecundity reductions, then the likelihood of fixation of novel rearrangements by random processes is low. A significant conclusion from these simulations is that, when population size is reduced to five individuals, the extinction rate may be higher than 40%; and when population size is reduced to ten, extinction is still a significant problem.

Results presented in this paper indicate that random processes alone are not sufficient to explain the magnitude of chromosomal evolution in many organisms and support the conclusion of Bengtsson and Bodmer (1976 p. 276) that "... fixation of chromosomal mutations by drift only occurs under special, and presumably very rare, circumstances." However, the results do not elucidate which other factors may be more important for explaining fixation of alternative chromosomal rearrangements. Empirical data fail to support any particular causes or consequences of chromosomal evolution in natural populations (John, 1981). It is likely that models that incorporate combinations of factors will provide more realistic predictions for chromosomal evolution.

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