

SIMULATION OF GENETIC SYSTEMS BY AUTOMATIC DIGITAL COMPUTERS

IV. SELECTION BETWEEN ALLELES AT A SEX-LINKED LOCUS

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Summary

A programme simulating selection between two alleles at a sex-linked locus has been developed for an automatic digital computer (the SILLIAC). It introduces selection and chance effects at four stages of the life cycle.

Two experiments on competition between sex-linked alleles have been simulated, viz. selection between (i) the "sex ratio" and standard X-chromosomes of *Drosophila pseudoobscura* (Wallace 1948) and (ii) *yellow* and its wild-type allele in *D. melanogaster* (Merrell and Underhill 1956).

(i) Wallace's data includes estimated overall selective values and selective values for various of the components of fitness. From the latter, specific selective values appropriate to the four stages of selection in the programme have been calculated. Two sets of simulated populations, one using the overall selective values, the other the specific, gave similar results. Further, though completely dissimilar to the experimental population, they were very similar to the theoretical curve of change in frequency of sex ratio. The difficulties of estimating selective values from studies of the components of fitness are discussed and the need for an overall measure of fitness emphasized.

(ii) The simulated populations for competition between *yellow* and wild type agreed closely with the experimental. The importance of selective mating in this competition has been considered.

The results show that it is possible to simulate the operations of selection between two alleles at a sex-linked locus.

I. INTRODUCTION

Changes in gene frequency due to differential selection of alleles at a sex-linked locus have been reported by Buzzati-Traverso (1955), L'Héritier and Tiessier (1934, 1937), Ludwin (1951), Merrell (1953*a*, 1953*b*), Merrell and Underhill (1956), Reed and Reed (1948, 1950), and Wallace (1948). Of these, Merrell, Reed and Reed, and Wallace have attempted to determine the selective forces operating in their populations. In most cases, however, one can only note that there is a fitness differential between the alleles but cannot determine the nature or extent of this differential.

Fraser (1957*a*, 1957*b*) first introduced the Monte Carlo method to the simulation of genetic systems by automatic digital computers. The method was used

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by Barker (1958) in the analysis of selection between alleles in a population where, for given selection coefficients, it is possible to simulate the operations of selection and generate selection curves. The results showed that the simulated selection curves, which involve chance effects at the various stages of selection, closely resemble the selection curves obtained in experimental populations. Selection between alleles at an autosomal locus was discussed.

This method has now been adapted to the study of selection between alleles at a sex-linked locus. The programme for the SILLIAC simulates selection between two alleles segregating in a bisexual population in which males are the heterogametic sex and there is no overlap of generations.

TABLE I
INFORMATION CONCERNING ZYGOTES

Genotype	No. of Males	Zygote Selective Value	Genotypic Reproductive Coefficient
A/Y	N_{m_1}	w_m	x_{m_1}
a/Y	N_{m_2}	$w_m(1-s_m)$	x_{m_2}
Totals	N_m		1

II. OPERATIONS OF THE PROGRAMME

The selection processes are as defined by Barker (1958) for selection between autosomal alleles, viz.:

- (i) Zygote selection;
- (ii) Genotypic reproductive selection;
- (iii) Selection between gametes at meiosis in heterozygotes;
- (iv) Gamete selection at fertilization.

Essentially, the operations of this programme are the same as those of the autosomal selection programme. The operations for females are identical but they differ slightly for males as there are only two male genotypes. The operations of selection will be considered briefly for males only. Designate the segregating alleles as A and a . At the start, which is taken as the moment of fertilization, the numbers of A/Y and a/Y males are specified (Y representing the Y -chromosome). The information required about zygotes is given in Table 1.

To determine the numbers of males which reach sexual maturity, N_{m_1} and N_{m_2} are multiplied by the appropriate zygote selective values to give the expected numbers of males. Chance effects are introduced as before (Barker 1958) to determine the actual numbers of males at sexual maturity, viz. N'_{m_1} of A/Y and N'_{m_2} of a/Y , with a total of N'_m .

At this stage, a device is introduced which allows population size to tend to the specified expected size (E), but letting it fluctuate around this according to chance. The average number of offspring of each male is made to be E/N'_m . The relative genotypic reproductive coefficients are also effective at this stage. Let the average numbers of offspring of the two genotypes be P_1 and P_2 so that

$$(P_1 + P_2)/2 = E/N'_m.$$

As

$$x_{m_1} + x_{m_2} = 1,$$

$$2E/N'_m \times x_{m_1} = P_1,$$

and

$$2E/N'_m \times x_{m_2} = P_2.$$

From each genotype the numbers of gametes which take part in fertilization are generated as before (Barker 1958). This gives the total numbers of gametes from A/Y males (designated M_1) and from a/Y males (designated M_2). These have to be sorted into gametes containing A , a , or Y . Take, for example, A/Y males. If there is selection between the gametes at meiosis with selection coefficients of A equal to r_{m_1} , and of Y equal to r_{m_3} , the expected proportions of A and Y gametes will be $M_1/2 \times r_{m_1} : M_1/2 \times r_{m_3}$. Use of the random transform then generates the actual numbers of A and Y gametes produced by A/Y males, viz. M'_A of A , M'_{YA} of Y .

Similarly for a/Y males, where the selection coefficient of a is r_{m_2} , the numbers of a and Y gametes are generated, viz. M'_a of a , M'_{Ya} of Y .

Selection between gametes at fertilization is then introduced, where the selective values are t_{m_1} for A , t_{m_2} for a , and t_{m_3} for Y . The procedure is as above for selection between gametes at meiosis. Thus the actual numbers of gametes of each type that take part in fertilization are generated, namely M_A of A , M_{YA} of Y (from A/Y males), where $M_A + M_{YA} = M_1$; M_a of a , M_{Ya} of Y (from a/Y males), where $M_a + M_{Ya} = M_2$; and $M_1 + M_2 = M'$, the total number of male gametes generated.

The numbers of gametes produced by females are F_A of A , F_a of a , where $F_A + F_a = F'$.

The processes are not such that F' necessarily equals M' , while for fertilization, there must be equal numbers of male and female gametes. However, they are not likely to be very different, and the number of offspring generated is set to equal F' or M' , whichever is the smaller.

Fertilization is performed in two stages, though in each stage the method is the same as that in the autosomal selection programme. First, fertilization by gametes from A/Y males is carried out. This gives the following progeny genotypes: males, A/Y , a/Y ; females, AA , Aa .

The numbers of each of these are counted as they are produced. When this is completed, the remaining female gametes are fertilized by gametes from a/Y males, giving the following genotypes: males, A/Y , a/Y ; females, Aa , aa .

This method is not entirely satisfactory for when F' is less than M' , some gametes from a/Y males will not be used in fertilization, while all those from A/Y males will be used. There is then a possibility of bias in the results, the degree of this bias depending on how often F' is less than M' , and on the extent of the difference between them. Although this bias is quite small, the programme has since been altered to remove this deficiency. This has been done by using a total of F' male gametes when F' is less than M' . Gametes from A/Y and a/Y males are used in proportion to the numbers of each previously generated. The possible degree of bias in the results due to the fertilization method used can be seen in the following. One of the simulated populations to be discussed later has been re-run for three generations using the amended programme. With the original programme, the gene frequencies were:

Generation	Males	Females	Overall
1	0.513	0.496	0.504
2	0.423	0.418	0.420
3	0.411	0.370	0.391

while the amended programme gave:

Generation	Males	Females	Overall
1	0.526	0.487	0.506
2	0.416	0.425	0.421
3	0.401	0.371	0.386

Another simulated population gave results with the amended programme identical to those previously obtained; in this case F' was not less than M' in any generation. There will be no bias when M' is less than F' (i.e. when there are unused female gametes), because female A and a gametes are used in a random order.

From the results of the two stages of fertilization, the total numbers of progeny of each of the five genotypes are obtained and then the gene frequencies of A in males, females, and overall are calculated. The programme prints out this information on the number of progeny individuals of each genotype and gene frequencies. These are used to produce the following generation, and so on. The programme can be set to run for any number of generations.

The time taken by the SILLIAC to do these computations may be of interest. At an expected population size (E) of 180, 17 generations took 9 min, while when E equalled 4000, 10 generations took 22 min.

III. RESULTS AND DISCUSSION

The aim so far has been to show that this programme can simulate the processes of selection between sex-linked alleles. Merrell (1953*a*, 1953*b*), Merrell and Underhill (1956), Reed and Reed (1950), and Wallace (1948) have estimated the nature and extent of the selective forces operating in their experimental populations. These estimated selection coefficients can be used as specifications for the programme, allowing the results of the simulated populations to be compared with those of the experimental populations. Two such experiments have been simulated.

As in the case of the autosomal selection, experiments using different population sizes have been selected, viz.: selection studied in large populations by Wallace (1948) and in small populations by Merrell and Underhill (1956).

(a) *Large Population Size*

Wallace made an extensive analysis of selection between the "sex ratio" and standard *X*-chromosomes of *D. pseudoobscura*, studying competition between these chromosomes in population cages of the type described by Wright and Dobzhansky (1946), which at 25°C support a population of about 4000 adults. In addition, he analysed selective differences by studying larval competition, adult longevity, fecundity, sexual activity, and egg hatchability. From these data, estimates of the selective values of the genotypes were made.

From Wallace's Table 16 (which summarizes the selective values he determined) specific selective values appropriate to the four stages of selection in the programme were calculated as follows for selection at 25°C.

(i) *Zygote Selective Values Used*

- (1) *Males*.—Selective values for larval competition.
- (2) *Females*.—Larval competition × egg hatchability.

(ii) *Genotypic Reproductive Coefficients Used*

- (1) *Males*.—Longevity × sexual activity—maximum estimate of latter.
- (2) *Females*.—Longevity × fecundity—maximum estimate of latter.

These values were then adjusted so that coefficients for males and females both sum to 1.

(iii) *Selection between Gametes at Meiosis in Heterozygotes*

(1) *Males*.—Darlington and Dobzhansky (1942) found that at 25°C, males comprise 6.2 per cent. of the total offspring of sex ratio males. Therefore the selective values of gametes from sex ratio males would be 0.938 for sex ratio (*SR*) *X*-chromosomes, and 0.062 for *Y*-chromosomes, these values being in the ratio 1 : 0.066. However, in setting up the programme specifications, this ratio was taken inadvertently as 1 : 0.1. The effect of this will be noted later. The selective values were thus specified as 1.0 for *SR* and 0.1 for *Y*. As there is no known fitness difference between the standard *X*-chromosome and the *Y*, the selective value for *ST* was taken also as 0.1. In this case, there is no direct comparison between these fitnesses of sex ratio and standard, both are relative to the *Y*. This may be seen by considering the programme operations at this stage. The total number of gametes produced by *ST/Y* males is determined and these are then apportioned according to the selective values into the numbers of *ST* and *Y*. As the selective values are equal, this subdivision is essentially on a 1 : 1 expectation. Therefore, the selective values operate as 1.0 for *SR* and 0.1 for *Y* in sex ratio males, and 0.5 for *ST* and 0.5 for *Y* in standard males, giving a ratio of 2 : 1 for the selective values of *SR* : *ST*. This is the ratio expected from the results of Sturtevant and Dobzhansky (1936). They showed that the *Y*-chromosome fails to be included in the spindle at the meiotic divisions

during spermatogenesis and is lost. The X -chromosome, which shows a four-parted structure at the first metaphase, undergoes two equational divisions during the course of meiosis resulting in the formation of four sperm, each containing a sex ratio X -chromosome. Thus a male of this type will produce only (or mainly) female offspring but these will be as numerous as the combined sexes in progeny of males with the normal X -chromosome.

(2) *Females*.—No differential selection so that coefficients are taken as 1.0.

(iv) *Gamete Selective Values*

No differential selection so that coefficients are taken as 1.0.

TABLE 2
MAXIMUM SELECTIVE VALUES AT 25°C FOR COMPETITION BETWEEN
SEX RATIO (SR) AND STANDARD (ST)
Values obtained from data of Wallace (1948)

Selective Values	Males		Females		
	SR	ST	SR/SR	SR/ST	ST/ST
Overall (fitnesses)	0.724	1	0.021	1	0.314
Specific					
Zygote	0.407	1	0.036	1	0.511
Genotypic reproductive coefficients	0.471	0.529	0.200	0.500	0.300
	Male Gametes			Female Gametes	
	SR	ST	Y	SR	ST
Selection between gametes at meiosis in heterozygotes	1	0.100	0.100	1	1
Gamete selective values at fertilization	1	1	1	1	1

The selective values used as specifications for the programme are shown in Table 2. The overall selective values are the maximum values at 25°C given by Wallace and are used in the programme as zygote selective values with no differential selection at the other stages. For both the overall and specific values, the expected population size was taken as 4000 and the initial population was as in the experimental population (cage No. 11) viz. 500 of each of the genotypes SR and ST males and SR/SR and SR/ST females. Four replicate runs were done with each set of selective values. The results are shown in Figures 1 and 2. Generation length in the experimental population was assumed to be 25 days (Wallace 1948; Dobzhansky and Pavlovsky 1953). Use of specific and overall selective values allows a comparison of the effectiveness of the simulation with each, as well as comparison of experimental and simulated populations.

Figure 1 shows striking differences between the experimental and simulated populations. Sex ratio had been eliminated from the experimental population by generation 9, while in the simulated populations, the frequency of sex ratio is tending to an equilibrium. From the given overall selective values, the expected curve

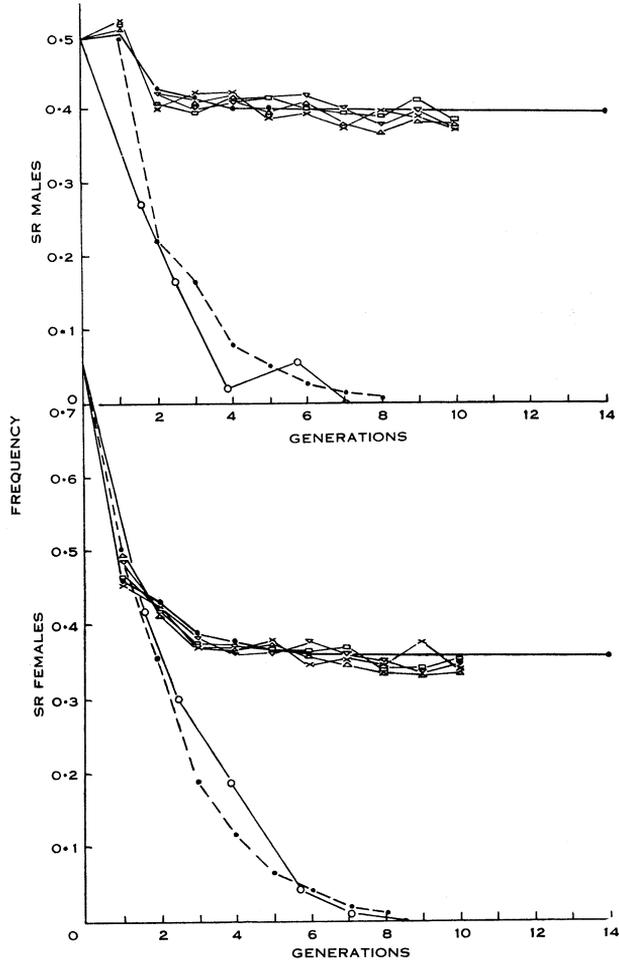


Fig. 1.—Results of competition between sex ratio (*SR*) and standard (*ST*) X-chromosomes in *D. pseudoobscura* at 25°C. Maximum overall selective values used in the simulated populations. ○ Wallace's experimental population (cage No. 11). ×, □, △, ▽ Simulated populations. ●—● Calculated theoretical curve for overall selective values of Wallace. ●—● Calculated theoretical curve for selective values of 0.95 in *SR* and 1 in *ST* males, and 0 in *SR*/*SR*, 0.4 in *SR*/*ST*, and 1 in *ST*/*ST* females.

of frequency change has been calculated for the first six generations. Bennett (1957) presented formulae which, for given selective values, allow determination of whether an equilibrium is expected, and if so, what will be the equilibrium gene frequencies. If the maximum overall selective values at 25°C are used in these formulae, the equilibrium gene frequencies of sex ratio are 0.393 in males and 0.356 in females.

These values are shown in Figures 1 and 2. The simulated populations in Figure 1 agree closely with one another and fluctuate at random around the expected curve. That is, the simulation provides, for given selective values, an accurate description of the expected changes in frequency in a large population.

The simulated populations using overall selective values (Fig. 1) may be compared with those using specific selective values (Fig. 2). Identity of the curves would not be expected as different sets of random numbers are used in the simulation of chance effects. The curves for males are, however, fairly similar though those in Figure 2 do have a slight excess of values lower than the expected curve.

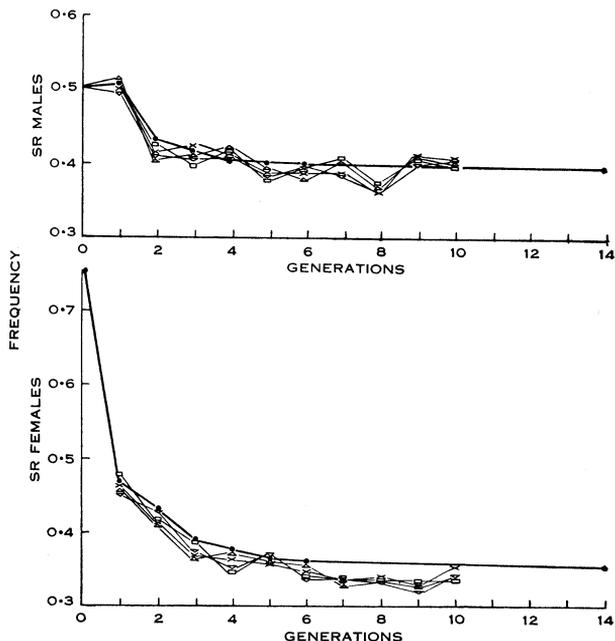


Fig. 2.—Results of competition between sex ratio (*SR*) and standard (*ST*) X-chromosomes in *D. pseudoobscura* at 25°C. Maximum specific selective values used in the simulated populations. Designation of populations as in Figure 1.

This could be a chance effect but in females the curves from specific selective values are generally below the expected curve, the difference averaging about 0.02–0.03 in the gene frequency. This could result from the selective values taken for selection between gametes at meiosis in males. The values of 1.0 for *SR* and 0.1 for *Y* in *SR/Y* males will give a bias in favour of *Y*; that is, a possible reduction in the production of *SR*-containing gametes from these males each generation. This bias may be somewhat more than is apparent from the earlier discussion based on Darlington and Dobzhansky's (1942) finding that males comprise 6.2 per cent. of the offspring of sex ratio males. This percentage of male offspring varies for different sex ratio males, and Wallace states that the sex ratio chromosomes used in the experimental population came from 16 males which gave offspring consisting of 0.5 per cent. males. Although the bias would be small, it could build up over a

few generations and its effects would, of course, be more noticeable in females than in males. It is reasonable to conclude that the methods of simulation of selection used are adequate and that specific or overall selective values may be used to study any given genetic situation.

The differences between the results of the experimental and simulated populations emphasize the inadequacy of available methods of estimating fitnesses of competing genotypes. An attempt has been made to determine fitnesses that would fit the experimental population. The calculated curve for the following values

Males		Females	
<i>SR</i>	0.95	<i>SR/SR</i>	0
<i>ST</i>	1	<i>SR/ST</i>	0.4
		<i>ST/ST</i>	1

is shown in Figure 1.

The calculated curve is sufficiently similar to the experimental that these fitness values may be taken as approximating the true fitnesses. They are quite different to the fitnesses (overall selective values in Table 2) experimentally determined by Wallace. The factors of larval competition, longevity, etc., that Wallace studied are clearly important components of fitness, but the fitnesses calculated from them do not fit the observed elimination of sex ratio in the experimental population. Both maximum and minimum estimates of the fitnesses are given by Wallace while only the maximum have been used in the simulated populations. However, even the minimum estimates would not give a selection curve similar to the experimental population as these values would result in an equilibrium frequency of sex ratio in males of 0.405 and in females of 0.363. Wallace states that the factors he studied are obviously not all the components of fitness and mentions various others that could be of importance. These other components may be responsible for the difference between the true fitnesses and the estimated ones. On the other hand, the difference may also be due to errors in estimation. These could result from sampling errors in that generally only small numbers of flies were taken from the cage to start the various estimates. In addition, the estimation procedures may cause errors. For example, the components studied (except for larval competition) cannot be measured under conditions that approach those of a population cage. The relative fitnesses in a cage could be quite different to those as measured in vials. For example, the estimated zygote selection coefficient for *SR/SR* females of 0.036 could have a true value of zero under cage conditions. It is difficult to see to what extent cage conditions would alter the other components.

To attempt to estimate fitness by studying its components separately will usually give doubtful results because all the components are not necessarily understood, and many whose effects are realized are very difficult to measure accurately. A major requirement is some simple method of estimating overall fitness of different genotypes. Knight and Robertson (1957) have taken one step in this direction by devising a technique for *Drosophila* which involves competition of the genotype under test with a stock marked with two dominant genes (Curly and Plum) and the final assessment is called "the competitive index". Further, the programmes developed here are being used to generate families of selection curves for a wide range of

selective values. Therefore, from the results of experimental populations involving competition between genotypes, it will be possible to obtain estimates of the relative selective values (fitnesses) of the competing genotypes by comparison against the selection curves for series of simulated populations.

(b) *Small Population Size*

Merrell and Underhill (1956) analysed competition between the sex-linked mutant *yellow* (*y*) of *D. melanogaster* and its wild-type allele. The populations were maintained in population bottles (Reed and Reed 1948). The relative viabilities of the genotypes and the degree of selective mating were determined. These results can be converted to selective values appropriate for use in the programme. The data given for relative viability of mutant and wild type sibs is:

	Numbers of Sib Progeny	
	+ or +/y	y or y/y
Males	444	477
Females	475	440

and, from this, zygote selective values have been taken as

Males		Females	
+	1	+/+	1
y	1	+/y	1
		y/y	0.926

Table 3 gives results of selective mating experiments (Merrell 1949). The male choice experiments show that wild-type males mated at random with either female type, while the *yellow* males mated significantly more often with the *y/y* females than with the +/y females. However, where the females have a choice of males (female-choice experiment) the majority of females of both genotypes mate with the wild-type male. There is no way of combining the data from these two experiments (except subjectively) to determine the degree of selective mating when all four genotypes are present. However, in this case the preference of *y/y* females for + males will probably greatly exceed that of *y* males for *y/y* females. +/y and +/+ females will be expected to have the same genotypic reproductive coefficients and it appears simplest to give all three female genotypes equal coefficients, with the selective mating operating only through the male reproductive coefficients. The relative sexual activity of *y* males to + males with *y/y* females is 1 : 9 approximately. However, *y* males, being more distasteful to + females, are twice as likely to fertilize *yellow* females as +, so that with + females their relative activity is 1 : 19. In setting up programme specifications, only one overall comparison of + to *y* males is made so that an average estimate must be used. The genotypic reproductive coefficients have been taken as:

Males		Females	
+	0.92	+/+	0.33
y	0.08	+/y	0.33
		y/y	0.33

It must be emphasized that these values are subjective and approximate. True

estimates could only be obtained from multiple-choice experiments on selective mating.

There is no information on differential selection at the gamete stage so that these coefficients were all taken as 1. E was specified as 180. The initial population was taken as 1 wild-type male, 99 *yellow* males, 100 *yellow* females, which correspond closely to the experimental populations where 1 wild-type male was added to an established *yellow* population estimated to contain about 200 individuals. Ten replicate runs were done using these specifications. Eight of these simulated populations became homozygous for y , the wild-type allele being lost from four of them

TABLE 3
RESULTS OF SELECTIVE MATING EXPERIMENTS BETWEEN YELLOW AND WILD TYPE
Results quoted from Merrell (1949). Tests carried out with freshly emerged flies
except where indicated

Female-choice Experiment			Male-choice Experiment		
Female Genotype	Successful Males (%)		Male Genotype	Fertilized Females (%)	
	y	+		y/y	$+/y$
y/y	10.5	89.5	y	69.8	30.2
y/y^*	11.8	88.2	y^*	72.0	28.0
$+/y$	4.6	95.4	+	56.1	43.9
$+/y^*$	7.8	92.2	$+^*$	49.4	50.6

* Males and females aged 7 days.

in generation 1, from three in generation 2, and from the other in generation 3. In the remaining two populations, the frequency of y decreased until the populations became homozygous for $+$. This is shown in Figure 3 which compares the results of the experimental and simulated populations. Generation length in the experimental populations was taken as 24 days (Merrell 1953b).

Merrell and Underhill (1956) started nine populations of competition between *yellow* and wild-type allele, but the wild-type became established in only three populations (see Fig. 3). Unfortunately, they did not state how long this allele remained in the other six populations before it was eliminated. However, the simulated and experimental populations show close agreement in this as, in eight of the 10 simulated, the wild-type allele was eliminated. The remaining simulated and experimental populations show similar trends in the elimination of *yellow* (Fig. 3).

In this case, the selective values estimated by Merrell and Underhill are sufficient to explain the observed gene frequency changes. However, Morpurgo and Nicoletti (1955, 1956) have queried the importance of selective mating as a factor in gene frequency changes in experimental populations. Their doubts are based on results with *white* and its wild-type allele only, so that they do not necessarily apply to other mutants. Perhaps, as they suggest, different selective values would give similar results. However, as the independently calculated selective values

give results in the simulated populations very similar to the experimental ones, they probably are essentially correct. Selective mating is thus a factor of major importance in this competition. A further argument can be deduced from the early generations of competition. After a varying number of generations where the frequency of *yellow* males remains near 100 per cent., this percentage suddenly decreases. In one generation then, there is a large production of + males, which can only be progeny of +/y or +/+ females. If, by chance, the number of +/y females increases in one generation, they will preferentially mate with + males. This will cause an increase in the number of +/y and +/+ females in the following generation, and an increase in the number of + males in the next. Morpurgo and Nicoletti's argument is that differential viability in the larval stage is more important than

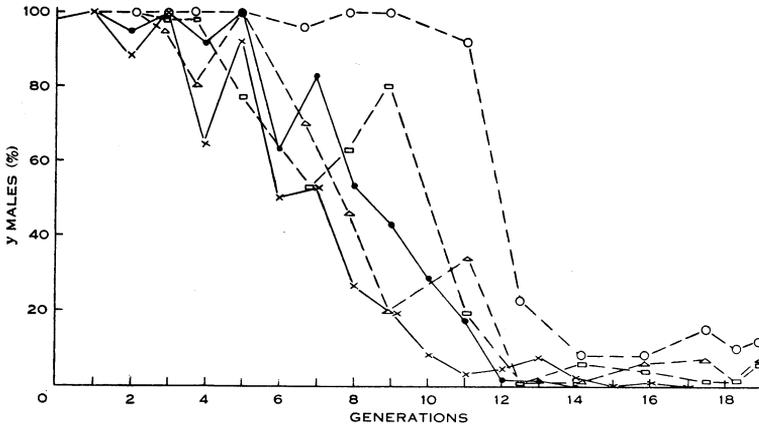


Fig. 3.—Results of competition between *y* and its wild-type allele in *D. melanogaster*. O, □, △ Experimental populations. ●, × Simulated populations.

Merrell and Underhill would consider it. In these early generations, the numbers of +/+ and +/y eggs produced will be still quite small relative to the numbers of *y/y*. It is difficult to see then how increased viability of the former relative to the latter could give a sudden increase in one generation in the number of +/+ and +/y females.

Comparisons of Figures 1 and 3 shows a greater degree of variation between simulated populations at the smaller population size. Variation in the large population (Fig. 1) is low but cannot be compared with experimental population variation as there is only one such population. In the small populations (Fig. 3) the experimental populations show greater variation than the simulated but with so few populations, this difference may not be real. The whole problem of the interrelation of selective values and population size with variance of the selection curves is being investigated in detail.

In general, the results show that it is possible to simulate in an automatic digital computer the operations of selection between two alleles at a sex-linked locus. This programme is being used in further studies of such selection.

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