SELECTION AT SEX-LINKED LOCI. I. A METHOD OF ESTIMATING TOTAL FITNESSES

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SUMMARY

A method of estimating fitness values from population data for sex-linked loci is presented. It possesses several particular characteristics devised to avoid the apparition of spurious frequency-dependent fitnesses due to the existence of incompletely-selected stages or to the utilization of a too simple population model. Overall fitnesses are estimated in each generation by using zygotic frequencies so that the absence of post-observational selection is warranted. Moreover, the method is based on a general population model that takes into account different selection in sexes and any pattern of mating. Some of the current problems for measuring selection are discussed in connection with the method presented here.

1. INTRODUCTION

Natural selection, one of the main forces acting on the genetic variability present in populations, has focussed the attention of many workers since the early days of population genetics. It is not surprising, given the necessity of understanding the mode of action of natural selection for explanations of organismic evolution. Nevertheless, the conceptual framework of theoretical population genetics, including the deterministic theory of selection (see Li, 1967*a*), has been often developed without taking into consideration the experimental problems associated with the estimation of parameters used by the models. In any case, some of the current methods to estimate selective values are based on very restrictive assumptions for both experimental and natural populations.

The usual approach to the estimation of fitnesses or adaptive values from population data consists basically of recording the changes in genotypic frequencies produced by selection. However, the subtle problems in the estimation of fitness values by this method were not perceptible until Prout's (1965) fundamental paper. Prout (1965, 1969) and later Christiansen *et al.*, (1977) have shown that apparent frequency-dependent fitnesses can arise using genotypic frequencies to estimate adaptive values, if the population is sampled when the selection process is only partially completed. In this sense, it is necessary to emphasize that fertility and other late components of fitness have been shown to play a very important role in populations (Anderson and Watanabe, 1974; Anderson and McGuire, 1978; Anderson *et al.*, 1979) and these precisely constitute the post-observational selection which leads to erroneous fitness estimations.

Another source of error in fitness estimation from population data can arise in connection with the assumptions of the model involved in the estimation. Prout (1969) has pointed out that spurious frequency-dependent fitness will also appear when an over-simple model is assumed. This

is the case when mating is not random or the mode of selection is sex-dependent and fitnesses are estimated by using the "classical model", which assumes random mating and sex-independent selection.

The particular case of selection at sex-linked loci has received the attention of many workers from experimental and theoretical points of view (Haldane, 1924; Merrell, 1953; Bennett, 1957; Mandel, 1959; Haldane and Jayakar, 1964; Li, 1967b; Anderson, 1969b; Hedrick, 1976; Christiansen et al., 1977; and others), but a model of estimation of total fitness values for X-linked genes has not been worked out (see Barker, 1977). This paper is an attempt to estimate overall fitnesses for sex-linked loci by means of a general model which uses completed selected stages, in such a manner that the main errors associated with the measurement of selection are avoided.

2. THE MODEL

The main problem to be considered in estimating overall or total fitness values, from genotypic frequencies recorded at the same stage in two successive generations, consists of choosing the observational period in a way that selection has been completed at that moment. Otherwise, serious errors will appear in the estimations, as shown by Prout (1965). Ideally, it would be desirable to sample the population when no fitness component remains to act, but this is not possible by sampling adults given that fertility connects parents with their zygotic offspring. Obviously, the only way to avoid these problems related with post-observational components is to sample the population at the zygotic stage; otherwise total fitness has to be partitioned into Early and Late components, which increases the number of parameters to be estimated. Nevertheless, a new difficulty arises when genotypic frequencies are recorded immediately after mating. It is that genotypic frequencies are disturbed by mating and so no reliable information about selection is obtained from them; on the other hand, allele frequencies remain unchanged and therefore they could be used from egg samples to obtain information about selection.

Undoubtedly, an infinite set of fitness values could explain a given change in allelic frequencies from one generation to the next. However, with a minimum number of two transitions (three successive generations), this problem of indetermination can be solved, as has been pointed out by Prout (1969). A method using transitions to estimate total fitness values from zygotic frequencies was devised by Levene (in Dobzhansky and Levene, 1951) for autosomal loci, and this method avoids the post-observational selection problems.

In accordance with the arguments we have been considering, we develop a method to estimate total fitness values for sex-linked loci by using zygotic frequencies from egg samples. In organisms such as Drosophila, zygotic frequencies can be easily obtained by growing a sample of eggs under optimal conditions. In this way, the serious biases derived from the existence of incomplete selection at the time of observation can be avoided.

The assumptions on which the selection model we are considering is based are:

(a) A population of diploid, sexually reproducing organisms with discrete generations is considered, with A_1 and A_2 being the alleles at the sex-linked locus.

(b) The selective values of the genotypes are supposed to be constant during the transitions we need for calculations. Also, it is considered that the fecundity of a mating is determined by the genotype of the female parent, and that any male fertility differences affect only differential contributions to males to the gene pool.

(c) No drift, mutation, or gametic selection are considered. Also, segregation of alleles at meiosis is assumed to be normal in both sexes.

The selection model for a sex-linked locus in which genotypic frequencies are recorded in egg samples is shown in table 1. Overall fitnesses are expressed as relative ones in each sex, by which three parameters W_1, W_2 and V_1 must be estimated. In this way, complex modes of selection due to sex-dependent adaptive values are being considered by the model.

For a sex-linked locus, under no selection, the following equations are established:

$$q_{f(t+1)} = \tfrac{1}{2}q_{f(t)} + \tfrac{1}{2}q_{m(t)} \tag{1}$$

$$q_{m(t+1)} = q_{f(t)}. \tag{2}$$

When selection is operating, equation (2) is maintained only between male gene frequency at zygotic stage and female gene frequency of the previous generation after selection is completed, and so becomes:

$$q_{m(t+1)} = \frac{C_t W_2 + \tfrac{1}{2}B_t}{A_t W_1 + B_t + C_t W_2}. \tag{3}$$

Thus, we have an expression with W_1 and W_2 as parameters to be estimated, and so another transition is needed.

$$q_{m(t+2)} = \frac{C_{t+1} W_2 + \tfrac{1}{2}B_{t+1}}{A_{t+1} W_1 + B_{t+1} + C_{t+1} W_2}. \tag{4}$$

Therefore, solving for W_1 and W_2 in equations (3) and (4) female fitness values can be obtained, which are the same as the maximum likelihood estimates:

$$\hat{W}_1 = \frac{B_t C_{t+1}(1 - q_{m(t+2)})(1 - 2q_{m(t+1)}) - B_{t+1}C_t(1 - q_{m(t+1)})(1 - 2q_{m(t+2)})}{2[A_t C_{t+1}q_{m(t+1)}(1 - q_{m(t+2)}) - A_{t+1}C_t q_{m(t+2)}(1 - q_{m(t+1)})]} \tag{5}$$

$$\hat{W}_2 = \frac{A_{t+1}B_t q_{m(t+2)}(1 - 2q_{m(t+1)}) - A_t B_{t+1}q_{m(t+1)}(1 - 2q_{m(t+2)})}{2[A_t C_{t+1}q_{m(t+1)}(1 - q_{m(t+2)}) - A_{t+1}C_t q_{m(t+2)}(1 - q_{m(t+1)})]}. \tag{6}$$

In samples of large size, the variances of $\hat{W}_1$ and $\hat{W}_2$ calculated by statistical differentials ("delta method"), will be approximately

$$\text{Var } \hat{W}_1 = (1/T_{m(t+1)})\left(\frac{A_t\hat{W}_1 + B_t + C_t\hat{W}_2}{A_t}\right)^2\left(\frac{A_t\hat{W}_1 + \tfrac{1}{2}B_t}{C_t\hat{W}_2 + \tfrac{1}{2}B_t}\right)$$

$$+ (1/T_{m(t+2)})\left(\frac{A_{t+1}\hat{W}_1 + B_{t+1} + C_{t+1}\hat{W}_2}{A_{t+1}}\right)^2\left(\frac{A_{t+1}\hat{W}_1 + \tfrac{1}{2}B_{t+1}}{C_{t+1}\hat{W}_2 + \tfrac{1}{2}B_{t+1}}\right) \tag{7}$$

TABLE 1

Selection model for an X-linked locus

Genotype	Females				Males		
	A_1A_1	A_1A_2	A_2A_2	Gene frequency $A_2 = q_f$	A_1Y	A_2Y	Gene frequency $A_2 = q_m$
Zygotic frequencies observed at generation t:	A_t	B_t	C_t	$\dfrac{C_t + \frac{1}{2}B_t}{A_t + B_t + C_t}$	M_t	N_t	$\dfrac{N_t}{M_t + N_t}$
Total fitness values:	W_1	1	W_2		1	V_1	
After selection:	A_tW_1	B_t	C_tW_2	$\dfrac{C_tW_2 + \frac{1}{2}B_t}{A_tW_1 + B_t + C_tW_2}$	M_t	N_tV_1	$\dfrac{N_tV_1}{M_t + N_tV_1}$
Zygotic frequencies observed at generation $t+1$:	A_{t+1}	B_{t+1}	C_{t+1}	$\dfrac{C_{t+1} + \frac{1}{2}B_{t+1}}{A_{t+1} + B_{t+1} + C_{t+1}}$	M_{t+1}	N_{t+1}	$\dfrac{N_{t+1}}{M_{t+1} + N_{t+1}}$

$$\text{Var } \hat{W}_2 = (1/T_{m(t+1)})\left(\frac{A_t\hat{W}_1+B_t+C_t\hat{W}_2}{C_t}\right)^2\left(\frac{C_t\hat{W}_2+\frac{1}{2}B_t}{A_t\hat{W}_1+\frac{1}{2}B_t}\right)$$

$$+ (1/T_{m(t+2)})\left(\frac{A_{t+1}\hat{W}_1+B_{t+1}+C_{t+1}\hat{W}_2}{C_{t+1}}\right)^2\left(\frac{C_{t+1}\hat{W}_2+\frac{1}{2}B_{t+1}}{A_{t+1}\hat{W}_1+\frac{1}{2}B_{t+1}}\right) \quad (8)$$

where T_m is the total number of males at the given generation.

The covariance of these female fitness estimates in large samples will be approximately

$$\text{Cov }(\hat{W}_1, \hat{W}_2) = (1/T_{m(t+1)})\left(\frac{(A_t\hat{W}_1+B_t+C_t\hat{W}_2)^2}{A_tC_t}\right)$$

$$+ (1/T_{m(t+2)})\left(\frac{(A_{t+1}\hat{W}_1+B_{t+1}+C_{t+1}\hat{W}_2)^2}{A_{t+1}C_{t+1}}\right).$$

Finally, in order to obtain the male fitness value (V_1), only one transition is necessary, since when selection is operating equation (1) holds between female gene frequency at zygotic stage and male and female gene frequencies of the previous generation, provided that selection is completed. Therefore, female gene frequency in (1) becomes:

$$q_{f(t+1)} = \frac{1}{2}q_{m(t+1)} + \frac{1}{2}\frac{N_tV_1}{M_t+N_tV_1} \quad (9)$$

and, solving (9) for V_1, the male fitness value is obtained, which is also the maximum likelihood estimate:

$$\hat{V}_1 = \frac{M_t(q_{m(t+1)}-2q_{f(t+1)})}{N_t(2q_{f(t+1)}-q_{m(t+1)}-1)}. \quad (10)$$

In large samples, the variance of $\hat{V}_1$ derived by using the "delta method" is approximately

$$\text{Var } \hat{V}_1 =$$

$$\frac{(M_t+N_t\hat{V}_1)^2[q_{m(t+1)}(M_t+N_t\hat{V}_1)+N_t\hat{V}_1][(2-q_{m(t+1)})(M_t+N_t\hat{V}_1)-N_t\hat{V}_1]}{N_t^2M_t^2T_{f(t+1)}} \quad (11)$$

where T_f is the total number of females at the corresponding generation.

In this way, total fitness estimates for each sex, with the corresponding variances are given.

(i) Computer simulations

Maximum likelihood estimators possess several asymptotic properties specially useful for statistical purposes. For large samples, the maximum likelihood estimators are asymptotically unbiased, approximately normally distributed and their asymptotic variances can be calculated (Elandt-Johnson, 1971). In connection with the formulas that we have derived to characterize the mode of action of selection on a sex-linked locus, it is necessary to know the sample size required for the formulas to give good approximations and therefore to be useful to an experimenter. Consequently, we have conducted Monte Carlo simulations to test whether our large-sample formulas for fitness and variances are accurate for samples of the size commonly used by population geneticists.

Three sets of fitnesses were considered in the simulations. A case of overdominance ($W_1 = 0.5$, $W_2 = 0.5$ and $V_1 = 0.5$) satisfying the condition of stable equilibrium for sex-linked loci (see Li, 1967), and two cases of intermediate heterozygote with different intensities of selection ($W_1 = 1.5$, $W_2 = 0.5$, $V_1 = 0.9$ and $W_1 = 1.2$, $W_2 = 0.8$, $V_1 = 0.8$) in which a stable equilibrium is not maintained. Computer simulations were performed in accordance with the procedure of maximum likelihood used to estimate the three fitnesses. Input genotypic frequencies in generation t and the true fitnesses were used to calculate the male and female allelic frequencies in generations $t + 1$ and $t + 2$. For male fitness estimation, the simulation of the random choice of either 100 or 200 females from a population with the true female allele frequencies in generation $t + 1$ was carried out with the binomial sampling error expected under random sampling. For female fitnesses, random sampling of either 100 or 200 males was carried out in generations $t + 1$ and $t + 2$ in accordance with the true male frequencies of these two generations. One hundred simulations were generated for each set of fitnesses and for each sample size to represent 100 samples. The 100 estimates of W_1, W_2 and V_1 for each case were used to calculate the respective means and their corresponding variances about the true values (empirical variances). The means of the estimates will show how accurately the true values are estimated and whether a serious bias exists in the estimation. This is an important question, given that most of the maximum likelihood estimators calculated from small samples are biased (Elandt-Johnson, 1971). The empirical variances of the estimates were compared with the values from the formulas (7), (8) and (11) for the asymptotic sampling variances in order to know the degree of approximation of these formulas. The comparison was performed by means of a chi-square test, given that the ratio ($N \times$ empirical variance)/(sampling variance) will be distributed as χ^2 with N degrees of freedom. The results of simulations are compared with the values calculated by maximum likelihood theory in table 2. Simulations were performed for several input genotypic frequencies but, for simplicity, only the results corresponding to frequencies 0.7, 0.2, 0.1, 0.8 and 0.2 (for A_1A_1, A_1A_2, A_2A_2, A_1Y and A_2Y, respectively) are given in table 2. The results obtained with other input frequencies were very similar to those presented in table 2. In general, the means of $\hat{W}_1$ and $\hat{W}_2$ and $\hat{V}_1$ are quite close to the true values, although a slight bias is observed specially for $\hat{W}_1$ and $\hat{W}_2$ in samples of size 100. The distributions of $\hat{W}_1$, $\hat{W}_2$ and $\hat{V}_1$ estimated from the simulations were examined and a chi-square test of goodness-of-fit was employed to test the fit to a normal curve. The distributions of the three fitness estimates were slightly skewed and wider than the normal distribution, and the chi-square tests detected statistically significant differences for the two sample sizes considered in this study. The ratios of empirical variance to sampling variance were, in general, smaller than unity which could provide a conservative test for the significance of the selection. In fact, empirical variances were significantly smaller than sampling variances in the majority of the cases. Nevertheless, in some of the cases in which input frequencies are intermediate (not presented in table 2) empirical variances of $\hat{W}_1$ and $\hat{W}_2$ were significantly larger than the corresponding sampling variances even if sample size is 200.

In summary, the computer simulations show no evidence of serious bias in the estimation of W_1, W_2 and V_1 at least when 200 males and 100

TABLE 2

Means of fitnesses and their variances estimated in 100 populations simulated by computer, compared with the true fitnesses and their asymptotic sampling variances

True fitnesses	Sampling variances of true fitness		Mean fitness values estimated from simulations		Empirical variances of estimated fitness values		Empirical variance / Sampling variance	
	$N = 100$	$N = 200$	$N = 100$	$N = 200$	$N = 100$	$N = 200$	$N = 100$	$N = 200$
W_1 0·500	0·0500	0·0250	0·5408	0·4982	0·0458	0·0129	0·92†	0·52
W_2 0·500	2·0134	1·0067	0·4939	0·4922	0·0106	0·0052	0·01	0·01
V_1 0·500	0·1517	0·0758	0·5231	0·5190	0·1018	0·0310	0·67	0·41
W_1 1·500	0·5694	0·2847	1·6715	1·6132	0·6185	0·2626	1·09†	0·92†
W_2 0·500	4·8769	2·4384	0·5296	0·5246	0·0746	0·0268	0·02	0·01
V_1 0·900	0·1833	0·0916	0·9087	0·9247	0·0656	0·0409	0·36	0·45
W_1 1·200	0·2959	0·1480	1·3247	1·2420	0·5125	0·1092	1·73	0·74
W_2 0·800	3·1499	1·5750	0·8518	0·8399	0·1275	0·0510	0·04	0·03
V_1 0·800	0·1817	0·0908	0·8018	0·8173	0·0610	0·0384	0·34	0·42

† not significant at the 5% level

females are sampled, and therefore it indicates the validity of the formulas for these three fitness estimates. Unfortunately, the poor fit to the normal curve presented by the distributions of the estimates together with the irregularity showed by the asymptotic sampling variances of $\hat{W}_1$ and $\hat{W}_2$ will constitute a serious limit to the statistical power of the estimation. Moreover, it should be noted that experimental errors and other sources of variation are not considered by the asymptotic variances, by which the significance of selection has to be analyzed on the basis of the observed variation within replicated experiments, as it is usual in several methods for fitness estimation (Prout, 1971; Bundgaard and Christiansen, 1972). The analysis of trends judged from the point of view of empirical variation observed within replicates will be more proper way to establish the significance of selection.

(ii) *Partial fitness components*

Total fitness can be partitioned into Early and Late components which, in our case, can be easily estimated by a very simple modification of the model, recording an additional set of genotypic frequencies between zygotes of two succeeding generations. When young adults are sampled, Early and Late components will correspond, approximately, to viability and fertility respectively. In this case, viability fitnesses can be easily obtained by comparing zygote and adult genotypic frequencies, as it is usual (see Anxolabehere *et al.*, 1982).

In order to obtain fertility estimates, zygote genotypic frequencies in formulas of the model must be substituted by the genotypic frequencies in adult stage. In this way $\hat{W}_1$, $\hat{W}_2$ and $\hat{V}_1$ will estimate properly the late component of fitness and equations (7), (8) and (11), will give the corresponding variances.

3. DISCUSSION

Estimation of adaptive values is one of the main goals in the analysis of selective mechanisms. Surprisingly, the literature on the subject is not very abundant and only few cases where a reduced number of parameters have to be determined, as with lethal genes (Chung, 1964; Anderson, 1969*a*; Polivanov and Anderson, 1969), have been resolved in detail. In dealing with more complex cases, the number of parameters increases and the models become less and less mathematically manageable and, in addition, their assumptions become more unrealistic. In this paper we present a method of estimating net fitnesses for sex-linked loci which is both simple and realistic.

The model described above makes use of zygotic frequencies which assures that the selection is completed at the time of observation. It fulfills, in addition, a set of conditions which make it useful for being applied to population studies. First of all, it produces overall fitness estimations, which is of paramount importance given that partial fitness components do not supply enough information about selection. In population genetics the analysis of selection in terms of the early fitness components (such as viability) has been habitual, but these studies must be regarded with caution because several authors have proved the absence of correlation between

early and late fitness components (Sved and Ayala, 1970; Sved, 1971; Tracey and Ayala, 1974). In addition, these works are the most drastic demonstration that we can not rely on viability to be the main fitness component.

Another important point to be considered is the assumption of constant selective values. Early methods on fitness estimation as Wright's one (in Wright and Dobzhansky, 1946), and also DuMouchel and Anderson's one (1968), are based on this supposition, but its validity has been called into question since the discovery of a great deal and diversity of frequency-dependent selection mechanisms (Kojima, 1971; Ayala and Campbell, 1974). This is specially true for sex-linked loci, because many cases of frequency-dependent fitness have been demonstrated to occur for morphological (Petit, 1951, 1954; Alvarez *et al.*, 1979; Alvarez and Fontdevila, 1981) as well as for allozyme loci (Fontdevila and Méndez, 1979) located on the X chromosome. In this context, the method presented here is sensitive to any form of non constant fitnesses. However, we calculate female fitness values by supposing no change in selective values during two transitions, but this restriction could produce only a small error if change in fitnesses are not too large in each pair of transitions. On the contrary, male fitness estimations are obtained without this restriction and therefore they are free of this type of error.

The "classical model" for fitness estimation assumes sex-independent selection and random mating, and these are two serious restrictions in order to obtain a realistic view of the action of natural selection. Thus, Prout (1969) has shown that if some of these conditions do not hold, spurious frequency-dependent fitness will arise. Unlike the "classical model", the method we propose works with different selection in females and males, since for X-linked loci sex-independent selection is not expected to occur in many instances. In addition, it is not necessary to assume any particular pattern of mating in the model, since fitness estimates are obtained from genotypic frequencies at input zygotes to allelic frequencies at zygotes of the succeeding generation (output frequencies) in each generation. In this point, it is necessary to emphasize that, as it has been pointed out by Anderson and McGuire (1978), pattern of mating has not to be confounded with mating success. Pattern of mating is confined to choice of mate, so that it will not affect the output of allelic frequencies. Mating success involves frequency of mating and so it is a component of natural selection which will be included in the total fitness estimates of the model. Thus, true fitnesses are estimated irrespective of the pattern of mating of the population. Departures from random mating, such as consanguineous or assortative matings, will not disturb fitness estimates. In this way, the method is free of two of the most restrictive assumptions involved in fitness estimation.

A final point to be quoted here is the suggestion by Prout (1969) about splitting up total selection in various partial fitness components which can be estimated in a separate set of experiments outside the population, as it was done by Prout (1971) and Bundgaard and Christiansen (1972). This approach presents the inconvenience of requiring a great experimental effort and, moreover, it is unlikely that the conditions of such experiments are like those in the population itself. The method presented here, of estimating fitnesses from population data, takes advantage of reduced

amount of experimental work and, in addition, it produces adaptive values which are estimated under the genuine conditions of a population.

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