THE EFFECTS OF LINKAGE, EPISTASIS, AND INBREEDING ON POPULATION CHANGES UNDER SELECTION[1]

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IN studies of population genetic theory a number of complications arise when consideration shifts from single locus to multilocus situations. In multilocus situations, the possibility of interaction between loci (epistasis) is one obvious complicating factor, and the amount of recombination between loci (linkage) is another such factor. A number of recent investigations of multilocus models (KIMURA 1956; KOJIMA 1959a,b; LEWONTIN and KOJIMA 1960; BODMER and PARSONS 1962; LEWONTIN 1964a,b, 1965) have shown that interactions between linkage and epistasis can in fact have significant effects on the structure of large, random-mating populations and that some of the features of such populations can be understood only if the interactions between linkage and epistasis are taken into account.

Another factor that is likely to be of real importance in understanding population structure is deviation from panmixia. Although it is not known how widespread the various types of deviation from panmixia are relative to one another, there can be little doubt that inbreeding is an extremely common phenomenon. Inbreeding can occur not only as a result of one or another type of control of the mating system, such as those that lead to predominant self-fertilization in many plant species, but also in regularly outcrossing species owing to regular or sporadic restrictions in population size, isolation by distance, and so on. Further, it is easily demonstrated that the position and stability of adaptive peaks corresponding to gene-frequency equilibria vary markedly with the level of inbreeding (e.g. ALLARD and WEHRHAHN 1964). This introduces the possibility that deviations from panmixia may influence interactions between linkage and epistasis and hence that they must be taken into account in attempts to understand multigenic systems.

In view of the importance of inbreeding and the probability of compound interactions amongst inbreeding, epistasis and linkage, it seemed worthwhile to determine the combined effects of these factors on multilocus systems. The plan adopted was to examine a variety of heterotic and optimum models to determine in what ways relaxation of the assumption of panmixia affects various aspects of population structure. Both two-locus and six-locus models have been investigated. Results from two-locus models with large population size will be considered in

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this paper. Some additional features revealed by six-locus stochastic models will be discussed in a later paper.

Definitions and Procedures

The basic features of population dynamics for the discrete generation case have been treated in detail by LEWONTIN and KOJIMA (1960) and more recently by LEWONTIN (1964a,b, 1965). Hence, only main points need be recapitulated in extending the models to include inbreeding. Assume two loci with two alleles each (A,a and B,b). Let gene frequencies be p_1, q_1 and p_2, q_2, respectively, and let the four gametic types AB, Ab, aB, and ab have frequencies g_1, g_2, g_3 and g_4, immediately following meiosis in any generation and let c be the recombination value between the two loci. There are ten possible genotypes with frequencies (f_i) and selective values (w_{ij}) as follows:

	AA	Aa	aa
BB	f_1	f_4	f_8
	w_{22}	w_{12}	w_{02}
Bb	f_2	$f_5(AB/ab), f_6(Ab/aB)$	f_9
	w_{21}	w_{11}	w_{01}
bb	f_3	f_7	f_{10}
	w_{20}	w_{10}	w_{00}

(1)

The selective value is the relative probability that a zygote of given genotype will contribute a zygote to the next generation. The mean fitness of a population ($\overline{W}$) is given by the weighted sum of the individual w_{ij}'s.

Linkage equilibrium: The concept of linkage equilibrium is essential to a discussion of genetic models involving two or more loci. Linkage equilibrium is defined as the condition in which the equilibrium gametic frequencies correspond to the products of the appropriate gene frequencies, i.e., at linkage equilibrium

$$\begin{aligned} \hat{g}_1 &= \hat{p}_1\hat{p}_2, & \hat{g}_3 &= \hat{q}_1\hat{p}_2, \\ \hat{g}_2 &= \hat{p}_1\hat{q}_2, & \hat{g}_4 &= \hat{q}_1\hat{q}_2, \end{aligned} \tag{2}$$

where $\hat{p}_1$, $\hat{p}_2$ are the equilibrium gene frequencies ($\Delta p_1 = \Delta p_2 = 0$). For non-equilibrium situations the gametic frequencies under *any* mating system are given by the relation

$$\begin{aligned} \hat{g}_1 &= \hat{p}_1\hat{p}_2 + D, & \hat{g}_3 &= \hat{q}_1\hat{p}_2 - D, \\ \hat{g}_2 &= \hat{p}_1\hat{q}_2 + D, & \hat{g}_4 &= \hat{q}_1\hat{q}_2 - D, \end{aligned} \tag{3}$$

where $D = \hat{g}_1\hat{g}_4 - \hat{g}_2\hat{g}_3$. D can vary from $-.25$ (all Ab and aB) to .25 (all AB and ab). D, thus defined, is a measure of linkage disequilibrium. It should be noted that the term "linkage disequilibrium" is a misnomer in two respects. First, D can take values other than zero even in the absence of linkage. Second, a population can be in linkage disequilibrium, i.e., $D \neq 0$, even though it is in

gene frequency equilibrium. The term *gametic phase unbalance* might be a more appropriate term for the parameter denoted by D.

One difficulty with D as a measure of gametic phase unbalance is its sensitivity to gene frequencies such that changes in D reflect not only real changes in gametic phase unbalance but also changes in gene frequency (LEWONTIN 1964a). LEWONTIN suggested an adjustment in D based on the ratio $D' = D/\varepsilon$, where ε is the largest possible value of the product of the appropriate gene frequencies. With $p_1 = p_2 = \frac{1}{2}$, ε is always $\frac{1}{4}$. D', therefore, expresses the extent of gametic phase unbalance relative to the maximum possible value for the equilibrium gene frequencies. When it is appropriate, this relative value, D', will be given along with D.

Selective models: Twenty-four different models of selection have been examined as shown in Table 1. It should be noted that literal solutions for equilibrium gene or genotypic frequencies do not exist in general for the matrix of selective values w_{ij}, even for two loci under random mating. It has therefore been necessary to resort to numerical methods to establish change in the f_i, g_i, D and $\bar{W}$ and to determine their values at equilibrium.

Inbreeding: We have imposed inbreeding on our populations by assuming that selfing or random outcrossing occur in the proportion s and t, respectively ($s + t = 1$). Thus there is a constant probability t that any individual in the population will mate with any other individual and a constant probability $s = 1 - t$ that any individual in the population will produce progeny by selfing. The recurrence expressions relating genotypic frequencies in generations n and $n + 1$ are:

$$
\begin{aligned}
&AABB\text{: } f_1^{(n+1)} \propto w_{22}\,[s\{f_1^{(n)} + \tfrac{1}{4}(f_2^{(n)} + f_4^{(n)} + c^2 f_6^{(n)} + (1-c)^2 f_5^{(n)})\} + tg_1^2] = f_1'^{(n+1)},\\
&AABb\text{: } f_2^{(n+1)} \propto w_{21}\,[s\{\tfrac{1}{2}f_2^{(n)} + \tfrac{1}{2}c(1-c)(f_5^{(n)} + f_6^{(n)})\} + 2tg_1g_2] = f_2'^{(n+1)},\\
&AAbb\text{: } f_3^{(n+1)} \propto w_{20}\,[s\{f_3^{(n)} + \tfrac{1}{4}(f_2^{(n)} + f_7^{(n)} + c^2 f_5^{(n)} + (1-c)^2 f_6^{(n)})\} + tg_2^2] = f_3'^{(n+1)},\\
&AaBB\text{: } f_4^{(n+1)} \propto w_{12}\,[s\{\tfrac{1}{2}f_4^{(n)} + \tfrac{1}{2}c(1-c)(f_5^{(n)} + f_6^{(n)})\} + 2tg_1g_3] = f_4'^{(n+1)},\\
&AB/ab\text{(coupling): } f_5^{(n+1)} \propto w_{11}\,[\tfrac{1}{2}s\{(1-c)^2 f_5^{(n)} + c^2 f_6^{(n)}\} + 2tg_1g_4] = f_5'^{(n+1)},
\end{aligned}
\tag{4}
$$

$$
\begin{aligned}
&Ab/aB\text{(repulsion): } f_6^{(n+1)} \propto w_{11}\,[\tfrac{1}{2}s\{c^2 f_5^{(n)} + (1-c)^2 f_6^{(n)}\} + 2tg_2g_3] = f_6'^{(n+1)},\\
&Aabb\text{: } f_7^{(n+1)} \propto w_{10}\,[s\{\tfrac{1}{2}f_7^{(n)} + \tfrac{1}{2}c(1-c)(f_5^{(n)} + f_6^{(n)})\} + 2tg_2g_4] = f_7'^{(n+1)},\\
&aaBB\text{: } f_8^{(n+1)} \propto w_{02}\,[s\{f_8^{(n)} + \tfrac{1}{4}(f_4^{(n)} + f_9^{(n)} + c^2 f_5^{(n)} + (1-c)^2 f_6^{(n)})\} + tg_3^2] = f_8'^{(n+1)}.\\
&aaBb\text{: } f_9^{(n+1)} \propto w_{01}\,[s\{\tfrac{1}{2}f_9^{(n)} + \tfrac{1}{2}c(1-c)(f_5^{(n)} + f_6^{(n)})\} + 2tg_3g_4] = f_9'^{(n+1)},\\
&aabb\text{: } f_{10}^{(n+1)} \propto w_{00}\,[s\{f_{10}^{(n)} + \tfrac{1}{4}(f_7^{(n)} + f_9^{(n)} + (1-c)^2 f_5^{(n)} + c^2 f_6^{(n)})\} + tg_4^2] = f_{10}'^{(n+1)}.
\end{aligned}
$$

The proportionalities (4) become equations when the frequencies f'_i are normalized to add to unity by dividing the f'_i by their sum $\bar{W}' = \Sigma f'_i$, so that $f_i^{(n+1)} = f'^{(n+1)}_i/\bar{W}'$. Genotypic frequencies f'_i are those obtained soon after selection and before the next cycle of matings.

Numerical solutions: The system of nonhomogeneous, nonlinear equations (4) has been solved only for certain special cases, e.g. when $t = 0$ (SHIKATA 1963). However, for more general models numerical solutions are possible on digital computers by the use of standard iteration procedures (e.g. NEWTON-RAPHSON's), or by repeated substitution into the recursion equations until successive generations show no further change in genotypic frequencies. For one cycle of frequency changes

$$f_i^{(n)} \text{——}(R)\text{——}\rightarrow g_i^{(n)} \text{——}(M)\text{——}\rightarrow z_i'^{(n+1)} \text{——}(S)\text{——}\rightarrow f_i'^{(n+1)} \text{——}(N)\text{——}\rightarrow f_i^{(n+1)},$$

genotypic frequencies; gametic frequencies; zygotic output; genotypic frequencies in next generation

where R, M, S and N are linkage, mating, selection and normalizing operators, respectively, and at equilibrium $f_i^{(n+1)} = f_i^{(n)}$ (LEWONTIN 1964a). By such a procedure, changes were determined in the f_i, the g_i and for D and $\overline{W}$; their values at equilibrium were also determined. Other quantities of interest were levels of heterozygosity at the two loci ($f_{Aa..} = R_1$, $f_{..Bb} = R_2$) and the excess or deficiency of double heterozygotes as given by KIMURA's (1958) parameter

TABLE 1

Sets of selective values

	AA	*Aa*	*aa*
BB	w_{22}	w_{12}	w_{02}
Bb	w_{21}	w_{11}	w_{01}
bb	w_{20}	w_{10}	w_{00}

Intermediate optimum model												
.6	.8	1.0	.8	.9	1.0	.6	.9	1.0	.800	.925	1.000
.8	1.0	.8	.9	1.0	.9	.9	1.0	.9	.925	1.000	.925
1.0	.8	.6	1.0	.9	.8	1.0	.9	.6	1.000	.925	.400
	1(a)			1(b)			1(c)			1(d)	
Heterotic models												
.6	.8	.6	.8	.9	.8	.9	1.0	.7	.95	1.0	.55
.8	1.0	.8	.9	1.0	.9	.8	1.0	.8	.75	1.0	.75
.6	.8	.6	.8	.9	.8	.7	1.0	.9	.55	1.0	.95
	2(a)			2(b)			3(a)			3(b)	
	↖——Nonepistatic——↗						↖——Kimura's model——↗				
.5	.7	.5	.5	.7	.4	.4	.6	.3	.4	.7	.3
.7	1.0	.7	.7	1.0	.6	.6	1.0	.5	.7	1.0	.6
.5	.7	.5	.5	.7	.4	.5	.7	.4	.5	.8	.4
	4(a)			4(b)			4(c)			4(d)	
	↖——————Cumulative heterosis——————↗										
.5	.9	.5	.5	.9	.4	.50	.90	.40	.40	.90	.30
.9	1.0	.9	.9	1.0	.9	.90	1.00	.80	.90	1.00	.80
.5	.9	.5	.5	.9	.6	.60	.95	.50	.50	.95	.40
	5(a)			5(b)			5(c)			5(d)	
	↖——————Diminutive heterosis——————↗										
Mixed overdominance, underdominance												
.9	.2	.9	.8	.6	.8	.8	.5	.8	.8	.5	.8
.2	1.0	.2	.6	1.0	.6	.9	1.0	.9	.6	1.0	.5
.9	.2	.9	.8	.6	.8	.8	.5	.8	.7	.6	.6
	6(a)			6(b)			6(c)			6(d)	
Intermediate optimum model, with heterozygote advantage												
.50	.70	.85	.50	.80	.75	.78	.97	.94	.50	.90	.85
.70	1.00	.70	.80	1.00	.80	.97	1.00	.97	.90	1.00	.95
.85	.70	.50	.75	.80	.50	.94	.97	.78	.80	.95	.50
	7(a)			7(b)			7(c)			7(d)	

$\theta_{11} = (f_{AaBb} - R_1R_2)/p_1p_2q_1q_2$. Several different values of the parameters t and c were taken for each selection model. Also, several different initial compositions of population were assumed as follows: (I) coupling heterozygotes only (all $AB/ab, D^{(0)} = .25$); (II) repulsion heterozygotes only (all $Ab/aB, D^{(0)} = -.25$); (III) Hardy-Weinberg proportions with $p_1^{(0)} = p_2^{(0)} = 0.5$ $(D^{(0)} = 0)$; (IV) Hardy-Weinberg proportions with $p_1^{(0)} = p_2^{(0)} \neq 0.5$. All numerical results in this paper were based on computations on an IBM 7040 that involve round-off errors beyond eight decimal points.

RESULTS

In our present study of the effects of linkage and inbreeding on changes in gene and genotypic frequencies at two loci under selection, two quantities of primary interest are the amount of gametic phase unbalance (D) and mean population fitness given by $\overline{W}$ for populations at equilibrium. The results bearing on these relations are presented below for each type of model. Second, the conditions for permanent gametic unbalance and stable equilibria are considered in relation to the requirements in terms of linkage intensity, level of inbreeding or the type of selection model. Third, changes in level of homozygosis, excess or deficiency of double heterozygotes and gene frequencies at equilibria are used in comparing several of these models.

Optimizing selection: Under optimizing selection it is assumed that the fitness of any individual declines as its phenotype for some metrical character departs increasingly from an intermediate optimum value Φ. Thus phenotypic fitness values, w_{ij}, on a secondary scale are related to genotypic values, γ_{ij}, on an underlying additive scale such that $w_{ij} = 1 - F(\gamma_{ij} - \Phi)$, where F denotes some function of $(\gamma_{ij} - \Phi)$. In the four optimum models given in Table 1 the optimum Φ was taken equal to a fixed value on the primary scale (Table 2). Models 1a and 1b assume the w_{ij}'s to be linearly proportional to the deviation from Φ, whereas models 1c and 1d conform to WRIGHT's quadratic deviation model in that selective values are a function of squared deviations from the optimum, $-(\gamma_{ij} - \Phi)^2$.

Selection models 1a, 1b and 1c can be represented by the matrix

$$\begin{matrix} \alpha & \delta & \gamma \\ \beta & 1 & \beta \\ \gamma & \delta & \alpha \end{matrix} ,$$

and by virtue of the symmetry, literal solutions for D and $\overline{W}$ are possible for the random mating case. At equilibrium $g_1 = g_4$, $g_2 = g_3 = .5 - g_1$ and $D = \pm (.25 - g_1)$. Values of g_1 can be obtained by solving the cubic equation

$$2g^3_1 (\alpha - 2\beta + \gamma - 2\delta + 2) + g^2_1 (-\alpha + 3\beta - 2\gamma + 3\delta - 3) + \tfrac{1}{2} g_1 (-\beta + \gamma - \delta + 1 + 2c) - \tfrac{1}{4} c = 0, \tag{5}$$

and mean population fitness can be obtained by solving the quadratic equation

TABLE 2

First degree statistics for dominance and epistatic deviations

Model	Secondary scale: dominance d_a	Secondary scale: dominance d_b	Secondary scale: epistasis e_{22}	Secondary scale: epistasis e_{21}	Secondary scale: epistasis e_{12}	Secondary scale: epistasis e_{11}	Primary scale: dominance a	Primary scale: dominance b	Primary scale: epistasis ε_{ij}	Optimum value ϕ
Intermediate optimum model										
1(a)	.10	.10	0	—.40	—.40	0	0	0	0	2.0
1(b)	.05	.05	0	—.20	—.20	0	0	0	0	2.0
1(c)	.10	.10	—.20	—.20	—.20	—.20	0	0	0	2.0
1(d)	.10	.10	—.05	—.15	—.15	—.45	.5	.5	0	2.5
Heterotic models										
2(a)	.20	.20	0	0	0	0				
2(b)	.10	.10	0	0	0	0				
3(a)	.20	0	.1	.1	.1	.1				
3(b)	.25	0	.2	.2	.2	.2				
4(a)	.25	.25	.1	—.1	—.1	.1				
4(b)	.30	.25	.1	—.1	—.1	.1				
4(c)	.35	.25	.2	—.2	—.2	.2				
4(d)	.35	.25	0	0	0	0				
5(a)	.25	.25	—.3	.3	.3	—.3				
5(b)	.25	.25	—.3	.3	.4	—.2				
5(c)	.288	.211	—.30	.25	.30	—.25				
5(d)	.338	.262	—.40	.35	.40	—.35				
Mixed underdominance, overdominance										
6(a)	.05	.05	1.5	—1.5	—1.5	1.5				
6(b)	.10	.10	.6	—.6	—.6	.6				
6(c)	—.10	.30	.4	—.4	—.4	.4				
6(d)	.138	.138	.7	—.5	—.8	.5				
Intermediate optimum, with overdominance on fitness scale										
7(a)	.162	.162	.10	—.45	—.45	.10				
7(b)	.188	.188	—.10	—.15	—.15	—.10				
7(c)	.070	.070	—.16	0	0	—.16				
7(d)	.169	.169	—.30	.05	0	—.40				

$d_a = (w_{1.} - w_{2.} + w_{0.})/2$, $d_b = (w_{.1} - w_{.2} + w_{.0})/2$, $e_{22} = w_{22} + w_{11} - w_{21} - w_{12}$, $e_{21} = w_{21} + w_{10} - w_{20} - w_{11}$, $e_{12} = w_{12} + w_{01} - w_{02} - w_{11}$, and $e_{11} = w_{11} + w_{00} - w_{10} - w_{01}$. (cf. COCKERHAM 1954).

$$\overline{W} = 2g^2_1 (\alpha - 2\beta + \gamma - 2\delta + 2) + 2g_1 (\beta + \gamma + \delta - 1) + \tfrac{1}{2} (1 + \gamma). \quad (6)$$

Specifically for models 1a and 1b, $\alpha = 1 - 2x$, $\beta = \delta = 1 - x$ and $\gamma = 1$ with $x = 0.2$ and 0.1, respectively. Thus equation (5) becomes

$$4xg^3_1 - 6xg^2_1 + g_1 (x + c) = \tfrac{1}{4} c = 0. \quad (7)$$

Equation (7) has only one solution in the range $0 < g_1 < \tfrac{1}{4}$, and this solution corresponds to $D < 0$. Note that taking Φ different from the mean $\overline{y}$, as KOJIMA (1959b) has done, introduces asymmetry and may lead to more than one stable equilibrium. For model 1c, $\alpha = 1 - 4x$, $\beta = \delta = 1 - x$ and $\gamma = 1$, so that equation (5) reduces to the quadratic equation

$$4xg^2_1 - g_1 (x + c) + \tfrac{1}{4} c = 0. \quad (8)$$

Again, equilibrium values of D are negative and gametic balance ($D = 0$) is not obtained. This is a feature of all intermediate optimum models.

First degree statistics measuring dominance and epistatic deviations (COCKERHAM 1954) are given in Table 2. The primary scale is entirely additive for models 1a, 1b and 1c but dominance on the primary scale is a feature of model 1d. Positive values of d_a and d_b and non-zero values of certain of the e_{ij} indicate dominance and epistasis on the secondary (or fitness) scale for all four intermediate optimum models.

LEWONTIN (1964b), using numerical methods, reached the following conclusions regarding optimizing selection under random mating: (1) gene frequencies and gametic frequencies are sensitive to changes in linkage intensity, particularly in the range from very low to intermediate recombination values; (2) the effect of linkage is to increase the proportion of repulsion phase gametes; (3) the large amount of epistasis which optimum models generate on the fitness scale results in gametic phase unbalance even in the absence of linkage and; (4) the effect of tightening linkage is an increase in mean fitness ($\overline{W}$).

To test whether inbreeding makes a substantial difference to these conclusions we have examined models 1a to 1d numerically under a range of values of t, including the case of $t = 1$ (random mating). The results were similar for all four models and hence can be illustrated with only a sample of the data, as given in Table 3 and Figures 1 and 2.

It should be noted that there is only a single gene frequency equilibrium for each of the four intermediate optimum models. This equilibrium in each case

TABLE 3

Values of various parameters at gene frequency equilibria under models 1(a) and 1(d)

		Model 1(a)				Model 1(d)					
t	c	$\hat{g}_1=\hat{g}_4$	$\hat{g}_2=\hat{g}_3$	D	$\overline{W}$	$\hat{g}_1$	$\hat{g}_2=\hat{g}_3$	$\hat{g}_4$	D	D'	$\overline{W}$
.10	.01	.0016	.4984	—.2484	.9988	.0030	.4977	.0016	—.2477	—.9908	.9990
	.10	.0134	.4866	—.2366	.9895	.0254	.4808	.0130	—.2308	—.9233	.9912
	.25	.0271	.4729	—.2229	.9789	.0508	.4622	.0248	—.2124	—.8502	.9827
	.50	.0406	.4594	—.2094	.9702	.0754	.4448	.0350	—.1952	—.7821	.9748
.30	.01	.0043	.4957	—.2457	.9966	.0089	.4932	.0047	—.2432	—.9728	.9971
	.10	.0377	.4623	—.2123	.9710	.0752	.4441	.0366	—.1945	—.7792	.9764
	.25	.0761	.4239	—.1739	.9438	.1453	.3953	.0641	—.1469	—.5915	.9562
	.50	.1111	.3889	—.1389	.9210	.2045	.3566	.0823	—.1103	—.4479	.9406
.90	.01	.0113	.4887	—.2387	.9910	.0284	.4751	.0214	—.2251	—.9004	.9919
	.10	.1031	.3969	—.1469	.9256	.1967	.3480	.1073	—.1000	—.4032	.9512
	.25	.1809	.3191	—.0691	.8815	.2814	.2906	.1374	—.0458	—.1871	.9332
	.50	.2161	.2839	—.0339	.8621	.3178	.2667	.1488	—.0238	—.0980	.9258
1.0	.01	.0125	.4875	—.2375	.9901	.0325	.4697	.0281	—.2197	—.8788	.9908
	.10	.1141	.3859	—.1359	.9192	.2096	.3348	.1208	—.0868	—.3500	.9493
	.25	.1917	.3083	—.0583	.8760	.2857	.2834	.1475	—.0382	—.1558	.9338
	.50	.2226	.2774	—.0274	.8616	.3168	.2630	.1573	—.0193	—.0792	.9277

corresponds to $\hat{p}_1 = \hat{p}_2$ and an excess of repulsion phase gametes, leading to the negative values of D. It should be noted that these equilibria are obtained from initially equal gene frequencies, i.e., $p_1^{(0)} = p_2^{(0)}$ (Sets I, II, III, IVa,b) and are maintained only as long as the condition of exact equality of gene frequencies is satisfied. This special class of metastable equilibria has been termed *isoplethic* (JAIN and ALLARD, 1965). The general properties of optimum models discussed below, however, apply equally to the truly stable equilibria.

Table 3 gives the pertinent parameters of gene and genotypic frequency equilibrium ($\Delta p_i = 0, \Delta f_i = 0$) for one symmetrical model (1a) and one asymmetrical model (1d). The most significant feature of the results given in this table is the striking interaction between inbreeding and linkage. Under random mating ($t = 1$) the results follow the pattern described by LEWONTIN (1964b), i.e., the excess of repulsion phase gametes which occurs under tight linkage decreases rapidly as linkage loosens to intermediate values, and virtually disappears under free recombination. This pattern is only slightly altered under mild inbreeding ($t = .90$). But as the level of inbreeding increases, the extent of gametic phase unbalance becomes increasingly important, especially with loose linkage. For example, there is only a small excess of repulsion gametes under random mating ($t = 1$) and free recombination but with $t = .10$, and $c = .50$, about 90% of the gametes are in repulsion phase. Complete selfing ($t = 0$) leads to $D = -.25$ under optimum models when initial gene frequencies are $p_1^{(0)} = p_2^{(0)} = .5$, regardless of the recombination value.

Table 3 reveals another effect of inbreeding under optimizing selection, namely, that increased levels of inbreeding lead to increased mean fitness, $\overline{W}$, of populations. The extent of this effect is not the same for all recombination values but, as in the case of D', the effect is particularly large with tight linkages.

Figure 1 illustrates some differences among the optimum selection models

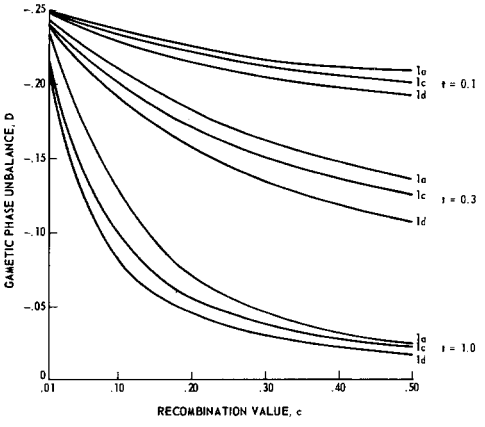

FIGURE 1.—Effect of recombination (c) and partial selfing ($1—t$) on gametic phase unbalance (Models 1a, 1c, 1d).

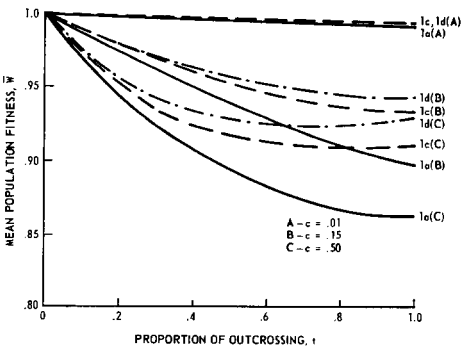

FIGURE 2.—Effect of recombination (c) and partial selfing ($1—t$) on mean population fitness at gene frequency equilibrium (Models 1a, 1c, 1d).

respecting the extent of gametic phase unbalance (D). Under random mating ($t = 1$) the values of D for the different models are most nearly alike under loose linkage ($c > .40$) and most different with intermediate values of c ($c = .10$ to .20). With inbreeding, however, the values of D are most different with free recombination. The asymmetrical selective values of model 1d seem to have no effect on the general relationship between D and c.

Figure 2 illustrates the relationship between mean fitness, $\overline{W}$, and level of inbreeding, for models 1a, 1c and 1d. With tight linkage ($c = .01$), $\overline{W}$ hardly changes over the entire range from complete selfing to random mating, irrespective of model. With intermediate linkage values (e.g. $c = .15$) $\overline{W}$ falls off more rapidly for models 1a and 1c than for 1d as t increases and for loose linkage $\overline{W}$ decreases as t increases to intermediate values; thereafter further increase in t leads to increase in $\overline{W}$. In general $\overline{W}$ is higher as D departs further from zero but increases in gametic unbalance do not always result in proportional changes in $\overline{W}$. For example, the usual relationship between D and $\overline{W}$ is reversed for $c = .50$ and t in the range .50 to .90 for models 1c and 1d. Thus, $\overline{W}$ is lower for these models than for model 1a for tight linkage but higher than for model 1a if linkage is loose.

The general pattern that emerges is that tightening of linkage or increasing the level of inbreeding have much the same effect under optimizing selection. An effect of both is to increase the proportion of repulsion phase gametes, so bringing the mean closer to the optimum, which in turn leads to an increase in fitness. The relationships amongst the variables t, c, D are, however, not simple and their interactions with each other and with selection (as expressed in the model) influence $\overline{W}$ in complex ways.

It should be noted that the tests for stability of equilibria developed by KOJIMA (1959a) indicate that stable equilibria do not exist for the four intermediate optimum models we have investigated. However, numerical checks based on simulation indicate that there is in fact a single isoplethic equilibrium, corresponding to $\hat{p}_1 = \hat{p}_2 = .5$ for each of the models, 1a to 1c, provided $p_1^{(0)} = p_2^{(0)} = 0.5$. The failure of KOJIMA's conditions to identify the stability of this equilibrium is associated with his assumption that gametic phase unbalance (D) has negligible effects. The effects of ignoring D on stability conditions will be discussed in more detail in a later section.

Heterotic Models

We have determined the effects of inbreeding, linkage and selection under five types of heterotic models as follows: (1) Models which involve overdominance at both loci, but no epistasis (all $e_{ij} = 0$, $\alpha = \gamma$, $\beta = \delta > \alpha$), such as models 2a and 2b; (2) Models which show overdominance at only one locus but involve epistasis as indicated by the quantities $e_{ij} > 0$ (Table 2). Models 3a and 3b are examples. (3) Models of cumulative heterosis in which the heterotic effect at one locus is enhanced by heterozygous phase at the other locus. Examples are

Models 4a, 4b, 4c (epistatic) and 4d (nonepistatic); (4) Models of diminutive heterosis in which the heterotic effect at each of two loci is proportionately decreased in the double heterozygote. Models 5a, 5b, 5c and 5d represent variations of this situation respecting symmetry and dominance; (5) Models of mixed over- and under-dominance in which it is assumed that all four homozygotes are superior to single heterozygotes but inferior to the double heterozygote. Examples are models 6a to 6d.

Heterotic models with no epistasis: One of the major points made by LEWONTIN and KOJIMA (1960) and by LEWONTIN (1964a) is that linkage does not affect the final equilibrium of random mating populations in the absence of epistasis. With $t = 1$ (random mating) our results with models 2a and 2b gave $D = 0$ over the entire range of linkage values, which is in conformity with expectations based on the theory developed by LEWONTIN and KOJIMA. With inbreeding, however, there is a range of linkage values under which permanent gametic phase unbalance ($D \neq 0$) occurs in nonepistatic heterotic models, as shown in Table 4. With very heavy inbreeding, such as that produced by $t = .01$, gametic phase unbalance occurs over a wider range of linkage values. As the level of inbreeding decreases, increasingly tighter linkage is required to maintain permanent gametic phase unbalance at gene frequency equilibrium. For example with $t = .10$ a crossover value of $c = .05$ is no longer adequate to maintain permanent gametic

TABLE 4

Values of various parameters at gene frequency equilibria under model 2a

$t > 0$ (Initial Sets: I, II)*					$t=0$†			
t	c	D	$\overline{W}$	$\hat{R}_1=\hat{R}_2$	Initial set	c	D	$\hat{p}_1=\hat{p}_2$
0.01	.001	±.2447	.6104	.0426	I, II	.01	±.2310	
	.01	±.1909	.6093	.0370		.10	±.1234	
	.05	0	.6075	.0279		.25	±.0483	.5000
	.50	0	.6066	.0230		.40	±.0139	
0.10	.001	±.2432	.6619	.2328		.50	0	
	.01	±.1712	.6577	.2093	III	.01 to .50	0	.5000
	.05	0	.6528	.1820	IVa	.01	.0030	.7465
	.50	0	.6496	.1645	($p_1=p_2=.8$)	.10	.0009	.7551
0.05	.001	±.2332	.7492	.4918		.25	—.0002	.7571
	.01	0	.7436	.4367		.40	—.0005	.7592
	.05	0	.7434	.4342		.50	—.0006	.7608
	.50	0	.7424	.4241	IVb	.01	.00052	.5736
0.90	.001	±.1320	.7912	.5610	($p_1=p_2=.6$)	.10	.00017	.5785
	.01	0	.7909	.5433		.25	.00001	.5805
	.05	0	.7908	.5430		.40	—.00006	.5814
	.50	0	.7908	.5414		.50	—.00011	.5820
1.00	.001 to .50	0	.8000	.5625				

* Initial sets IIII, IV gave $D=0$ for all values of c.

† Equilibria had all four homozygotes in various proportions, with $\overline{W}=.60$ in all cases.

phase unbalance. For inbreeding less intense than that resulting from $t = .20$, extremely tight linkage is required to maintain permanent gametic phase unbalance. With extremely tight linkage ($c = .001$) gametic phase unbalance occurs even with very little inbreeding, say $t = .90$.

Note that LEWONTIN and KOJIMA's general solution of cubic equation (5) is given by $g_1 = \frac{1}{4} \pm \frac{1}{4}\{1 - 4c/(1 + \alpha - \beta - \delta)\}^{\frac{1}{2}}$, which implies $D = 0$ when $(1 + \alpha - \beta - \delta) = 0$, i.e., no epistasis; this restriction on selective values does not hold as soon as any inbreeding is involved. It is therefore clear that epistasis is not a requirement for $D \neq 0$ for cases involving inbreeding.

Table 4 reveals another effect of inbreeding on models 2a and 2b. Under random mating ($t = 1$) linkage has no effect on equilibrium gene frequencies (p_1, p_2), on the extent of heterozygosity (R_1, R_2), on the mean population fitness ($\bar{W}$) nor, as noted above, on gametic phase unbalance (D). When, however, even mild inbreeding is imposed (say $t = .90$), $\hat{p}_1$, $\hat{p}_2$, R and $\bar{W}$ are influenced by linkage. The important effect of tighter linkage for any given level of inbreeding ($t < 1.0$) is to increase the proportion of heterozygotes and thus to increase $\bar{W}$, since in these models heterozygotes have higher fitness. This effect of linkage on $\bar{W}$ can occur even when $D = 0$, in contrast to the situation under random mating, where $D \neq 0$ is prerequisite to the effect of linkage on $\bar{W}$. Thus, under inbreeding the genotypic frequency equilibria can be influenced by linkage through genotypic associations of the type discussed by BENNETT and BINET (1956) in spite of the completely balanced gametic arrays. These two different sources of a correlated gene distribution at linked loci should be distinguished under inbreeding.

Table 4 also gives a sample of results obtained with model 2a when the mating system is one of complete self-fertilization ($t = 0$). Even though the models are symmetrical with respect to selection, equilibrium gene frequencies and D depend on initial genotypic frequencies. This result is expected in view of the demonstration by BENNETT and BINET (1956) that initial discrepancy between the frequency of coupling and repulsion linkages persists even without selection under complete selfing. These results make it clear that the case of complete selfing ($t = 0$) is qualitatively different from any mixed mating system, and the case of $t = 0$ cannot be regarded as the limiting case in inbreeding, as has been done by BODMER and PARSONS (1960). The distinctive properties of the complete selfing system often make it inaccurate to draw inferences about predominantly selfing systems from the case of $t = 0$.

Models involving heterozygote advantage at one locus, plus epistasis: In this type of model a pair of alleles at one locus (A,a) is kept in balanced polymorphism by virtue of heterozygote advantage in fitness. Another pair of alleles (B,b) at a second locus is assumed to interact with the first locus in such a way that A is advantageous in combination with B but the situation is reversed with respect to allele a, i.e., the homozygotes *AABB* and *aabb* are superior to *AAbb* and *aaBB*. Models of this sort ($\delta = 1$, $\alpha > \beta > \gamma$) were investigated by KIMURA (1956). Our models 3a and 3b are examples. For symmetrical cases, say with $\alpha = 1 + x - y$, $\beta = 1 - y$, $\gamma = 1 - x - y$, the cubic equation (5) reduces to

$$x g_1^2 + (c - .5x) g_1 - .25 c = 0, \quad (9)$$

and the only admissible solution is

$$g_1 = \tfrac{1}{2} [\tfrac{1}{2} - c/x (\tfrac{1}{4} + c^2/x^2)^{\frac{1}{2}}],$$

giving mean fitness

$$\bar{W} = 1 - \tfrac{1}{2} (x + y) + 2 x g_1.$$

As shown by KIMURA (1956) for the random-mating case, a stable nontrivial equilibrium is possible only for low values of c, i.e., the second locus will remain polymorphic only when linkage is very tight. For models 3a and 3b the upper bound on c, under random mating, is given by the inequality, $c < (\gamma^2 - x^2/4\gamma)$ so that stable equilibrium is possible for model 3a only when the crossover value is less than .0375 and for model 3b when $c < .0225$. For larger values of c, locus b goes to fixation when $p_1^{(0)} = p_2^{(0)}$ (e.g. as with initial condition IV). When, however, $p_1^{(0)} = p_2^{(0)} = .5$ (initial conditions I, II, and III) larger values of c result in metastable equilibria for which $D \neq 0$ and other population parameters are also affected as shown in Table 5. On the computer such metastable equilibria may persist for hundreds of generations but ultimately the round-off

TABLE 5

Values of various parameters at gene frequency equilibria under models 3a, 3b

		Model 3(a)				Model 3(b)			
t	c	D	$\bar{W}$	$\hat{R}_1$	$\hat{R}_2$	D	$\bar{W}$	$\hat{R}_1$	$\hat{R}_2$
0.10	.01	.2462	.9087	.1090	.1078	.2479	.9536	.0993	.0983
	.02	.2425	.9076	.1093	.1069	.2460	.9525	.0995	.0976
	.04	.2357	.9055	.1098	.1053	.2422	.9504	.0999	.0963
	.10	.2191	.9003	.1110	.1018	.2328	.9450	.1010	.0932
	.50	.1707*	.8852	.1149	.0949	.2018*	.9276	.1047	.0866
0.30	.01	.2389	.9211	.2626	.2585	.2441	.9587	.2464	.2435
	.02	.2286	.9183	.2640	.2561	.2384	.9558	.2476	.2420
	.04	.2099	.9131	.2664	.2520	.2278	.9503	.2499	.2392
	.10	.1673*	.9014	.2720	.2444	.2012*	.9364	.2558	.2330
	.50	.0789*	.8768	.2848	.2356	.1242*	.8960	.2747	.2234
0.50	.01	.2313	.9295	.3679	.3605	.2401	.9621	.3511	.3461
	.02	.2143	.9253	.3702	.3565	.2308	.9576	.3533	.3438
	.04	.1850	.9180	.3742	.3505	.2134	.9493	.3575	.3398
	.10	.1262	.9034	.3826	.3420	.1718*	.9292	.3681	.3324
	.50	.0413*	.8822	.3955	.3370	.0748*	.8821	.3955	.3270
0.90	.01	.2116	.9395	.5059	.4908	.2298	.9654	.4916	.4816
	.02	.1800	.9329	.5097	.4838	.2114	.9573	.4958	.4772
	.04	.1335	.9233	.5153	.4765	.1797*	.9445	.5031	.4071
	.10	.0691*	.9099	.5233	.4722	.1165*	.9184	.5182	.4645
	.50	.0154*	.8987	.5302	.4734	.0303*	.8826	.5405	.4689
1.00	.01	.2050	.9410	.5313	.5140	.2262	.9655	.5179	.5062
	.02	.1693	.9338	.5354	.5064	.2050	.9570	.5225	.5011
	.04	.1202*	.9240	.5411	.4995	.1693*	.9427	.5304	.4945
	.10	.0590*	.9118	.5484	.4966	.1036*	.9164	.5456	.4891
	.50	.0125*	.9025	.5540	.4988	.0248*	.8849	.5650	.4951

* Metastable equilibria.

errors cause gene frequencies to deviate from 0.5. Once this occurs the locus b inevitably goes to fixation (BB or bb), gametic phase unbalance disappears ($D \rightarrow 0$) and the value of $\overline{W}$ is governed by locus a. In real situations it is doubtful whether such metastable equilibria would become established or persist for a long period should they become established. Thus, under random mating, gametic phase unbalance and the associated effects on $\overline{W}$ are not likely to be of any real importance under selection models 3a and 3b except for very tightly linked genes.

The imposition of inbreeding under selection models 3a and 3b has substantial effects on several parameters of population structure, as can be seen from Table 5. As t becomes smaller, linkage need be less tight to maintain both loci unfixed, i.e., stable equilibrium is possible with looser linkage. (Note that when $p_1^{(0)} = p_2^{(0)} = .5$, metastable equilibria occur above the critical values of c). As under random mating these equilibria are characterized by an excess of coupling gametes, i.e., $D > 0$, and this gametic phase unbalance is accompanied by an increase in mean fitness ($\overline{W}$). In selection models of this type it is obvious that the more tightly the locus b is linked to the heterotic locus a, the more likely that locus b will remain unfixed. The data of Table 5 show that for any given linkage value, locus b is less likely to become fixed as inbreeding becomes more intense, i.e., inbreeding enhances the effect of linkage in allowing a nonheterotic locus to avoid fixation.

Models with cumulative heterosis: Selection models 4a to 4d show *cumulative* heterosis in that heterozygote advantage in fitness at one locus is enhanced in association with the heterozygous phase at the other locus. These four models differ from one another with respect to symmetry (Table 1), degree of dominance and kind and amount of epistasis (Table 2). LEWONTIN (1964a) has investigated model 4c for the random-mating case.

The main population parameters for models 4a and 4b are given in Table 6. Certain features are common to both models: (1) Stable equilibria in which $D \neq 0$ exist only with tight linkage; (2) With progressively greater inbreeding the tightness of linkage required for stable equilibrium decreases. The relaxation of the requirement for equilibrium of $c < e_{22}/4$ is slightly greater for model 4a (a symmetrical model) than 4b, but is not large in either case; (3) When requirements for equilibrium with $D \neq 0$ are satisfied there exist two stable conjugate equilibria for each value of t and c, one with D positive (excess of coupling gametes) and one with D negative (excess of repulsion gametes). Which of these two equilibrium points will be reached depends on initial genotypic frequencies. If the initial population is composed entirely of coupling double heterozygotes (Initial Condition I, $D = .25$), or if $p_a^{(0)} = p_b^{(0)} \neq .5$ so that both dominant alleles equally frequent (Initial Condition IV), D will be positive at gene frequency equilibrium. Conversely if the initial population is composed entirely of repulsion double heterozygotes (Initial Condition II) or $p_a = q_b \neq .5$, an excess of repulsion phase gametes results ($D < 0$). If, however, the initial population satisfies the Hardy-Weinberg rule with $p_a = p_b = .5$ (Initial Condition III) $D = 0$ at gene

TABLE 6

Values of various parameters at gene frequency equilibria under models 4a, 4b

		4(a)			4(b)						
t	c	$\pm D$	$\overline{W}$	$\hat{R}_1=\hat{R}_2$	$\pm D$	$\pm D'$	$\overline{W}$	$\hat{R}_1$	$\hat{R}_2$	$\hat{p}_1$	$\hat{p}_2$
.10	.01	.2201	.5934	.3119	.1882	.2314	.5698	.3171	.3229	.6822	.6399
	.02	.1856	.5871	.2909	.1436	.2056	.5617	.2756	.2918	.7164	.6152
	.04	.0829	.5750	.2500	0	0	.5491	.1780	.2324	.8018	.5000
	.06	0	.5706	.2347	0	0	.5418	.1586	.2209	.8275	.5000
	.10	0	.5674	.2236	0	0	.5386	.1281	.2049	.8580	.5000
.30	.01	.2143	.6519	.4605	.2009	.2258	.6278	.4716	.4770	.6119	.5732
	.02	.1718	.6442	.4366	.1547	.1916	.6193	.4356	.4483	.6607	.5737
	.04	.0072	.6303	.3924	0	0	.6050	.3710	.4005	.6679	.5000
	.06	0	.6292	.3889	0	0	.6039	.3656	.3962	.6822	.5000
	.10	0	.6274	.3830	0	0	.6017	.3565	.3889	.6876	.5000
.50	.01	.2089	.6866	.5357	.1993	.2188	.6627	.5454	.5502	.5850	.5493
	.02	.1578	.6780	.5094	.1470	.1769	.6540	.5103	.5201	.6086	.5308
	.04	0	.6664	.4728	0	0	.6425	.4638	.4804	.6336	.5000
	.10	0	.6649	.4679	0	0	.6408	.4574	.4743	.6362	.5000
.90	.01	.1970	.7315	.6206	.1890	.2080	.7088	.6266	.6299	.5687	.5266
	.02	.1232	.7218	.5896	.1148	.1347	.6996	.5902	.5941	.5831	.5112
	.04	0	.7154	.5690	0	0	.6940	.5686	.5721	.5902	.5000
	.10	0	.7152	.5683	0	0	.6938	.5678	.5713	.5904	.5000
1.0	.01	.1936	.7400	.6351	.1853	.2039	.7177	.6402	.6429	.5656	.5231
	.02	.1118	.7300	.6027	.1018	.1188	.7083	.6029	.6052	.5787	.5084
	.04	0	.7250	.5862	0	0	.7042	.5868	.5883	.5834	.5000
	.10	0	.7250	.5862	0	0	.7042	.5868	.5883	.5834	.5000

frequency equilibrium; (4) Values of D (or D') are consistently higher under inbreeding than with random mating and high values of D are accompanied by high values of $\overline{W}$; (5) Tighter linkage leads to higher levels of heterozygosity for any given level of t. This effect is more pronounced for model 4b than model 4a, probably as a result of the higher degree of dominance in model 4b; (6) In model 4b, which is asymmetrical, gene frequencies at the two loci tend to be similar at equilibrium when linkage is tight but quite different when linkage is loose.

Results for models 4c and 4d are given in Table 7 for the range of linkage values $c = .01$ to $c = .10$. Results for looser linkages ($c = .10$ to .50) for model 4(c) are given in Figure 3. Several points are worth noting. First, even though model 4d does not involve epistasis, gametic phase unbalance ($D \neq 0$) occurs under inbreeding. A similar result was noted above for models 2a and 2b. Second, when linkage is very tight, there are two possible equilibria for each recombination value. These pairs of equilibria have unequal and opposite-signed values of D, and different mean fitnesses. The coupling equilibria (D positive) were obtained from populations in initial condition I; all other initial conditions (II, III, IV) led to a negative D for model 4c. A third point to note with respect to these cumulative heterotic models is that like optimum models, they are con-

TABLE 7

Values of various parameters at gene frequency equilibrium under models 4c and 4d

		Model 4(c)—I				Model (4(c)—II, III, IV				Model 4(d)			
t	c	D'	$\overline{W}$	$\hat{p}_1$	$\hat{p}_2$	D'	$\overline{W}$	$\hat{p}_1$	$\hat{p}_2$	D'	$\overline{W}$	$\hat{p}_1$	$\hat{p}_2$
0.10	.01	+.2351	.5433	.5553	.4316	—.2334	.5551	.7604	.2370	—.2214	.5553	.7573	.2329
	.02	—.2164	.5482	.7713	.2229	—.2164	.5482	.7713	.2227	—.1912	.5486	.7647	.2141
	.04	—.1827	.5357	.7954	.1915	—.1827	.5357	.7954	.1915	—.1325	.5378	.7794	.1738
	.10	—.1161	.5115	.8888	.0826	—.1161	.5115	.8888	.0826	—.0517	.5518	.8202	.0826
0.20	.01	+.2093	.5766	.5300	.4604	—.2321	.5872	.6947	.3018	—.2142	.5872	.6906	.2931
	.02	+.1396	.5610	.5927	.3773	—.2132	.5798	.6998	.2925	—.1716	.5802	.6913	.2743
	.04	—.1728	.5663	.7098	.2715	—.1728	.5663	.7098	.2715	—.0812	.5705	.6922	.2433
	.10	—.0724	.5420	.7340	.2118	—.0724	.5420	.7340	.2118	—.0190	.5640	.6982	.2154
0.30	.01	+.2142	.6002	.5236	.4678	—.2311	.6103	.6608	.3352	—.2053	.6104	.6551	.3225
	.02	+.1683	.5884	.5579	.4209	—.2108	.6026	.6638	.3274	—.1454	.6032	.6535	.3033
	.04	—.1652	.5881	.6690	.3100	—.1652	.5881	.6690	.3100	—.0408	.5962	.6523	.2848
	.10	—.0480	.5650	.6745	.2716	—.0480	.5650	.6745	.2716	—.0090	.5932	.6549	.2746
0.50	.01	+.2175	.6348	.5186	.4740	—.2294	.6444	.6237	.3720	—.1730	.6446	.6142	.3521
	.02	+.1800	.6244	.5411	.4423	—.2067	.6360	.6249	.3658	—.0485	.6385	.6131	.3388
	.04	—.1524	.6200	.6260	.3515	—.1524	.6200	.6260	.3515	—.0092	.6376	.6130	.3374
	.10	—.0240	.6003	.6210	.3337	—.0240	.6003	.6210	.3337	—.0024	.6367	.6139	.3350
0.90	.01	+.2184	.6812	.5148	.4791	—.2264	.6899	.5884	.4071	—.0007	.6967	.5772	.3911
	.02	+.1830	.6714	.5306	.4568	—.1993	.6805	.5881	.4025	—.0003	.6967	.5772	.3911
	.04	—.1287	.6622	.5863	.3925	—.1287	.6622	.5863	.3925	—.0001	.6966	.5773	.3912
	.10	—.0087	.6491	.5790	.3898	—.0087	.6491	.5790	.3898	—.0004	.6966	.5773	.3912
1.00	.01	+.2182	.6901	.5142	.4799	—.2225	.6986	.5829	.4127	0	.7086	.5715	.4000
	.02	+.1827	.6804	.5290	.4589	—.1975	.6890	.5823	.4084	0	.7086	.5715	.4000
	.04	—.1227	.6704	.5801	.3994	—.1337	.6704	.5801	.3994	0	.7086	.5715	.4000
	.10	—.0072	.6588	.5730	.3985	—.0072	.6588	.5730	.3985	0	.7086	.5715	.4000

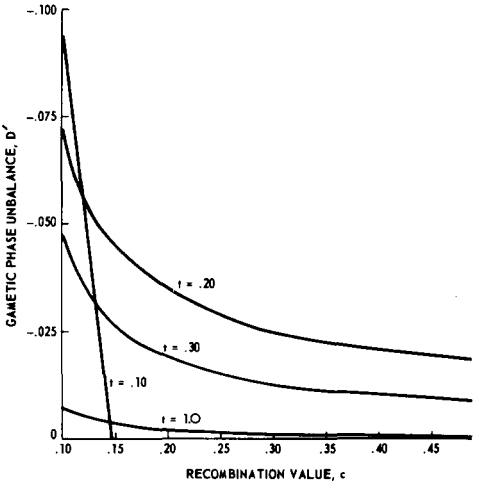

FIGURE 3.—Effect of recombination (c) and partial selfing ($1-t$) on gametic phase unbalance (Model 4c).

ducive of gametic phase unbalance, i.e., they lead to large values of D under tight linkage and also produce $D \neq 0$ under very loose linkage. An exception to this generalization occurs when selection is highly asymmetrical and inbreeding is intense. Under this circumstance inbreeding leads to homozygosity and selection tends to fix the superior homozygote. It is also significant to note that under cumulative heterosis there are no metastable equilibria such as those found with models 3a and 3b.

Models with diminutive heterosis: In models 5a to 5d the degree of heterosis at locus a is less in the presence of Bb than in the presence of BB or bb. A similar inequality holds for the locus b. These four models are therefore examples of diminutive heterosis in which increase in fitness is proportionately less than expected on the basis of increase in number of heterozygous loci. Such models are not expected to be particularly favorable to the development of permanent gametic phase unbalance and the analysis of the present examples show that this is the case. Model 5a, a symmetrical selection model, gave equilibria with $D = 0$ for all values of c and t. However, it is interesting to note that the introduction of asymmetry into the models, as in models 5b, 5c, and 5d, changed the situation drastically respecting equilibrium such that under model 5b, for example, even $c = .50$ yielded $D \neq 0$ over the entire range of values to t. With model 5b the amount of gametic phase unbalance is substantial, particularly for tight linkages and rather close inbreeding (Figure 4). In general, however, the amount of gametic phase unbalance and its effects on other population parameters were rather small for these models of diminutive heterosis (Figure 5). It should be noted that there is a single stable equilibrium for each value of t and c and that $D > 0$ for model 5b and $D < 0$ for models 5c and 5d.

Models of mixed over- and underdominance: Models 6a, 6b and 6d are similar to one another in that single heterozygotes are selectively inferior to homozygotes whereas double heterozygotes are favored over all other genotypes. Model 6c represents a different pattern in that single heterozygotes have an advantage over

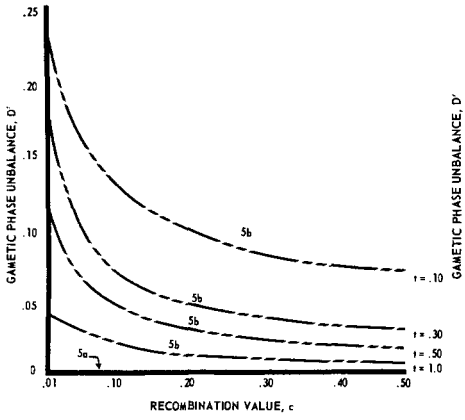

FIGURE 4.—Effect of recombination (c) and partial selfing ($1—t$) on gametic phase unbalance (Models 5a, 5b).

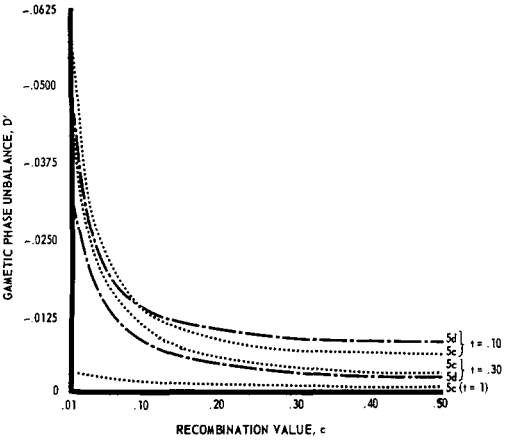

FIGURE 5.—Effect of recombination (c) and partial selfing ($1—t$) on gametic phase unbalance (Models 5c, 5d).

homozygotes at locus a and are selectively inferior to homozygotes at locus b ($d_a = -.10$, $d_b = .30$; see Table 2). Other variations in the models involve symmetry of selection, intensity of selection, level of dominance, and the relative magnitudes and sign of the quantities e_{ij} (Table 2).

LEWONTIN (1964a) investigated model 6a for the random-mating case only and found that for any linkage value $c \leq .10$ stable equilibrium occurs with intense gametic phase unbalance. (LEWONTIN gave $c = .10$ as the upper critical bound but when c is plotted at intervals of .01, it is found that this bound is near .15). As in other heterotic symmetrical models these are two conjugate equilibria, one in coupling ($D > 0$) and one in repulsion ($D < 0$). With c in the range of 0.15 to .375 ($\leq e_{22}/4$) there are no stable equilibria with $D \neq 0$. A point not brought out by LEWONTIN is that equilibria with $D \neq 0$ do not develop under his model irrespective of the value of c, unless the starting population shows gametic array unbalance. Thus, initial conditions I and II give $D > 0$ for tight linkage but $D \neq 0$ fails to develop for initial conditions III and IV, even when c is in the critical tight linkage range of $c = 0$ to .15.

The effect of inbreeding on model 6a is given in Table 8. It is interesting to note that the critical bound on c (i.e., $c \leq .15$) for stable equilibria is not changed by inbreeding. Inbreeding does, however, tend to raise the upper critical bound on c below which metastable equilibrium occurs. For example, for $t = .10$, all values of c above .15, including those in the range .375 to .50, give metastable equilibria with $D \neq 0$. Under inbreeding, as with random mating, the initial composition of the population affects the ultimate equilibrium. If initial gene frequencies are $p_1 = p_2 = .5$, and $D = 0$ (Initial condition III), stable nontrivial equilibrium (termed isoplethic) in which there is no gametic phase unbalance is possible. If, however, initial gene frequencies differ from $p_1 = p_2 = .5$, as under Initial condition IV, the population always goes to fixation of the homozygote

TABLE 8

Values of various parameters at gene frequency equilibria under model 6a

		Initial sets I, II		Initial sets III, IV		
t	c	$\pm D$	$\overline{W}$	D	$\overline{W}$	Region of metastability
0	.01	.2486	.90	0	.90	
	.10	.2266	.90	0	.90	
	.25	.1572	.90	0	.90	none
	.40	.0625	.90	0	.90	
	.50	0	.90	0	.90	
.10	.01	.2486	.9078	0	.8652	
	.10	.2331	.8916	0	.8588	
	.25	.1965*	.8731	0	.8530	$.15 \leqslant c < .50$
	.40	.1469*	.8609	0	.8506	
	.50	0	.8502	0	.8502	
.30	.01	.2479	.9191	0	.7963	
	.10	.2268	.8780	0	.7818	
	.25	.1824*	.8238	0	.7673	$.15 < c < .44$
	.40	.1227*	.7847	0	.7606	
	.50	0	.7594	0	.7594	
.90	.01	.2468	.9380	0	.6036	
	.10	.2154	.8528	0	.5986	
	.25	.1487*	.7133	0	.5926	$.15 < c < .375$
	.40	0	.5894	0	.5894	
	.50	0	.5888	0	.5889	
1.0	.01	.2466	.9400	0	.5750	
	.10	.2141	.8500	0	.5750	
	.25	.1443*	.6300	0	.5750	$.15 < c < .375$
	.40	0	.5750	0	.5750	
	.50	0	.5750	0	.5750	

* Metastable equilibria.

nearest to the initial point. In nature, this model should lead to fixation since exact equality of intial gene frequency is necessary for nontrivial equilibrium. In summary, either tight or rather loose linkage are more favorable than intermediate linkage for maintenance of genetic variability with model 6a under random mating. Under inbreeding, however, populations are not likely to avoid fixation unless linkage is tight because stable equilibria with $D = 0$ are replaced by metastable types. Results with models 6b and 6c differ from these with 6a only in detail and hence will not be considered specifically.

Results with the asymmetrical model 6d have a number of interesting features as shown in Table 9. Stable equilibria with a relative excess or deficiency of coupling gametes are obtained for various combinations of linkage (c) and inbreeding ($1 - t$), depending on the initial composition of the population. The critical range of values of c is relatively narrower for heavy than for mild inbreeding and it is interesting to note that, even though the course of genetic change toward equilibrium depends on the initial composition in complicated ways, there are at most two equilibrium points for any given set of values of t

TABLE 9

Values of various parameters at gene frequency equilibrium under model 6d

t	c	Initial frequency set*	D	D'	$\bar{W}$	$\hat{p}_1$	$\hat{p}_2$
.10	.01–.10	I, II, III, IV, V	0	0	.80	0	1.0
	.15–.50		0	0	.80	1.0	1.0
.30	.01		—.1572	—.2451	.8182	.2026	.7989
	.10		0	0	.80	0	1.0
	.15–.50		0	0	.80	1.0	1.0
.50	.01		—.2090	—.2439	.8387	.3127	.6883
	.10		—.1195	—.1724	.7944	.1051	.8063
	.15–.50		0	0	.80	1.0	1.0
.60	.01	I, II, V	.1740	.2431	.8320	.7659	.7644
		III, IV	—.2185	—.2435	.8467	.3412	.6595
	.10	I, II, V	.0621	.1868	.7964	.9077	.9007
		III, IV	—.1442	—.1864	.7916	.2818	.7308
	.15–.50	I, II, III, IV, V	0	0	.80	1.0	1.0
.70	.01	I, II, IV, V	.1899	.2431	.8396	.7329	.7311
		III	—.2244	—.2433	.8537	.3620	.6387
	.10	I, II, IV, V	.0965	.1825	.7934	.8401	.8267
		III	—.1550	—.1800	.7894	.3342	.6768
	.15–.50	I, II, III, IV, V	0	0	.80	1.0	1.0
.90	.01	I, II, IV, V	.2083	.2431	.8524	.6874	.6852
		III	—.2310	—.2428	.8654	.3902	.6100
	.10	I, II, IV, V	.1269	.1759	.7892	.7529	.7297
		III	—.1605	—.1708	.7862	.4002	.6083
	.15	I, II, III, IV, V	.0834	.1478	.7742	.8228	.7958
	.25–.50		0	0	.80	1.0	1.0
1.0	.01	I, II, IV, V	.2139	.2431	.8578	.6711	.6688
		III	—.2329	—.2426	.8704	.4004	.5998
	.10	I, II, IV, V	.1337	.1736	.7877	.7234	.6964
		III	—.1602	—.1670	.7850	.4219	.5844
	.15	I, II, III, IV, V	.0933	.1378	.7641	.7678	.7293
	.25		0	0	.80	1.0	1.0
	.50	I, II, III, IV	.0046	.0158	.7121	.6495	.5513
		V	0	0	.80	1.0	1.0

* Initial frequency sets: I—all coupling *AB/ab*; II—all repulsion *Ab/aB*; III—Hardy-Weinberg proportions with $p_1=p_2=.5$; IV, $p_1=p_2=.2$, $D=0$; V, $p_1=p_2=.8$, $D=0$.

and c. The mean fitness of the population ($\bar{W}$) appears to be independent of the direction of gametic unbalance and gene frequencies at equilibrium differ markedly from one equilibrium point to another. An important feature to note is that different values of c can lead to fixation of different genotypes under heavy inbreeding, even for identical initial conditions.

Intermediate Optimum Models with Heterozygote Advantage

This type of model was apparently first proposed by WRIGHT (1952) who studied a case with $w_{22} = 1 - 4x$, $w_{21} = w_{12} = w_{01} = 1 - x + y$, $w_{20} = w_{02} = 1$

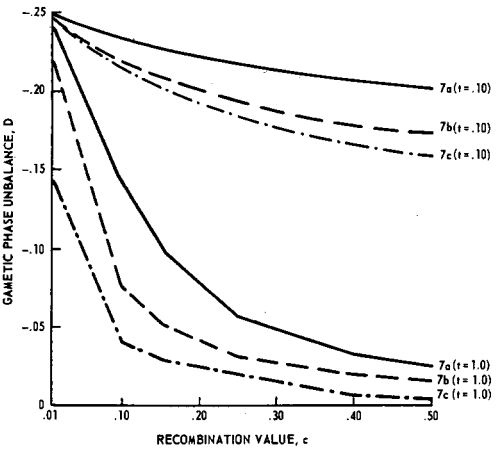

FIGURE 6.—Effect of recombination (c) and partial selfing ($1—t$) on gametic phase unbalance (Models 7a, 7b, 7c).

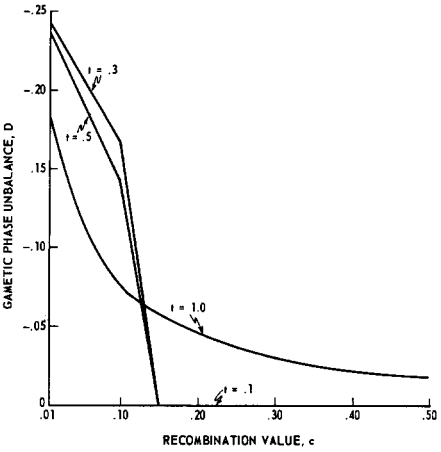

FIGURE 7.—Effect of recombination (c) and partial selfing ($1—t$) on gametic phase unbalance (Model 7d).

and $w_{11} = 1 + 2\gamma$, i.e., an increment γ is added to the fitness of heterozygotes on the secondary scale. Our models 7a, 7b, 7c, and 7d are examples of models in which heterozygote advantage is superimposed on basically intermediate optimum models. The variations amongst these four examples are reflected in the measures of dominance and epistatic components, the d_i's and e_{ij}'s (Table 2).

The values of D obtained with our models 7a, 7b, and 7c for varying values of t and c are given in Figure 6. These results are similar to those obtained with the nonheterotic intermediate optimum models discussed earlier, i.e., there is an excess of repulsion phase gametes at gene frequency equilibrium ($p_1 = p_2 = .5$) and this unbalance is greater with high than with low levels of inbreeding. There is, however, one feature in which the heterotic and nonheterotic intermediate optimum models differ: under random mating and tight linkage D tends to be lower for the heterotic models. This result is not surprising since the effectiveness of linkage in producing gametic phase unbalance tends to decrease as heterozygote advantage increases (e.g. LEWONTIN and KOJIMA 1960). The present results show that this effect of heterozygote advantage is less marked under inbreeding and they also indicate that there is a wider range of conditions under which gametic phase unbalance can develop under inbreeding than under random mating. Thus LEWONTIN's (1964a) conclusion that "tight linkage and strong epistasis are necessary for maintaining permanent linkage disequilibrium" is less applicable under inbreeding than under random mating for symmetrical cases such as models 7a, 7b, and 7c.

WRIGHT, who assumed small selective differences amongst genotypes, concluded that, beside allowing for stability, the addition of the γ increment had little effect on gametic unbalance. Results with model 7d indicate circumstances under which this conclusion does not hold, namely, asymmetry in fitness values of the two alleles at a locus. Under heavy inbreeding asymmetry in selective

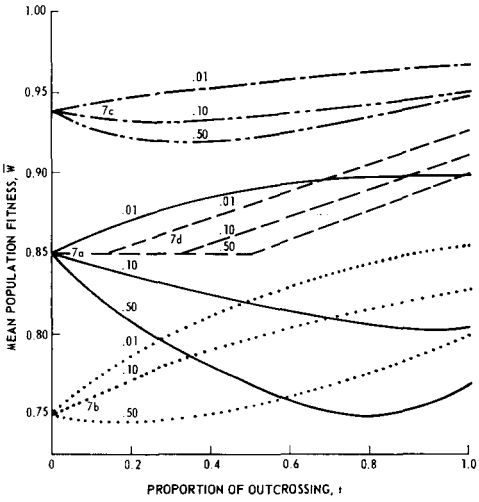

FIGURE 8.—Effect of recombination (c) and partial selfing ($1—t$) on mean population fitness at gene frequency equilibrium (Models 7a, 7b, 7c, 7d).

values is a strong force leading to fixation of the favored allele so that the critical range of crossover values (c) under which permanent gametic unbalance occurs is narrower than under random mating. Thus, for model 7d, $t = .10$ gave equilibria with $D' = 0$ for all values of c, $t = .2$ and .3 yielded non-zero D' only for tight linkage, while there was permanent gametic unbalance even for free recombination ($c = .5$) under random mating (Figure 7).

Mean population fitness values at gene frequency equilibrium are shown in Figure 8 for models 7a to 7d. It is seen that high fitness is in general associated with tight linkage and random mating. Under model 7a, which has a smaller heterotic component than model 7b, the relationship between t and $\bar{W}$ is reversed for relatively loose linkages. It therefore appears that gametic phase unbalance does not always result in higher $\bar{W}$ at equilibria under mixed selection models involving intermediate optima as well as heterozygote advantage on the fitness scale.

Multiciplicity of equilibrium points: An important feature of multiple gene systems involving epistatic interactions and linkage is the multiplicity of possible peaks on the adaptive surface given by the distribution of $\bar{W}$. When there is no gametic phase unbalance (i.e., $D = 0$) genotypic frequencies can be computed as the product of the appropriate gene frequencies and the fitness values of individual genotypes (LEWONTIN and WHITE 1960). $\bar{W}$ can be put in the form of a topography in which the two horizontal dimensions represent the frequencies of the two genes and the vertical distance above the base represents mean population fitness. Thus an adaptive landscape is formed with peaks, valleys, ridges and saddles. Peaks and saddles are particularly interesting because they correspond to stable and unstable equilibrium points, respectively. This method of plotting adaptive surfaces is clearly inaccurate when there is gametic phase unbalance because $D \neq 0$ implies that genotypic frequencies are no longer a simple function of gene frequencies. Hence, when D departs from zero, this

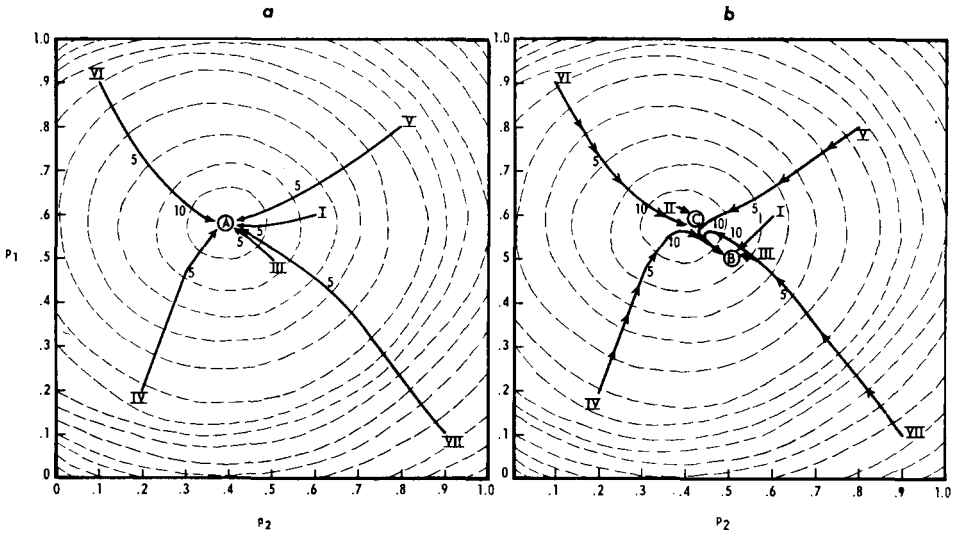

FIGURE 9.—Adaptive topographies for Model 4c for $c = .50$ (a—left) and $c = .001$ (b—right). The isoadapts (dotted contour lines) in both figures were computed assuming $D = 0$. Numbers along the trajectories give the generation at which the population point reached the position indicated. Initial gene frequency sets were: I, $p_1 = p_2 = .6$, $D = .25$ (all coupling gametes); II, $p_1 = .6$, $p_2 = .4$, $D = -.25$ (all repulsion gametes); III, $p_1 = p_2 = .5$, $D = 0$; IV, $p_1 = p_2 = .2$, $D = 0$; V, $p_1 = p_2 = .8$, $D = 0$; VI, $p_1 = .9$, $p_2 = .1$, $D = 0$, and VII, $p_1 = 1$, $p_2 = .9$, $D = 0$. With $c = .50$ (Figure 9a), all initial sets lead to a peak at $\hat{p}_1 = .572$, $\hat{p}_2 = .399$, with $D = -.0008$ and $\overline{W} = .659$. Note that this peak is near A ($\hat{p} = .575$, $\hat{p} = .400$, $\overline{W} = .658$), which is the expected position of the peak when it is assumed $D = 0$. With tight linkage ($c = .001$) there are two peaks as shown in Figure 9b. Initial gene frequency sets II, III and VII reach gene frequency equilibrium at peak c ($\hat{p}_1 = .583$, $\hat{p}_2 = .416$, $D = -.2406$, $\overline{W} = .707$), which is near the peak expected under the assumption $D = 0$. Initial gene frequency sets I, IV, V and VII reach gene frequency equilibrium at peak B ($\hat{p}_1 = .501$, $\hat{p}_2 = .498$, $D = .2467$, $\overline{W} = .699$) which lies at some distance from the peak expected when D is assumed to be zero.

method not only locates peaks and saddles incorrectly but the entire topography is affected.

Some effects on adaptive topographies of ignoring D are illustrated for model 4c in Figures 9a and 9b, and for model 6d in Figures 10a to 10d. In all of these figures the isoadapts were computed on the incorrect assumption that $D = 0$. With $c = .50$ both models give a rather small value of D and it is therefore not surprising that the singular stable equilibrium point, in both cases (Figures 9a and 10a), lies close to the peaks given by the respective $\overline{W}$-surfaces. With tight linkage ($c = .001$) D takes much larger values with both models. Actual trajectories of gene frequency changes indicate that there are in fact two distinct peaks in the topography (at A and B) and that initial gene frequencies determine which of these peaks (stable equilibrium points) the population will ultimately reach. Note that several of the trajectories approach the peak at B from the neighborhood of C. This shows that C has a rather steep slope facing B. Correct contour lines might perhaps be drawn by taking a large number of initial sets

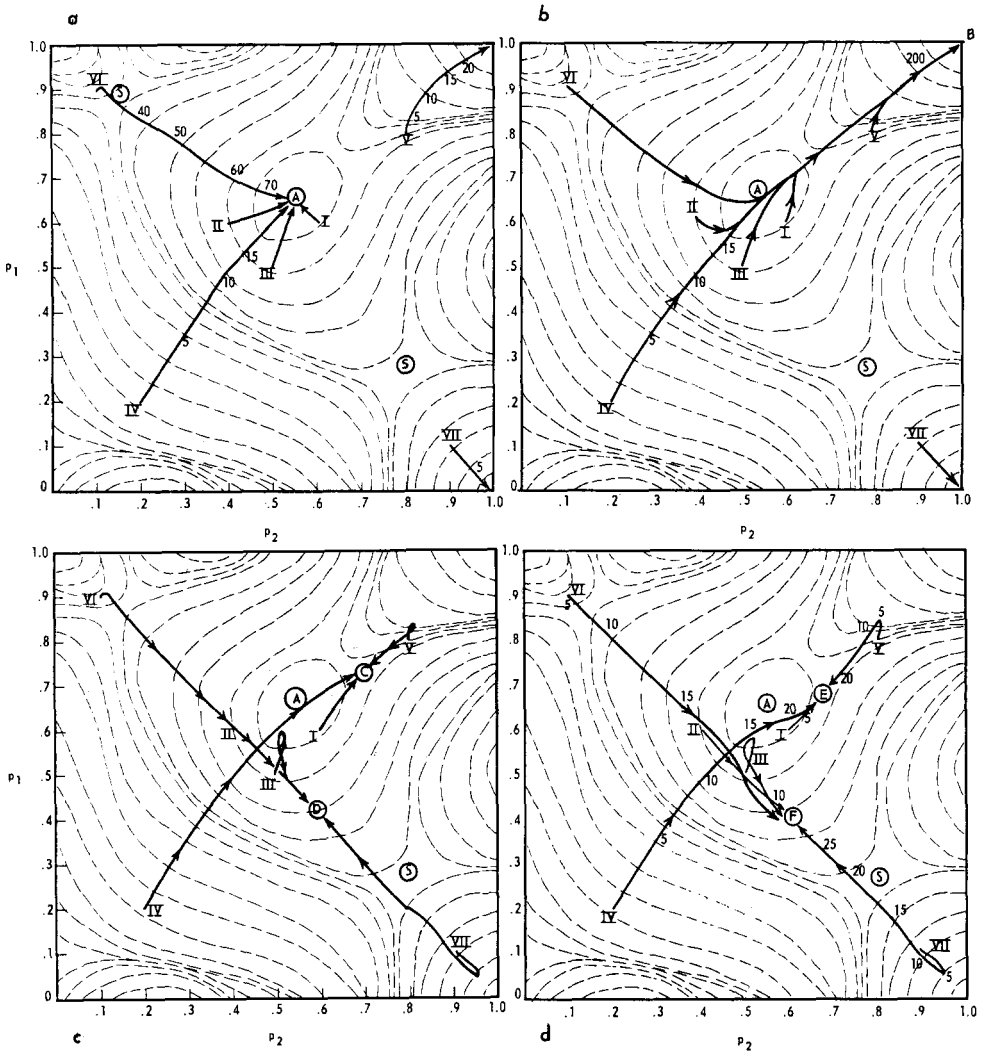

FIGURE 10.—Adaptive topographies for Model 6d for $c = .50$ (a—upper left), $c = .25$ (b—upper right), $c = .10$ (c—lower left) and $c = .001$ (d—lower right). The isoadapts (dotted contour lines) shown in all four topographies were computed on the assumption that $D = 0$. This topography indicates a peak at A and saddles at S. Numbers by trajectories give the generation at which the population point reached the positions indicated. Initial gene frequency sets are the same as for Figure 9. For $c = .50$ (Figure 10a) initial sets I, II, III, IV, and VI approached gene frequency equilibrium at the peak near A ($\hat{p}_1 = .650$, $\hat{p}_2 = .551$, $D = .0046$, $\bar{W} = .712$) whereas initial sets V and VII go to fixation at *AABB* and *aaBB*, respectively. With $c = .25$ the peak near A disappears and all intial gene frequency sets lead to fixation (Figure 10b). With tighter linkage ($c = .10$), there are peaks at C and D (Figure 10c) corresponding to stable equilibria at $\hat{p}_1 = .723$, $\hat{p}_2 = .696$, with $D = .1337$ and $\bar{W} = .788$, and $\hat{p}_1 = .422$, $\hat{p}_2 = .584$ with $D = -.1602$ and $\bar{W} = .785$, respectively. With still tighter linkage ($c = .001$) there are peaks at E and F (Figure 10d) corresponding to stable equilibria at $\hat{p}_1 = \hat{p}_2 = .667$, $D = .2214$, $\bar{W} = .866$ and $\hat{p}_1 = .400$, $\hat{p}_2 = .600$, $D = -.2393$, $\bar{W} = .879$, respectively. It is clear that ignoring D when it takes values other than zero leads to incorrect adaptive topographies.

of gene frequencies over the entire range $0 < p_1, p_2 < 1$. The work involved might not be worthwhile, however, because points of stable equilibrium are of primary interest and they can be determined with relatively few sets of initial gene frequencies.

Rates of change are indicated in Figures 9 and 10 by generation numbers along the trajectories. In general gene frequencies shift from Hardy-Weinberg proportions toward equilibrium frequencies rapidly until equilibrium is approached. However, it then usually takes many generations to attain ultimate equilibrium values of D, especially under tight linkage.

Figures 10b to 10d illustrate the effect of varying c, and hence also of varying D, on the position of peaks under model 6d. It is interesting to note that with $c = .25$, there are peaks in the corners only whereas with tighter linkages there are two distinct peaks which seem to replace the peak A and saddle S of the topography obtained assuming $D = 0$. The trajectories do not seem to follow the shortest or steepest paths, as was also found by LEWONTIN and KOJIMA (1960). It is clearly inaccurate to draw adaptive topographies assuming $D = 0$ in such cases. With inbreeding the situation becomes even more complex because the values taken by $\overline{W}$ are influenced by interactions of inbreeding with the other factors.

Conditions for stability of equilibria: Using a model of two-locus epistasis, KOJIMA (1959a) derived the following conditions for stability of gene frequency equilibria:

$$\frac{\partial^2 \overline{W}}{\partial p^2_1} < 0, \quad \frac{\partial^2 \overline{W}}{\partial p^2_2} < 0, \text{ and } \left(\frac{\partial^2 \overline{W}}{\partial p_1 \partial p_2}\right)^2 - \left(\frac{\partial^2 \overline{W}}{\partial p^2_1} \cdot \frac{\partial^2 \overline{W}}{\partial p^2_2}\right) < 0.$$

These inequalities require: (1) overdominance on the marginal means of the three genotypes at each locus; and (2) that the additive × additive component of genotypic variance for fitness (σ^2_w) be smaller than geometric mean of the dominance components. In his derivation, KOJIMA assumed gametic phase unbalance (D) to be negligible in populations in approximate equilibrium. For the case $D \neq 0$ a generalized verification of KOJIMA's second condition appears to be difficult until methods become available for partitioning the epistatic components.

A start has been made in determining stability conditions using numerical methods. From numerical analysis of a model similar to our model 4a LEWONTIN and KOJIMA (1960) suggested that marginal overdominance was necessary for stability of equilibrium. Although explicit general conditions have not been worked out, a similar numerical check can be made for our various models under both random mating and inbreeding. In this connection models 1a, 3a and 6a are of particular interest because they involve both stable and metastable equilibria with different values of c. Table 10 gives estimates of dominance effects (d_a, d_b) at equilibrium for various combinations of values of t and c. Note that while $d_a, d_b > 0$ for all stable equilibria, marginal overdominance does not ensure stability (e.g. isoplethic equilibria occur with model 1a, and also with model 6a when $t = 1$, $c = .35$). Thus KOJIMA's condition (1) seems to be a necessary but not a sufficient condition for stability.

TABLE 10

Estimates of marginal dominance (d_a, d_b) *at gene frequency equilibrium*

Model 1(a)			Model 3(a)				Model 6(a)		
t,c	D	$\hat{d}_a=\hat{d}_b$	t,c	D	$\hat{d}_a$	$\hat{d}_b$	t,c	D	$\hat{d}_a=\hat{d}_b$
.10,.01	—.2484*	—.0028	.10,.01	.2461	.1013	.0949	.10,.01	.2486	.0900
.10,.01	—.2366*	—.0225	.10,.10	.2191	.1107	.0620	.10,.10	.2331	.0067
.10,.50	—.2094*	—.0481	.10,.50	.1707†	.1378	.0230	.10,.15	.2223†	—.0346
							.10,.40	.1469†	—.1990
.90,.01	—.2387*	0	.90,.01	.2116	.1153	.0613	.90,.01	.2468	.0978
.90,.10	—.1469*	.0154	.90,.10	.0691†	.1721	—.0052	.90,.15	.1957	.0668
.90,.50	—.0339*	.0710	.90,.50	.0154†	.1935	—.0011	.90,.35	.0779†	.0231
							.90,.40	0	.0148
1.0,.01	—.2375*	.0002	1.0,.01	.2050	.1180	.0524	1.0,.01	.2466	.0987
1.0,.10	—.1259*	.0208	1.0,.10	.0590†	.1764	—.0125	1.0,.15	.1936	.0800
1.0,.50	—.0274*	.0793	1.0,.50	.0125†	.1950	—.0045	1.0,.35	.0646†	.0533
							1.0,.40	0	.0500

* Isoplethic equilibria (stable as long as $\hat{p}_1 = \hat{p}_2$).

† Metastable equilibria (stable as long as $\hat{p}_1 = \hat{p}_2 = .5$).

DISCUSSION

Major emphasis in this study of multilocus genetic systems was on the evolutionary implications of the complexities which result from interactions amongst linkage, epistasis and inbreeding. The choice of optimum, heterotic and mixed optimum-heterotic models on which to base the study was influenced by the general experience that the modes of selection implied by these models are widespread in occurrence.

Results from the study of two-locus models show that the patterns of interaction amongst dominance, linkage, mode of selection, inbreeding and other parameters which were varied are complex. Variations in the amount of crossing over, for example, can affect the extent of gametic phase unbalance and the nature and number of gene frequency equilibria, especially in mixed selection models. The initial composition of a population can also influence the final equilibrium which is attained. The intricacies which can develop are well illustrated in Figures 10b to 10d from which it can be seen that trajectories of population change cross one another. This shows that the evolutionary futures of populations which have identical gene frequencies can be very different as a result of differing evolutionary histories.

Many of the controversies that have developed in population genetics appear to have their basis in the fact that various factors have been considered singly. The present results give numerical substance to the often expressed idea that multigenic systems cannot be dealt with by analyzing the isolated effect of any single variable but only through characterization of the interplay of various factors acting simultaneously.

SUMMARY

The joint effects of linkage, level of dominance, epistasis and inbreeding on the genotypic constitution of large populations were investigated for a variety of selection models by simulation on a digital computer. Results were expressed primarily in terms of the extent of gametic phase unbalance (linkage disequilibrium), mean population fitness and the number and nature of gene frequency equilibria. Conditions for stability of equilibria were determined by varying the initial genotypic frequency set or by disturbing equilibrium frequencies. Some of the findings are: (1) permanent gametic phase unbalance can occur under a wide range of conditions respecting dominance (or overdominance), linkage and epistasis; (2) the amount of unbalance in gametic arrays tends to increase with inbreeding, particularly under symmetrical selection; (3) for intense inbreeding there are many recombination values under which permanent gametic phase unbalance is possible, even without epistasis; (4) optimum models and certain mixed selection models are more favorable than heterotic models for the development and maintenance at equilibrium of gametic phase unbalance; (5) overdominance on marginal means appears to be a necessary condition for the stability of equilibria; however, lesser levels of marginal overdominance appear to be necessary for stability of equilibria under inbreeding than with random mating.—The results indicate that complex interactions occur amongst the various factors that were varied, including inbreeding, and hence that it is the totality of all variables that determines the genetic structure of populations.

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