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Selection, Linkage, and Dominance in Small Populations

I. Effects on Coefficient of Inbreeding

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Summary. Linkage, dominance, and selection interact significantly to alter the mean coefficient of inbreeding. The effect of one is not predictable without the other two. Close linkage between adjacent loci in the presence of intense selection caused a different response with overdominant gene action from with partial dominance. When selection was random, effects of linkage and dominance on the coefficient of inbreeding were nonexistent; but when selection was by either phenotype or genotype, linkage and dominance became important. Joint effects between linkage, dominance, and selection are illustrated in specific simulated populations.

Plans of selection for genetic improvement of economic traits depend upon genetic variances, covariances, and means. These characteristics of the population are influenced by method of selection, frequencies of genes, modes of gene action, and system of mating. Relatively simple models for mathematical description of relationships among these elements usually are restricted by unrealistic pretensions such as infinite size of population, equal numbers of parents of each sex, no linkage, no interactions between nonallelic genes, and random or regular systems of mating. Various theoreticians have relaxed one or more pretenses, but because of complexity rarely have they considered many simultaneously.

Simulation of genetic populations by computer has enabled assessing effects of several factors interacting on genetic parameters. For example, Fraser (1957, 1960a, b, c) considered effects of linkage and selection; linkage, dominance, and epistasis; and reproductive rate and selection intensity of genetic structure. Gill (1965a, b, c) evaluated the effects of population size, selection intensity, linkage and nonadditive variability upon genetic change. Jain and Allard (1966) reported the effects of linkage, epistasis and inbreeding on population changes from selection. Lewontin (1964a, b) dealt with the interaction of selection and linkage. Many others have published on one or two factors that affect genetic parameters.

This study was proposed to ascertain how linkage, dominance and mode of selection affect gene frequency, genotypic mean, genotypic variance, coefficient of inbreeding, and genotypic covariance of relatives in small populations. The model, simulation program, and results for the coefficient of inbreeding are discussed in this paper. Other results will be in later communications.

Methods and Procedure

The Model

The model was a 3^3 factorial plan. Variable factors were:

1. *Linkage:* One autosome was simulated with recombination fractions of 0.50, 0.26, or 0.02 between adjacent loci. Functionally, 0.50 is equivalent to having one locus per autosome.

2. *Dominance:* Three models of gene action were partial dominance, complete dominance, and overdominance. More precisely, $[h - (d + r)/2] = 2$, 4, and 6, respectively, where d, h, and r represent genotypic values of homozygous dominant, heterozygous, and homozygous recessive genotypes, $r = 0$ and mean $= 6$ for a ratio of 1:2:1 for each locus.

3. *Mode of selection:* Eight individuals from each population of 48 were selected to become parents of the succeeding generation by one of three methods. Selection was at random, or for largest genotypic values, or for largest phenotypic values. Expected environmental variance in phenotypes was three times as large as the genotypic variance in the original population. This is equivalent to an initial heritability of 0.25 (in the broad sense).

Three replicates (populations) per factorial combination were simulated, and trends and interactions of quantitative factors were evaluated with orthogonal polynomial contrasts. Orthogonal polynomials for unequally spaced independent variables were used for assessing effects of linkage.

A parental population included four individuals of each sex; an individual contained a single pair of autosomes with 50 loci, two alleles per locus. Simulation forced initial Hardy-Weinberg equilibrium at each locus with gene frequency of one-half. Initial linkage disequilibrium was not controlled.

Of individuals selected to be parents, each male was paired with each female to produce three offspring. This generated a population of 48 offspring which included 48 possible full-sib pairs, 432 half-sib pairs, and 648 non-sib pairs. Parental genes were "transferred" to offspring one locus at a time with probability of recombination between adjacent loci specified by the linkage. From the 48 offspring, eight individuals were selected to be parents for the next generation. The first four selected individuals were assigned one sex, and the remaining four, the opposite sex. Choice of male or female for the first group of four was random. Each population continued for 20 generations.

Additional restrictions were: (1) no interlocus interactions (epistasis); (2) linkage for adjacent loci only (no interference); (3) no multiple alleles; and (4) individuals were unisexual and diploid.

Note on Degree of Linkage

All studies we reviewed defined intensity of linkage as the probability of crossing over between adjacent loci on one autosome. Intensity may be defined by the average probability of recombination between $n (n - 1)/2$ pairs of loci. The probability of recombination for all possible pairs of loci is $r_{a,b} = [1 - (1 - 2r)^{b-a}]/2$, where a and b are linearly ordered loci numbered consecutively on an autosome, and r is the probability of recombination between adjacent loci. All probabilities of recombination between loci on different autosomes are 0.50. Rowe (1966) defined the average probability of recombination for loci on the same autosome:

$$\bar{r}_i = \{1 - [(1 - 2r)/n_i r] + (1 - 2r)^2 [1 - (1 - 2r)^{(n_i - 1)}]/2 n_i (n_i - 1) r^2\}/2 ,$$

where n_i is the number of loci per autosome. For n loci distributed over several autosomes, the average recombination probability is:

$$\bar{r} = 0.5 + \sum [n_i (n - 1) (\bar{r}_i - 1/2)/n (n - 1)] .$$

Only recombination rates between adjacent loci can be controlled easily in simulated populations, but the treatment above shows the high probability of recombination among a large number of loci in a polygenic system. Low recombination rates, such as 0.05 and 0.005, between adjacent loci do not cause a major reduction in average recombination value. Because all linkages between loci must be considered in evaluating the effect of various recombination rates on different genetic parameters, the average recombination rate seems more descriptive of the linkage intensity than the rate between adjacent loci only.

Average recombination rates were 0.185, 0.481, and 0.500, respectively, for populations with recombination rates between adjacent loci of 0.02, 0.26, and 0.50.

Mechanism of Simulation

A general purpose digital computer, Control Data 3600, was used for the simulation. Magnetic core provided 65,536 48-bit words of storage capacity. "Packing" a single word stored complete information about one allele, including parental origin, whether the allele was dominant or recessive, and unique identification of the origin of the allele in the initial population. Only 800 unique "genes" were present in any population. At time of pairing of chromosomes, unique identification as well as dominance or recessive symbol for an allele was transferred to the offspring.

Our system for generation of uniformly distributed pseudo-random numbers from 0 to 1 was first proposed by Lehmer in 1951 and modified by Rotenberg (1960) and Greenberger (1961). The equation, by the multiplicative congruential method, is $X_{i+1} = (2^p + 1) X_i + C$, with $p > 2$ and C odd. Initial X_i must be supplied. Improved generators recently have been proposed by Marsaglia and Bray (1968).

Evaluation of Population Parameters

Frequency of the favored allele, genotypic mean and variance were evaluated per generation of offspring. Because each replicate population was an inbred line, parameters were averaged within lines. Genotypes of offspring were evaluated by masking operations. These operations compared two operands (chromosomes) bit by bit (locus by locus) and assigned either a zero or one at that location to two logical variables depending on the particular logical operation and bit structure. Operations and resulting bit values were:

Operands		Logical Operation	
B_1	B_2	B_1 .AND. B_2	B_1 .OR. B_2
1	1	1	1
1	0	0	1
0	1	0	1
0	0	0	0

B_1 and B_2 represent masking operands while .AND. and .OR. represent logical masking operators.

By this process each locus was identified as homozygous dominant (1,1), homozygous recessive (0,0), or heterozygous (0,1) or (1,0). Genotypic values were assigned to each locus according to the genotype of the locus and level of dominance. Genotypic values per locus were:

Genotype		Level of Dominance		
		Partial	Complete	Over
11	(*AA*)	10	8	6
10	(*Aa*)	7	8	9
01	(*aA*)	7	8	9
00	(*aa*)	0	0	0
Initial Mean (per locus)		6	6	6
Initial Variance (per locus)		13.5	12.0	13.5

Parameters of relationship were measured each generation for full-sibs, half-sibs, and non-sibs. All 48 pairs of full-sibs, 48 chosen at random from 432 possible pairs of half-sibs, and 48 chosen at random from 648 pairs of non-sibs were included in measuring genotypic covariances between individuals in respective sib groups.

Malécot (1948) gave a precise probabilistic definition to the concept of "alikeness by descent" or "identity by descent" and, thus, clarified inbreeding and relationship. Two alleles a and b, for example, are alike by descent if they are copies of a single allele in some previous generation or one is a copy of the other. The probability of a and b being alike by descent is $P\ (a = b)$. This probability is relative to some base population in which all alleles are unlike by descent.

An individual X has at a certain locus a genotype which may be represented as $A_{xd}\,A_{xs}$ where the subscripts indicate the origin of the alleles; A_{xs} was transmitted to X by its sire, and A_{xd} was obtained from the dam of X. The coefficient of inbreeding, F_x of individual X, is the probability that the two genes of X at a certain locus are alike by descent; i.e., $F_x = P\ (A_{xs} = A_{xd})$, where $A_{xs} = A_{xd}$ is "A_{xs} is like A_{xd} by descent". Malécot also defined the "coefficient de parenté" (r_{xy}) between individuals X and Y as the probability that a randomly chosen gene from Y at a given locus is by descent like a randomly chosen gene from X at the same locus. Where the genotype of Y is $A_{ys}A_{yd}$ and of X is $A_{xs}\,A_{xd}$, r_{xy} may be represented as:

$$r_{xy} = [(P\ (A_{xs} = A_{ys}) + P\ (A_{xs} = A_{yd}) + P\ (A_{xd} = A_{ys}) + P\ (A_{xd} = A_{yd})]/4\ .$$

The u_{xy} in the covariances between relatives in random mating populations (Kempthorne 1954, 1957) is defined by probabilities as:

$$u_{xy} = P\ (A_{xs} = A_{ys} \neq A_{xd} = A_{yd}) + P\ (A_{xs} = A_{yd} \neq A_{xd} = A_{ys})\ .$$

Harris (1964), in like manner, added four additional probabilities of alikeness by descent to r_{xy}, u_{xy}, F_x, F_y. These are:

$$s_{xy} = [P\ (A_{xs} = A_{xd} = A_{ys}) + P\ (A_{xs} = A_{xd} = A_{yd})]/2\ ,$$

$$s_{yx} = [P\ (A_{ys} = A_{yd} = A_{xs}) + P\ (A_{ys} = A_{yd} = A_{xd})]/2\ ,$$

$$t_{xy} = P\ (A_{xd} = A_{xs} = A_{yd} = A_{ys})\ , \quad \text{and}$$

$$v_{xy} = P\ (A_{xs} = A_{xd} \neq A_{ys} + A_{yd})\ .$$

s_{xy} is the probability that both genes of X by descent are like a randomly chosen gene of Y at a certain locus; s_{yx} is the probability that both genes of Y by descent are like a randomly chosen gene of X; t_{xy} is the probability that all four genes by descent are like each other; and v_{xy} is the probability that the two genes of X by descent are like each other, the two genes of Y by descent are like each other, but the genes of X are not like the genes of Y by descent. Also, t_{xy} equals t_{yx} and v_{xy} equals v_{yx}, but s_{xy} is not necessarily equal to s_{yx}.

Discussion of Results

The mean coefficients of inbreeding in generations 3, 8, 13, and 18 for each of the 28 combinations of selection, linkage, and dominance are in Tables 1 through 4. Averages are for the specified generation and the two preceding and two succeeding generations for three replications. Therefore, each result is the mean of 36,000 binomial events, each occurring at one locus in one individual. A sample analysis of variance of the mean coefficient of inbreeding is in Table 5.

Table 1. *Coefficients of inbreeding with probability 0.50 of recombination between adjacent loci*

Selection	Dominance	Generation 3	8	13	18
Random	Partial	.12	.31	.51	.64
	Complete	.12	.31	.49	.62
	Over	.10	.30	.45	.57
Genotypic	Partial	.16	.42	.65	.79
	Complete	.16	.46	.66	.75
	Over	.12	.33	.50	.59
Phenotypic	Partial	.13	.36	.52	.67
	Complete	.12	.37	.50	.64
	Over	.10	.33	.52	.64
Standard error*		±0.018	±0.031	±0.038	±0.036

* Standard error of each mean coefficient in that column.

Table 2. *Coefficients of inbreeding with probability 0.26 of recombination between adjacent loci*

Selection	Dominance	Generation 3	8	13	18
Random	Partial	.13	.33	.50	.63
	Complete	.09	.31	.46	.61
	Over	.14	.41	.55	.67
Genotypic	Partial	.15	.41	.62	.78
	Complete	.15	.45	.64	.79
	Over	.14	.38	.52	.60
Phenotypic	Partial	.12	.28	.48	.62
	Complete	.13	.41	.54	.67
	Over	.12	.32	.48	.60
Standard error*		±0.018	±0.031	±0.038	±0.036

* Standard error of each mean coefficient in that column.

Table 3. *Coefficients of inbreeding with probability 0.02 of recombination between adjacent loci*

Selection	Dominance	Generation 3	8	13	18
Random	Partial	.09	.35	.49	.65
	Complete	.09	.26	.51	.65
	Over	.09	.33	.44	.54
Genotypic	Partial	.21	.49	.71	.82
	Complete	.14	.38	.50	.55
	Over	.14	.35	.42	.48
Phenotypic	Partial	.11	.41	.59	.74
	Complete	.07	.32	.50	.66
	Over	.10	.29	.43	.51
Standard error*		±0.018	±0.031	±0.038	±0.036

* Standard error of each mean coefficient in that column.

Interaction of Selection with Dominance

The interaction of selection and dominance was prominent. Interaction of selection with the linear effect of dominance was the largest source of variation among orthogonal polynomial fractions. Populations affected by partial dominance achieved the highest inbreeding regardless of mode of selection (Table 4). Differences in inbreeding between populations with complete dominance or overdominance and those with partial dominance were largest when selection was on genotypic value, intermediate when selection was on phenotypic value, and negligible when individuals were selected at random.

Inbreeding should be proportional to the efficiency of selection because animals selected as parents should have more advantageous genes alike by descent when selection is efficient. Selection should locate less effectively animals with homozygous superior genes in populations affected by complete dominance than in populations affected less by dominance. When genes exhibit overdominance, heterozygous individuals have the highest merit; thus, selected individuals tend to be the least inbred in the population. Even when selection was under perfect heritability, the mean coefficient of inbreeding, averaged over all recombination rates, in populations affected by overdominance was less in the twentieth generation than for populations where selection was random.

Populations selected by phenotypic value at all levels of dominance had coefficients of inbreeding between those of populations selected by genotypic merit and at random. Efficient and inefficient selection are contrasted by populations affected by partial dominance and selected on genotypic value and populations selected on a phenotypic basis with complete dominance. Selection in the latter is less effective because of dominance and environmental variation.

Interaction of Linkage with Dominance

A large fraction of variation in inbreeding caused by the interaction of linkage and dominance was attributable to interaction of linear effects of each factor (see bottom section of Table 4). Over all modes of selection and all populations excepting those selected randomly and exhibiting overdominance, for a given degree of dominance, inbreeding was similar for the two higher rates of recombination ($\bar{r} = 0.50$ and $\bar{r} = 0.48$). However, among populations with partial dominance, populations with tight linkage were more inbred than those with less linkage and were more inbred than populations having complete dominance or overdominance. Populations exhibiting overdominance and selected by genotype had significantly lower inbreeding than other populations with the two higher recombination rates. The average restriction in inbreeding for tight linkage and complete dominance or overdominance was caused mostly by populations selected on genotypic values. For any degree of linkage, the average inbreeding was highest for populations with partial dominance, nearly as high for those with complete dominance, and lowest for those with overdominance. A non-significant exception was slightly higher inbreeding with complete dominance than with partial dominance when linkage was moderate ($\bar{r} = 0.48$); (Table 4).

Table 4. *Coefficients of inbreeding for combinations of selection, linkage, and dominance — 18th generation*

		Dominance			
Selection	Recombination	Partial	Complete	Over	Average
Random	0.50	.64[1]	.62	.57	.61[2]
	0.26	.63	.61	.67	.64
	0.02	.65	.65	.54	.61
	Average	.64[2]	.63	.59	.62[3]
Genotypic	0.50	.79	.75	.59	.71
	0.26	.78	.79	.60	.72
	0.02	.82	.55	.48	.62
	Average	.80	.70	.56	.69
Phenotypic	.50	.67	.64	.64	.65
	0.26	.62	.67	.60	.63
	0.02	.74	.66	.51	.64
	Average	.68	.66	.59	.64
2-way Averages	0.50	.70[2]	.67	.60	.66[3]
	0.26	.68	.69	.63	.67
	0.02	.74	.62	.51	.62
Main effect Averages		.71[3]	.66	.58	.65 ±0.007

[1] Standard error for 3-way subclass averages = ±0.036
[2] Standard error for 2-way averages = ±0.021
[3] Standard error for main effect averages = ±0.012

Table 5. *Analysis of variance of coefficients of inbreeding — 18th generation*

Source	d.f.	S.S.		F Ratio
Selection (S)	2	0.0602		7.8**
Dominance (D)	2	0.2221		28.8**
Linkage (L)	2	0.0302		3.9**
$S \times D$	4	0.0957		6.2**
$S \times D_{\text{Linear}}$	2		0.0950	12.2**
$S \times D_{\text{quadratic}}$	2		0.0007	<1.0
$S \times L$	4	0.0405		
$S \times L_{\text{Linear}}$	2		0.0351	4.5**
$S \times L_{\text{quadratic}}$	2		0.0055	<1.0
$D \times L$	4	0.0789		
$D \times L$ linear × linear	1		0.0669	17.3**
$D \times L$ linear × quadratic	1		0.0068	1.8
$D \times L$ quadratic × linear	1		0.0034	<1.0
$D \times L$ quadratic × quadratic	1		0.0018	<1.0
$S \times L \times D$	8	0.0630		2.00
Residual	54	0.2083		

** Significant at $P < 0.01$.
* Significant at $P < 0.05$.

Interaction of Selection with Linkage

Interaction of selection and linkage was primarily attributable to interaction of selection with the linear effect of linkage. The slowing of inbreeding by tight linkage was significant only when selection was effective (genotypic).

Interaction of Selection with Linkage and Dominance

Although the three-way interaction was statistically significant only at $P < 0.08$, differences between coefficients of inbreeding within populations selected for genotypic value, for various degrees of dominance, were sufficiently different to warrant comment. Tight linkage retarded rates of inbreeding for populations with complete dominance or overdominance but not in populations with partial dominance.

Tight linkage with intense selection should affect inbreeding in different ways with varying degrees of dominance. When genes act additively or nearly so, as with partial dominance, selected individuals should have more advantageous alleles for the trait than if genotypic values were affected by either complete or overdominance. But with tight linkage a genetically superior individual also will transmit to the following generation more unfavorable alleles than if recombination were not restricted. The unfavorable alleles will not be removed from the population as rapidly when linkage is tight as in free recombination. As a result, the finite size of population allows random sampling more opportunity to fix some of these undesirable alleles along with favorable ones. Tight linkage should also tend to limit increases in the frequencies of favored alleles unless overdominance is present.

Complete dominance and overdominance cause selection to favor heterozygous individuals as much or more than homozygotes. If recombination is hindered, the population will not recover as large a proportion of homozygotes in the next generation as if recombination were free. Thus, the increase of inbreeding in the populations is restricted for both complete dominance and overdominance.

Comparisons with Other Studies

Populations with partial dominance should have more fixation than populations with complete dominance or overdominance when recombination is restricted. The lack of a larger difference in this study might be attributed to deliberately mating less related animals then expected in random mating. When eight individuals were selected for parents, the first four were one sex, and the last four, the opposite sex. This caused pairs of full sibs 1—2, 2—3, 3—4, and 5—6, 6—7, 7—8 to be one sex and did not allow any individuals within a pair to be mated with the other in the same pair. If selection were efficient, as for partial dominance, then two individuals within a pair or within one sex would tend to be more related than two individuals of the eight chosen at random or than one from the one sex with any other of the other sex. This deviation could account for the lack of expected increase in fixation caused by tight linkage.

For random selection and selection on phenotype, linkage had little effect on fixation. Variances within combinations differed considerably. Populations with tight linkage and little or no directional selection varied considerably more in inbreeding than others. Average inbreeding within populations in which selection was random with linkage tight was largest for partial dominance and smallest for overdominance. For both random selection and selection on phenotypic value, populations with tight linkage were intermediate to the other two levels of recombination in amount of inbreeding. For both of these modes of selection the degree of linkage appeared to have little or no effect on inbreeding.

Wright (1951) showed that the fraction of a population that is heterozygous decreases each generation by a proportion which is approximately $[1/(2N)]$, where N is the size of the breeding population. The amount of heterozygosity is proportional to P or $(1 - F)$ for inbred populations derived from random mating populations where F is the coefficient of inbreeding. Wright (1951) called F the fixation index and P the panmictic index. For random mating with effective population size N, $F_t = [(1 + F_{t-2})/2N] + [1 - (1/N)]\ F_{t-1}$ and $P_t = [P_{t-2}/2N] + [1 - (1/N)]\ P_{t-1}$. After t generations of inbreeding the panmictic index would become (for moderately large N) approximately $P_t = P_0\, e^{-t/2N}$, as given by Malécot (1948). For the randomly selected parents, the effective size of the breeding population is eight. By Malécot's approximation, the expected values of F are 0.12, 0.35, 0.53, and 0.65 for generations 3, 8, 13, and 18 where the number of generations of inbreeding is one less than the number of a particular generation in this case. By Wright's recurrence relation, the corresponding expected values are 0.12, 0.34, 0.51, and 0.64. For random selection and free recombination the observed inbreeding values were consistently less than the values expected by Malécot's approximation, but the differences were not statistically significant. In the second generation the coefficient of inbreeding was slightly lower than expected (0.06). Since inbreeding is cumulative, the early discrepancy may have been responsible for results in later generations.

The effect of selection on inbreeding did not agree well with projected figures from Robertson's theory (1961). He showed that selection for a character with high heritability can cause important reduction in effective population size and, thus, increase inbreeding. However, Robertson specified that genes act additively, whereas all models in this study included dominance. Also, two-thirds of the populations had linkage, which was not considered in Robertson's theory. The effective number "N_e", which Robertson found to be a function of heritability and selection intensity, for perfect heritability (genotypic selection) was 3.5 in our study. For this value, Malécot's approximation gave an expected inbreeding of 0.91 for the 18th generation. The corresponding figure from Wright's equation was 0.90. The group of populations with partial dominance (selected on genotype) had inbreeding closer than others to the theoretical coefficient in the 18th generation (Table 4). Since gene action was not completely additive, one should not expect perfect agreement with theoretical figures. Also, parents were selected on genotype, and the first four selected were of one sex. Forcing relatives to be the same sex violated specifications in the derivation of the prediction formula.

Where environmental variation constituted three-fourths of the total phenotypic variation in the first generation (phenotypic selection), N_e was 4.3, and the expected inbreeding in the 18th generation was 0.86. The group selected on phenotype did not approach the theoretical F in the 18th generation as closely as the group selected on genotype. Part of the divergence of the group selected on phenotype can be explained by the decrease in heritability from reduced genotypic variance within the line after several generations of selection. Essentially, selection became less and less effective in this group; and as it did, selected individuals were not as closely related as they would have been if heritability had been constant.

Gill and Clemmer (1966) found a definite increase in inbreeding when there was tight linkage between adjacent loci, but our study does not show the same trend. They also reported that linkage and selection jointly caused an increase in inbreeding in early generations, an effect evident in this study only in later generations for populations with partial dominance and phenotypic selection.

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