# ATTAINMENT OF QUASI LINKAGE EQUILIBRIUM WHEN GENE FREQUENCIES ARE CHANGING BY NATURAL SELECTION

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RECENTLY, a number of papers on population genetics have been published treating the effect of linkage and epistasis on selection (LEWONTIN and KOJIMA 1960; BODMER and PARSONS 1962; PARSONS 1963; LEWONTIN 1964a,b; NEI 1964a,b; WRIGHT 1965; FELSENSTEIN 1965 and others). These papers mainly treat particular problems and little is yet known about the general principles governing linked gene systems in evolution. The problem of finding such principles might appear to be difficult, since the recent paper by MORAN (1964) seems to show that WRIGHT's conception of an "adaptive topography" is untenable, at least as it stands.

The main purpose of the present paper is to show that linked gene systems own a remarkable property of rapidly settling to a state which I would like to call quasi linkage equilibrium. This state is attained if gene frequencies are changing under loose linkage and relatively weak epistatic interactions. On the other hand, linkage disequilibrium may be built up indefinitely when linkage is tight, epistatic interactions are relatively strong and gene frequencies are changing toward fixation.

I would like to show further that for a genetic system evolving under quasi linkage equilibrium, both WRIGHT's conception of an "adaptive topography" and FISHER's fundamental theorem of natural selection indeed hold.

Throughout this paper I will consider a very large random mating population and assume that the fitnesses of individual genotypes are constant, though not necessarily the same. Furthermore, I will restrict my consideration to the case of two linked loci, each with a pair of alleles, $A_1$ and $A_2$ in the first locus and $B_1$ and $B_2$ in the second, leaving more complex cases to future investigations.

## *Haploid population*

Let us consider a population of a haploid organism and designate by $x$, $y$, $z$, and $u$ the respective frequencies of four genotypes, $A_1B_1$, $A_2B_1$, $A_1B_2$ and $A_2B_2$, in the population before selection. Their respective frequencies after the selection will be denoted by capital letters, $X$, $Y$, $Z$, and $U$. We will assume that meiosis follows immediately after fertilization, to form the next generation.

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If $w_o$, $w_a$, $w_b$ and $w_{ab}$ are respectively the fitnesses of these genotypes measured in selective values (= viabilities if there are no fertility differences), then

$$\left.\begin{aligned} X &= xw_o/\bar{w} \\ Y &= yw_a/\bar{w} \\ Z &= zw_b/\bar{w} \\ U &= uw_{ab}/\bar{w} \end{aligned}\right\} \text{after selection,} \tag{1}$$

and

$$\left.\begin{aligned} x' &= X - cD \\ y' &= Y + cD \\ z' &= Z + cD \\ u' &= U - cD \end{aligned}\right\} \text{ after recombination,} \tag{2}$$

where primed letters indicate values in the next generation. In the above formulae, $\bar{w}$ is the mean selective value of the population,

$$\bar{w} = w_o x + w_a y + w_b z + w_{ab} u, \tag{3}$$

$D$ is half the difference of the frequencies of the coupling and repulsion double heterozygotes after fertilization,

$$D = XU - YZ, \tag{4}$$

and $c$ is the recombination fraction between the two loci.

From (1) and (2), we have

$$\begin{aligned} \Delta x &= \frac{x(w_o - \bar{w})}{\bar{w}} - cD \\ \Delta y &= \frac{y(w_a - \bar{w})}{\bar{w}} + cD \\ \Delta z &= \frac{z(w_b - \bar{w})}{\bar{w}} + cD \\ \Delta u &= \frac{u(w_{ab} - \bar{w})}{\bar{w}} - cD \end{aligned} \tag{5}$$

where $\Delta$ is the finite difference operator with respect to time, measured by one generation as unit, so that $\Delta x = x' - x$, $\Delta y = y' - y$ etc.

Now, let us put

$$r = \frac{xu}{yz}, \tag{6}$$

$$R = \frac{XU}{YZ} = \left(\frac{w_o w_{ab}}{w_a w_b}\right) r \tag{7}$$

and consider the change of $\log r$ in one generation, assuming that changes in gene frequencies are going on.

Since

$$\Delta \log r = \Delta \log x - \Delta \log y - \Delta \log z + \Delta \log u,$$

we have, neglecting higher order terms,

$$\Delta \log r = \frac{\Delta x}{x} - \frac{\Delta y}{y} - \frac{\Delta z}{z} + \frac{\Delta u}{u}. \tag{8}$$

Then, using (5), we obtain

$$\bar{w}\Delta log\, r = (w_o - w_a - w_b + w_{ab}) - c\bar{w}D(\frac{1}{x}+\frac{1}{y}+\frac{1}{z}+\frac{1}{u}) \qquad (9)$$

$$= (w_o - w_a - w_b + w_{ab}) - c\bar{w}YZ(R-1)(\frac{1}{x}+\frac{1}{y}+\frac{1}{z}+\frac{1}{u})$$

or, noting (7), we have

$$\bar{w}\Delta log\, R = \varepsilon - cH(R-1)\ , \qquad (10)$$

where

$$\varepsilon = w_o - w_a - w_b + w_{ab} \qquad (11)$$

and

$$H = \bar{w}YZ\,(\frac{1}{x}+\frac{1}{y}+\frac{1}{z}+\frac{1}{u}). \qquad (12)$$

Let us consider the process of change in $R$ using equation 10. Without losing generality we can assume that $\varepsilon$ in the equation is non-negative, because if $\varepsilon$ is negative we may redefine $R^{-1}$ as $R$ and $-\varepsilon$ as $\varepsilon$ to carry out the same argument. Suppose that $R$ is less than unity, then the right side of (10) is positive and therefore *log R* will increase. When $R$ reaches unity, *log R* will increase roughly at the rate of $\varepsilon$ per generation if selection is mild. Thereafter, the rate of increase in *log R* will diminish, since the second term on the right side of (10) starts to produce negative contribution to $\Delta log\, R$. However, if the epistatic effect $\varepsilon$ is very much larger than the recombination fraction $c$, the right side of (10) may remain positive and $R$ will increase indefinitely. On the other hand, if $\varepsilon$ is much smaller than $c$, term $cH(R\text{-}1)$ will approach $\varepsilon$ quickly, with the result that an equilibrium state will soon be reached, where

$$\Delta log\, R = 0. \qquad (13)$$

This state is stable, because if $R$ starts from a value which is larger than its equilibrium value ($\hat{R}$), it will decrease until $R=\hat{R}$. Deviation of $R$ from $\hat{R}$ will be reduced roughly by fraction $c$ in each generation.

It should be noted here that (13) is an approximation, since $H$ in (10) is not strictly a constant. However, in such a state, the change in $R$ may be so slow that we may treat $R$ as practically constant even if gene frequencies are changing. I would like to call such state, quasi linkage equilibrium. Furthermore, if selection coefficients are small, the equilibrium value of $R$ is expected to be near unity, with the result that $H$ is roughly unity and we have

$$\varepsilon - c(R-1) = 0$$

or

$$\hat{R} = 1 + \varepsilon/c \qquad (14)$$

approximately.

Though the above arguments are based on the assumption of nonnegative $\varepsilon$, equation 14 holds also for negative $\varepsilon$ as long as $|\varepsilon| \ll c$.

In order to check the validity of the above arguments, an extensive numerical study using a high-speed computer has been carried out. Table 1 shows an example with $w_o = 1.0$, $w_a = w_b = 0.98$, $w_{ab} = 1.06$ and $c = 0.5$. Namely, the two

TABLE 1

*A numerical example showing some properties of the quasi linkage equilibrium. Selective values,* $w_0 = 1.00$, $w_a = w_b = 0.98$, $w_{ab} = 1.06$; *recombination fraction,* $c = 0.5$

| Generation $t$ | Percent chromosome frequency before selection $x\times10^2$ | $y(=z)\times10^2$ | $u\times10^2$ | Linkage disequilibrium $R$ | $D\times10^2$ | Change in population fitness $\Delta\bar{w}\times10^4$ | Additive and epistatic variances $V_A\times10^4$ | $V_{EP}\times10^4$ |
|---|---|---|---|---|---|---|---|---|
| 0 | 49.0000 | 21.0000 | 9.0000 | 1.10371 | 0.4419 | 2.63 | 0.42 | 4.41 |
| 5 | 47.8124 | 21.0096 | 10.1683 | 1.21565 | 0.9184 | 0.71 | 0.63 | 4.66 |
| 10 | 45.9617 | 21.4762 | 11.0860 | 1.21930 | 0.9752 | 0.81 | 0.80 | 4.88 |
| 20 | 41.5594 | 22.496 | 13.4485 | 1.21895 | 1.0662 | 1.30 | 1.29 | 5.34 |
| 40 | 29.5776 | 24.2446 | 21.9332 | 1.21811 | 1.2228 | 3.57 | 3.54 | 6.18 |
| 80 | 3.1992 | 14.0789 | 68.6430 | 1.22280 | 0.3955 | 10.77 | 11.07 | 2.13 |
| 100 | 0.2827 | 4.7859 | 90.1454 | 1.22814 | 0.0453 | 5.11 | 5.36 | 0.25 |
| 200 | 0.0000 | 0.0022 | 99.9955 | 1.23141 | 0.0000 | 0.00 | 0.00 | 0.00 |

loci are independent and either $A_2$ or $B_2$ alone decreases fitness by 2% but the two together increase fitness by 6%. The initial frequencies of $A_2$ and $B_2$ are each assumed to be 30% and also the initial frequencies of the four chromosomes are assumed to be in "linkage equilibrium" so that $x = 49\%$, $y = z = 21\%$ and $u = 9\%$ (i.e. $r = 1.0$ in the 0th generation). It may be seen from the table that quasi linkage equilibrium is reached after a few generations of random mating and then $R$ changes extremely slowly until it reaches the limiting value of 1.23141 . . . . The approximate value of $\hat{R}$ given by (14) is 1.20 because $\varepsilon = 1.0 - 0.98 - 0.98 + 1.06 = 0.1$ and $c = 0.5$. On the other hand, $D$ changes extensively throughout the process of selection.

Table 1 also shows another important property of quasi linkage equilibrium. Namely, the rate of change of population fitness ($\Delta\bar{w}$) is equal to the additive genetic variance ($V_A$), that is to say, the additive component of the total genotypic variance. This is again an approximation, but, as seen from the table, the agreement between these two quantities is close enough to rule out the existence of any appreciable contribution from epistatic variance ($V_{EP}$), except for the 0th generation for which $\Delta\bar{w} = V_A + \frac{1}{2} V_{EP}$ holds. This last relationship, however, is the result of artificially imposing "linkage equilibrium" ($r = 1.0$) where such an equilibrium can not be realized if the change in gene frequencies is kept going on due to natural selection.

The important property,

$$\Delta\bar{w} = V_A \tag{15}$$

at the state of quasi linkage equilibrium may be derived as follows: Since $\Delta log\, r = \Delta log\, R = 0$ in this state, we have, from equation 9,

$$\varepsilon - c\bar{w}DI = 0, \tag{16}$$

where $I = x^{-1} + y^{-1} + z^{-1} + u^{-1}$.

Thus

$$\begin{aligned}\Delta\bar{w} &= w_o\Delta x + w_a\Delta y + w_b\Delta z + w_{ab}\Delta u \\ &= \frac{1}{\bar{w}}(w_o{}^2 x + w_a{}^2 y + w_b{}^2 z + w_{ab}{}^2 u - \bar{w}^2) - cD\varepsilon \qquad \text{(using (5))}\end{aligned}$$

$$=(V_T - c\bar{w}D\varepsilon)/\bar{w}$$
$$=(V_T - \frac{\varepsilon^2}{I})/\bar{w} \qquad \text{(using (16))}$$
$$=(V_T - V_{EP})/\bar{w}$$

and therefore

$$\Delta\bar{w} = V_A/\bar{w}, \tag{17}$$

where $V_T$ is the total genotypic variance and $V_{EP}$ is the epistatic variance. The additive genetic variance $V_A=V_T-V_{EP}$ is the variance due to the additive effects of the genes (see Appendix I). Since we assume small selection coefficients, we may put $\bar{w}\approx 1$ and (15) follows from (17). It is interesting to note in the above derivation that the amount of linkage disequilibrium is such that the term $-c\bar{w}D\varepsilon$ exactly cancels out the epistatic component of variance in fitness. This means that however small the epistatic effect may be, the assumption of "linkage equilibrium" is inappropriate here.

In the above example, free recombination ($c=0.5$) was assumed, but for closer linkage, the approach to quasi linkage equilibrium may be slower. Table 2 gives an example with the recombination fraction, $c=0.2$ and selective values, $w_0=1.00$, $w_a=w_b=0.99$, $w_{ab}=1.02$, i.e., $A_2$ or $B_2$ singly reduces fitness by 1% but in combination they increase fitness by 2%. It is assumed that initial frequencies of $A_2$ and $B_2$ are respectively 0.25 and 0.20, and that the four chromosome types are in linkage equilibrium so that $x=0.60$, $y=0.20$, $z=0.15$ and $u=0.05$. The table shows that at generation 40, $\Delta\bar{w}$ and $V_A$ agree with the error of about 4%, while $V_{EP}$ is more than 100 times as large as $\Delta\bar{w}$. The error is reduced to about 2% in generation 200.

### *Diploid population*

The essential part of the foregoing argument can be extended to cover the diploid population, as I would like to show in this section.

Let us denote by $X_1$, $X_2$, $X_3$ and $X_4$ the frequencies of four chromosome types $A_1B_1$, $A_2B_1$, $A_1B_2$ and $A_2B_2$ immediately after fertilization. It may be convenient

TABLE 2

*An example similar to that of Table 1, but with closer linkage. Selective values,* $w_0 = 1.00$, $w_a=w_b = 0.99$, $w_{ab} = 1.02$; *recombination fraction,* $c = 0.2$

| Generation | Percent chromosome frequency before selection | | | | Linkage disequilibrium | Change in population fitness | Additive and epistatic variances | |
|---|---|---|---|---|---|---|---|---|
| $t$ | $x\times10^2$ | $y\times10^2$ | $z\times10^2$ | $u\times10^2$ | $R$ | $\Delta\bar{w}\times10^7$ | $V_A\times10^7$ | $V_{EP}\times10^7$ |
| 0 | 60.0000 | 20.0000 | 15.0000 | 5.0000 | 1.04 | 392.6 | 7.500 | 480.0 |
| 5 | 60.4542 | 19.5306 | 14.7174 | 5.2970 | 1.16 | 138.1 | 5.302 | 493.1 |
| 10 | 60.6582 | 19.2918 | 14.6605 | 5.3895 | 1.20 | 50.59 | 4.629 | 496.8 |
| 20 | 60.8672 | 19.0073 | 14.7211 | 5.4044 | 1.22 | 9.388 | 4.042 | 496.9 |
| 40 | 61.1902 | 18.5743 | 14.9044 | 5.3312 | 1.23 | 3.576 | 3.441 | 492.5 |
| 80 | 61.9243 | 17.8173 | 15.1281 | 5.1303 | 1.23 | 3.353 | 3.153 | 480.1 |
| 160 | 64.0225 | 16.4390 | 14.9974 | 4.5410 | 1.23 | 5.811 | 5.678 | 440.4 |
| 200 | 65.5113 | 15.7009 | 14.6467 | 4.1411 | 1.23 | 9.015 | 8.816 | 411.6 |

TABLE 3

*Designation of chromosome frequencies and selective values of genotypes*

| | | $X_1$ $A_1B_1$ | $X_2$ $A_2B_1$ | $X_3$ $A_1B_2$ | $X_4$ $A_2B_2$ |
|---|---|---|---|---|---|
| $X_1$ | $A_1B_1$ | $w_{11}$ | $w_{12}$ | $w_{13}$ | $w_{14}$ |
| $X_2$ | $A_2B_1$ | $w_{21}$ | $w_{22}$ | $w_{23}$ | $w_{24}$ |
| $X_3$ | $A_1B_2$ | $w_{31}$ | $w_{32}$ | $w_{33}$ | $w_{34}$ |
| $X_4$ | $A_2B_2$ | $w_{41}$ | $w_{42}$ | $w_{43}$ | $w_{44}$ |

to give these chromosomes the numbers 1, 2, 3 and 4 so that the frequency of chromosome $i$ is $X_i$ ($i$=1,2,3,4). We will designate by $w_{ij}$ the selective values of the genotype formed by the union of chromosomes $i$ and $j$ as shown in Table 3 ($i, j$=1, . . . , 4). As before, the recombination fraction between the two loci will be denoted by $c$. Then the amount of change in one generation of these chromosome frequencies may be given by the following set of equations.

$$\begin{aligned}
\Delta X_1 &= \frac{X_1(w_{1.} - \bar{w}) - cD_W}{\bar{w}} \\
\Delta X_2 &= \frac{X_2(w_{2.} - \bar{w}) + cD_W}{\bar{w}} \\
\Delta X_3 &= \frac{X_3(w_{3.} - \bar{w}) + cD_W}{\bar{w}} \\
\Delta X_4 &= \frac{X_4(w_{4.} - \bar{w}) - cD_W}{\bar{w}}
\end{aligned} \tag{18}$$

where $w_{i.}$ is the average selective value of chromosome $i$, ($i$=1, 2, 3, 4), that is

$$w_{i.} = \sum_{j=1}^{4} w_{ij} X_j, \tag{19}$$

$\bar{w}$ is the average selective value of the population

$$\bar{w} = \sum_{i=1}^{4} w_{i.} X_i = \sum_{i,j} w_{ij} X_i X_j \tag{20}$$

and

$$D_W = w_{14} X_1 X_4 - w_{23} X_2 X_3. \tag{21}$$

The above set of equations (18) is slightly more general than the one given by KIMURA (1956) but equivalent to that given by BODMER and PARSONS (1962). Since equations 18 are a natural extension of equations 5, we again let

$$R = \frac{X_1 X_4}{X_2 X_3} \tag{22}$$

and consider the rate of change of $log\ R$ per generation as in the case of the haploid population. This leads to

$$\bar{w}\Delta log\ R = \bar{\varepsilon} - cD_W(X_1^{-1} + X_2^{-1} + X_3^{-1} + X_4^{-1}) \tag{23}$$

or

$$\bar{w}\Delta log\ R = \bar{\varepsilon} - c(w_{14} R - w_{23})\left(\frac{X_1 + X_4}{R} + X_2 + X_3\right), \tag{23'}$$

TABLE 4

*A numerical example showing the attainment of quasi linkage equilibrium in a diploid population (completely recessive mutations). Selective values,* $w_{11}=w_{12}=w_{21}=w_{13}=w_{31}=w_{14}=w_{41}=w_{23}=w_{32}=1.00$, $w_{22}=w_{24}=w_{42}=0.99$, $w_{33}=w_{34}=w_{43}=0.985$, $w_{44}=1.02$; *Recombination fraction,* $c=0.5$

| Generation | Percent chromosome frequencies | | | | Linkage disequilibrium | Change in fitness | Additive and epistatic chromosomal variances | |
|---|---|---|---|---|---|---|---|---|
| $t$ | $X_1\times10^2$ | $X_2\times10^2$ | $X_3\times10^2$ | $X_4\times10^2$ | $R$ | $\Delta\bar{w}\times10^5$ | $V_{AC}\times10^5$ | $V_{EPC}\times10^5$ |
| 0 | 20.0000 | 20.0000 | 30.0000 | 30.0000 | 1.000000 | 2.926 | 0.726178 | 2.18700 |
| 10 | 20.1063 | 20.4041 | 29.1205 | 30.3691 | 1.02766 | 0.661 | 0.658748 | 2.24996 |
| 50 | 19.6403 | 22.3886 | 26.6847 | 31.2864 | 1.02852 | 0.455 | 0.452730 | 2.40233 |
| 100 | 18.5716 | 24.2562 | 24.3791 | 32.7932 | 1.02990 | 0.370 | 0.365753 | 2.61448 |
| 200 | 14.6145 | 25.9359 | 20.9553 | 38.4943 | 1.03511 | 0.933 | 0.914888 | 3.32151 |
| 300 | 7.2680 | 22.8986 | 16.2207 | 53.6127 | 1.04908 | 5.7138 | 5.64348 | 4.45057 |
| 400 | 0.5350 | 8.4571 | 5.0317 | 85.9762 | 1.08091 | 15.29 | 15.4166 | 1.36214 |
| 500 | 0.0018 | 0.6407 | 0.2544 | 99.1031 | 1.09538 | 1.68 | 1.71846 | 0.00709 |
| 1500 | 0.0000 | 0.0000 | 0.0000 | 100.0000 | 1.09642 | 0.00 | 0.00000 | 0.00000 |

where

$$\bar{\varepsilon} = w_{1.} - w_{2.} - w_{3.} + w_{4.} \tag{24}$$

is the epistatic effect involving four chromosome types.

Let us consider a situation in which gene frequencies are changing slowly under loose linkage and weak selection. We may see from equation 23′ that starting from an arbitrary positive value, $R$ will be adjusted quickly to attain the quasi linkage equilibrium, where

$$\Delta log\, R = 0 \tag{25}$$

or

$$R = \text{constant}. \tag{26}$$

Either of these is an approximation but seems to be good enough for practical purposes, though the accuracy might be less as compared with the haploid case, if $\bar{\varepsilon}$ does not behave nicely. A considerable number of numerical examples have been studied by computers and the results have shown that the assumption of quasi linkage equilibrium is satisfactory. Table 4 shows an example in which the two loci are independent ($c$=0.5) and both mutant alleles $A_2$ and $B_2$ are recessive. It is assumed that $A_2$, when homozygous, decreases fitness by 1%, and similarly, $B_2$ when homozygous, decreases fitness by 1.5%, while $A_2$ and $B_2$ in combination as double mutants increase fitness by 2%. In the 0th generation, frequencies of $A_2$ and $B_2$ are respectively 50% and 60%.

Also "linkage equilibrium" ($R$=1) is assumed between the two loci in the 0th generation so that $X_1$=0.2, $X_2$=0.2, $X_3$=0.3, $X_4$=0.3 at the start. The computation was carried out until generation 1,500. The quasi linkage equilibrium is attained in a few generations and then $R$ changes extremely slowly, as shown in the table. The table also reveals an important property of the quasi linkage equilibrium, i.e.

$$\Delta\bar{w} = V_{AC}, \tag{27}$$

where $V_{AC}$ is the additive chromosomal variance as defined in Appendix II. The

above relationship can be derived as follows: From equation 20, we have, neglecting higher order terms,

$$\Delta\bar{w} = 2\sum_{i=1}^{4} w_{i.}\,\Delta X_i. \tag{28}$$

Substituting (18) for $\Delta X_i$, we get

$$\Delta\bar{w} = \frac{2}{\bar{w}}\left[\sum_{i=1}^{4}(w_{i.}-\bar{w})^2 X_i - cD_W\bar{\varepsilon}\right]. \tag{29}$$

Now, from the assumption of quasi linkage equilibrium,

$$\bar{w}\Delta log\, R = \bar{\varepsilon} - cD_W(X_1^{-1} + X_2^{-1} + X_3^{-1} + X_4^{-1}) = 0, \quad \text{(cf. equation 23)}$$

and therefore

$$cD_W = \bar{\varepsilon}/J, \tag{30}$$

where $J = X_1^{-1} + X_2^{-1} + X_3^{-1} + X_4^{-1}$. From Appendix II,

$$V_{TC} = 2\sum_{i=1}^{4}(w_{i.}-\bar{w})^2 X_i, \tag{31}$$

$$V_{EPC} = 2\bar{\varepsilon}^2/J, \tag{32}$$

and

$$V_{AC} = V_{TC} - V_{EPC}. \tag{33}$$

Thus, substituting (30) in (29), and noting (31), (32) and (33), we get

$$\begin{aligned}\Delta\bar{w} &= \frac{2}{\bar{w}}\left[\sum_{i=1}^{4}(w_{i.}-\bar{w})^2 X_i - \bar{\varepsilon}^2/J\right] \\ &= (V_{TC} - V_{EPC})/\bar{w} \\ &= V_{AC}/\bar{w},\end{aligned} \tag{34}$$

or assuming that selection coefficients are small so that $\bar{w}$ is approximately unity, we obtain $\Delta\bar{w} = V_{AC}$, as was to be shown. I would like to point out here that the good agreement found in Table 4 at the 0th generation between $\Delta\bar{w}$ and the total chromosomal variance $(V_{AC} + V_{EPC})$ comes from the artificial assumption of "linkage equilibrium" $(R = 1)$. When gene frequencies are changing under natural selection, no "linkage equilibrium" could be attained if epistatic effects in fitness are involved. KOJIMA and KELLEHER (1961) studied the rate of change of mean fitness of a population in a similar situation to that studied in the present paper. They argued that the correction term (corresponding to our $-2cD_W\bar{\varepsilon}$ in equation 29) may make positive or negative contribution to the rate, with the result that when the number of loci involved gets large, correction factors would tend to cancel each other and the rate of change in fitness would become twice the marginal variance (corresponding to our $V_{TC}$). However, under quasi linkage equilibrium $-2cD_W\bar{\varepsilon}$ is just enough for cancelling out the epistatic component of $V_{TC}$. More generally, when gene frequencies are changing under natural selection $D_W$ and $\bar{\varepsilon}$ would tend to have the same sign and $-cD_W\bar{\varepsilon}$ to make a negative contribution to the rate of increase in fitness as suggested by the recent work of FELSENSTEIN (1965).

The attainment of quasi linkage equilibrium is not restricted to the case in which the gene frequencies are changing toward fixation. It can also be attained

TABLE 5

*A numerical example showing the attainment of quasi linkage equilibrium when overdominance is involved. Selective values,* $w_{11}=w_{22}=w_{33}=w_{44}=w_{23}=w_{32}=1.00$, $w_{12}=w_{21}=w_{13}=w_{31}=w_{24}=w_{42}=w_{34}=w_{43}=1.01$, $w_{14}=w_{41}=1.05$; *Recombination fraction,* $c=0.5$. *Chromosome frequencies at the 0 generation,* $X_1=0.6$, $X_2=X_3=0.0$, $X_4=0.4$

| Generation | Percent chromosome frequencies $X_2\times10^2=$ | | | Linkage disequilibrium | Change in fitness | Additive and epistatic chromosomal variances | |
|---|---|---|---|---|---|---|---|
| $t$ | $X_1\times10^2$ | $X_3\times10^2$ | $X_4\times10^2$ | $R$ | $\Delta\bar{w}\times10^5$ | $V_{AC}\times10^5$ | $V_{EPC}\times10^5$ |
| 1 | 47.4609 | 12.3047 | 27.9297 | 8.75510 | —319.76 | 2.24232 | 6.91295 |
| 5 | 35.9730 | 23.4166 | 17.1937 | 1.12797 | —17.30 | 0.599233 | 7.48018 |
| 10 | 34.9579 | 24.1481 | 16.7460 | 1.00390 | —0.04 | 0.502889 | 7.40367 |
| 20 | 34.3155 | 24.2625 | 17.1595 | 1.00029 | 0.43 | 0.445136 | 7.44652 |
| 30 | 33.7330 | 24.3458 | 17.5753 | 1.00025 | 0.39 | 0.395017 | 7.48770 |
| 40 | 33.1869 | 24.4200 | 17.9731 | 1.00022 | 0.34 | 0.352348 | 7.52441 |
| 50 | 32.6752 | 24.4860 | 18.3529 | 1.00020 | 0.30 | 0.313724 | 7.55707 |
| 60 | 32.1956 | 24.5446 | 18.7151 | 1.00018 | 0.27 | 0.272736 | 7.58614 |
| 70 | 31.7464 | 24.5967 | 19.0602 | 1.00016 | 0.24 | 0.252879 | 7.61195 |
| 80 | 31.3255 | 24.6429 | 19.3886 | 1.00014 | 0.22 | 0.221015 | 7.63488 |
| 90 | 30.9312 | 24.6840 | 19.7009 | 1.00012 | 0.19 | 0.197671 | 7.65524 |
| 99 | 30.5978 | 24.7169 | 19.9685 | 1.00011 | 0.18 | 0.175360 | 7.67159 |

when gene frequencies are changing toward intermediate equilibrium values, as shown in Table 5. In this example, overdominance is assumed.

A single heterozygote has 1% selective advantage; the double heterozygote has 5% advantage in the coupling phase, but none in the repulsion phase. The initial population (0th generation) is assumed to contain only two types of chromosomes, $A_1B_1$ and $A_2B_2$ with respective frequencies of 60% and 40% so that $R=\infty$ and $\bar{w}=1.024$. Also free recombination ($c=0.5$) is assumed. The table shows the process of change in the genetic constitution of the population for the succeeding 99 generations. Since the population starts from excess of the coupling phase and since only this phase is assumed to have selective advantage in double heterozygotes, the population fitness $\bar{w}$ decreases rather rapidly for the first few generations as shown in the table. However, the decrease stops at the 10th generation and then $\bar{w}$ starts to increase. By the 20th generation, quasi linkage equilibrium seems to have been established, as suggested by the good agreement between $\Delta\bar{w}$ and $V_{AC}$. Actually, change of $R$ is very slow from the 20th generation onward as the table shows.

It is important to note that the concept of quasi linkage equilibrium does not apply unless gene frequencies are changing. Change of chromosome frequencies alone is not enough. To show this, an example is given in Table 6, in which selective values and recombination fraction are exactly the same as in the above example (Table 5), but initial chromosome frequencies are $X_1=X_4=0.5$, $X_2=X_3=0.0$. In this example, there is no change in gene frequencies because they are equal to the equilibrium value of 0.5 from the start. Chromosome frequencies alone are changing and as the frequency of repulsion phase increases, the mean

TABLE 6

*An example in which the mean fitness of population* ($\bar{w}$) *is always decreasing*

| Generation $t$ | Percent chromosome frequencies $X_1\times10^2=X_4\times10^2$ | $X_2\times10^2=X_3\times10^2$ | Linkage disequilibrium $R$ | Change in fitness $\Delta\bar{w}\times10^5$ |
|---|---|---|---|---|
| 0 | 50.0000 | 0.0000 | $\infty$ | —735.51 |
| 1 | 37.1951 | 12.8049 | 8.43764 | —332.72 |
| 2 | 30.9918 | 19.0082 | 2.65836 | —157.35 |
| 4 | 26.4582 | 23.5418 | 1.26312 | —37.21 |
| 6 | 25.3561 | 24.6439 | 1.05864 | —9.03 |
| 8 | 25.0870 | 24.9130 | 1.01402 | —2.20 |
| 10 | 25.0213 | 24.9787 | 1.00341 | —0.54 |
| 12 | 25.0052 | 24.9948 | 1.00083 | —0.13 |
| 14 | 25.0013 | 24.9987 | 1.00020 | —0.03 |
| 16 | 25.0003 | 24.9997 | 1.00005 | —0.01 |
| 18 | 25.0001 | 24.9999 | 1.00001 | —0.00 |
| 20 | 25.0000 | 25.0000 | 1.00000 | —0.00 |

There is no change in gene frequencies, and therefore the concept of quasi linkage equilibrium is irrelevant in this case. Selective values and the recombination fractions are exactly the same as in Table 5, but the initial chromosome frequencies are $X_1=X_4=0.5$ and $X_2=X_3=0.0$.

fitness decreases until all the chromosome frequencies are in equilibrium. On the other hand, if we start from excess of the repulsion phase such as $X_1 = X_4 = 0.0$ and $X_2 = X_3 = 0.5$, the frequency of the coupling phase, and therefore the mean fitness of the population, would increase from generation to generation. Again, the concept of quasi linkage equilibrium is irrelevant because of no change in gene frequencies throughout the process.

Finally, I would like to show an example in which the recombination fraction is much smaller than the epistatic interaction and linkage disequilibrium is built

TABLE 7

*An example in which linkage disequilibrium is built up indefinitely. Selective values,* $w_{11}=w_{12}=w_{21}=w_{13}=w_{31}=w_{14}=w_{41}=w_{23}=w_{32}=1.0$, $w_{22}=w_{33}=w_{24}=w_{42}=w_{34}=w_{43}=0.95$, $w_{44}=1.10$; *Recombination fraction,* $c=0.01$

| Generation $t$ | Percent chromosome frequencies $X_2\times10^2=$ $X_1\times10^2$ | $X_3\times10^2$ | $X_4\times10^2$ | Linkage disequilibrium $R$ | Change in fitness $\Delta\bar{w}\times10^5$ | Additive, epistatic and total chromosomal variances $V_{AC}\times10^5$ | $V_{EPC}\times10^5$ | $V_{TC}\times10^5$ |
|---|---|---|---|---|---|---|---|---|
| 0 | 25.000 | 25.000 | 25.000 | 1.00 | 31.84 | 0.002 | 31.25 | 31.25 |
| 10 | 27.776 | 21.805 | 28.614 | 1.67 | 38.762 | 1.456 | 40.26 | 41.72 |
| 20 | 29.365 | 18.526 | 33.583 | 2.87 | 53.561 | 8.790 | 52.52 | 61.31 |
| 40 | 26.299 | 11.441 | 50.819 | $1.02\times10^1$ | 144.62 | 79.88 | 88.86 | 168.73 |
| 80 | 2.474 | 0.702 | 96.122 | $4.83\times10^2$ | 82.82 | 76.65 | 22.64 | 99.29 |
| 100 | 0.325 | 0.086 | 99.503 | $4.38\times10^3$ | 11.59 | 11.01 | 3.00 | 14.01 |
| 120 | 0.040 | 0.010 | 99.940 | $3.81\times10^4$ | 1.41 | 1.35 | 0.36 | 1.71 |
| 140 | 0.005 | 0.001 | 99.993 | $3.22\times10^5$ | 0.17 | 0.17 | 0.04 | 0.21 |
| 200 | 0.000 | 0.000 | 100.000 | $1.82\times10^8$ | 0.00 | 0.00 | 0.00 | 0.00 |
| 400 | 0.000 | 0.000 | 100.000 | $2.59\times10^{17}$ | 0.00 | 0.00 | 0.00 | 0.00 |
| 450 | 0.000 | 0.000 | 100.000 | $5.03\times10^{19}$ | 0.00 | 0.00 | 0.00 | 0.00 |

up indefinitely as time goes on so that quasi linkage equilibrium is not attained. This is shown in Table 7. In this case, both mutant genes $A_2$ and $B_2$ are recessive and each in single homozygote reduces fitness by 5% but in combination they increase fitness by 10% in double mutant homozygotes. A tight linkage with recombination fraction $c = 0.01$ is assumed. The value of $R$ which is unity at generation 0 reaches $5.03 \times 10^{19}$ at generation 450, and it will continue to increase indefinitely. Note here that $D$ tends to zero as $R$ tends to infinity. Throughout the process, $\Delta\bar{w}$ is roughly equal to the total chromosomal variance ($V_{TC}$) and neither $V_{AC}$ nor $V_{EPC}$ alone fails to give good approximation to $\Delta\bar{w}$. This is understandable, since the two loci may behave as if they were a single locus under tight linkage and relatively strong epistatic interaction.

## DISCUSSION

I hope that the above demonstrations are enough to show that *when gene frequencies are changing slowly* under loose linkage and relatively weak epistatic interaction, the state is quickly realized in which chromosome frequencies are changing in such a way that $R =$ constant, where $R$ is the ratio between the frequencies of coupling and repulsion phases, i.e., $R = (X_1X_4)/(X_2X_3)$. The state is termed quasi linkage equilibrium and though its formulation is an approximation, it seems to be good enough for practical purposes. It may be most useful in the treatment of cases in which two loci are segregating independently and selection coefficients are at most of the order of a few percents. The term "quasi linkage equilibrium" should not be confused with "quasi gene frequency equilibrium" used by BODMER and PARSONS (1962) to denote an equilibrium for which $D$ is small. Furthermore, it may be noted that a small $D$ is not necessarily equivalent to a small $(R - 1)$, as shown by the example in Table 7. Generally, $R$ is more sensitive to linkage disequilibrium than $D$ and less dependent on gene frequencies.

The assumption of quasi linkage equilibrium leads to some important conclusions. I have already shown one of them that is related to the rate of change in the mean fitness of the population. Namely,

$$\Delta\bar{w} = V_{AC}/\bar{w}, \tag{35}$$

as shown in (34). In this formula $V_{AC}$ is the additive chromosomal variance. For weak selection, $\bar{w}$ is near unity and we have $\Delta\bar{w} = V_{AC}$ as a good approximation. It might be thought here that the additive chromosomal variance contains, besides the genic (or additive genetic) variance $V_g$, some epistatic components of variance in fitness. However, as shown in Appendix III, $V_{AC}$ is exactly equal to $V_g$ under random matings, so that we have

$$\Delta\bar{w} = V_g/\bar{w}, \tag{36}$$

even if linkage disequilibrium is present.

For overlapping generations, fitness may be measured in Malthusian parameters and the corresponding formulation should be

$$d\bar{a}/dt = v_g, \tag{37}$$

where $\bar{a}$ is the mean fitness of the population and $v_g$ is the genic variance in fit-

ness. This means that FISHER's fundamental theorem of natural selection (cf. FISHER 1958) holds under quasi linkage equilibrium.

In one of my previous papers treating the change of population fitness by natural selection (KIMURA 1958), I attempted to resolve $d\bar{a}/dt$ into three components, one of which was $v_g$. I also suggested that the case of random mating with linkage may be approached by considering "additive chromosomal variance." At that time the remarkable property of quasi linkage equilibrium was not noticed and I could only carry out a formal analysis of the problem assuming general conditions.

Another important conclusion that follows from the assumption of quasi linkage equilibrium is that the direction of change in gene frequencies by natural selection is such that the mean fitness of the population is increased. This is derived from (35) noting that $V_{AG}$ is nonnegative and therefore

$$\Delta\bar{w} \geqq 0. \tag{38}$$

This result is significant, since it suggests that the stable equilibrium corresponds to the local maximum of $\bar{w}$ with respect to the change in gene frequencies. To be sure, one can find easily an example in which this inequality does not hold, when some unnatural value is artificially imposed upon $R$, as shown by the example in Table 5. In such an example, $R$ will change rapidly in a few generations, but as long as gene frequencies are changing, the quasi linkage equilibrium will soon be attained where (38) holds. Nature is simpler than some artificial examples suggest. MORAN (1964) gave an example in which $\bar{w}$ increases steadily from generation to generation until an equilibrium is reached if one starts from one set of chromosome frequencies, but decreases steadily toward the same equilibrium, if one starts from another set of chromosome frequencies. It turns out that in his example, only $R$ is changing and there is no change in gene frequencies. So the situation is exactly the same as explained by using the example of Table 6.

From his example, MORAN argues that WRIGHT's conception of an "adaptive topography" is not correct since populations do not in general tend to maximize their mean fitness if the latter is dependent on more than one locus. He also tries to show that stationary populations do not in general correspond to stationary values of $\bar{w}$ and that it is unlikely that equations giving equilibrium frequencies can be derived from any principle which maximizes a function of gametic frequencies.

I would like to assert that once the concept of quasi linkage equilibrium is introduced, the classical picture of adaptive topography remains to be useful for studying the change of gene frequencies in a population. For example, equilibrium chromosome frequencies can be derived by considering the stationary points of $\bar{w}$ and the stability of an equilibrium can be tested by seeing if $\bar{w}$ has a local maximum at the equilibrium point, *provided that the side condition of* R = *constant is imposed*, in addition to the ordinary condition that chromosome frequencies add up to unity.

However, a more exact specification of conditions under which quasi-linkage equilibrium holds in such a situation has to be worked out in future.

I would like to thank Dr. M. Nei for stimulating discussions during preparation of the manuscript.

SUMMARY

In a large random mating population, if gene frequencies are changing by natural selection, under loose linkage and relatively weak epistatic interactions, a state is quickly realized in which chromosome frequencies change in such a way that $R$ is kept constant, where $R$ is the ratio between the frequencies of coupling and repulsion phases. Such a state was termed *quasi linkage equilibrium*, and it was shown that several important conclusions follow from its formulation, namely: (1) The rate of change in the mean fitness of a population is equal to the additive genetic variance in fitness. So. Fisher's fundamental theorem holds. (2) The direction of change in gene frequencies by natural selection is such that the mean fitness is increased. (3) The stable equilibrium of gene frequencies corresponds to the local maximum of the mean fitness and Wright's classical picture of "adaptive topography" continues to be useful if the concept of quasi linkage equilibrium is taken into account.

In order to corroborate the above points, an extensive numerical study was carried out with the help of high speed computers and some of the results are presented.

APPENDIX I. *Analysis of variances in fitness with two segregating loci each with a pair of alleles in a haploid population*

Let $\alpha$ be the average effect of substituting $A_2$ for $A_1$ and let $\beta$ be that of substituting $B_2$ for $B_1$. If we designate fitnesses and frequencies of four genotypes as in Table A.1, additive values $w$, $\alpha$ and $\beta$ may be obtained by minimizing

$$Q = (w_o-w)^2x + (w_a-w-\alpha)^2y + (w_b-w-\beta)^2z + (w_{ab}-w-\alpha-\beta)^2u.$$

Thus, from $\partial Q/\partial w = \partial Q/\partial\alpha = \partial Q/\partial\beta = 0$, we obtain

$$(w_o-w)x = -(w_a-w-\alpha)y = -(w_b-w-\beta)z = (w_{ab}-w-\alpha-\beta)u \equiv K,$$

where

$$K = \varepsilon/I$$

in which $\varepsilon = w_o-w_a-w_b+w_{ab}$ and $I = x^{-1}+y^{-1}+z^{-1}+u^{-1}$. The epistatic variance ($V_{EP}$) is the sum of squares of deviations from additive approximation, i.e. the minimum value of $Q$:

$$V_{EP} = K^2x^{-1}+K^2y^{-1}+K^2z^{-1}+K^2u^{-1} = K^2I = \varepsilon^2/I.$$

The additive genetic variance ($V_A$) is the variance due to the additive values and can be shown to be equal to $V_T-V_{EP}$, where

$$V_T = w_o^2x+w_a^2y+w_b^2z+w_{ab}^2u-\bar{w}^2$$

is the total genotypic variance.

TABLE A.1

| Genotype | Fitness | Additive value | Frequency |
|---|---|---|---|
| $A_1B_1$ | $w_o$ | $w$ | $x$ |
| $A_2B_1$ | $w_a$ | $w+\alpha$ | $y$ |
| $A_1B_2$ | $w_b$ | $w+\beta$ | $z$ |
| $A_2B_2$ | $w_{ab}$ | $w+\alpha+\beta$ | $u$ |

TABLE A.2

| Chromosome | $(i)$ | Average value | Additive value | Frequency |
|---|---|---|---|---|
| $A_1B_1$ | (1) | $w_{1.}$ | $W$ | $X_1$ |
| $A_2B_1$ | (2) | $w_{2.}$ | $W+A$ | $X_2$ |
| $A_1B_2$ | (3) | $w_{3.}$ | $W+B$ | $X_3$ |
| $A_2B_2$ | (4) | $w_{4.}$ | $W+A+B$ | $X_4$ |

APPENDIX II. *Additive and epistatic chromosomal variances in a population of a diploid organism.*

Let $w_{i.}$ be the average selective value of chromosome $i$ as defined in (19), that is

$$w_{i.} = \sum_{j=1}^{4} w_{ij} X_j \qquad (i=1, \ldots, 4)$$

The total chromosomal variance, $V_{TC}$, may be defined as twice the variance due to $w_{i.}$'s, because each individual has two homologous chromosomes (considering only autosomes);

$$V_{TC} = 2 \sum_{i=1}^{4} (w_{i.}-\bar{w})^2 X_i.$$

In order to extract the additive component from this, let $W$, $A$, and $B$ be additive values as shown in Table A.2, and choose these parameters so that

$Q=X_1(w_{1.}-W)^2+X_2(w_{2.}-W-A)^2+X_3(w_{3.}-W-B)^2+X_4(w_{4.}-W-A-B)^2$

is minimized. From $\partial Q/\partial W = \partial Q/\partial A = \partial Q/\partial B = 0$, we obtain

$(w_{1.}-W)X_1 = -(w_{2.}-W-A)X_2 = -(w_{3.}-W-B)X_3 = (w_{4.}-W-A-B)X_4 \equiv K,$

where $K=\bar{\varepsilon}/J$

in which $\bar{\varepsilon}=w_{1.}-w_{2.}-w_{3.}+w_{4.}$ and $J=X_1^{-1}+X_2^{-1}+X_3^{-1}+X_4^{-1}$. Then it can be shown that the minimum value of $Q$ is

$$Q_m = \bar{\varepsilon}^2/J.$$

It can also be shown that, if we define the additive chromosomal variance, $V_{AC}$, as twice the variance due to the additive values, and the epistatic chromosomal variance as twice the minimum value of $Q$, then

$$V_{AC} = V_{TC} - V_{EPC},$$

where $V_{EPC} = 2\bar{\varepsilon}^2/J.$

Parameters $A$ and $B$ may be obtained by solving the following set of equations:

$$\begin{aligned} p_1p_2A + DB &= C_p \\ DA + q_1q_2B &= C_q, \end{aligned} \qquad \text{(A II.1)}$$

where $p_1$ and $p_2$ are frequencies of $A_1$ and $A_2$ in the first locus, $q_1$ and $q_2$ are those of $B_1$ and $B_2$ in the second locus and

$$\begin{aligned} C_p &= X_2(w_{2.}-\bar{w}) + X_4(w_{4.}-\bar{w}) \\ C_q &= X_3(w_{3.}-\bar{w}) + X_4(w_{4.}-\bar{w}) \end{aligned}$$

In terms of $A$ and $B$, the additive chromosomal variance is

$$V_{AC} = 2A^2p_1p_2 + 4ABD + 2B^2q_1q_2, \qquad \text{(A II.2)}$$

where $D = X_1X_4 - X_2X_3.$

APPENDIX III. *Proof that under random mating the additive component of the total chromosomal variance is equal to the genic or additive genetic variance.*

TABLE A.3

| Genotype | Fitness | Additive value | Frequency |
|---|---|---|---|
| $A_1B_1/A_1B_1$ | $w_{11}$ | $\omega$ | $X_1^2$ |
| $A_1B_1/A_2B_1$ | $w_{12}$ or $w_{21}$ | $\omega+\alpha$ | $2X_1X_2$ |
| $A_1B_1/A_1B_2$ | $w_{13}$ or $w_{31}$ | $\omega+\beta$ | $2X_1X_3$ |
| $A_1B_1/A_2B_2$ | $w_{14}$ or $w_{41}$ | $\omega+\alpha+\beta$ | $2X_1X_4$ |
| $A_2B_1/A_2B_1$ | $w_{22}$ | $\omega+2\alpha$ | $X_2^2$ |
| $A_2B_1/A_1B_2$ | $w_{23}$ or $w_{32}$ | $\omega+\alpha+\beta$ | $2X_2X_3$ |
| $A_2B_1/A_2B_2$ | $w_{24}$ or $w_{42}$ | $\omega+2\alpha+\beta$ | $2X_2X_4$ |
| $A_1B_2/A_1B_2$ | $w_{33}$ | $\omega+2\beta$ | $X_3^2$ |
| $A_1B_2/A_2B_2$ | $w_{34}$ or $w_{43}$ | $\omega+\alpha+2\beta$ | $2X_3X_4$ |
| $A_2B_2/A_2B_2$ | $w_{44}$ | $\omega+2\alpha+2\beta$ | $X_4^2$ |

Let $\alpha$ be the additive effect of substituting $A_2$ for $A_1$ and let $\beta$ be that of substituting $B_2$ for $B_1$ as shown in Table A.3. Parameters, $\omega$, $\alpha$ and $\beta$ are determined in such a way that the sum of squares of deviation from additive expectation is minimized. This leads to the following equations for $\alpha$ and $\beta$:

$$p_1p_2\alpha + D\beta = C_p$$
$$D\alpha + q_1q_2\beta = C_q, \qquad \text{(A III.1)}$$

where $p_1=X_1+X_3$, $p_2=X_2+X_4$, $q_1=X_1+X_2$, $q_2=X_3+X_4$, $D=X_1X_4-X_2X_3$, and

$$C_p = X_2(w_{2\cdot}-\bar{w}) + X_4(w_{4\cdot}-\bar{w})$$
$$C_q = X_3(w_{3\cdot}-\bar{w}) + X_4(w_{4\cdot}-\bar{w}).$$

The genic or additive genetic variance, denoted by $V_g$, is the sum of squares due to additive values, $\alpha$ and $\beta$. It can be shown that

$$V_g = 2\alpha^2p_1p_2 + 4\alpha\beta D + 2\beta^2q_1q_2 \qquad \text{(A III. 2)}$$

Comparison of A( III.1) with (A II.1) shows that $A=\alpha$ and $B=\beta$. Therefore, it is clear from the comparison of (A III.2) with (A II.2) that $V_{AC}=V_g$.

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