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Mathematical Frameworks for Phenotypical Selection and Epistasis

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A mathematical approach to interactions between genotypes and phenotypes in a multilocus multiallele population is developed. No *a priori* information on a fitness function is required. In particular, some structural definitions of epistasis and the position effect are given in terms of a decomposition of phenotypical structures. On this base a distance to the additive non-epistasis is introduced and an explicit formula for it is obtained. A class of phenotypical structures including multilocus dominance is described in terms of directed graphs. The evolutionary equations are adjusted to a fitness function compatible with a phenotypical structure. Some results on the finiteness of the equilibria set are presented.

1. General Notions

The concepts of genotype and phenotype are both fundamental in theoretical population genetics. Moreover, as it was emphasized by Lewontin (1974, Chapter 1), the phenotypical variables must be substantially taken into account in the dynamical theory of evolution. In Yablokov (1986) the *phenetics* is developed in a purely biological context. In the present communication we discuss an adequate mathematical design for the phenotypical selection and consider some related evolutionary problems. The most complicated mathematical proofs of some statements we quote can be found in Lyubich *et al.* (2001).

Let Z be the set of all zygote genotypes (*zygotes*, for short) in a multilocus multiallele population. A classical principle states that *the phenotypes of individuals are determined by their genotypes* (up to a statistical deviation we ignore here). Thus, there is a set Φ of phenotypes and a *genotype–phenotype mapping*, (*GP-map*) $\varphi : Z \to \Phi$, so that for any zygote $z \in Z$ its phenotype is $\varphi(z) \in \Phi$. We call the triple (Z, Φ, φ) the *phenotypical structure* of the population.

Given a phenotypical structure (Z, Φ, φ) and a phenotype $f \in \Phi$, the set of all z with phenotype f is called a *phenotypical class*. The set Z is the union of pairwise distinct phenotypical classes which form the *phenotypical partition* of Z. Later on we do not distinguish phenotypical structures with the same partition, i.e. *isomorphic* in this sense.

Any partition of Z determines the phenotypical structure for which Φ is the set of classes of the partition. Then for every zygote z the phenotype $\varphi(z)$ is the class containing z. This is an universal way of obtaining all phenotypical structures up to isomorphism.

Note that a similar abstract scheme is applicable to modern genomics with the DNA sequences as genotypes and the secondary RNA structures or the corresponding proteins

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as phenotypes (cf. Wright, 1968; Schuster *et al.*, 1994; Fontana & Shuster, 1998).

Let (Z, Φ, φ) and (Z, Ψ, ψ) be two phenotypical structures with the same zygote set Z. We say that (Z, Ψ, ψ) is *larger* than (Z, Φ, φ) or, equivalently, (Z, Φ, φ) is *finer* than (Z, Ψ, ψ), if every (Z, Ψ, ψ)-class is the union of some (Z, Φ, φ)-classes. In terms of *GP*-maps this means that there exists a mapping $\theta\Phi \to \Psi$ such that $\psi(z) = \theta(\varphi(z)), z \in Z$.

In the simplest situation all zygotes are of the same phenotype. We call such a phenotypical structure *neutral*. This structure is the largest one, i.e. this is the enlargement of every phenotypical structure with the same Z.

In the opposite situation the phenotypes of distinct zygotes are distinct. We call such a phenotypical structure *separative*. This structure is the finest one, i.e. this is the refinement of every phenotypical structure with the same Z.

2. One-locus Phenotypical Structures

Consider a diallele locus with alleles A and a. There are three zygotes AA, aa, $Aa \equiv aA$ and five phenotypical structures: (1) *neutral*: the only class is $\{AA, aa, Aa\}$; (2) *separative*: the classes are: $\{AA\}$, $\{aa\}$, $\{Aa\}$; (3) *numerical*: $\{AA, aa\}$, $\{Aa\}$ where the phenotypes can be identified with the numbers 1 or 2 of different alleles; (4) *Mendelian dominant*: $\{AA, Aa\}$, $\{aa\}$ or $\{AA\}$, $\{aa, Aa\}$.

In general, the alleles at a locus are $a_1, ..., a_m$ where $m \geqslant 2$. Then the zygotes are $a_i a_k \equiv a_k a_i$. Thus, the number of zygote genotypes is $m(m+1)/2$, namely, there are m homozygotes $a_i a_i$ and $m(m-1)/2$ heterozygotes $a_i a_k$ $i<k$. It is clear that the total number of phenotypical structures rapidly increases with the growth of m. Yet the number of phenotypical structures with just two phenotypes is equal to

$$2^{\frac{m(m+1)}{2}-1} - 1.$$

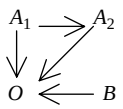
See Cotterman (1955) and Bennet (1957) for more information.

Fortunately, the most interesting phenotypical structures are rather special. In particular, some classical one-locus phenotypical structures are determined by *dominance*. We will describe this phenomenon in terms of a directed graph (the *dominance graph*) with vertices $a_1, ..., a_m$ and arcs $a_i \to a_k (i \neq k)$ meaning "a_i dominates a_k", i.e. the phenotypes of the heterozygote $a_i a_k$ and the homozygote $a_i a_i$ coincide. Let the homozygous phenotypes be pairwise distinct. Then the dominance graph turns out to be *antisymmetric*, i.e. $a_i \to a_k$ is incompatible with $a_k \to a_i$. In addition, if some a_i and a_k are *codominant* (i.e. a_i does not dominate a_k and a_k does not dominate a_i) then there are no arcs between a_i and a_k in both directions. The *completely codominant* situation is just the separative phenotypical structure.

For example, at the locus controlling the MN blood group system the genotypes MM, NN, MN are recognized by two antisera: anti-M and anti-N. In absence of anti-N the separative phenotypical structure effectively turns into the Mendelian dominant $\{MM, MN\}, \{NN\}$. The graph for the latter is $M \to N$. This observed phenotypical structure is larger than the hidden one which is observed in the presence of both antisera.

For the classical blood group system with three alleles A, B, O, the dominance graph is $A \to O \leftarrow B$, in particular, A and B are codominant. The corresponding phenotypical classes are $\{OO\}$, $\{AA, AO\}$, $\{BB, BO\}$, $\{AB\}$.

In fact, it is known that the allele A is a family of several alleles, for example, A_1 and A_2, where A_1 dominates A_2 (Li, 1976, Chapter 5, Section 10). The corresponding dominance graph is



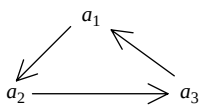
The phenotypes are {OO}, {A_1A_1, A_1A_2, A_1O}, {A_2A_2, A_2O}, {BB, BO}, {A_1B}, {A_2B}. By enlargement {OO}, {A_1A_1, A_1A_2, A_1O, A_2A_2, A_2O}, {BB, BO}, {A_1B, A_2B} and identification $A_1 \equiv A_2 (\equiv A)$ we return to the initial system.

Antisymmetry is a characteristic property of dominance graphs. Indeed, we can start with any directed antisymmetric graph D with vertices $a_1, ..., a_m$ and then we can recover the phenotypical structure the dominance graph of which is D. Namely, we attribute some pairwise distinct phenotypes f_i to the homozygotes $a_i a_i$ $1 \leqslant i \leqslant m$.

Then the same f_i becomes the phenotype of the heterozygote a_ia_k such that $a_i \to a_k$ in D. (There is no collision since D is antisymmetric.) In absence of arcs between a_i and a_k the heterozygote a_ia_k gets a specific phenotype $f_{ik} = f_{ki}$. ("Specific" means "different from all other phenotypes".)

The extreme situation arises if the graph D has no arcs at all (the *empty graph*). The corresponding phenotypical structure is separative.

For a directed graph D antisymmetry means that there are no oriented cycles of length 2 in D. If there are no oriented cycles at all, the graph is called *acyclic*, see Harary *et al.* (1965). In the following example an antisymmetric graph is not acyclic:



Actually, this is a cycle of length 3. Here we have a non-standard situation: a_1 dominates a_2 and a_2 dominates a_3 and, finally, a_3 dominates a_1. The corresponding phenotypical structure is $\{a_1a_1, a_1a_2\}$, $\{a_2a_2, a_2a_3\}$, $\{a_3a_3, a_3a_1\}$.

Obviously, the empty graph is acyclic. All the above-mentioned concrete dominance graphs are acyclic.

Actually, a directed (not necessary antisymmetric) graph G can be associated with an arbitrary phenotypical structure (Z, Φ, φ). Its vertices are $a_1, ..., a_m$, as before, and $a_i \to a_k (i \neq k)$ if and only if there exists a_j such that the phenotypes of zygotes a_ia_i and a_ja_k coincide, i.e. $\varphi(a_ja_k) = \varphi(a_ia_i)$. In the case of dominance $a_j = a_i$, therefore, $G = D$. For example, $A \leftrightarrow a$ for the neutral diallele structure while $A \to a$ or $a \to A$ for the diallele Mendelian dominant structure. For both separative and numerical structures the graphs are empty. It immediately follows from the above definition that *for any number m of alleles the graph G is empty if and only if the homozygous phenotypes are specific.* By the way, we see that the same graph can correspond to more than one phenotypical structure.

In general, the graph G describes those interactions between alleles which are immanent for the phenotypical structure. We call G the *graph of phenotypical heredity*. Two phenotypical structures with the same graph G should be determined by some additional factors other than the above-mentioned interactions.

We conclude this section with one more illustrative example. Consider a locus with three alleles a_1, a_2, a_3. The graph of the phenotypical structure

$$\{a_1a_1, a_2a_3\},\ \{a_2a_2\},\ \{a_3a_3\},\ \{a_1a_2, a_1a_3\}$$

is $a_2 \leftarrow a_1 \to a_3$. This is also the dominance graph coming from the phenotypical structure where a_1 dominates both a_2 and a_3 but a_2 and a_3 are codominant so, the classes are

$$\{a_1a_1, a_1a_2, a_1a_3\},\ \{a_2a_2\},\ \{a_3a_3\},\ \{a_2a_3\}.$$

An interpretation of the first phenotypical structure is: a_1a_2 and a_1a_3 are lethal while a_1a_1 and a_2a_3 survive.

3. Multilocus Phenotypical Structures

We use the following convenient mathematical description of multilocus genotypes (cf. Lyubich, 1992, Section 6.1). Let $L = \{1, \ldots, l\}$ be a set of autosomal loci with alleles a_{ik} at the i-th locus, $1 \leqslant i \leqslant l$, $1 \leqslant k \leqslant m_i$, $m_i \geqslant 2$. The gamete genotypes (*gametes*, for short) are commutative combinations of the form $g = a_{1k_1}, \ldots, a_{lk_l}$. Every pair of gametes (g, h) determines a zygote z. Conversely, for any zygote z the corresponding pair (g, h) is determined up to permutations of homologous chromosome. However, we will write $z = (g, h)$ for simplicity. In particular, the homozygotes are (h, h).

For each subset $U \subset L$ and for any gamete g the *subgamete* g_U is the combination of those genes from g which are situated in U. For any $U \subset L$ and $V = L \setminus U$ we have $g_U g_V = g$ (up to a reordering of the combined genes). The partitions $U|V$ correspond to all formally possible crossing-overs. The probability of a partition $U|V$ is denoted by $r(U|V)$, so that

$$r(U|V) \geqslant 0,\ \sum_{U|V} r(U|V) = 1.$$

(In real populations most of the crossing-overs have very small probabilities.)

Under the crossing-over $U|V$ a zygote $z = (g, h)$ produces the recombinant gametes $g_U h_V$

and $h_U g_V$ with equal probabilities $r(U|V)/2$. The probabilities $r(U|V)$ form the *linkage distribution*. This distribution must be consistent with independent segregation of homologous chromosomes in meiosis, see Lyubich, (1992, Section 6.1) for an adequate mathematical formulation. The subset of loci which belong to the same chromosome is called a *linkage group*. The linkage groups form the *chromosomal partition* of the loci set L.

The set Z of all zygotes provided with a linkage distribution $r = \{r(U/V)\}$ is what we call the *genotypical structure* of the population. A phenotypical structure (Z, Φ, φ) is a superstructure over (Z, r). In what follows the probabilities $r(U|V)$ do not explicitly enter the picture before the evolutionary equations appear (Section 6). However, the presence/absence of linkage is significant since without this information the zygote genotypes are not well determined.

Some multilocus phenotypical structures are in a sense the products of structures with lesser numbers of loci. Consider a partition $L_1|L_2$ of the loci set L and assume that three phenotypical structures $(Z_{L_1}, \Phi_1, \varphi_1)$, $(Z_{L_2}, \Phi_2, \varphi_2)$ and (Z, Φ, φ) are given for the loci sets L_1, L_2 and L, respectively. Consider the Cartesian product $\Phi_1 \times \Phi_2$ of the phenotype sets i.e. the set of all ordered pairs (f_1, f_2) where $f_1 \in \Phi_1$ and $f_2 \in \Phi_2$. Let there exist a bijective mapping $\theta : \Phi_1 \times \Phi_2 \to \Phi$ such that

$$\varphi(g, h) = \theta(\varphi_1(g_{L_1}, h_{L_1}), \varphi_2(g_{L_2}, h_{L_2}))$$

for all zygotes $z = (g, h)$. Then we say that the phenotypical structure (Z, Φ, φ) is *decomposable with the constituents* $(Z_{L_1}, \Phi_1, \varphi_1)$ and $(Z_{L_2}, \Phi_2, \varphi_2)$. This definition means that the classes of zygotes relating to the whole loci set L are in a 1–1 correspondence with the pairs of classes relating to L_1 and L_2. Hence, $n = n_1 n_2$ where n, n_1, n_2 are the number of classes for L, L_1, L_2 respectively.

If $\Phi = \Phi_1 \times \Phi_2$ and θ is the identity mapping then (Z, Φ, φ) is called the *direct product* of $(Z_{L_1}, \Phi_1, \varphi_1)$ and $(Z_{L_2}, \Phi_2, \varphi_2)$,

$$(Z, \Phi, \varphi) = (Z_{L_1}, \Phi_1, \varphi_1) \times (Z_{L_2}, \Phi_2, \varphi_2).$$

Any decomposable phenotypical structure is isomorphic to a direct product.

The decomposability with more than two constituents can be defined quite similarly. We say that the phenotypical structure is *completely decomposable* if it is decomposable with one-locus constituents. In this case the *GP*-map can be treated as a result of independently acting one-locus *GP*-maps.

A completely decomposable phenotypical structure whose constituents are determined by some dominance graphs can be called *multilocus dominant*. For instance, so is the multilocus Mendelian dominant structure, the direct product of one-locus ones.

Below in this section we focus on the two-locus diallele situation where the above introduced general concepts become especially clear. Let the alleles be A and a at the first locus and B and b at the second one. Then the two-locus genotypes are the homozygotes

$$AABB,\ AAbb,\ aaBB,\ aabb \tag{1}$$

and the simple heterozygotes

$$AaBB, Aabb, AABb, aaBb \tag{2}$$

and, finally, the double heterozygotes

$$AaBb, AabB. \tag{3}$$

If the loci are unlinked then the double heterozygote genotypes coincide and then the total number of genotypes is equal to nine instead of ten in the case of linked loci.

Obviously, *the neutral two-locus phenotypical structure is decomposable* with neutral one-locus constituents.

The separative two-locus structure with unlinked loci is decomposable with separative one-locus constituents, according to the decomposition $9 = 3 \times 3$. For instance, the class $\{AaBb\}$ corresponds to the pair of classes $\{Aa\}$ and $\{Bb\}$.

The separative structure with linked loci is indecomposable, otherwise, a one-locus constituent would consist of at least 5 classes. Indeed, there are no decompositions of the number 10 other than $10 = 2 \times 5 = 1 \times 10$. However, the maximal number of one-locus classes with two alleles is $3 < 5$.

We see that the decomposability depends on linkage.

A realistic example we describe in our terms is the *MNS* blood group system. According to Li (1976, Chapter 5, Section 11) there are the alleles M, N at the first locus and S, s at the second one, the loci are linked. With four antisera against M, N, S and s one can detect all genotypical differences except for the double heterozygotes. Thus, the phenotypical structure corresponding to this experimental situation consists of 9 classes: $\{MMSS\}$, $\{MMSs\}$, $\{MMss\}$, $\{NNSS\}$, $\{NNSs\}$, $\{NNss\}$, $\{MNSS\}$, $\{MNss\}$, $\{MNSs, MNsS\}$. This structure is decomposable with separative constituents but it is not separative *per se*.

If there are three antisera against M, N, S but the anti-s is not available, then the phenotypes are $\{MMSS, MMSs\}$, $\{MMss\}$, $\{NNSS, NNSs\}$, $\{NNss\}$, $\{MNSS, MNSs, MNsS\}$, $\{MNss\}$. This structure is decomposable with the separative constituent at the first locus and the Mendelian dominant at the second one (according to the decomposition $6 = 3 \times 2$). Thus, the structure is two-locus dominant.

If a phenotypical structure is decomposable with respect to a partition $L = L_1|L_2$, we say that *there is no descriptive epistasis* between the loci groups L_1 and L_2. The completely decomposable phenotypical structure can be considered as a *descriptively nonepistatic* one. In Section 5 we introduce a quantitative (metrical) characterization of the epistasis. See Wagner *et al.* (1998) for a different approach to this problem.

The position effect can also be treated in terms of decomposability. The *absence of the position effect* means that the allele transpositions at each locus do not affect the phenotypes. In this case the phenotype only depends on the set of genes situated in the homologous chromosomes irrespective of how the genes are distributed between the chromosomes. For instance, in the separative two-locus structure there is no position effect if the loci are unlinked loci in contrast to the case of linked loci.

Proposition 1. *There is no position effect in a phenotypical structure if and only if it is an enlargement of the decomposable phenotypical structure with one-locus separative constituents.*

Proof. The "if" part immediately follows from the definitions. Now let (Z, Φ, φ) be a direct product of one-locus separative structures and let (Z, Ψ, ψ) be a phenotypical structure with no position effect. Then, if $\varphi(g, h) = \varphi(g', h')$ then the one-locus subgametes $g_i \leftrightarrow h_i$ and $g_i' \leftrightarrow h_i'$ coincide up to the transpositions $g_i \leftrightarrow h_i, g_i' \leftrightarrow h_i'$ $(1 \leqslant i \leqslant l)$.

The latter do not change the phenotypes $\psi(g, h)$ and $\psi(g', h')$, respectively. Hence, $\psi(g, h) = \psi(g', h')$. We have proved that $\psi(z)$ is a function of $\varphi(z)$. □

It is interesting that a phenotypical structure with no position effect can be descriptively epistatic (indecomposable). An example of this is the two-locus *numerical* phenotypical structure

$$\{AABB, AAbb, aaBB, aabb\},$$

$$\{AaBB, Aabb, AABb, aaBb\}, \{AaBb, AabB\}. \quad (4)$$

If it were decomposable then one of the constituents would be neutral while the other is separative (according to the only decomposition $3 = 1 \times 3$). This contradicts eqn (4).

Returning to the multilocus theory we generalize the notion of the *graph of phenotypical heredity*. Let (Z, Φ, φ) be a phenotypical structure. For some different gametes g, h we write $h \to g$ if g is produced by a zygote $\zeta = (\chi, \gamma)$ of the same phenotype as the homozygote (h, h). More formally, there is a (χ, γ) and a crossing-over $U|V$ such that $g = \chi_U \gamma_V$ and $\varphi(\chi, \gamma) = \varphi(h, h)$. It remains to identify the gametes with the vertices of a directed graph G where the arcs $h \to g$ are as above.

A phenotypical structure (Z, Φ, φ) is called *acyclic* if its graph G is acyclic. In particular, *a phenotypical structure is acyclic if the homozygous phenotypes are specific* (the case of the empty graph). *A fortiori*, all separative phenotypical structures are acyclic. In contrast, any neutral phenotypical structure is not acyclic.

Note that *if a phenotypical structure is acyclic then the homozygous phenotypes are pairwise distinct*. Indeed, if $\varphi(g, g) = \varphi(h, h)$ then $h \to g$ and $g \to h$ by definition, so that a cycle of length 2 appears.

It is easy to see that *any decomposable phenotypical structure with acyclic constituents is acyclic.*

4. Fitness Functions

Denote by R_+ the set of nonnegative real numbers. Let Z be the set of all zygotes in a multilocus multiallele population. A fitness function λ of the population is a mapping $Z \to R_+$. The value $\lambda(z)$ is the fitness of the zygote z. At least one of these values must be different from zero. We suppose that *given a phenotypical structure* (Z, Φ, φ)*, the fitness* $\lambda(z)$ *only depends on phenotype* $\varphi(z)$. In other words,

$$\lambda(z) = \Lambda(\varphi(z)), \tag{5}$$

where Λ is a mapping from Φ into R_+. For example, in the case of diallele Mendelian dominance we have $\lambda(AA) = \lambda(Aa) = \Lambda(\{AA, Aa\})$ and $\lambda(aa) = \Lambda(\{aa\})$.

In the neutral phenotypical structure all zygotes have the same fitness, $\lambda(z) = \text{const}$.

For any phenotype f the value $\Lambda(f)$ is called its *fitness.* Let n be the total number of phenotypes. The n-tuple $(\Lambda(f) : f \in \Phi)$ is called the *phenotype fitness vector.* The *phenotype fitness space* is the set of all fitness vectors, i.e. it is the set $\mathbf{R}_+^n$ of all non-zero n-tuples with nonnegative components.

The fitness of the phenotypes is a substantial factor in the evolutionary equations we consider below. These equations are invariant with respect to the multiplication of all values $\lambda(z)$ by the same constant. This allows us to identify all proportional fitness vectors. One of them can be chosen as a representative of all of them. A normalization, say $\Sigma\{\Lambda(f) : f \in \Phi\} = 1$, is a way to specify a standard representative.

Under assumption (5) the phenotypical structure (Z, Φ, φ) is called λ-*compatible* and also λ is called (Z, Φ, φ)-*compatible*. For instance, any fitness function is compatible with the separative phenotypical structure but the latter is too fine, in general. The largest λ-compatible phenotypical structure is such that the zygotes z and ζ are of the same phenotype if and only if $\lambda(z) = \lambda(\zeta)$. This phenotypical structure is uniquely determined by the fitness function which allows us to say that the largest λ-compatible phenotypical structure is λ-*determined.* For example, at a single locus with alleles A and a such that $\lambda(AA) = \lambda(Aa) \neq \lambda(aa)$ the Mendelian dominant phenotypical structure is λ-determined. However, if $\lambda(AA) = \lambda(Aa) = \lambda(aa)$ then the λ-determined phenotypical structure is neutral.

The fitness function plays a subordinate role with respect to a phenotypical structure. Moreover, the exact (or well approximated) fitness function is usually unknown (Wright, 1968; Lewontin, 1974). In this situation it is especially important to develop some structural approaches (cf. Lyubich *et al.*, 2001; Stadler *et al.*, 2001). Below we follow this way.

As before, let the loci be $1, \ldots, l$. Given a function $P : \mathbf{R}_+^n \to \mathbf{R}_+$, a multilocus fitness function λ is called *P-decomposed* if

$$\lambda(z) = P(\lambda^{(1)}(z_1), \ldots, \lambda^{(l)}(z_l)), \tag{6}$$

where z_i is the genotype of z at the i-th locus provided with a fitness function $\lambda^{(i)}, 1 \leqslant i \leqslant l$. The most popular examples are: the *additive selection*

$$\lambda(z) = \lambda^{(1)}(z_1) + \cdots + \lambda^{(l)}(z_l), \tag{7}$$

and the *multiplicative selection*

$$\lambda(z) = \lambda^{(1)}(z_1) \ldots \lambda^{(l)}(z_l). \tag{8}$$

The latter is a particular case of the *monomial selection* which we introduce as

$$\lambda(z) = [\lambda^{(1)}(z_1)]^{v_1} \ldots [\lambda^{(l)}(z_l)]^{v_l}, \tag{9}$$

where v_k are positive integers.

In Karlin (1979) a "mixture" of additive and multiplicative selection was introduced and called the *generalized non-epistatic selection*. This is

$$\lambda(z) = \sum_{U \subset L} c(U) \prod_{k \in U} \lambda^{(k)}(z_k), \tag{10}$$

where $c(U)$ are some nonnegative coefficients, at least one of which is positive. For $c(U) = \delta_{|U|,1}$ or $c(U) = \delta_{U,L}$ formula (10) turns into the additive or multiplicative selection respectively. (Here we use the standard Kronecker's symbol: $\delta_{x,y} = 0$ for $x \neq y$, otherwise, $\delta_{x,y} = 1$.)

Proposition 2. *Let a l-locus phenotypical structure be descriptively non-epistatic. Suppose that a fitness function* $\lambda(z)$ *is P-decomposed where*

$\lambda^{(1)}(z_1), \ldots, \lambda^{(l)}(z_l)$ are compatible with the corresponding one-locus constituents. Then this structure is λ-compatible.

Thus, our structural definition of non-epistasis is consistent with the quantitative version (6), in particular, with eqns (7)–(10).

Proof. Suppose that two zygotes z and z' are of the same phenotype in the given descriptively non-epistatic ($\equiv$ completely decomposable) phenotypical structure:

$$\varphi_k(z_k) = \varphi_k(z'_k), \quad 1 \leqslant k \leqslant l,$$

where φ_k are the one-locus GP-maps. Since the one-locus constituents are $\lambda^{(k)}$-compatible, we have

$$\lambda^{(k)}(z_k) = \lambda^{(k)}(z'_k), \quad 1 \leqslant k \leqslant l.$$

Hence, $\lambda(z) = \lambda(z')$ by eqn (6). □

In particular, the additive selection is compatible with any descriptively non-epistatic phenotypical structure if its summands are compatible with the one-locus constituents. Traditionally, the additive selection is a standard pattern for the "quantitative non-epistasis" expressed in terms of fitness function, see e.g. Moran (1965, Section 9). Here we propose to *measure the epistasis by the Euclidean distance of a fitness vector from the manifold of additive fitness vectors*. We call this the *epistatic distance*. This distance is automatically zero for the additive selection. All fitness vectors (functions) under consideration are supposed to be compatible with an *a priori* given descriptively non-epistatic phenotypical structure.

In the next section we explicitly determine the epistatic distance for any decomposable two-locus phenotypical structure.

In principle, any P-decomposed fitness function can be chosen as a pattern for a quantitative non-epistasis. However, in order to find the corresponding epistatic distance some difficult nonlinear problems have to be solved. Nevertheless, the "multiplicative" epistasis distance can be found in a structurally simple situation, see Appendix B.

5. The Epistatic Metric

Let us start with the two-locus Mendelian dominant structure. Let the alleles be A, a and B, b at the first and at the second locus, respectively. This is the direct product of one-locus Mendelian dominant structures. For the classes

$$\{AABB, AABb, AaBB, AaBb\},$$

$$\{AAbb, Aabb\}, \ \{aaBB, aaBb\}, \ \{aabb\} \qquad (11)$$

the additive fitness values are $\alpha + \gamma$, $\alpha + \delta$, $\beta + \gamma$, $\beta + \delta$ where

$$\alpha = \lambda^{(1)}(AA) = \lambda^{(1)}(Aa), \ \beta = \lambda^{(1)}(aa)$$

and

$$\gamma = \lambda^{(2)}(BB) = \lambda^{(2)}(Bb), \ \delta = \lambda^{(2)}(bb).$$

The whole fitness space corresponding to the phenotypical structure (11) consists of all non-negative non-zero 4-dimensional vectors $\lambda = (\lambda_1, \lambda_2, \lambda_3, \lambda_4)$. The manifold $\mathscr{A}$ of additive fitness vectors is the intersection of $\mathbf{R}^4_+$ with the *additive subspace* $\tilde{\mathscr{A}}$ the equation of which is

$$\lambda_1 - \lambda_2 - \lambda_3 + \lambda_4 = 0,$$

so that $\tilde{\mathscr{A}}$ is a hyperplane.

The *epistatic distance d in the two-locus Mendelian dominant structure is the Euclidian distance from* $\lambda \in \mathbf{R}^4_+$ to $\mathscr{A}$,

$$d = \mathrm{dist}(\lambda, \mathscr{A}).$$

Since $\mathscr{A} \subset \tilde{\mathscr{A}}$ we have the lower bound

$$d \geqslant \mathrm{dist}(\boldsymbol{\lambda}, \tilde{\mathscr{A}}). \qquad (12)$$

The hyperplane $\tilde{\mathscr{A}}$ consists of all vectors λ which are orthogonal to the vector $v = \frac{1}{2}(1, -1, -1, 1)$. The latter is normalized, $||v|| = 1$. Hence,

$$\mathrm{dist}(\boldsymbol{\lambda}, \tilde{\mathscr{A}}) = |\rho|,$$

$$\rho \equiv (\boldsymbol{\lambda}, \mathbf{v}) = (\lambda_1 - \lambda_2 - \lambda_3 + \lambda_4), \qquad (13)$$

where $(\boldsymbol{\lambda}, \boldsymbol{v})$ is the standard inner product. By the way, the *oriented distance* ρ distinguishes the *superadditive* selection ($\rho > 0$) from the *subadditive* one ($\rho < 0$).

It is easy to prove that inequality (12) turns into equality, i.e.

$$d = \mathrm{dist}(\lambda, \tilde{\mathscr{A}}), \tag{14}$$

if the constraints

$$-4\min(\lambda_1, \lambda_4) \leqslant \lambda_1 - \lambda_2 - \lambda_3 + \lambda_4 \leqslant 4\min(\lambda_2, \lambda_3) \tag{15}$$

are satisfied.

Let us consider the separative phenotypical structure corresponding to a pair of unlinked diallele loci. Here the result turns out to be more complicated than above, the fitness vectors are 9-dimensional, say $\lambda = (\lambda_k)_1^9$, where the components $\lambda_1, \ldots, \lambda_9$ are enumerated according to the list of genotypes (1)–(3) with $AabB \equiv AaBb$.

Now the additive subspace $\tilde{\mathscr{A}}$ is described by the system of equations

$$\lambda_1 - \lambda_2 - \lambda_3 + \lambda_4 = 0, \lambda_1 - \lambda_2 - \lambda_5 + \lambda_6 = 0,$$
$$\lambda_1 - \lambda_3 - \lambda_7 + \lambda_8 = 0, \lambda_1 - \lambda_5 - \lambda_7 + \lambda_9 = 0. \tag{16}$$

Indeed, let the one-locus fitness values be $\alpha_1, \alpha_2, \alpha_3$ for *AA, aa, Aa*, respectively and $\beta_1, \beta_2, \beta_3$ for *BB*, *bb*, *Bb*. The additive two-locus values are $\lambda_1 = \alpha_1 + \beta_1, \lambda_2 = \alpha_1 + \beta_2, \lambda_3 = \alpha_2 + \beta_1, \lambda_4 = \alpha_2 + \beta_2, \lambda_5 = \alpha_3 + \beta_1, \lambda_6 = \alpha_3 + \beta_2, \lambda_7 = \alpha_1 + \beta_3, \lambda_8 = \alpha_2 + \beta_3, \lambda_9 = \alpha_3 + \beta_3$.

Let us introduce the oriented distances to hyperplanes (16), namely,

$$\rho_1 = \tfrac{1}{2}(\lambda_1 - \lambda_2 - \lambda_3 + \lambda_4),$$
$$\rho_2 = \tfrac{1}{2}(\lambda_1 - \lambda_2 - \lambda_5 + \lambda_6) \tag{17}$$

and

$$\rho_3 = \tfrac{1}{2}(\lambda_1 - \lambda_3 - \lambda_7 + \lambda_8),$$
$$\rho_4 = \tfrac{1}{2}(\lambda_1 - \lambda_5 - \lambda_7 + \lambda_9), \tag{18}$$

respectively. By some linear algebra calculations [see Section Appendix B, part (a)] we obtain

$$[\mathrm{dist}(\boldsymbol{\lambda}, \tilde{\mathscr{A}})]^2 = \tfrac{4}{9}[4(\rho_1^2 + \rho_2^2 + \rho_3^2 + \rho_4^2) - 4(\rho_1 + \rho_4)(\rho_2 + \rho_3) + 2(\rho_1\rho_4 + \rho_2\rho_3)]. \tag{19}$$

Both bound (12) and (under some constraints) equality (14) remain in force but with $\mathrm{d}(\boldsymbol{\lambda}, \tilde{\mathscr{A}})$ given by eqn (19).

Remarkably, the oriented distance ρ_1 coincides with the measure E_{AB} introduced in Wagner *et al.* (1998). According to the latter the quantity $\rho_1 = E_{\mathrm{AB}}$ measures the absolute effect of subsequent substitutions $A \rightsquigarrow a$ and $B \rightsquigarrow b$ on the genotypic values (the fitness values, for instance) at the loci **B** and **A**, respectively. Note that the only homozygous values are accounted in ρ_1 in contrast to ρ_2, ρ_3, ρ_4.

It is interesting to compare results (19) and (20). One can try to measure the epistasis in the two-locus Mendelian dominant structure using formula (19) for the separative structure but with the "dominance conditions"

$$\lambda_1 = \lambda_5 = \lambda_7 = \lambda_9, \ \lambda_2 = \lambda_6, \ \lambda_3 = \lambda_8 \tag{20}$$

corresponding to structure (11). Then eqns (17) and (18) reduce to $\rho_1 = \rho, \rho_2 = \rho_3 = \rho_4 = 0$ where ρ is defined by eqn (12). By substitution into eqn (19) we obtain

$$\mathrm{dist}(\boldsymbol{\lambda}, \tilde{\mathscr{A}}) = \tfrac{4}{3}|\rho|,$$
$$\boldsymbol{\lambda} = (\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_1, \lambda_2, \lambda_1, \lambda_3, \lambda_1). \tag{21}$$

According to eqn (20), in the separative structure the fitness vector $\boldsymbol{\lambda}$ represents the vector $(\lambda_1, \lambda_2, \lambda_3, \lambda_4)$ from the Mendelian dominant structure. Formula (21) includes the coefficient 4/3 as opposed to 1 in the "intrinsic" formula (13).

Similarly, the epistatic distance in the direct product of the one-locus Mendelian dominant structure and the separative structure appears in eqn (19) with the additional factor $\sqrt{4/3}$.

Thus, *the value of the epistatic distance substantially depends on a preexisting phenotypical structure*. We continue to discuss this phenomenon in Section Appendix B, part (b).

All the formulas for epistatic distances we have obtained are some particular cases of a general formula concerning the direct product of two arbitrary one-locus multiallele phenotypical structures. In order to write such a formula we denote the classes of those one-locus structures by $C_1^{(1)}, ..., C_s^{(1)}$ and $C_1^{(2)}, ..., C_t^{(2)}$, respectively. Then the classes in their direct product can be described as the formal products $C_i^{(1)} C_k^{(2)}$, $1 \leqslant i \leqslant s, 1 \leqslant k \leqslant t$. The total number of them is $n = st$. Let λ_{ik} be the fitness value of the class $C_i^{(1)} C_k^{(2)}$. Consider the oriented distance

$$\rho_{ik} = \tfrac{1}{2}(\lambda_{11} - \lambda_{1i} - \lambda_{k1} + \lambda_{ik}), \tag{22}$$

where $2 \leqslant i \leqslant s, 2 \leqslant k \leqslant t$. The corresponding additive subspace is

$$\tilde{\mathscr{A}} = \{\lambda \in \mathbf{R}^n : \rho_{ik} = 0,\ 2 \leqslant i \leqslant s,\ 2 \leqslant k \leqslant t\}. \tag{23}$$

Theorem 1. *The formula*

$$[\mathrm{dist}(\boldsymbol{\lambda}, \tilde{\mathscr{A}})]^2 = \frac{4}{n}\Big[(s-1)(t-1)\sum_{j,l}\rho_{jl}^2 - (s-1)\sum_{j,l,\,k\neq l}\rho_{jl}\rho_{jk} - (t-1)\sum_{j,l,i\neq j}\rho_{jl}\rho_{il} + \sum_{j,l,i\neq j,\,k\neq l}\rho_{jl}\rho_{ik}\Big] \tag{24}$$

holds.

For the proof see Section 8, part (c).

A remarkable property of formula (24) is that the structure of its right-hand side is uniquely determined by the class numbers s and t. For example, eqn (13) is valid for the direct product of one-locus numerical structures. Meanwhile, in this direct product the content of the classes is different from that in the two-locus Mendelian dominant structure.

6. The evolutionary Equations under Phenotypical Selection

We start with the evolutionary equations determined by an arbitrary given fitness function $\lambda(g, h)(\equiv \lambda(h, g))$, see Lyubich (1992, eqn 9.5.1). We adjust these equations to any λ-compatible phenotypical structure.

A *state* of a population on the gamete level is a distribution $p(g)$ of probabilities of gametes. The evolutionary equations yield the state $p'(g)$ for the offspring generation in terms of the state $p(g)$ in the parental generation.

For any gamete g we denote by $\Phi(g)$ the set of phenotypes f such that g is a recombinant gamete for a zygote the phenotype of which is f. More formally,

$$\Phi(g) = \{f \in \Phi | \exists(\chi, \gamma), U|V : f = \varphi(\chi, \gamma), \chi_U \gamma_V = g\}. \tag{25}$$

Then under panmixia

$$p'(g) = \frac{Q_g(p)}{W(p)}. \tag{26}$$

Here

$$W(p) = \sum_{g,h} \lambda(g, h) p(g) p(h) \tag{27}$$

is the *mean fitness* of the population and

$$Q_g(p) = \sum_{f \in \Phi(g)} \Lambda(f) \sum_{\varphi(\gamma,\chi)=f} \pi_{\gamma\chi,g} p(\gamma) p(\chi). \tag{28}$$

The coefficient

$$\pi_{\gamma\chi,g} = \sum_{\gamma_U \chi_V = g} r(U|V) \tag{29}$$

is the probability for the gamete pair γ, χ to produce g by recombination.

The quantity $Q_g(p)$ is the contribution of the gamete g to the mean fitness $W(p)$:

$$\sum_g Q_g(p) = W(p), \tag{30}$$

so that $W(p)$ can be expressed in terms of phenotypical fitnesses $\Lambda(f)$ as well. The linkage distribution $r(U|V)$ being fixed, the only parameters in the evolutionary eqns (26) are the phenotypical fitnesses $\Lambda(f)$. However, the dynamical variables $p(g)$ are related to the genotypes. It is known that, in general, *there is no definite dynamics in terms of phenotypical probabilities* (Lewontin, 1974, Chapter 1; Lyubich, 1992, Section 1.2).

7. The Equilibrium Set. The Finiteness Problem

For an equilibrium p we have $p'(g) = p(g)$. According to eqn (26) p is an equilibrium if and only if

$$p(g)W(p) - Q_g(p) = 0. \tag{31}$$

The equilibrium set may be infinite. The classical example is the Hardy–Weinberg parabola. More generally, *the equilibrium set is infinite for any selection free population,* i.e. for the neutral phenotypical structure.

Actually, there are a lot of problems in evolutionary theory, where the finiteness of the equilibrium set is a needed condition *a priori*. For instance, under this condition the number of equilibria can be evaluated explicitly (Karlin & Feldman, 1970; Lewontin, 1974; Renaud & Morton, 1991; Lyubich, 1992). Also, under the finiteness condition the problem of convergence to equilibrium can be essentially simplified (Blackley, 1964; Lyubich, 1992}

A standard "philosophical" opinion is that the equilibrium set under "effective" selection is finite "as a rule". However, there are only a few exact statements of this kind for the multilocus multiallele populations, in particular, for the additive or almost additive selection (Kun & Lyubich, 1980; Kun, 1988; Lyubich, 1992, Chapter 9; Nagylaki *et al.*, 1999). The following result has been recently established (Lyubich *et al.*, 2001).

Theorem 2. *For any acyclic phenotypical structure the equilibrium set is finite generically in the phenotype fitness space.*

In particular, we have

Corollary 1. *If the phenotype of every homozygote is specific* (*in particular*, *if the phenotypical structure is separative*) *then the equilibrium set is finite generically.*

Corollary 2. *For any multilocus phenotypical structure with acyclic constituents the equilibrium set is finite generically.*

Also in Lyubich & Kirzhner (2002) a theorem of generic finiteness of the equilibrium set in Karlin's model (10) was obtained from Theorem 1.

The following theorem has been proved in Kirzhner & Lyubich (2000).

Theorem 3. *Under monomial* (*in particular*, *multiplicative*) *selection the equilibrium set is finite generically.*

In all the above-mentioned cases *the total number of equilibria does not exceed* 3^{n-1}, *where n is the total number of gamete genotypes in the population.*

On the other hand, the best possible upper bound for the total number of equilibria cannot be less than 2^n–1 since the latter number is attained.

Example. At a locus with allele $a_1, \ldots, a_m$ we consider the phenotypical structure with phenotypes $f_1 \ldots f_m$ for the homozygotes and with one more phenotype f_{m+1} for all heterozygotes. This structure is acyclic since the phenotypes of homozygotes are specific. The compatible fitness vector is $\{\lambda_1, \ldots \lambda_m, \lambda_{m+1}\}$. We assume these fitness values pairwise distinct, so the phenotypical structure under consideration is λ-determined.

Now the equilibrium equations (25) take the form

$$\lambda_i p_i^2 + \lambda_{m+1} \sum_{k:k\neq i} p_i p_k = p_i W,\ 1 \leqslant i \leqslant m, \tag{32}$$

where $p_1, \ldots, p_m$ are the probabilities of the alleles $a_1, \ldots, a_m$, respectively.

With $I = \{i : p_i \neq 0\}$ the system of eqn (32) reduces to

$$\lambda_i p_i + \lambda_{m+1}(1 - p_i) = W, i \in I. \tag{33}$$

Under the normalizing condition $\Sigma\{p_i : i \in I\} = 1$ the only solution of eqn (33) is

$$p_i = \frac{1}{\lambda_i - \lambda_{m+1}} \left(\sum_{i \in I} \frac{1}{\lambda_i - \lambda_{m+1}} \right)^{-1},\ i \in I. \tag{34}$$

This is a unique equilibrium with prescribed set I if all differences $\lambda_i - \lambda_{m+1}$ are of the same sign. With this property for all $i, 1 \leqslant i \leqslant m$, the equilibrium set is enumerated by non-empty subsets of $\{1, \ldots, m\}$. Accordingly, the total number of equilibria is 2^m –1 in this case.

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Appendix A

Proofs to Section 5

(a) Here we derive the distance formula (19). It is convenient to rewrite eqns (16) as

$$(\boldsymbol{\lambda}, \mathbf{v}_k) = 0, 1 \leqslant k \leqslant 4, \tag{A.1}$$

where $\mathbf{v}_k$ are those normalized vectors which are orthogonal to the corresponding hyperplanes. Namely,

$$\mathbf{v}_1 = \tfrac{1}{2}(1,-1,-1,1,0,0,0,0,0),$$
$$\mathbf{v}_2 = \tfrac{1}{2}(1,-1,0,0,-1,1,0,0,0),$$
$$\mathbf{v}_3 = \tfrac{1}{2}(1,0,-1,0,0,0,-1,1,0),$$
$$\mathbf{v}_4 = \tfrac{1}{2}(1,0,0,0,-1,0,-1,0,1).$$

Respectively, the oriented distances (17) and (18) are

$$\rho_k = (\boldsymbol{\lambda}, \mathbf{v}_k),\ 1 \leqslant k \leqslant 4.$$

Equations (A.1) determine the additive subspace $\tilde{\mathscr{A}} \subset \mathbf{R}^9$. In order to find the distance from a vector $\lambda \in \mathbf{R}^9$ to $\mathscr{L}$ we use the orthogonal decomposition

$$\boldsymbol{\lambda} = \left(\sum_{k=1}^{4} \xi_k \mathbf{v}_k\right) \oplus \boldsymbol{\omega},\ \boldsymbol{\omega} \in \tilde{\mathscr{A}} \tag{A.2}$$

The coefficients ξ_k in eqn (A.2) can be found from the system of linear equations

$$\sum_{k=1}^{4} g_{ik}\xi_k = \rho_i,\ 1 \leqslant i \leqslant 4, \tag{A.3}$$

where $g_{ik} = (\mathbf{v}_i, \mathbf{v}_k)$ are the entries of the Gram matrix

$$G = \frac{1}{4}\begin{pmatrix} 4 & 2 & 2 & 1 \\ 2 & 4 & 1 & 2 \\ 2 & 1 & 4 & 2 \\ 1 & 2 & 2 & 4 \end{pmatrix}.$$

The inverse matrix is

$$G^{-1} = \frac{4}{9}\begin{pmatrix} 4 & -2 & -2 & 1 \\ -2 & 4 & 1 & -2 \\ -2 & 1 & 4 & -2 \\ 1 & -2 & -2 & 4 \end{pmatrix}.$$

Now we can solve eqn (A.3) and find

$$\left.\begin{aligned} \xi_1 &= \tfrac{4}{9}(4\rho_1 - 2\rho_2 - 2\rho_3 + \rho_4) \\ \xi_2 &= \tfrac{4}{9}(-2\rho_1 + 4\rho_2 + \rho_3 - 2\rho_4) \\ \xi_3 &= \tfrac{4}{9}(-2\rho_1 + \rho_2 + 4\rho_3 - 2\rho_4) \\ \xi_4 &= \tfrac{4}{9}(\rho_1 - 2\rho_2 - 2\rho_3 + 4\rho_4) \end{aligned}\right\}. \tag{A.4}$$

It follows from eqns (A.2) and (A.3) that

$$\begin{aligned} [\mathrm{dist}(\lambda, \tilde{\mathscr{A}})]^2 &= \|\sum_{k=1}^{4} \xi_k v_k\|^2 \\ &= \sum_{i,k=1}^{4} g_{ik}\xi_i\xi_k = \sum_{i=1}^{4} \xi_i\rho_i. \end{aligned} \tag{A.5}$$

It remains to insert eqn (A.4) into eqn (A.5) in order to get eqn (19).

(b) There is a deep reason for the divergence between the epistatic distances (13) and (21) which related to the two-locus Mendelian dominant structure. Formula (13) was obtained directly in this structure while eqn (21) is the epistatic distance in the separative structure specialized by means of eqn (20). Actually, we have the linear mapping $T : \mathbf{R}^4 \to \mathbf{R}^9$,

$$\begin{aligned} &T(\lambda_1, \lambda_2, \lambda_3, \lambda_4) \\ &\quad = (\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_1, \lambda_2, \lambda_1, \lambda_3, \lambda_1), \end{aligned} \tag{A.6}$$

which transfers the fitness vectors from the two-locus Mendelian dominant structure to the separative one. Obviously, T maps the additive hyperplane

$$\mathscr{H} = \{\boldsymbol{\lambda} \in \mathbf{R}^4 : \lambda_1 - \lambda_2 - \lambda_3 + \lambda_4 = 0\}$$

into the additive subspace $\tilde{\mathscr{A}} \subset \mathbf{R}^9$. However, *$T$ is not isometric*, its action does not preserve the lengths of vectors and the angles between them. In particular, for the vector $\mathbf{v}$ which is normalized and orthogonal to $\mathscr{H}$, we obtain

$$Tv = \tfrac{1}{2}(1, -1, -1, 1, 1, -1, 1, -1, 1).$$

We see that $\|Tv\| = 3/2$ while $\|v\| = 1$. Moreover, Tv is not orthogonal to $\tilde{\mathscr{A}}$. Indeed, otherwise, Tv would be a linear combination of $\boldsymbol{v}_k, 1 \leqslant k \leqslant 4$, but this is false. For this reason the constant $c = \mathrm{dist}(T\mathbf{v}, \tilde{\mathscr{A}})$ could be different from $\mathrm{dist}(\mathbf{v}, \mathscr{H}) = 1$. They are really different since $c = 4/3$ according to eqn (21). Note that eqn (21) can be rewritten in the apparent geometrical form

$$\mathrm{dist}(T\boldsymbol{\lambda}, \tilde{\mathscr{A}}) = \frac{4}{3}\mathrm{dist}(\boldsymbol{\lambda}, \mathscr{H}),\ \boldsymbol{\lambda} \in \mathbf{R}^4. \tag{A.7}$$

(c) Here we prove Theorem 5.1. Before doing so let us verify eqn (23) for the additive subspace. First, with

$$\lambda_{ik} = \alpha_i + \beta_k,\ 1 \leqslant i \leqslant s,\ 1 \leqslant k \leqslant t, \tag{A.8}$$

all equations in eqn (23) are valid. Secondly, this system of equations for the additive selection is complete. Indeed, eqn (A.8) defines a linear mapping $\mathbf{R}^{s+t} \to \mathrm{R}^{st}$ with all $\lambda_{ik} = 0$ if and only if all α_i are equal to some α while all $\beta_k = -\alpha$. Hence, the number of independent equations for the additive subspace is $st - (s + t) + 1 = (s - 1)(t - 1)$, just the same as in eqn (23).

Now we introduce the vector $\boldsymbol{v}_{ik} (2 \leqslant i \leqslant s, 2 \leqslant k \leqslant t)$ as the $(s-1) \times (t-1)$ matrix with the entry $\frac{1}{2}$ at the northwest corner as well as at the intersection of the i-th row and the k-th column; with the entries $-\frac{1}{2}$ at the intersection of the 1st row and k-th column as well as of the i-th row and the 1st column; with the entries 0 at all other places. Then eqn (22) takes the form

$$\rho_{ik} = (\boldsymbol{\lambda}, \mathbf{v}_{ik}),\ 2 \leqslant i \leqslant s,\ 2 \leqslant k \leqslant t. \tag{A.9}$$

The Gram matrix of the system $\{\boldsymbol{v}_{ik}\}$ is $G = (g_{ik,\,jl})$ where

$$g_{ik,\,jl} = (\mathbf{v}_{ik}, \mathbf{v}_{jl}) = \tfrac{1}{4}(1 + \delta_{ij})(1 + \delta_{kl}). \tag{A.10}$$

The orthogonal decomposition

$$\boldsymbol{\lambda} = \left(\sum_{i,k} \xi_{ik}\mathbf{v}_{ik}\right) \oplus \boldsymbol{\omega},\ \boldsymbol{\omega} \in \tilde{\mathscr{A}} \tag{A.11}$$

yields the system of linear equations

$$\sum_{i,k} g_{ik,\,jl}\xi_{ik} = \rho_{jl},\ 2 \leqslant i \leqslant s,\ 2 \leqslant k \leqslant t. \tag{A.12}$$

(It is suffitient to multiply eqn (A.11) by $\boldsymbol{v}_{jl}$ and use $(\boldsymbol{\omega}, \boldsymbol{v}_{jl}) = 0$.)

By eqn (A.10), system eqn (A.12) can be rewritten as

$$\xi_{jl} + \sigma_j + \tau_l + \sigma = 4\rho_{jl},$$
$$2 \leqslant i \leqslant s,\ 2 \leqslant k \leqslant t, \tag{A.13}$$

where

$$\sigma_j = \sum_k \xi_{jk},\ \tau_l = \sum_i \xi_{il},\ \sigma = \sum_{i,k} \xi_{ik}, \tag{A.14}$$

so that

$$\sum_j \sigma_j = \sum_l \tau_l = \sigma. \tag{A.15}$$

By summation over all indices in eqn (A.13) and application of eqns (A.14) and (A.15) we obtain

$$\sigma = \tfrac{4}{st} \sum_{j,l} \rho_{jl} = \tfrac{4}{n} \sum_{j,l} \rho_{jl}. \tag{A.16}$$

In turn, the summation over l in eqn (A.13) yields

$$\sigma_j = \tfrac{4}{t} \sum_l \rho_{jl} - \sigma \tag{A.17}$$

and, similarly, the summation over j yields

$$\tau_l = \tfrac{4}{s} \sum_j \rho_{jl} - \sigma \tag{A.18}$$

Finally, ξ_{il} are determined by eqns (A.13) and (A.16)–(A.18).

Coming back to eqn (A.11) we obtain

$$[dist(\lambda, \tilde{\mathscr{A}})]^2 = \| \sum_{i,k} \xi_{ik} v_{ik} \|^2$$
$$= \sum_{i,k,j,l} g_{ik,jl} \xi_{ik} \xi_{jl} = \sum_{j,l} \xi_{jl} \rho_{jl} \tag{A.19}$$

by eqn (A.12). In principle, it remains to substitute ξ_{jl} we have found. However, elementary algebraic machinery is also needed to obtain the final result eqn (A.15). Let us omit it.

Appendix B

Epistatic Distance to a Multiplicative Pattern

Consider the two-locus Mendelian dominant structure (11) but with the multiplicative fitness values $\alpha\gamma, \alpha\delta, \beta\gamma, \beta\delta$ instead of additive ones. The manifold $\mathscr{M}$ of multiplicative fitness vectors is the intersection of $\mathbf{R}^4_+$ with the multiplicative manifold $\tilde{\mathscr{M}}$ the equation of which is

$$\lambda_1\lambda_4 - \lambda_2\lambda_3 = 0.$$

This manifold is a quadric in $\mathbf{R}^4$, not a linear subspace. We are going to find the Euclidian distance of an arbitrary point $\boldsymbol{\mu} = (\mu_1, \mu_2, \mu_3, \mu_4)$ to $\tilde{\mathscr{M}}$.

Let $\varepsilon_k = \lambda_k - \mu_k, 1 \leqslant k \leqslant 4$, where $\lambda = (\lambda_1, \lambda_2, \lambda_3, \lambda_4)$ is the closest to $\boldsymbol{\mu}$ point of $\tilde{\mathscr{M}}$. The vector $\boldsymbol{\varepsilon} = (\varepsilon_1, \varepsilon_2, \varepsilon_3, \varepsilon_4)$ has to be orthogonal (normal) to $\tilde{\mathscr{M}}$ at the point λ. Hence, $\boldsymbol{\varepsilon}$ is proportional to $(\lambda_4, -\lambda_3, -\lambda_2, \lambda_1)$. We obtain the following system of equations with unknown $\varepsilon_k, 1 \leqslant k \leqslant 4$:

$$(\mu_1 + \varepsilon_1)(\mu_4 + \varepsilon_4) = (\mu_2 + \varepsilon_2)(\mu_3 + \varepsilon_3) \tag{B.1}$$

$$\frac{\mu_4 + \varepsilon_4}{\varepsilon_1} = -\frac{\mu_3 + \varepsilon_3}{\varepsilon_2} = -\frac{\mu_2 + \varepsilon_2}{\varepsilon_3} = \frac{\mu_1 + \varepsilon_1}{\varepsilon_4}. \tag{B.2}$$

To solve eqns (B.1) and (B.2) we introduce the common value τ of all fractions involved in eqn (B.2). Then eqn (B.1) reduces to

$$\varepsilon_1\varepsilon_4 = \varepsilon_2\varepsilon_3 \tag{B.3}$$

and eqn (B.2) yields the system of linear equations

$$\varepsilon_1\tau - \varepsilon_4 = \mu_4, \varepsilon_4\tau - \varepsilon_1 = \mu_1,$$
$$\varepsilon_2\tau + \varepsilon_3 = -\mu_3,\ \varepsilon_3\tau + \varepsilon_2 = -\mu_2.$$

Then

$$\varepsilon_1 = \frac{\mu_1 + \mu_4\tau}{\tau^2 - 1},\ \varepsilon_2 = \frac{\mu_2 - \mu_3\tau}{\tau^2 - 1},$$
$$\varepsilon_3 = \frac{\mu_3 - \mu_2\tau}{\tau^2 - 1},\ \varepsilon_4 = \frac{\mu_4 + \mu_1\tau}{\tau^2 - 1} \tag{B.4}$$

with the (non-essential) constraint $\tau \neq 1$.

By substitution into eqn (B.3) we obtain a quadratic equation

$$r\tau^2 + D^2\tau + r = 0, \tag{B.5}$$

where the coefficients are

$$r = \mu_1\mu_4 - \mu_2\mu_3,\ D^2 = \sum_{k=1}^{4} \mu_k^2. \tag{B.6}$$

Note, that r is the multiplicative analog of the oriented distance ρ we have in the additive situation, cf. eqn (13).

The multiplicative epistatic distance in question is determined by the formula

$$[\mathrm{dist}(\boldsymbol{\mu}, \tilde{\mathscr{M}})]^2 = \sum_{k=1}^{4} \varepsilon_k^2 = \frac{D^2\tau^2 + 4r\tau + D^2}{(\tau^2 - 1)^2} \tag{B.7}$$

by eqn (B.4). Using eqn (B.5) one can subsequently eliminate τ^2 from eqn (B.7) obtaining

$$[\mathrm{dist}(\boldsymbol{\mu}, \tilde{\mathscr{M}})]^2 = -r\tau^{-1}, \tag{B.8}$$

where τ is a root of eqn (B.5), i.e.

$$\tau = -\frac{D^2 \pm \sqrt{\Delta}}{2r},\ \Delta = D^4 - 4r^2. \tag{B.9}$$

It is follows from eqn (B.6) that

$$\Delta = [(\mu_1 - \mu_4)^2 + (\mu_2 + \mu_3)^2]$$
$$[(\mu_1 + \mu_4)^2 + (\mu_2 - \mu_3)^2 0. \tag{B.10}$$

By eqn (B.9) $\Delta < D^4$ and the signs of τ and r are opposite. This fact is consistent with eqn (B.8) where the left-hand side has to be positive. As a result,

$$[\mathrm{dist}(\boldsymbol{\mu}, \tilde{\mathscr{M}})]^2 = |r\tau^{-1}| = \frac{2r^2}{D^2 + \sqrt{\Delta}}. \tag{B.11}$$

The choice of sign in eqn (B.9) provides the smallest value eqn (B.11).