The Fundamental Theorem of Natural Selection in Ewens' Sense (Case of Fertility Selection)

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ABSTRACT

We show that the Fundamental Theorem of Natural Selection in Ewens' sense is valid in the case of fertility selection: the additive genetic variance in fertility divided by the mean fertility is exactly equal to the partial change in the mean fertility from the current generation to the next. This partial change is the increase in the mean additive value caused by frequency changes from one generation to the next but keeping unchanged the additive values. The only hypothesis on mating is that it does not affect the allelic frequencies in the sense that these are the same before and after mating in the parental generation, which occurs for a wide range of mating patterns going from random mating to several regular systems of inbreeding and cases of assortative mating. The fertility of couples is determined by the genes at an arbitrary number of loci, and the additive (average) allelic effects are defined by a linear system of equations, which is used to extend Ewens' optimality principle to the case of fertility selection.

THE Fundamental Theorem of Natural Selection (FTNS) as interpreted by EWENS (1989) in the case of viability selection in an infinite diploid population undergoing discrete nonoverlapping generations states that the partial change in the mean fitness is exactly equal to the ratio of the additive genetic variance in fitness to the mean fitness. The theorem holds for any mating scheme, random or not, as long as there is no change between the allelic frequencies in the adults just before mating and in the offspring just after reproduction, and it is true no matter the number of loci involved in fitness determination and no matter the number of alleles at these loci. Some of the key elements in the analysis are the equations satisfied by the additive (average) allelic effects (see EWENS 1992; CASTILLOUX and LESSARD 1995, for corrected equations). This analysis can also be used to deduce optimality principles, a matter that we also take up.

In this paper we study the case of fertility selection as suggested in EWENS (1989), which was thought to be more difficult (W. J. EWENS, personal communication) but certainly interesting since it is known that the mean fertility does not generally increase over successive generations. As for the mean viability, the partial change in the mean fertility is obtained by replacing the exact fertility values by the associated additive fertility values and by keeping these values constant from one generation to the next. It is shown that this partial change is exactly equal to $\sigma_A^2/\bar{f}$, where σ_A^2 is the additive genetic variance in fertility and $\bar{f}$ is the mean fertility. A linear system of equations for the additive allelic effects on fertility determined at several loci is deduced and EWENS' (1992) optimality principle is shown to hold in this case. The arguments are valid whether mating is random or not as long as it does not change the allelic frequencies in the adults of the parental generation as in cases of mating based on kinship or assortment.

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MODEL AND NOTATION

Let $A_1^{(m)}, \ldots, A_{s_m}^{(m)}$ be the s_m alleles of a gene at locus m for $m = 1, \ldots, n$ in a sexual diploid population of infinite size. A genotype in this n locus system is made of two gametes, i and j, of the form

$$i = (i_1, \ldots, i_n),$$

$$j = (j_1, \ldots, j_n),$$

with $1 \leq i_m \leq s_m$ and $1 \leq j_m \leq s_m$, for $m = 1, \ldots, n$. The appearance of the parameter i_m at the mth component of gamete i means that the allele $A_{i_m}^{(m)}$ is present at locus m of this gamete, for $m = 1, \ldots, n$, and similarly for gamete j. If we do not distinguish the origin (maternal or paternal) of the gametes, then the genotype is represented by the nonordered pair $\{i, j\}$. The frequency of this genotype at conception is assumed to be identical for females and for males and is represented by $2g_{ij}$, if $j \neq i$, and by g_{ii}, if $j = i$. If we order at random the gametes of the nonordered genotype $\{i, j\}$, then we get the ordered genotype (i, j) with probability $1/2$ and the ordered genotype (j, i) with probability $1/2$. Then the frequency of the ordered genotype (i, j) is g_{ij} for all i, j.

The frequency of gamete i at conception is represented by p_i. We have

$$p_i = \sum_j g_{ij}.$$

We represent the frequency at conception of allele $A_{i_m}^{(m)}$ at locus m by p_{mi_m}. We get this frequency by summing p_i over all gametes i that contain the fixed i_m at the mth component, that is

$$p_{mi_m} = \sum_{i \ni i_m} \sum_j g_{ij}.$$

A mated pair of individuals consisting of a female of genotype $\{i, j\}$ and of a male of genotype $\{k, l\}$ is represented by the ordered couple $(\{i, j\}, \{k, l\})$. The frequency of this couple after mating is represented by $4X_{ij,kl}$, if $j \neq i$ and $l \neq k$, $2X_{ii,kl}$, if $j = i$ and $l \neq k$, $2X_{ij,kk}$, if $j \neq i$ and $l = k$, $X_{ii,kk}$, if $j = i$ and $l = k$. If we order the genotypes as above, then the frequency of the couple $((i, j), (k, l))$ is $X_{ij,kl}$ for all i, j, k, l. We assume $X_{ij,kl} > 0$ for all i, j, k, l. Moreover, we have the symmetry conditions

$$X_{ij,kl} = X_{ij,lk} = X_{ji,kl} = X_{ji,lk}.$$

But, we may have $X_{ij,kl} \neq X_{kl,ij}$. In the particular case of random mating, we have $X_{ij,kl} = g_{ij}g_{kl}$.

The frequency of genotype (i, j) in mated females is $\Sigma_{k,l}X_{ij,kl}$ and the corresponding frequency in mated males is $\Sigma_{k,l}X_{kl,ij}$. Then the frequency of gamete i is $\Sigma_{j,k,l}X_{ij,kl}$ in mated females and $\Sigma_{j,k,l}X_{kl,ij}$ in mated males, in such a way that the overall frequency of gamete i in mated individuals is

$$\sum_{j,k,l} (X_{ij,kl} + X_{kl,ij})/2.$$

If we assume that mating does not change the allelic frequencies from the time of conception to the time of reproduction, and this is the case for several mating patterns, then we have

$$p_{mi_m} = \sum_{i \ni i_m} \sum_{j,k,l} (X_{ij,kl} + X_{kl,ij})/2. \tag{1}$$

Now let $f_{ij,kl}$ be the fertility of couple $((i, j), (k, l))$. This parameter, which may be frequency-dependent, can be interpreted as the expected number of offspring in the progeny. The progeny sex ratio is assumed to be one-to-one, which means that there are as many males as females in the progeny on the average. We have the symmetry conditions

$$f_{ij,kl} = f_{ji,kl} = f_{ij,lk} = f_{ji,lk},$$

for all i, j, k, l. But, we may have $f_{ij,kl} \neq f_{kl,ij}$, which means that the sexes of the parents matter. The mean fertility in the population is

$$\bar{f} = \sum_{i,j,k,l} X_{ij,kl} f_{ij,kl}.$$

If p'_{mi_m} denotes the frequency of $A_{i_m}^{(m)}$ at the beginning of the next generation, then we have, assuming Mendelian segregation and no gametic selection,

$$p'_{mi_m} = \sum_{i \ni i_m} \sum_{j,k,l} (X_{ij,kl} f_{ij,kl} + X_{kl,ij} f_{kl,ij})/(2\bar{f}), \tag{2}$$

for $i_m = 1, \ldots, s_m$ and $m = 1, \ldots, n$. Therefore, the change in the frequency of $A_{i_m}^{(m)}$ from the mother generation to the daughter generation is

$$\Delta p_{mi_m} = p'_{mi_m} - p_{mi_m}$$

$$= \frac{1}{2\bar{f}} \sum_{i \ni i_m} \sum_{j,k,l} [X_{ij,kl}(f_{ij,kl} - \bar{f}) + X_{kl,ij}(f_{kl,ij} - \bar{f})], \tag{3}$$

for $i_m = 1, \ldots, s_m$ and $m = 1, \ldots, n$.

ADDITIVE ALLELIC EFFECTS

The additive allelic effects on fertility are obtained by the classical least-square method (see, *e.g.*, FISHER 1918, 1930; KEMPTHORNE 1957; EWENS 1979). We write the fertility parameter $f_{ij,kl}$ in the form

$$f_{ij,kl} = \bar{f} + \sum_r (\alpha_{ri_r} + \alpha_{rj_r} + \alpha_{rk_r} + \alpha_{rl_r}) + \gamma_{ij,kl}, \tag{4}$$

such that

$$S = \sum_{i,j,k,l} X_{ij,kl} \left[f_{ij,kl} - \bar{f} - \sum_r (\alpha_{ri_r} + \alpha_{rj_r} + \alpha_{rk_r} + \alpha_{rl_r}) \right]^2$$

is minimum under the constraint

$$\sum_{i_r} \alpha_{ri_r} p_{ri_r} = 0, \tag{5}$$

for $r = 1, \ldots, n$. The parameter α_{ri_r} represents the additive effect of allele $A_{i_r}^{(r)}$ on fertility, while $\gamma_{ij,kl}$ measures the effect of all interactions between genes carried by i, j, k, l. Using Lagrange multipliers, the additive allelic effects have to minimize

$$\tilde{S} = \sum_{i,j,k,l} X_{ij,kl} \left[f_{ij,kl} - \bar{f} - \sum_r (\alpha_{ri_r} + \alpha_{rj_r} + \alpha_{rk_r} + \alpha_{rl_r}) \right]^2 + \sum_r \lambda_r \sum_{i_r} \alpha_{ri_r} p_{ri_r},$$

for some λ_r for $r = 1, \ldots, n$. The partial derivatives of $\tilde{S}$ are given by

$$\frac{\partial \tilde{S}}{\partial \alpha_{mi_m}} = -4 \sum_{i \ni i_m} \sum_{j,k,l} X_{ij,kl} \left[f_{ij,kl} - \bar{f} - \sum_r (\alpha_{ri_r} + \alpha_{rj_r} + \alpha_{rk_r} + \alpha_{rl_r}) \right]$$

$$- 4 \sum_{i \ni i_m} \sum_{j,k,l} X_{kl,ij} \left[f_{kl,ij} - \bar{f} - \sum_r (\alpha_{ri_r} + \alpha_{rj_r} + \alpha_{rk_r} + \alpha_{rl_r}) \right] + \lambda_m p_{mi_m},$$

for $i_m = 1, \ldots, s_m$ and $m = 1, \ldots, n$. By equating these partial derivatives to 0 and by summing over i_m for each m, we find

$$\lambda_m = 4 \sum_{i,j,k,l} X_{ij,kl}\left[f_{ij,kl} - \bar{f} - \sum_r (\alpha_{ri_r} + \alpha_{rj_r} + \alpha_{rk_r} + \alpha_{rl_r})\right]$$
$$+ 4 \sum_{i,j,k,l} X_{kl,ij}\left[f_{kl,ij} - \bar{f} - \sum_r (\alpha_{ri_r} + \alpha_{rj_r} + \alpha_{rk_r} + \alpha_{rl_r})\right]$$
$$= 8\left[\sum_{i,j,k,l} X_{ij,kl} f_{ij,kl} - \bar{f} - 4 \sum_r \sum_{i_r} \alpha_{ri_r} p_{ri_r}\right] = 0,$$

for $m = 1, \ldots, n$. According to (3), we have

$$\sum_{i \ni i_m} \sum_{j,k,l} X_{ij,kl}(f_{ij,kl} - \bar{f}) + \sum_{i \ni i_m} \sum_{j,k,l} X_{kl,ij}(f_{kl,ij} - \bar{f})$$
$$= 2\bar{f}\Delta p_{mi_m}. \quad (6)$$

Then the equality

$$\frac{\partial \tilde{S}}{\partial \alpha_{mi_m}} = 0,$$

for $i_m = 1, \ldots, s_m$ and $m = 1, \ldots, n$ is equivalent to the equation

$$2\bar{f}\Delta p_{mi_m} = \sum_{i \ni i_m} \sum_{j,k,l} (X_{ij,kl} + X_{kl,ij}) \times \sum_r (\alpha_{ri_r} + \alpha_{rj_r} + \alpha_{rk_r} + \alpha_{rl_r}), \quad (7)$$

for $i_m = 1, \ldots, s_m$ and $m = 1, \ldots, n$.

By developing the right hand side of (7), one obtains

$$2\bar{f}\Delta p_{mi_m} = \alpha_{mi_m} \sum_{i \ni i_m} \sum_{j,k,l} (X_{ij,kl} + X_{kl,ij})$$
$$+ \sum_{r \neq m} \sum_{i_r} \alpha_{ri_r} \sum_{i \ni i_r, i_m} \sum_{j,k,l} (X_{ij,kl} + X_{kl,ij})$$
$$+ \sum_r \sum_{j_r} \alpha_{rj_r} \sum_{i \ni i_m} \sum_{j \ni j_r} \sum_{k,l} (X_{ij,kl} + X_{kl,ij})$$
$$+ 2 \sum_r \sum_{k_r} \alpha_{rk_r} \sum_{i \ni i_m} \sum_{k \ni k_r} \sum_{j,l} (X_{ij,kl} + X_{kl,ij}).$$

This can be written in the form

$$\bar{f}\Delta p_{mi_m} = \alpha_{mi_m} p_{mi_m} + \sum_{r \neq m} \sum_{i_r} \alpha_{ri_r} P_{mi_m, ri_r}$$
$$+ \sum_r \sum_{j_r} \alpha_{rj_r} Q_{mi_m, rj_r} + 2 \sum_r \sum_{k_r} \alpha_{rk_r} R_{mi_m, rk_r}, \quad (8)$$

where

$$P_{mi_m, ri_r} = \sum_{i \ni i_r, i_m} \sum_{j,k,l} (X_{ij,kl} + X_{kl,ij})/2,$$
$$Q_{mi_m, rj_r} = \sum_{i \ni i_m} \sum_{j \ni j_r} \sum_{k,l} (X_{ij,kl} + X_{kl,ij})/2$$

and

$$R_{mi_m, rk_r} = \sum_{i \ni i_m} \sum_{k \ni k_r} \sum_{j,l} (X_{ij,kl} + X_{kl,ij})/2.$$

The quantity P_{mi_m, ri_r} is the frequency of all gametes in mated individuals carrying $A_{i_m}^{(m)}$ at locus m and $A_{i_r}^{(r)}$ at locus r, Q_{mi_m, rj_r} is the frequency of all genotypes among mated individuals carrying $A_{i_m}^{(m)}$ at locus m on one gamete chosen at random and $A_{j_r}^{(r)}$ at locus r on the other gamete and R_{mi_m, rk_r} is the frequency of all couples carrying $A_{i_m}^{(m)}$ at locus m on one gamete chosen at random in one of the parents chosen at random and $A_{k_r}^{(r)}$ at locus r on one gamete chosen at random in the other parent.

A more compact form for (8) is

$$\bar{f}\Delta p_{mi_m} = \sum_r \sum_{j_r} \alpha_{rj_r} T_{mi_m, rj_r}, \quad (9)$$

where

$$T_{mi_m, rj_r} = P_{mi_m, rj_r} + Q_{mi_m, rj_r} + 2R_{mi_m, rj_r},$$

when $r \neq m$,

$$T_{mi_m, mj_m} = Q_{mi_m, mj_m} + 2R_{mi_m, mj_m},$$

when $j_m \neq i_m$, and

$$T_{mi_m, mi_m} = p_{mi_m} + Q_{mi_m, mi_m} + 2R_{mi_m, mi_m}.$$

In every case, with reference to the above definitions, the element T_{mi_m, rj_r} can be interpreted as follows. This element is four times the probability that two genes chosen at random and independently, the first one at locus m and the second one at locus r, in a same couple chosen at random, be $A_{i_m}^{(m)}$ and $A_{j_r}^{(r)}$ in this order. This is so since then the two genes will be chosen on the same gamete with probability $1/4$, on two different gametes in a same individual with probability $1/4$ and on two different gametes in two different individuals of a same couple with probability $1/2$. Moreover, if the two genes are chosen at the same locus m on the same gamete, then they are different with probability 0 and they are the same gene $A_{i_m}^{(m)}$ with probability p_{mi_m}, which is the frequency of that gene in the population. Equation 9 for $i_m = 1, \ldots, s_m$ and $m = 1, \ldots, n$, characterizes the additive allelic effects on fertility.

DECOMPOSITION OF GENETIC VARIANCE

Let σ_T^2 be the total genetic variance of fertility. Then we have

$$\sigma_T^2 = \sum_{i,j,k,l} X_{ij,kl}(f_{ij,kl} - \bar{f})^2$$
$$= \sum_{i,j,k,l} X_{ij,kl}\left[f_{ij,kl} - \bar{f} - \sum_r (\alpha_{ri_r} + \alpha_{rj_r} + \alpha_{rk_r} + \alpha_{rl_r})\right]^2$$
$$+ \sum_{i,j,k,l} X_{ij,kl}\left[\sum_r (\alpha_{ri_r} + \alpha_{rj_r} + \alpha_{rk_r} + \alpha_{rl_r})\right]^2$$
$$+ 2 \sum_{i,j,k,l} X_{ij,kl}\left[f_{ij,kl} - \bar{f} - \sum_r (\alpha_{ri_r} + \alpha_{rj_r} + \alpha_{rk_r} + \alpha_{rl_r})\right]$$
$$\times \sum_s (\alpha_{si_s} + \alpha_{sj_s} + \alpha_{sk_s} + \alpha_{sl_s}).$$

But, by using (3) and (7), we find

$$\sum_{i,j,k,l} X_{ij,kl}\left[f_{ij,kl} - \bar{f} - \sum_r (\alpha_{ri_r} + \alpha_{rj_r} + \alpha_{rk_r} + \alpha_{rl_r})\right]$$

$$\times \sum_s (\alpha_{si_s} + \alpha_{sj_s} + \alpha_{sk_s} + \alpha_{sl_s}) = 2 \sum_s \sum_{i_s} \alpha_{si_s}$$

$$\times \sum_{i \ni i_s} \sum_{j,k,l} [X_{ij,kl}(f_{ij,kl} - \bar{f}) + X_{kl,ij}(f_{kl,ij} - \bar{f})]$$

$$- 2 \sum_r \sum_{i_r} \alpha_{ri_r} \sum_{i \ni i_r} \sum_{j,k,l} (X_{ij,kl} + X_{kl,ij})$$

$$\times \sum_s (\alpha_{si_s} + \alpha_{sj_s} + \alpha_{sk_s} + \alpha_{sl_s}) = 4\bar{f} \sum_s \sum_{i_s} \alpha_{si_s} \Delta p_{si_s}$$

$$- 4\bar{f} \sum_r \sum_{i_r} \alpha_{ri_r} \Delta p_{ri_r} = 0.$$

Therefore we have

$$\sigma_T^2 = \sigma_R^2 + \sigma_A^2, \tag{10}$$

where

$$\sigma_R^2 = \sum_{i,j,k,l} X_{ij,kl}\left[f_{ij,kl} - \bar{f} - \sum_r (\alpha_{ri_r} + \alpha_{rj_r} + \alpha_{rk_r} + \alpha_{rl_r})\right]^2$$

and

$$\sigma_A^2 = \sum_{i,j,k,l} X_{ij,kl}\left[\sum_r (\alpha_{ri_r} + \alpha_{rj_r} + \alpha_{rk_r} + \alpha_{rl_r})\right]^2.$$

The quantity σ_R^2 is the variance of the interaction effects, also called the residual genetic variance, and σ_A^2 is the variance of the additive allelic effects, called the additive genetic variance. Moreover, by using (7), we have

$$\sigma_A^2 = \sum_{i,j,k,l} X_{ij,kl}\left[\sum_r (\alpha_{ri_r} + \alpha_{rj_r} + \alpha_{rk_r} + \alpha_{rl_r})\right]^2$$

$$= 2 \sum_{i,j,k,l} (X_{ij,kl} + X_{kl,ij}) \sum_r \alpha_{ri_r}$$

$$\times \sum_s (\alpha_{si_s} + \alpha_{sj_s} + \alpha_{sk_s} + \alpha_{sl_s}) = 2 \sum_r \sum_{i_r} \alpha_{ri_r}$$

$$\times \sum_{i \ni i_r} \sum_{j,k,l} (X_{ij,kl} + X_{kl,ij}) \sum_s (\alpha_{si_s} + \alpha_{sj_s} + \alpha_{sk_s} + \alpha_{sl_s})$$

$$= 4\bar{f} \sum_r \sum_{i_r} \alpha_{ri_r} \Delta p_{ri_r}. \tag{11}$$

PARTIAL CHANGE IN MEAN FERTILITY

Let us consider the change in the mean fertility from one generation to the next. This change can be caused by a change in the frequency of the couple $((i, j), (k, l))$, noted $\Delta X_{ij,kl}$, by a change in the fertility of the couple $((i, j), (k, l))$, noted $\Delta f_{ij,kl}$, or by a change in these two quantities simultaneously, and this for every couple $((i, j), (k, l))$ in the population. To resume, we have

$$\Delta \bar{f} = \sum_{i,j,k,l} (\Delta X_{ij,kl}) f_{ij,kl} + \sum_{i,j,k,l} X_{ij,kl}(\Delta f_{ij,kl}) + \sum_{i,j,k,l} (\Delta X_{ij,kl})(\Delta f_{ij,kl}). \tag{12}$$

Let $f_{ij,kl}^{(A)}$ be the additive fertility corresponding to $f_{ij,kl}$, that is

$$f_{ij,kl}^{(A)} = \bar{f} + \sum_r (\alpha_{ri_r} + \alpha_{rj_r} + \alpha_{rk_r} + \alpha_{rl_r}),$$

such that, according to (4), we have

$$f_{ij,kl} = f_{ij,kl}^{(A)} + \gamma_{ij,kl}.$$

Then the first term on the right hand side of (12) becomes

$$\sum_{i,j,k,l} (\Delta X_{ij,kl}) f_{ij,kl}^{(A)} + \sum_{i,j,k,l} (\Delta X_{ij,kl}) \gamma_{ij,kl}.$$

We consider the change in the mean fertility only through the changes of couple frequencies and by replacing the fertilities by the corresponding additive fertilities. Therefore, we consider the following partial change in the mean fertility:

$$\Delta_{part}\bar{f} = \sum_{i,j,k,l} (\Delta X_{ij,kl}) f_{ij,kl}^{(A)}$$

$$= \sum_{i,j,k,l} (\Delta X_{ij,kl}) \left[\bar{f} + \sum_r (\alpha_{ri_r} + \alpha_{rj_r} + \alpha_{rk_r} + \alpha_{rl_r})\right]$$

$$= \sum_{i,j,k,l} (\Delta X_{ij,kl}) \sum_r (\alpha_{ri_r} + \alpha_{rj_r} + \alpha_{rk_r} + \alpha_{rl_r})$$

$$= 2 \sum_r \sum_{i_r} \alpha_{ri_r} \sum_{i \ni i_r} \sum_{j,k,l} \Delta(X_{ij,kl} + X_{kl,ij})$$

$$= 4 \sum_r \sum_{i_r} \alpha_{ri_r} \Delta p_{ri_r}. \tag{13}$$

From the above expressions for σ_A^2 and $\Delta_{part}\bar{f}$, we conclude that

$$\Delta_{part}\bar{f} = \frac{\sigma_A^2}{\bar{f}}. \tag{14}$$

Therefore, the partial change in the mean fertility is always exactly equal to the ratio of the additive genetic variance in fertility over the mean fertility. In particular, this partial change is always nonnegative.

OPTIMALITY PRINCIPLE

We may now ask if we could derive an optimality principle for fertility selection similar to that of EWENS (1992) for viability selection. That is, we would like to find a quadratic function of gene frequency changes, $d_{11}, \ldots, d_{ns_n}$, that is minimized, subject to some constraint, at the natural selection values, $\Delta p_{11}, \ldots, \Delta p_{ns_n}$.

The gene frequency changes from one generation to the next caused by fertility selection are characterized by (9) for $i_m = 1, \ldots, s_m$ and $m = 1, \ldots, n$. In matrix form, we have

$$\bar{f}\boldsymbol{\delta} = \mathbf{T}\boldsymbol{\alpha}, \tag{15}$$

where

$$\boldsymbol{\delta} = (\delta_1, \ldots, \delta_n) \quad \text{with } \delta_r = (\Delta p_{r1}, \ldots, \Delta p_{rs_r}) \quad \text{for } r = 1, \ldots, n,$$

$$\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_n) \quad \text{with } \alpha_r = (\alpha_{r1}, \ldots, \alpha_{rs_r}) \quad \text{for } r = 1, \ldots, n,$$

$$\mathbf{T} = \|T_{m,r}\|_{m,r=1}^{n} \quad \text{with } T_{m,r} = \|T_{mi_m rj_r}\|_{i_m j_r=1}^{s_m s_r} \quad \text{for } m, r = 1, \ldots, n.$$

It is shown in the APPENDIX that $\mathbf{T}$ is a nonnegative definite symmetric matrix whose nullspace, the space of all $\boldsymbol{\xi}$ such that $\mathbf{T}\boldsymbol{\xi} = 0$, is

$$\mathcal{N} = \left\{ \boldsymbol{\xi} = (\xi_1, \ldots, \xi_n): \xi_r = (\xi_{r1}, \ldots, \xi_{rs_r}) = c_r (1, \ldots, 1) \text{ for } r = 1, \ldots, n \text{ and } \sum_r c_r = 0 \right\}.$$

Moreover, owing to (11), we have

$$4\boldsymbol{\delta}^T\boldsymbol{\alpha} = \frac{\sigma_A^2}{\bar{f}}. \tag{16}$$

Therefore, we consider any vector of gene frequency changes

$$\mathbf{d} = (d_1, \ldots, d_n), \quad \text{with } d_r = (d_{r1}, \ldots, d_{rs_r}) \quad \text{and} \quad \sum_{i_r} d_{ri_r} = 0 \quad \text{for} \quad r = 1, \ldots, n,$$

satisfying

$$4\mathbf{d}^T\boldsymbol{\alpha} = \frac{\sigma_A^2}{\bar{f}}. \tag{17}$$

Owing to (14), this condition fixes the value of the partial change in the mean fertility to be achieved by the changes of gene frequencies at the n loci given by $\mathbf{d}$. We claim the following principle.

MINIMIZING PRINCIPLE. *The quadratic form* $\mathbf{d}^T\mathbf{T}^{-1}\mathbf{d}$ *is minimized at* $\boldsymbol{\delta}$ *over the set of all vectors of gene frequency changes satisfying* (17).

Observe that the quadratic form $\mathbf{d}^T\mathbf{T}^{-1}\mathbf{d}$ is well defined for every vector $\mathbf{d}$ of gene frequency changes, since such a $\mathbf{d}$ is perpendicular to the nullspace $\mathcal{N}$ of $\mathbf{T}$.

Let

$$g(\mathbf{d}) = \mathbf{d}^T\mathbf{T}^{-1}\mathbf{d} - 4\lambda\mathbf{d}^T\boldsymbol{\alpha} - \sum_r \mu_r \sum_{i_r} d_{ri_r},$$

where λ and $\mu_1, \ldots, \mu_n$ are Lagrange multipliers. The partial derivatives of $g(\mathbf{d})$ with respect to the components of $\mathbf{d}$ are

$$2\mathbf{T}^{-1}\mathbf{d} - 4\lambda\boldsymbol{\alpha} - \boldsymbol{\mu},$$

where the ri_r element of the vector $\boldsymbol{\mu}$ is μ_r for $i_r = 1, \ldots, s_r$ and $r = 1, \ldots, n$. Therefore, for all partial derivatives to be 0, we must have

$$\mathbf{d} = 2\lambda\mathbf{T}\boldsymbol{\alpha} + \frac{\mathbf{T}\boldsymbol{\mu}}{2}. \tag{18}$$

But, as shown in the APPENDIX for a vector in the form of $\boldsymbol{\mu}$, we have

$$\mathbf{T}\boldsymbol{\mu} = (\mu_1 + \cdots + \mu_n)\mathbf{p}, \tag{19}$$

where $\mathbf{p}$ is the vector of gene frequencies given by

$$\mathbf{p} = (p_1, \ldots, p_n) \text{ with } p_r = (p_{r1}, \ldots, p_{rs_r}), p_{ri_r} > 0 \text{ for } i_r = 1, \ldots, s_r \text{ and } \sum_{i_r} p_{ri_r} = 1 \text{ for } r = 1, \ldots, n.$$

Owing to (15) and (19) and recalling that $\mathbf{d}$ is a vector of gene frequency changes, the summation of all components in the vector equation (18) yields

$$0 = (\mu_1 + \cdots + \mu_n)n,$$

which is possible only if

$$(\mu_1 + \cdots + \mu_n) = 0.$$

Therefore, $\mathbf{T}\boldsymbol{\mu} = \mathbf{0}$ and (18) reduces to

$$\mathbf{d} = 2\lambda\mathbf{T}\boldsymbol{\alpha}. \tag{20}$$

Then, using (15), we get

$$\mathbf{d} = 2\lambda\bar{f}\boldsymbol{\delta},$$

which shows that $\mathbf{d}$ is a multiple of $\boldsymbol{\delta}$. This is compatible with (16) and (17) only if

$$\mathbf{d} = \boldsymbol{\delta},$$

which is the case if

$$\lambda = \frac{1}{2\bar{f}}.$$

Therefore the quadratic form $\mathbf{d}^T\mathbf{T}^{-1}\mathbf{d}$ is minimized at $\boldsymbol{\delta}$ over the set of all vectors of gene frequency changes that would give the same partial change in the mean fertility.

The above minimizing principle can be stated in an equivalent converse form:

MAXIMIZING PRINCIPLE. *Subject to the constraint*

$$\mathbf{d}^T\mathbf{T}^{-1}\mathbf{d} = \frac{\sigma_A^2}{4\bar{f}^2}, \tag{21}$$

the vector $\mathbf{d}$ *of gene frequency changes that maximizes the partial change in mean fertility given by* $4\mathbf{d}^T\boldsymbol{\alpha}$ *is* $\boldsymbol{\delta}$.

To prove the equivalence, let

$$h(\mathbf{d}) = 4\mathbf{d}^T\boldsymbol{\alpha} - \lambda\mathbf{d}^T\mathbf{T}^{-1}\mathbf{d} - \sum_r \mu_r \sum_{i_r} d_{ri_r},$$

where λ and $\mu_1, \ldots, \mu_n$ are Lagrange multipliers. The

partial derivatives of $h(\mathbf{d})$ with respect to the components of $\mathbf{d}$ are

$$4\boldsymbol{\alpha} - 2\lambda\mathbf{T}^{-1}\mathbf{d} - \boldsymbol{\mu}.$$

Equating all partial derivatives to 0 produces

$$\mathbf{d} = \frac{2\mathbf{T}\boldsymbol{\alpha}}{\lambda} - \frac{\mathbf{T}\boldsymbol{\mu}}{2\lambda}. \tag{22}$$

As shown above, we have $\mathbf{T}\boldsymbol{\mu} = \mathbf{0}$, so that

$$\mathbf{d} = \frac{2\mathbf{T}\boldsymbol{\alpha}}{\lambda} = \frac{2\bar{f}\boldsymbol{\delta}}{\lambda}. \tag{23}$$

Then (21) becomes

$$\frac{4\bar{f}^2}{\lambda^2}\boldsymbol{\delta}'\mathbf{T}^{-1}\boldsymbol{\delta} = \frac{\sigma_A^2}{4\bar{f}^2},$$

which gives, owing to (15) and (16),

$$\lambda = 2\bar{f},$$

and hence

$$\mathbf{d} = \boldsymbol{\delta}.$$

Remark. The Hessian matrix of $g(\mathbf{d})$ is $2\mathbf{T}^{-1}$ while the Hessian matrix of $h(\mathbf{d})$ is $-2\mathbf{T}^{-1}$. To ensure that $g(\mathbf{d})$ is minimized while $h(\mathbf{d})$ is maximized at the critical point $\mathbf{d} = \boldsymbol{\delta}$, we have to check that the matrix $\mathbf{T}^{-1}$ is positive definite, or equivalently that the matrix $\mathbf{T}$ is positive definite, on the set of all vectors of gene frequency changes. This is shown in the APPENDIX. Note also that the Hessian matrix of $\bar{S}$ is $8\mathbf{T}$, which is positive definite on the set of all α satisfying (5). This guarantees that the additive allelic effects minimize $\bar{S}$.

DISCUSSION

FISHER (1930, 1958) stated his Fundamental Theorem of Natural Selection (FTNS) in a context of Malthusian individual fitness in continuous-time models in the following words: *"The rate of increase in fitness of any organism at any time is equal to its genetic variance in fitness at that time."* By genetic variance, Fisher meant what we call today additive genetic variance or genic variance.

Analyzing a multiallele one-locus model, KIMURA (1958) found that the total rate of increase in fitness is exactly equal to the additive genetic variance only if the Malthusian fitness parameters are constant and there is no dominance or, if there is dominance, then the coefficients of departure from Hardy-Weinberg proportions for genotypic frequencies are constant. In the case of several loci, there must be in addition no epistatic effects or, otherwise, constant coefficients of departure from random combinations of alleles at different loci. Under the hypotheses of constant fitness parameters and random combinations of alleles intra- and interlocus, KIMURA (1958) also showed the following Maximum Principle (see also CROW and KIMURA 1970): *"For a given short time interval* [. . .], *natural selection causes gene frequency changes* [. . .] *in such a way that the increase of population fitness* [. . .] *shall be maximum under the restriction* [that a relation between the gene frequency changes and the additive genetic variance be satisfied; see below for a precise statement in the case of discrete-time models]". Finally, it was claimed, without proof, that this principle could be extended to more general situations.

For discrete-time models with random mating and individual fitness expressed by constant selective values understood as expected contributions to the next generation and determined at a single multiallelic locus, WRIGHT (1937, 1942) had shown that a gene increases in frequency from one generation to the next if and only if an infinitesimal increase of this gene alone, all other genes decreasing in frequency at the same relative rate, would increase the mean fitness. His conclusion is the following (WRIGHT 1942): *"the mean selective values of possible random breeding populations form a surface* [. . .], *the gradient of which determines the way in which the population tends to change under the influence of selection"*. Such a surface has been called an adaptive topography. It was proved later, under the same assumptions, that the mean fitness increases from one generation to the next (MULHOLLAND and SMITH 1959; SCHEUER and MANDEL 1959; KINGMAN 1961). This increase is given exactly by the ratio of the additive genetic variance over the mean fitness, which is always nonnegative, plus another term that may be negative but without exceeding the first one in absolute value (see, *e.g.*, LI 1969). With nonrandom mating, there is an extra term that is generally nonnegligible (see, *e.g.*, KEMPTHORNE 1957). More terms have to be added for the change of the mean fitness if selective values are variable or determined at two or several loci in discrete-time as well as continuous-time models with or without random mating (see, *e.g.*, KIMURA 1958; CROW and NAGYLAKI 1976; NAGYLAKI 1989). In such cases, it is well known that the mean fitness may decrease (see, *e.g.*, WRIGHT 1942; KOJIMA and KELLEHER 1961; MORAN 1964; KIMURA 1965) and cycles may exist (HASTINGS 1981; AKIN 1982). With selection for fecundity of mating pairs, steady decreases or oscillations of the mean fitness can occur even in the case of constant selection parameters determined at a single locus in random mating populations (see, *e.g.*, HADELER and LIBERMAN 1975; POLLAK 1978), but then the selection parameters must not be products of two factors associated with the genotypes of the mates irrespective of sex, which lead to a situation equivalent to a viability model complying with the steady increase of the mean value (BODMER 1965; see EWENS 1979 and NAGYLAKI 1992, for more details). Thus there are several difficulties associated with the conventional interpretation of the fundamental theorem.

But if a theorem is to be called the Fundamental Theorem of Natural Selection, it should be of general

validity. One view is to consider that the FTNS is a good approximation if selection is weak enough (see, *e.g.*, CROW and KIMURA 1970; NAGYLAKI 1992). It has been shown, for instance, that the change in the mean fitness in discrete-time models is approximately given by the additive genetic variance at least after enough generations and away enough from equilibrium in cases of viability selection parameters close enough to 1 and determined at several linked loci (NAGYLAKI 1993) and in cases of sex-differentiated viability and fertility selection parameters close enough to 1 and determined at a single multiallelic locus if the mean fitness is defined in an appropriate way (NAGYLAKI 1987; LESSARD 1993). To the order of the approximations, these results entail the increase of the mean fitness as long as there is enough genetic variability.

Another view is to consider that the FTNS is exact but *"the rigour of the demonstration requires that the terms employed should be used strictly as defined"* (FISHER 1958). This is the view of PRICE (1972) for continuous-time models and EWENS (1989) for discrete-time as well as continuous-time models. According to PRICE (1972), the FTNS concerns the change in mean fitness due to natural selection (that is, due to additive effects of changes in gene frequencies) and not the total change that also comprises the change due to environment effects (including dominance and epistasis). The change in mean fitness due to natural selection is equal to what EWENS (1989) has called the partial change in mean fitness. This change can be obtained by replacing the fitness of every genotype by the corresponding additive fitness (*"the value of the genotype as best predicted from the genes present"*) (FISHER 1958) and by considering the change in the mean value only through changes in genotypic frequencies. This is in agreement with the equations in FISHER's (1958) proof of the FTNS but not necessarily with Fisher's words and his derivation of the FTNS as made clear by PRICE (1972). According to EWENS (1989), the FTNS is about the partial change in mean fitness and is not limited to continuous-time models. For discrete-time models he claims that the following interpretation applies. The partial change in mean fitness is equal to the ratio of the additive genetic variance in fitness over the mean fitness. This was shown originally in the case of viability differences among individuals determined at any number of loci with any number of alleles at these loci and without any assumption of random mating. It is remarkable that the same statement exactly holds in the case of fertility selection on mating pairs. Hence EWENS' interpretation of the FTNS proves to be applicable to an important class of models without restrictive assumptions on the number of loci and number of alleles at these loci and on the mating scheme. The only condition on mating is that the gene frequencies be the same before and after mating, which is the case with several regular systems of inbreeding and some uniform patterns of assortative mating. Since there is no viability selection in the paper at hand, this condition means that the gene frequencies do not change from the time of conception to the time of reproduction. With viability selection from the time of conception to the time of mating but no fertility selection, nor meiotic and gametic selection, the same condition would mean invariant gene frequencies from the time of mating to the time of conception of the next generation. This is the assumption made in EWENS (1989).

The equations characterizing the additive allelic effects on fertility determined at several loci, linked or not, and without any assumption of random mating, are of prime interest. These equations involve only the mean fertility, the vector of gene frequency changes and a nonnegative definite symmetric matrix, noted $\mathbf{T}$, that depends on the genetic structure in couples, specifically on the joint distributions of all pairs of genes in couples. The part of this matrix that concerns pairs of genes in individuals has already been found, and has been noted $\mathbf{V}$, in the equations characterizing the additive allelic effects on viability determined at many loci without the assumption of random mating (CASTILLOUX and LESSARD 1995). At least if every possible couple type has a positive frequency, the matrix $\mathbf{T}$ is positive definite on the set of all vectors of gene frequency changes and therefore invertible on this set. This is also the case for the matrix $\mathbf{V}$ at least if every possible genotype has a positive frequency.

The matrix $\mathbf{T}$ plays a central role in optimality principles associated with fertility selection. If we write

$$(\mathbf{d} - \boldsymbol{\delta})^T\mathbf{T}^{-1}(\mathbf{d} - \boldsymbol{\delta}) = \mathbf{d}^T\mathbf{T}^{-1}\mathbf{d} - 2\mathbf{d}^T\mathbf{T}^{-1}\boldsymbol{\delta} + \boldsymbol{\delta}^T\mathbf{T}^{-1}\boldsymbol{\delta}, \quad (24)$$

where $\boldsymbol{\delta}$ is the vector of gene frequency changes resulting from fertility selection, then it is clear that, over the set of all vectors of gene frequency changes,

$$\text{minimizing } \mathbf{d}^T\mathbf{T}^{-1}\mathbf{d} \quad \text{subject to} \quad \mathbf{d}^T\mathbf{T}^{-1}\boldsymbol{\delta} = \frac{\sigma_A^2}{4\bar{f}^2} \quad (25)$$

gives the same solution $\mathbf{d} = \boldsymbol{\delta}$ as

$$\text{maximizing } \mathbf{d}^T\mathbf{T}^{-1}\boldsymbol{\delta} \quad \text{subject to} \quad \mathbf{d}^T\mathbf{T}^{-1}\mathbf{d} = \frac{\sigma_A^2}{4\bar{f}^2}, \quad (26)$$

since

$$\boldsymbol{\delta}^T\mathbf{T}^{-1}\boldsymbol{\delta} = \frac{\boldsymbol{\delta}^T\boldsymbol{\alpha}}{\bar{f}} = \frac{\sigma_A^2}{4\bar{f}^2}, \quad (27)$$

owing to (15) and (16), where σ_A^2 is the additive genetic variance in fertility, and

$$(\mathbf{d} - \boldsymbol{\delta})^T\mathbf{T}^{-1}(\mathbf{d} - \boldsymbol{\delta}) \geq 0 \text{ with equality if and only if } \mathbf{d} = \boldsymbol{\delta}, \quad (28)$$

if $\mathbf{d}$ is to be a vector of gene frequency changes. This shows the equivalence of the two optimality principles.

If we make the change of variables

$$\mathbf{a} = \bar{f}\mathbf{T}^{-1}\mathbf{d}, \tag{29}$$

defined such that

$$\mathbf{a} = (a_1, \ldots, a_n) \quad \text{with} \quad a_r = (a_{r1}, \ldots, a_{rs_r}) \quad \text{for} \quad r = 1, \ldots, n$$

satisfies

$$\sum_{i_r} a_{ri_r} p_{ri_r} = 0 \quad \text{for} \quad r = 1, \ldots, n, \tag{30}$$

then the quadratic form (24) becomes

$$\frac{1}{\bar{f}^2}(\mathbf{a} - \bar{f}\mathbf{T}^{-1}\boldsymbol{\delta})^T\mathbf{T}(\mathbf{a} - \bar{f}\mathbf{T}^{-1}\boldsymbol{\delta}), \tag{31}$$

whose partial derivatives with respect to the components of $\mathbf{a}$ are given by

$$\frac{2}{\bar{f}^2}(\mathbf{T}\mathbf{a} - \bar{f}\boldsymbol{\delta}^T\mathbf{a}), \tag{32}$$

which gives also the partial derivatives of

$$\frac{1}{4\bar{f}^2}\sum_{i,j,k,l} X_{ij,kl}\left[f_{ij,kl} - \bar{f} - \sum_r (a_{ri_r} + a_{rj_r} + a_{rk_r} + a_{rl_r})\right]^2, \tag{33}$$

owing to (6), (7) and (9). But (31) is obviously minimum when

$$\mathbf{a} = \bar{f}\mathbf{T}^{-1}\boldsymbol{\delta}, \tag{34}$$

which gives the additive allelic effects. Therefore, the optimality principles for fertility selection have the same biological grounds (the definition of additive allelic effects) as the corresponding principles for viability selection (EWENS 1992, 1995).

Notice that

$$\boldsymbol{\delta}^T\mathbf{T}^{-1}\mathbf{d} = \frac{\mathbf{d}^T\boldsymbol{\alpha}}{\bar{f}}, \tag{35}$$

where $\boldsymbol{\alpha}$ is the vector of the additive allelic effects given by (15). This is a multiple of the partial change in the mean fertility corresponding to changes in gene frequencies given by $\mathbf{d}$, which is $4\mathbf{d}^T\boldsymbol{\alpha}$. Therefore, (26) shows that the vector of gene frequency changes $\mathbf{d}$ that maximizes the partial change in the mean fertility is the vector of gene frequency changes $\boldsymbol{\delta}$ resulting from natural selection, under the constraint

$$\mathbf{d}^T\mathbf{T}^{-1}\mathbf{d} = \frac{\sigma_A^2}{4\bar{f}^2}. \tag{36}$$

Observe that the quadratic form $\mathbf{d}^T\mathbf{T}^{-1}\mathbf{d}$ defines a metric on the set of all vectors of gene frequency changes, since $\mathbf{T}^{-1}$ is positive definite on this set.

If there is random mating, then $\mathbf{T}$ takes the form

$$\mathbf{T} = D_\mathbf{p} + \mathbf{P} + \mathbf{Q} + 2\mathbf{p}\mathbf{p}^T, \tag{37}$$

where $\mathbf{p}$ is the vector of gene frequencies at n loci, which is a positive vector in the form

$$\mathbf{p} = (p_1, \ldots, p_n) \quad \text{with} \quad p_r = (p_{r1}, \ldots, p_{rs_r}), \sum_{i_r} p_{ri_r} = 1, \quad \text{for } r = 1, \ldots, n,$$

$D_\mathbf{p}$ is the diagonal matrix with the components of $\mathbf{p}$ on the diagonal, $\mathbf{P}$ is the matrix whose (mi_m, rj_r) element is the frequency of all gametes in mated individuals carrying $A_{i_m}^{(m)}$ at locus m and $A_{j_r}^{(r)}$ at locus r for $i_m = 1, \ldots, s_m$ and $i_r = 1, \ldots, s_r$ for m, $r = 1, \ldots, n$ $(m \neq r)$ and whose (mi_m, mj_m) element is 0 for $i_m, j_m = 1, \ldots, s_m$ for $m = 1, \ldots, n$, and $\mathbf{Q}$ is the matrix whose (mi_m, rj_r) element is the frequency of all genotypes among mated individuals carrying $A_{i_m}^{(m)}$ at locus m on one gamete chosen at random and $A_{j_r}^{(r)}$ at locus r on the other gamete for $i_m = 1, \ldots, s_m$ and $j_r = 1, \ldots, s_r$ for m, $r = 1, \ldots, n$.

If there is random mating and fertilities are multiplicative, being products of two factors associated with the genotypes of the mates irrespective of sex, then

$$\mathbf{Q} = \mathbf{p}\mathbf{p}^T$$

and

$$\mathbf{T} = \mathbf{D}_\mathbf{p} + \mathbf{P} + 3\mathbf{p}\mathbf{p}^T. \tag{38}$$

This model is equivalent to a viability model without sex differences. In this case, if $\mathbf{d}$ is a vector of gene frequency changes in the form

$$\mathbf{d} = (d_1, \ldots, d_n) \quad \text{with} \quad d_r = (d_{r1}, \ldots, d_{rs_r}), \sum_{i_r} d_{ri_r} = 0, \quad \text{for} \quad r = 1, \ldots, n,$$

then the vector

$$\mathbf{b} = \mathbf{T}^{-1}\mathbf{d}$$

can be chosen in the form (see the APPENDIX)

$$\mathbf{b} = (b_1, \ldots, b_n) \quad \text{with} \quad b_r = (b_{r1}, \ldots, b_{rs_r}) \quad \text{and} \quad \sum_{i_r} b_{ri_r} p_{ri_r} = 0 \quad \text{for} \quad r = 1, \ldots, n.$$

Then $\mathbf{b}$ satisfies

$$\mathbf{T}\mathbf{b} = (D_\mathbf{p} + \mathbf{P})\mathbf{b} = \mathbf{d}, \tag{39}$$

from which we have

$$\mathbf{b} = (D_\mathbf{p} + \mathbf{P})^{-1}\mathbf{d} \tag{40}$$

and

$$\mathbf{d}^T\mathbf{T}^{-1}\mathbf{d} = \mathbf{d}^T(D_\mathbf{p} + \mathbf{P})^{-1}\mathbf{d}. \tag{41}$$

This reduces to the Riemannian metric used by SHAHSHAHANI (1979) to interpret Kimura's Maximum Principle, but only in the case of a single locus for which

$$\mathbf{d}^T(D_\mathbf{p} + \mathbf{P})^{-1}\mathbf{d} = \mathbf{d}^T D_\mathbf{p}^{-1}\mathbf{d}. \tag{42}$$

As a matter of fact, in this particular case, the maximizing principle corresponds to KIMURA's (1958) principle and the minimizing principle to EDWARDS' (1974) equivalent principle. It suffices to replace the factor 4 by a factor 2 and to change fertility for fitness to get the exact corresponding statement (see EWENS 1992). In general, with two or more loci, the metric (41) differs from the SHAHSHAHANI metric used to study linkage and epistasis in viability models with random mating, which is obtained from the inverse of the diagonal matrix with the gametic frequencies on the diagonal (see, *e.g.*, AKIN 1979).

Finally, our results can be applied to fertility-viability selection models with general fertilities and sex-differentiated viabilities in nonrandom mating populations since sex-differentiated viability selection and nonrandom mating can be incorporated into fertility selection models with random pairings of males and females if fertility parameters, possibly frequency-dependent, are appropriately defined. This is done by ROUX (1977) for one-locus models (see HOFBAUER and SIGMUND 1988). The extension to multilocus models with recombination appears to be straightforward.

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APPENDIX

Recall that $\mathbf{T}$ is a matrix whose (mi_m, rj_r) element is four times the probability that two genes chosen at random and independently, the first one at locus m and the second one at locus r, in a same couple chosen at random, be $A_{i_m}^{(m)}$ and $A_{j_r}^{(r)}$ in this order. Conditioning on the couple type, we get the expression

$$\mathbf{T} = 4 \sum_{i,j,k,l} X_{ij,kl} \mathbf{N}_{ij,kl} \mathbf{N}_{ij,kl}^T, \qquad \text{(A1)}$$

where $X_{ij,kl}$ is the frequency of couple $((i, j), (k, l))$ and $\mathbf{v}_{ij,kl}$ is the vector of allelic frequencies in couple $((i, j), (k, l))$. More precisely, the $r\gamma_r$ element of $\mathbf{v}_{ij,kl}$ gives the frequency of $A_{\gamma_r}^{(r)}$ among the genes carried by the gametes i, j, k, l at locus r for $\gamma_r = 1, \ldots, s_r$ and $r = 1, \ldots, n$. Therefore the components of $\mathbf{v}_{ij,kl}$ can take as values $0, {}^1/_4, {}^1/_2, {}^3/_4, 1$ and the ones associated to the same locus sum up to 1, that is,

$$\mathbf{v}_{ij,kl}^{(r\gamma_r)} = 0 \text{ or } {}^1/_4 \text{ or } {}^1/_2 \text{ or } {}^3/_4 \text{ or } 1,$$

$$\text{for} \quad \gamma_r = 1, \ldots, s_r, \qquad \text{(A2)}$$

and

$$\sum_{\gamma_r} \mathbf{v}_{ij,kl}^{(r\gamma_r)} = 1, \quad \text{for} \quad r = 1, \ldots, n. \qquad \text{(A3)}$$

Note that, since $\mathbf{T}$ is a linear combination of nonnegative definite symmetric matrices with nonnegative coefficients, it is necessarily a nonnegative definite symmetric matrix. Therefore, $\boldsymbol{\xi} = (\xi_1, \ldots, \xi_n)$ with $\xi_r = (\xi_{r1}, \ldots, \xi_{rs_r})$ for $r = 1, \ldots, n$ is in the nullspace of $\mathbf{T}$, noted $\mathcal{N}$, that is, satisfies $\mathbf{T}\boldsymbol{\xi} = 0$, if and only if $\boldsymbol{\xi}^T\mathbf{T}\boldsymbol{\xi} = 0$. But, we have

$$\boldsymbol{\xi}^T\mathbf{T}\boldsymbol{\xi} = 4 \sum_{i,j,k,l} X_{ij,kl}(\mathbf{v}_{ij,kl}^T\boldsymbol{\xi})^2, \tag{A4}$$

and this is equal to 0 if and only if

$$\mathbf{v}_{ij,kl}^T\boldsymbol{\xi} = 0 \tag{A5}$$

as soon as $X_{ij,kl} > 0$, which is the case for all i, j, k, l by assumption. In particular, for i, j, k, l such that

$$\mathbf{v}_{ij,kl}^{(m\gamma_m)} = 1$$

and for $\tilde{i}, \tilde{j}, \tilde{k}, \tilde{l}$ such that

$$\mathbf{v}_{\tilde{i}\tilde{j},\tilde{k}\tilde{l}}^{(m\beta_m)} = 1 \quad \text{for} \quad \beta_m \neq \gamma_m$$

and

$$\mathbf{v}_{\tilde{i}\tilde{j},\tilde{k}\tilde{l}}^{(r\gamma_r)} = \mathbf{v}_{ij,kl}^{(r\gamma_r)} \quad \text{for} \quad \gamma_r = 1, \ldots, s_r \quad \text{and} \quad r \neq m,$$

we have, recalling (A2) and (A3), that

$$\begin{aligned} 0 &= \mathbf{v}_{ij,kl}^T\boldsymbol{\xi} - \mathbf{v}_{\tilde{i}\tilde{j},\tilde{k}\tilde{l}}^T\boldsymbol{\xi} \\ &= \sum_r \sum_{\gamma_r} [\mathbf{v}_{ij,kl}^{(r\gamma_r)} - \mathbf{v}_{\tilde{i}\tilde{j},\tilde{k}\tilde{l}}^{(r\gamma_r)}]\xi_{r\gamma_r} \\ &= \xi_{m\gamma_m} - \xi_{m\beta_m}. \end{aligned} \tag{A6}$$

We conclude that every $\boldsymbol{\xi}$ in the nullspace of $\mathbf{T}$ must be in the form

$$\boldsymbol{\xi} = (\xi_1, \ldots, \xi_n) \quad \text{with} \quad \xi_r = c_r(1, \ldots, 1) \quad \text{for} \quad r = 1, \ldots, n. \tag{A7}$$

But then, owing to (A1) and (A3), we have

$$\begin{aligned} \mathbf{T}\boldsymbol{\xi} &= 4 \sum_{i,j,k,l} X_{ij,kl}\mathbf{v}_{ij,kl}\left(\sum_r c_r\right) \\ &= 4\left(\sum_r c_r\right)\mathbf{p}, \end{aligned} \tag{A8}$$

where $\mathbf{p}$ is the vector of gene frequencies in the population, that is,

$$\mathbf{p} = (p_1, \ldots, p_n), \quad p_r = (p_{r1}, \ldots, p_{rs_r})$$

$$\text{for} \quad r = 1, \ldots, n, \quad p_{ri_r} > 0 \quad \text{for} \quad i_r = 1, \ldots, s_r \quad \text{and} \quad \sum_{i_r} p_{ri_r} = 1 \quad \text{for} \quad r = 1, \ldots, n.$$

In such a case, we get

$$\boldsymbol{\xi}^T\mathbf{T}\boldsymbol{\xi} = 4\left(\sum_r c_r\right)^2,$$

and this is 0, that is $\boldsymbol{\xi}$ in the form (A7) is in the nullspace $\mathcal{N}$ of $\mathbf{T}$, if and only if

$$\sum_r c_r = 0. \tag{A9}$$

As a consequence, the image space of $\mathbf{T}$, which is the subspace perpendicular to $\mathcal{N}$, necessarily contains the set of all vectors of gene frequency changes. Moreover, $\mathbf{T}$ is positive definite, and invertible, on its image space.

By convention, we can choose

$$\mathbf{b} = \mathbf{T}^{-1}\mathbf{d}, \tag{A10}$$

where $\mathbf{d}$ is a vector of gene frequency changes, such that

$$\mathbf{b} = (b_1, \ldots, b_n) \quad \text{with} \quad b_r = (b_{r1}, \ldots, b_{rs_r}) \quad \text{and} \quad \sum_{i_r} b_{ri_r}p_{ri_r} = 0 \quad \text{for} \quad r = 1, \ldots, n.$$

If this is not the case, it suffices to replace $\mathbf{b}$ by

$$\tilde{\mathbf{b}} = \mathbf{b} - \boldsymbol{\xi}, \tag{A11}$$

where

$$\boldsymbol{\xi} = (\xi_1, \ldots, \xi_n) \quad \text{with} \quad \xi_r = c_r(1, \ldots, 1) \quad \text{and} \quad c_r = \sum_{i_r} b_{ri_r}p_{ri_r} \quad \text{for} \quad r = 1, \ldots, n.$$

Then, the vector

$$\tilde{\mathbf{b}} = (\tilde{b}_1, \ldots, \tilde{b}_n) \quad \text{with} \quad \tilde{b}_r = (\tilde{b}_{r1}, \ldots, \tilde{b}_{rs_r}) \quad \text{for} \quad r = 1, \ldots, n$$

satisfies

$$\sum_{i_r} \tilde{b}_{ri_r}p_{ri_r} = \sum_{i_r} (b_{ri_r} - c_r)p_{ri_r} = \sum_{i_r} b_{ri_r}p_{ri_r} - c_r = 0,$$

for $r = 1, \ldots, n$. Moreover, we have

$$\mathbf{T}\tilde{\mathbf{b}} = \mathbf{T}\mathbf{b} - \mathbf{T}\boldsymbol{\xi} = \mathbf{T}\mathbf{b}, \tag{A12}$$

since, owing to (A8) and (A10), we have

$$\begin{aligned} \mathbf{T}\boldsymbol{\xi} = 4\left(\sum_r c_r\right)\mathbf{p} = 4(\mathbf{p}^T\mathbf{b})\mathbf{p} &= 4\left[\left(\frac{\mathbf{T}\mathbf{1}}{4n}\right)^T\mathbf{T}^{-1}\mathbf{d}\right]\mathbf{p} \\ &= \frac{1}{n}(\mathbf{1}^T\mathbf{d})\mathbf{p} = 0, \end{aligned} \tag{A13}$$

where $\mathbf{1}$ is the vector with every component equal to 1. Equation A13 means that $\boldsymbol{\xi}$ is in the nullspace of $\mathbf{T}$ and (A12) means that the image of $\tilde{\mathbf{b}}$ is the same as the image of $\mathbf{b}$, which is $\mathbf{d}$ by (A10), that is

$$\mathbf{T}\tilde{\mathbf{b}} = \mathbf{d}$$

or

$$\tilde{\mathbf{b}} = \mathbf{T}^{-1}\mathbf{d}.$$