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Perspective

The change in a mean measurement that is invariant under reshuffling of genes

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Abstract

Fisher's fundamental theorem of natural selection continues to be widely cited in the literature but there is still misunderstanding about its interpretation and significance. Even though it is now recognized that the additive genetic variance in its statement captures only a partial rate of change in mean fitness, the original terms and arguments used to present it remain unclear, not to mention its real meaning. Here, we revisit the interpretation of this partial rate of change. Applying the properties of the additive genetic values and residual addends of a quantitative trait to the relative growth rate of genotype frequency in a diploid population, and comparing two reproductive systems, clonal reproduction and sexual reproduction with either random union of gametes or random mating with additive fecundities of mating types, we argue that this additive genetic rate of change corresponds to the change that is invariant under reshuffling of genes. We show that this is actually the case for the partial rate of change in the mean of any measurement given by the additive genetic covariance with fitness. We focus on the one-locus multiallele setting in continuous time without age effects for simplicity, but the conclusion can be extended to multilocus settings with age effects in continuous time as well as discrete time.

Keywords: average allelic effect, constant genic environment, covariance formulas, fundamental theorems of natural selection, relative growth rate, additive genetic component

Introduction

It has been pointed out that the additive genetic variance in fitness in Fisher's (1930, 1958) fundamental theorem of natural selection (FTNS) accounts for only part of the change in mean fitness (Edwards, 1994, 2002; Ewens, 1989; Frank & Slatkin, 1992; Lessard, 1997; Price, 1972). As a matter of fact, the total change generally involves other terms (Kempthorne, 1957; Kimura, 1958; Lessard, 1997). These extra terms cannot be neglected even with constant genotypic fitnesses in random mating populations in a constant environment unless selection is very weak (Nagylaki, 1976, 1992, 1993).

The importance given to the FTNS in population genetics comes a great deal from its name and the status of R.A. Fisher, one of the founders of the field. Nevertheless, the exact significance of the change meant in its statement is still debated nowadays (Birch, 2016; Edwards, 2014, 2016; Ewens & Lessard, 2015; Frank, 2014; Frank & Fox, 2020; Garcia-Pintos, 2024; Grafen, 2018, 2021; Lessard & Ewens, 2019; Queller, 2017; Smith, 2023; van Veelen, 2018). In Lessard & Ewens (2019), it was argued that this change in the mean of the population does not fully capture the change due to all changes in gene frequencies even as a change in a constant environment including a constant genic environment. This concept based on constraints on changes in genotype frequencies was presented in Fisher (1941) to clarify the difference between the average effect and the average excess of a gene substitution. A condition for a constant genic environment in a multilocus multialle setting was proposed in Lessard (1997) but this condition does not reduce to the condition at each marginal locus given in Fisher (1941) in the case of two alleles at each locus. Moreover, it was noticed in Lessard & Ewens (2019) that the concept itself looks like a tautology, since the genic environment is constant when the relative change in genotype frequency is approached by average allelic effects, while the change in the mean of any measurement depends only on average allelic effects when the genic environment is constant.

In a recent review, Ewens (2024) rejects the idea that Fisher (1930, 1958) meant a partial change in mean fitness in his statement of the FTNS, but a total change. He concludes that it "was not correct" and "should be banned from the literature." Although we remain very critical about the significance of the FTNS, we do not adhere to this view. The debate on the subject, however, deserves constant attention since many still believe that the FTNS implies an increase in the mean fitness. Moreover, this "theorem" is widely cited not only in population genetics but also in many related fields such as molecular biology and immunology (Bukkuri & Brown, 2023; Bukkuri et al., 2023; Schuster & Stadler, 2023), not to mention less related fields having little to do with Mendelian genetics such as economics (Koyama, 2020), game theory (Jaćimović, 2023) and even philosophy (McLoone, 2024; Okasha, 2008).

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The assumptions made by Fisher (1930, 1958) to deduce the FTNS are not recalled in its statement, and we have to resort to the terms and definitions used in its proof to understand its exact meaning. First, the change that the FTNS concerns is simply said to be "produced by Natural Selection" (Fisher, 1930, p. 42, 1958, p. 45). Second, it is generally described as a change "due to all changes in gene [frequencies]" (Fisher, 1930, p. 35, 1958, p. 37). Third, and not the least, the change in question is actually explained by gene substitution used to introduce the concept of an average allelic effect before the statement of the FTNS. With multiple alleles at a single locus, this effect is interpreted as the amount of the difference produced, on the average, in the total measurement of the population, "[by] substituting [the] chosen gene for a random selection of the genes homologous with it" (Fisher, 1958, p. 35) or, in the particular case of two alleles, "by the substitution of the one gene to the other" (Fisher, 1930, p. 31). Mathematically, the values of the average allelic effects are obtained by the least-mean-squares method as "the best additive system for predicting the genotypic value from the actual genes present in any individual" (Fisher, 1958, p. 35).

The proof of the FTNS in a continuous-time setting relies essentially on the claim that "any increase dp in the frequency of [a] chosen gene will be accompanied by an increase $2\alpha dp$ in the average fitness of the species" (Fisher, 1958, p. 37), where α is the average allelic effect. In Price [1972, Equation (5.8)], this claim is interpreted as meaning that 2α is a kind of partial derivative of the average fitness with respect to the frequency of the chosen gene. Then the partial change in mean fitness can be obtained by replacing the genotypic fitness by its best linear prediction from the genes present in the genotype and by keeping this predicted value constant. A similar approach is used in Ewens (1989) for a discrete-time version of Price's (1972) interpretation. See also Castilloux & Lessard (1995) for the equation that characterizes the average allelic effects in a multilocus setting.

In Fisher (1941), however, the partial change in the simplest continuous-time one-locus two-allele setting is obtained in a different way by keeping the genotypic fitness fixed and by assuming no change in the ratio of the squared frequency of the heterozygotes over the product of the frequencies of both homozygotes. This defines a change in a constant environment, including a constant genic environment. In Lessard (1997), this approach is shown to be equivalent to replacing the relative changes in genotype frequencies by their best linear predictions and is extended to multilocus multiallelle models in discrete time with or without overlapping generations as well as in continuous time with or without age effects. Moreover, the approach can be applied to the change in the mean of any measurement correlated with fitness to get Robertson's (1966) secondary theorem of natural selection, STNS (see, e.g., Crow & Nagylaki, 1976; Nagylaki, 1993, and references therein), which is related to a covariance formula for the change in the frequency of an allele (Li, 1967, Price, 1970).

Nevertheless, the concept of constant genic environment is still widely misunderstood as suggested by recent papers on the interpretation and significance of the FTNS (Ewens, 2024; Grafen, 2018; Lessard & Ewens, 2019). The objective here is to bring some clarification on this concept and propose a new interpretation for the partial change in the mean of any measurement that is suggested by this concept.

In the next sections, we consider any constant measurement determined at a single multiallelic locus and explain how to get the partial rate of change in its mean in a continuous-time model in a constant genic environment. Applying this to the Malthusian parameter measuring fitness without age effects and comparing two reproductive systems, namely, clonal reproduction and sexual reproduction with either random union of gametes or random mating with additive fecundities of mating types, we come back to the interpretation of the additive genetic variance in fitness. The interpretation proposed can be extended to more general settings in continuous time as well as discrete time (multilocus determination and age effects) and applied more generally to the additive genetic covariance with fitness, which gives a partial rate of change (or partial change in discrete time) in the mean of any measurement. We conclude with a discussion section on the implication and significance of this interpretation.

Rate of change of a mean measurement

In order to be as close as possible to Fisher's (1941) framework, we consider a very large diploid population in continuous time and any individual measurement represented by m determined at a single locus in this population. Moreover, we assume multiple allelic types at this locus as in Fisher (1958). Denoting the alleles by $A_1, \ldots, A_n$, the measurement associated with the ordered genotype A_iA_j is represented by $m_{ij} = m_{ji}$, and the frequency of this genotype in the population at time $t \geq 0$ by $P_{ij} = P_{ji}$, for $i, j = 1, \ldots, n$. The corresponding frequency of allele A_i is given by $p_i = \sum_{j=1}^{n} P_{ij}$ for $i = 1, \ldots, n$.

Assuming that the measurement takes constant values that do not depend on age and do not change over time, the total rate of change of its mean $\bar{m} = \sum_{i,j=1}^{n} m_{ij}P_{ij}$ can be expressed as

$$\frac{d\bar{m}}{dt} = \sum_{i,j=1}^{n} m_{ij}\frac{dP_{ij}}{dt} = \sum_{i,j=1}^{n} (m_{ij} - \bar{m})\frac{dP_{ij}}{dt}$$

$$= \sum_{i,j=1}^{n} (m_{ij} - \bar{m})r_{ij}P_{ij}, \tag{1}$$

where

$$r_{ij} = \frac{d}{dt}\log P_{ij} = \frac{1}{P_{ij}}\frac{dP_{ij}}{dt} \tag{2}$$

for $i, j = 1, \ldots, n$. Then, since

$$\bar{r} = \sum_{i,j=1}^{n} r_{ij}P_{ij} = \sum_{i,j=1}^{n} \frac{dP_{ij}}{dt} = \frac{d}{dt}\left(\sum_{i,j=1}^{n} P_{ij}\right) = 0, \tag{3}$$

we have

$$\frac{d\bar{m}}{dt} = \mathrm{cov}(m, r). \tag{4}$$

Here, r represents the relative growth rate of genotype frequency.

Now, using the least-mean-squares method for linear regression on the number of genes of each type in an individual (0, 1, or 2, see Supplementary Material, Section 1), we have the decompositions $m = \bar{m}$ α δ and $r = \beta$, where α and β are the additive genetic values of m and

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r, respectively. These can be expressed as $\alpha = 2\sum_{i=1}^{n} \alpha_i f_i$ and $\beta = 2\sum_{i=1}^{n} \beta_i f_i$, where α_i and β_i denote here the average effects of allele A_i on m and r, respectively, and f_i is the frequency of A_i in the individual, for $i = 1, \ldots, n$. This means that α and β take the values $\alpha_i \quad \alpha_j$ and $\beta_i \quad \beta_j$, respectively, for an individual of genotype A_iA_j for $i, j = 1, \ldots, n$. Moreover, the covariances of α and β with the residual addends δ and $\quad$ are all equal to 0, since $\mathrm{cov}(f_i, \delta) = 0$ and $\mathrm{cov}(f_i, \quad) = 0$ for $i = 1, \ldots, n$. As for the average allelic effects, they are determined by the linear equations $\mathrm{cov}(f_i, m) = 2\sum_{j=1}^{n} \alpha_j \mathrm{cov}(f_i, f_j)$ and $\mathrm{cov}(f_i, r) = 2\sum_{j=1}^{n} \beta_j \mathrm{cov}(f_i, f_j)$ for $i = 1, \ldots, n$ under the constraints $\sum_{i=1}^{n} \alpha_i p_i = 0$ and $\sum_{i=1}^{n} \beta_i p_i = 0$, respectively.

Applying the bilinearity property of the covariance and the uncorrelation between the additive genetic values and the residual addends, Equation (4) can be decomposed as

$$\frac{d\bar{m}}{dt} = \mathrm{cov}(\alpha, \beta) \quad \mathrm{cov}(\delta, \quad). \tag{5}$$

Moreover, since

$$\mathrm{cov}(f_i, \beta) = \mathrm{cov}(f_i, r) = \sum_{j=1}^{n} r_{ij} P_{ij} = \sum_{j=1}^{n} \frac{dP_{ij}}{dt} = \frac{dp_i}{dt} \tag{6}$$

for $i = 1, \ldots, n$, we conclude that

$$\mathrm{cov}(\alpha, \beta) = 2\sum_{i=1}^{n} \alpha_i \mathrm{cov}(f_i, \beta) = 2\sum_{i=1}^{n} \alpha_i \frac{dp_i}{dt}. \tag{7}$$

This additive genetic covariance gives a partial rate of change of the mean measurement $\bar{m}$.

Since $\mathrm{cov}(\bar{m} \quad \alpha, \beta \quad) = \mathrm{cov}(\alpha, \beta)$, the above partial rate of change of $\bar{m}$ is obtained if m_{ij} in Equation (1) is replaced by $\bar{m} \quad \alpha_i \quad \alpha_j$ and is kept constant for $i, j = 1, \ldots, n$ (as in Price, 1972 and Ewens, 1989, for fitness as measurement). The corresponding partial change in a discrete-time setting was called the additive genetic component in Grafen (2018).

Notice that, since $\mathrm{cov}(\bar{m} \quad \alpha \quad \delta, \beta) = \mathrm{cov}(\alpha, \beta)$, the above partial rate of change in the continuous-time setting is also obtained if r_{ij} in Equation (1) is replaced by $\beta_i \quad \beta_j$ for $i, j = 1, \ldots, n$ (as in Lessard, 1997, where the above decomposition of the total rate of change can be found; see also Kimura, 1958; Nagylaki, 1992, p. 90, and Denniston, 1978, for alternative decompositions involving changes of variables).

As suggested in Fisher (1941) and argued in Lessard (1997) (see also Lessard & Ewens, 2019), we can consider that the residual addend of r captures all the effects of interactions between genes on changes in genotype frequencies so that ignoring this residual addend in a rate of change leaves a partial rate of change in a constant genic environment. In other words, the genic environment is constant when the residual addend $\quad$ of r is kept equal to 0 in which case $\mathrm{cov}(\delta, \quad) = 0$ for any variable δ (see Supplementary Material, Section 2). More importantly, this approach will allow us to give an interpretation of the additive genetic rate of change in the mean of any measurement given in Equation (7).

Mean Malthusian parameter

Fisher (1930, 1941, 1958) considered the Malthusian parameter m as measurement of fitness. In the simplest setting without age effects on fecundity and mortality determined at a single locus, this parameter for a genotype A_iA_j is given by $m_{ij} = b_{ij} - d_{ij}$, where b_{ij} is a birth rate and d_{ij} a death rate, for $i, j = 1, \ldots, n$.

Introducing the quantities $N_{ij} = P_{ij}N$ and $N_i = p_iN$ for $i, j = 1, \ldots, n$, where N represents the population size or density, and using the identity

$$\frac{dN_i}{dt} = \sum_{j=1}^{n} m_{ij} N_{ij} \tag{8}$$

for $i = 1, \ldots, n$, we find that

$$\mathrm{cov}(f_i, m) = \sum_{j=1}^{n} m_{ij} P_{ij} - p_i \bar{m} \tag{9}$$

$$= \frac{1}{N}\frac{dN_i}{dt} - \frac{N_i}{N^2}\sum_{j=1}^{n} \frac{dN_j}{dt} = \frac{dp_i}{dt} \tag{9}$$

for $i = 1, \ldots, n$. Then, the additive genetic rate of change of $\bar{m}$ is

$$2\sum_{i=1}^{n} \alpha_i \frac{dp_i}{dt} = 2\sum_{i=1}^{n} \alpha_i \mathrm{cov}(f_i, m) = \mathrm{cov}(\alpha, m) = \mathrm{cov}(\alpha, \alpha), \tag{10}$$

where

$$\mathrm{cov}(\alpha, \alpha) = 4\sum_{i,j=1}^{n} \alpha_i \alpha_j \mathrm{cov}(f_i, f_j) = \sum_{i,j=1}^{n} P_{ij}(\alpha_i \quad \alpha_j)^2 \tag{11}$$

is called today the additive genetic variance in fitness.

This is the genetic variance in the statement of the FTNS (Fisher, 1930, p. 35, 1958, p. 37) that is claimed to be equal to the rate of increase in fitness "produced by Natural Selection" (Fisher, 1930, p. 42, 1958, p. 45), or "ascribable to natural selection" (Fisher, 1941, p. 57). This is understood as the rate of increase ascribable only to changes in gene frequencies in a "constant genic environment" (Fisher, 1941, p. 56).

Particular modes of reproduction

The partial rate of change in the mean Malthusian parameter obtained in the previous section does not depend on the mating system and reproduction. This suggests that natural selection concerns only changes in gene frequencies excluding "fortuitous fluctuations in genetic composition" (Fisher, 1930, p. 35) that may be brought about by any reshuffling of genes.

Some insight on the significance of the additive genetic rate of change in the mean of any measurement can be gained by considering two particular reproduction methods, namely, clonal reproduction and sexual reproduction with either random union of gametes or random mating of individuals. In both cases, we assume below a Malthusian parameter $m_{ij} = b_{ij} - d_{ij}$ with birth rate b_{ij} and death rate d_{ij} for $i, j = 1, \ldots, n$.

In the case of clonal reproduction, the per capita growth rate of the number of individuals with the ordered genotype

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A_iA_j, namely, $(dN_{ij}/dt)/N_{ij}$, is given by m_{ij} so that

$$r_{ij} = \frac{1}{P_{ij}}\frac{dP_{ij}}{dt} = m_{ij} - \bar{m} \tag{12}$$

for $i, j = 1, \ldots, n$, where

$$\bar{m} = \bar{b} - \bar{d} = \sum_{i,j=1}^{n} b_{ij}P_{ij} - \sum_{i,j=1}^{n} d_{ij}P_{ij}. \tag{13}$$

In the case of sexual reproduction, r_{ij} generally depends on the mating type frequencies (see, e.g., Nagylaki & Crow, 1974; Nagylaki, 1992, Section 4.10, Ewens, 2004, Section 2.7). In the particular case of random union of gametes, it is easy to see that

$$r_{ij} = \frac{\bar{b}}{P_{ij}}\left(p_i^* p_j^* - P_{ij}\right) - (d_{ij} - \bar{d}) \tag{14}$$

for $i, j = 1, \ldots, n$, where

$$p_i^* = \sum_{j=1}^{n} \frac{b_{ij}P_{ij}}{\bar{b}} \tag{15}$$

for $i = 1, \ldots, n$. Similarly, in the case of random mating with additive fecundities of mating types, it can be shown [see Equation (2.44) in Ewens, 2004] that

$$r_{ij} = \frac{\bar{b}}{P_{ij}}\left(p_i p_j^* \quad p_i^* p_j - p_i p_j - P_{ij}\right) - (d_{ij} - \bar{d}) \tag{16}$$

for $i, j = 1, \ldots, n$.

The relative growth rate r_{ij} in all the above cases has the same additive genetic value $\beta_i \quad \beta_j$ for $i, j = 1, \ldots, n$. This is because the rates of change in the allele frequencies that determine this value are the same in all these cases. They are given by

$$\frac{dp_i}{dt} = \sum_{j=1}^{n}\frac{dP_{ij}}{dt} = \bar{b}\left(p_i^* - p_i\right) - \bar{d}\left(p_i^{**} - p_i\right), \tag{17}$$

where p_i^* is the frequency of A_i in individuals being born defined in Equation (15), and similarly

$$p_i^{**} = \sum_{j=1}^{n}\frac{d_{ij}P_{ij}}{\bar{d}} \tag{18}$$

the frequency of A_i in individuals going dead, for $i = 1, \ldots, n$. As for the residual addend $_{ij}$ of r_{ij}, it depends on the way that the individuals mate and reproduce even when the genotype frequencies are currently in Hardy–Weinberg proportions (see Supplementary Material, Section 3).

Notice that the above claim about the additive genetic value of r follows directly from Equation (6), which does not depend on mating and reproduction. More importantly, Equation (17) shows that any reshuffling of genes in individuals being born or in individuals going dead will have no effect on the rates of change in allele frequencies. This implies that the additive genetic value of the relative growth rate r remains invariant under any reshuffling of genes.

Extensions

The average effects of multiple alleles at multiple loci can be defined in a similar way as in Section 2. Then the covariance between the additive genetic value of any measurement determined at those loci and the additive genetic value of the relative growth rate in genotype frequency gives a partial rate of change in the mean measurement that is genically additive and invariant under reshuffling of genes at the same loci. Moreover, this applies to the Malthusian parameter with age-specific birth and death rates if the individuals are weighted by reproductive values. As for discrete-time models, an analogous result hold with changes in genotype frequencies and gene frequencies from one time step to the next replacing the corresponding instantaneous rates of change (see Supplementary Material, Section 4, and references therein).

Discussion

Additive genetic rate of change

It is rather surprising that it took so long before recognizing that Fisher's FTNS stating that "the rate of increase in fitness of any organism at any time is equal to its genetic variance at that time" (Fisher, 1930, p. 35, 1958, p. 37) can account only for a partial rate of change in mean fitness (Ewens, 1989; Ewens & Lessard, 2015; Price, 1972; Lessard, 1997). This should have been obvious since the beginning considering the fact that no assumption is made about reproduction and mating. The general terms used in the aforequoted statement may explain the initial confusion. Moreover, even though the population fitness may tend to increase under the effect of selection, since more fit individuals leave more successful gametes that carry parental genes determining fitness, the total rate of change in a Mendelian diploid population depends on the ways that genes are combined and interact within individuals and with the environment. The effects of all these interactions may play against an increase in mean fitness.

Similarly, stating that the partial change in mean fitness is the increase due to changes in gene frequencies as in Grafen (2018) without adding that this is in a "constant environment," a concept introduced in Fisher (1941, p. 56), is incomplete. Even though all changes in genotype frequencies may be functions of changes in allele frequencies, only parts of those changes lead to a rate of change in mean fitness equal to the additive genetic variance in fitness as shown in Lessard & Ewens (2019). As we have recalled, these parts can be obtained by keeping solely track of the additive genetic value β in the relative rate of change of genotype frequency r, which is a linear function of the rates of change of gene frequencies. This is the condition for an infinitesimal change dp_i in the frequency of an allele A_i to entail an infinitesimal change $2\alpha_i dp_i$ in the mean of any measurement m, and in particular in the mean fitness. Here, α_i is interpreted as the average effect on the measurement m of substituting allele A_i for a gene chosen at random at the same locus in the population in a constant environment for $i = 1, \ldots, n$ (see Supplementary Material, Section 1). Summing over all alleles at the locus determining m yields the additive genetic rate of change of its mean, which can be expressed as $\mathrm{cov}(m, \beta) = \mathrm{cov}(\alpha, \beta)$, where $\alpha = 2\sum_{i=1}^{n} f_i\alpha_i$ is the additive genetic value of m. This additive genetic covariance is non-negative and given by the additive genetic variance in fitness, when the measurement is the Malthusian parameter. Moreover, it is generally different from the total rate of change given by $\mathrm{cov}(m, r)$.

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It is tempting to view $2\alpha_i$ as a derivative of the mean measurement $\bar{m}$ with respect to the current frequency p_i of allele A_i for $i = 1, \ldots, n$. But this view encounters difficulties of interpretation since $\bar{m}$ is generally a function of genotype frequencies that does not reduce to a function of allele frequencies alone. This is exactly the point that was addressed by Fisher (1941) in connection with a formula proposed by Wright (1937) for the change in the frequency of an allele, which involves a derivative of mean fitness with respect to the allele frequency. His explanation in terms of average effects of gene substitution on fitness relies on particular expressions for the relative rates of change of genotype frequencies that correspond exactly to their additive genetic values. However, his concept of a constant genic environment for these particular expressions to hold is difficult to grasp since it actually involves partial relative rates of change instead of total ones (see Supplementary Material, Section 2).

The same additive genetic rate of change in the mean $\bar{m}$ can be obtained by keeping solely track of the additive genetic value α in the measurement m itself since $\mathrm{cov}(\alpha, \beta) = \mathrm{cov}(\alpha, r)$. This expression for the partial rate of change corresponds to the interpretation given in Price (1972) and Ewens (1989) for fitness as measurement. In Grafen (2018), the corresponding partial change in a discrete-time setting was called the additive genetic component. See also Ewens (2024) for an alternative expression for the residual rate of change, which involves time derivatives of additive allelic effects on fitness that include the mean fitness.

Keeping solely track of the additive genetic value in the relative growth rate r, however, yields a partial change in the mean of any measurement m even if this measurement has little to do with changes in genotype frequencies. This is what makes the condition on r so remarkable and, perhaps, why it was used in Fisher (1941) to define a constant genic environment. It remains to interpret this condition.

Connection with the Robertson-Li-Price covariance formula

The equality $\mathrm{cov}(f_i, m) = dp_i/dt$ in Equation (9), where m is the Malthusian parameter, f_i the frequency of allele A_i in an individual and p_i this frequency in the whole population, is a continuous-time version of a covariance formula for the change in the frequency of an allele (Li, 1967, Price, 1970). This equality holds if m is replaced by the relative growth rate of genotype frequency r owing to Equation (6) (see Lessard, 1990, for a discrete-time analog). This implies that r and the Malthusian parameter m share the same average allelic effects, and therefore the same additive genetic value β. As a consequence, the additive genetic rate of change in the mean of any measurement M determined at a single multi-allelic locus with additive genetic value $\gamma = 2\sum_{i=1}^{n} \gamma_i f_i$, given by $\mathrm{cov}(\gamma, \beta)$ according to Equation (7), is equal to $\mathrm{cov}(\gamma, m)$. This corresponds to Robertson's (1966) secondary theorem of natural selection, STNS. Our study sheds more light on the interpretation of this partial rate of change. Notice also that the total rate of change, given here by $\mathrm{cov}(M, r)$, is generally different from $\mathrm{cov}(M, m)$. This is not surprising since the Malthusian parameter alone is not sufficient to determine the rate of change in genotype frequency.

Invariance under reshuffling of genes

We can say that the additive genetic value of the relative growth rate of genotype frequency r is the best linear prediction of r from the genes present in the genotype of an individual in the least-mean-squares sense. This is true for any measurement including fitness, but r is a very special measurement since it captures the dynamics of genotype frequencies.

The key property $\mathrm{cov}(f_i, r) = dp_i/dt$ for $i = 1, \ldots, n$ from Equation (6) implies that the average allelic effects on r are linear functions of dp_i/dt for $i = 1, \ldots, n$, and so is the additive genetic value β of r. Therefore, this value is invariant under any reshuffling of genes that does not change the allele frequencies. This invariance is transferred to the partial rate of change in the mean of any measurement m given by $\mathrm{cov}(m, \beta) = \mathrm{cov}(\alpha, \beta)$, where $\alpha = 2\sum_{i=1}^{n} f_i\alpha_i$ is the additive genetic value of m.

In conclusion, the additive genetic rate of change in the mean of any measurement is a part of the total rate of change that is invariant under reshuffling of genes. This part depends linearly on the rates of change in allele frequencies.

A similar conclusion was reached in Ewens (2011) with viability as measurement m in a population undergoing discrete, non-overlapping generations by expressing the partial change in the mean as $\sum_{i,j=1}^{n}(\Delta^* P_{ij})(\bar{m} \quad \alpha_i \quad \alpha_j)$, or equivalently $2\sum_{i=1}^{n}(\Delta^* p_i)\alpha_i$, in a one-locus multi-allele setting. Here, Δ^* is used to indicate an intra-generational change in frequency from the time of conception to the time of reproduction. Observing that "gene frequencies in a daughter generation at its time of conception are identical to those in the parental generation at its age of reproduction, whatever the mating scheme in the parental population might be," Ewens (2011) concludes that the partial change in mean viability "does not depend on the mating scheme." See Ewens and Lessard (2015) for some further discussion on this property.

It is easy to show that the partial change in the previous paragraph can be expressed as $\sum_{i,j=1}^{n}(\beta_i \quad \beta_j)m_{ij}P_{ij}$, where $\beta_i \quad \beta_j$ is the additive genetic value of the relative change $(\Delta P_{ij})/P_{ij}$ from one generation to the next, for $i, j = 1, \ldots, n$. This additive genetic value depends only on the genotype frequencies in the current generation and the changes in allele frequencies from this generation to the next one represented by Δp_i for $i = 1, \ldots, n$.

The above approach can be extended to more general models in continuous time as well as discrete time with overlapping generations and applied to any measurement m determined at any number of loci in a whole-genome framework (see Supplementary Material, Section 4). The situation is more complicated with overlapping generations, however, since then only a fraction of the population is replaced at a time. As illustrated in Section 4 by comparing clonal reproduction and sexual reproduction with either random union of gametes or random mating with additive fecundities of mating types, the invariance of the additive genetic value of r is not only with respect to reshuffling of genes in the flow of individuals entering the population through birth but also in the flow of individuals exiting the population through death. This may look strange but reshuffling of genes in individuals going dead has similar effects on the relative growth rate of genotype frequency as reshuffling of genes in individuals being born. Such a reshuffling of genes has nothing to do with the mating system, but viability selection is connected

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to reproduction since individuals must survive in order to reproduce.

Final thoughts

There are omissions and flaws in Fisher's (1930, 1958) work about the FTNS (see, e.g., Edwards, 1994; Price, 1972). The statement itself is even false if one considers that it concerns a total rate of change (Ewens, 2024). However, the explanations given by Fisher (1941) in relation with the key concept of an average allelic effect and his criticism of a derivative of mean fitness with respect to an allele frequency in Wright's (1937) formula do not agree with this view. Moreover, the rate of change in the statement is not presented as a time derivative of mean fitness but only as a part of it (Fisher, 1930, p. 42, 1958, p. 45), while the total increase in fitness mentioned just before the statement most likely refers to a sum of changes over all loci, called factors. But then, what part of the total rate of change is it about?

In a haploid population, the effect of natural selection is captured by the growth rate theorem (Edwards, 1994): "In a subdivided population, the rate of change in the overall growth-rate is proportional to the variance in growth rates." The main contribution of Fisher (1930, p. 35, 1958, p. 37) is to have proposed the variance of the additive genetic value, called the genetic variance, for the corresponding rate of change in the fitness of a Mendelian diploid population. This is interpreted as a rate of change due to all changes in gene frequencies in a constant environment including a constant genic environment (Fisher, 1941). This agrees with a gene-centred view of evolution (Edwards, 2014). A passage from the Fisher-Kempthorne correspondence found by A.W.F. Edwards (personal communication) leaves little doubt about this point of view: "... the only evolutionary effect, either in increased fitness or in anything else, that I can recognize as such, is constituted by changes in gene ratio" (R.A. Fisher to O. Kempthorne, 18 February 1955, from Bennett, 1983, p. 229).

We may presume that this view comes from linear regression and the analysis of variance (Fisher, 1918). Indeed, the additive genetic variance on the right-hand side of Fisher's FTNS suggests its inductive nature as recalled in Frank (2014): "Fisher's theorem shows that the change in mean fitness by selection is invariant to all details of variability in the population except the variance associated with the transmissible predictors." Here, the predictors are the gene frequencies. Nevertheless, this does not necessarily imply that the additive genetic variance captures all the effects of changes in gene frequencies. See also Edwards (2016) and Frank & Fox (2020) for further discussion.

The difficulty with Fisher's FTNS comes from its left-hand side, which is the interpretation of the additive genetic variance as a partial rate of change in mean fitness (Ewens, 1989; Ewens & Lessard, 2015; Grafen, 2018; Lessard, 1997; Lessard & Ewens, 2019; Price, 1972). In this paper, we have shown that this partial rate of change possesses the property of being invariant under reshuffling of genes. This can be viewed as a consequence of the additivity property with respect to gene frequencies that comes from linear regression. This component changes over time, however, so that no conclusion can be drawn about the increase or decrease of the mean fitness from this component alone.

The same conclusion holds more generally for Robertson's (1966) STNS about the mean of any measurement M whose partial rate of change is given by the covariance between the additive genetic value of the measurement and the additive genetic value of fitness measured by the Malthusian parameter m. This is the case because this additive genetic covariance is the same if fitness is measured by the relative rate of change of genotype frequency r (Denniston, 1978). Moreover, it suffices to add the covariance between the residual addend of M and the residual addend of r to get the total rate of change in the mean of any measurement kept constant [see Equation (7)]. Here, the analogy with the scalar product in analytic geometry is clear, the residual addends being uncorrelated to the additive genetic values representing the best linear predictions from the genes present. In the case of r, the residual addend captures the effects of interactions between genes, representing the genic environment, on the dynamics of genotype frequencies irrespective of the measurement considered. As for the significance of the partial rate of change in the mean measurement given by the additive genetic covariance, it is like trying to understand the meaning of sentences only from the numbers of the different letters that they contain.

Supplementary material

Supplementary material is available online at *Evolution*.

Data availability

No new data were generated or analysed in support of this research.

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Conflict of interest

The author declares no conflict of interest.

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