Refinements to the partitioning of the inbred genotypic variance

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Natural gene flow is often localised because of gamete dispersal limitations, and the quantity and structure of the genotypic variance in such populations is a key to predicting the advance from selection, in both evolution and artificial breeding programmes. Earlier derivations of this variance have shown that the total dominance variance may increase with inbreeding despite the fact that heterozygosity is decreasing. This anomaly has been corrected following the *de novo* biometrical derivation presented in this paper. The whole population also subdivides into descendant lineages that differ in allele frequencies and means because of the

dispersion caused by genetic drift and continuing localisation of gamodemes. The paper defines for the first time the among-line and within-line partitions of the dominance variance; and corrects anomalies in the total genic (additive genetic) variance, and its underlying inbred average allel-substitution effect. The revisions also clarify the connections between the Fisher – Falconer, Mather – Hayman, and Wright approaches to defining the inbred genotypic variance. Relationships are discussed between the population dispersion structure and genetic efficiency in selection.

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Introduction

It is necessary still to focus on the inheritance of phenotypes, because sexual gene exchange and the observed properties of whole organisms remain the central issues for selection, evolution, ecology, and human families. Such natural genetics (ie, heredity through sexual reproduction between individuals in groups) will certainly continue for a long time as the predominant means of gene flow for the higher organisms on Earth. Population genetics addresses the population summaries of this sexual exchange, accounting for central issues such as mating system, selection, fundamentals of genetics, and the consequences of mutation and transgenesis. Quantitative genetics incorporates all of this, and adds a crucial element – phenotypic *quantity* – to complete the link to the macrocosm of real-life biology. Molecular genetics intrinsically provides a microcosmic outlook to genetics, and the connecting of the two approaches is of ultimate concern. One method of doing this may be to utilise the large body of knowledge already extant in quantitative genetics, and to link it via coefficients of determination to metabolic pathways between the gene and the phenotype. This essentially would be quantifying the concepts of Koehn *et al* (1983). Therefore, we need to ensure that quantitative population genetics continues to be researched and improved to make it as useful as possible, both for its own utility and for this ultimate synthesis.

Genetic neighbourhoods

One of the issues in population genetics is that gene flow is often *not* panmictic (as often assumed, despite limited validity eg. Gordon, 2000) but restricted to small genetic neighbourhoods (gamodemes) – ‘islands’ of gene exchange (Levin and Kerster, 1974; Richards, 1986). All genes subject to sexual exchange are affected by this mating system, including transgenes that have become stabilised within the nucleus genome. The consequences of this are of major importance, and include binomial sampling of allele frequencies (genetic drift), dispersion into descendant lineages (‘lines’, or ‘families’), and a general rise in the frequency of homozygosity (inbreeding) (Wright, 1921, 1943; Crow and Kimura, 1970; Falconer and Mackay, 1996). This dispersion and associated allele sampling lead to descendant lines that may be vigorous, average, or depressed, each with known probabilities dependent on the initial allele frequencies and the rate of inbreeding (Wright, 1951; Crow and Kimura, 1970). The general mean (of the overall mixture of dispersion lines) is always depressed (Crow and Kimura, 1970; Falconer and Mackay, 1996), but the vigorous lines within the mixture can be isolated for the future by selection and reproductive separation. Concurrently, the genotypic variance generally increases, and can be partitioned into among-line (AL) and within-line (WL) components (Wright, 1951).

Genotypic variance partitions

Another form of partitioning the genotypic variance is independent of inbreeding dispersion, but has a strong influence on it nevertheless. This is Fisher’s partitioning (1930, 1941) into genic variance (σ^2_{λ}), based on the

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average effect (α) of allele substitution under panmictic equilibrium, and a genotypic 'residual'. Other workers popularised this approach (Kempthorne, 1957; Falconer, 1960, 1985; Falconer and Mackay, 1996), and the residual became known as the 'dominance' variance (σ_D^2). When the dispersion variance was elaborated, it was the genic variance which was the focus, and the total 'dominance' variance was estimated by difference (as statistical residuals commonly are). Although the Fisher – Falconer partitioning predominates, another approach is extant (Mather and Jinks, 1971), and its dispersion partitions are also available (Mather and Jinks, 1971, p 246). It turns out to have greater genetical utility than the predominant form (Gordon, 1999).

The genic variance dispersion partitions are $2\phi\sigma_a^2$ (the homozygote variance – Gordon, 1999) for the AL component, and $(1-\phi)\sigma_A^2$ for the WL component, where ϕ is the inbreeding coefficient (Wright, 1951; Kempthorne, 1957; Falconer, 1960; Crow and Kimura, 1970). Many inbreeding possibilities have been investigated for ϕ (Wright, 1921, 1943, 1951; Crow and Kimura, 1970, pp 101–111), enabling coverage of a wide range of genetic neighbourhood situations. At the same time, the total dispersed genic variance was estimated as $(1+\phi)\sigma_{A\phi}^2$, based on an inbred average allele effect α_ϕ (Crow and Kimura, 1970, p 131; Falconer, 1985). The dominance variance was defined again as a difference: between this total inbred genic variance and a total inbred genotypic variance $\sigma_{G\phi}^2$ (Wright, 1951; Crow and Kimura, 1970, pp 130–131).

This approach of estimating the dominance variance by difference, coupled with a small discrepancy in obtaining the total dispersed genic variance, led to the problem that this paper addresses: that hitherto dominance variance theoretically has appeared to *increase* early in inbreeding (Falconer and Mackay, 1996, pp 128, 266–267) despite the fact that heterozygosis is actually *decreasing*. This paper corrects the total dispersed genic variance, and, at the same time, presents a direct derivation of the dominance variance, together with its partitioning into AL and WL components. During this rederivation of partitioning, the Mather and Jinks approach re-emerges also, confirming both their earlier results (Mather and Jinks, 1971) and its genetical efficacy.

Gene-effect models

Many phenotypic attributes have a polygenic system underlying them, and digenic and polygenic models have been developed to study them (Seyffert, 1966; Jana, 1971), with some being presented in the form of biometrical expectations (Cockerham, 1954; Kempthorne, 1957; Hayman, 1958). The expectations are of two types: genetical (homozygote and heterozygote deviations from a homozygote midpoint for each locus) and statistical (deviations between genetical effects and actual genotype expectations, that is, epistasis).

The genotypic variance of a natural mating system requires, however, that deviations be defined instead with respect to the *population mean*. Therefore, it is necessary to include a correction factor based on the second moment of that population mean. This requirement has made complicated the definition of the genotypic variance, especially where epistasis is in-

cluded. The most widely used definition is based on any single random universal gene affecting the attribute (Fisher, 1930; Wright, 1951; Falconer, 1960; Mather and Jinks, 1971). In a polygenic attribute, this approach accounts for each of the genes in turn, but separately; and they can be simply accumulated (Hayman, 1958; Mather and Jinks, 1971). In order to account for epistatic variance, two (or more) factors need to be considered *jointly*, but this whole issue still requires further development. For the current problem, we present the single factor case, in line with the bulk of work on quantitative genetics, and thereby account for the general homozygote and heterozygote effects of any single universal gene. Extension to account for cumulation and interaction (epistasis) deviations awaits further research.

Methods

The phenotypic expectations of the three genotypes possible from any two random alleles in any one random gene effecting the attribute define its *quantity*. The midpoint between the two opposite homozygotes is MP, and the deviation from MP to each genotype expectation defines the *gene effects*, a , d , and $(-a)$, for the 'more' homozygote (A_1A_1), heterozygote (A_1A_2), and lesser homozygote (A_2A_2), respectively. They constitute the vector $\mathbf{g}$.

The population considered here consists of several small randomly fertilised (RF) gamodemes, the reproductive outcomes of which are summarised by an appropriate definition of the overall inbreeding coefficient (ϕ) (Wright, 1951; Crow and Kimura, 1970). The overall mean frequency of the allele causing 'more' in the phenotype (A_1) is p , while that of any alternative allele (A_2) is q , and there is no omission ($p + q = 1$). The reproductively defined genotype frequencies overall for this population are $\mathbf{f}' = [p^2 + \phi pq, 2pq(1-\phi), (q^2 + \phi pq)]$ for the same respective genotypes; and the overall mean of this inbred population is

$$\overline{G_\phi} = \gamma = (p - q)a + (1 - \phi) 2pq d$$

(Falconer, 1985; Falconer and Mackay, 1996). Dispersion will be accommodated by partitioning the total genic and dominance variances into WL and AL components.

Results

Partitions of the inbred genotypic variance

Under the present universal unitary-gene model, the dispersed small-gamodeme RF genotypic variance has the expectation

$$\sigma_G^2 = \sum_{i \leq i'}^3 f_{ii'} g_{ii'}^2 - \gamma^2$$

where the respective right-hand terms are an unadjusted sum-of-squares (USS) and a correction factor (CF). The sum-of-squares (SS) thus defined is immediately seen also to be the variance as frequencies are used instead of counts. This expectation is expanded in the following, where the vectors $\mathbf{f}$ and $\mathbf{g}$, and the scalar γ , have been defined previously. The matrix $\mathbf{g}^A$ in the following

is $\mathbf{g}^{\text{diag}}$:

$$\begin{aligned}\sigma_{G_\phi}^2(SS) &= \mathbf{f}'\mathbf{g}^A\mathbf{g} - \gamma^2 \\ &= \phi 2pqa^2 + 2pqa^2 - (1-\phi)4p^2qad + (1-\phi)4pq^2ad \\ &\quad + (1-\phi)2pqd^2 - (1-2\phi)4p^2q^2d^2 - \phi^2 4p^2q^2d^2 \\ &= (1+\phi)2pqa^2 + (1-\phi)(q-p)4pqad \\ &\quad + (1-\phi)2pqd^2 - (1-\phi)^2 4p^2q^2d^2\end{aligned}\quad (1)$$

Equation (1) completes the biometrical partitioning to the point presented by Mather and Jinks (1971, p 246). If we rewrite their components into the terminology of Falconer and Mackay (1996), the components of equation (1) become $(1+\phi)\frac{1}{2}D$, $(1-\phi)\frac{1}{2}F'$ (where $F' = -F$ of Mather), $(1-\phi)\frac{1}{2}H_1$, and $(1-\phi)^2\frac{1}{4}H_2$, respectively. These are the same results as those of Mather and Jinks (1971).

Relations with the Wright components

We now proceed from equation (1) to show the relation between the Mather and Jinks (1971) components, and the Wright (1951) and Falconer (1960) partitioning of the genic variance (σ_A^2). At the same time we will complete the direct partitioning of the dominance variance (σ_D^2):

$$\begin{aligned}\sigma_{G_\phi}^2 &= (1+\phi)2pqa^2 + (1-\phi)(q-p)4pqad \\ &\quad + (1-\phi)2pqd^2(1-2pq(1-\phi)) \\ &= 2\phi 2pqa^2 + (1-\phi)2pqa^2 + (1-\phi)(q-p)4pqad \\ &\quad + (1-\phi)(q-p)^2 2pqd^2 + \phi(1-\phi)(2pq)^2 d^2 \\ &\quad + (1-\phi)(2pq)^2 d^2\end{aligned}\quad (2)$$

$$\begin{aligned}&= 2\phi 2pqa^2 + (1-\phi)2pq[a + (q-p)d]^2 \\ &\quad + (\phi - \phi^2)(2pq)^2 d^2 + (1-\phi)(2pq)^2 d^2\end{aligned}\quad (3)$$

Recalling the definitions of $\sigma_{A_\phi}^2$, α , $\sigma_{A_\phi}^2$, and σ_D^2 (Falconer and Mackay, 1996; Gordon, 1999), equation (3)

becomes

$$\sigma_{G_\phi}^2 = 2\phi\sigma_A^2 + (1-\phi)\sigma_A^2 + (\phi - \phi^2)\sigma_D^2 + (1-\phi)\sigma_D^2 \quad (4)$$

The first two terms in equation (4) are the AL and WL genic variances, respectively, and confirm the results of Wright (1951) and of Falconer (1960). The last two terms are the new AL and WL dominance variances, respectively. The terms of the whole equation can be written in Mather terminology as, respectively, $(2\phi)\frac{1}{2}D$, $(1-\phi)\frac{1}{2}D_R$, $(\phi - \phi^2)\frac{1}{4}H_2$ and $(1-\phi)\frac{1}{4}H_2$. The $D_R = \sigma_A^2 = (\frac{1}{2}D + \frac{1}{2}F' + \frac{1}{2}H_3)$, which can be shown to be the same as Hayman's (1958) expression of $D_R = (\frac{1}{2}D - \frac{1}{2}F + \frac{1}{2}H_1 - \frac{1}{2}H_2)$.

Total genic and dominance variances

Direct estimation of the total genic variance involves the definition of an average allele effect (α_ϕ) adjusted for inbreeding in the dispersed RF bulk population. We can derive this by recommencing equation (2), and gathering its terms in a way which specifies total genic variance (as well as total dominance variance):

$$\begin{aligned}\sigma_{G_\phi}^2 &= 2pq[(1+\phi)a^2 + (1-\phi)(q-p)2ad \\ &\quad + (1-\phi)(q-p)^2 d^2] + (1-\phi)(2pq)^2 d^2[1+\phi] \\ &= (1+\phi)2pq\left[a^2 + \frac{(1-\phi)}{(1+\phi)}(q-p)(2ad + (q-p)d^2)\right] \\ &\quad + (1-\phi^2)(2pq)^2 d^2\end{aligned}\quad (5)$$

$$= (1+\phi)\sigma_{A_\phi}^2 + (1-\phi^2)\sigma_D^2 \quad (6)$$

With continued dispersion and inbreeding, and partial dominance, the genic variance generally increases at a faster rate (approximately at $(1+\phi)$) than the rate of decline $(1-\phi^2)$ of the dominance variance, and therefore the total genotypic variance generally increases.

The revised total dominance variances for $\phi = 0.125$ –1, and also for $\phi = 0$, are shown in Figure 1a. This is

Figure 1 Total dominance variance (σ_D^2) in bulked populations of dispersing randomly fertilised small gamodemes with an overall inbreeding coefficient of ϕ , and graphed across the universe of possible overall allele frequencies (p). (The unlabelled line is $\phi = 0.125$; and $\phi = 0$ is the nondispersing panmixia.) The corrected variances are given in (a); and the previous versions are in (b) in which is evident the *ad hoc* nesting with respect to ϕ , and the erroneous increase in dominance variance (in the p -tail regions) with inbreeding, especially so for low ϕ .

compared with the previous version of these variances in Figure 1b. Partial dominance is used for both ($a = 10$ and $d = 7.5$).

These revised curves (Figure 1a) reveal a symmetrical nesting, and a general decrease of the dominance variance with inbreeding. The inbred dominance variance is never greater than that for panmixia ($\phi = 0$). All of these properties contrast strongly with those of the previous biased expressions for the dominance variance (Figure 1b). The refinements of derivation in this paper completely remove these anomalies.

Bias in the older version of the inbred average allele effect is also removed by this rederivation. The bracketed section of equation (5) furnishes a corrected definition of this α_ϕ , as follows:

$$\alpha_\phi = \left[a^2 + \frac{(1-\phi)}{(1+\phi)} 2(q-p)ad + \frac{(1-\phi)}{(1+\phi)} (q-p)^2 d^2 \right]^{1/2} \quad (7)$$

Graphing equation (7) shows that α_ϕ decreases with inbreeding when $p < 0.5$, but increases with inbreeding when $p > 0.5$. The upper and lower curves are not quite symmetrical, however. At $p = \frac{1}{2}$, or when $\phi = 1$, the value of α_ϕ is simply equal to the homozygote effect (a).

Discussion

Inbreeding and the average allele effect

Previously, the definition of α_ϕ of Crow and Kimura (1970, p 131) has been the common basis of defining the total inbred genic variance; and it has also been central, therefore, in defining the inbred dominance variance, as pointed out earlier. The discrepancy in the previous dominance variance must reflect a bias in the earlier definition of this inbred average-allele effect, and it is important therefore to compare this previous definition with the present one.

Crow and Kimura (1970) give α_ϕ as follows:

$$\alpha_\phi = \frac{(p + \phi q)(a_{11} - a_{12}) + (q + \phi p)(a_{12} - a_{22})}{1 + \phi} \quad (8)$$

where a_{11} , a_{12} , and a_{22} are the gene effects, expressed as deviates from the RF mean (G), for the genotypes A_1A_1 , A_1A_2 , and A_2A_2 , respectively. By expanding these effects in terms of the definition gene effects, and after substituting these into the α_ϕ equation (of Crow and Kimura, 1970), we obtain

$$\begin{aligned} \alpha_\phi &= \frac{(pa - pd + \phi qa - \phi qd) + (qa + qd + \phi pa + \phi pd)}{1 + \phi} \\ &= \frac{a(1 + \phi) + d((q - p)(1 - \phi))}{1 + \phi} \\ &= a + \frac{1 - \phi}{1 + \phi} (q - p)d \end{aligned}$$

This is now identical with Falconer's definition (1985), where it is linked to Fisher's foundational concepts (Fisher, 1930, 1941).

These earlier definitions can be compared with equation (7) (which presents a variance-based unbiased definition of α_ϕ). This comparison is facilitated by squaring the older definition, as seen inside the brackets

in the following.

$$\alpha_\phi = \left[a^2 + \frac{(1-\phi)}{(1+\phi)} 2(q-p)ad + \left(\frac{(1-\phi)}{(1+\phi)} (q-p) \right)^2 d^2 \right]^{1/2}$$

The earlier bias is seen to lie in the d^2 coefficients, with the revised α_ϕ (equation (7)) being larger. This means that the previous inbred average allele effect (equation (8)) underestimated the total dispersed genic variance.

Total genotypic and dominance variances

Previous definition of the total inbred dominance variance was based on the difference between the total genotypic variance adjusted for inbreeding (Wright, 1951; Crow and Kimura, 1970) and the inbred total genic variance. We have noted in the previous section that the latter was previously underestimated, suggesting overestimation of this dominance variance. To finalise this matter, we need also to examine if there is any bias in the previous inbreeding-adjusted genotypic variance. However, this mostly is of historical interest, because, with the results in this paper, we have instead *direct* estimators for this dominance variance and do not need to resort to estimating by difference.

The total genotypic variance adjusted for inbreeding is first given by Wright (1951) from a derivation based on population means. Crow and Kimura (1970, p 99) re-present it in a clearer nomenclature, which we use in the following:

$$\sigma_{G_\phi}^2 = (1 - \phi)\sigma_{G_0}^2 + \phi\sigma_{G_1}^2 + \phi(1 - \phi)(\bar{Y}_0 - \bar{Y}_1)^2$$

In this expression, ϕ is the inbreeding coefficient, and the other right-hand terms are, respectively, the genotypic variance prior to inbreeding ($\phi = 0$), the genotypic variance at full inbreeding ($\phi = 1$), the population mean at $\phi = 0$, and the population mean at $\phi = 1$. Definitions for each of these exist (Wright, 1951; Falconer and Mackay, 1996 and herein), and can be substituted into the expression as follows:

$$\begin{aligned} \sigma_{G_\phi}^2 &= (1 - \phi)(\sigma_A^2 + \sigma_D^2) + \phi(4pqa^2) \\ &\quad + (\phi - \phi^2)[\mu + a(q - p) + 2pqd - \mu - a(q - p)]^2 \\ &= (1 - \phi)\sigma_A^2 + (1 - \phi)\sigma_D^2 + \phi 2\sigma_a^2 + (\phi - \phi^2)\sigma_D^2 \end{aligned}$$

where all terms are defined previously. This is identical with equation (4), showing that the total genotypic variance in the older form is the same as that in this paper. Therefore, the bias in the earlier definition of the total inbred dominance variance is due solely to the discrepancies in the earlier α_ϕ and the subsequent total inbred genic variance (discussed in the previous section). The result is overestimation of the inbred dominance variance by the earlier method based on difference.

Dispersion structure

As the presence of small genetic neighbourhoods leads to dispersion into descendant lineages (lines), it is of interest to monitor the rate of change across generations of the dispersion structure for the population bulk. This can be achieved from combined graphs of the AL and WL genotypic variances across generations (or even ϕ), and quantified with the ratio

$$\Psi = \frac{\sigma_{G_{AL}}^2}{\sigma_{G_{WL}}^2}$$

Apart from its intrinsic interest, dispersion structure has utility in plant and animal breeding, where it can be

an aid in deciding which selection strategy (AL, individual, and a combination of them both) to use at any generation (Falconer and Mackay, 1996). While combined selection has the most genetic advance (Falconer and Mackay, 1996), it may be more expensive to perform (as it may require two passes through the nursery, or extensive data collection prior to decision-making). Under conditions of low inbreeding (and weak dispersion structure), individual selection may be as efficient as combined selection in its genetic advance: while for high levels of inbreeding (and strong dispersion structure) AL selection may be as efficient. The cheaper strategies may be preferable. The author has found that $0.25 < \psi < 5.0$ is a good indicator for preferring combined selection in plant breeding practice.

In evolutionary genetics also, the existence of finite genetic neighbourhoods would tend to enhance genetic advance from selection, owing to incipient combined selection. This would be so especially in conjunction with any propagation dispersal which spatially (ie, reproductively) separates gamodeme progenies. Such selection has a parallel with Kimura's neutral theory of evolution (1983), which incorporates a genetic drift process. The present localisation of demes also includes genetic drift as part of the dispersion, but the additional opportunity for combined selection would be expected to enhance local differentiation, and adaptation, to a greater extent than simple random drift. Combined selection operates at the external phenotype rather than at the primary gene product, being separated from it by all the physiology and biochemistry in between. If there is a low coefficient of determination between the two levels, even the mutant 'neutrality' of Kimura's theory is supported.

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