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# Additive genetic variation and evolvability of a multivariate trait can be increased by epistatic gene action

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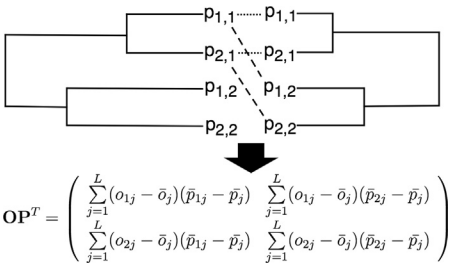
## HIGHLIGHTS

- We explore how epistasis affects heritable multivariate trait variation and evolvability.
- Epistatic genetic effects map differently genealogically than additive genetic effects.
- Which leads to less relative covariance in genotypic and breeding values between individuals.
- Which allows for greater heritable multivariate variation and evolvability.

## GRAPHICAL ABSTRACT

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## ABSTRACT

Epistatic gene action occurs when mutations or alleles interact to produce a phenotype. Theoretically and empirically it is of interest to know whether gene interactions can facilitate the evolution of diversity. In this paper, we explore how epistatic gene action affects the additive genetic component or heritable component of multivariate trait variation, as well as how epistatic gene action affects the evolvability of multivariate traits. The analysis involves a sexually reproducing and recombining population. Our results indicate that under stabilizing selection conditions a population with a mixed additive and epistatic genetic architecture can have greater multivariate additive genetic variation and evolvability than a population with a purely additive genetic architecture. That greater multivariate additive genetic variation can occur with epistasis is in contrast to previous theory that indicated univariate additive genetic variation is decreased with epistasis under stabilizing selection conditions. In a multivariate setting, epistasis leads to less relative covariance among individuals in their genotypic, as well as their breeding values, which facilitates the maintenance of additive genetic variation and increases a population's evolvability. Our analysis involves linking the combinatorial nature of epistatic genetic effects to the ancestral graph structure of a population to provide insight into the consequences of epistasis on multivariate trait variation and evolution.



## 1. Introduction

A multivariate trait is a feature of an organism that is composed of a set of characters (Kirkpatrick, 2009), where a character is a univariate measure of phenotype. A canonical example of a multivariate trait is the wing of a fruit fly (Mezey and Houle, 2005; McGuigan and Blows, 2007) or the flower of a plant (Bradshaw et al., 1998; Caruso, 2004). Flight properties of a wing are a function of a set of characters that make up the wing (Vogel, 1966) and pollinator preference is a function of a set of characters that make up a flower (Schemske and Bradshaw, 1999). Therefore, to understand variation in fitness within a species sometimes requires understanding the causes and consequences of variation in a multivariate trait.

Variation in a multivariate trait is often measured using a covariance matrix of the set of characters that make up the trait. By itself a covariance matrix can be difficult to interpret. Two multivariate traits

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may be composed of the same number of characters and have the same character-level variances, but may differ in the pattern, signs and magnitudes of covariances. Differences in the pattern, signs and magnitudes of covariances can result in different levels of multivariate trait variation between traits or for a shared multivariate trait between populations or species.

A gestalt approach to measuring multivariate trait variation is to perform a principal components analysis (PCA), or equivalently an eigen decomposition (ED), of the trait. PCA and ED find independent combinations of characters that explain from the most to the least amount of variance of the trait. If the sum of the variances associated with the principal components of a trait are equal between two populations or species, then variation at the character level is equal on average between populations. But, the evenness or uniformity in variances may be different, such that in one population only a few principal components express variation and the others express little variation, while in the second population each principal component expresses similar levels of variation, but with a slight decline. Here the second population would be more diverse because more principal components express variation. ED has been directly applied in studies of population-level multivariate trait variation (see below), and is the basis of the Flury hierarchical approach that compares multivariate variation between populations (Phillips and Arnold, 1999, Arnold and Phillips, 1999). Other approaches that compare multivariate trait variation involve predicted responses to selection, which is a function of variation and the direction of selection (Cheverud and Marroig, 2007; Calsbeek and Goodnight, 2009; Hansen and Houle, 2008).

In the context of wing shape, Mezey and Houle (2005) measured 20 component characters in *Drosophila melanogaster* and found significant phenotypic and additive genetic variance associated with all 20 principal components. Nevertheless, there was approximately a two to three order of magnitude drop in variance from the leading principal component to the last principal component. In *Drosophila bunnanda* McGuigan and Blows (2007) found less multivariate trait variation in wing shape. Their study measured 10 component characters of wing shape, some of which were in common with the Mezey and Houle (2005) study, but found that although at the phenotypic level there was significant variation across 10 principal components, up to only five had significant additive genetic variance (although some technical aspects of variance estimates may have biased estimates to be low). Nevertheless, the works of Mezey and Houle (2005) and McGuigan and Blows (2007) indicate that there may be differences in multivariate trait variation, particularly additive genetic variation, between species.

Several processes could cause differences in additive genetic multivariate trait variation between species. Previously, genealogical structure and a lack of recombination were shown to decrease additive multivariate genetic variation in a diploid sexually reproducing population (Griswold et al., 2007). In this paper, we explore theoretically how epistatic gene action may affect additive multivariate genetic variation. Epistatic gene action occurs when mutations or alleles at loci interact to produce a phenotype. Multiple terms in the literature are used to indicate epistatic gene action, including molecular epistasis, physiological epistasis and functional epistasis. A diagnostic measure of epistatic gene action is to introduce mutants singly and in combination and measure their phenotypic outcomes. If the phenotype of a combination of mutants is different from the sum of their single effects, then epistasis occurs.

Epistatic gene action contributes to quantitative trait variation, both additive (or heritable) and epistatic variance components, depending on allele frequencies in a population. An important aspect of this paper is to distinguish and recognize that while epistatic gene action, such as molecular interactions, are numerous and can contribute substantially to additive genetic variation, they contribute to additive genetic variation differently than purely additive genetic effects in a multivariate setting.

In the context of multivariate traits and wing shape, in particular, there is molecular and quantitative genetic evidence of epistatic genetic effects (Dworkin et al., 2009; Chari and Dworkin, 2013; Chandler et al., 2014). There is also evidence that epistatic gene action causes differences in floral inflorescence architecture, for instance, between teosinte (the ancestor to maize) and maize (Doebley et al., 1995; Lukens and Doebley, 1999).

Griswold and Henry (2012) showed that epistasis can increase additive multivariate trait variation in a haploid population experiencing asexual reproduction, no genomic recombination and stabilizing selection. An underlying mechanism for the increase in multivariate variation with epistasis is how epistatic genetic effects map genealogically. Griswold and Eisner (2012) showed that epistatic genetic effects map proportionally more towards the tips of a genealogical tree, which decreases the relative level of genotypic covariance and allows for greater multivariate diversity.

In this paper we focus our attention on how epistasis affects heritable multivariate trait variation in a sexually reproducing population with recombination. With sexual reproduction and recombination, the genealogical history of genotypes is not tree-like, but instead an ancestral graph with tree-like substructure that depends on the rate of recombination (e.g. Hudson, 1983, Griffiths, 1991). It is therefore unclear whether epistasis will have the same effect on multivariate trait variation in sexually reproducing and recombining diploid populations compared to asexual and nonrecombining haploid populations.

In our multivariate analysis, the extent of variation is measured as the uniformity or evenness of the eigenvalues of the additive genetic variance-covariance matrix (**G** matrix). This uniformity can be quantified in several ways, one of which is simply a rank-ordered plot of the eigenvalues of the **G** matrix (as in Mezey and Houle, 2005); a more rapid decline in eigenvalues indicates less uniformity, all else being equal. A second measure of multivariate trait variation is the determinant of the **G** matrix, which is the product of the eigenvalues of **G** and follows the general approach to characterizing multivariate variation introduced by Wilks (1932). In addition, we quantify the effect of epistasis on the evolvability of a multivariate trait using a measure of evolvability introduced by Hansen and Houle (2008) that characterizes a population's ability to adaptively respond to the direction of a random selection gradient. This study assumes that the characters that make up a multivariate trait have the same underlying distribution of mutational effects and are measured on the same scale. In natural or experimental settings, an approach to scale characters such that comparisons can be made to this work (and others) is to measure characters on a standard deviation scale (Hansen and Houle, 2008).

Our study consists of a combination of simulation and analytical analyses. The simulation analysis is presented in the main body of the paper and involves a diploid sexually reproducing and recombining population. The simulation analysis is supported by an analytical treatment that is presented in the Appendix. Given the complexity of combining both sex and recombination with a multivariate analysis, the analytical treatment is limited to a haploid recombining population and small sample sizes. Nevertheless, the analytical treatment gives insight into general mechanisms that occur under more complex conditions explored in simulations. In the results and discussion, links between results from the simulation analysis are made with the analytical analysis.