Prerequisites 1

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Let no one unversed in statistics enter here

It is interesting that one can obtain some results without invoking Mendelism at all, but merely use purely statistical ideas of correlation and regression. One can go further, I believe. The whole area of selection can be approximated by purely statistical ideas of correlation and regression. The ideas of Mendelism merge with these ideas, as Fisher showed (more or less), and the fact that the theory does not need Mendelism in some respects, and one can almost say, does not use Mendelism intimately is, I think, a reason for it having a moderate degree of robustness in relation to assumptions. Apart from a difficulty I shall mention later, one could proceed as follows.

Let there be a population; let rules of forming mating couples be defined in terms of metric traits of individuals and/or in terms of relationship; let there be selection of individuals on the basis of metric traits or metric traits of related individuals; and finally let the offspring be measured. Then without an atom of formal Mendelism and with a large data set, the joint distribution of offspring and parents can be determined. One can examine this distribution and determine a prediction equation, which one can then apply for a few generations. The only flies in the ointment for this proposal are that every covariance would have to be determined from data and not inferred from, say, a coefficient of relationship and heritability, and large data sets would be needed to control sampling error.

So one could have a completely empirical selection procedure and a purely empirical process of obtaining a prediction of the result of continued selection. I suggest that this type of thinking should not be dismissed as a cranky idea. The reason that some predictions of the results of selection theory seem to work is that they are based on a process rather close to what I have sketched.

Oscar Kempthorne (1976)

This chapter aims at showing that quantitative genetics theory is built upon many theories from many other fields. Reading and understanding of this book does not need full mastery of those other fields. But if the reader is inclined to further develop the quantitative genetics theory, then deeper understanding of other fields is necessary.

There are some concepts of biochemistry, statistics, molecular genetics, Mendelian genetics, etc. that you should know. These are listed below.

1.1 Mendelian genetics

Mendelian genetics in this book is defined as the study of the inheritance of specific alleles in simple matings (crosses) or limited pedigrees. The focus of interest in Mendelian genetics is the genotype of an individual. Therefore, we either follow the process of inheritance of certain specific alleles from parents with known genotypes to their offspring, or alternatively we trace back the origin of certain specific alleles from offspring with known genotypes to their parents.

A little bit of history

There are some doubts about the claims of *independent* re-discovery by these three gentlemen, and also if they had a correct understanding of Mendel's work (FIND REF).

Many ideas within the field of QG have their roots in a time before the *re-discovery* of Mendel's rules (Mendel (1866), and *c.f.*, Bateson (1901)) in 1900 by Correns, Tschermak, and deVries. As an example, the reliance on the normal distribution can be traced back to the work of Galton (1886).

It took 18 years from the *re-discovery* of Mendel's rules until a formal and general reconciliation of Mendelian genetics and normality of observation for continuously distributed traits was formulated by Fisher (1918). The Mendelian concepts that Fisher used were very few and very simple *i.e.*:

- Bi-allelic inheritance;
- Alleles within a locus may show statistical interaction (any degree of dominance / recessive relationship);
- Alleles across loci may show statistical interaction (any degree of epistasis);
- Different loci may have some degree of linkage.

Fisher (1918) showed that the loci underlying continuously distributed traits follow the usual rules of Mendelian inheritance. However, the usual Mendelian ratios cannot be observed for these traits because many loci are involved. Therefore, Kempthorne (1976) is justified to downplay the role of *Mendelism*, because Fisher (1918) did not rely heavily on the rules of Mendelian genetics.

There is, however, an educational / pedagogical source of misunderstanding among new students of QG who have just a little knowledge of Mendelian genetics. The reason is that many textbook examples of Mendelian genetics concepts might lack generality. An example will make this point more clear.

The concept of dominance is most often introduced in the genetic textbooks by examples of an allele in a locus being completely dominant or recessive compared to the other allele in that locus. The seven traits used by Mendel in his experiments are usually the first examples. By the time that other related concepts (such as partial dominance, expressivity, and penetrance) are introduced the student has a firm understanding of the complete dominance with many examples in the mind. This may lead to the misunderstanding that complete dominance is the rule, while in fact complete dominance is just an exception. The same argument (though somewhat more complicated) can be used for epistasis.

In summary, development and understanding of QG theory does not need a lot of knowledge from Mendelian genetics. However, the more knowledge you have from Mendelian genetics, it becomes easier to understand the rationale behind assumptions of QG.

There are many good introductory genetics textbooks that cover Mendelian genetics quite well. Any of the following textbooks (and many similar ones) can be consulted to cover the needs:

- Griffiths *et al.* (2015) *An Introduction to Genetic Analysis*
- Pierce (2012) *Genetics: A conceptual approach*
- Sanders and Bowman (2015) *Genetic Analysis - An Integrated Approach*

1.2 Molecular genetics

The term *molecular genetics* is used here for a wide group of fields that use the DNA/RNA structure (and other molecules), in any form and length, to address many important biological questions. As such, molecular genetics is not needed for the development of QG theory. The majority of QG models are dependent on the involvement of many loci in expression of continuously distributed traits. The evidence provided by recent advances of molecular genetics certainly justify such QG models.

For the time being, general rules of how the phenotype (trait measurements) are mapped to genome are still not available. The reason is that there are many categories of DNA/RNA sequences, for which the details of how they affect the phenotype have not been elucidated yet. For example, the role of three dimensional structure of the chromosomes and its relationship with the position effects (expression) of sequence variants are are not fully understood yet (see *e.g.* Collas *et al.* (2019), Meaburn and Misteli (2019), Rowley and Corces (2018), and Zheng and Xie (2019)). Another example is related to the role of repetitive sequences in the position effect phenomena (see *e.g.* Keel *et al.* (2019); Liu, X. Chang, *et al.* (2019)).

Therefore, there are reasons to believe that the black-box theory of QG is still valid, and useful. A good grasp of molecular genetics, however, contributes to better understanding of underlying assumptions of QG. The general textbooks mentioned above provide enough information about molecular genetics as well. Additionally, the following textbooks (and many similar ones) can be consulted:

- Alberts *et al.* (2015) *Molecular Biology of the Cell*
- Strachan *et al.* (2015) *Genetics and Genomics in Medicine*

1.3 Biochemistry and biochemical genetics

Much of the biochemistry related to genetics is covered by the books mentioned in the previous two sections. There is a part of biochemistry, enzyme kinetics, that is most often not covered by genetic books. Understanding of the enzyme kinetics, specially models such as Metabolic Control Analysis (**MCA**), introduced by Kacser and Burns (1981), are very important to understand both dominance and epistasis. The following textbooks have enough coverage of the enzyme kinetics to understand models such as MCA:

- Lehninger *et al.* (2013) *Lehninger principles of biochemistry*
- Tymoczko *et al.* (2015) *Biochemistry, a short course*

1.4 Mathematical / Statistical genetics

Development of QG theory has required many, for biologists, complicated mathematical /statistical concepts. It is noteworthy that many contributions to QG theory have been made by scientists who have actually been statisticians (or have had very strong statistical backgrounds). However, this book restricts itself to the simplified versions of equations that require ordinary college level of mathematics / statistics. In order to keep the level of complexity at an acceptable level, for the general biologists, derivation of equations from first principles are not shown (and the reader is referred to other sources for the derivations). For basic mathematical statistical matters the following books (and many similar ones) can be consulted:

- Casella and Berger (2002) *Statistical inference*
- Hogg *et al.* (2019) *Introduction to mathematical statistics*
- Larsen and Marx (2017) *An Introduction to Mathematical Statistics and Its Applications*
- Lehmann and Casella (1998) *Theory of point estimation*
- Maindonald and Braun (2010) *Data Analysis and Graphics Using R - an Example-Based Approach*
- Wackerly *et al.* (2008) *Mathematical Statistics*

Another issue is that although many QG concepts can be shown in simple equations, the estimation of variables included in those equations may not be trivial, and may need sophisticated methods. For example, the concept of heritability can be shown by several simple equations, including $h^2 = V_A/V_P$. But, given the nature and structure of the data, the estimation can be quite tricky. It can be argued that the *estimation* and *prediction* are outside of the domain of pure QG. For these matters the following sources are essential:

- Mrode (2013) *Linear models for the prediction of animal breeding values*
- Schaeffer (2019) *Animal models*
- Sorensen and Gianola (2002) *Likelihood, Bayesian and MCMC methods in quantitative genetics*

1.5 Population genetics

In this book, population genetics is defined asthe branch of genetics studying changes of allele and genotype frequencies in populations. Like any other branch of genetics, population genetics rests firmly on the foundations laid down by the Mendelian genetics.

The focus of interest in population genetics is the frequency of alleles or genotypes in populations. Therefore, we either follow the process of inheritance of certain specific alleles from one generation to the next, or alternatively we trace back the patterns of allele and genotype frequencies in one generation to the processes that have been at work in the previous generations. Even though individuals are building blocks of a group, the genotype of any specific individual is of less interest in comparison to the dynamics of change in allele and genotype frequencies in the population.

What is important in population genetics is not what genotype any individual has, but how and why the frequency of alleles and genotypes in one generation or population differs from the frequency of alleles and genotypes in another generation or population. Population genetics is all about processes that are the causes of changes and the patterns that they create. It's all about processes and patterns, patterns and processes.

Population genetics

Population genetics is the study of allele and genotype frequencies across space (populations) and time (generations).

Population genetics is the science of patterns of allele and genotype frequencies, and the processes that change these patterns.

A central subject in population genetics is the relationship between allele and genotype frequencies in one or more loci, and (Darwinian) fitness. Of course, there is no necessity for all alleles and loci to confer a non-zero fitness value, *i.e.* many alleles and loci are not under selection and have no adaptive role. The theory of QG stands directly on the foundation laid down by population genetics, except for the fact that it is the mean and variance of phenotypic measurements that are under under scrutiny. Similarly quantitative genetics can be defined as:

Quantitative genetics

Quantitative genetics is the study of phenotypic means and variances across space (populations) and time (generations).

Quantitative genetics is the science of patterns of phenotypic means and variances, and the processes that change these patterns.

Thus, a good knowledge of population genetics is of utmost importance for development of QG theory, and understanding QG's present status. Further, if (and only if) there is a gap in the QG theory, one can conveniently use population genetics theory if an answer can be found there. The only thing that one needs to consider is the relationship between the fitness value (often symbolized by w or s) and selection differential (often symbolized by S or i; Robertson (1966), and Price (1970), see also Walsh and Lynch (2018) (Chapter 6)).

At the undergraduate level, the following books (and many similar ones) can be used by the readers:

- Hamilton (2009) *Population genetics*

At the postgraduate level, the following books (and many similar ones) can be used by the readers:

- Crow and Kimura (2009) *An introduction to population genetics theory*
- Ewens (2004) *Mathematical population genetics. 1: Theoretical introduction*
- Hartl and Clark (2007) *Principles of population genetics*
- Nielsen and Slatkin (2013) *An introduction to population genetics - Theory and application*

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