Report on the meeting
"100 years of quantitative genetics theory and its applications: celebrating the centenary of Fisher 1918"

October 9, 2018
Wolfson Hall, Royal College of Surgeons, Nicolson St., Edinburgh EH8 9DW

Sponsored by
The *Fisher Memorial Trust*, the *Genetics Society*, the *Galton Institute*, the *London Mathematical Society* and the *Royal Statistical Society*

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Ronald A. Fisher's 1918 paper, entitled "The correlation between relatives on the supposition of Mendelian inheritance" and published in the Transactions of the Royal Society of Edinburgh, set the foundations for the study of the genetics of quantitative traits. 100 years later, we celebrate Fisher's contribution and reflect on the advances made since this classical paper first emerged.

Context

Prior to R.A. Fisher's famous contribution, the genetic basis of evolutionary change was vigorously disputed between biometricians and Mendelians. In support of Darwin's theory of evolution by natural selection, biometricians believed evolution to be a continuous process, having developed much of modern statistical methods such as regression and correlation to describe the inheritance of biometric (continuous or quantitative) traits. After the rediscovery of Mendel's work on inheritance, the Mendelians argued against these views by vehemently supporting discontinuous evolution via Mendelian (discontinuous) traits controlled by the segregation of major genetic factors. The first attempts to reconcile the two opposing schools of thought were made independently by George Udny Yule in 1902 and Wilhelm Weinberg in 1910, whose studies were largely overlooked by both biometricians and Mendelians, blinded by the ongoing conflict. It was only in 1918 that the first comprehensive synthesis of Mendelism and biometry was put forth by Fisher.

Fisher (1918) presented the mathematical relationships between the principles of biometric measures of *heredity* (correlations between relatives), Mendelian *inheritance* of genetic factors and Darwinian evolution. He believed biometric heredity to be a special case of Mendelian segregation of genetic factors, and therefore reformulated it in terms of the Mendelian principles of inheritance, such that variation in a single trait could result from the segregation of one or multiple Mendelian factors. We now refer to Mendelian factors as loci, and to traits as Mendelian if determined by a few loci with clearcut segregation of alleles, or as quantitative if determined by so many loci that segregation at individual loci cannot be observed.

Traits can be determined by several components, including those with a genetic basis and those without (often described as environmental components). Among the genetic components is the *additive genetic* component which describes how the genotype of a parent affects the phenotype of its offspring. The magnitude of these components cannot be directly measured for a given individual. Instead, by comparing phenotypes among related individuals, the cause of phenotypic variation can be tracked. These statistical tools were introduced by biometricians to describe whether differences between individuals could be ascribed to differences between their parents. In his 1918 paper, Fisher coined the term *variance,* and extended these statistical tools to an *analysis of variance* framework to show that the (co)variance among traits can be decomposed into different components, such as between and within-family components (which include genetic and environmental components) and that these components could be quantified. Strikingly, the within-family variance estimates were largely consistent with those expected under a scenario with a large number of additive Mendelian factors, suggesting that traits are often determined by multiple loci.

The concepts introduced by Fisher (1918) opened the horizon to an explosion of studies in genetics and evolutionary biology that resulted in a large body of theoretical and empirical work. Among these studies are those concerned with fundamental aspects of evolution, such as the genetic architecture of traits and the effect of evolutionary forces on different components of the phenotype. More applied studies have been concerned with topics such as animal and plant breeding, and have contributed to much of the theory of quantitative genetics as well as to practical advances.

The meeting

The meeting started with an introduction by the lead organizer, Brian Charlesworth (University of Edinburgh, UK), about R. A. Fisher and some of the key concepts introduced by his work that are still widely used to this day. This introduction was followed by a series of talks representative of the diversity of topics that have developed from Fisher's classical 1918 paper. Talks were given by speakers from several countries, of which 7 were invited speakers: Nick Barton (Institute of Science and Technology, Austria), Josephine Pemberton (University of Edinburgh, UK), Sharon Browning (University of Seattle, USA), Heather Cordell (University of Newcastle, UK), Ed Buckler (Cornell University, USA), Richard Mott (University College London, UK) and Jarrod Hadfield (University of Edinburgh, UK). 4 were early career speakers: Josselin Clo (University of Montpellier, France), Chandana Basu Mallick (Roslin Institute, UK), Himani Sachdeva (IST, Austria) and Daniel Crouch (University of Oxford, UK). The meeting closed with a Fisher Memorial Lecture, introduced by the Chairman of the Fisher Memorial Trust, Sir Walter Bodmer (University of Oxford, UK), and given by Michael Goddard (University of Melbourne, Australia). Additionally, there were 9 contributed posters: Juliane Friedrich (Roslin Institute, UK), Emanuele Giorgi (Lancaster University, UK), Richard Oppong (University of Edinburgh, UK), David Clark (University of Edinburgh, UK), Jing Chen (University of Birmingham, UK), Keira Johnston (University of Glasgow, UK), Anna-Margarete Staehler (University of St Andrews, UK), Sandy Ayoub (University of London, UK) and Gabriela Gomes (Liverpool School of Tropical Medicine, UK).

Fisher (1918) realised that most traits are likely to be determined by many *independently inherited* loci with additive effects. Fisher arrived at this conclusion given the similarity between his estimates with those expected under the "infinitesimal model", which describes the extreme case where traits are determined by an indefinite number of loci, each contributing a small fraction of the phenotypic variance. Nick Barton presented an exhaustive analysis of the generality of the infinitesimal model in predicting the inheritance of quantitative traits. By formulating the infinitesimal model in terms of the distribution of phenotypes in a population, rather than the distribution of additive effects of the underlying loci, he showed that phenotypes *within* families are normally distributed without making assumptions about the distribution of phenotypes *across* the population. This work showed the infinitesimal model to preserve its generality in the presence of selection, drift, mutation, population structure and epistasis. Himani Sachdeva later spoke about the effects of selection and recombination on the introgression (exchange of genetic material between divergent gene pools) of blocks of linked loci, by assuming an infinitesimal model that considers *linkage*.

One of the main applications of the analysis of genetic variance into its different components introduced by Fisher (1918) is the estimation of additive genetic values and variance components given the genetic relatedness between individuals of a population. Estimating the relatedness between closely related individuals can be performed using pedigree information or from DNA sequence similarity. However, the task becomes more difficult among distantly related individuals: the effect of missing individuals in pedigrees becomes more significant as the distance between individuals increases and tests of sequence similarity among individuals become less powerful at detecting shared ancestry. Sharon Browning and Heather Cordell presented sophisticated computational methods for estimating the relatedness between individuals, using coalescent theory and genetic marker data to estimate the identity by descent (IBD) of genetic variants among individuals. From the notion that recombination breaks down linkage between loci and causes the decay of haplotypes (blocks of linked loci) over time, these methods use the frequency and length of shared haplotypes to inform about IBD. For example, long and common haplotypes are likely to be more identical by descent than those that are short and rare.

In experimental populations, whether in farm or in laboratory settings, reasonably good information about the genetic relationships between individuals as well as the environment experienced by them, is attainable. The next step is then to use this information to predict breeding (additive genetic) values and components of phenotypic variance, which can then be used to predict the response to selection using genomic selection. Animal and plant breeders were the first to make use of such predictions for artificial selection of traits and genetic improvement. Michael Goddard is one of the world leaders in quantitative genetics applied to animal breeding. Over the years, his work has made great contributions to the genetic improvement of cattle by making use of theoretical genetic considerations for the development of cost-efficient breeding programs. Michael presented the Fisher Memorial Lecture, where he spoke about how the use of densely distributed single nucleotide polymorphism (SNP) data has revolutionised our understanding of the genetic architecture of traits, i.e. the number and effects of loci that determine traits. SNP data allow us to not only estimate the additive genetic variance of a quantitative trait, as well as to detect large effect loci. Consistent with Fisher's ideas, the immense SNP data that has been collected

across numerous populations and species has shown most quantitative genetic variation to be caused by many polymorphisms with small effects. Mutations typically have weak or almost neutral effects on the phenotype, and those that have large effects are often deleterious and thus removed by selection. It is only in rare instances that these large effect mutations can be favoured by selection. Focusing on maize, one of the largest production crops worldwide, Ed Buckler spoke about how we can use machine learning tools and functional information to estimate breeding values more accurately and thus to predict the response to artificial selection over time.

The study of quantitative traits in wild populations is more complicated. The environment in these populations is uncontrolled and the genetic relationships among individuals are hard to determine. Josephine Pemberton, one of the pioneers of quantitative genetics in the wild, spoke about the challenges involved in estimating variance components in such populations, and described advances in using these to predict the effects of selection. Using two wild animal populations from islands off the coast of Scotland, the Soay sheep on St Kilda and the red deer on the Isle of Rhum, a joint effort by a large team of researchers has assembled detailed pedigrees using microssatelite-based parentage as well as genomic inference, and has collected a vast amount of genomic and phenotypic data. Focussing on *fitness* itself as a quantitative trait, the Pemberton group has made advances in understanding the causes of differences in fitness between individuals and genetic variation within populations, showing how conventional approaches to predicting the effects of selection can be misleading.

Traits that are subject to selection are to some degree causative of fitness, and are often described in terms of indirect genetic effects (IGE) on fitness. Jarrod Hadfield spoke about how the kin selection models developed by William Hamilton in 1964 are in essence a special case of IGE models. These models describe a process by which an individual's fitness benefits from the fitness of its relatives. As such, a social interaction (e.g. altruism) that *directly* benefits a relative's fitness thus *indirectly* benefits its own. Indirect genetic effects can come at a cost and it is the balance between the costs and benefits that determines the degree to which an individual can benefit from the indirect genetic effects of a correlated trait (e.g. a social interaction). These models assume that social interactions are determined by single traits, but break down when they are determined by multiple traits. Using a framework developed by Lande (1979) for selection on multiple correlated traits, Jarrod showed how the evolution of social interactions can be modelled when they are determined by multiple quantitative traits.

As Fisher proposed, most quantitative traits, with some exceptions, are determined by many loci of small effect. However, different loci can have different magnitudes of effect and large effect loci can sometimes be detected. Chandana Basu Mallick and Daniel Crouch spoke about the detection of major effect loci affecting two human traits. Chandana presented her work on the genetic basis of hair shape, using the mouse as a model for quantitative trait locus validation. For over 100 years, the mouse has been a powerful model system for the study of human genetics, due to the high genomic similarities between the two species as well as the ease of genomic manipulation in mice. A locus with a major effect on hair shape is present in humans, associated with genetic variation within European and East Asian populations. Chandana described knock-out experiments in mice that confirm

that this gene (*Prss53*) is involved in the control of hair-shape. Daniel presented his work on the genetic basis of human facial features, using a novel approach to Genome Wide Association Mapping. Using phenotypic data on several facial features, three loci with major effects were detected in the UK population.

Virtually any genetic or environmental variable can affect the expression of a quantitative trait. In most quantitative genetic studies, phenotypic variance is decomposed in an additive genetic component, other non-additive genetic components and an environmental component. Recent work by Richard Mott has shown that additive genetic variance in a trait can be caused by genetic variants other than SNPs. He showed how structural variants, including transposable element insertions, can be detected by treating read counts from short-read sequences as a quantitative trait. When applied to the model plant species *Arabidopsis thaliana*, structural variants were found to contribute significantly to heritable variation in quantitative traits.

The magnitude of additive genetic variance in a population is determined by the joint effect of the evolutionary forces of drift, selection, mutation and migration. Consequently, features of populations that affect these forces indirectly influence such variance. Josselin Clo spoke about his work on the effects of *self-fertilization*, which occurs when an individual mates with itself, on the magnitude of additive genetic variance. The study found selfing in plant populations to reduce the additive genetic variance and total genetic variance of quantitative traits and consequently to reduce the potential of populations to respond to selection.

The meeting was attended by approximately 200 people, including PhD students, early career researchers, and senior researchers among which renown scientists whose contributions have greatly marked the field of quantitative genetics. Filled with intense scientific discussions, the meeting radiated excitement and curiosity. In moments of reflection throughout the meeting it became clear to me, and perhaps to most attendees, how much we owe to Ronald A. Fisher's work.