

**Quantitative Genetics, Version 3.0: Where Have We Gone
Since 1987 And Where Are We Headed?**

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Header: Quantitative Genetics: Past, Present, and Future

Abstract

The last twenty years since the previous World Congress have seen tremendous advancements in quantitative genetics, in large part due to the advancements in genomics, computation, and statistics. One central theme of this last twenty years has been the exploitation of the vast harvest of molecular markers – examples include QTL and association mapping, marker-assisted selection and introgression, scans for loci under selection, and methods to infer degree of coancestry, population membership, and past demographic history. One consequence of this harvest is that phenotyping, rather than genotyping, is now the bottleneck in molecular quantitative genetics studies. Equally important have been advances in statistics, many developed to effectively use this treasure trove of markers. Computational improvements in statistics, and in particular Markov Chain Monte Carlo (MCMC) methods, have facilitated many of these methods, as have significantly improved computational abilities for mixed models. Indeed, one could agree that mixed models have had at least as great an impact in quantitative genetics as have molecular markers. A final important theme over the past twenty years has been the fusion of population and quantitative genetics, in particular the importance of coalescence theory with its applications for association mapping, scans for loci under selection, and estimation of the demography history of a population.

What are the future directions of the field? While obviously important surprises await us, the general trend seems to be moving into higher and higher dimensional traits and, in general, dimensional considerations. We have methods to deal with infinite-dimensional traits indexed by a single variable (such as a trait varying over time), but the future will require us to treat much more complex objects, such as infinite-dimensional traits indexed over several variables and with graphs and dynamical networks. A second important direction is the interfacing of quantitative genetics with physiological and developmental models as a step towards both the gene-phenotype map as well as predicting the effects of environmental changes. The high-dimensional objects we will need to consider almost certainly have most of their variation residing on a lower (likely much lower) dimensional subspace, and how to treat these constraints will be an important area of future research. Conversely, the univariate traits we currently deal with are themselves projections of more complex structures onto a lower dimensional space, and simply treating these as univariate traits can result in serious errors in understanding their selection and biology.

As a field, our future is quite bright. We have new tools and techniques, and (most importantly) new talent with an exciting international group of vibrant young investigators who have received their degrees since the last Congress. One cloud for concern, however, has been the replacement at many universities of plant and animal breeders with plant and animal molecular biologists. Molecular tools are now an integral part of breeding, but breeding is not an integral part of molecular biology.

Introduction: The Current State of Quantitative Genetics

We meet here at Zhejiang University in Hangzhou, China for the Third International Congress on Quantitative Genetics, over thirty years since the first Congress at Iowa State University in Ames in 1976 (Pollak et al. 1977) and twenty years since the last Congress at North Carolina State University in Raleigh (Weir et al. 1988). Much has happened since we last met. Over the last twenty years molecular biology has fully flowered into genomics. We have seen truly awesome advances in computer speed and performance, to the point where the laptops carried by conference participants are far more powerful than the vast majority of mainframes at the time of the last congress. Somewhat less appreciated, but equally important, have been major advances in statistics. Indeed, the magnitude and impact of these advances in statistics are very comparable to the advances in molecular biology over the last twenty years. Finally, these three areas of major advancements have had strong synergistic interactions. For example, analysis of high-dimensional genomic data required the development of new statistical methods that were only computationally feasible on today's computers.

Given this background of staggering change and scientific advances, how has quantitative genetics fared? Extremely well. Indeed, quantitative genetics is more relevant than ever, extremely vibrant with an entirely new arsenal of tools and techniques, and well-stocked with a very talented pool of young international scientists with degrees since the last congress (many of whom are on display here). We have seen important convergences between quantitative and population genetics and increased cross-talk among the important subfields of quantitative genetics (animal breeding, forestry genetics, plant breeding, evolutionary biology, and human genetics). Quantitative genetics is now an integral part of genomics, especially functional genomics, and the high-dimensional data sets generated by this fusion have sparked important advances in statistical theory. Most importantly, there are still important challenges and key unanswered questions to tackle, given our new tools, techniques, and talent.

Here we briefly review some of the major advances over the last twenty years, examine important on-going work, and try (futility, of course) to peer into the next twenty years of quantitative genetics. We conclude with an admittedly idiosyncratic list of a few "grand challenge" questions for the field to answer, which will hopefully spark others to offer their own important, and unresolved, questions for us to consider.

The options presented here may track with the general view of most of the community on some issues and be almost completely orthogonal on others. My goal is not to give a general community consensus, but rather to perhaps poke and prod others into commenting as to just how absurd some of my notions truly are. The best testament to the success of this presentation would be that it sparks a very open-ended and far-ranging discussion as to who we are, where we have been, and where we think we are going.

Where Have We Been?

Just what has the field of quantitative genetics (QG) been doing over the last twenty years? I offer a few general remarks and trends, as opposed to any attempt at an exhaustive review (which would certainly be a book!). We can loosely classify endeavors in QG over the last twenty years into (i) more of the same, only (hopefully) better, (ii) applications of old ideas that are now feasible because of

technological advances, and (iii) new directions not foreseen as of the last congress. A few examples of each are given below.

More of the Same, Only Better

One example are long-term selection experiments on a grander scale (longer term, larger effective population sizes). Experiments in bacteria (e.g., Cooper et al. 2003, Lenski 2004) span tens of thousands of generations, with the added benefit that population samples can be frozen at any point in time, and rescued for future experiments. Another example is Weber's (Weber and Diggins 1990, Weber 1996) experiments on wing-speed in *Drosophila*. Through the ingenious use of artificial wind tunnels, Weber was able to use much larger effective population sizes than most previous artificial selection experiments, and found that selection response continues for at least several hundred generations.

A second example is the explosion at the interface between ecology and evolution, largely from the work of Lande (1976, 1979). In particular, the paper of Lande and Arnold (1983), describing how to use quadratic regressions to measure direct and indirect linear and quadratic selection, has been widely applied over the last twenty years. Indeed, a recent review by Kingsolver et al. (2001) contained over 2,500 estimates of these directional and quadratic selection gradients. While there are some serious caveats with this approach, it still provides biologists with a powerful tool to estimate which traits are under selection and the nature of selection on such traits.

Another example inspired by the work of Lande is comparison of \mathbf{G} matrices — matrices of the additive genetic variances and covariances of traits of interest. The motivation is two fold. Lande (1979) showed that the breeders' equation can be written in multivariate form as $\mathbf{R} = \mathbf{G}\mathbf{P}^{-1}\mathbf{S} = \mathbf{G}\boldsymbol{\beta}$. The vector $\boldsymbol{\beta}$ is the direction that selection is trying to move the population mean, while the response vector for changes in the mean in the offspring is $\mathbf{G}\boldsymbol{\beta}$, a (potential) rotation and scaling of $\boldsymbol{\beta}$ imposed by \mathbf{G} . Thus, one concern is how common genetic constraints are, while a second is the stability of \mathbf{G} over time. If \mathbf{G} is relatively stable over time, one can take an observed vector \mathbf{R}^* of population divergences and estimate the required direction of past selection $\boldsymbol{\beta}^*$ by noting that $\boldsymbol{\beta}^* = \mathbf{G}^{-1}\mathbf{R}^*$. A flurry of methods for comparison of \mathbf{G} matrices between different populations have been proposed (and applied) over the last twenty years, and the stability (or lack thereof) of \mathbf{G} remains a topic of active discussion.

Our final example is breeding value and variance component estimation. While BLUP/REML methodology was widely entrenched in animal breeding at the time of the last congress, they were just starting to be applied to evolutionary biology and awaiting their use in plant breeding. One interesting recent use of BLUP (by a number of different groups) has been to study selection in natural populations of marked individuals that have been followed for (in some cases) decades. A striking observation that emerges from such studies is the apparent lack of selection response for many heritable traits under (relatively) constant directional selection (Merilä et al. 2001). One suggestion for such stasis is that selection is on an environmental, rather than genetic or phenotypic, component. For example, better nutrition results in larger antlers and better fighting (and hence more mates), generating a correlation between antler size (a heritable trait) and mating ability (a fitness component). However, no change in antler size occurs, as selection is on a nonheritable environmental component (nutrition) of antler size (Kruuk et al. 2002). Looking in a population of red deer showing stasis in antler size, Kruuk et al. found a correlation between the phenotypic

value of antler size and mating success, but no such correlation when the estimated breeding value of antlers is used, consistent with selection being on a non-genetic component of antler size. Put another way, selection is on a character phenotypically, but not genotypically, correlated with antler size.

Old Ideas, Now Feasible

The second broad class of advances in quantitative genetics has been to apply old ideas which are now feasible thanks to advances in technology. Far and away, the most significant tool for quantitative geneticists from genomics are essentially unlimited supply of dense (i.e., closely linked) markers for just about any species/population for which we care to invest some modest resources. There is no more striking example of this than the explosion of QTL mapping, which is a historically very old idea (Payne 1918, Sax 1923, Thoday 1961). The problem with applying it was the lack of markers. Statistical advancements in QTL mapping closely followed marker availability. In the first studies in the late 1980's using a modest number of allozyme markers, ANOVA methods worked just fine. As marker densities increased, so that linked markers were the norm rather than the exception, the field saw the development of first interval mapping, and then composite interval mapping, and finally multipoint mapping. While these important statistical advances were new and novel, they are also a natural extension of the increased density of markers that quickly became available.

A second example of an old idea becoming feasible with new technologies/advancements has been the Bayesian explosion in genetics, which arose because MCMC methods became computational feasible and powerful improvements, such as Gibbs sampling, were developed. If one looks over the statistical history of quantitative genetics, the field was largely governed by methods-of-moment approaches (such as ANOVA) until the mid 1970s. At that point, computers had advanced to the point that rather complex maximum likelihood calculations (such as segregation analysis tests for the presence of a segregating major allele in a complex pedigree) became feasible. Similarly, the realization that MCMC methods could easily be used to generate draws from just about any Bayesian posterior distribution, coupled with the computing power to do so, has led to Bayesian methods becoming more and more dominant in quantitative genetics. It is worth noting, however, that although quantitative geneticists now have a very rich statistical toolbox from which to draw from, most are pragmatists, just as happy to use ANOVA (when appropriate) as to worry about a full-blown Bayesian analysis. Thus the "Bayesian revolution" in quantitative genetics is much more due to pragmatical, rather than ideological, reasons.

New Directions

Perhaps the most important new direction over the last twenty years is a change in perception. Quantitative genetics has transformed from a field where the focus was on estimating and exploiting summary statistics (e.g., variance components, breeding values, inbreeding depression and heterosis values) to a new focus on finding and exploiting genes of even modest effect. Just how successful the latter has been (to date) remains debatable, but there is no question that, as a field, our focus has significantly shifted. It is extremely instructive to look back to one of the brightest minds in the field, Oscar Kempthorne, and his review of the field for the Second Congress in 1987 (Kempthorne

1988), who stated:

“What has been the impact of post-DNA genetics on quantitative genetic theory? Nothing, I surmise. Why? My suggestion is that the field has been trapped in a very narrow tunnel, thinking about the very old classical beanbag model [of genetics]”

This shift in focus is almost entirely a consequence of ever-increasingly dense marker maps for just about any species of interest. A corollary has been the application of quantitative-genetic thinking to genomic traits, such as the entire expression array of genes within a genome through the analysis of microarrays. Similar analysis of genome-wide protein and metabolic panels has already started and will certainly explode in the very near future.

However, it is also important to look beyond this obvious new genomics direction. Other important advancements are also out there, partly obscured by the bright light shined on all things molecular. Two particular topics are especially worth highlighting. First, there has been an explosion of linear (especially mixed) models for the analysis of genotype-environment interaction, especially in large MET (multi-environmental trials) experiments for the suitability of new lines across a target population of environments. The basic structure of all of these models starts with

$$y_{ijk} = \mu + G_i + E_k + GE_{ij} + e_{ijk}$$

for the mean value (in plot k) of genotype i in environment k . Estimation of the all of the $G \times E$ terms can be problematic, at best. Further, the environments E_k are not simply replicable locations but also different years, which are far less (if ever!) replicable. All of this makes prediction of performance in a new environment especially challenging. AMMI (additive main effects, multiple interaction models), and other bilinear regressions (Gauch 1988, Cooper and DeLacy 1994, van Eeuwijk 1995), attempt to partition the $G \times E$ terms by using the first few principal components of the residuals after fitting main effects,

$$GE_{ij} = \sum_{k=1}^n \lambda_k \gamma_{Gk} \delta_{Ek} + \epsilon_{ij}$$

These forms of the linear model can also be analyzed by ordination and clustering techniques, such as the biplot, and this sort of visualization can offer considerable insight into $G \times E$ (Kempton 1984).

The second, perhaps more important, class of developments are mixed models where the environmental covariance structure is more fully taken into account. This approach has been especially powerful for looking at QTL \times environment interactions (e.g., Piepho 2000, Malosetti et al. 2004, van Eeuwijk et al. 2005).

The second very interesting direction has been to consider *curves* as traits, and not simply by focusing on a particular parametric family (such as a growth curve), and then using standard multi-trait QG to find the curve parameters. Rather, the curve itself is treated as an infinite-dimensional object, indexed by some continuous variable (such as time). The resulting curve is described by continuous covariance function between time points. The analysis of such *infinite dimensional traits* was introduced by Kirkpatrick (Kirkpatrick and Heckman 1989; Kirkpatrick and Lofsvold 1989, 1992; Kirkpatrick et al. 1990; Gomulkiewicz and Kirkpatrick 1992) in evolutionary biology and independently developed as *random regressions* in animal breeding (Schaeffer and Dekkers 1994, Meyer and Hill 1997). As we discuss below, dealing with even more complex structures as the objects of estimation and selection is an important future direction of quantitative genetics.

Where Are We Now?

Although partly redundant with our previous discussion, this is a good place to take stock of the various new toys that we now have in our quantitative genetics toolbox.

Impact of Advances in Reproductive Technologies

Incorporation of advances in reproductive technologies, especially in animal breeding, has had a long role in quantitative genetics, for example AI and MOET. AI (Artificial Insemination) greatly facilitates progeny testing and the sale of genetic material from high-valued sires. Multiple Ovulation Embryo Transfer, or MOET (using hormonal treatment to cause a female to release more eggs than normal, which are then transferred to surrogate females) was recognized rather early on as a way to increase selection responses (Land and Hill 1975, Nicholas and Smith 1983).

In the last twenty years, some of the splashiest results from biotechnology have been in reproduction, for example in 1996 Dolly the sheep became the first mammal cloned. While there are some obvious advantages to clones, such as preserving highly favorable gene complexes, their role in quantitative genetics to date has been relatively minor. The other high-profile advance in reproductive technologies has been cross-species gene transfer. This has resulted in major commercial products (BT corn, round-up ready soybeans), interesting experiments (e.g., inducible growth hormone in fish and other animals), and significant public concern (rightly or wrongly) in a number of countries. From a research standpoint, mouse transgenics have proven very helpful and are likely to be an important tool in mammalian quantitative genetics, especially for mouse models of human diseases (with their significant funding making such experiments possible). Likewise, plant transgenics (esp. in *Arabidopsis*) also provide important tools for complex trait analysis.

Impact of Genomics

The last twenty years have seen the transition from the modest sequencing of a few genes to the post-genomic era of whole genome sequences almost on demand. Quantitative genetics, as with most of biology, has been forever transformed. However, the two highest-profile endeavors at the interface of genomics and quantitative genetics, QTL mapping and marker-assisted selection (MAS), rode in with much excitement and potential, yet remain largely bogged down in the quagmire of small sample size and poor resolution. QTL mapping has now moved to association mapping to use historical recombinations to partly compensate for sample size, while MAS has moved to very high density mapping in attempts to predict breeding value (genomic selection). The success of both of these transformations appears near, but the field felt this way with QTL mapping for almost a decade, so some healthy skepticism is not out of place. Ironically, as a field we are now at the stage where phenotyping, rather than genotyping, is the bottleneck. Further, sample size issues become even more critical. It is (or will soon be) relatively trivial to score a million SNPs but unless the sample size is correspondingly large, much of this genomic information is redundant. Indeed, for many studies we need to start thinking about *selective phenotyping*, wherein a large number of individuals are rapidly genotyped, and then we phenotype traits on those individuals showing the greatest genetic distances from each other.

The increasing flood of markers moves us from mapping to regions (QTL mapping with 20-40

cM resolution) to the potential to map to individual genes and, ultimately, individual nucleotides (the mythical QTN, quantitative trait nucleotide). As marker density allows us to move down to this scale, lack of independence caused by population structure becomes increasingly important, and indeed the driver required for many of these methods to work. Thus, one immediate consequence of dealing with variability in small (less than one cM) genetic regions is that the seemingly esoteric population genetic tools of coalescent theory and higher-order linkage disequilibrium measures have become extremely relevant to modern quantitative genetics. Likewise, using marker information to search for signatures of selection (for example, by reduction in the levels of variation around selected genes) has moved from a topic restricted to *Drosophila* population geneticists to first human geneticists, and then to breeders in the search for domestication genes. Marker information also offers the potential of estimating relatedness among individuals, allowing quantitative genetics without (initial) knowledge of relatedness.

Putting These Advances Together: Practical Applications

It is illustrative to show the potential practicality of some of the above advances. Consider a more general version of the basic breeders' equation $R = h^2 S$ to allow for the more realistic situation of overlapping generations and selection using additional information beyond simply the phenotype of an individual,

$$R_y = \left(\frac{i_s + i_d}{L_s + L_d} \right) \rho_{uA} \sigma_A$$

Here R_y is rate of response per year, L the generation interval (for a sire s or dam d), i the selection intensity, and ρ_{uA} selection accuracy, the correlation between the index of selection u and the breeding value A of the individual under consideration. What can we do to increase the rate of response? Short of introducing new variation (in the extreme by gene transformation), not much can be done about increasing σ_A^2 within a population. Response is increased by decreasing L and increasing ρ and i . However, there are tradeoffs between L and i , and between L and ρ . Clearly, the longer we wait to allow a parent to reproduce, the more accurately we can predict their breeding value, as information from other relatives and from progeny-testing accumulates over time. However, these increases in ρ also result in increases in L . The optimal selection program must balance all of these competing interests, so let's briefly examine how some of the above developments can influence each of these components.

Advances in reproductive technologies can improve accuracy (in the extreme through cloning), but more typically by allowing for larger number of offspring in progeny tests to estimate a sire's breeding value. AI has resulted in the potential for far greater selection intensities (and unfortunately far more inbreeding) than would be possible under natural insemination. Likewise, MOET schemes to increase the number of offspring from females potentially allow for increases in the selection intensity on dams as well as decreases in the generation interval.

The use of molecular markers can potentially decrease generation interval (by choosing individuals long before the trait appears), increase selection intensity (by allowing for selection in sexes/conditions where the trait is not itself expressed), and (perhaps most importantly) improve the accuracy, especially for lower heritability traits. Of course, while a breeder certainly wants to maximize rate of response, more important is the economic rate of response, getting the same (or greater) response for less money. Thus, the promise of genome selection is that while its accuracy

might not be as high as BLUP-based progeny testing, the costs may be significantly less. This allows more individuals to be screened more rapidly, reducing L and increasing i .

Impact of Advances in Statistics

It is not fully appreciated that the dramatic advancements in statistics over the last twenty years (in large part due to increased computational ability) largely have kept pace with the frenetic pace of change in genomics. Many of the widely-used methods of statistics today (mixed models, permutation tests, bootstrap sampling, MCMC, Bayesian posteriors, model selection, false discovery rates) would not be found in most textbooks twenty years ago, except perhaps for an occasional minor aside. There are four broad trends with implications for quantitative genetics. First, resampling and other (largely) distribution-free methods for assessing significance and assigning confidence intervals. Second, increased computational ability to work with highly parametric models, such as mixed models with tens of thousands to millions of observations. Third, MCMC methods (such as Metropolis-Hastings and Gibbs sampling) allow us to generate draws from just about any distribution of interest, no matter how complex, opening up Bayesian analysis. Finally, analysis of models where the number of parameters p to estimate is much larger than the sample size n . Let's consider some of the consequences of these advances in order.

First, the impact of resampling tests is obvious to anyone who has performed a QTL mapping study. Each study has its own unique covariance structure among the genetic markers due to the segregating populations being used and the composition and distribution of markers. Permutation tests easily allow this structure to be fully utilized during significance testing for (just about) any statistical model we wish to run on the data. Likewise, given that many distributions in quantitative genetics are highly skewed and do not neatly follow standard testing distributions, resampling methods allow for more precise analysis.

Second, the impact of increased computational ability to deal with highly parametric models cannot be overstated. Indeed, one could easily argue that this has been as important to quantitative genetics as the introduction of molecular markers. After all, such models are needed to analyze the marker data! Starting with the complex segregation analysis models from the human geneticists to follow potential major genes in pedigrees, ever-increasingly complex maximum likelihood calculations have made their way into quantitative genetics. This is certainly seen in QTL mapping, but an even more complex problem is using molecular markers to estimate coalescence structure and the demographic parameters of a population, as may be required for association mapping and tests of loci under selection. However, it is in allowing the more widespread use of complex mixed models (including, of course, purely random models as a special case) where this increased computational ability has most strongly impacted quantitative genetics. Mixed models are used for BLUP estimation of breeding values in animals (a long and proud tradition), plants (more recently), and natural populations; for QTL mapping in complex pedigrees; for association mapping in structured populations; and for the analysis of genotype-environment interactions (to name a few). The power of random-effects models is that the use of the covariance structure allows a very large number of parameters to be estimated, potentially exceeding the sample size, and that it corrects (shrinks) these predictors. Mixed-model approaches are also scalable, so that as quantitative genetics continues to consider ever higher dimensional traits, mixed models (especially in a Bayesian framework) can keep pace.

Third, MCMC methods allow us to generate samples from complex distributions, such as high-dimensional Bayesian posteriors. This has allowed Bayesian methods to truly flower over the last twenty years. While the widespread use of Bayesian statistics was initially bogged down in bickering over the importance and implications of priors, the strong practicality of a Bayesian analysis slowly became appreciated. Essentially, it is maximum likelihood exact for any sample size (so that we do not have to resort to large-sample approximations for hypothesis testing and confidence intervals). Further, the use of marginal Bayesian posteriors, wherein uncertainty in all of the estimated nuisance parameters (those we have to estimate but do not really care about) can be integrated out, gives us a distribution of uncertainty for the parameters of interest that fully accounts for all of the uncertainty introduced from estimation of the nuisance parameters. Finally, Bayesian methods are especially adept at handling high-dimensional problems. One caveat, however, is in order for Bayesian methods. While theory tells us that the MCMC sampler will indeed generate draws from the desired distribution, this is a large-sample property and hence some concern about convergence is required. Often, one simply looks at the MCMC trace and decides that it is sufficiently “well-mixed” that it has approached its ergotic value (and hence realizations are draws from the target distribution). Clearly, a very desirable trend would be for more formalism, and less eye-balling, for convergence diagnostics, especially when samplers are jumping dimensions.

Lastly, the real statistical challenge facing quantitative genetics is over-saturated models, where $p \gg n$. We can already measure far more markers (millions) in an organism than we can measure individuals of that organism (n in the thousands can become very difficult). Another example is in QTL or association mapping attempting to search for epistasis – interactions between markers – giving a huge model space. Thus, much of quantitative genetics, especially when working with molecular data, reduces to model selection problems. While MCMC searches (such as stochastic search variable selection) can be used, a more fruitful approach seems to be using shrinkage estimators wherein all of the parameters are estimated at once in a random model (or Bayesian) context, and then most are shrunk back to near zero. Analysis of such over-saturated models raises the issue of dealing with multiple comparisons. Exciting developments, such as the false discovery rate, offers one approach to handle this issue in some settings (but not others, such as linkage studies). The ultimate solution to the multiple comparison problem is simply to treat many of these methods as dimensional-reduction tools, filtering out a number of irrelevant parameters to generate a smaller enriched set for independent verification and future study.

Impact of Advances in Population Genetics

Population and quantitative genetics have long enjoyed a special relationship. Indeed, both fields share the same founding fathers (Fisher and Wright). Population-genetic modeling of selection response (moving beyond the infinitesimal model) and mutation-selection balance were prominent at the last Congress and have continued strong since. One hope is that dense marker information can somehow be used to estimate parameters of interest when dealing with response when the infinitesimal model does not apply, but rather a finite number of genes of varying effect (and frequency) account for the variation. A frustration, and indeed an embarrassment, is that we still cannot account for the observation of widespread genetic variation, despite an increasingly-sophisticated theory by some extremely bright people. The observed patterns and amounts of variation are inconsistent with what we know about mutation rates and strength of selection (Johnson and Barton

2005). Obviously, there is plenty of work ahead for theoretical population geneticists.

While “standard” population genetics has a long history of cohabitation with quantitative genetics, a much more recent partner is molecular population genetics. As quantitative geneticists rely upon dense marker maps for association mapping, the very fine details of the history of that population (Did it go through a bottleneck? Is there population structure? Migration?) became quite important. Likewise, a complementary approach to QTL/association mapping (wherein one knows the traits and tries to search for the genes) is a genomic scan for loci under selection. For example, the domestication of plant and animals can (in some cases) leave signatures of selection around genes that were increased to high frequency during domestication. This provides a character-free approach for searching for targets of selection. While there is a rich history of tests of selection (in reality, tests of departures from the standard neutral model of a population of constant size in mutation-selection equilibrium), applying these to natural or domesticated populations (such as humans or pigs) requires accounting for the past population history so as to construct the appropriate null distribution for the test statistics. Both these techniques, association mapping and scans for selection, thus strongly rely on coalescence theory, the distribution of genetic variation given information about the past history of a population (which is generally inferred from marker data).

Where Are We Going?

So just what does the future of quantitative genetics hold? Obviously, a lot of more of the same, only better, and a big dash of old ideas that are now technologically feasible. But what about new directions? My fuzzy crystal ball suggests that important new future directions in quantitative genetics are *dimensionality* and *connectivity*. Specifically, we need new ways of thinking about projections of complex objects onto lower dimensions, the analysis of new (high dimensional) objects such as networks and pathways, and better connectivity between developmental and physiological models on one hand and quantitative genetics on the other. Much of this is about geometry.

Escape from Flatland

Geometry has a long and important history in biology, from Fisher’s (1918) original orthogonal variance decomposition to D’Arcy Thompson’s classic (1917) *On Growth and Form*, from Fisher’s geometric model for the adaptation of new mutations (Fisher 1930) to the Wright-Simpson concept of a phenotypic adaptive topography (Wright 1932, Simpson 1944). A most instructive treatise about geometric thinking is Edwin Abbott’s classic *Flatland. A romance of many dimensions* (1884). In the two-dimensional world of Flatland, individuals take on different appearances depending upon the angle from which they are viewed. Likewise, when a sphere sojourns through Flatland, its projection into this lower-dimensional subspace starts out as a point, increases to a circle, and then decreases to a point before vanishing. The key point is this: when we view a complex geometric object through its projection onto a lower-dimensional space, we usually have a very misleading view.

What does all of this have to do with quantitative genetics? Think back to the \mathbf{G} matrix of all the pairwise covariances among a vector of n traits. Each trait can show significant additive genetic variation (the projection of \mathbf{G} onto a single dimension shows considerable variation), but there may be no genetic variation along the direction that selection is trying to move the vector of traits.

Geometrically, this means that most of the genetic variation resides on some lower dimensional subspace, so that if n traits are measured, most of the variation is found on a subspace of dimension less (potentially much less) than n .

This notion goes back to Dickerson (1955), wherein each component of an index can have significant genetic variation, but the index itself may have none. Lande's (1979) model for multivariate response also notes this. However, the general view by many was that such constraints were rather pathological, requiring a very improbable combination of covariances to make \mathbf{G} nearly singular when all of its diagonal elements are positive. However, recent estimation of \mathbf{G} for modest-dimensional traits shows that such constraints may be much more common than we originally anticipated. Two recent studies from Mark Blow's lab (Blows et al. 2004, Van Homright et al. 2007) measured cuticular hydrocarbons (CHC) in two species of Australian fruit-flies, *Drosophila serrata* and *D. bunnanda*, which are important cues in mate choice. In 8 CHC in *Drosophila serrata*, most of the usable genetic variance is close to right angles away from the direction β of natural selection, while for the 9 CHC in *Drosophila bunnanda* the angle between β and its projection onto the subspace of \mathbf{G} containing most (98%) of usable genetic variation is 88.3 degrees, again nearly orthogonal. In both cases, although there is considerable genetic variation in each component (and hence univariate theory suggests a response to selection), there is very little usable genetic variation along the direction of past selection and hence very little response. If we simply consider the univariate projections, with each trait showing significant additive variation, we might assume it was extremely unlikely that little usable genetic variation resides along the direction of selection. However, past selection appears to have indeed eroded variation along the direction of selection (Fisher's Fundamental Theorem), while still leaving considerable variation in each univariate trait. Returning to Flatland, a misleading view arises in not just the quantitative, but more importantly the qualitative, prediction of selection response when just considering the individual univariate projections. Thus, quantitative genetics must try to escape from Flatland by considering the subset of traits being followed as part of a (most likely) much higher dimensional structure. Treating this object simply through its projections onto lower dimensional spaces can be very misleading (Walsh 2007, Blows and Walsh 2008). Conversely, when we have a complex structure, much of its usable genetic variation likely resides on a lower dimensional subspace.

New Objects of Analysis: Complex Functions, Graphs/Networks

It's all well and good to point out that biological systems are complex, but just how can we get some sort of handle on the more complex structures within which our trait(s) of interest reside? One type of object to consider are graph and network models of regulation and metabolism. These are obviously an intermediate step towards the more complex structures our trait(s) of interest are embedded within, but a clear goal of functional genomics is the estimation and analysis of dynamical behavior on such graphs. Since there will clearly be between-individual variation, much in the same way that QG has been applied to microarray analysis, its applications towards graphs and networks is an obvious step, and indeed we will see some early applications at this meeting. The estimation issues involved with detecting variation on these new structures will certainly be daunting, but our new statistical tools may provide some help. The first estimation issue is the topology (the shape of the wiring diagram) of such graphs, with the likely possibility that different individuals will have slightly different topologies. One simple way to describe the wiring diagram

between any n elements (nodes) is with an $n \times n$ matrix, with element ij describing the connection between nodes i and j . This element could simply be a one if the two nodes are connected and zero if they are not. Likewise, we could replace one by some measure of the strength of the connection. Finally, the ij -th element could be signed if there is a direction on the graph (i.e., 1 for $i \rightarrow j$, -1 for $j \rightarrow i$). In all of these settings, an appropriate Bayesian shrinkage estimator could be used to estimate between-individual variation in these elements. The even more complex estimation issue is the dynamics of change given this topology (the rate of flow across each node at a particular point in time). Individuals may have the exact same wiring diagrams, but different rate coefficients on some (or all) of the nodes.

The second class of complex structures we need to consider are the natural extensions of the infinite-dimensional trait models of Kirkpatrick. We need to move from where the trait is indexed by a single continuous variable (such as time) to settings where the trait is indexed by multiple variables. For example, three spatial variables and time could be used to describe morphological shape changing over time. In these cases, we move from univariate covariance functions to multivariate covariance functions, and hence from covariance matrices to covariance tensors. Obviously much fun awaits here!

Incorporation of Explicit Models of Physiology and Development

Networks are one attempt to model complex biological phenomena, typically at the lowest-level of biological organization (e.g., within-cell features such gene regulation and metabolism). At the other end of the modeling hierarchy are explicit models of physiology and development, where the outputs are phenotypes. This has been especially successful in plant breeding, where detailed crop growth models have allowed the incorporation of physiological details with both environmental and genetic variation (e.g., Cooper and Hammer 1996, Yin et al. 2004, Hammer et al. 2006). Similarly, quantitative genetics has a long history of using threshold models for development, wherein an underlying continuous liability variable (influenced by both genetic and environmental factors) is mapped into a binary phenotype.

In all cases, these are attempts to map from genotype + environmental space into phenotype space. One nice feature of crop growth models is that easily quantified environmental variables such as temperature, humidity, soil moisture, and other physical factors can be mapped into measures of plant stress and growth. While much of the focus of quantitative genetics has been on genes, there is likely to be an increased focus on the environment as well. We see hints of this in the proposed “individual medicine” wherein particular drugs (environments) are prescribed to patients given both their phenotype and key genotypes. Physical features of the environment have always been of interest, but there is now also a growing appreciation of biological features of the environment. For example, extension of Griffin’s (1967) notion of the associate effects by Muir and colleges (Muir 2005, Bijma et al. 2007a,b) provides a way to select for a more benign biological environment in breeding situations, allowing selection for better individual, and group, performance.

Biological systems are perplexingly both malleable and stable. On one hand, they can respond to environmental clues to generate phenotypic plasticity. On the other, most biological traits are relatively canalized, and hence buffered to much of the environmental/genetic changes they encounter. Significant perturbations (such as a major gene) can often knock a population outside of its zone of canalization, revealing considerable genetic variation that is otherwise hidden. We need

more realistic models that account for these general phenomena. Further, one hope is that a better understanding of the mapping from basic genetic and environmental inputs to the final phenotype might account for at least some of the nonlinearities which arise (epistasis and $G \times E$). These nonlinearities cause significant problems in prediction. However, if the inputs are relatively linear and then mapped into nonlinearities by the gene-environment-phenotype map, an understanding of at least some features of this map may significantly improve our predictive ability.

Putting These Pieces Together: Complexity Breeds Simplicity?

Thus, my prediction is that the future of quantitative genetics is in dealing with even greater complexity. Some might feel that this is a relatively gloomy future with all of this complexity and considerations of high dimensional biological structures offering us relatively little extra in return for the extra effort required to unpack it. My own view is quite the opposite. Think back to our friends in Flatland. Even a complex structure can have most of its variation residing on a lower-dimensional space. If we know something about this space, this complexity actually breeds simplicity and greater insight. Einstein said it best when he remarked "make things as simple as possible, but no simpler". Sometimes we need to start with complexity and whittle down the pieces to get the sort of insight that cannot be gathered by starting simple and trying to build up. One reason why quantitative genetics has such a bright future is its ability to quantify and handle various sources of uncertainty. Such will certainly be the case for the analysis of the complex biological structures of the future.

One very interesting start in this direction is the work by Cooper and colleagues (Cooper et al. 2005) in modeling optimal strategies for plant breeding. Building on a gene network that allows for significant epistasis and $G \times E$, their model incorporates information from known genes (such as QTLs) and their expected performance in crop growth models, coupled with unknown genes drawn from a potentially complex network. They simulate a large number of such draws, and then examine which selection strategy works best over these ensemble sets. This type of connectivity between existing QG techniques, models of growth and development, and gene networks is obviously a very important future direction for QG.

Grand Challenge Questions

In closing, in thinking about the future, many fields find it fashionable to pose a series of "grand challenge questions". The appeal is, of course, obvious. A writer of modest intelligence can suggest grand-sweeping questions and then be frequently cited when far brighter individuals actually solve them! In keeping with this fine tradition of science, I modestly offer a few such questions, and would encourage others to do so as well.

Two obvious grand challenge questions have a long history in QG: What is the molecular basis to quantitative variation? and What maintains quantitative-genetic variation? Thus, we mention these simply for completeness. We propose a few (hopefully) less obvious, questions:

Grand Challenge Question 1: How do we measure constraints to selection and evolution beyond G (i.e., beyond the Gaussian infinitesimal model)?

Grand Challenge Question 2: To what extent can information from dense marker maps provide input on the past nature and future course of selection (i.e., in the prediction of long-term response)?

Grand Challenge Question 3: What is the effective dimensionality of a typical trait? Phrased another way, what is the dimension of the subspace upon which most of the genetic variation in the structure within our target traits(s) is embedded?

Grand Challenge Question 4: How do we build up from network models and build down from physiological/developmental models to produce more predictive models of the gene-environment to phenotype mapping?

Grand Challenge Question 5: How can we stably exploit modest genetic differences in the face of epistasis and $G \times E$?

Grand Challenge Question 6: What is the maximum useable information (for QG) from a genomic sequence? From K sequences?

Concerns for the Future

One final comment. Despite the very healthy state of the field, there are concerns. In particular, plant and animal breeders at many Universities are being replaced by plant and animal molecular biologists. In part, this represents a view (largely by non-breeders) that future crop and livestock improvement will largely be through gene transformation. While transformations certainly can have dramatic effects, minor details such as selection to reduce the deleterious side effects that often accompany major genes and modification of effects across environments means that, even if the future is largely transformations (which is highly suspect), there will still be a critical role for breeders. We are children of the genomics age, and as such, molecular training is now as much the part of a breeder's education as is statistics. However, the converse is not true, as molecular biologists are often very naive about breeding, and plant and animal improvement could suffer greatly if it is solely inherited by them. The future of quantitative genetics is in working with molecular biologists to integrate new insights on developmental and physiological pathways into our understanding of the inheritance and transmission of complex traits. Thus, this closing remark is by no means an anti-molecular biology one (far from it). Rather, I simply wish to emphasize the importance in striking a balance for future hires, a balance that seems (at present) far from equilibrium.

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