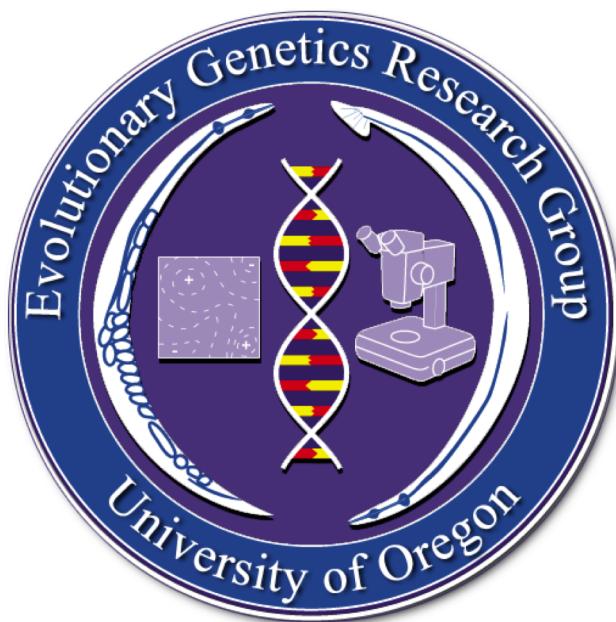


Molecular Quantitative Genetics

Theory and Practice

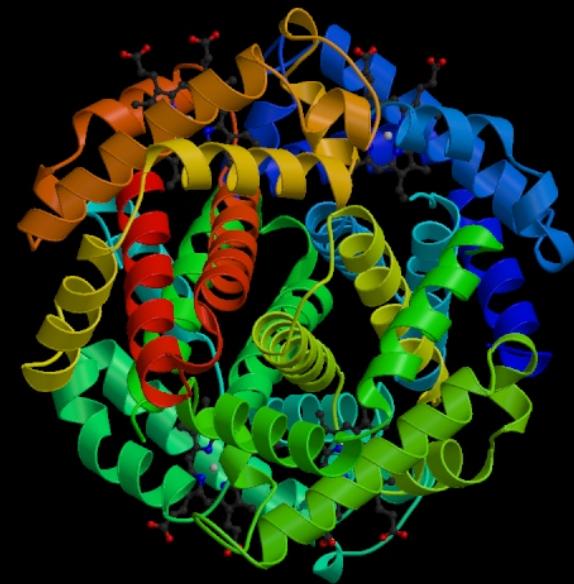
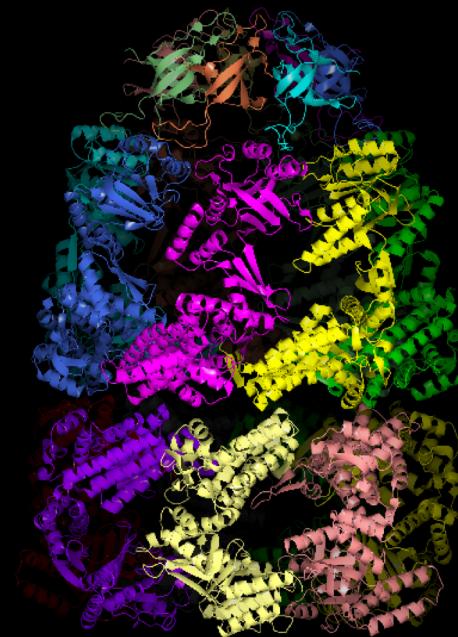
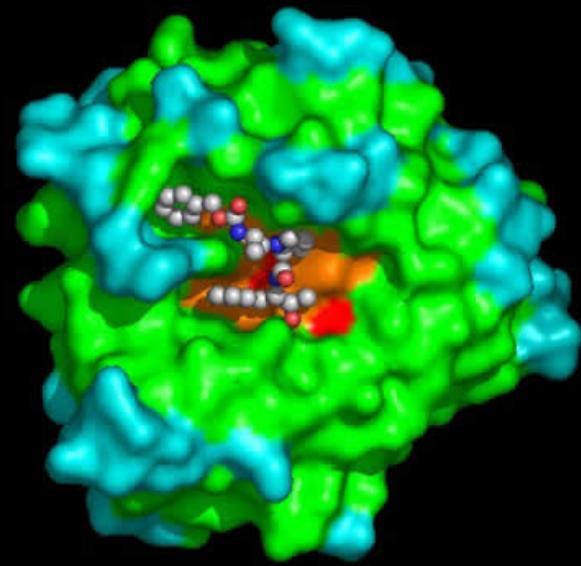
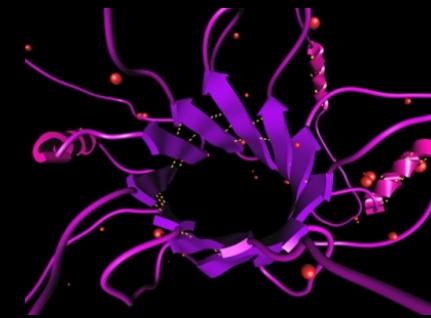
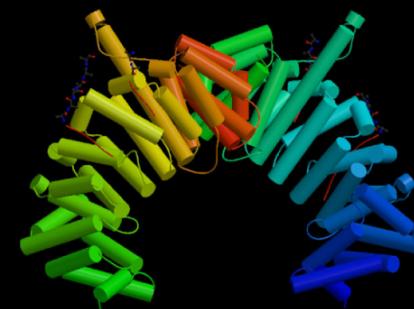
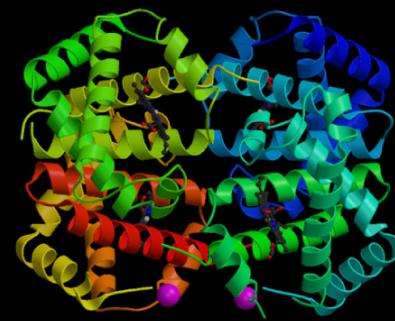
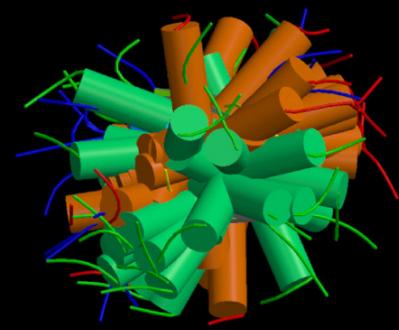
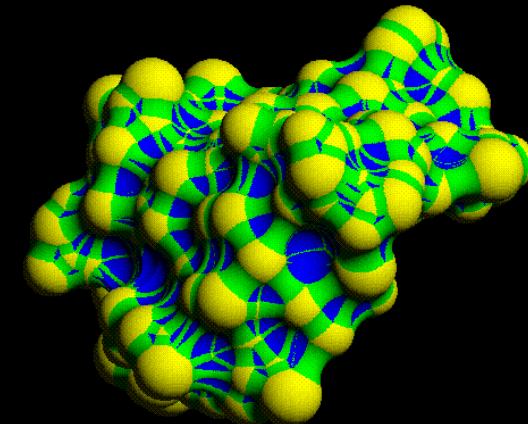
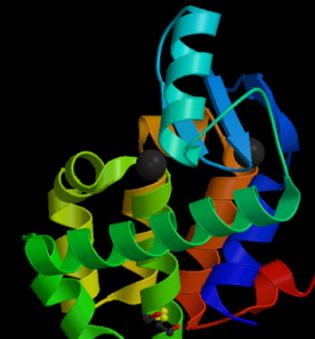
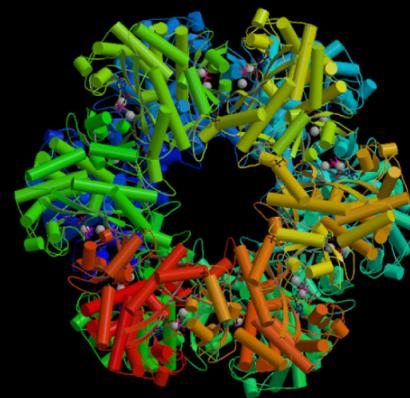
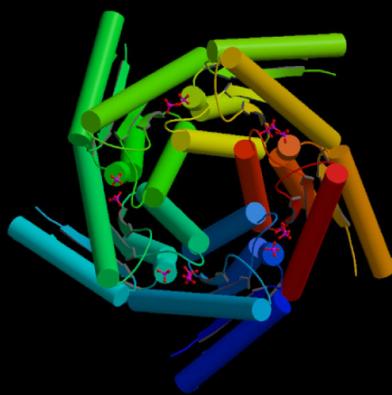


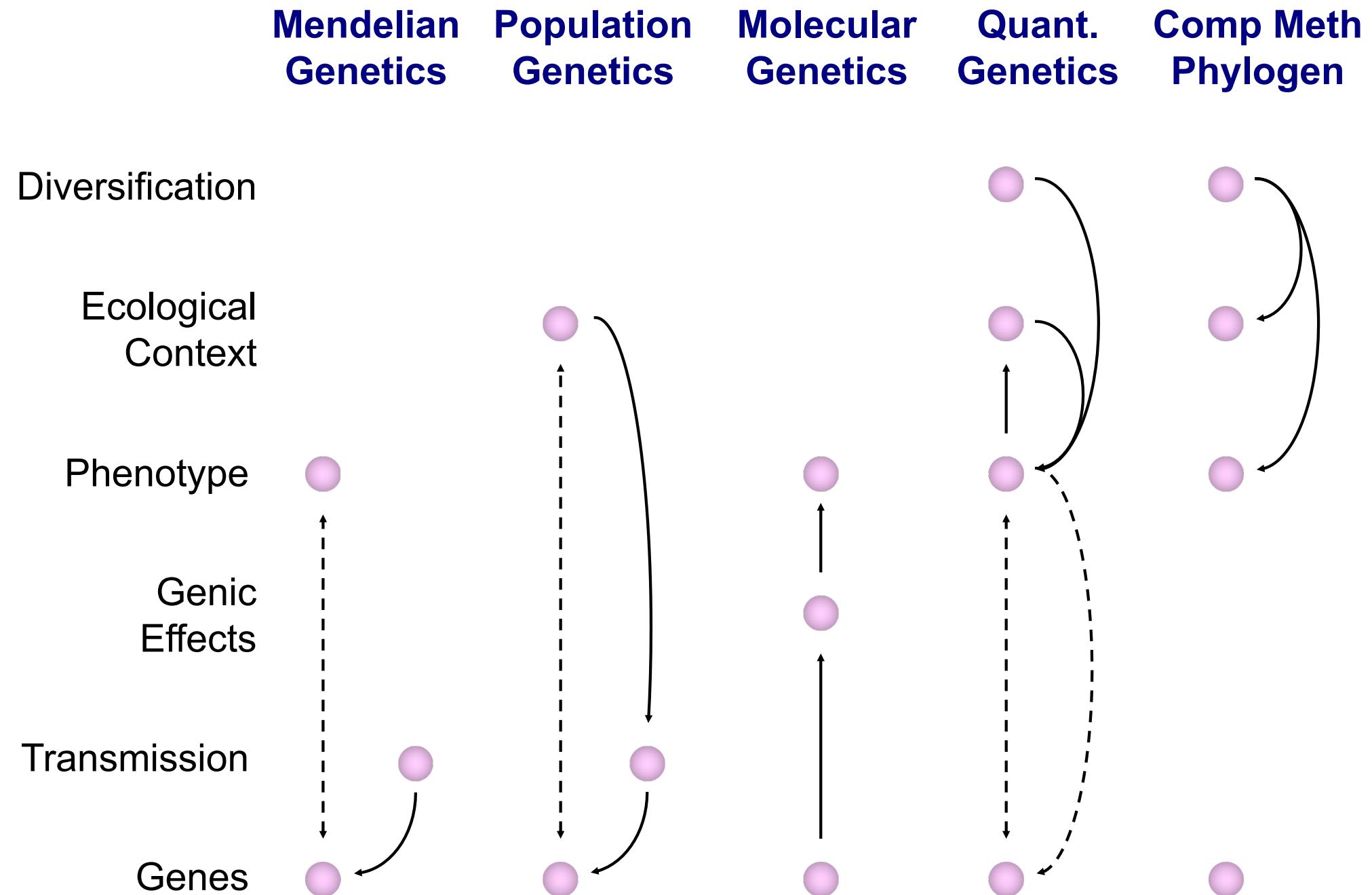
Patrick Phillips
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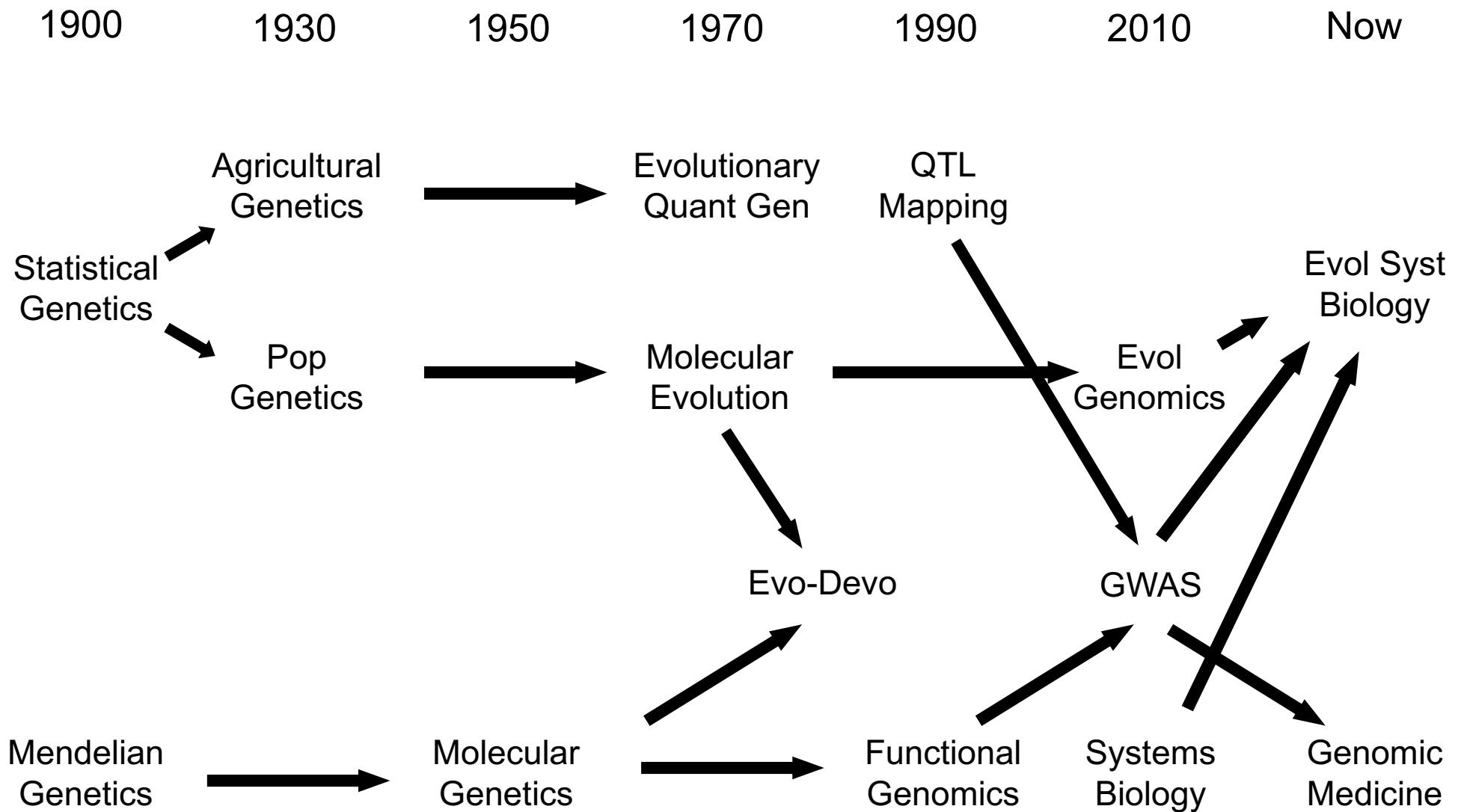


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The fundamental distinction

Fundamental genetic unit

- ◆ Mendelian/molecular biology
 - The locus
 - Comparison between wildtype and mutant (usually a knockout)
- ◆ Quantitative genetics
 - The allele
 - Each allele can have a quantitative effect that is independent of the effects of other alleles

Examples

◆ Pleiotropy

- *Mol bio*: property of a locus. Either pleiotropic or not
- *Quant gen*: property of an allele. Pleiotropy can be variable both within and between loci (and it can evolve)

◆ Epistasis

- *Mol bio*: Mutation at one locus blocks ("stands upon") effects of mutations at a second locus
- *Quant gen*: Many possible types of interaction, allele-by-allele across loci

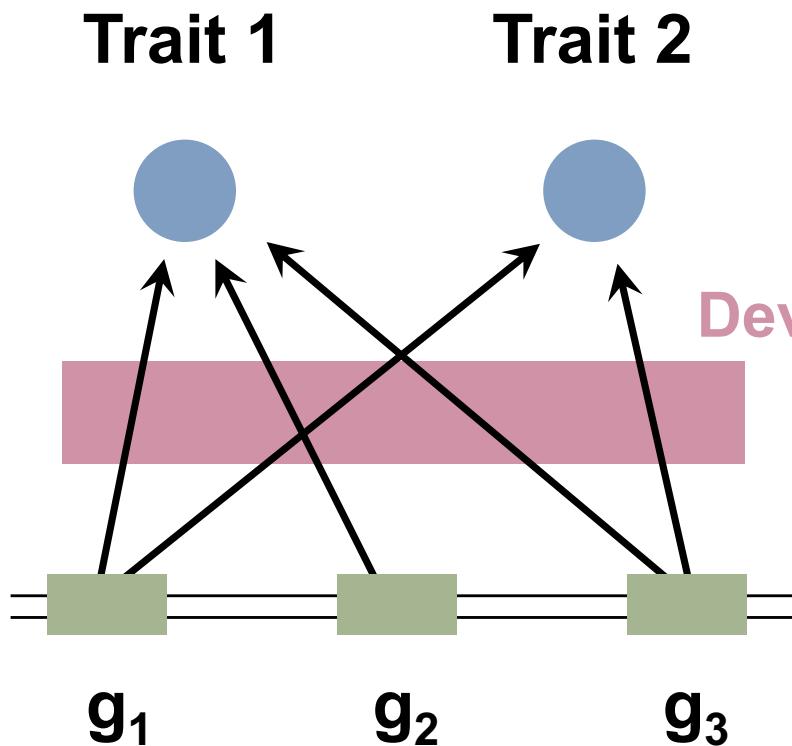
Multivariate selection

$$\Delta \bar{z} = G\beta$$

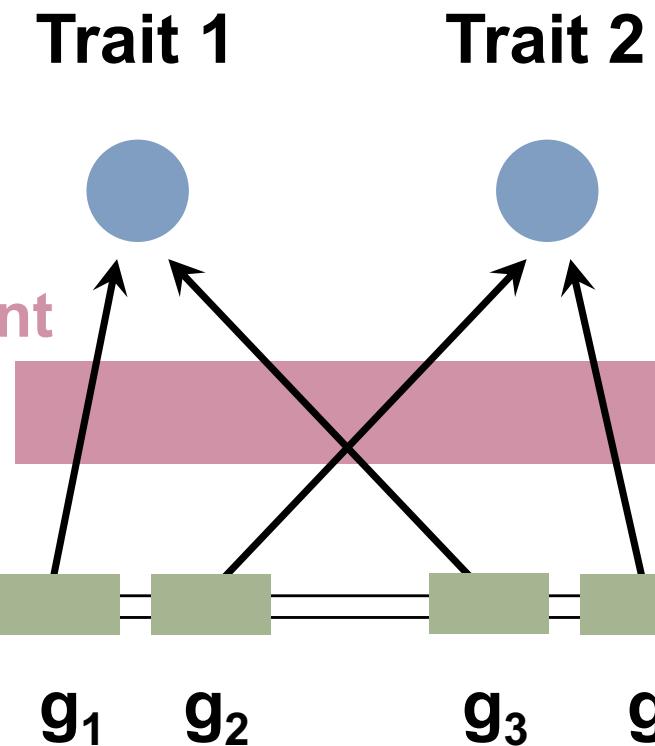
Lande 1979
Lande & Arnold 1983

Evolution of genetic architecture

Pleiotropy

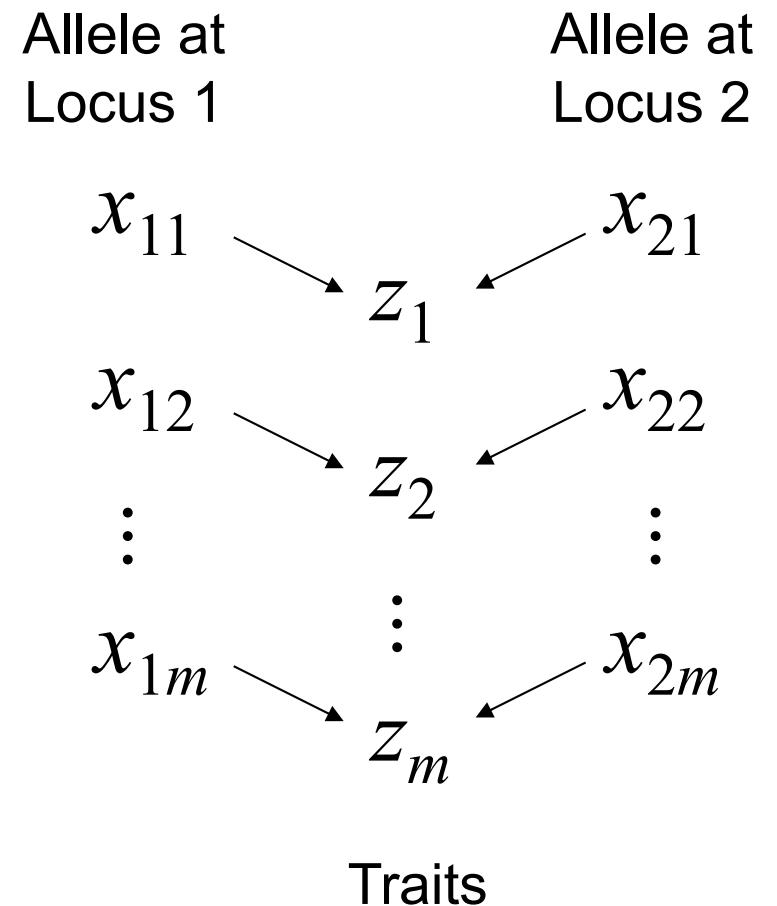
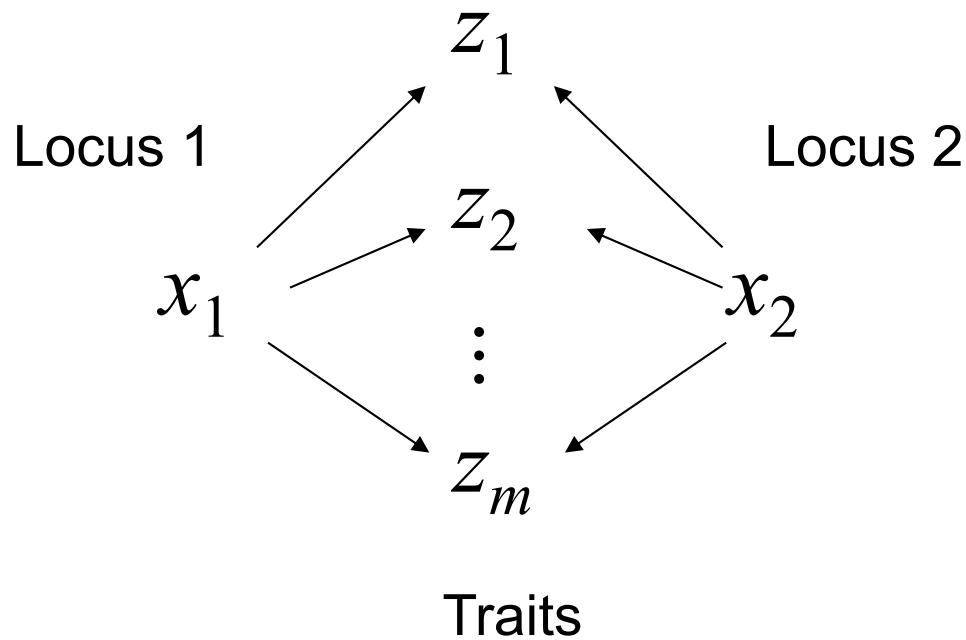


Linkage



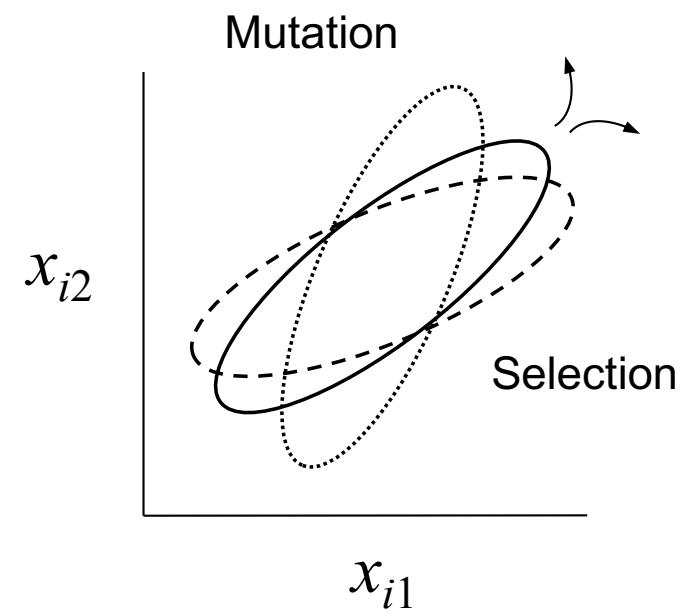
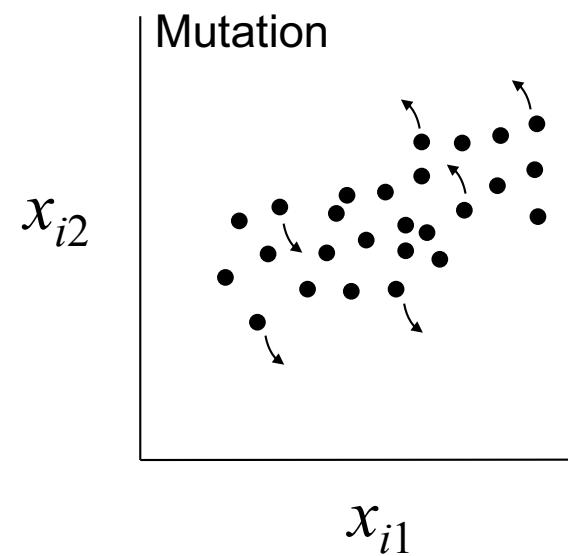
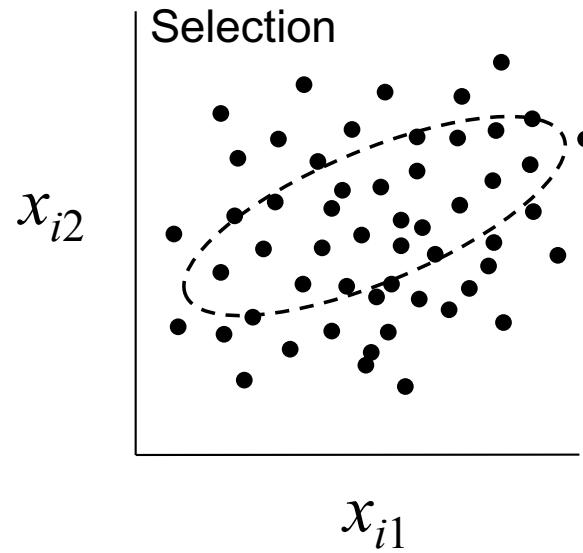
Development

Distributions of pleiotropic effects



Phillips and McGuigan 2006

Evolution of the G matrix



Finding the alleles that matter

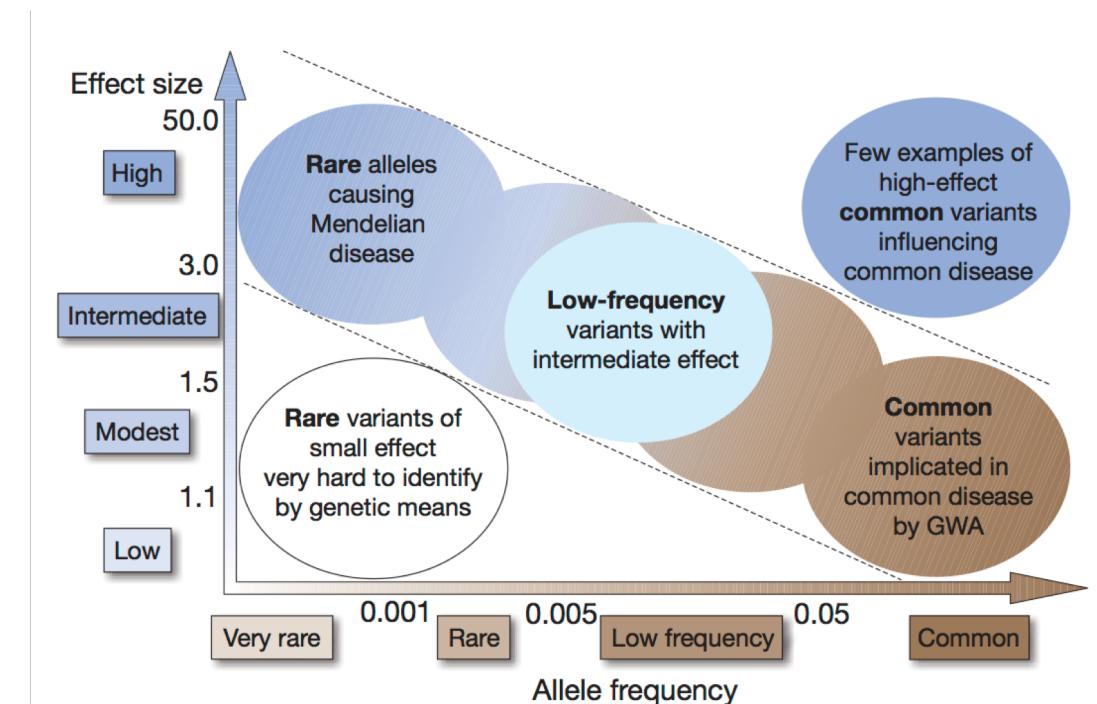
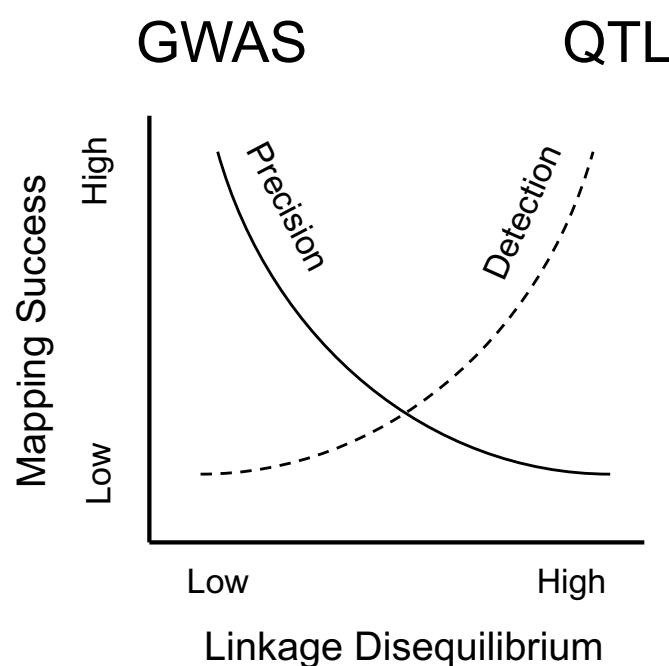
- ◆ Understand the functional basis of adaptation
 - Connect molecular evolution to phenotypic evolution
- ◆ Understand the role of historical processes in shaping evolutionary change
 - Connect phylogenetics and biogeography to phenotypic evolution
- ◆ Understand the distribution of allelic effects
- ◆ Understand and predict the structure of the genotype-phenotype map

Approaches

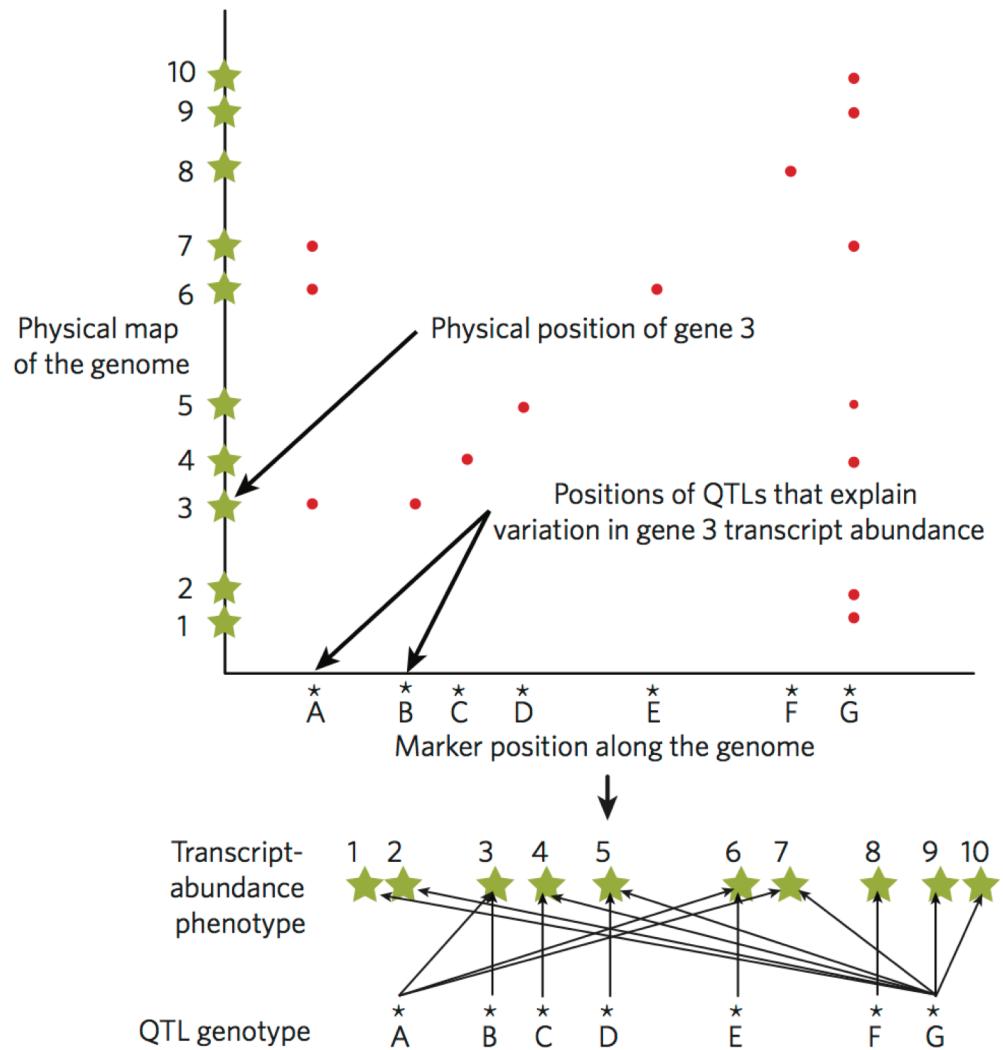
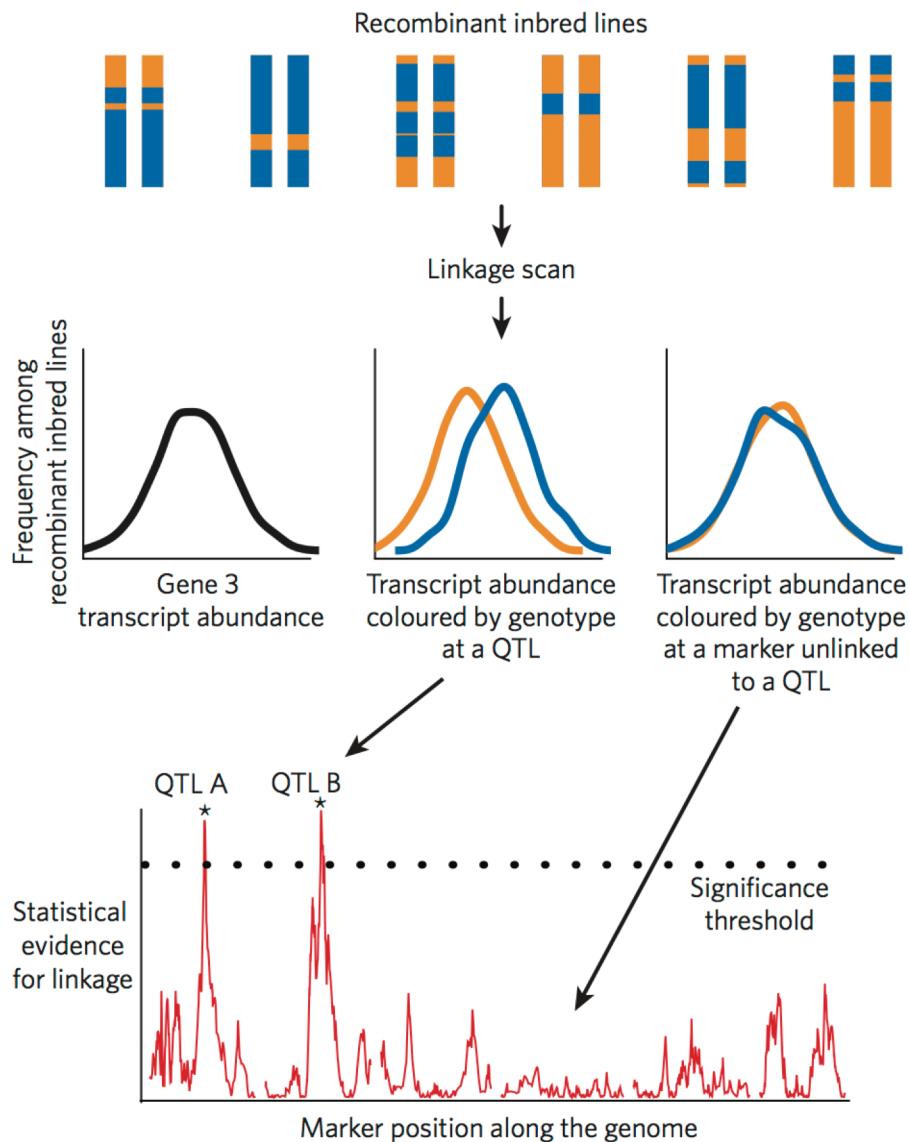
- ◆ **Quantitative trait locus (QTL) mapping**
 - *Strengths:* Controlled genetic crosses, strong linkage between markers and potential causal loci
 - *Weaknesses:* Limited sample of alleles, strong linkage can confound effects of different loci
- ◆ **Genome-wide association (GWAS) mapping**
 - *Strengths:* Potential to sample all relevant alleles, historical breakdown of linkage increases precision
 - *Weaknesses:* Genetic heterogeneity means large samples are required, undetected population structure can bias results
- ◆ **Evolve and re-sequence (experimental evolution)**
 - *Strengths:* Comparison to ancestor allows hypothesis testing and increased power, find alleles relevant to adaptation
 - *Weaknesses:* Only a subset of variants will be detected, selective sweeps could obscure signal, difficult to separate selection from drift

Challenges

- ◆ Structure of genetic architecture determines power of detection
- ◆ Tradeoff on the effects of linkage on detection and specification



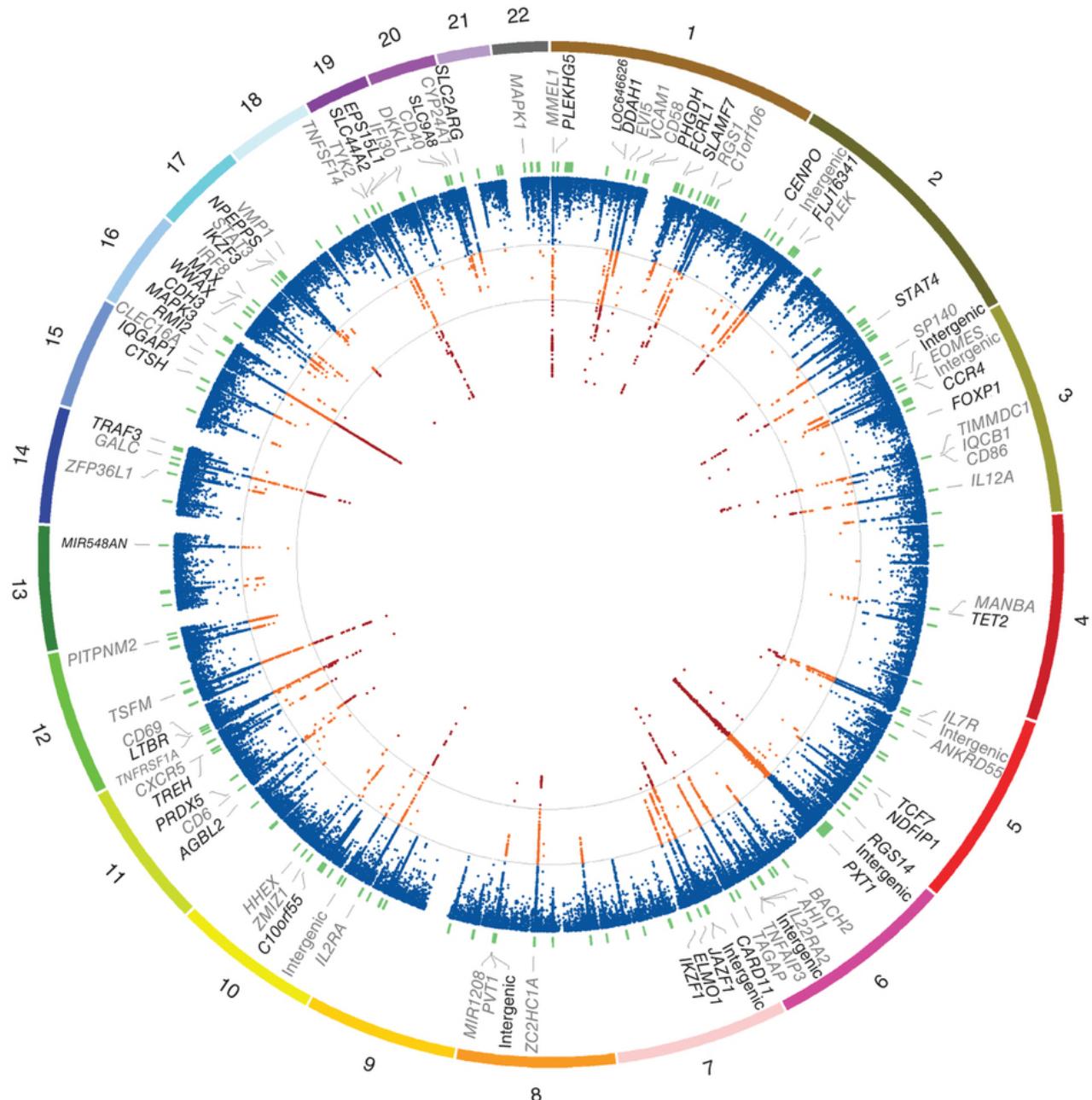
QTL Mapping



GWAS: Complexity of complex traits

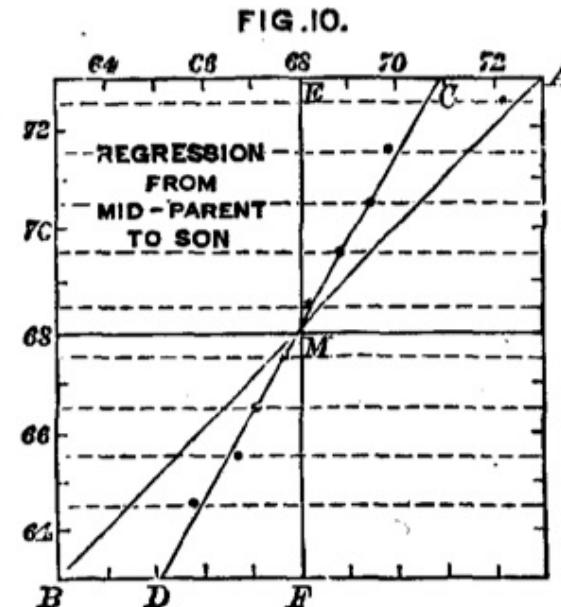
GWAS of multiple sclerosis

- 14,498 subjects
- 24,091 controls
- 161,311 SNPs
- 103 loci detected
- ~28% variation explained



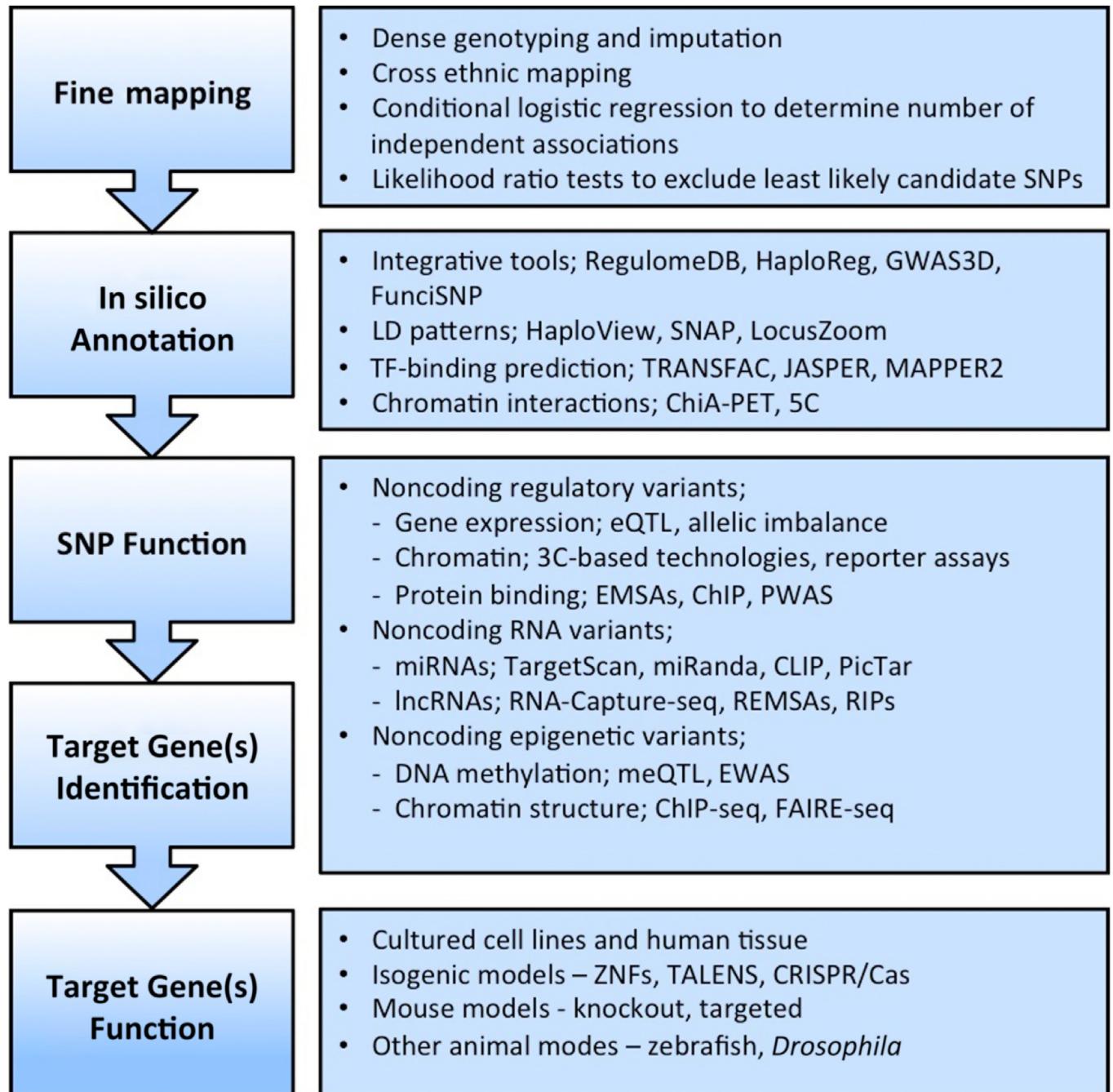
GWAS for human height

Francis Galton, Natural Inheritance (1889)

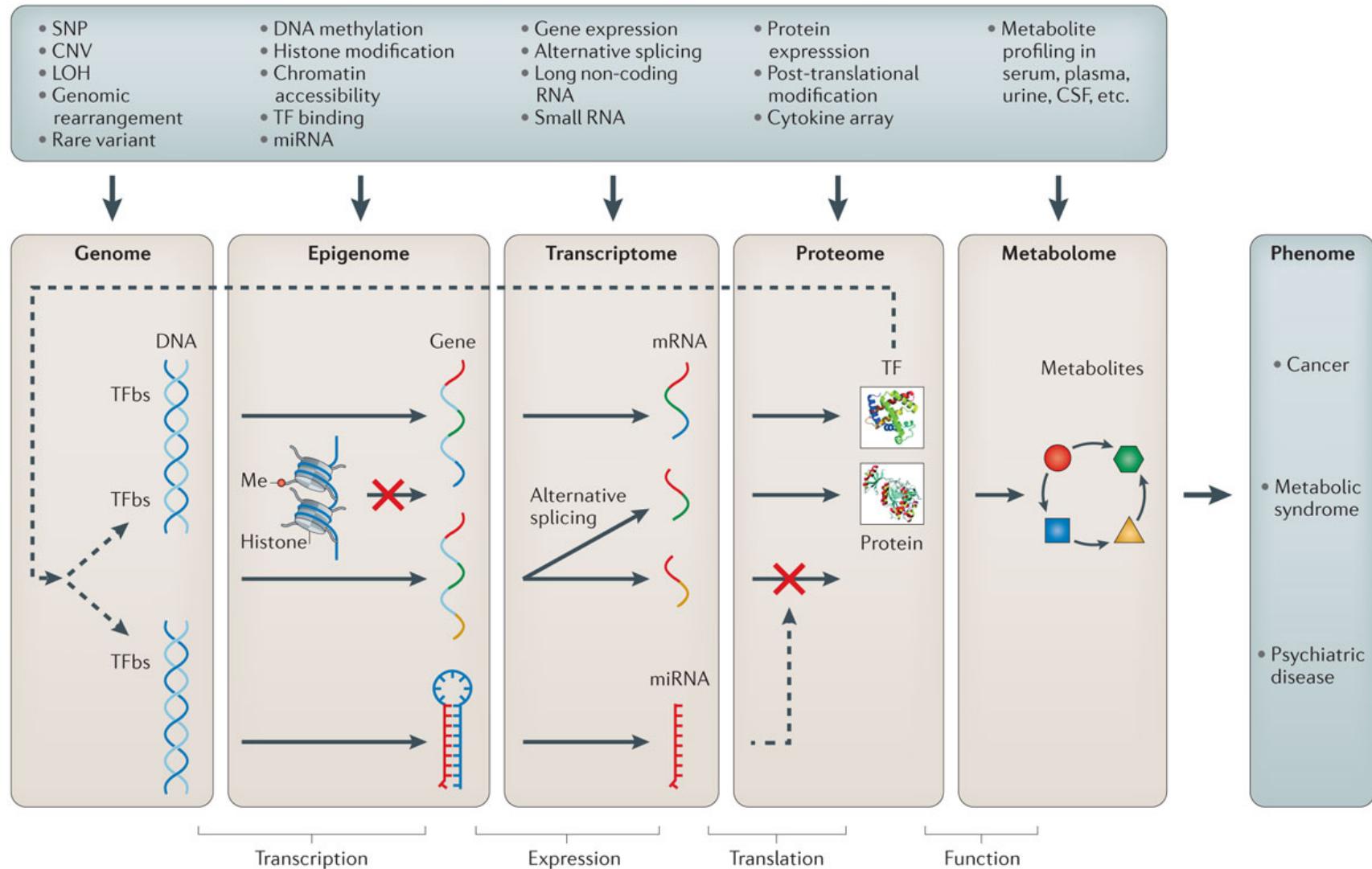


	Height	BMI
Genomes analyzed	693,000	681,000
Significant SNPs	3,290	716
Genes	712	416
Prediction accuracy	20%	4%
Variance explained	25%	5%

Determining SNP function



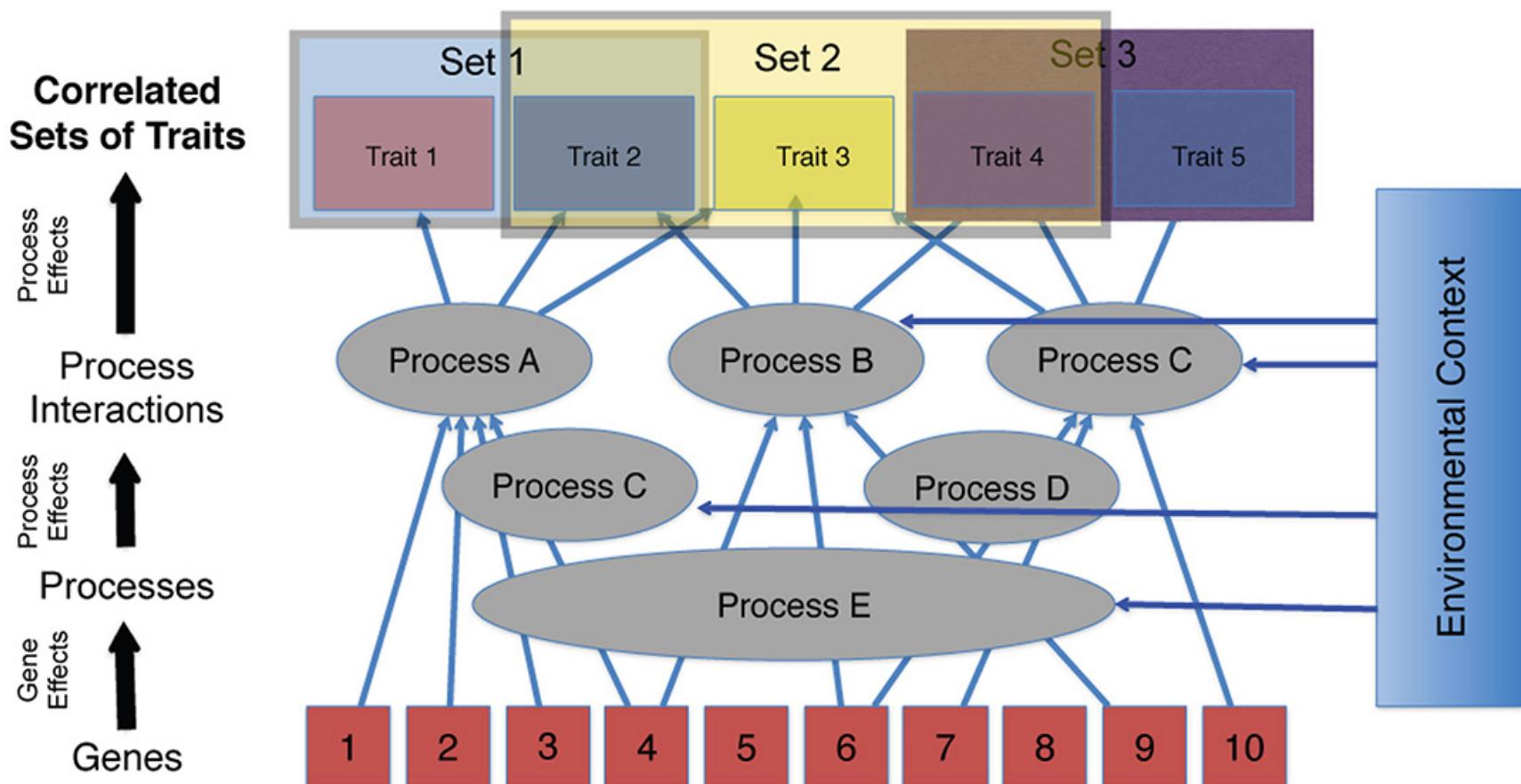
What is systems biology?



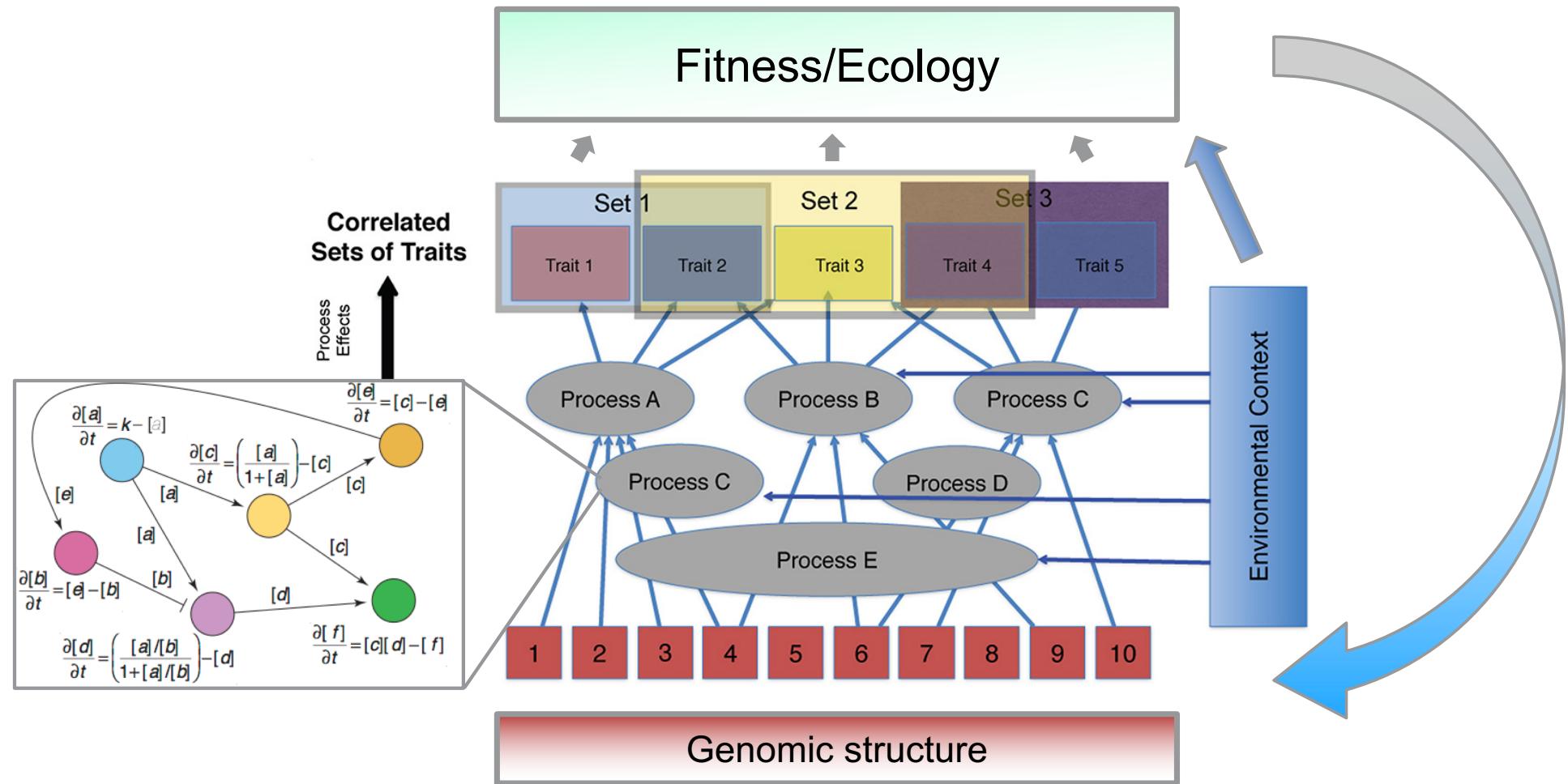
Nature Reviews | Genetics

Ritchie et al. 2015 Nat Rev Gen

Systems biology



Evolutionary systems biology



An assessment [of potential adaptive variation] will depend on an understanding of the relation between gene and organism that far transcends any present knowledge of development, physiology, and behavior. **In fact, it demands the answer to every other question that now lies open in biology.**

– Lewontin 1974

Open questions

- ◆ Is genetic variation polygenic enough (and additive enough) to allow application of traditional statistical-genetic approaches?
- ◆ How different is the genetic basis of adaptation from that of standing variation and disease?
- ◆ What is the relationship between the distribution of mutational effects and short and long term evolution?
- ◆ How important are genome-wide processes (e.g., recombination and linkage)?
- ◆ How central is the role of pleiotropy and how does it evolve?
- ◆ Does the genotype-phenotype map have coherent structure?
- ◆ What level of detail in gene function is necessary to understand long-term phenotypic evolution?