

Use and abuse of additive models in quantitative genetics

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Quantitative genetics

A statistical approach to the genetic architecture of complex traits

- Predict the response to artificial selection

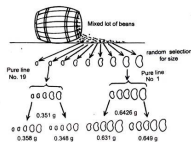
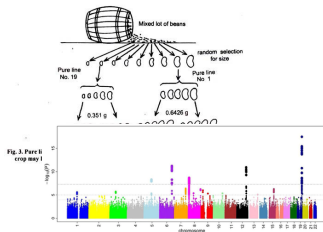


Fig. 3. Pure line selection in beans. The experiment demonstrated that a mixed population of a self-pollinated crop may be separated into pure lines inherently different, but that further selection with a pure line is ineffective in changing the genotype of the line.

Quantitative genetics

A statistical approach to the genetic architecture of complex traits

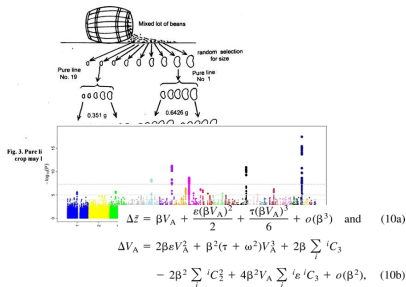
- Predict the response to artificial selection
- Statistical framework to detect candidate genes



Quantitative genetics

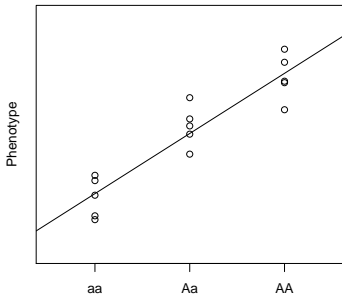
A statistical approach to the genetic architecture of complex traits

- Predict the response to artificial selection
- Statistical framework to detect candidate genes
- Powerful set of theoretical tools to understand evolution



Additive models

- The "additive effect" at a locus corresponds to the slope of a linear regression
- The variance explained by the regression is the "additive genetic variance"
- Summed up over all loci
→ prediction of the response to selection

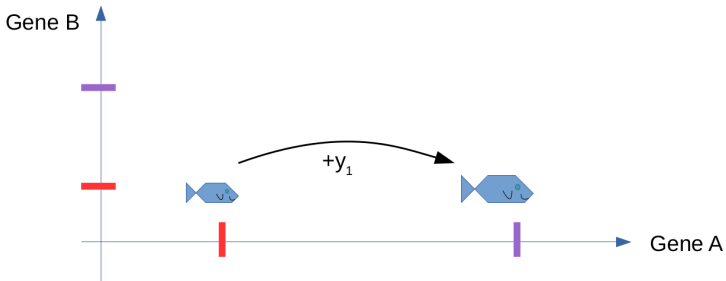


Epistasis

Genetics does not necessarily add up!

Dominance Intra-locus interactions

Epistasis Inter-locus interactions

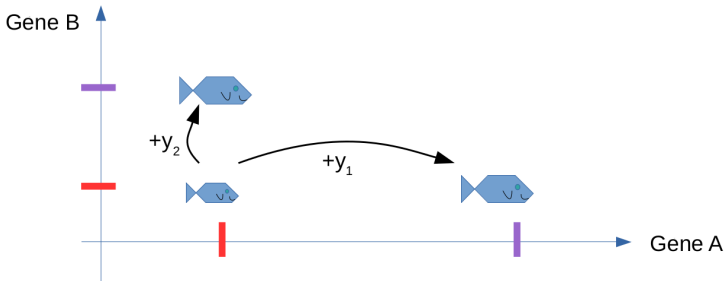


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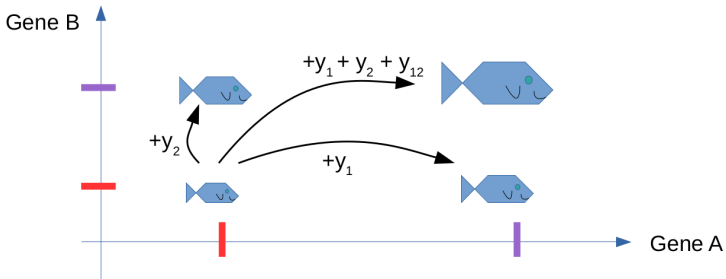


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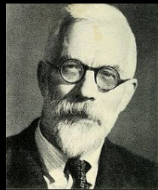


Is epistasis important ?

A century-old question !
(obviously a complex one)



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VS

Is epistasis important ?

Non-important

- Epistasis does not matter
 - Mathematically, epistasis just adds noise to the average gene effects
 - V_A is the only quantity that matters to predict evolution
- There is not so much epistasis
 - Very strong epistasis → No additive variance
 - QTL mapping reveals mostly additive genetic effects

Is epistasis important ?

Important

- Epistasis does matter
 - Epistasis is a major determinant in the evolution of V_A
 - Epistasis conditions evolutionary trajectories
- The absence of epistasis is impossible
 - Quantitative genetics is the only field in biology for which the additive hypothesis is reasonable

Developmental biology, Systems biology, Phylogeny, Physiology, Speciation genetics...

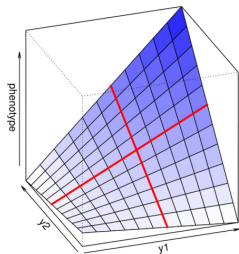
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Example 1 : Selection response and directional epistasis

Predicting the potential for selection response several generations ahead

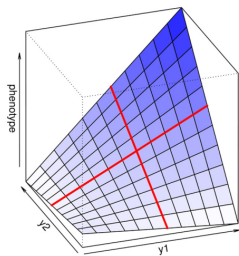
- Random epistasis does not affect selection response
- Non-random (directional) epistasis matters :
 - Synergistic
 - Antagonistic



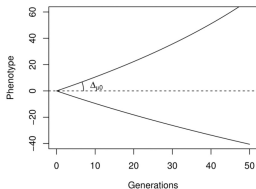
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Predicting the potential for selection response several generations ahead

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Theoretical response to selection
(positive directional epistasis)

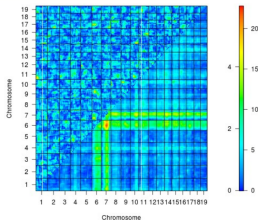


Example 2 : Gene mapping and sign epistasis



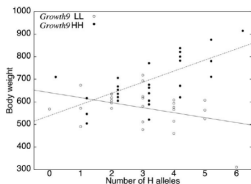
- QTL (linkage) mapping among two divergent chicken lines
Carlborg et al (2006)
- Traditional QTL scan : 1 significant QTL, 4% phenotypic difference

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- 2D-QTL scan : 4 significant QTLs, 40% phenotypic difference
- A major sign-epistasis locus involved

Many open questions in evolutionary biology

- How epistatic are real G-P maps?
- Missing heritability & the nature of heritable variance
- Long term vs. short-term responses to selection
- Evolution of mutational effects
 - Genetic robustness (canalization), evolvability...

Why not considering epistasis all the time ?

- Additional layer(s) of complexity in the models
- Feeling that additive models are satisfactory
- Unstable, unsatisfactory, and recent theoretical bases
- Much more data necessary to estimate epistasis
e.g. >1000 for linkage mapping, >10000 for GWAS
- Statistical issues (power, FDR) and computational burden

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