Statistical primer for systems genetics

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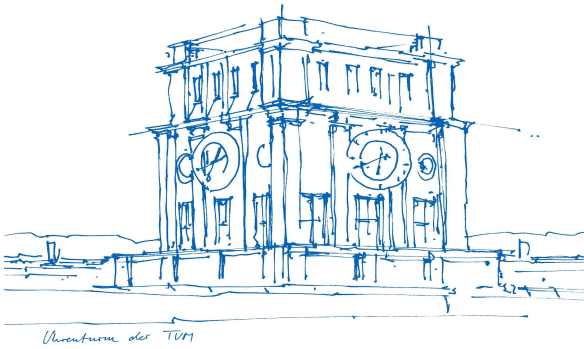
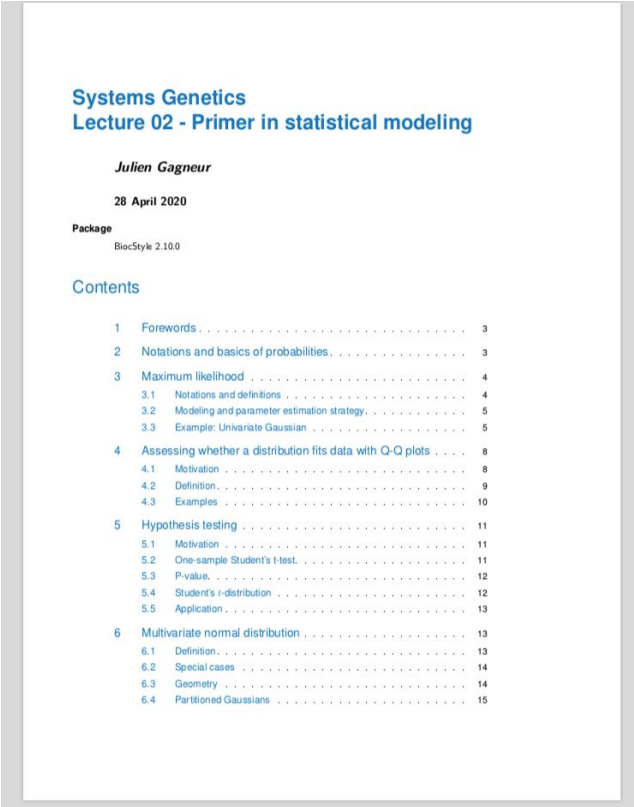
To understand the genetic basis of gene regulation and its implication in diseases



Motivation

- Lecture 02 provides a primer in statistical modeling covering topics necessary for the module
- This presentation gives an overview of the primer and how it connects to systems genetics modeling questions



Systems Genetics
Lecture 02 - Primer in statistical modeling

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Package
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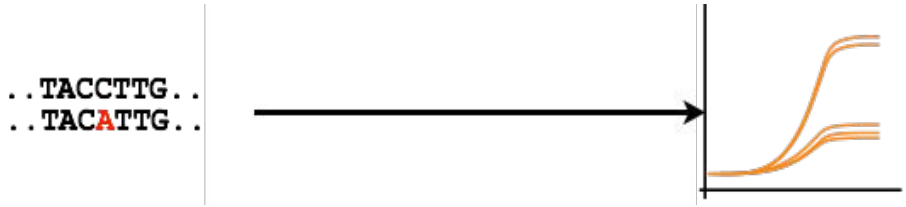
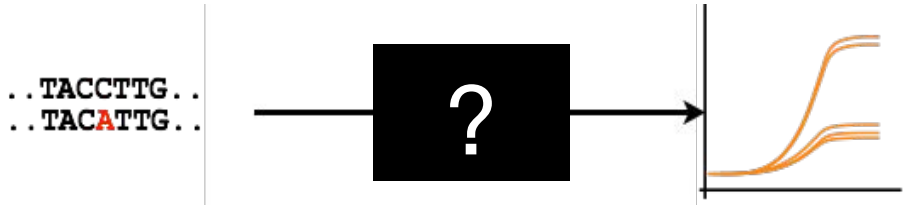
Goals of Systems Genetics



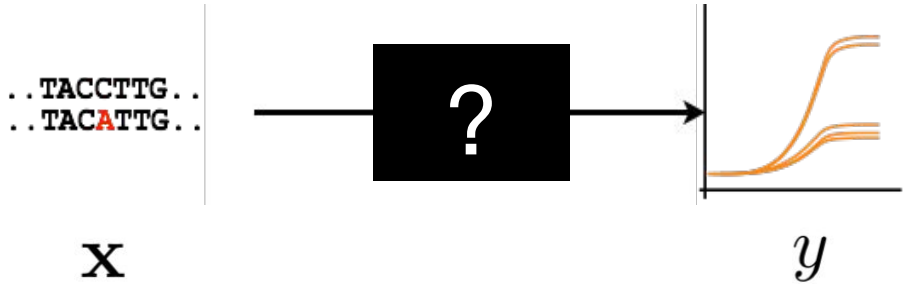
- Which genetic variants cause phenotypic variations?
- How strong are the effects?
- Through which molecular mechanisms?

Challenges of Systems Genetics



- Black box / complex biology

Modeling approach: data generative models



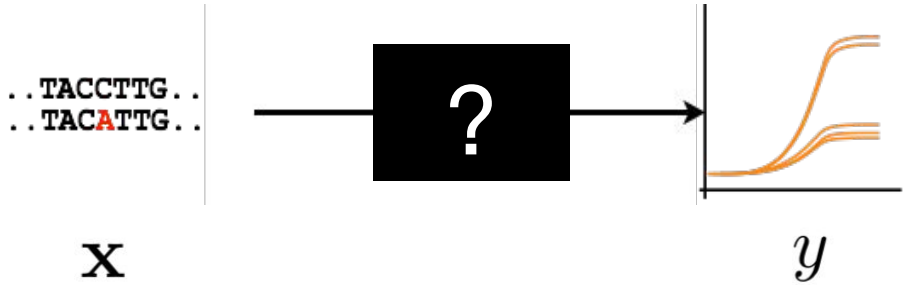
- Black box / complex biology
- Simple, high-level abstractions, often via linear models

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \epsilon$$

- **Data generative models** that describe the distribution of the phenotype y in function of genetic and other explanatory variables (x) and parameters (beta)

$$p(y|\mathbf{x}, \boldsymbol{\beta})$$

Parameter estimation



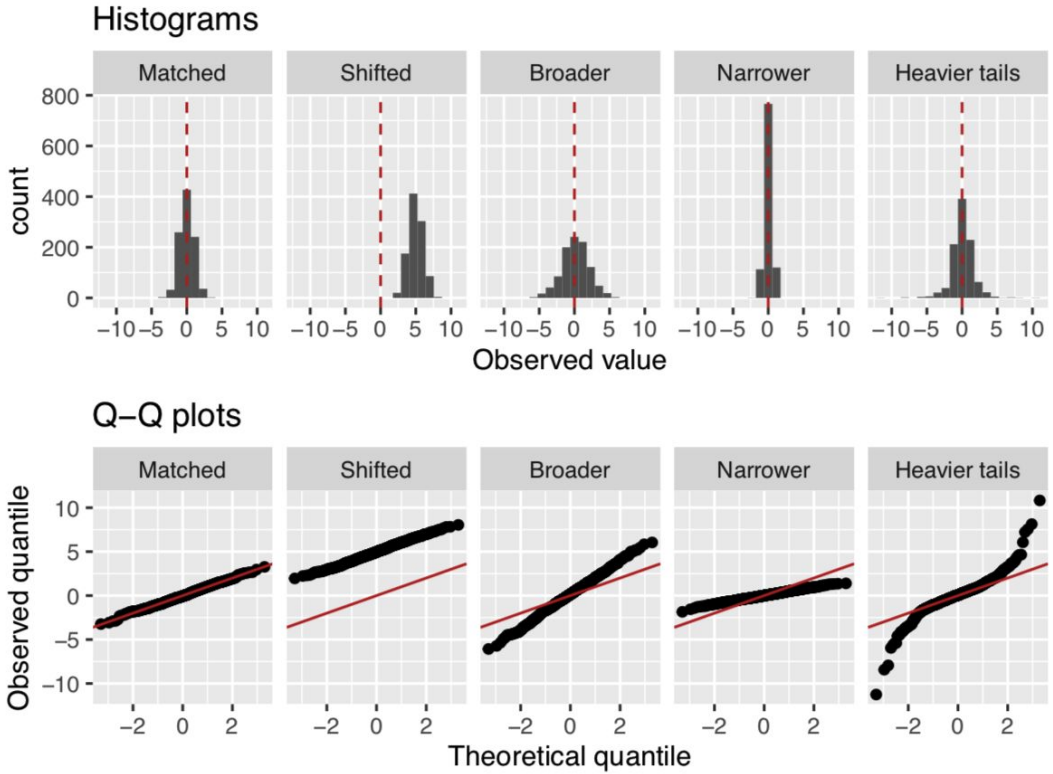
$$p(y|\mathbf{x}, \boldsymbol{\beta})$$

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \epsilon$$

- Parameter estimation (a.k.a model inference) aims at fitting a model to data
- **Maximum likelihood estimation** estimates the parameters that maximizes $p(y|\mathbf{x}, \boldsymbol{\beta})$
- Allows answering “How strong are the effects?”

Does the model distribution fits the data?

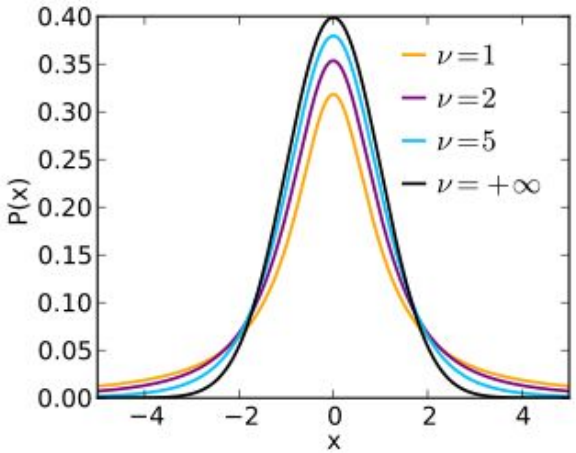
- Data generative models model the distribution of the data. Are they reasonable?
- **Quantile-quantile plots** allow comparing empirical data distribution compared to fitted distribution



Hypothesis testing

- Which genetic variants cause phenotypic variations?
- Inferring causality is hard. There will be lectures about it.
- For now: which effects are statistically significant? In other words, which effects would still be seen would the experiment be reproduced?
- **Hypothesis testing** allows answering this question.

$$P = p(t \geq t_{\text{obs}} | H_0)$$

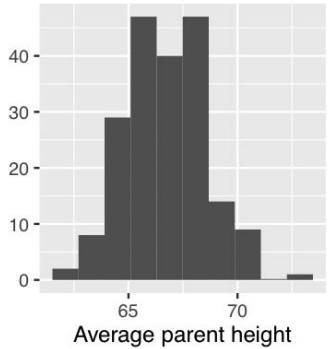


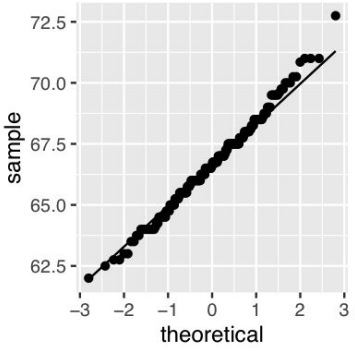
Multivariate Normal Distribution

- Normal distribution often arises among phenotypic traits

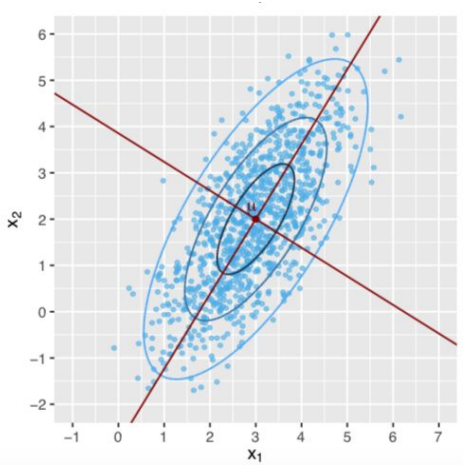
- Multivariate Normal (MVN) describes joint distributions
  - Multiple traits
  - Multi-omics

- The script describes properties of the MVN





Data from Galton, 1886

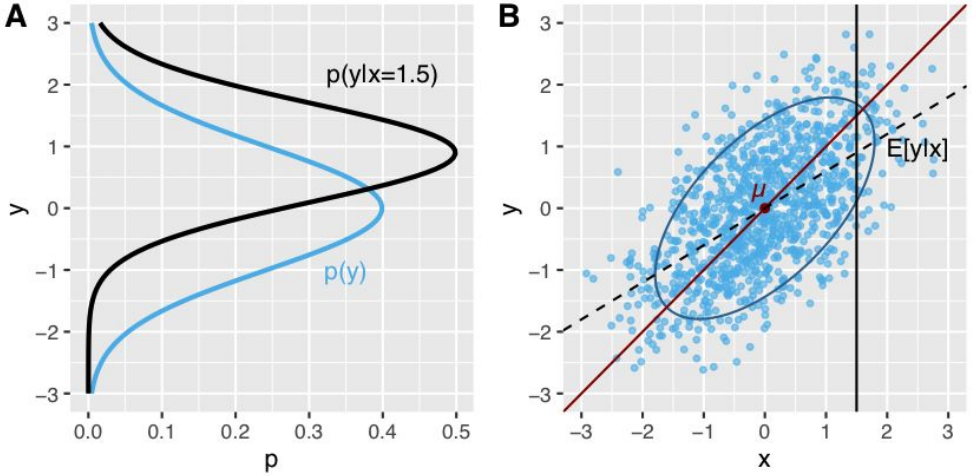


Conditioning and regression

- The **conditional distribution** is the distribution of one variable given (or conditioned on) the value of another one.

  E.g: How does cholesterol levels distribute among individuals with a specific BMI?

- Fundamentally related to the concept of **regression**, which aims at predicting a particular trait y given some explanatory variables x (genotype, sex, etc.)

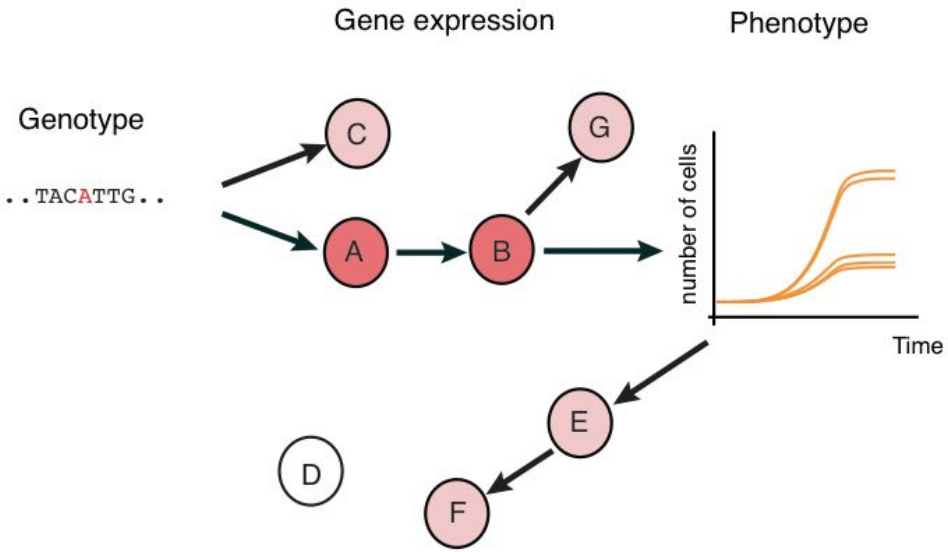


Linear systems

- Gaussian variables whose means are linear combinations of other Gaussian variables

$$p(\mathbf{x}) = \mathcal{N}\left(\mathbf{x}|\boldsymbol{\mu}, \boldsymbol{\Lambda}^{-1}\right)$$
$$p(\mathbf{y}|\mathbf{x}) = \mathcal{N}\left(\mathbf{y}|\mathbf{A}\mathbf{x} + \mathbf{b}, \mathbf{L}^{-1}\right)$$

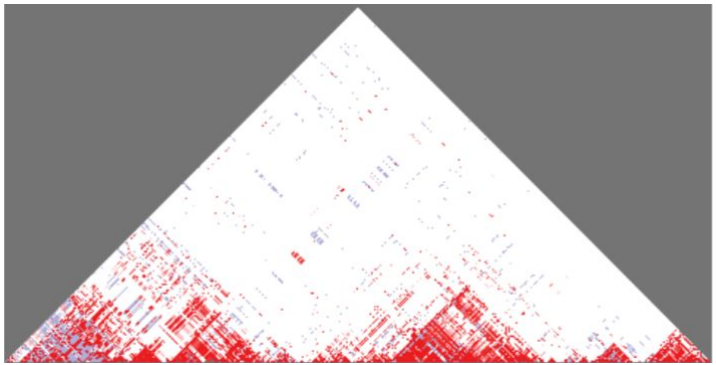
- E.g. in Bayesian networks that are used to model abundances of molecules, such as RNAs, proteins or metabolites



Estimating effects for millions of variants is hard

- Millions of genetic variants in human genome.
- Not enough data to estimate the entire model
- Strong genetic correlation in the population (e.g. ethnicity)

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + ...\beta_{1,000,000} x_{1,000,000} + \epsilon$$



Genotype correlation matrix

Chromosome

Estimating a single controlling for all others?

- Millions of genetic variants in human genome.
- Not enough data to estimate the entire model
- Strong genetic correlation in the population (e.g. ethnicity)
- Can we estimate effect of one variant controlling for all millions of other variants?

$$y = \beta_0 + \beta_1 x_1 + \boxed{\beta_2 x_2 + ...\beta_{1,000,000} x_{1,000,000}} + \epsilon$$

Marginalization with linear systems

- Millions of genetic variants in human genome.
- Not enough data to estimate the entire model
- Strong genetic correlation in the population (e.g. ethnicity)
- Can we estimate effect of one variant controlling for all millions of other variants?
- By assuming MVN distribution (mixed effect models) on other parameters and marginalizing out.

$$y = \beta_0 + \beta_1 x_1 + \boxed{\beta_2 x_2 + ...\beta_{1,000,000} x_{1,000,000}} + \epsilon$$

$$p(y|\mathbf{x}, \beta_1, \beta_2, ..., \beta_{10^6})$$

$$p(\beta_2, ..., \beta_{10^6}) = \mathcal{N}(\beta_2, ..., \beta_{10^6}|\boldsymbol{\mu}, \Sigma)$$

$$p(y|\mathbf{x}, \beta_1) = \int p(y|\mathbf{x}, \beta_1 x_1, \beta_2 x_2, ..., \beta_{10^6} x_{10^6}) d\beta_2 ... d\beta_{10^6}$$

Conclusion

- Genetics and statistics are old friends (Galton, Fisher, Pearson,...), driven by the need of detecting relationships in nature without having access to mechanistic details

- The primer gives you the necessary concepts and results for the module

- The exam does not involve complicated proofs

- The MVN formulae will be provided