Linear models for GWAS

II: Linear mixed models

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Microsoft Research

Current topics in computational biology
UCLA
October 15^{th}, 2012

Course structure

October 15^{th}

- Introduction
  - Terminology
  - Study design
  - Data preparation
  - Challenges and pitfalls
  - Course overview
- Linear regression
  - Parameter estimation
  - Statistical testing

October 17^{th}

- Basic probability theory
- Linear mixed models
  - Population structure correction
  - Parameter estimation
  - Variance component modeling
  - Phenotype prediction

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Probabilities

- Let X be a random variable, defined over a set $\mathcal{X}$ or measurable space.
- $P(X = x)$ denotes the probability that X takes value x, short $p(x)$.
  - Probabilities are positive, $P(X = x) \geq 0$
  - Probabilities sum to one

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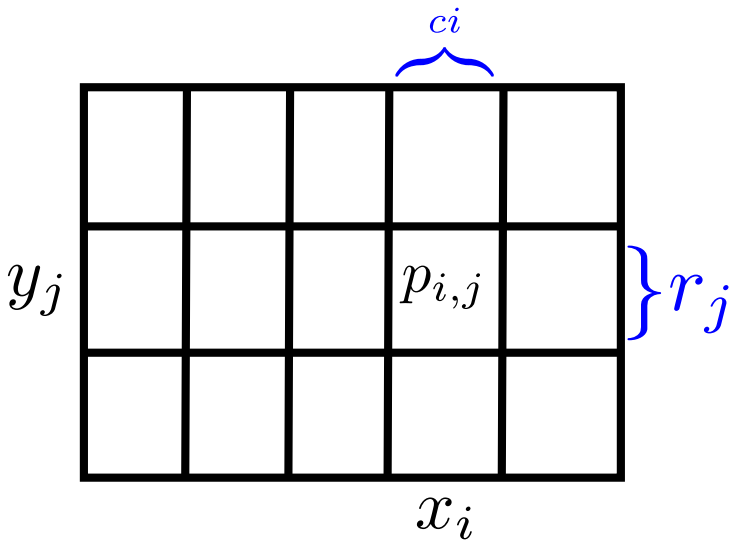
Probability Theory



Joint Probability

$$P(X = x_i, Y = y_j) = \frac{n_{i,j}}{N}$$

Marginal Probability

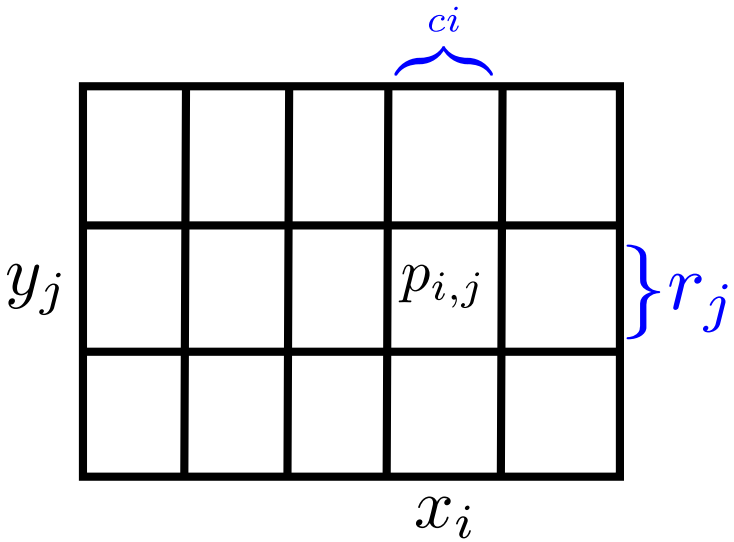
$$P(X = x_i) = \frac{c_i}{N}$$

Conditional Probability

$$P(Y = y_j \,|\, X = x_i) = \frac{n_{i,j}}{c_i}$$

(C.M. Bishop, Pattern Recognition and Machine Learning)

Probability Theory



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Product Rule

$$P(X = x_i, Y = y_j) = \frac{n_{i,j}}{N} = \frac{n_{i,j}}{c_i} \cdot \frac{c_i}{N}$$

$$= P(Y = y_j \,|\, X = x_i) P(X = x_i)$$

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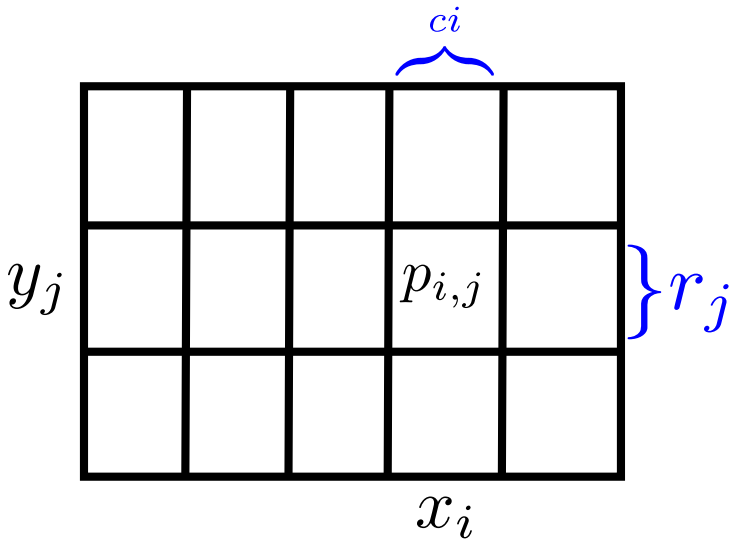

Sum Rule

$$P(X = x_i) = \frac{c_i}{N} = \frac{1}{N} \sum_{j=1}^{L} n_{i,j}$$

$$= \sum_{j} P(X = x_i, Y = y_j)$$

Product Rule

$$P(X = x_i, Y = y_j) = \frac{n_{i,j}}{N} = \frac{n_{i,j}}{c_i} \cdot \frac{c_i}{N}$$

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The Rules of Probability

Sum & Product Rule

Sum Rule	$p(x) = \sum_y p(x, y)$
Product Rule	$p(x, y) = p(y \mid x)p(x)$

The Rules of Probability

Bayes Theorem

- Using the product rule we obtain

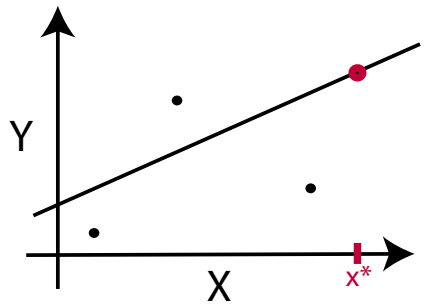
$$p(y \mid x) = \frac{p(x \mid y)p(y)}{p(x)}$$

$$p(x) = \sum_{y} p(x \mid y)p(y)$$

Bayesian probability calculus

- Bayes rule is the basis for inference and learning.
- Assume we have a model with parameters $\boldsymbol{\theta}$, e.g.

$$y = \theta_0 + \theta_1 \cdot x$$



- Goal: learn parameters $\boldsymbol{\theta}$ given Data $\mathcal{D}$.

$$p(\boldsymbol{\theta} \mid \mathcal{D}) = \frac{p(\mathcal{D} \mid \boldsymbol{\theta})\, p(\boldsymbol{\theta})}{p(\mathcal{D})}$$

  - Posterior
  - Likelihood
  - Prior

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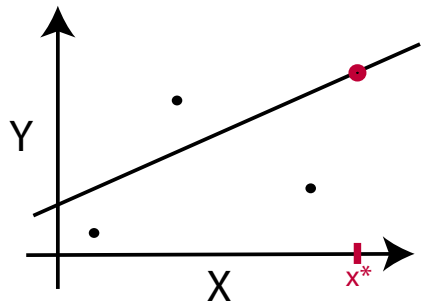

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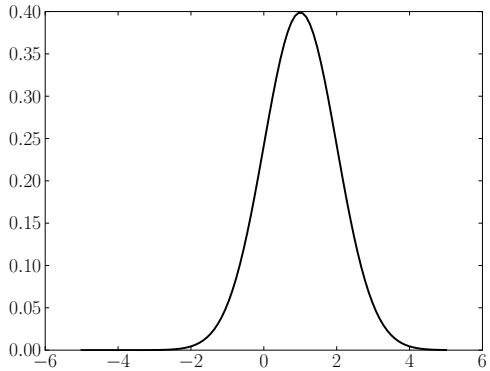
$$\text{posterior} \propto \text{likelihood} \cdot \text{prior}$$

- Posterior
- Likelihood
- Prior

Probability distributions

- Gaussian

$$p(x \mid \mu, \sigma^2) = \mathcal{N}(x \mid \mu, \sigma) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{1}{2\sigma^2}(x-\mu)^2}$$



- Multivariate Gaussian

$$p(x \mid \boldsymbol{\mu}, \boldsymbol{\Sigma}) = \mathcal{N}(\mathbf{x} \mid \boldsymbol{\mu}, \boldsymbol{\Sigma})$$
$$= \frac{1}{\sqrt{|2\pi\boldsymbol{\Sigma}|}} \exp\left[-\frac{1}{2}(\mathbf{x}-\boldsymbol{\mu})^{\mathrm{T}}\boldsymbol{\Sigma}^{-1}(\mathbf{x}-\boldsymbol{\mu})\right]$$

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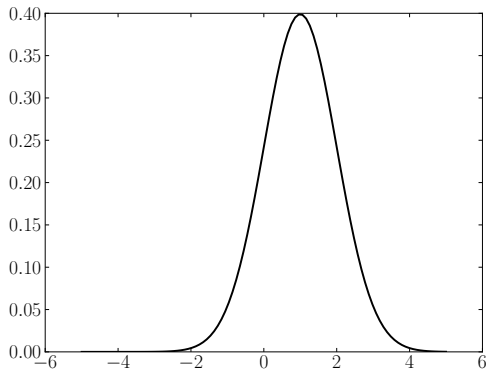

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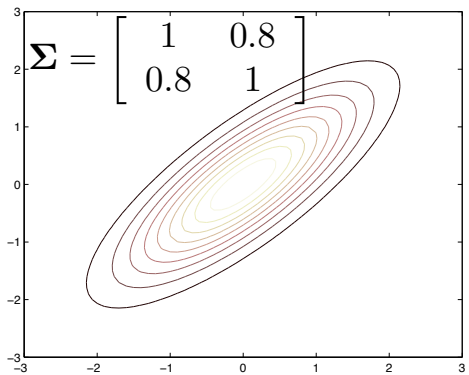
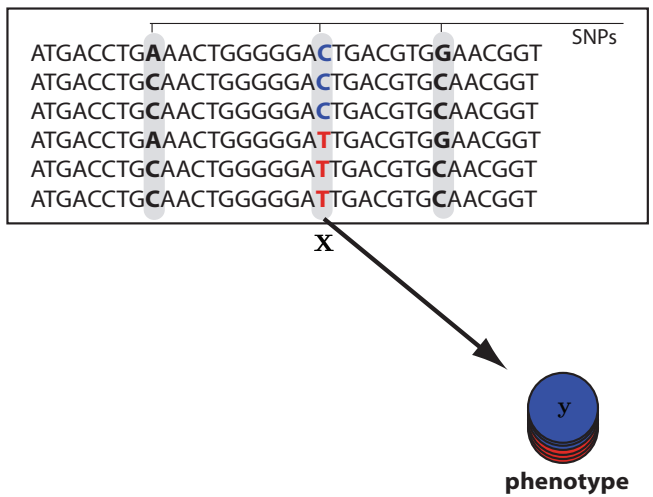


Genome wide association studies (GWAS)

- Identify associations between variable genetic loci and phenotypes.
  - Linear and logistic regression
  - Statistical dependence tests (F-test, likelihood ratio)



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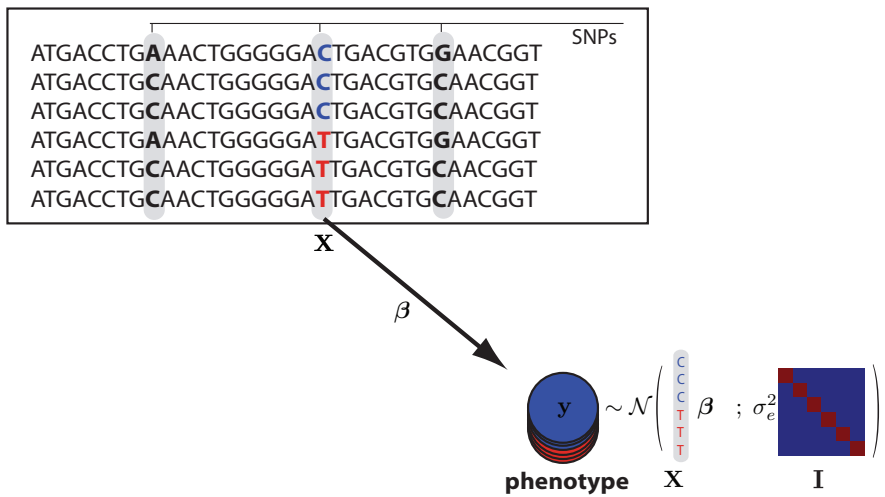
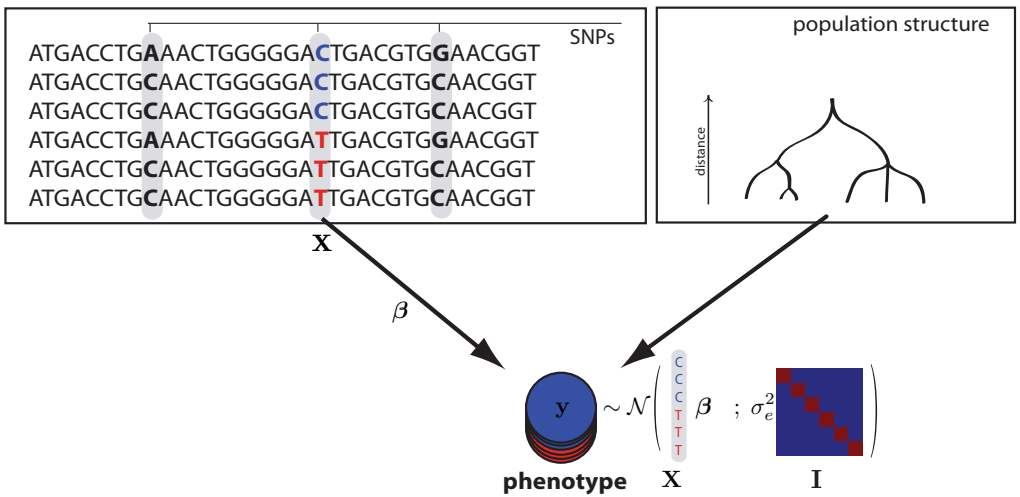
$$\frac{\mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta};\sigma_{\mathrm{e}}^{2}\mathbf{I}\right)}{\mathcal{N}\left(\mathbf{y}|\mathbf{0};\sigma_{\mathrm{e}}^{2}\mathbf{I}\right)} \qquad (1)$$



Population stratification

- Confounding structure leads to false positives.
  - Population structure
  - Family structure
  - Cryptic relatedness



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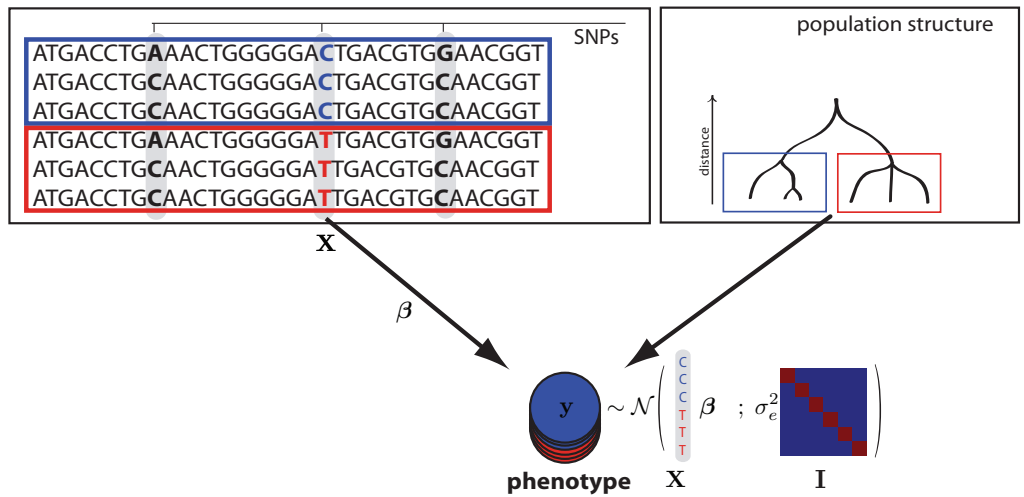

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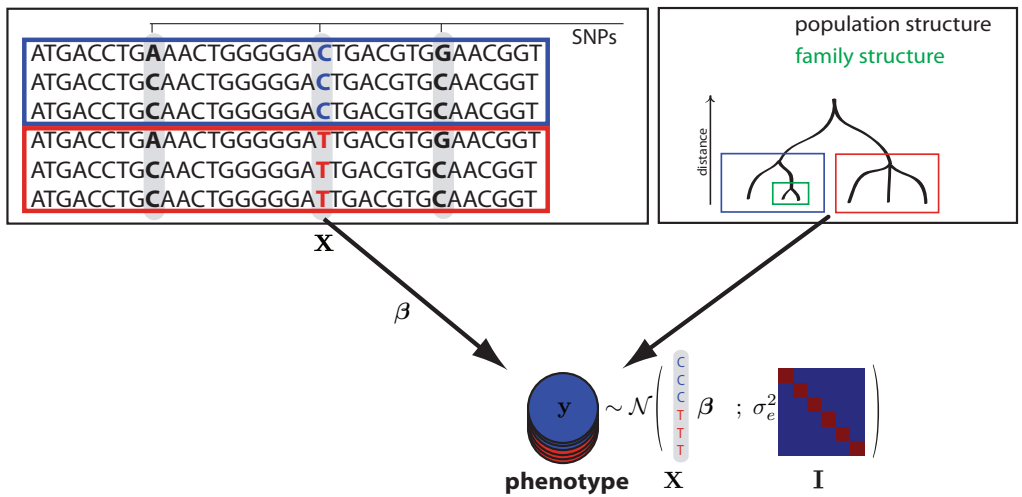

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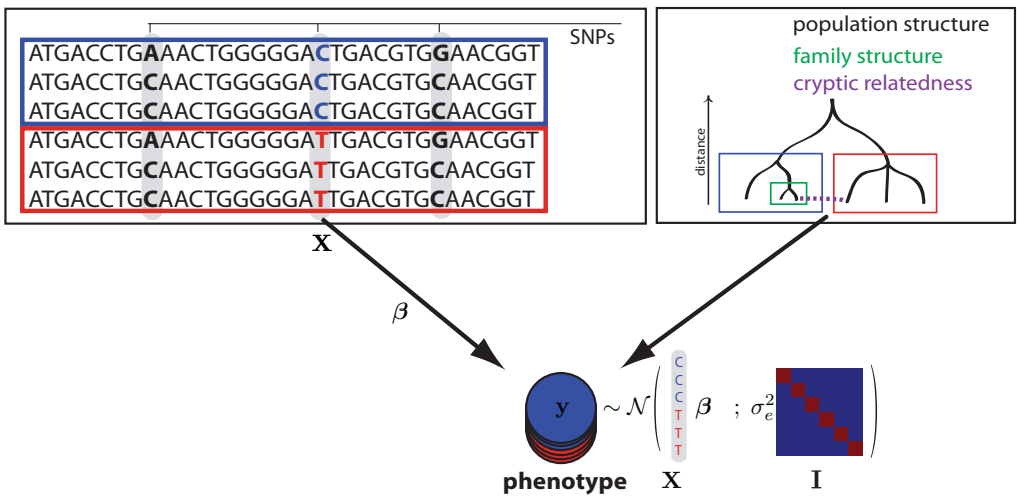

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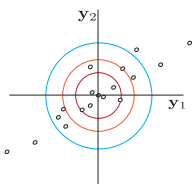

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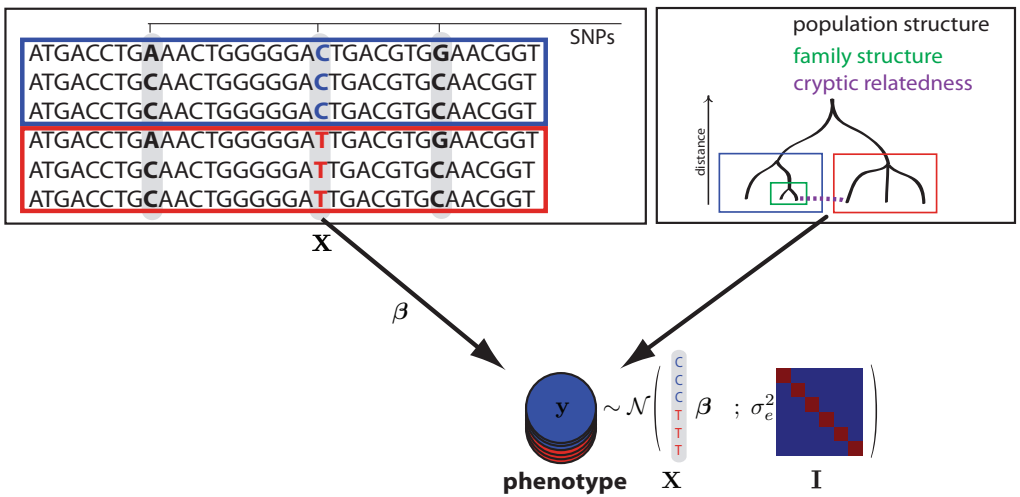

Population stratification

GWA on inflammatory bowel disease (WTCCC)

- 3.4k cases, 11.9k controls
- Methods
  - Linear regression
  - Likelihood ratio test

[Burton et al., 2007]

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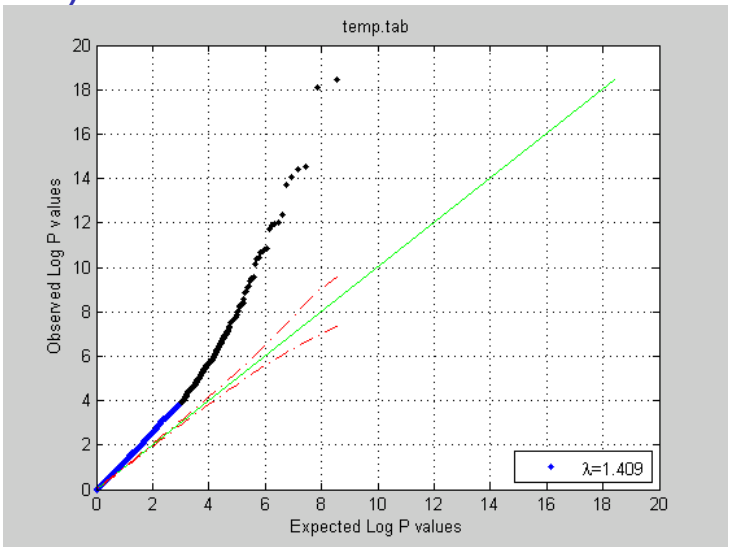
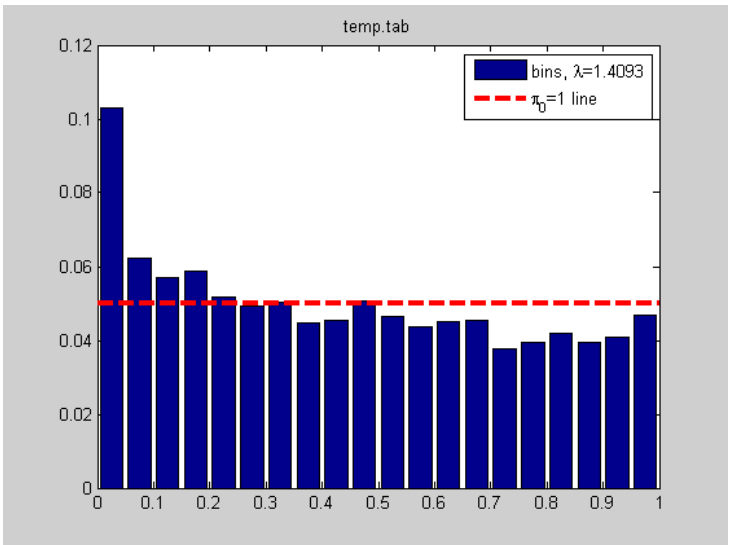




[Burton et al., 2007]

Outline

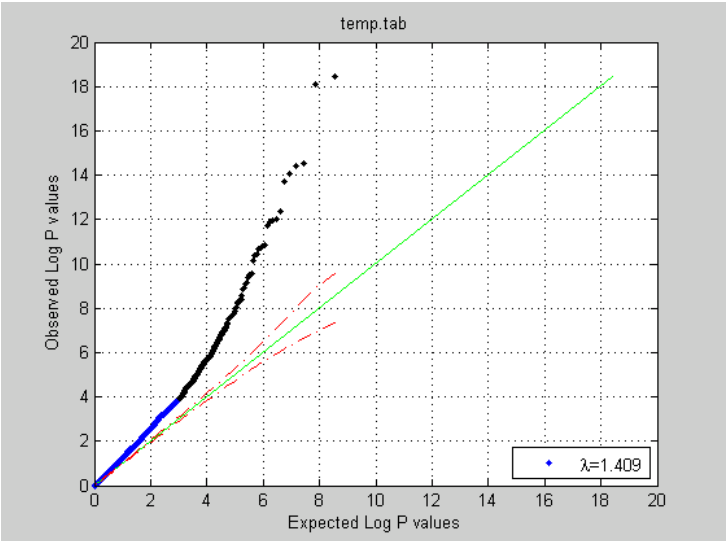
Genomic control [Devlin and Roeder, Biometrics 1999]

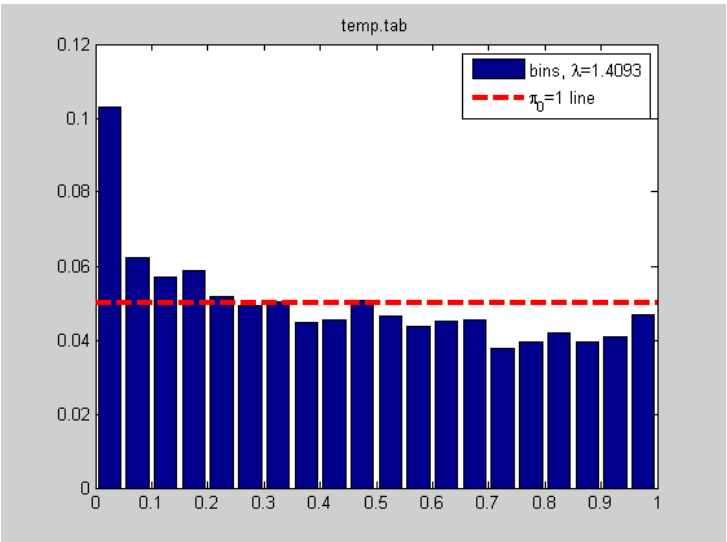
- Genomic control λ

$$\lambda = \frac{\text{median}(2LR)}{\text{median}(\chi^2)}.$$

  - $\lambda = 1$: Calibrated P-values
  - $\lambda > 1$: Inflation
  - $\lambda < 1$: Deflation

- Correct by dividing test statistic by λ.
- Applicable in combination with every method.
- Does not change (non-)uniformity of P-values.
- Very conservative.





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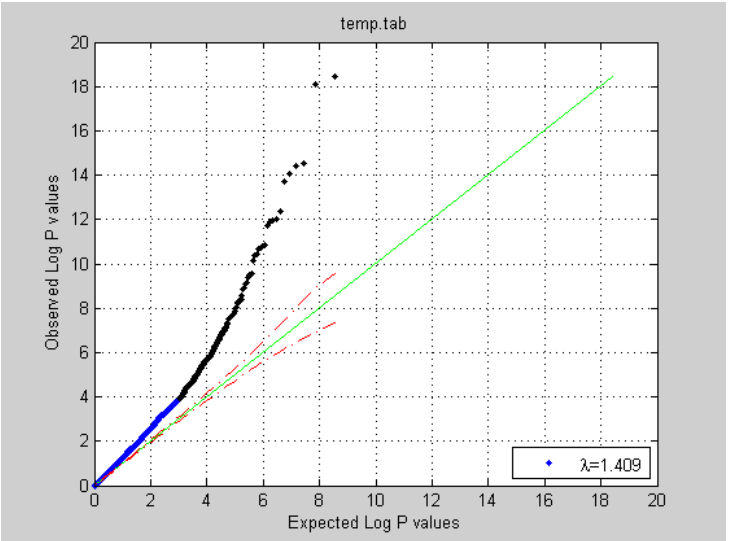

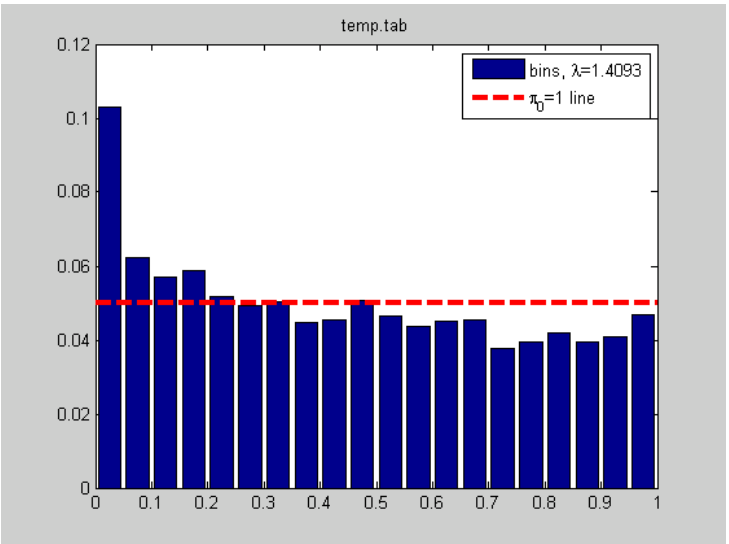

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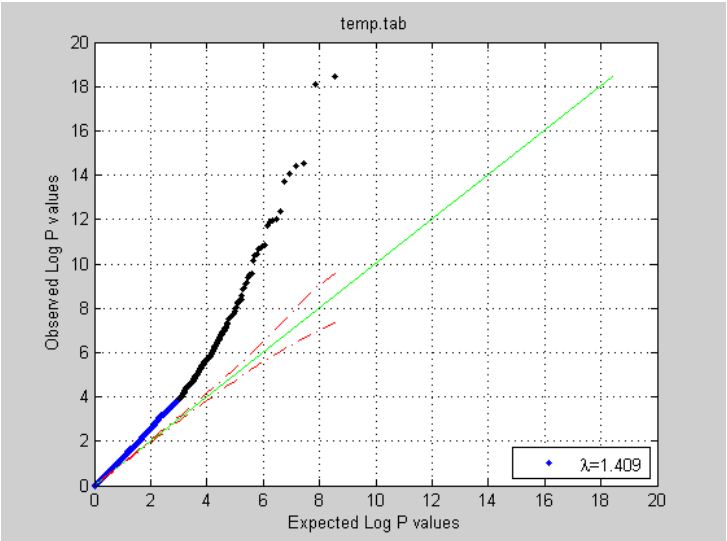

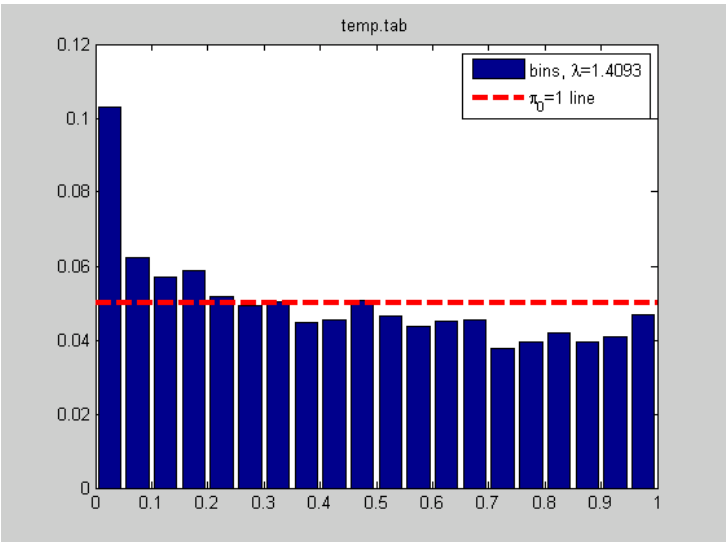

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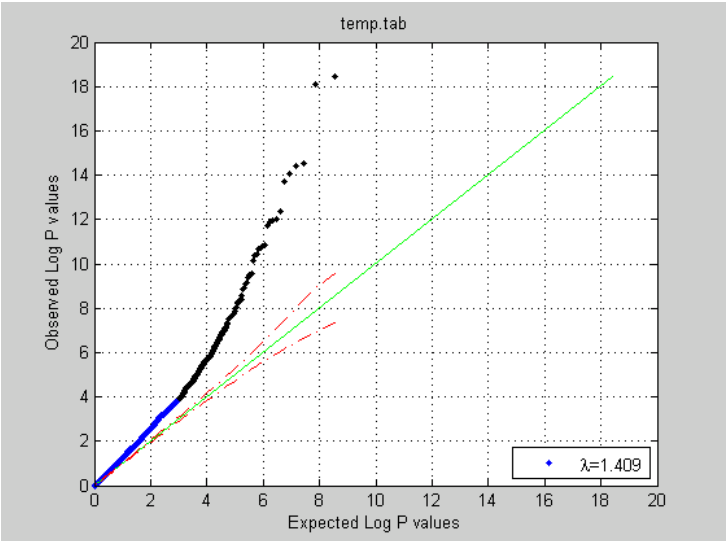

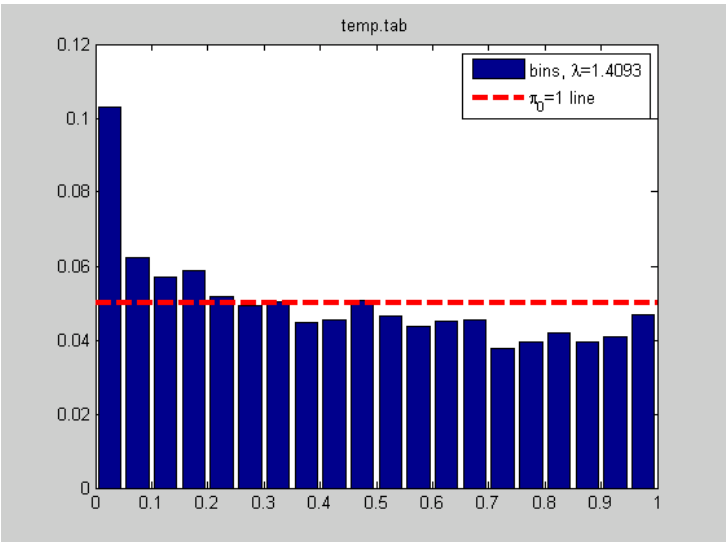

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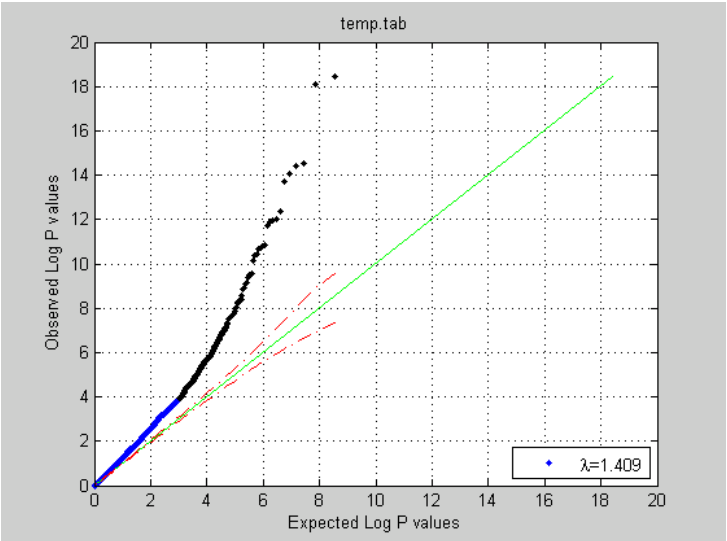

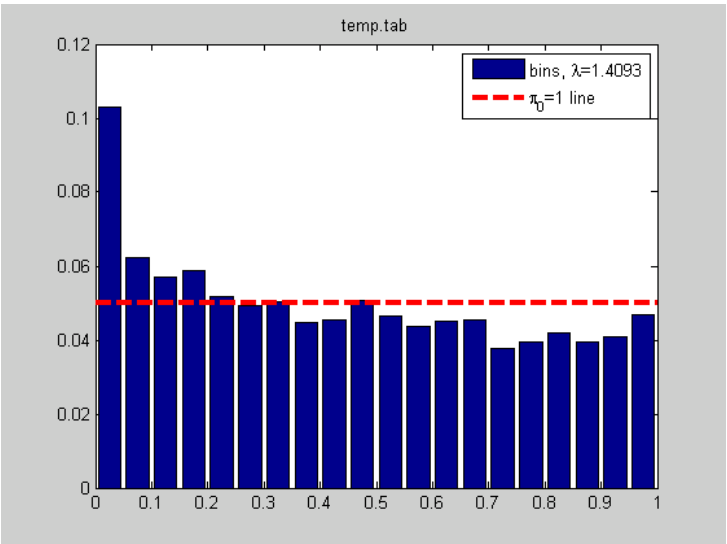

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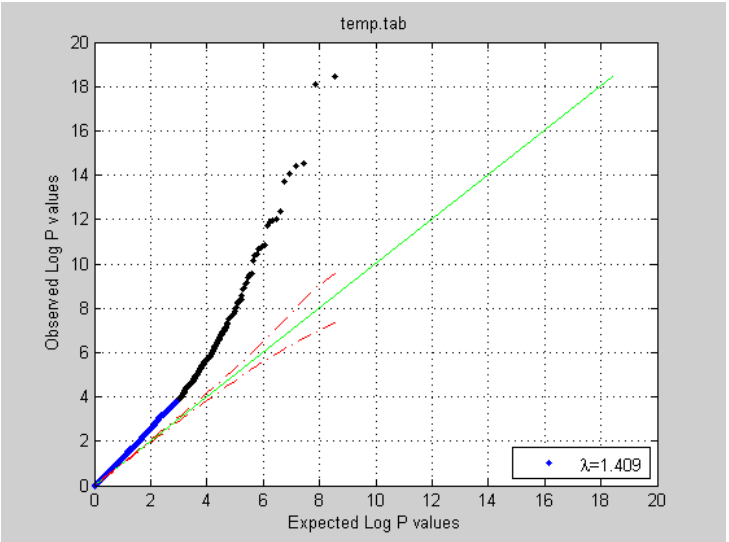

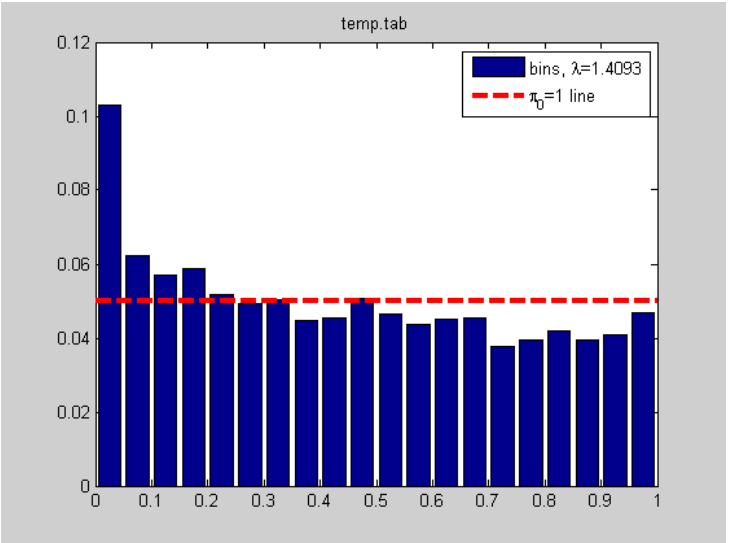

Eigenstrat

- Population structure causes genome-wide correlations between SNPs
- A large part of the total variation in the SNPs can be explained by population differences.
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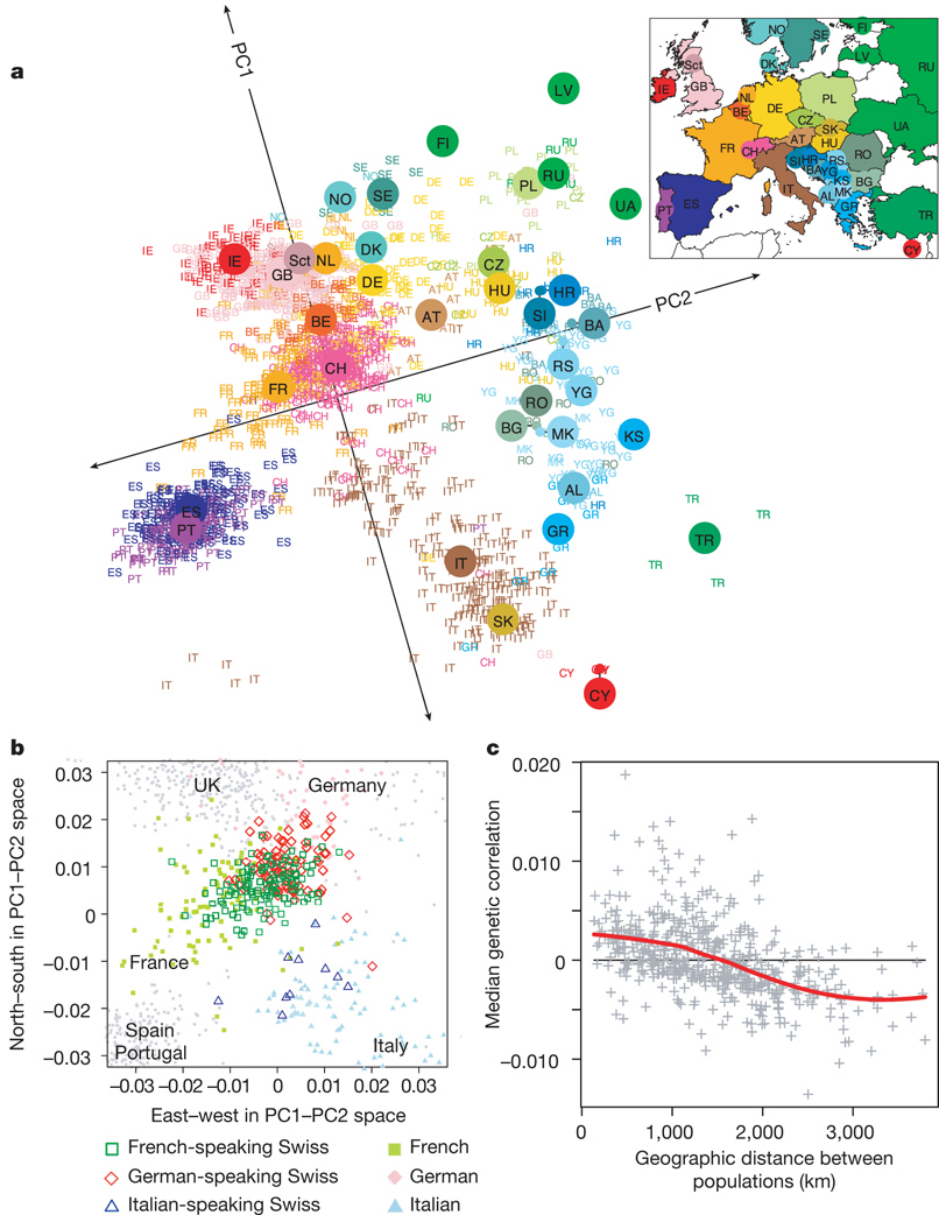

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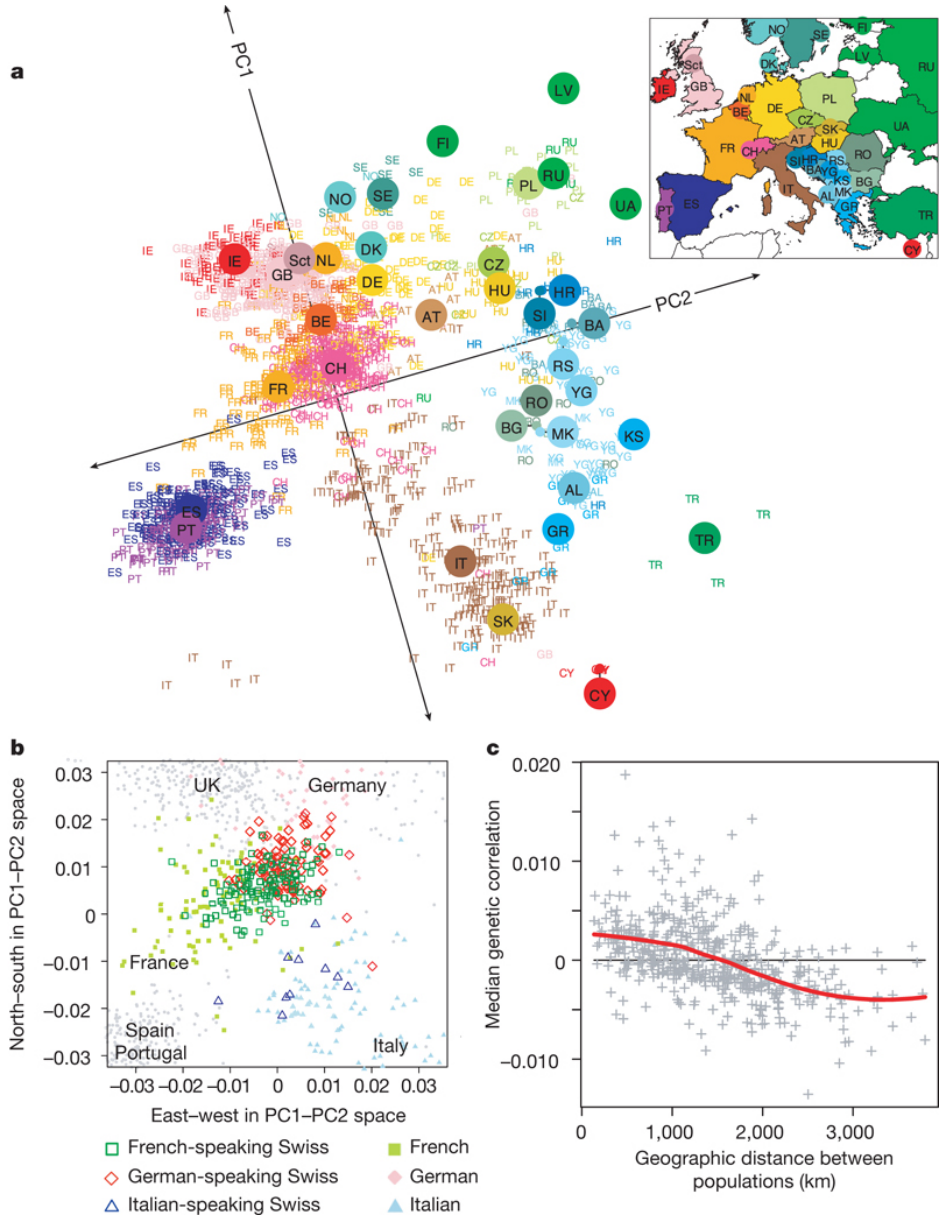

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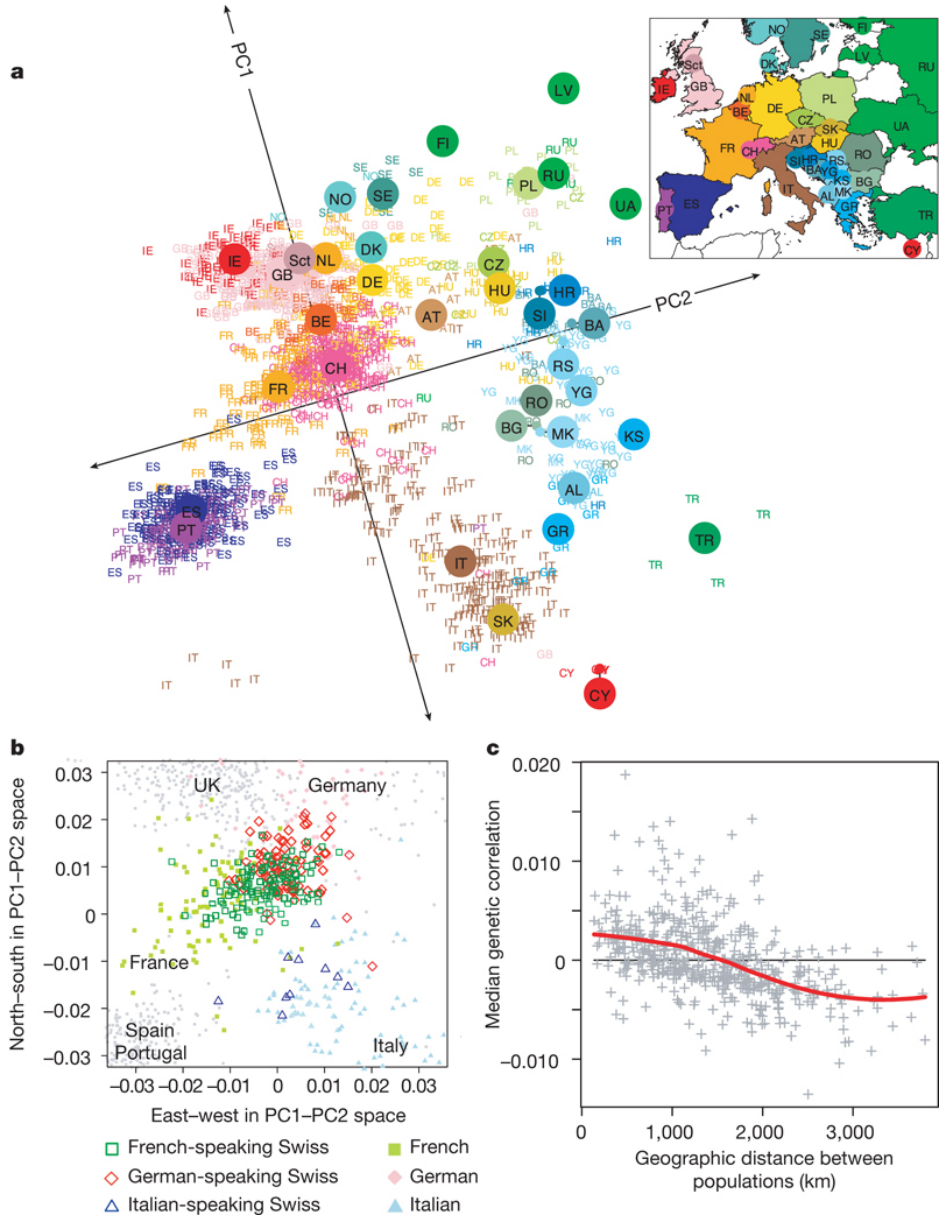

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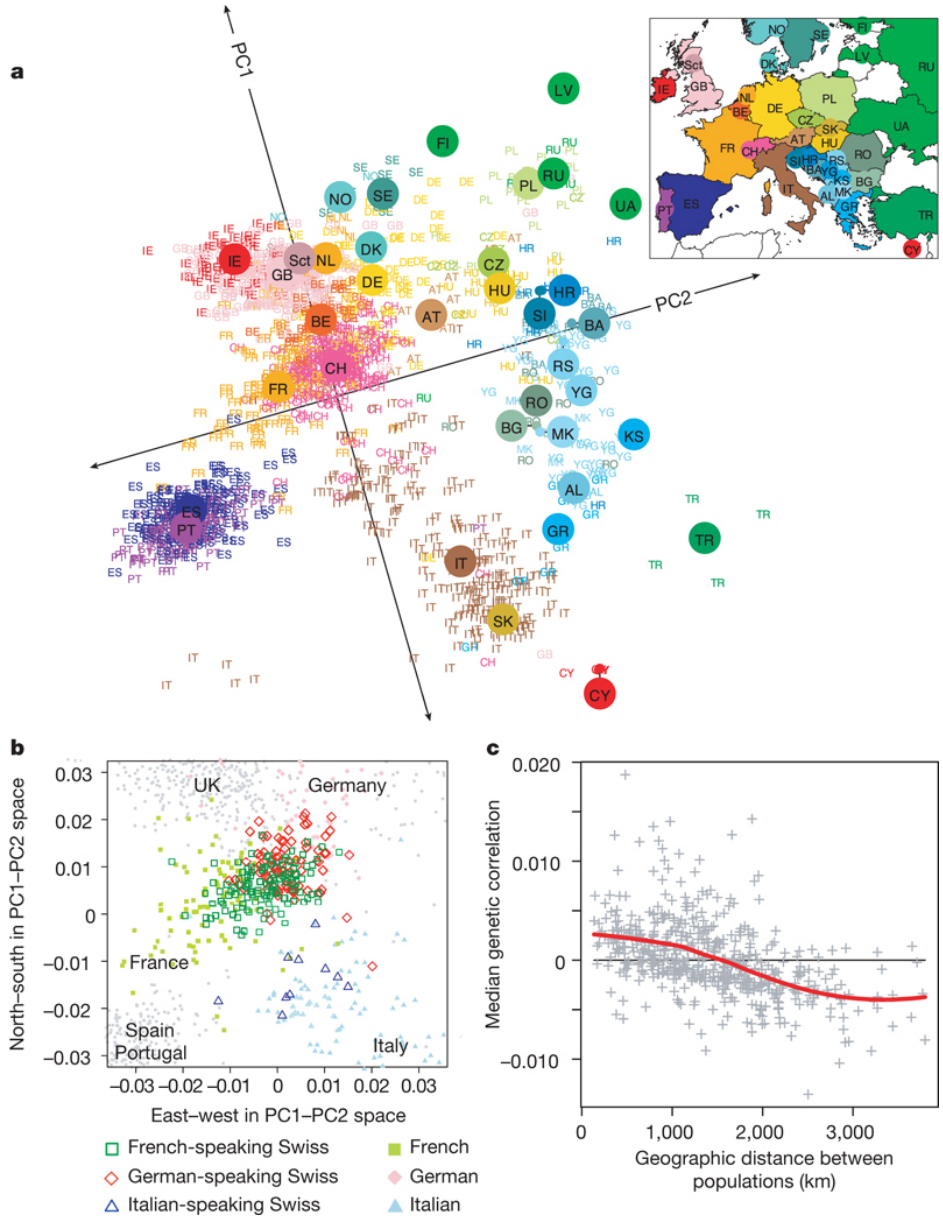

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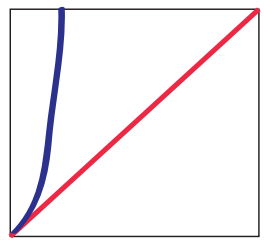

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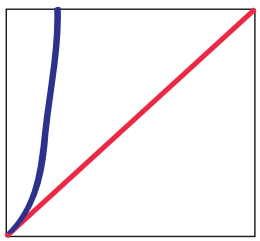

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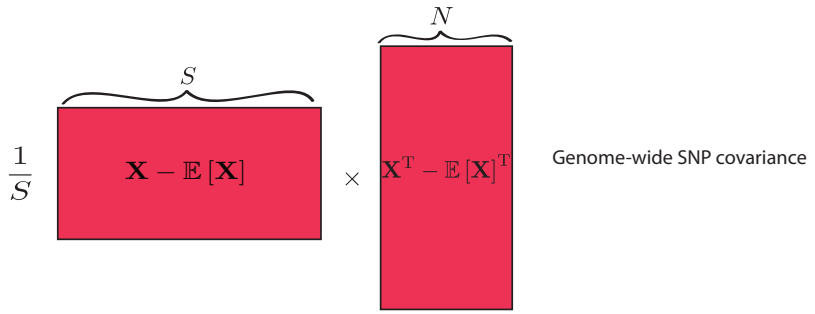

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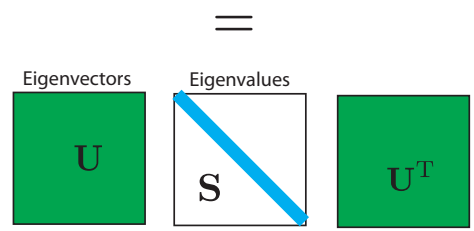

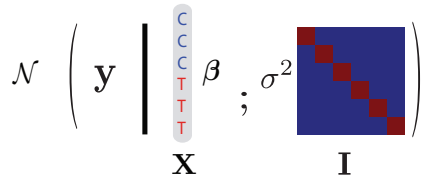

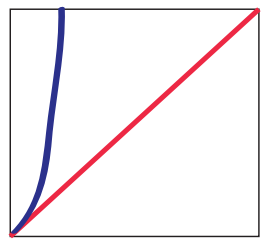

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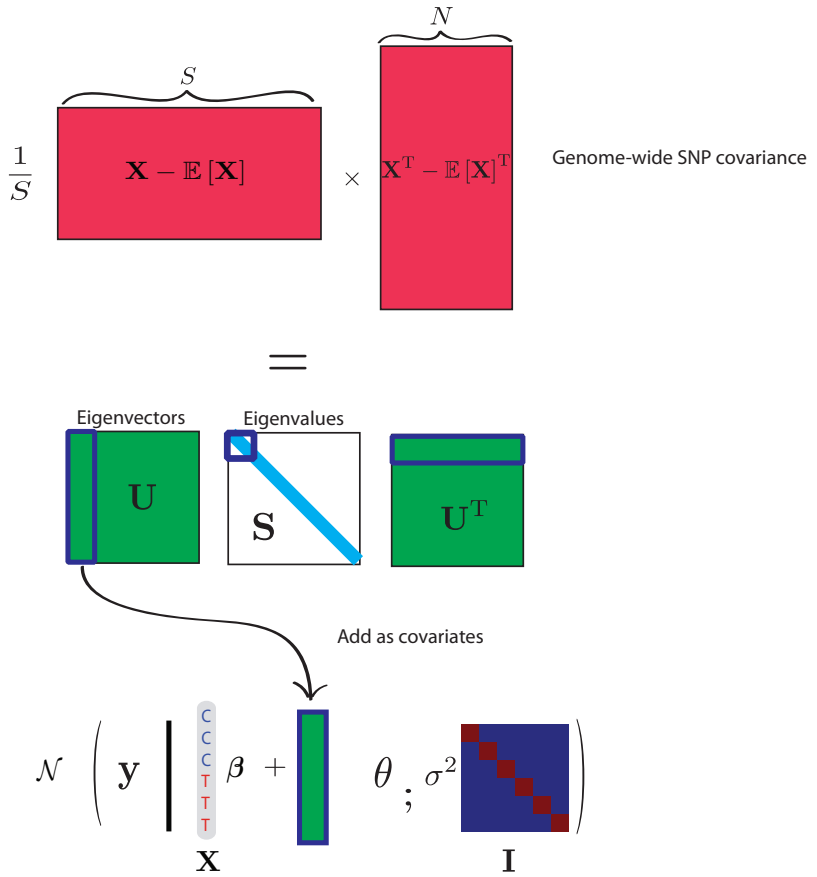

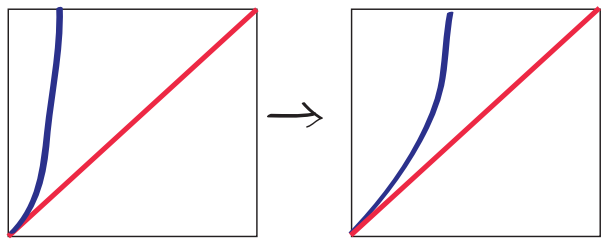

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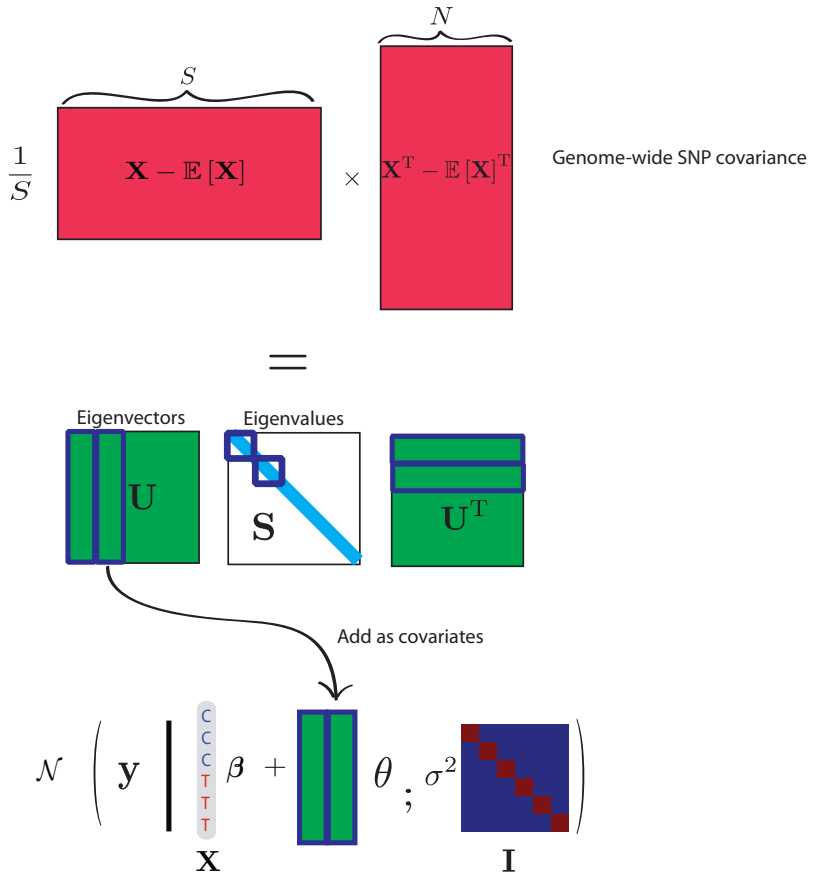

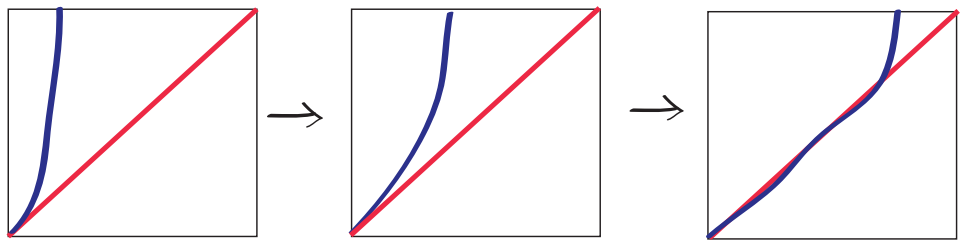

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Linear mixed models (LMM)

- Covariance matrix $\mathbf{K}$
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  - Realized relationship matrix (linear)
- Sample random effect $\mathbf{u}$.
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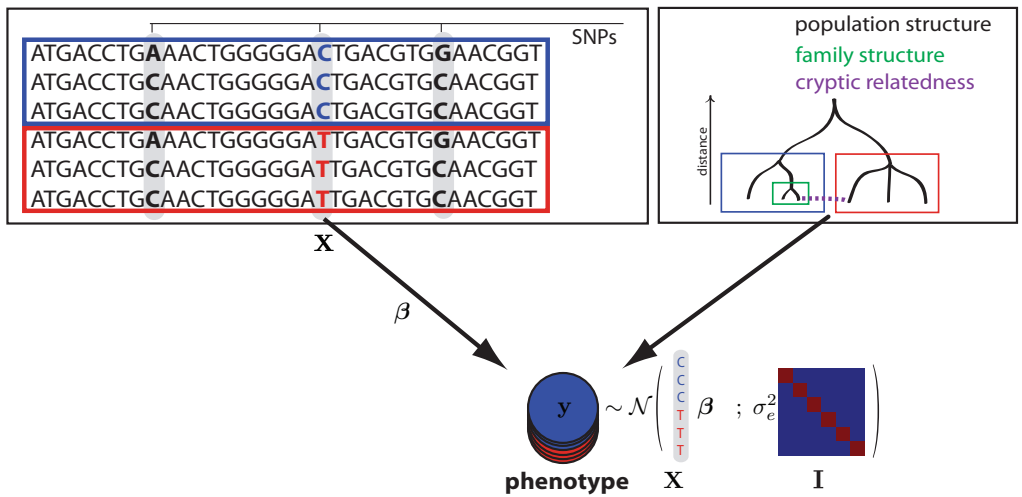

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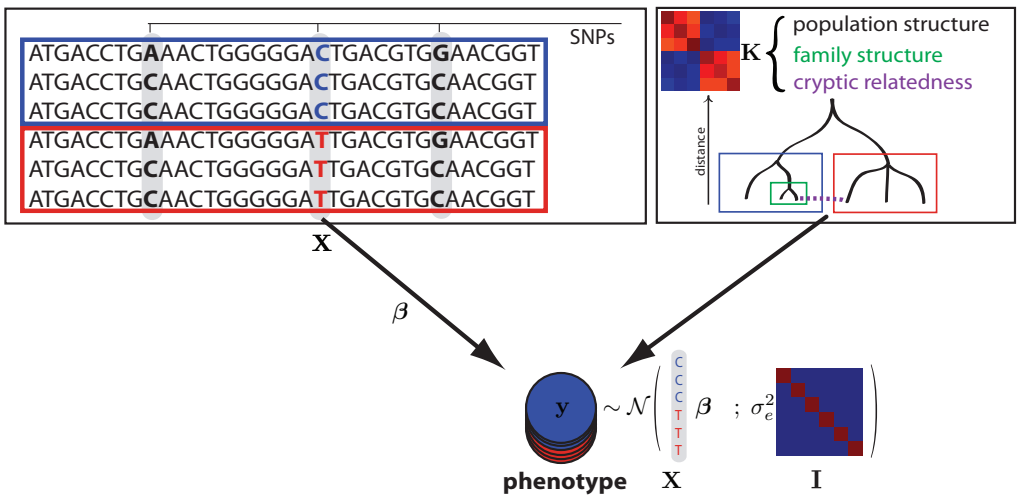

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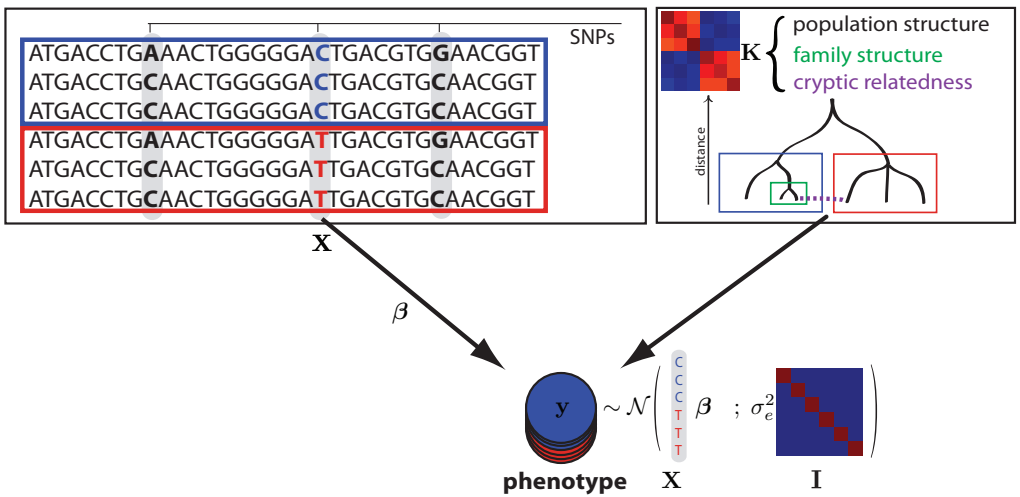

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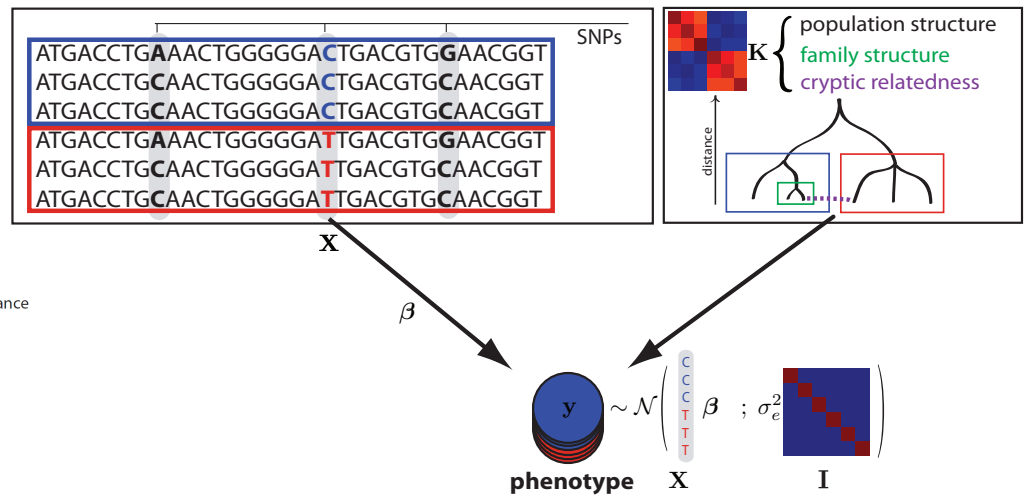

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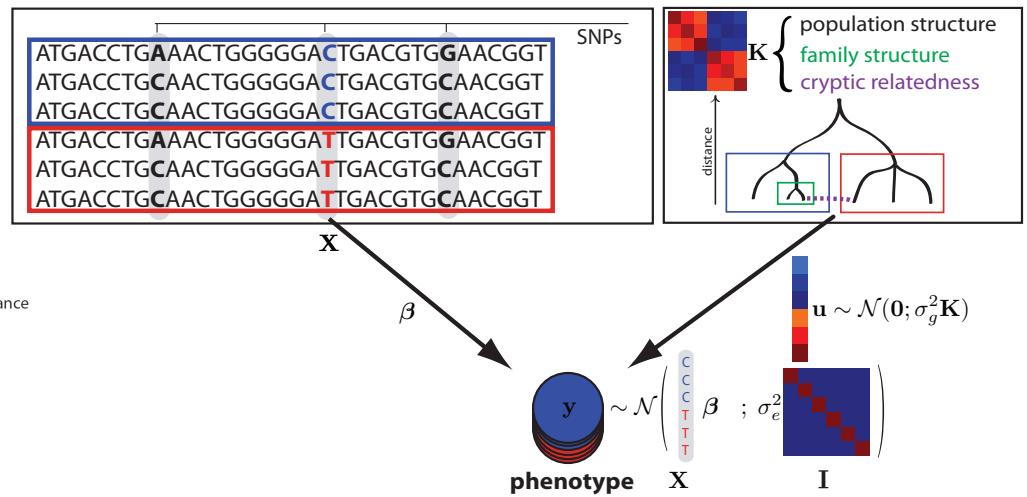

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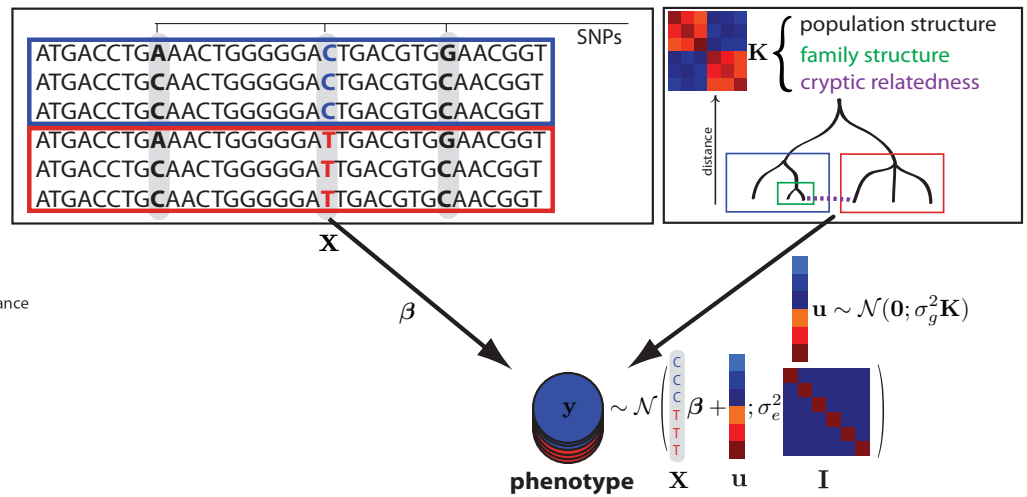

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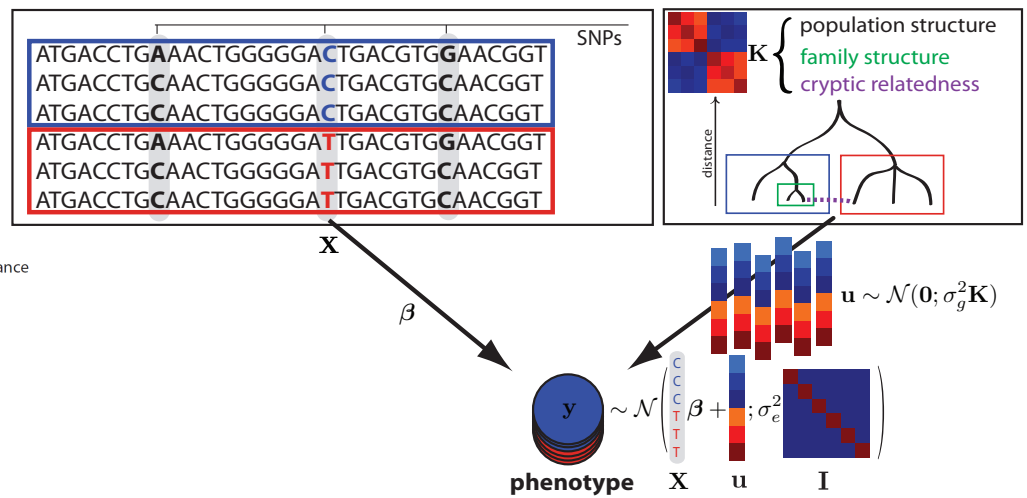

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$$\int_{\mathbf{u}} \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta} + \mathbf{u}; \sigma_{\mathrm{e}}^2\mathbf{I}\right)\mathcal{N}\left(\mathbf{u}|\mathbf{0}; \sigma_{\mathrm{g}}^2\mathbf{K}\right)$$

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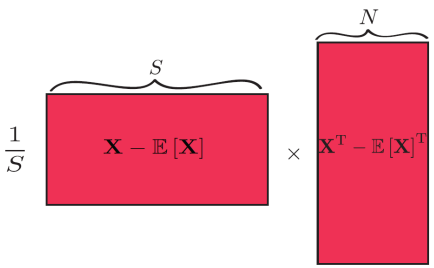

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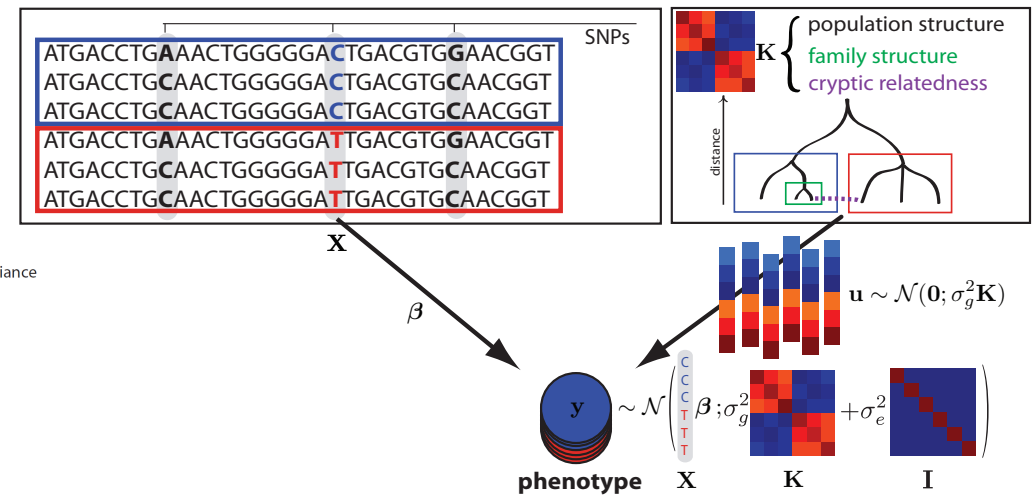

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Linear mixed models (LMM)

- Corrects for all levels of population structure.
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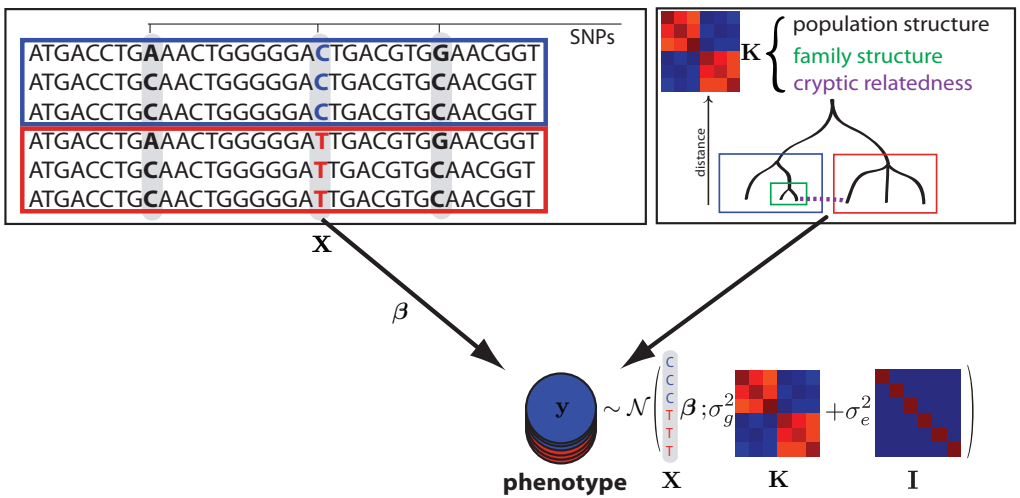

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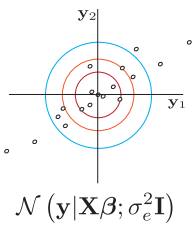

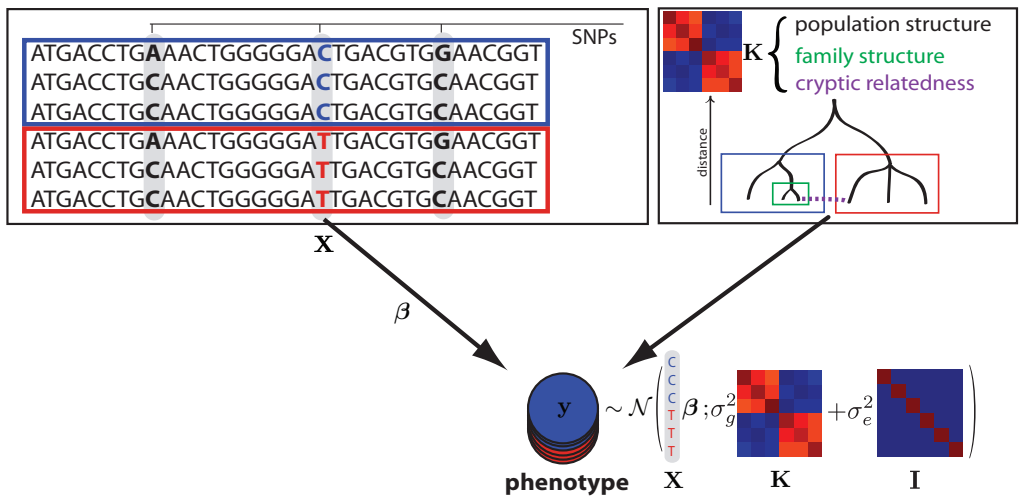

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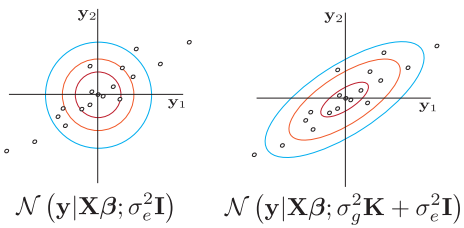

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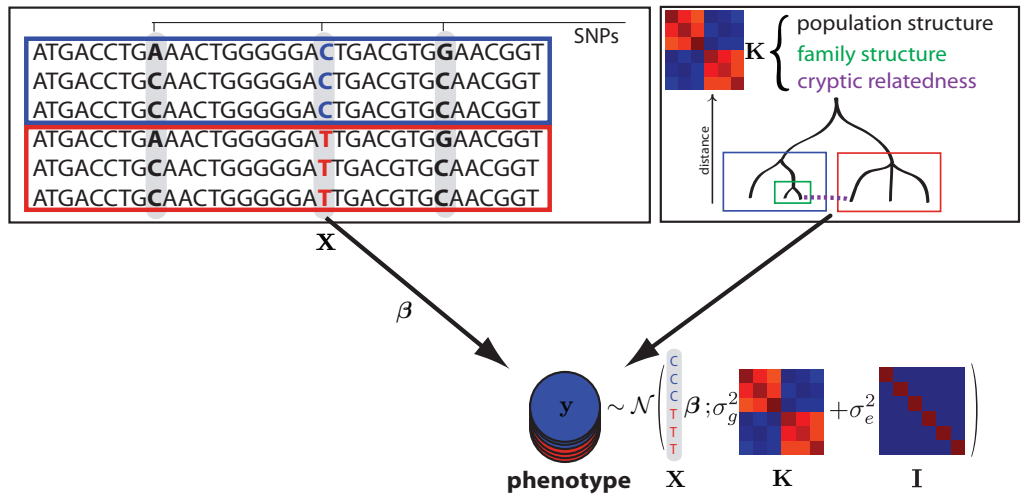

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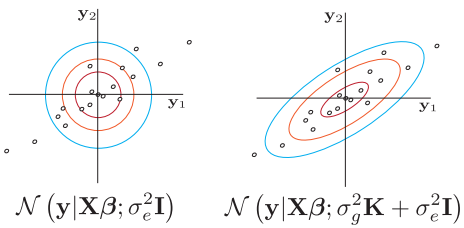

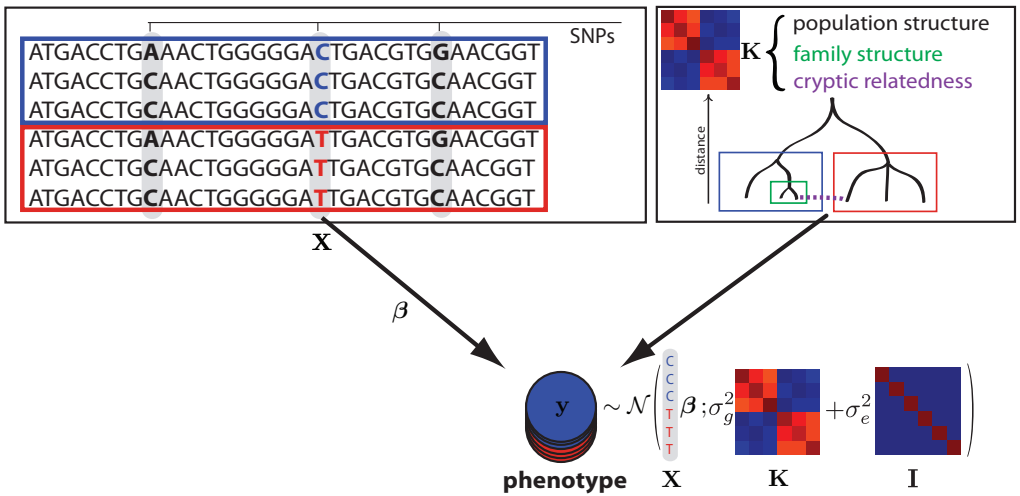

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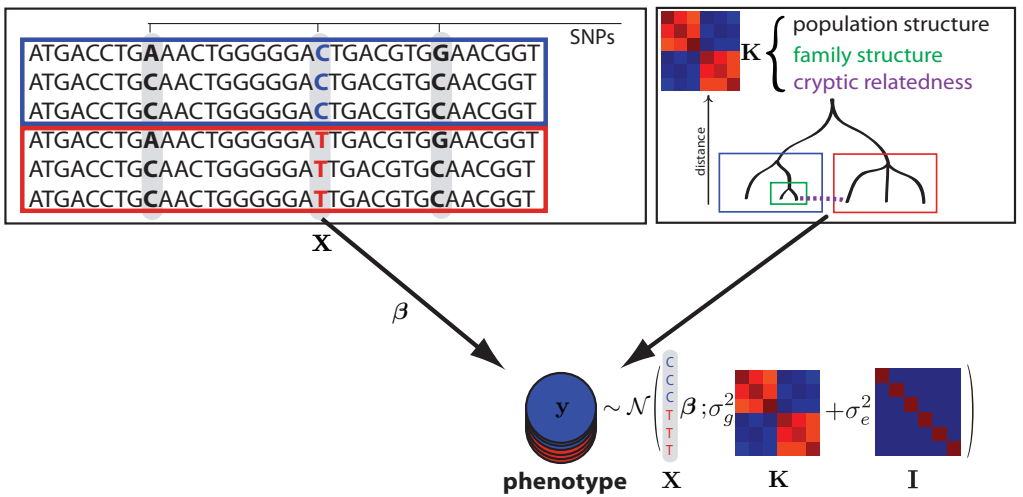
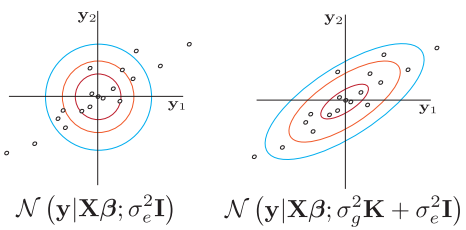
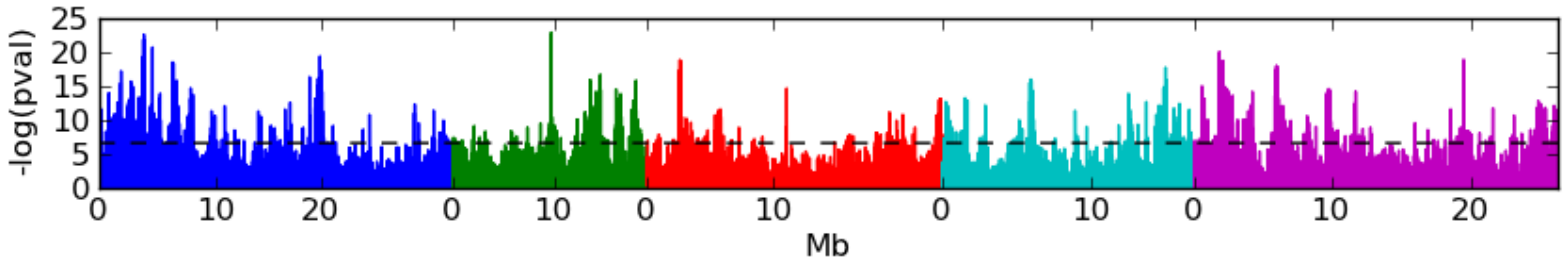




GWAS for Flowering Time in *Arabidopsis thaliana*

- Linear Model:



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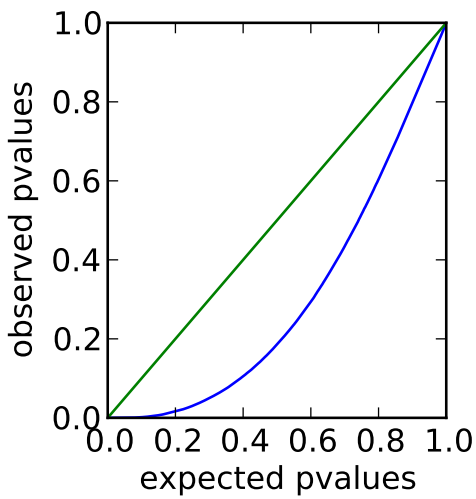

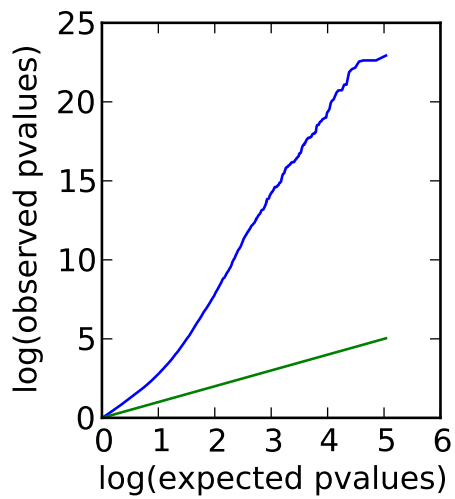

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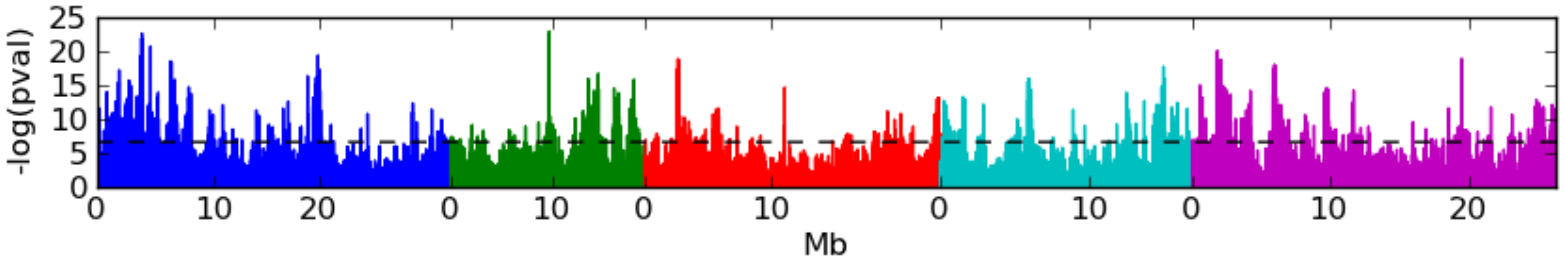

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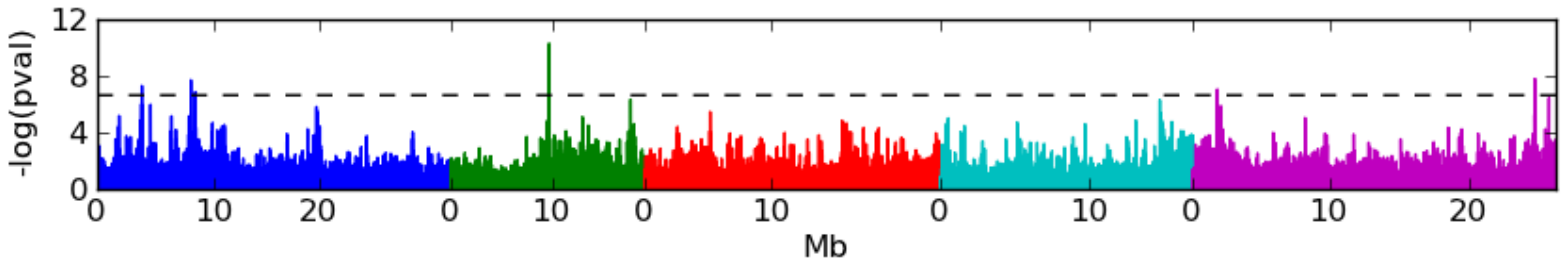

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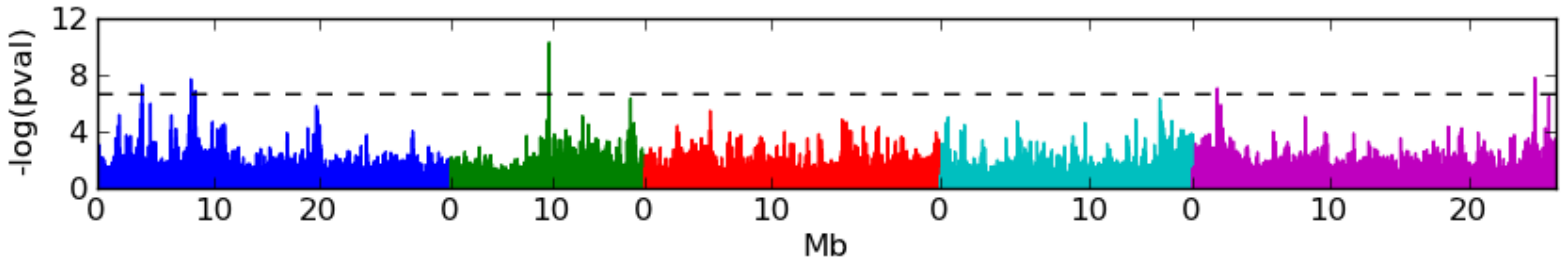

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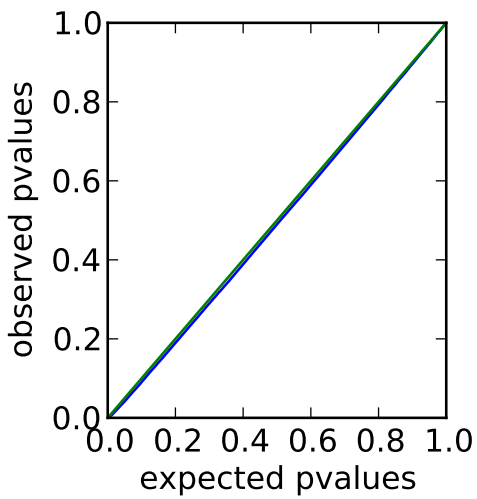

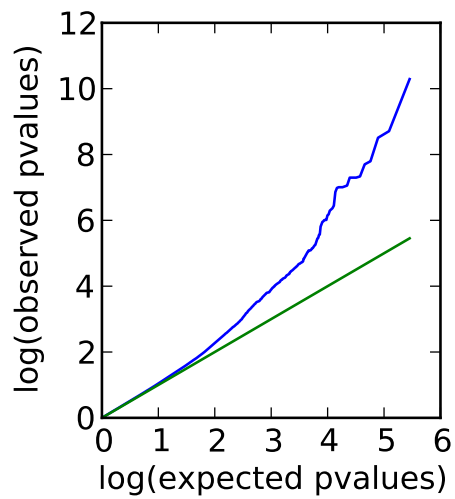

Linear mixed models (LMM)

- LMM log likelihood

$$LL(\boldsymbol{\beta}, \sigma_{\mathrm{g}}^2, \sigma_{\mathrm{e}}^2) = \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\mathbf{K} + \sigma_{\mathrm{e}}^2\mathbf{I}\right).$$

- Change of variables, introducing $\delta = \sigma_{\mathrm{e}}^2/\sigma_{\mathrm{g}}^2$:

$$LL(\boldsymbol{\beta}, \sigma_{\mathrm{g}}^2, \delta) = \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\left(\mathbf{K} + \delta\mathbf{I}\right)\right).$$

- ML-parameters $\hat{\boldsymbol{\beta}}$ and $\hat{\sigma_{\mathrm{g}}^2}$ follow in closed form.
- Use optimizer to solve 1-dimensional optimization problem over δ.

[Kang et al., 2008]

Linear mixed models (LMM)

- LMM log likelihood

$$LL(\boldsymbol{\beta}, \sigma_{\mathrm{g}}^2, \sigma_{\mathrm{e}}^2) = \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\mathbf{K} + \sigma_{\mathrm{e}}^2\mathbf{I}\right).$$

- Change of variables, introducing $\delta = \sigma_{\mathrm{e}}^2/\sigma_{\mathrm{g}}^2$:

$$LL(\boldsymbol{\beta}, \sigma_{\mathrm{g}}^2, \delta) = \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\left(\mathbf{K} + \delta\mathbf{I}\right)\right).$$

- ML-parameters $\hat{\boldsymbol{\beta}}$ and $\hat{\sigma_{\mathrm{g}}^2}$ follow in closed form.
- Use optimizer to solve 1-dimensional optimization problem over δ.

[Kang et al., 2008]

Linear mixed models (LMM)

- LMM log likelihood

$$LL(\boldsymbol{\beta}, \sigma_{\mathrm{g}}^2, \sigma_{\mathrm{e}}^2) = \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\mathbf{K} + \sigma_{\mathrm{e}}^2\mathbf{I}\right).$$

- Change of variables, introducing $\delta = \sigma_{\mathrm{e}}^2/\sigma_{\mathrm{g}}^2$:

$$LL(\boldsymbol{\beta}, \sigma_{\mathrm{g}}^2, \delta) = \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\left(\mathbf{K} + \delta\mathbf{I}\right)\right).$$

- ML-parameters $\hat{\boldsymbol{\beta}}$ and $\hat{\sigma_{\mathrm{g}}^2}$ follow in closed form.
- Use optimizer to solve 1-dimensional optimization problem over δ.

[Kang et al., 2008]

Linear mixed models (LMM)

- LMM log likelihood

$$LL(\boldsymbol{\beta}, \sigma_{\mathrm{g}}^2, \sigma_{\mathrm{e}}^2) = \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\mathbf{K} + \sigma_{\mathrm{e}}^2\mathbf{I}\right).$$

- Change of variables, introducing $\delta = \sigma_{\mathrm{e}}^2/\sigma_{\mathrm{g}}^2$:

$$LL(\boldsymbol{\beta}, \sigma_{\mathrm{g}}^2, \delta) = \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\left(\mathbf{K} + \delta\mathbf{I}\right)\right).$$

- ML-parameters $\hat{\boldsymbol{\beta}}$ and $\hat{\sigma_{\mathrm{g}}^2}$ follow in closed form.
- Use optimizer to solve 1-dimensional optimization problem over δ.

[Kang et al., 2008]

Linear mixed models (LMM)

ML parameters

Gradient of the LMM log likelihood w.r.t. $\boldsymbol{\beta}$

$$\begin{aligned}\nabla_{\boldsymbol{\beta}} \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\left(\mathbf{K}+\delta\mathbf{I}\right)\right) &= \nabla_{\beta} -\frac{1}{2\sigma_{\mathrm{g}}^2}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right) \\ &= \frac{1}{\sigma_{\mathrm{g}}^2}\left[-\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y}+\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\right]\end{aligned}$$

Linear mixed models (LMM)

ML parameters

Gradient of the LMM log likelihood w.r.t. $\boldsymbol{\beta}$

$$\begin{aligned}\nabla_{\boldsymbol{\beta}} \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\left(\mathbf{K}+\delta\mathbf{I}\right)\right) &= \nabla_{\boldsymbol{\beta}} - \frac{1}{2\sigma_{\mathrm{g}}^2}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right) \\ &= \frac{1}{\sigma_{\mathrm{g}}^2}\left[-\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y}+\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\right]\end{aligned}$$

Linear mixed models (LMM)

ML parameters

Gradient of the LMM log likelihood w.r.t. $\boldsymbol{\beta}$

$$\begin{aligned}\nabla_{\boldsymbol{\beta}} \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\left(\mathbf{K}+\delta\mathbf{I}\right)\right) &= \nabla_{\boldsymbol{\beta}} - \frac{1}{2\sigma_{\mathrm{g}}^2}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right) \\ &= \frac{1}{\sigma_{\mathrm{g}}^2}\left[-\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y} + \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\right]\end{aligned}$$

Linear mixed models (LMM)

ML parameters

Gradient of the LMM log likelihood w.r.t. $\boldsymbol{\beta}$

$$\begin{aligned}\nabla_{\boldsymbol{\beta}} \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\left(\mathbf{K}+\delta\mathbf{I}\right)\right) &= \nabla_{\boldsymbol{\beta}} - \frac{1}{2\sigma_{\mathrm{g}}^2}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right) \\ &= \frac{1}{\sigma_{\mathrm{g}}^2}\left[-\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y} + \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\right]\end{aligned}$$

set gradient to zero:

$$\begin{aligned}\mathbf{0} &= \frac{1}{\sigma_{\mathrm{g}}^2}\left[\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y} - \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\boldsymbol{\beta}\right] \\ \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\boldsymbol{\beta} &= \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y} \\ \boldsymbol{\beta}_{\mathrm{ML}} &= \left(\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\right)^{-1}\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y}\end{aligned}$$

Linear mixed models (LMM)

ML parameters

Gradient of the LMM log likelihood w.r.t. $\boldsymbol{\beta}$

$$\begin{aligned}\nabla_{\boldsymbol{\beta}} \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\left(\mathbf{K}+\delta\mathbf{I}\right)\right) &= \nabla_{\boldsymbol{\beta}} - \frac{1}{2\sigma_{\mathrm{g}}^2}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right) \\ &= \frac{1}{\sigma_{\mathrm{g}}^2}\left[-\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y} + \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\right]\end{aligned}$$

set gradient to zero:

$$\begin{aligned}\mathbf{0} &= \frac{1}{\sigma_{\mathrm{g}}^2}\left[\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y} - \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\boldsymbol{\beta}\right] \\ \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\boldsymbol{\beta} &= \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y} \\ \boldsymbol{\beta}_{\mathrm{ML}} &= \left(\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\right)^{-1}\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y}\end{aligned}$$

Linear mixed models (LMM)

ML parameters

Gradient of the LMM log likelihood w.r.t. $\boldsymbol{\beta}$

$$\begin{aligned}\nabla_{\boldsymbol{\beta}} \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\left(\mathbf{K}+\delta\mathbf{I}\right)\right) &= \nabla_{\boldsymbol{\beta}} - \frac{1}{2\sigma_{\mathrm{g}}^2}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right) \\ &= \frac{1}{\sigma_{\mathrm{g}}^2}\left[-\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y} + \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\right]\end{aligned}$$

set gradient to zero:

$$\begin{aligned}\mathbf{0} &= \frac{1}{\sigma_{\mathrm{g}}^2}\left[\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y} - \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\boldsymbol{\beta}\right] \\ \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\boldsymbol{\beta} &= \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y} \\ \boldsymbol{\beta}_{\mathrm{ML}} &= \left(\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\right)^{-1}\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y}\end{aligned}$$

Linear mixed models (LMM)

ML parameters

Gradient of the LMM log likelihood w.r.t. $\boldsymbol{\beta}$

$$\begin{aligned}\nabla_{\boldsymbol{\beta}} \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\left(\mathbf{K}+\delta\mathbf{I}\right)\right) &= \nabla_{\boldsymbol{\beta}} - \frac{1}{2\sigma_{\mathrm{g}}^2}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right) \\ &= \frac{1}{\sigma_{\mathrm{g}}^2}\left[-\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y} + \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\right]\end{aligned}$$

set gradient to zero:

$$\begin{aligned}\mathbf{0} &= \frac{1}{\sigma_{\mathrm{g}}^2}\left[\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y} - \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\boldsymbol{\beta}\right] \\ \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\boldsymbol{\beta} &= \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y} \\ \boldsymbol{\beta}_{\mathrm{ML}} &= \left(\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\right)^{-1}\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y}\end{aligned}$$

Linear mixed models (LMM)

ML parameters

Gradient of the LMM log likelihood w.r.t. $\boldsymbol{\beta}$

$$\begin{aligned}\nabla_{\boldsymbol{\beta}} \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\left(\mathbf{K}+\delta\mathbf{I}\right)\right) &= \nabla_{\boldsymbol{\beta}} - \frac{1}{2\sigma_{\mathrm{g}}^2}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right) \\ &= \frac{1}{\sigma_{\mathrm{g}}^2}\left[-\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y} + \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\right]\end{aligned}$$

set gradient to zero:

$$\begin{aligned}\mathbf{0} &= \frac{1}{\sigma_{\mathrm{g}}^2}\left[\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y} - \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\boldsymbol{\beta}\right] \\ \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\boldsymbol{\beta} &= \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y} \\ \boldsymbol{\beta}_{\mathsf{ML}} &= \left(\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\right)^{-1}\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y}\end{aligned}$$

Linear mixed models (LMM)

ML parameters

Gradient of the LMM log likelihood w.r.t. $\boldsymbol{\beta}$

$$\begin{aligned}\nabla_{\boldsymbol{\beta}} \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\left(\mathbf{K}+\delta\mathbf{I}\right)\right) &= \nabla_{\boldsymbol{\beta}} - \frac{1}{2\sigma_{\mathrm{g}}^2}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right) \\ &= \frac{1}{\sigma_{\mathrm{g}}^2}\left[-\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y} + \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\right]\end{aligned}$$

set gradient to zero:

$$\begin{aligned}\mathbf{0} &= \frac{1}{\sigma_{\mathrm{g}}^2}\left[\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y} - \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\boldsymbol{\beta}\right] \\ \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\boldsymbol{\beta} &= \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y} \\ \boldsymbol{\beta}_{\mathrm{ML}} &= \left(\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\right)^{-1}\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y}\end{aligned}$$

Note that this solution is analogous to the ML solution of the linear regression .

Linear mixed models (LMM)

ML parameters

Gradient of the LMM log likelihood w.r.t. $\boldsymbol{\beta}$

$$\begin{aligned}\nabla_{\boldsymbol{\beta}} \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\left(\mathbf{K}+\delta\mathbf{I}\right)\right) &= \nabla_{\boldsymbol{\beta}} - \frac{1}{2\sigma_{\mathrm{g}}^2}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right) \\ &= \frac{1}{\sigma_{\mathrm{g}}^2}\left[-\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y} + \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\right]\end{aligned}$$

set gradient to zero:

$$\begin{aligned}\mathbf{0} &= \frac{1}{\sigma_{\mathrm{g}}^2}\left[\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y} - \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\boldsymbol{\beta}\right] \\ \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\boldsymbol{\beta} &= \mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y} \\ \boldsymbol{\beta}_{\mathrm{ML}} &= \left(\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{X}\right)^{-1}\mathbf{X}^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\mathbf{y}\end{aligned}$$

Note that this solution is analogous to the ML solution of the linear regression $\left(\mathbf{X}^{\mathrm{T}}\mathbf{X}\right)^{-1}\mathbf{X}^{\mathrm{T}}\mathbf{y}$.

Linear mixed models (LMM)

ML parameters

Derivative of the LMM log likelihood w.r.t. σ_{g}^2

$$\frac{\partial}{\partial \sigma_{\mathrm{g}}^2} \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\left(\mathbf{K}+\delta\mathbf{I}\right)\right)$$

$$= -\frac{1}{2}\left[\frac{N}{\sigma_{\mathrm{g}}^2} - \frac{N}{\sigma_g^4}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)\right]$$

- **Bottleneck:** Inverting $N \times N$ matrix $\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}$
- If done naively, this is an $O(N^3)$ operation per SNP.

Linear mixed models (LMM)

ML parameters

Derivative of the LMM log likelihood w.r.t. σ_{g}^2

$$\frac{\partial}{\partial \sigma_{\mathrm{g}}^2} \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\left(\mathbf{K}+\delta\mathbf{I}\right)\right)$$

$$= -\frac{1}{2}\left[\frac{N}{\sigma_{\mathrm{g}}^2} - \frac{N}{\sigma_g^4}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)\right]$$

- **Bottleneck:** For every SNP we have to recalculate $(\mathbf{K}+\delta\mathbf{I})^{-1}$
- If done naively, this is an $O(N^3)$ operation per SNP.

Linear mixed models (LMM)

ML parameters

Derivative of the LMM log likelihood w.r.t. σ_{g}^2

$$\frac{\partial}{\partial \sigma_{\mathrm{g}}^2} \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\left(\mathbf{K}+\delta\mathbf{I}\right)\right)$$

$$= -\frac{1}{2}\left[\frac{N}{\sigma_{\mathrm{g}}^2} - \frac{N}{\sigma_g^4}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)\right]$$

set derivative to zero:

$$\begin{aligned} 0 &= -\frac{1}{2}\left[\frac{N}{\sigma_{\mathrm{g}}^2} - \frac{N}{\sigma_g^4}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)\right] \\ \sigma_{g\mathrm{ML}}^2 &= \frac{1}{N}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right) \end{aligned}$$

- **Bottleneck:** $(\mathbf{K}+\delta\mathbf{I})^{-1}$
- If done naively, this is an $O(N^3)$ operation per SNP.

Linear mixed models (LMM)

ML parameters

Derivative of the LMM log likelihood w.r.t. σ_{g}^2

$$\frac{\partial}{\partial \sigma_{\mathrm{g}}^2} \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\left(\mathbf{K}+\delta\mathbf{I}\right)\right)$$

$$= -\frac{1}{2}\left[\frac{N}{\sigma_{\mathrm{g}}^2} - \frac{N}{\sigma_g^4}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)\right]$$

set derivative to zero:

$$0 = -\frac{1}{2}\left[\frac{N}{\sigma_{\mathrm{g}}^2} - \frac{N}{\sigma_g^4}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)\right]$$

$$\sigma_{g\mathrm{ML}}^2 = \frac{1}{N}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)$$

- **Bottleneck:** how to compute the trace without the matrix calculation $(\mathbf{K}+\delta\mathbf{I})^{-1}$
- If done naively, this is an $O(N^3)$ operation per SNP.

Linear mixed models (LMM)

ML parameters

Derivative of the LMM log likelihood w.r.t. σ_{g}^2

$$\frac{\partial}{\partial \sigma_{\mathrm{g}}^2} \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\left(\mathbf{K}+\delta\mathbf{I}\right)\right)$$

$$= -\frac{1}{2}\left[\frac{N}{\sigma_{\mathrm{g}}^2} - \frac{N}{\sigma_g^4}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)\right]$$

set derivative to zero:

$$\begin{aligned} 0 &= -\frac{1}{2}\left[\frac{N}{\sigma_{\mathrm{g}}^2} - \frac{N}{\sigma_g^4}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)\right] \\ \sigma_{g\mathsf{ML}}^2 &= \frac{1}{N}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right) \end{aligned}$$

- **Bottleneck:** $\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}$
- If done naively, this is an $O(N^3)$ operation per SNP.

Linear mixed models (LMM)

ML parameters

Derivative of the LMM log likelihood w.r.t. σ_{g}^2

$$\frac{\partial}{\partial \sigma_{\mathrm{g}}^2} \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\left(\mathbf{K}+\delta\mathbf{I}\right)\right)$$

$$= -\frac{1}{2}\left[\frac{N}{\sigma_{\mathrm{g}}^2} - \frac{N}{\sigma_g^4}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)\right]$$

set derivative to zero:

$$\begin{aligned} 0 &= -\frac{1}{2}\left[\frac{N}{\sigma_{\mathrm{g}}^2} - \frac{N}{\sigma_g^4}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)\right] \\ \sigma_{g\mathrm{ML}}^2 &= \frac{1}{N}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right) \end{aligned}$$

- **Bottleneck:** For every SNP that we test we need to calculate $(\mathbf{K}+\delta\mathbf{I})^{-1}$.
- If done naively, this is an $O(N^3)$ operation per SNP.

Linear mixed models (LMM)

ML parameters

Derivative of the LMM log likelihood w.r.t. σ_{g}^2

$$\frac{\partial}{\partial \sigma_{\mathrm{g}}^2} \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\left(\mathbf{K}+\delta\mathbf{I}\right)\right)$$

$$= -\frac{1}{2}\left[\frac{N}{\sigma_{\mathrm{g}}^2} - \frac{N}{\sigma_g^4}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)\right]$$

set derivative to zero:

$$\begin{aligned} 0 &= -\frac{1}{2}\left[\frac{N}{\sigma_{\mathrm{g}}^2} - \frac{N}{\sigma_g^4}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)\right] \\ \sigma_{g\mathrm{ML}}^2 &= \frac{1}{N}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right) \end{aligned}$$

- **Bottleneck:** For every SNP that we test we need to calculate $\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}$.
- If done naively, this is an $O(N^3)$ operation per SNP.

Linear mixed models (LMM)

ML parameters

Derivative of the LMM log likelihood w.r.t. σ_{g}^2

$$\frac{\partial}{\partial \sigma_{\mathrm{g}}^2} \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\left(\mathbf{K}+\delta\mathbf{I}\right)\right)$$

$$= -\frac{1}{2}\left[\frac{N}{\sigma_{\mathrm{g}}^2} - \frac{N}{\sigma_g^4}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)\right]$$

set derivative to zero:

$$\begin{aligned} 0 &= -\frac{1}{2}\left[\frac{N}{\sigma_{\mathrm{g}}^2} - \frac{N}{\sigma_g^4}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)\right] \\ \sigma_{g\mathrm{ML}}^2 &= \frac{1}{N}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right) \end{aligned}$$

- **Bottleneck:** For every SNP that we test we need to calculate $\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}$.
- If done naively, this is an $O(N^3)$ operation per SNP. (Very expensive!)

Linear mixed models (LMM)

ML parameters

Derivative of the LMM log likelihood w.r.t. σ_{g}^2

$$\frac{\partial}{\partial \sigma_{\mathrm{g}}^2} \log \mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta}; \sigma_{\mathrm{g}}^2\left(\mathbf{K}+\delta\mathbf{I}\right)\right)$$

$$= -\frac{1}{2}\left[\frac{N}{\sigma_{\mathrm{g}}^2} - \frac{N}{\sigma_g^4}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)\right]$$

set derivative to zero:

$$\begin{aligned} 0 &= -\frac{1}{2}\left[\frac{N}{\sigma_{\mathrm{g}}^2} - \frac{N}{\sigma_g^4}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)\right] \\ \sigma_{g\mathrm{ML}}^2 &= \frac{1}{N}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathrm{T}}\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right) \end{aligned}$$

- **Bottleneck:** For every SNP that we test we need to calculate $\left(\mathbf{K}+\delta\mathbf{I}\right)^{-1}$.
- If done naively, this is an $O(N^3)$ operation per SNP. (very expensive!)

Linear mixed models (LMM)

ML parameters

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[Lippert et al., 2011]

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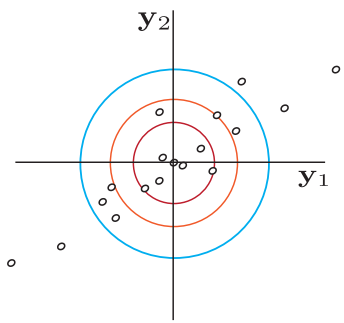

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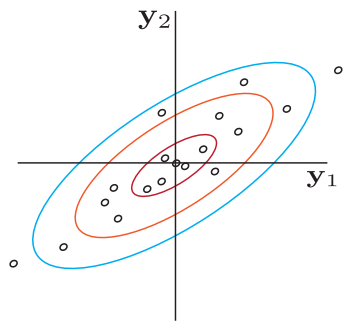

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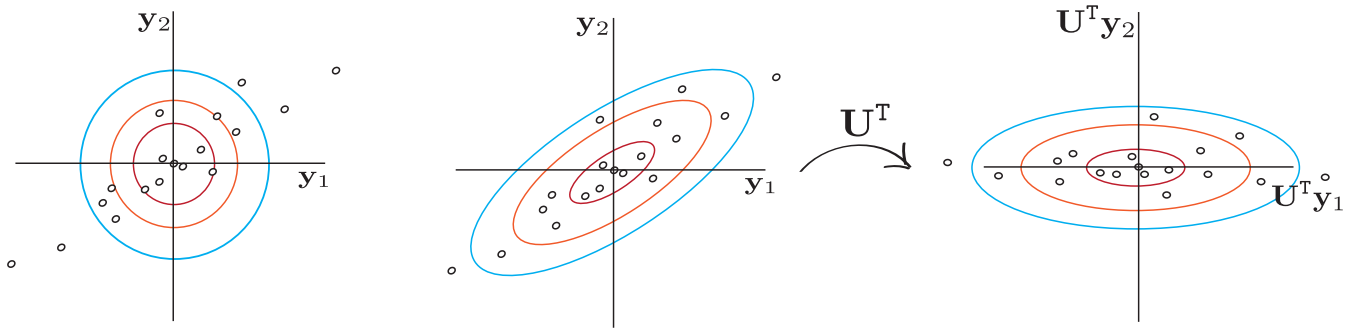

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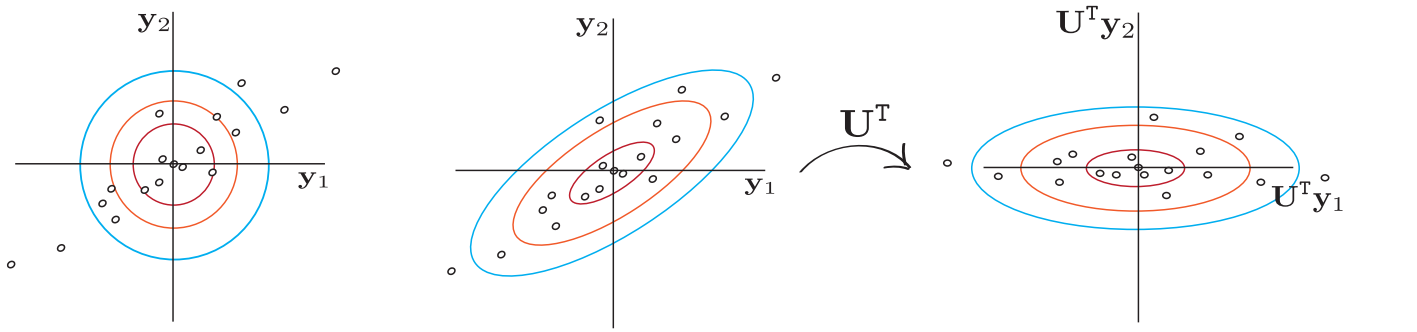

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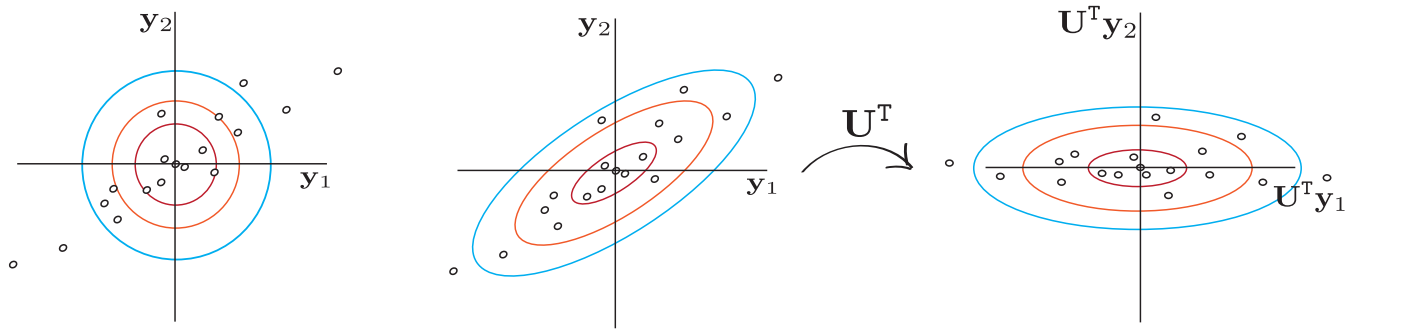

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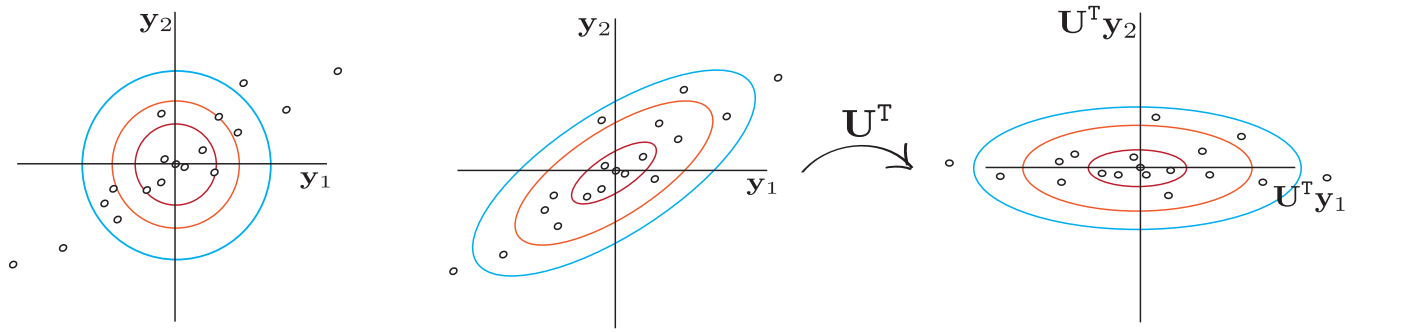

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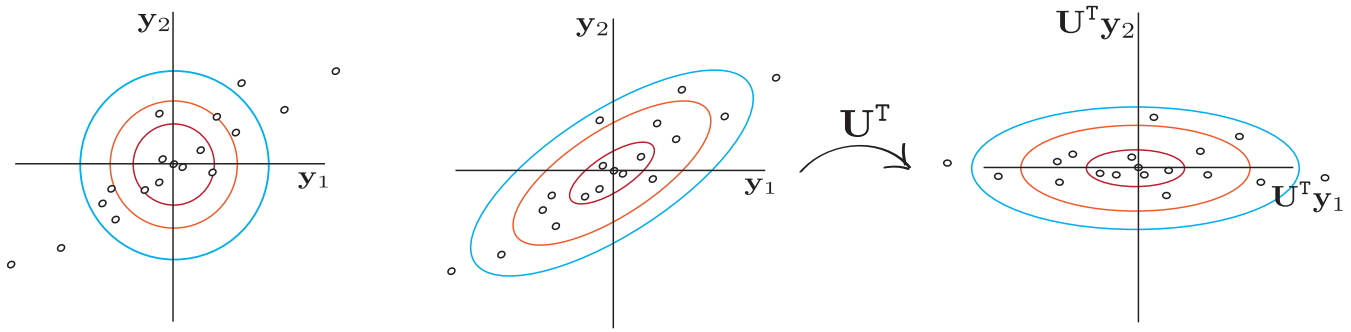

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Summary

Population structure correction

- Genomic control
  - Simple method
  - Works with any statistical test
  - Can be combined with other correction methods
  - Very conservative!
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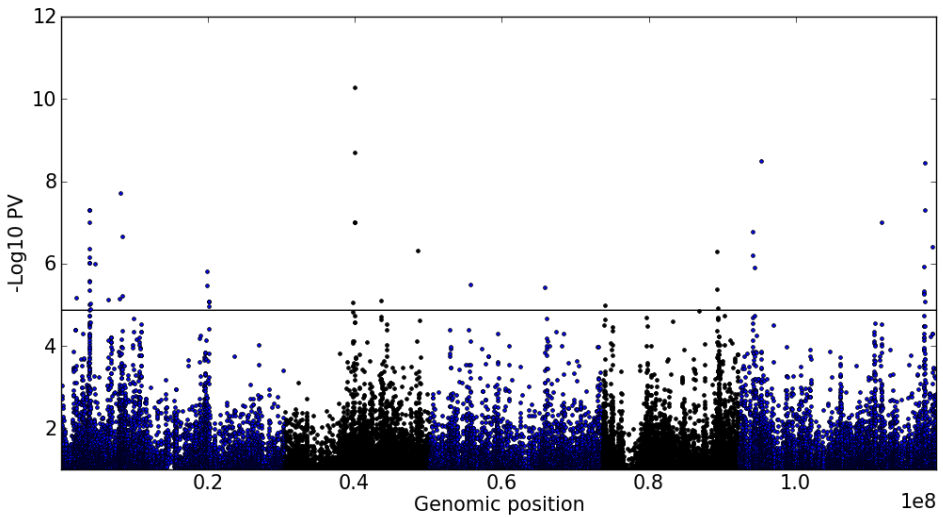

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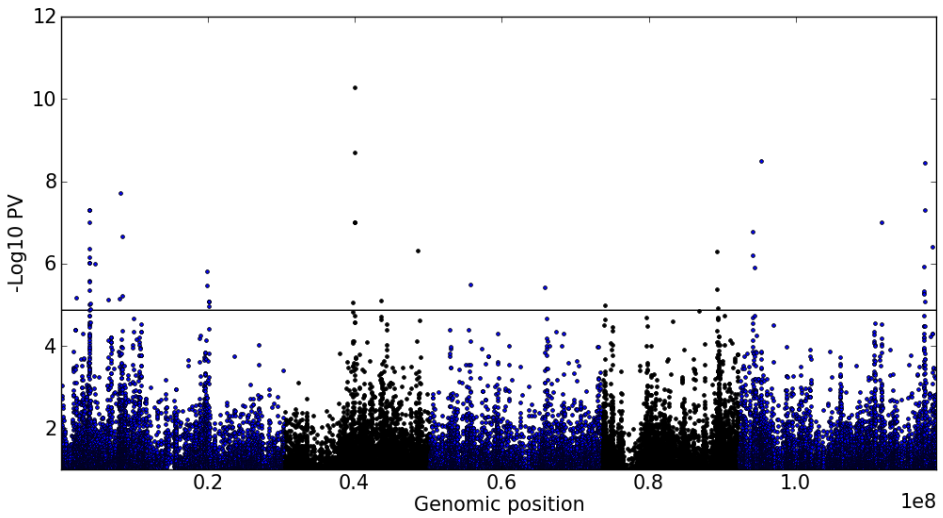

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Multi locus models

Remarks

$$p(\mathbf{y} \mid \mathbf{X}, \sigma_{\mathrm{g}}^2, \sigma_{\mathrm{e}}^2) = \mathcal{N}\left(\mathbf{y} \mid \mathbf{0}, \sigma_{\mathrm{g}}^2 \underbrace{\sum_{s=1}^{S} \mathbf{s}_s \mathbf{x}_s^{\mathrm{T}}}_{\mathbf{K}_g} + \sigma_{\mathrm{e}}^2 \mathbf{I}\right) \tag{3}$$

- $\mathbf{K}_g$ genotype covariance matrix.
  - Closely related to Kinship explaining population structure.
- Inference can be done my maximum likelihood.
- The ratio of σ_{g}^2 and σ_{e}^2 defines the narrow sense heritability of the trait

$$h^2 = \frac{\sigma_{\mathrm{g}}^2}{\sigma_{\mathrm{g}}^2 + \sigma_{\mathrm{e}}^2}.$$

Multi locus models

Remarks

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- $\mathbf{K}_g$ genotype covariance matrix.
  - Closely related to Kinship explaining population structure.
- Inference can be done my maximum likelihood.
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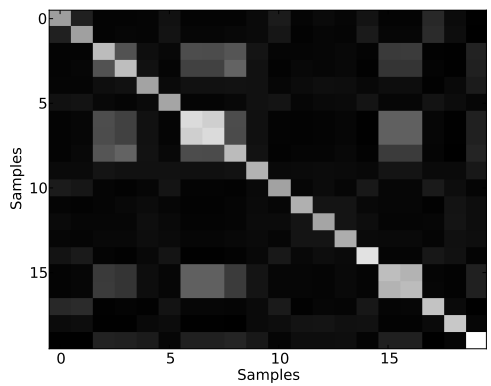

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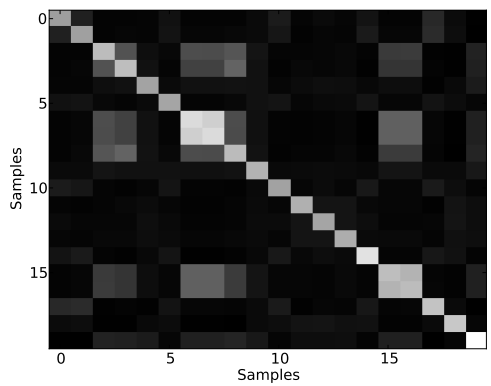

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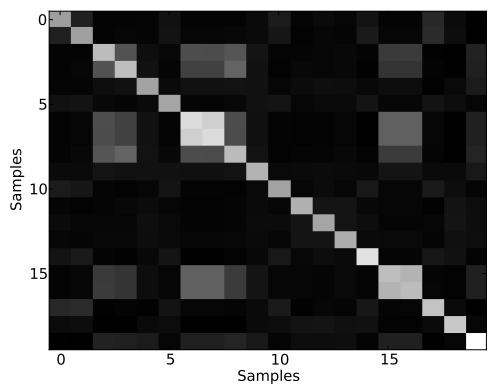

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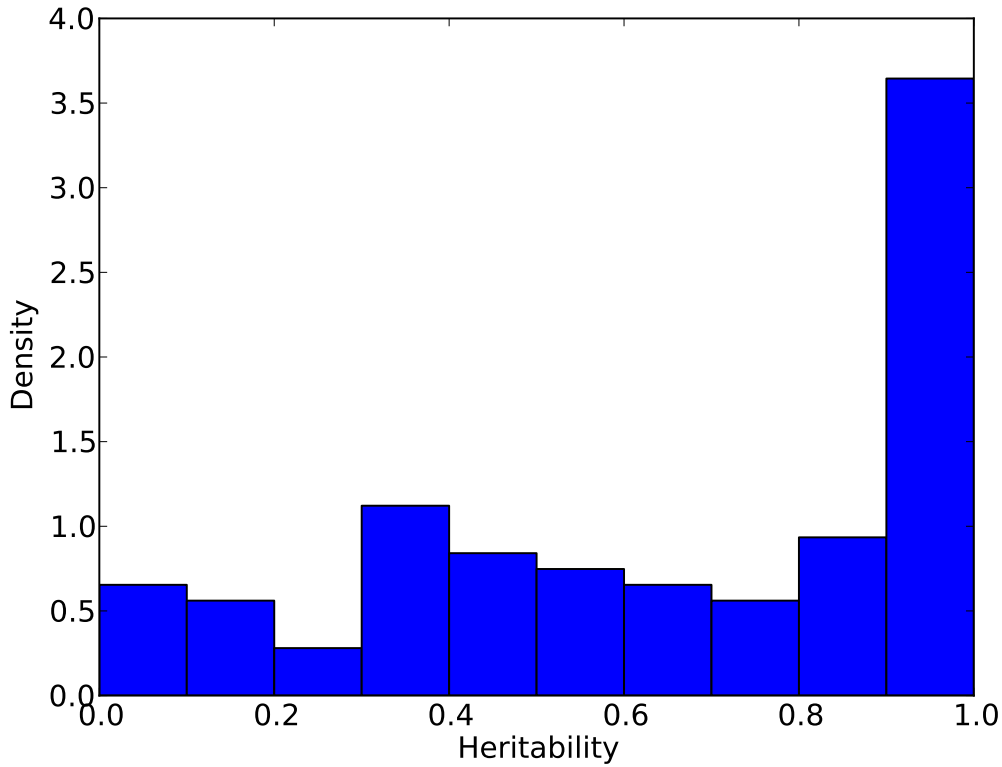
Heritability

Heritability estimated on 107 *A. thaliana* phenotypes

Global genetic heritability

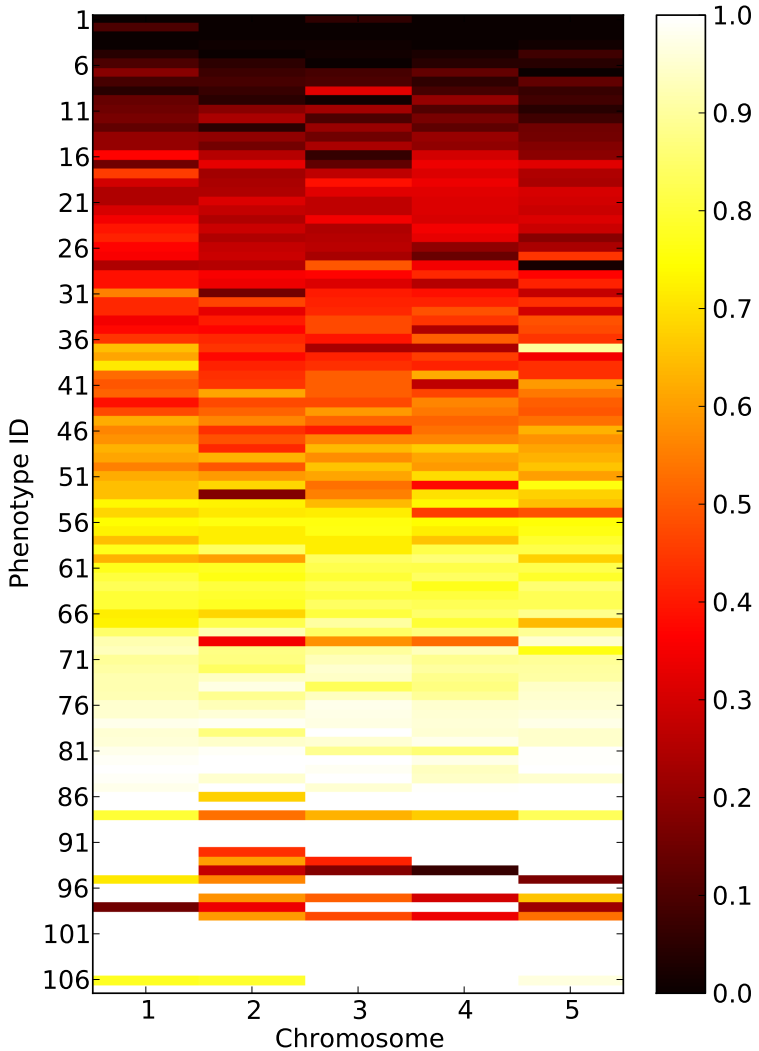


Heritability

Heritability estimated on 107 *A. thaliana* phenotypes

- Estimate can be restricted to a genomic region such as a single chromosome, etc.

$$\mathcal{N}\left(\mathbf{y} \,|\, \mathbf{0}, \sigma_{\mathrm{g}}^2 \sum_{s \in \mathrm{Chrom}} \mathbf{x}_s \mathbf{x}_s^{\mathrm{T}} + \sigma_{\mathrm{e}}^2 \mathbf{I}\right)$$



Window-based composite variance analysis

Region-based testing

- Just fitting a particular region ignores the genome-wide context
- Variance dissection with region-based separation

$$p(\mathbf{y} \mid W) = \mathcal{N}(\mathbf{y} \mid \mathbf{0}, \sigma_w^2 \underbrace{\sum_{s \in W} \mathbf{x}_s \mathbf{x}_s^{\mathrm{T}}}_{\mathbf{K}_w} + \sigma_g^2 \underbrace{\sum_{s \notin W} \mathbf{x}_s \mathbf{x}_s^{\mathrm{T}}}_{\mathbf{K}_g} + \sigma_{\mathrm{e}}^2 \mathbf{I})$$

- Explained variance components can be read off subject to suitable normalization of the covariances $\mathbf{K}_w$ and $\mathbf{K}_g$.
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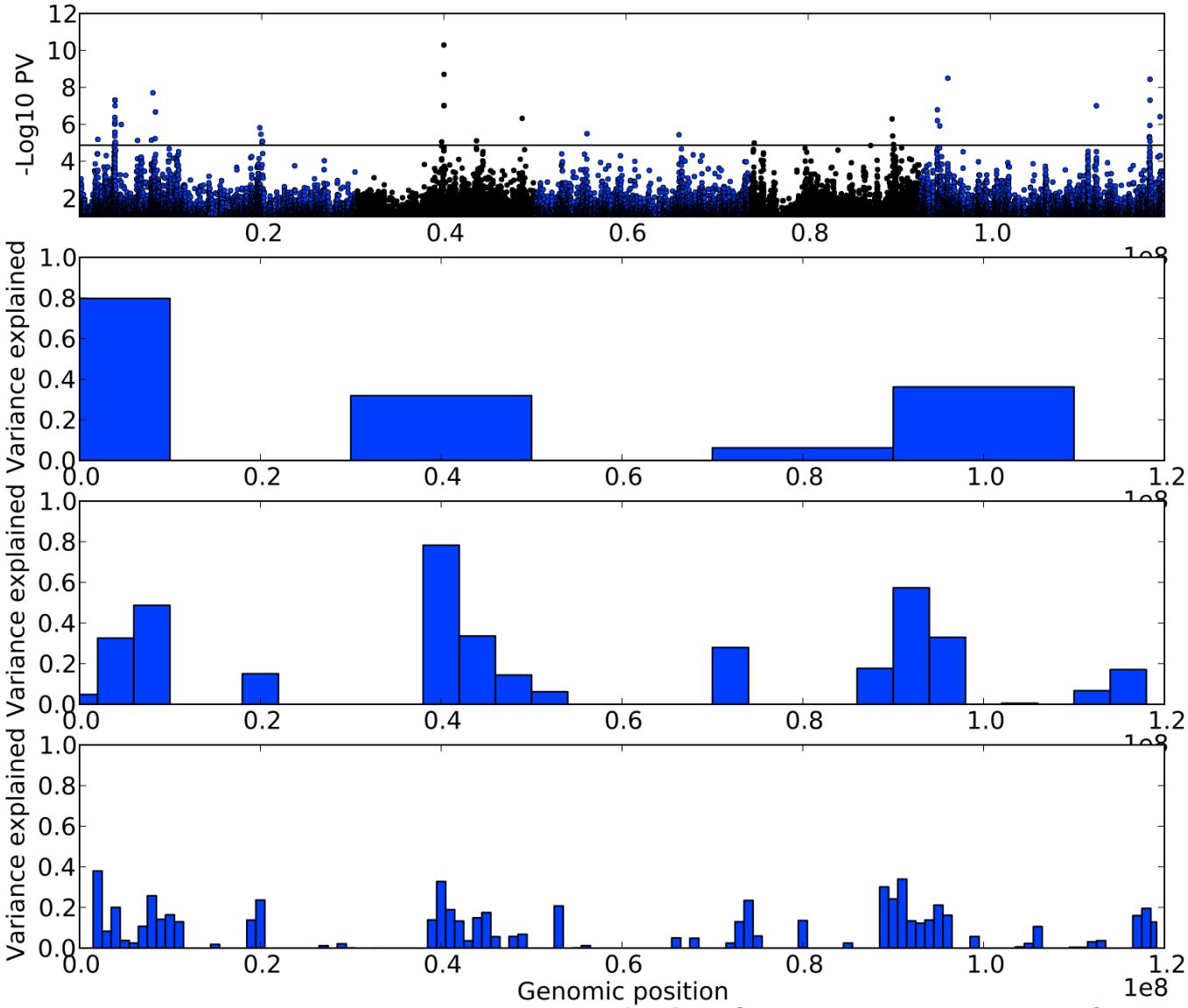

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Significance testing

- Analogously to fixed effect testing, the significance of a specific window can be tested.
- Likelihood-ratio statistics to score the relevance of a particular genomic region W

$$\mathrm{LOD}(W) = \frac{\mathcal{N}\left(\mathbf{y} \middle| \mathbf{0}, \sigma_w^2 \sum_{s \in W} \mathbf{x}_s \mathbf{x}_s^{\mathrm{T}} + \sigma_g^2 \sum_{s \notin W} \mathbf{x}_s \mathbf{x}_s^{\mathrm{T}} + \sigma_{\mathrm{e}}^2 \mathbf{I}\right)}{\mathcal{N}\left(\mathbf{y} \middle| \mathbf{0}, \sigma_g^2 \sum_{s \notin W} \mathbf{x}_s \mathbf{x}_s^{\mathrm{T}} + \sigma_{\mathrm{e}}^2 \mathbf{I}\right)}$$

- P-values can be obtained from permutation statistics or analytical approximation (variants of score tests or likelihood ratio tests).

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Making predictions with linear mixed models

- Linear model, accounting for a set of measured SNPs $\mathbf{X}$

$$p(\mathbf{y} \,|\, \mathbf{X}, \boldsymbol{\theta}, \sigma^2) = \mathcal{N}\left(\mathbf{y} \,\middle|\, \sum_{s=1}^{S} \mathbf{x}_s \theta_s, \sigma^2 \mathbf{I}\right)$$

- Prediction at unseen test input given max. likelihood weight:

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- Making predictions with linear mixed models?

The Gaussian distribution

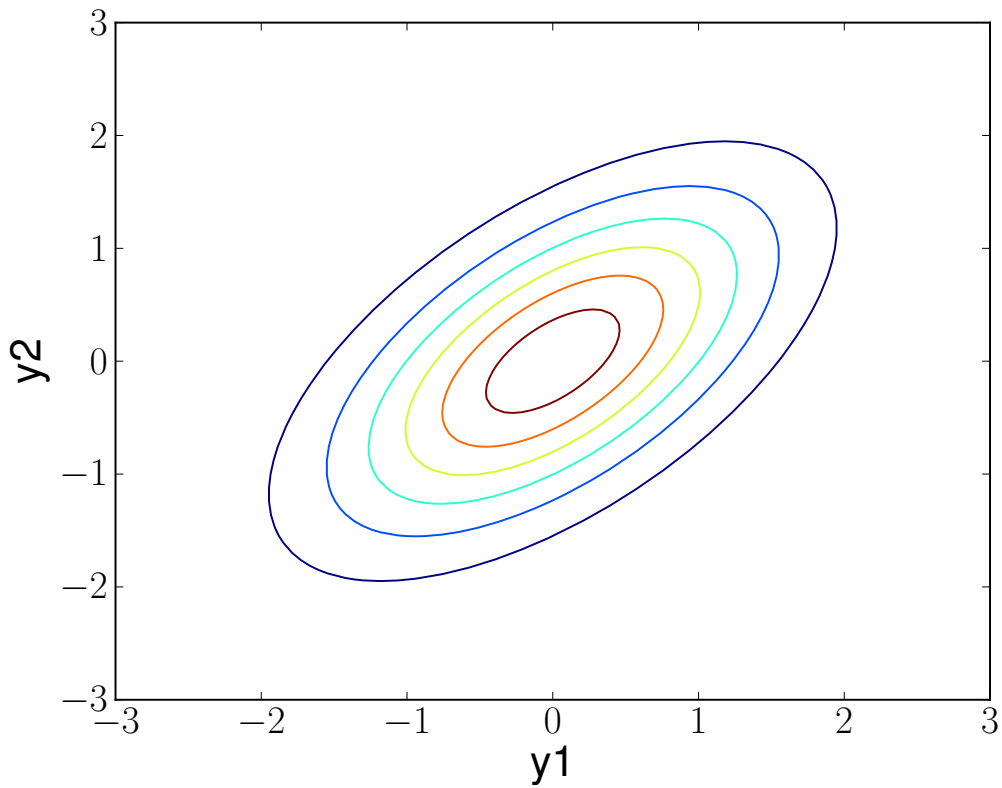
- Linear mixed models are merely based on the good old multivariate Gaussian

$$\mathcal{N}\left(\mathbf{x}\,\middle|\,\boldsymbol{\mu}, \mathbf{K}\right) = \frac{1}{\sqrt{|2\pi\,\mathbf{K}|}} \exp\left[-\frac{1}{2}(\mathbf{x}-\boldsymbol{\mu})^{\mathrm{T}}\,\mathbf{K}^{-1}(\mathbf{x}-\boldsymbol{\mu})\right]$$

- Covariance matrix or kernel matrix

A 2D Gaussian

- Probability contour
- Samples



$$\mathbf{K} = \begin{bmatrix} 1 & 0.6 \\ 0.6 & 1 \end{bmatrix}$$

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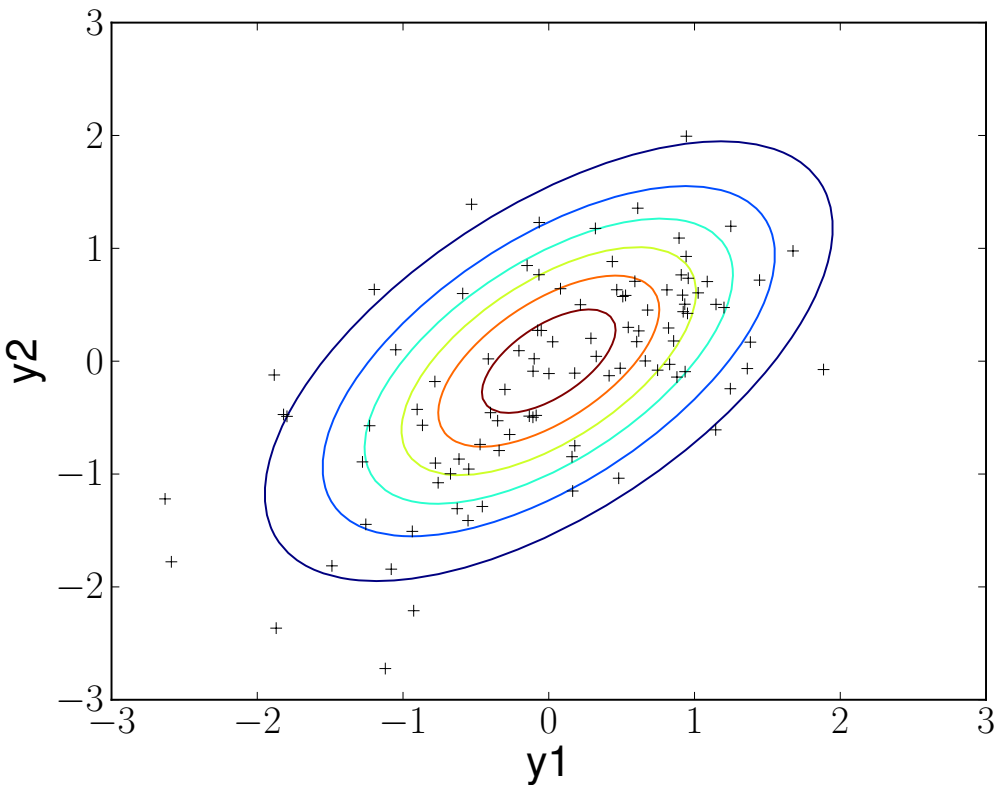

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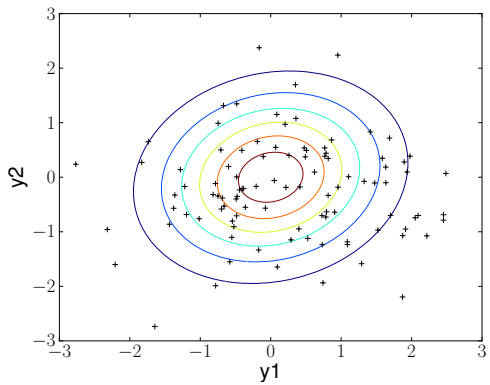
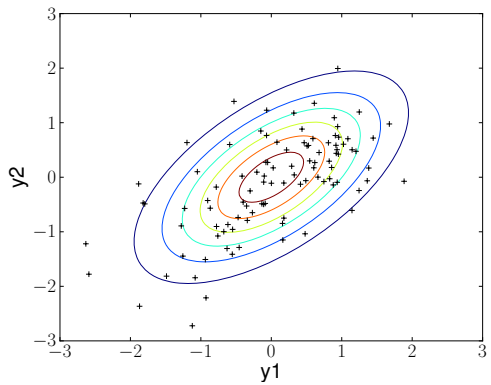
Varying the covariance matrix



$$\mathbf{K} = \begin{bmatrix} 1 & 0.14 \\ 0.14 & 1 \end{bmatrix}$$



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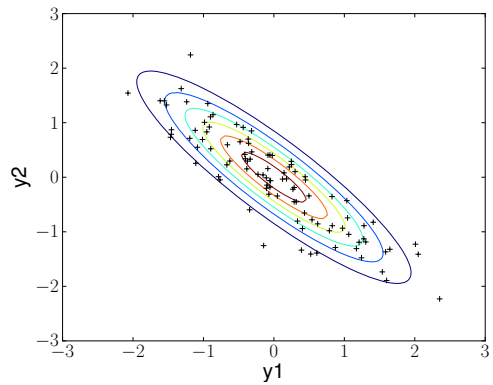

$$\mathbf{K} = \begin{bmatrix} 1 & -0.9 \\ -0.9 & 1 \end{bmatrix}$$

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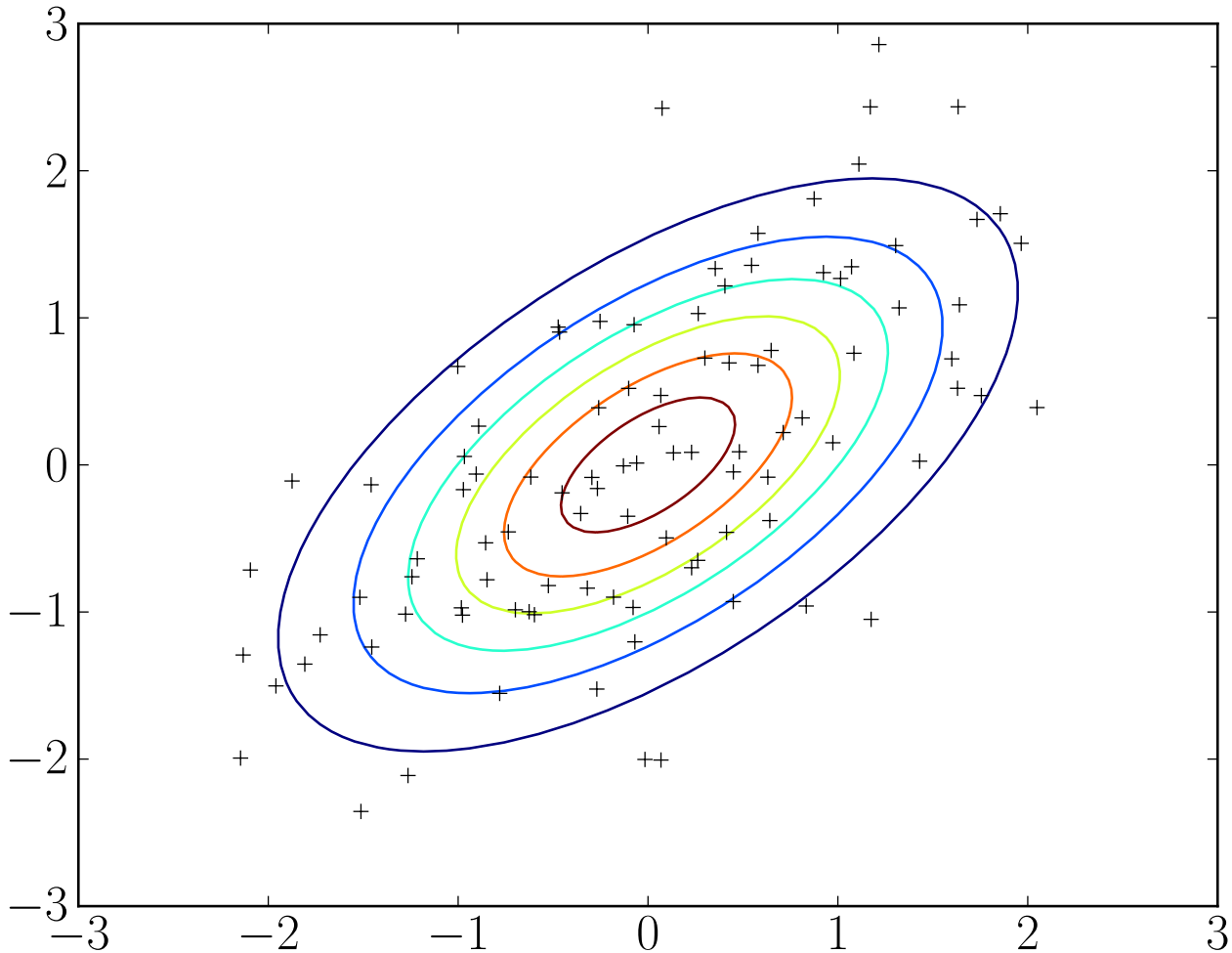
Inference



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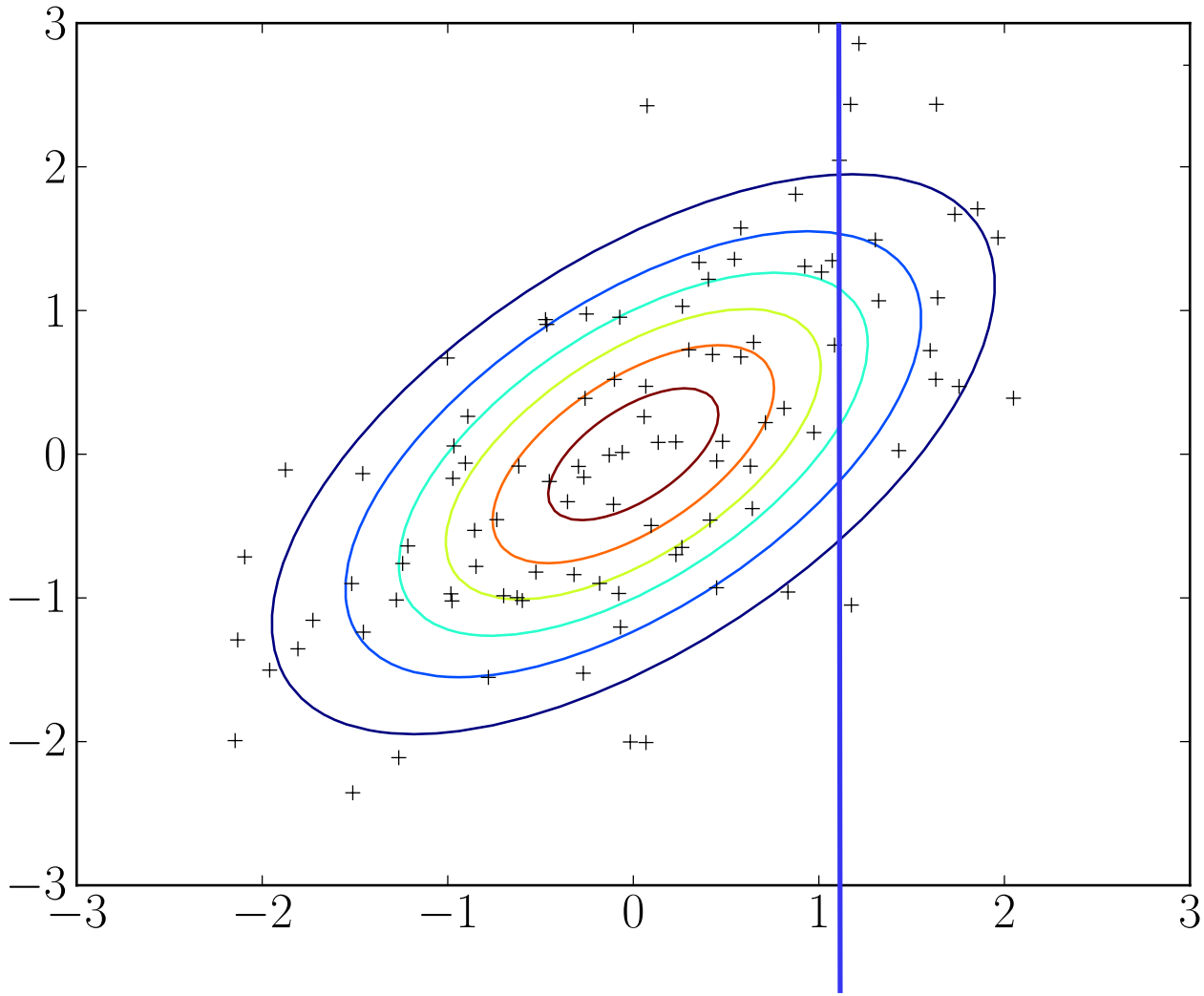

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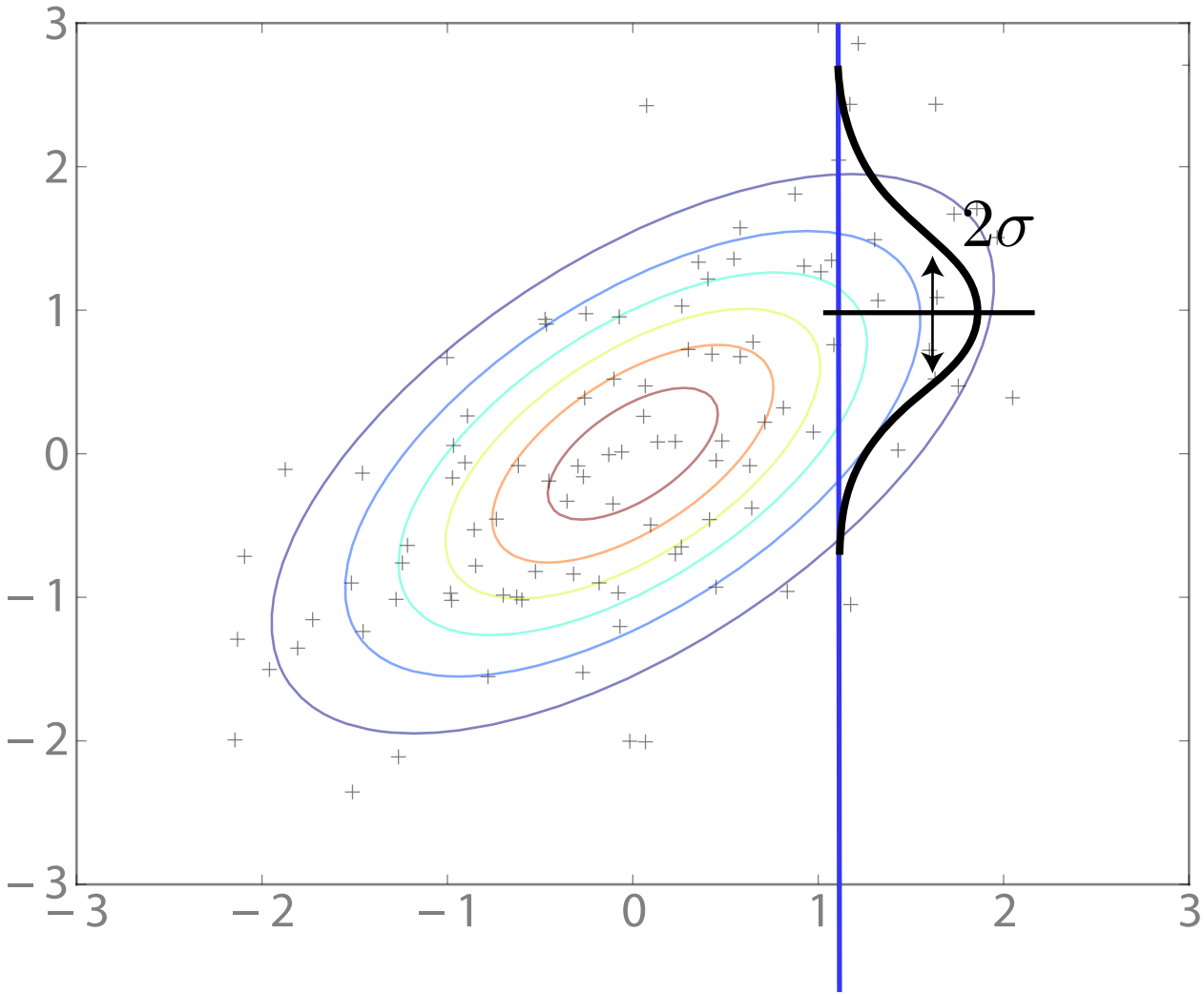

Phenotype prediction

Best linear unbiased prediction

- Given the phenotype values $\mathbf{y}$ of a set of individuals and the genetic relatedness, we can predict the genetic component of the phenotype of a new individual $\mathbf{y}^\star$.

- Use conditional probability distribution
- Note, that the result is again a Gaussian distribution!
- As a Gaussian distribution is always normalized, we can drop any constant terms, that do not contain $\mathbf{y}^\star$.
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$$P(\mathbf{y}^\star \,|\, \mathbf{y}) = \frac{P(\mathbf{y}, \mathbf{y}^\star)}{P(\mathbf{y})} = \frac{\mathcal{N}\left(\begin{bmatrix} \mathbf{y} \\ \mathbf{y}^\star \end{bmatrix} | \mathbf{0}, \sigma_g^2 \begin{bmatrix} \mathbf{K} & \mathbf{K}_{:,\star} \\ \mathbf{K}_{:,\star}^{\mathrm{T}} & \mathbf{K}^{\star,\star} \end{bmatrix} \sigma_e^2 \mathbf{I}\right)}{\mathcal{N}\left(\mathbf{0}, \sigma_g^2 \mathbf{K} + \sigma_e^2 \mathbf{I}\right)}$$

$$= \mathcal{N}\left(\mathbf{y}^\star \,|\, \boldsymbol{\mu}^\star, \boldsymbol{\Sigma}^\star\right) \propto \mathcal{N}\left(\begin{bmatrix} \mathbf{y} \\ \mathbf{y}^\star \end{bmatrix} | \mathbf{0}, \sigma_g^2 \begin{bmatrix} \mathbf{K} & \mathbf{K}_{:,\star} \\ \mathbf{K}_{:,\star}^{\mathrm{T}} & \mathbf{K}^{\star,\star} \end{bmatrix} \sigma_e^2 \mathbf{I}\right)$$

- Use conditional probability distribution
- Note, that the result is again a Gaussian distribution!
- As a Gaussian distribution is always normalized, we can drop any constant terms, that do not contain $\mathbf{y}^\star$.
- Completing the square identifies the mean $\boldsymbol{\mu}^\star$ and the variance $\boldsymbol{\Sigma}^\star$ of $\mathbf{y}^\star$ given $\mathbf{y}$.

Inference

Gaussian conditioning in 2D

$$p(y_2 \mid y_1, \mathbf{K}) = \frac{p(y_1, y_2 \mid \mathbf{K})}{p(y_1 \mid \mathbf{K})} \propto \exp\left\{-\frac{1}{2}[y_1, y_2]\,\mathbf{K}^{-1}\begin{bmatrix} y_1 \\ y_2 \end{bmatrix}\right\}$$

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Phenotype prediction

Best linear unbiased prediction

- Given the phenotype values of a set of individuals and the genetic relatedness, we can predict the genetic component of the phenotype of a new individual.
- $P(\mathbf{y}^\star \mid \mathbf{y}) = \mathcal{N}\left(\mathbf{y}^\star \mid \boldsymbol{\mu}^\star, \sigma_{\mathrm{g}}^2 \mathbf{V}_g^\star + \sigma_{\mathrm{e}}^2 \mathbf{I}\right)$
- Predictive mean: $\boldsymbol{\mu}^\star = \underbrace{\sigma_{\mathrm{g}}^2 \mathbf{K}_g^{\star,:} \left(\sigma_{\mathrm{g}}^2 \mathbf{K}_g + \sigma_{\mathrm{e}}^2 \mathbf{I}\right)^{-1}}_{\text{BLUP}} \mathbf{y}$
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Summary

- Basic probability theory
- Linear mixed models
  - Population structure correction
  - Parameter estimation
  - Variance component modeling
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  O. Stegle
- **FaST lmm**
  J. Listgarten, D. Heckerman

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