Mapping of high-dimensional traits: eQTL and beyond

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Basel
09. September 2012

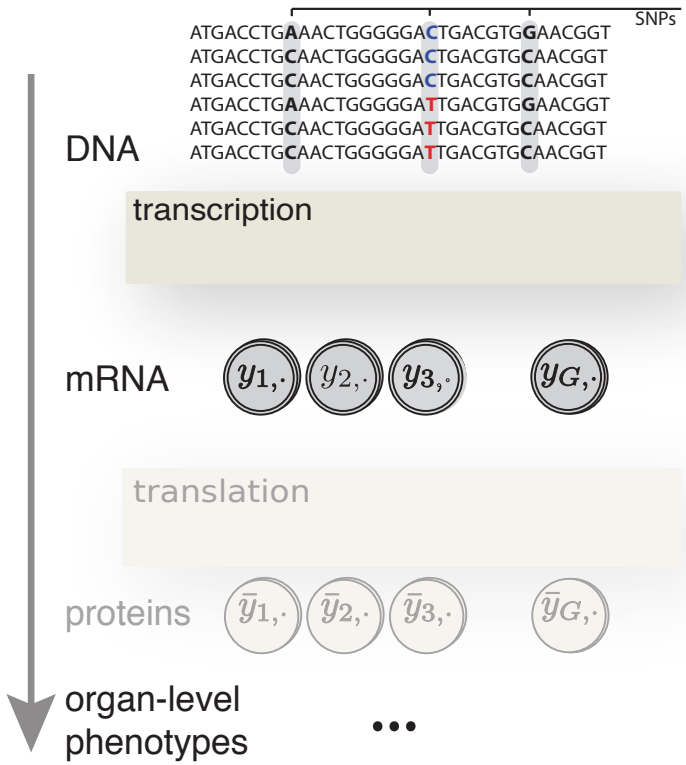
Microsoft Research

Models of molecular variation

Motivation

Goal:

- Dissect genetic GWAS signals
- Improve predictive models of quantitative traits
- Understand genetic architecture



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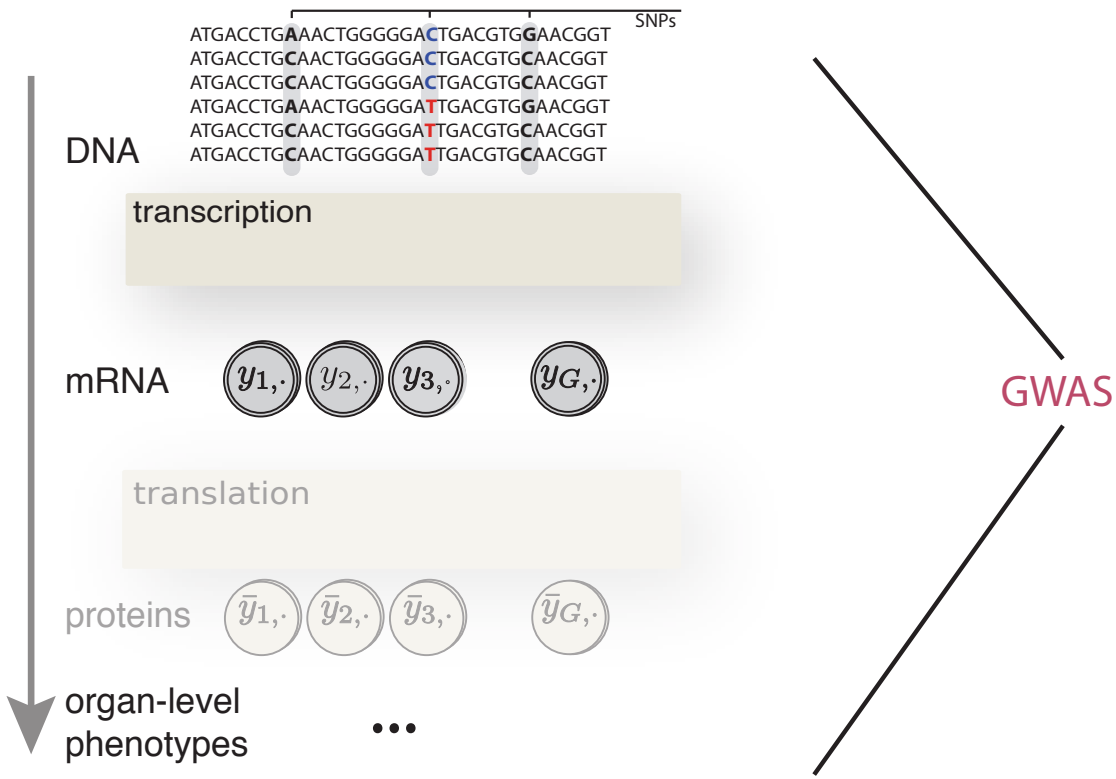

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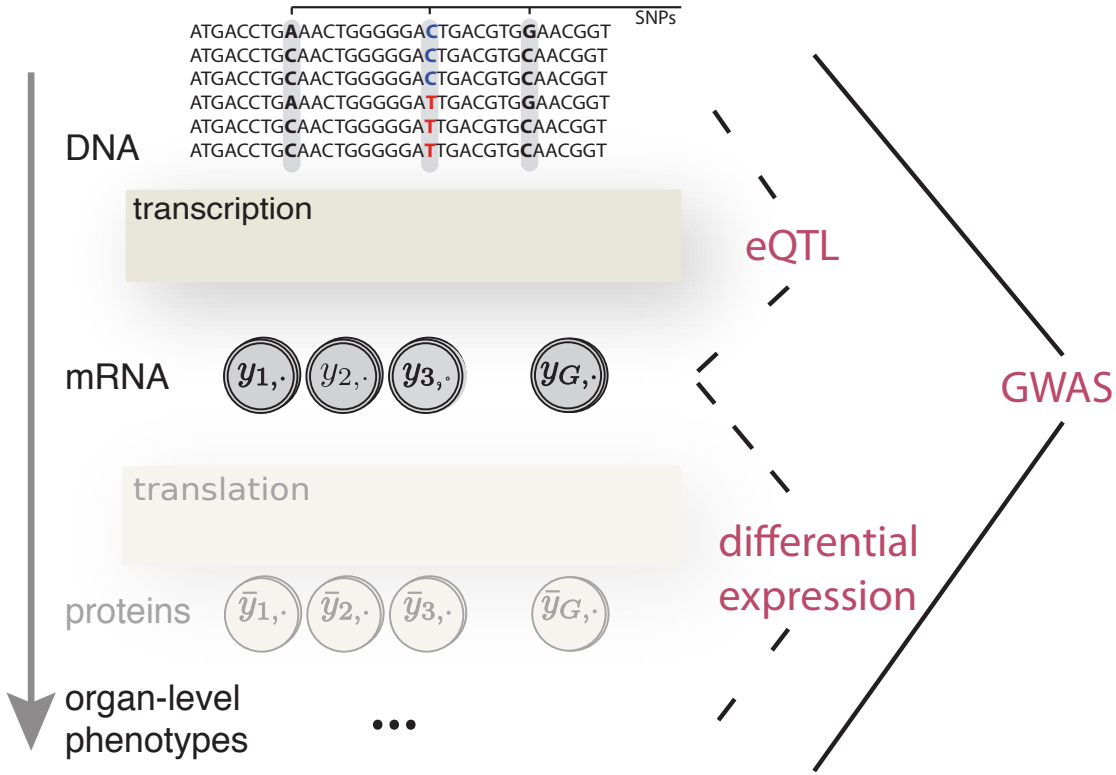

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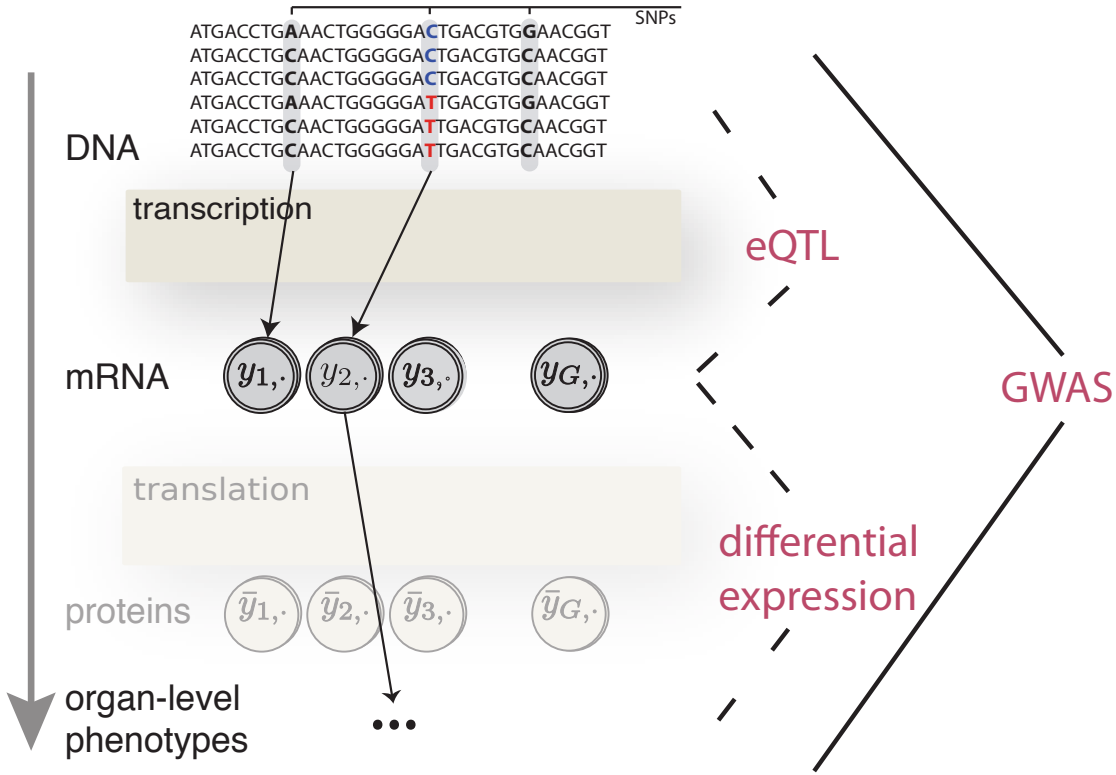
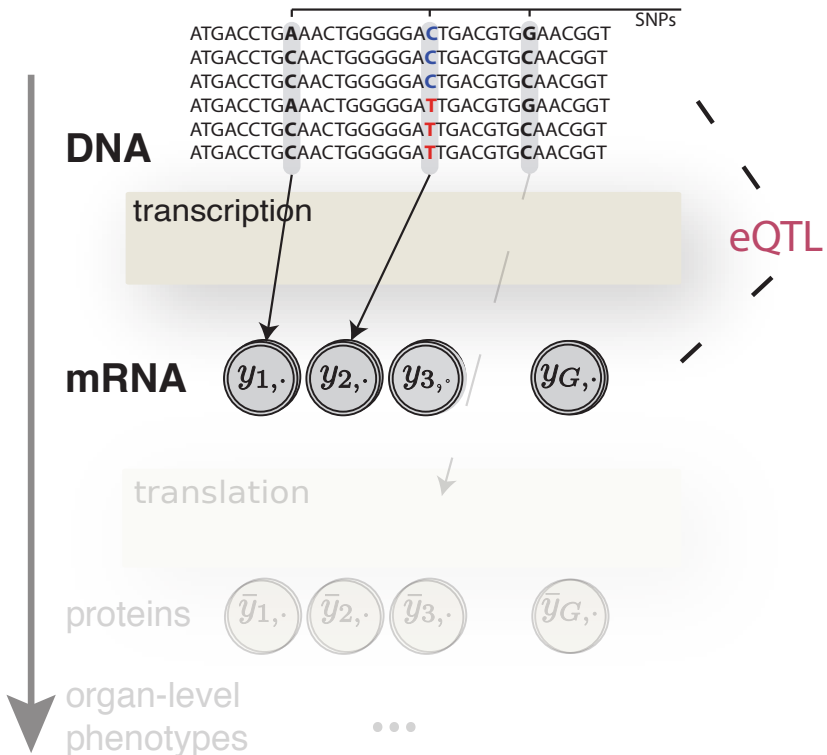


Models of molecular variation

eQTL

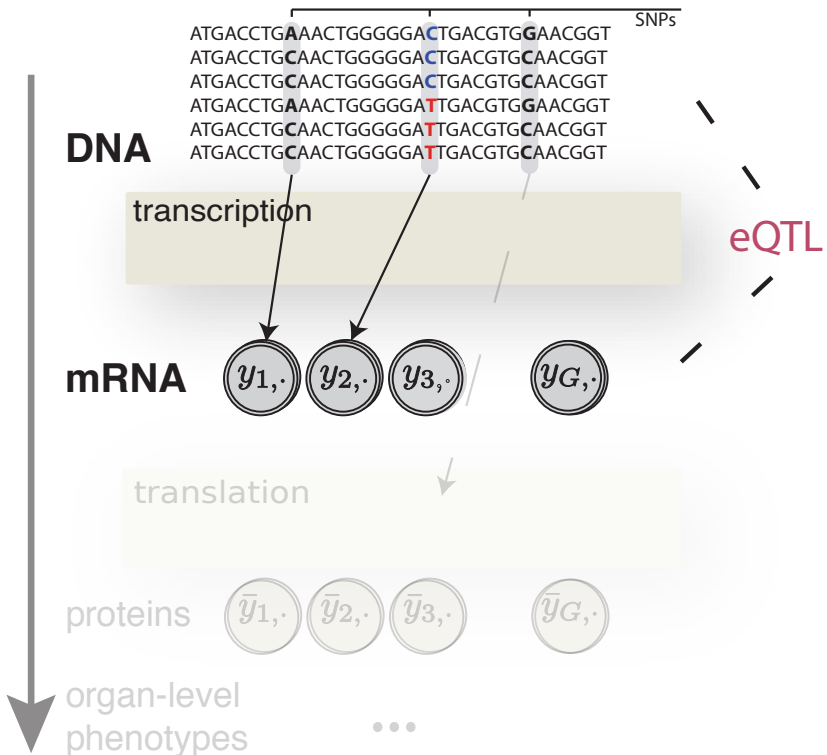


Models of molecular variation

eQTL

Statistical challenges:

- Large-scale ($N << p$ regime)
- Millions of tests
- Limited power



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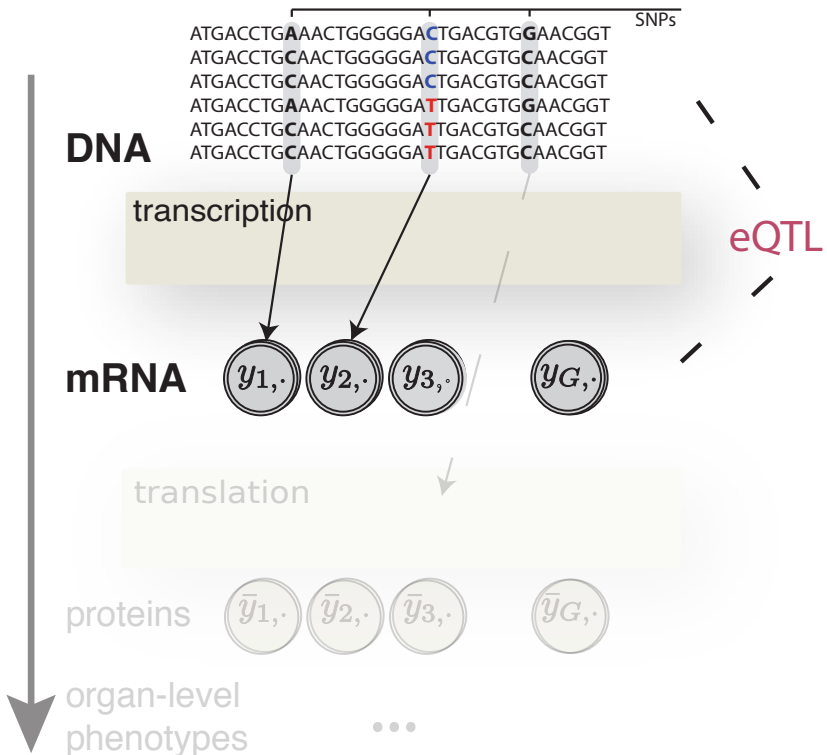

Models of molecular variation

eQTL

Statistical challenges:

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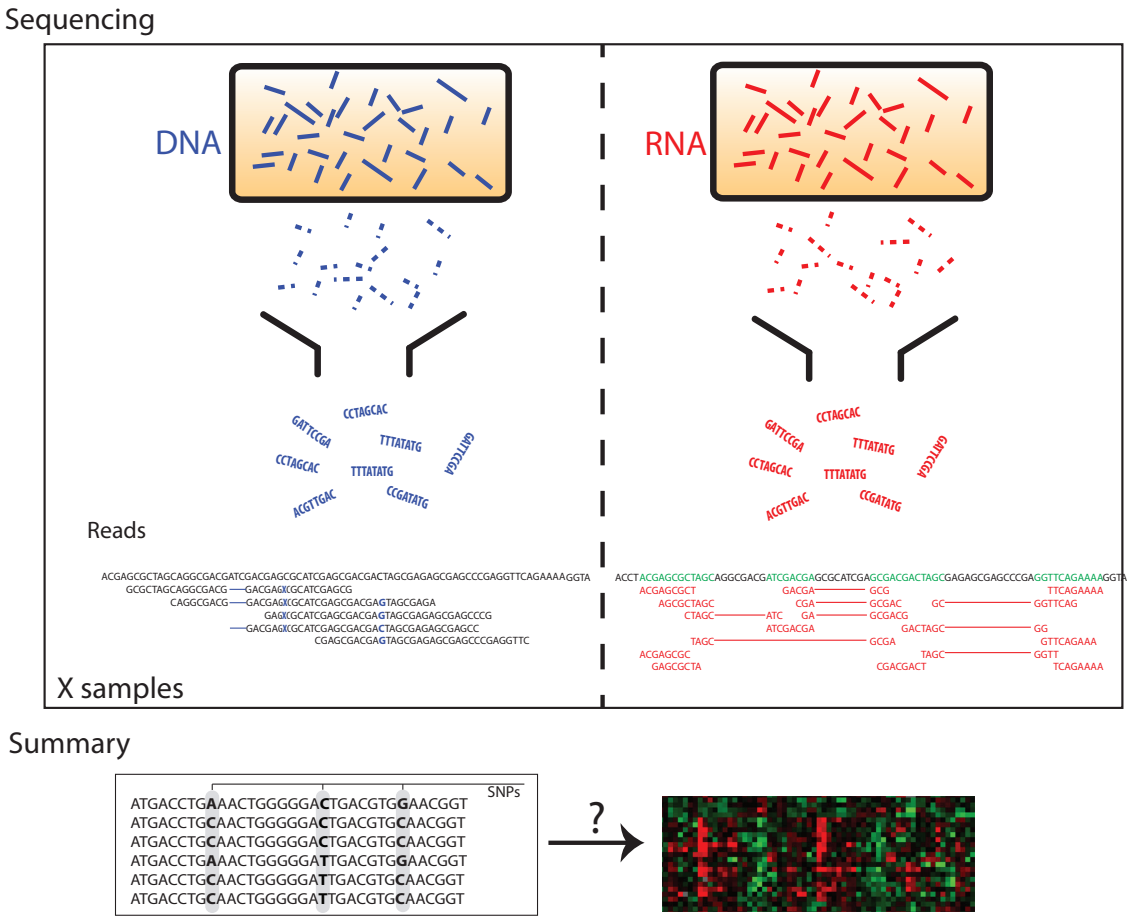
Bioinformatics challenges:

- Phenotyping
- Using NGS technologies



Outline

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Models of molecular variation

Univariate phenotypes, examples

- Single-marker mapping using linear models:

$$\mathbf{y}_g = \underbrace{\mathbf{x}_s \beta_{s,g}}_{\text{genetic}} + \underbrace{\mathbf{u}}_{\text{background}} + \underbrace{\boldsymbol{\epsilon}_g}_{\text{noise}}$$

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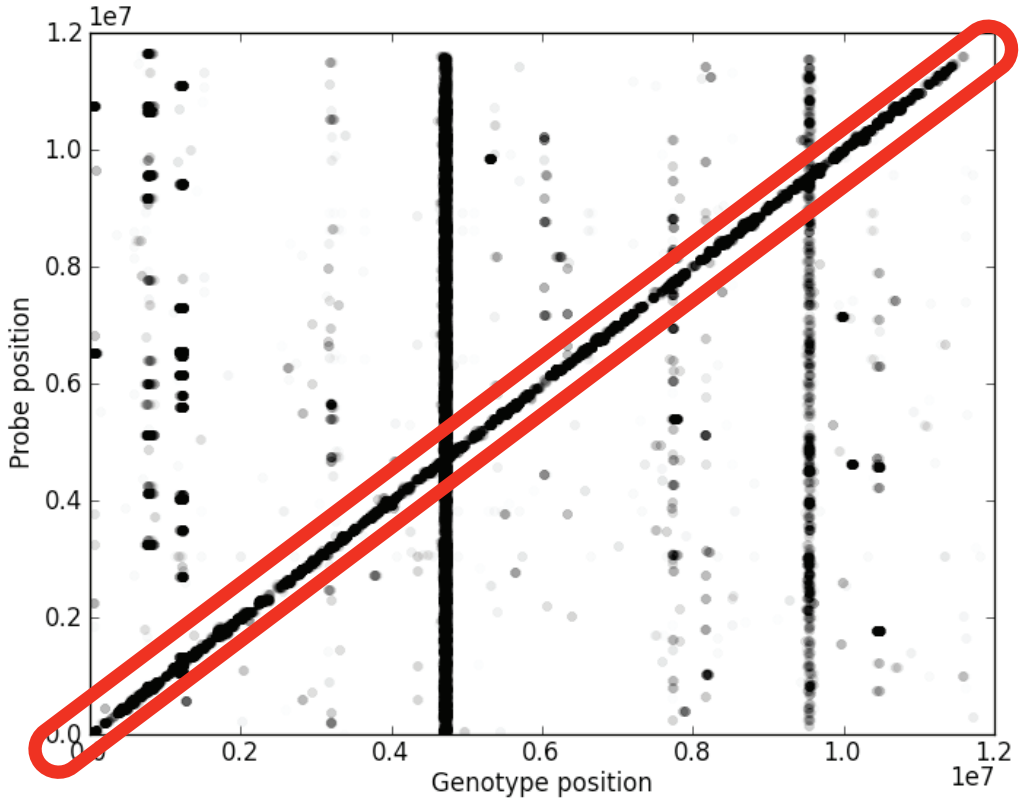
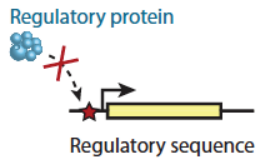


Local regulation



- promoter, RNA stability, chromatin structure
- typically *cis* mechanisms

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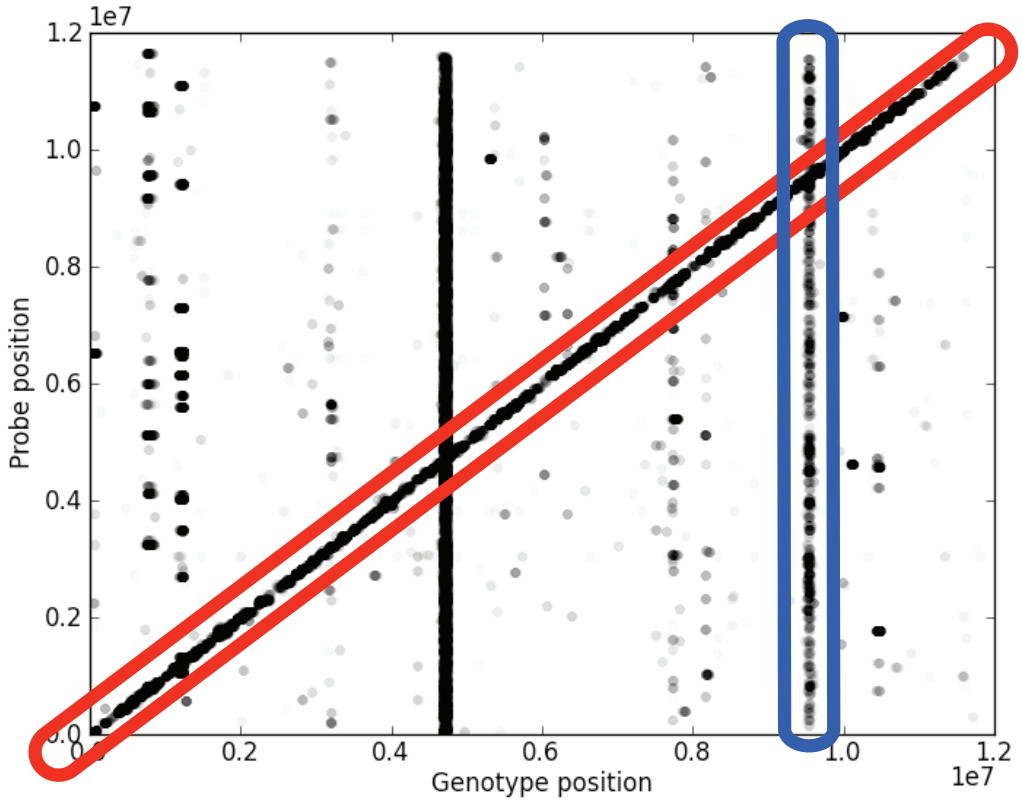

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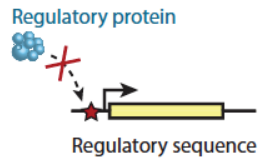

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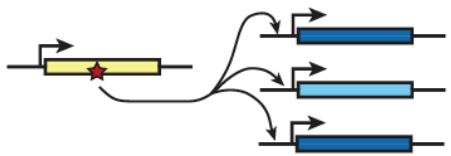
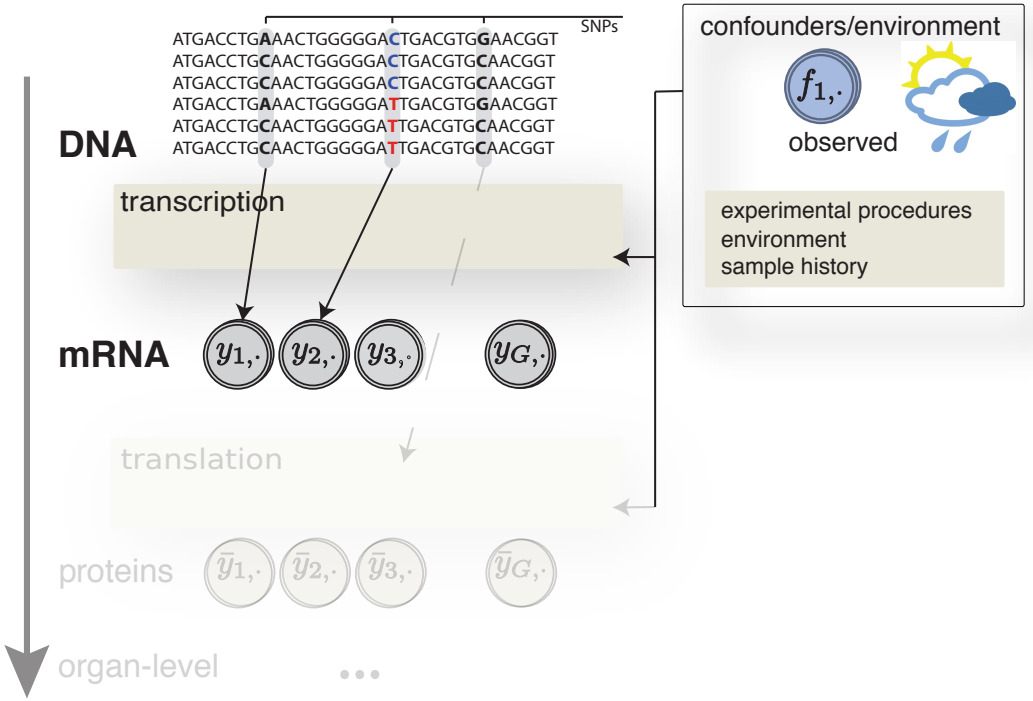
Distal regulation



- sequence of a TF,
- regulatory protein, pathway
- hotspots
- typically *trans* mechanisms

Known and unknown confounding in genomic analyses

- Standard to model *known factors*
  - Population background
  - Gender
- It is key to account for unknown hidden factors as well
  - Sample preparation
  - Sample history



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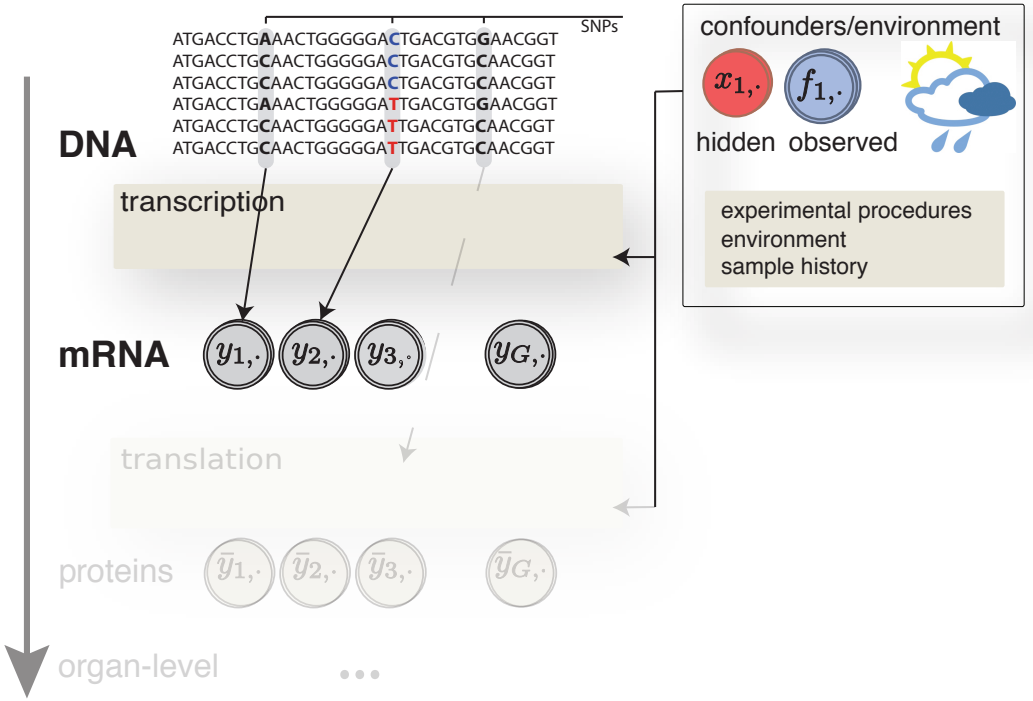
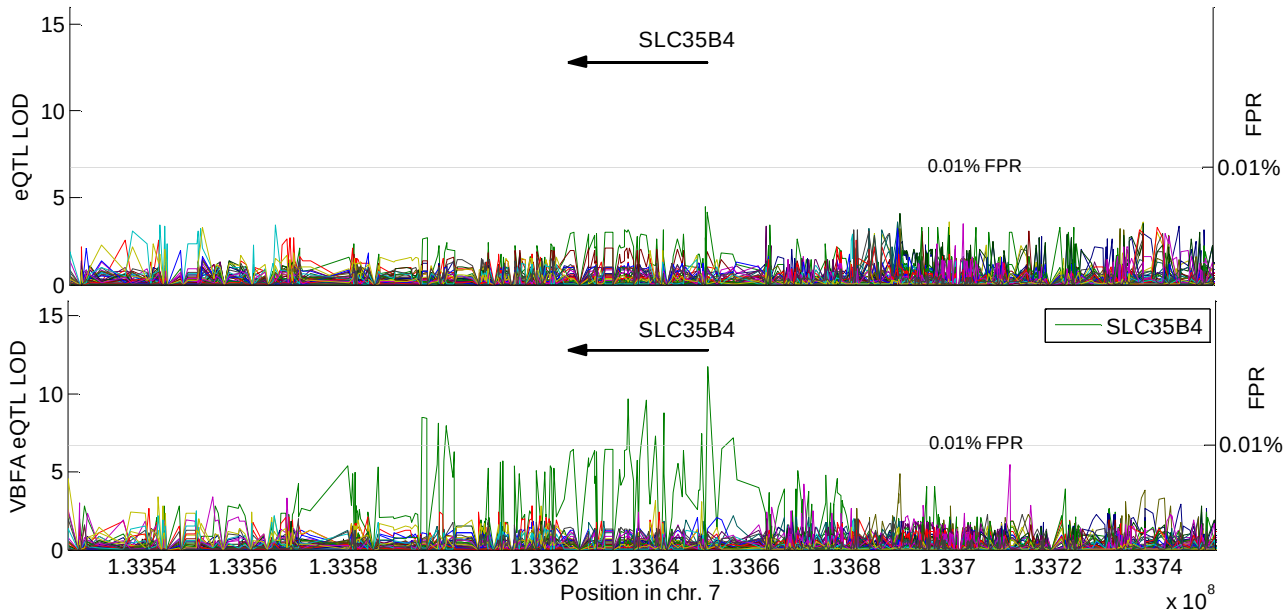


[Leek and Storey, 2007]

Example, Human

(a) Standard

(b) VBFA accounting for hidden factors



Association model

PEER: accounting for hidden factors

- Start with standard association model.
- Include (few) global hidden factors (confounders) in the model.
- Factors $\mathbf{H} = \{\mathbf{h}_1, \ldots, \mathbf{h}_K\}$ need to be learnt from the expression data.
- Controlling model complexity using hierarchical Bayesian modeling.

$$p(w_{g,k}, \alpha_k) = \mathcal{N}\left(w_{g,k} \middle| 0, \frac{1}{\alpha_k}\right) \Gamma(\alpha_k \,|\, a_k, b_k)$$

$$y_g^n = \overbrace{(x_s^n \beta_{s,g})}^{\text{genetic}} + \underbrace{\mathbf{f}^n \mathbf{v}_g}_{\text{known factors}} + \underbrace{\epsilon_g^n}_{\text{noise}}$$

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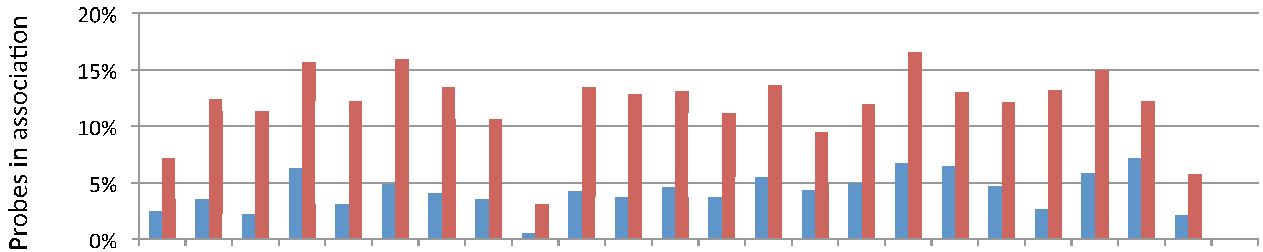
Use cases



Chr.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	X	Y
Probes	1009	644	540	384	449	571	468	338	387	380	545	520	189	330	348	426	549	154	618	266	120	238	328	15
Standard	25	23	12	24	14	28	19	12	2	16	20	24	7	18	15	21	37	10	29	7	7	17	7	0
VBQTL	72	80	61	60	55	91	63	36	12	51	70	68	21	45	33	51	91	20	75	35	18	29	19	0

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- Increased power
- Similarly on yeast, mouse, *A. thaliana*

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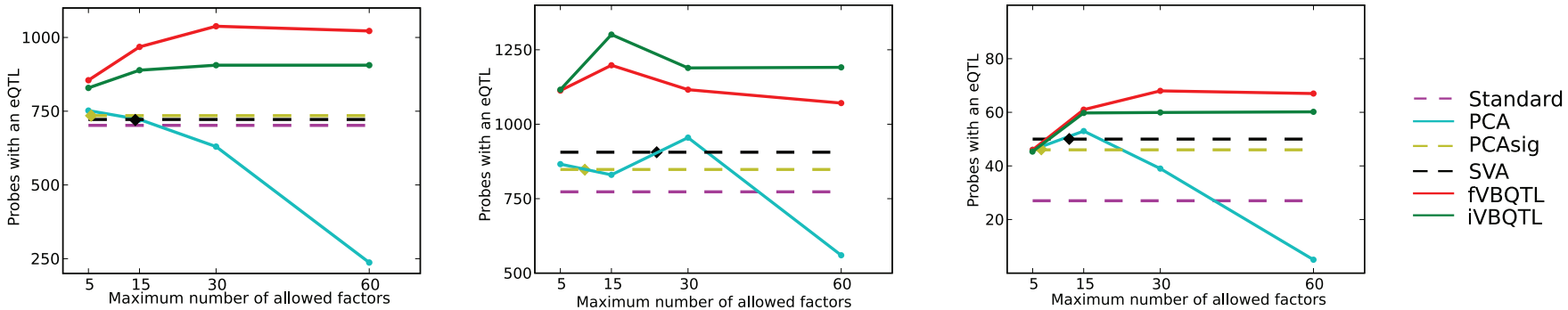

(a) Yeast *cis* eQTLs (b) Mouse *cis* eQTLs (c) Human *cis* eQTLs

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Mixed model implementation

$$\mathbf{y}_g = \underbrace{\mathbf{x}_s \beta_{s,g}}_{\text{SNP effect}} + \underbrace{\mathbf{vU}}_{\text{covariates}} + \underbrace{\mathbf{Hw}_g}_{\text{unknown confounding}} + \boldsymbol{\epsilon}_g$$

- Exploit large number of expression traits to estimate the empirical covariance structure.
- Iterative learning on the covariance structure induced by all traits.
  1. Learn confounders, explaining broad covariance within expression profiles.
  2. Test for genetic (SNP) control of learnt confounders.
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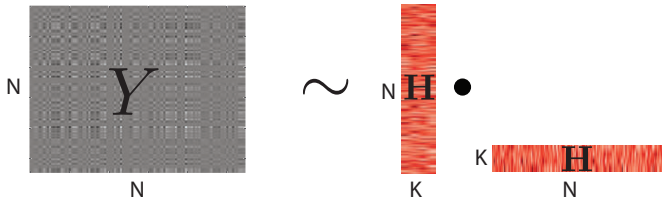

Gene expression hidden confounders

$+\psi$

noise

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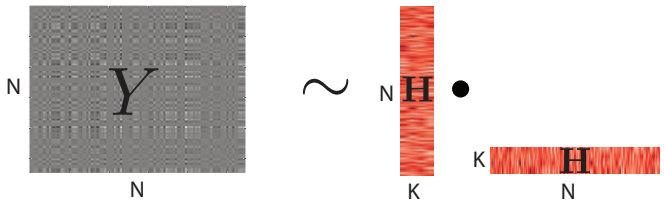

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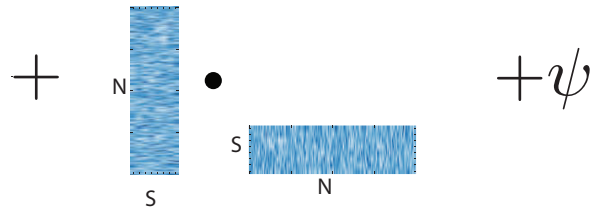

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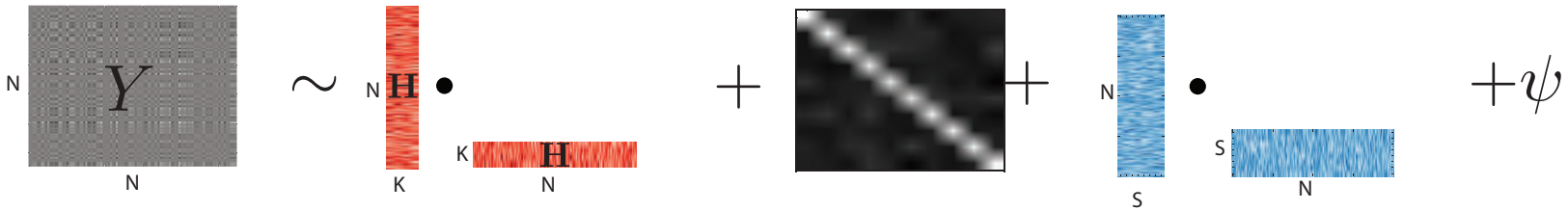

Gene expression hidden confounders population structure master regulators noise

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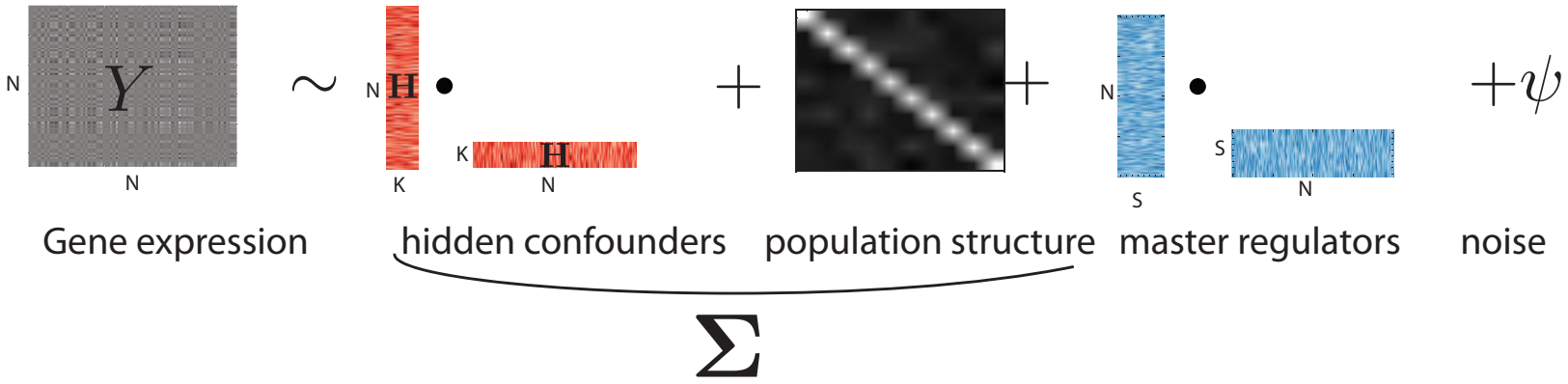

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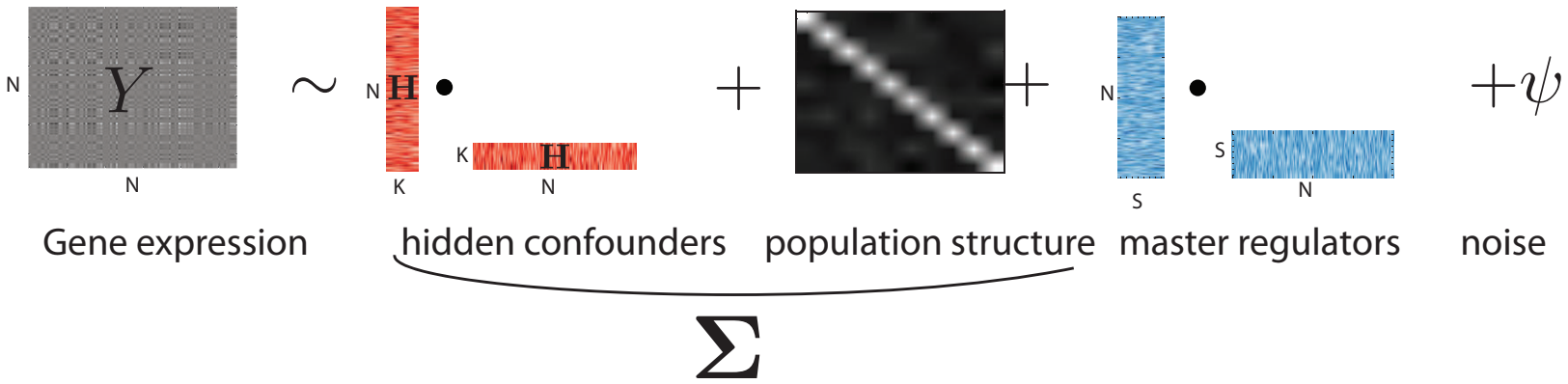
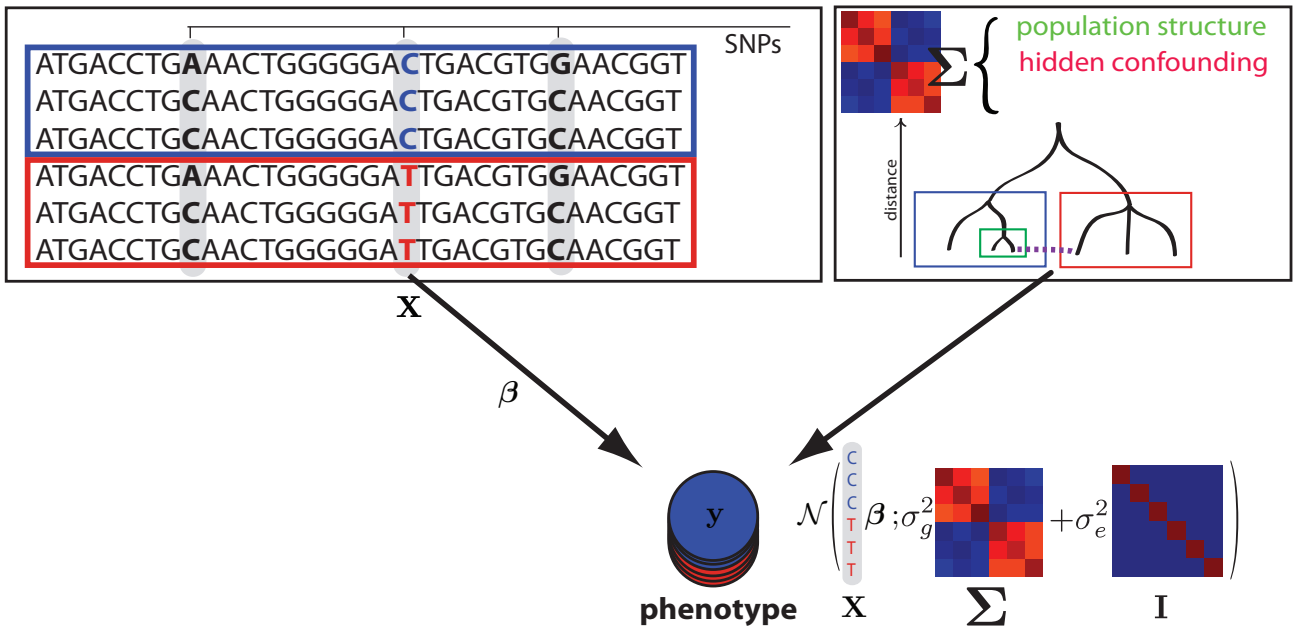


- Formally, the expression levels are independent given genotype, hidden factors and population structure.

$$P(\mathbf{Y} \mid \mathbf{X}, \mathbf{H},) = \prod_{g=1}^{G} \mathcal{N}\left(\mathbf{y}_{:,g} \,\middle|\, \mathbf{0}, \sigma_g^2 \sum_{s=1}^{S} \mathbf{x}_s \mathbf{x}_s^{\mathrm{T}} + \sigma_h^2 \sum_{k=1}^{K} \mathbf{h}_k \mathbf{h}_k^{\mathrm{T}} + \mathbf{K}_{\mathsf{pop}} + \sigma_e^2 \mathbf{I} \right)$$

Mixed model implementation

Testing strategies



- Mixed model likelihood ratio

$$\mathrm{LOD}_{g,s} = \log \frac{\mathcal{N}\left(\mathbf{y}_g \,\middle|\, \mathbf{x}_s\beta_{s,g}, \sigma_g^2\boldsymbol{\Sigma} + \sigma_e^2\mathbf{I}\right)}{\mathcal{N}\left(\mathbf{y}_g \,\middle|\, \mathbf{0} \quad , \sigma_g^2\boldsymbol{\Sigma} + \sigma_e^2\mathbf{I}\right)}$$

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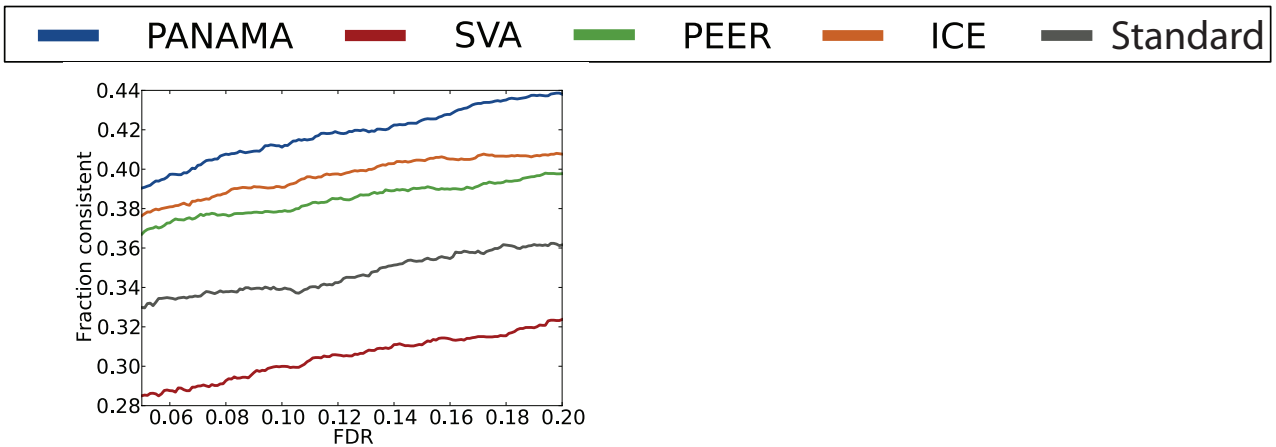
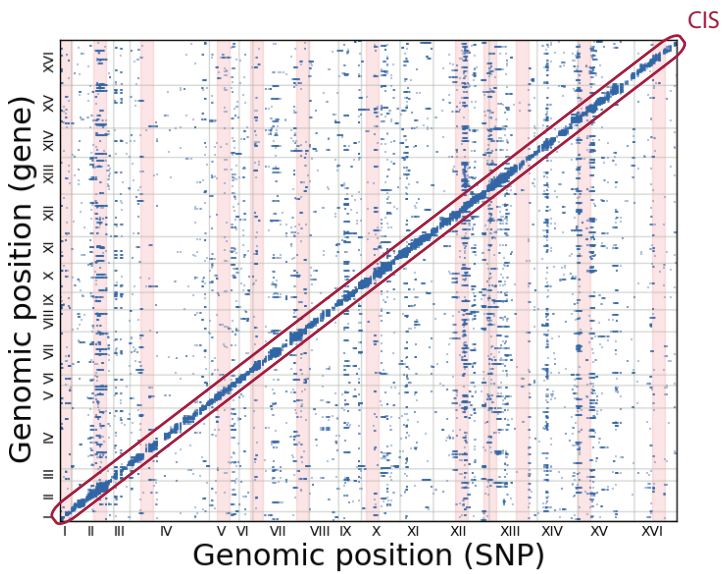


(d) Cis calling consistency

[Fusi et al., 2012]

- Increased power
- Improved consistency between studies
- Better calibrated test statistics



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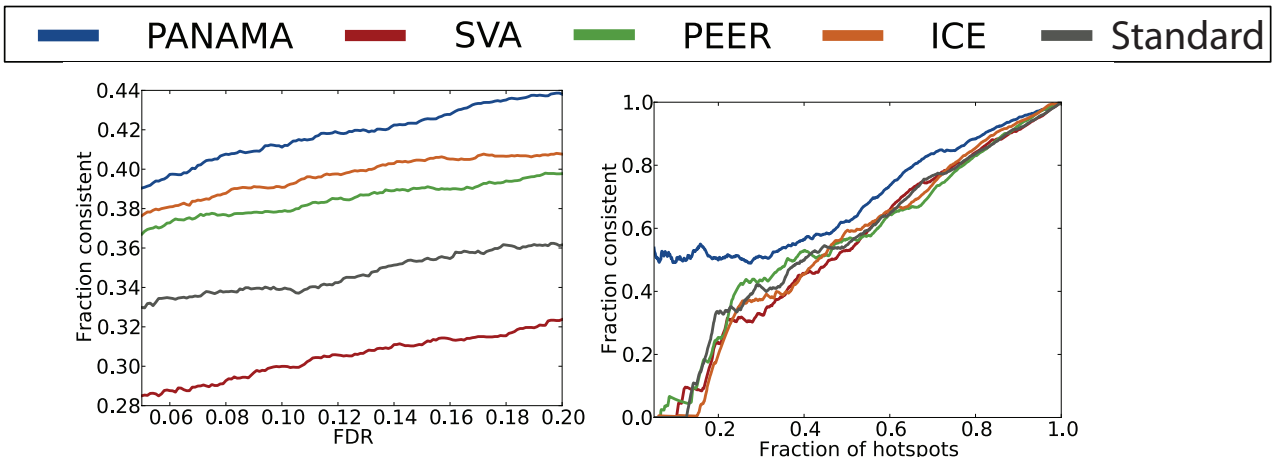

(d) Cis calling consistency (e) Trans calling consistency

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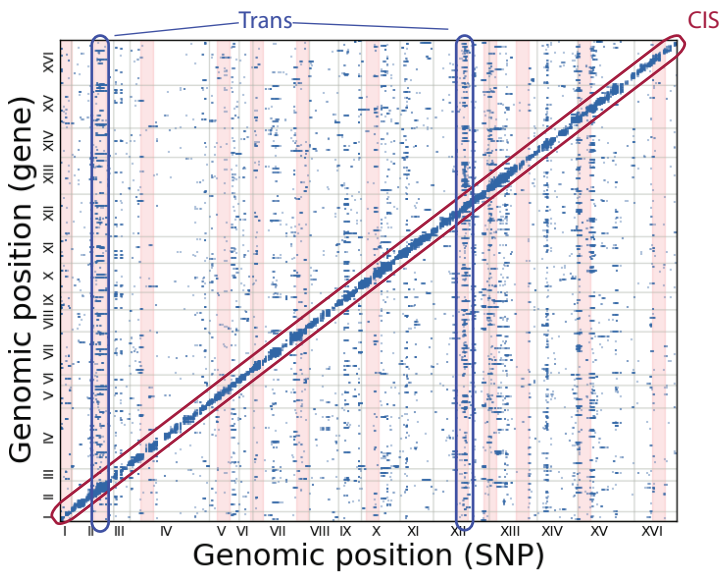

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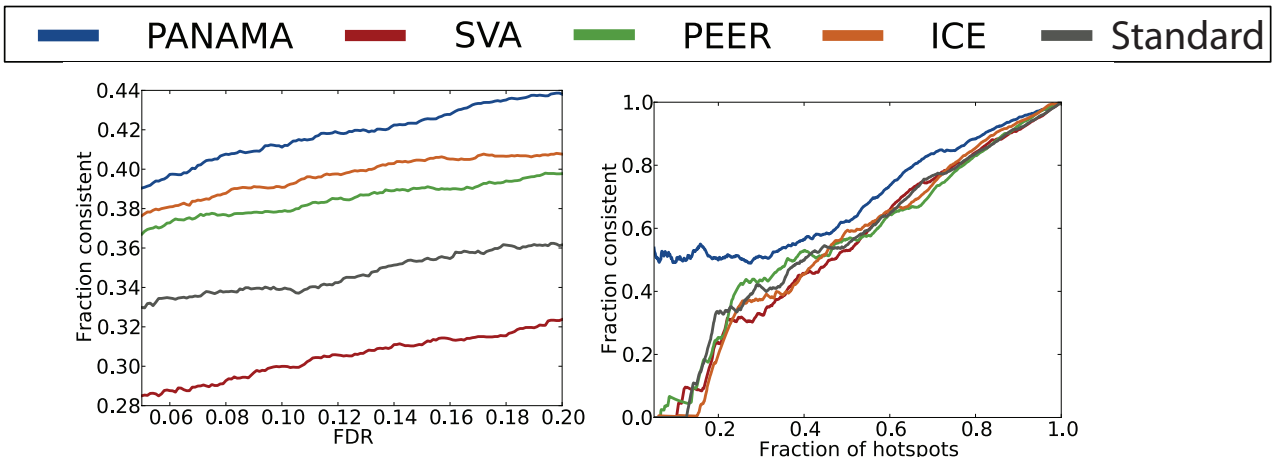

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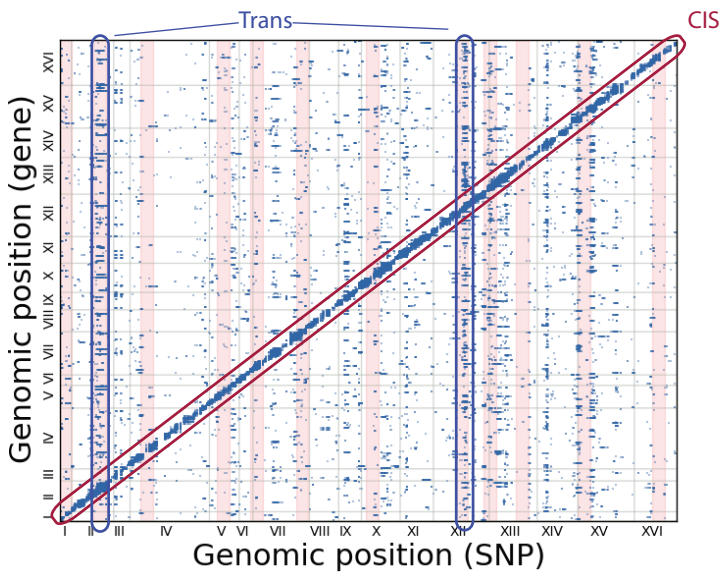

Summary

- Accounting for hidden factors can greatly increase the power and meaningfulness of analysis results.
- Open source **PEER** software package (Python, R, C++) [Stegle et al., 2012]

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- 1000 Genomes project

  A map of human genome variation from population-scale sequencing Nature (Nature, 1000 genomes consortium 2010)
- HapMap III expression analysis

  Patterns of Cis Regulatory Variation in Diverse Human Populations, PLoS Genet 2012
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Regulatory and external factors

- Confounding factors

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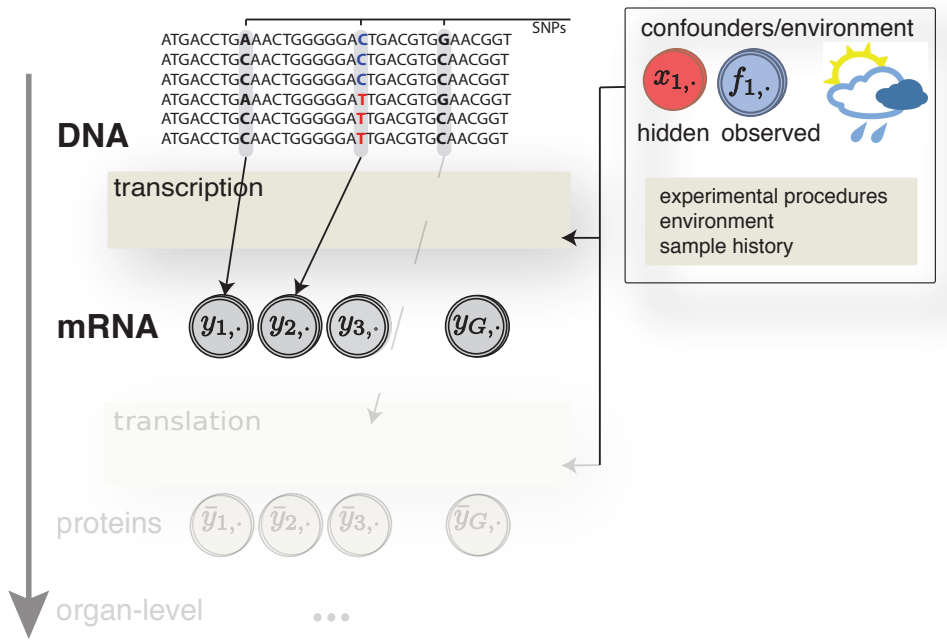
- Account for regulatory factors in transcription?

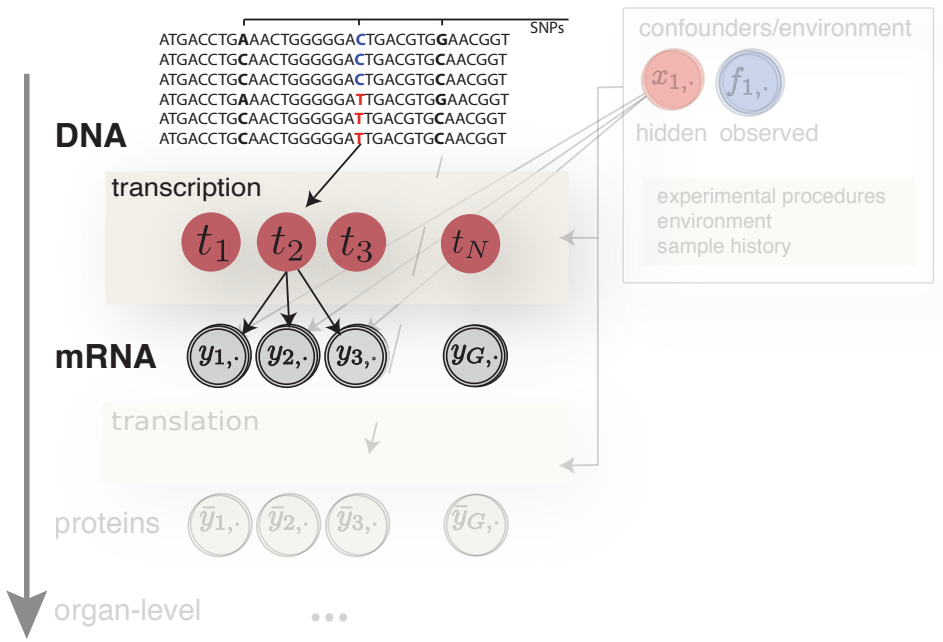


Regulatory and external factors

- Confounding factors

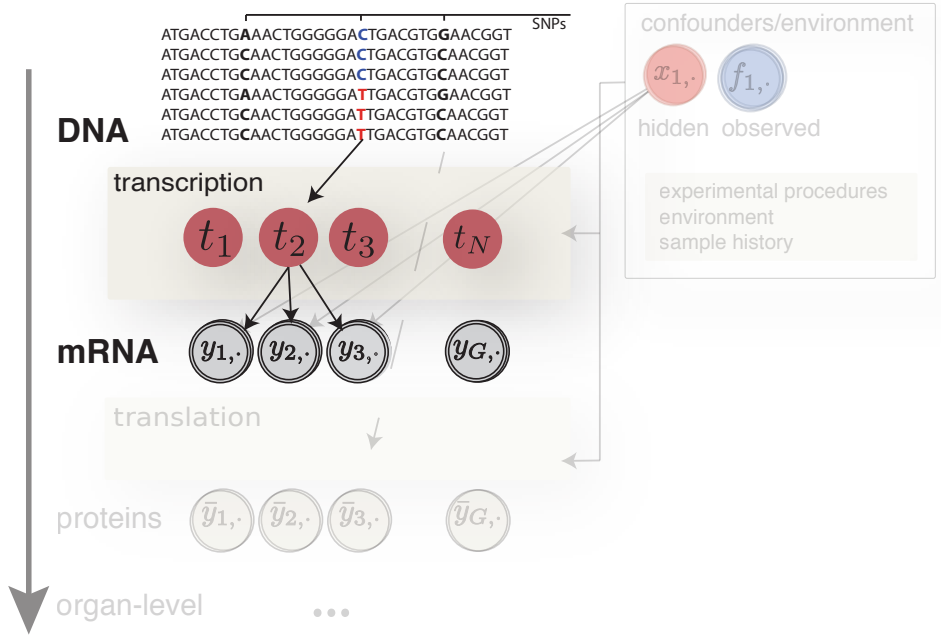
$$y_g^n = \overbrace{b_{n,g}\left(\mathbf{x}_s^n \theta_{n,g}\right)}^{\text{genetic}} + \underbrace{\mathbf{f}^n \mathbf{v}_g}_{\text{known factors}} + \underbrace{\mathbf{h}^n \mathbf{w}_g}_{\text{hidden factors}} + \underbrace{\epsilon_g^n}_{\text{noise}} .$$

- Account for regulatory factors in transcription?



Regulatory factors

- Regulatory factors:
  - Transcription factors
  - Pathway components
- Mechanistic hypothesis: regulatory factors mediate the association signals to target genes.
- Measuring $\mathbf{T}$?
  - Difficult and expensive
- Learn the unobserved factors $\mathbf{T}$



[Parts et al., 2011, Lee and Bussemaker, 2010]

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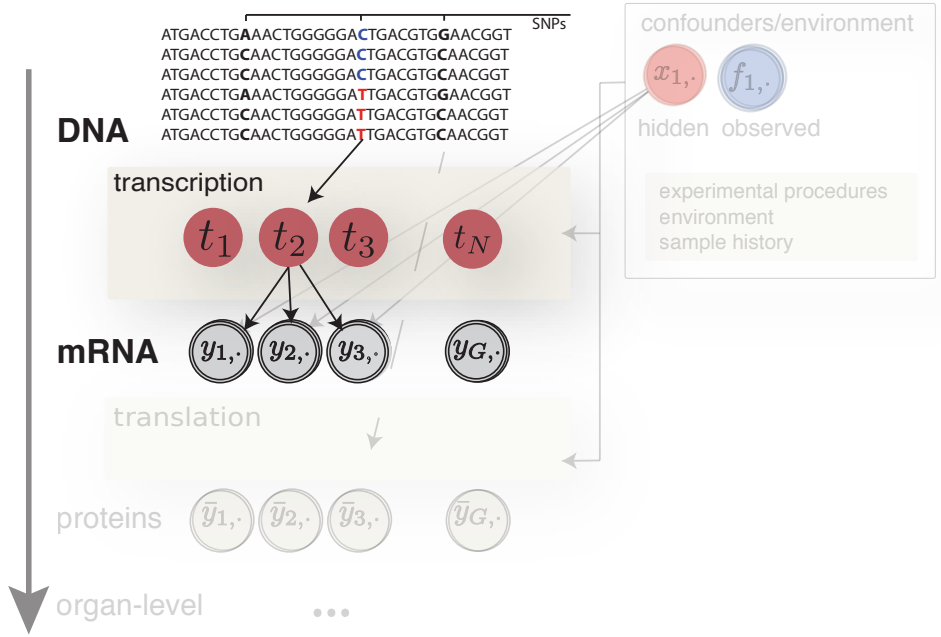

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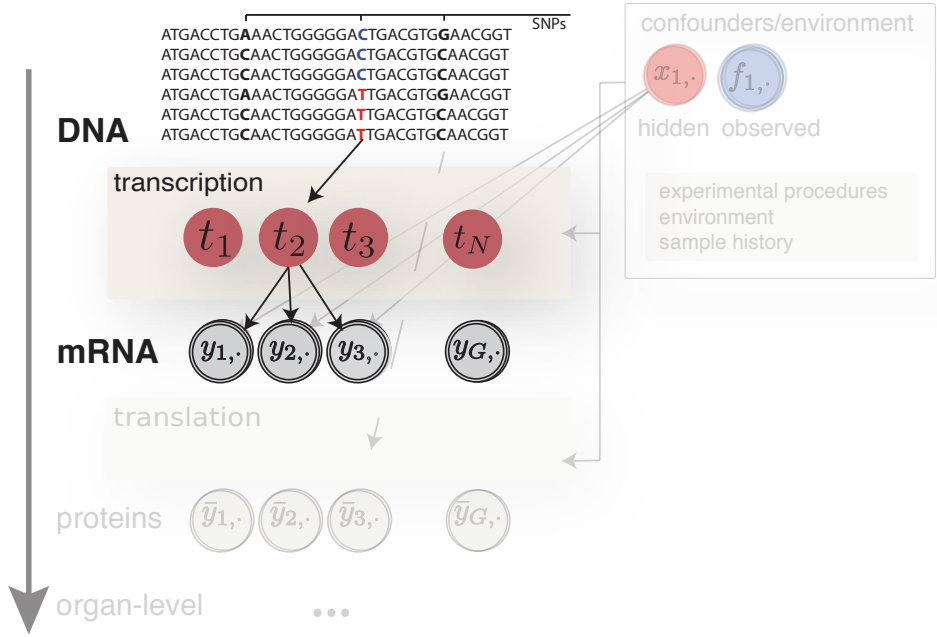

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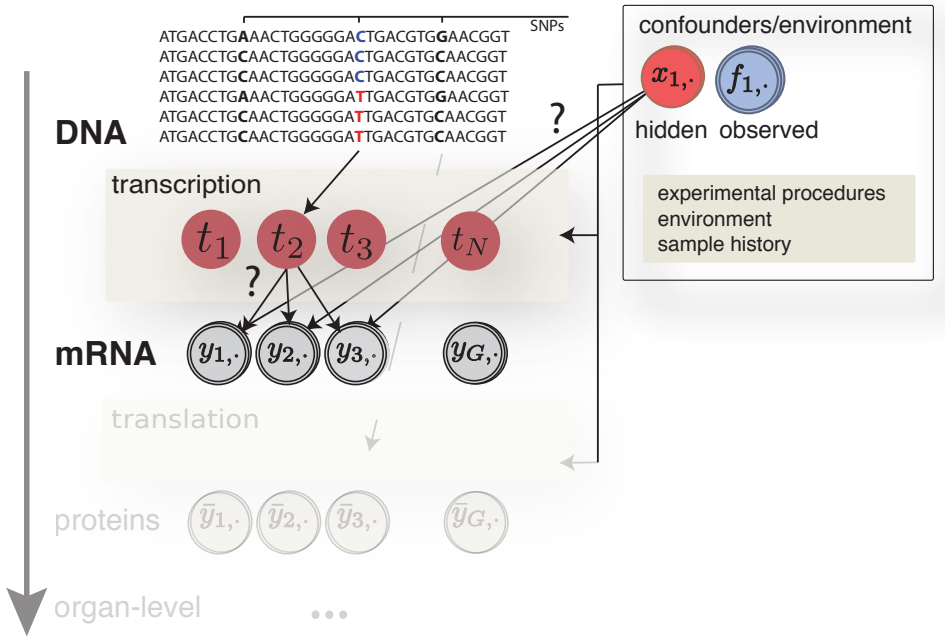
Regulatory factors

A linear model of gene regulation

- Inference of regulatory factors:

$$\underbrace{\mathbf{Y}_{J\cdot G}}_{\text{Expr.}} = \underbrace{\mathbf{T}_{J\cdot K}}_{\text{Factors}} \cdot \underbrace{\mathbf{W}_{K\cdot G}}_{\text{Weights}} + \underbrace{\mathbf{\Psi}_{J\cdot G}}_{\text{Noise}} \cdot$$

  - $\mathbf{W}$ is sparse; each factor regulates a specific subset of all genes.
- Incorporation of prior knowledge to render factors interpretable:
  - Transcription factor binding.



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Sparse factor analysis

Probabilistic model

- Graphical model $\mathbf{Y} = \mathbf{T} \cdot \mathbf{W} + \mathbf{\Psi}$.
- Indicators $z_{g,k}$ determine the sparsity pattern:

$$P(w_{g,k} \mid z_{g,k} = 0) = \mathcal{N}\left(w_{g,k} \mid 0, \sigma_0^2\right)$$
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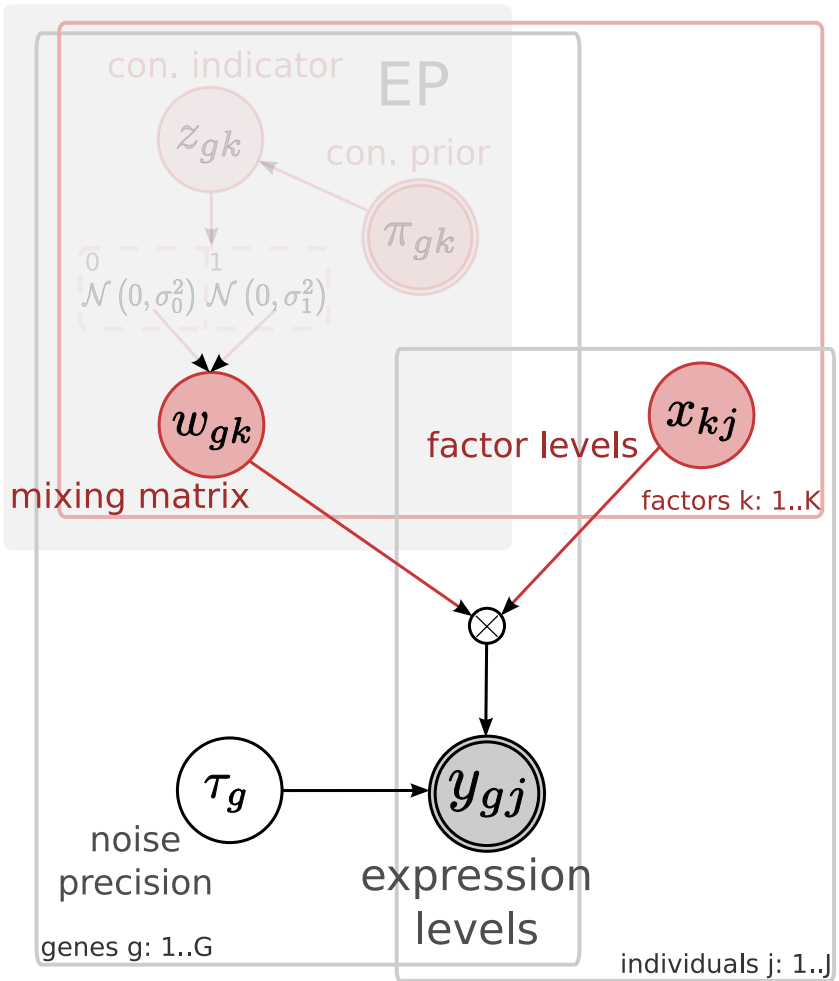

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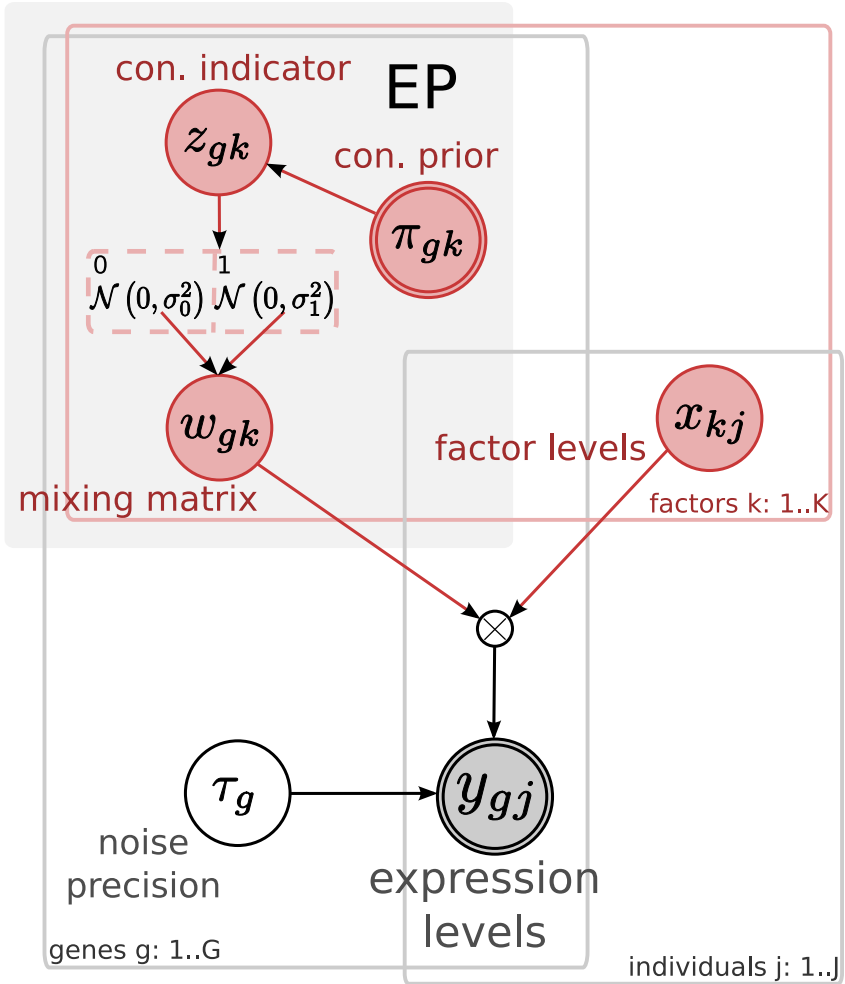

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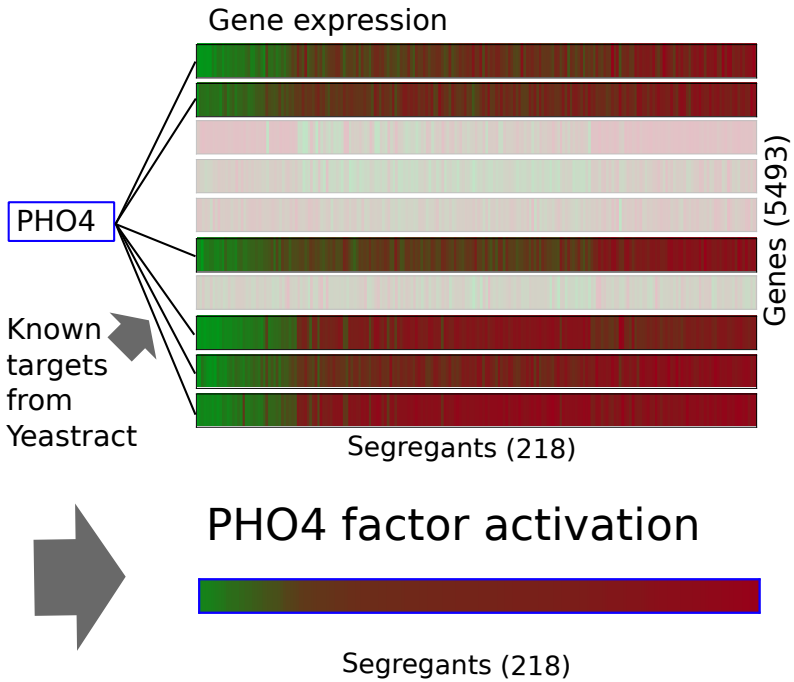
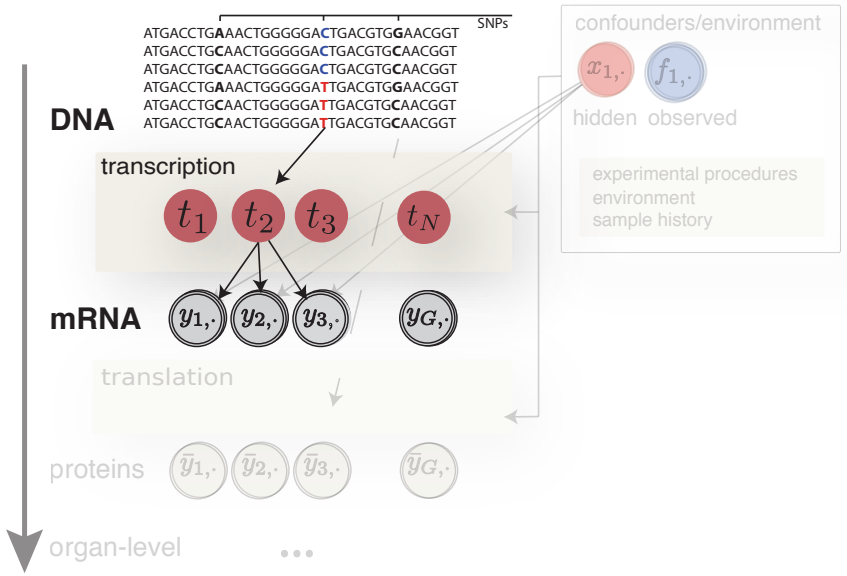


Application to yeast

Factor associations

- Application to 108 yeast strains.
  - Genotyped and expression profiled in 2 conditions.
  - Prior knowledge: TF binding affinities.
- Biological hypotheses
  1. Genetic variation (SNPs) may regulate factor activations.
  2. Genotype-specific regulation of target genes.



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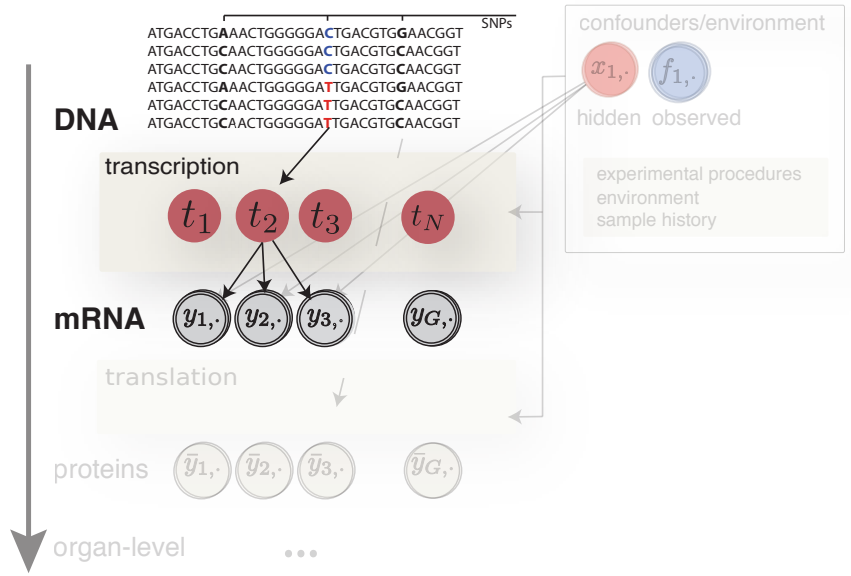

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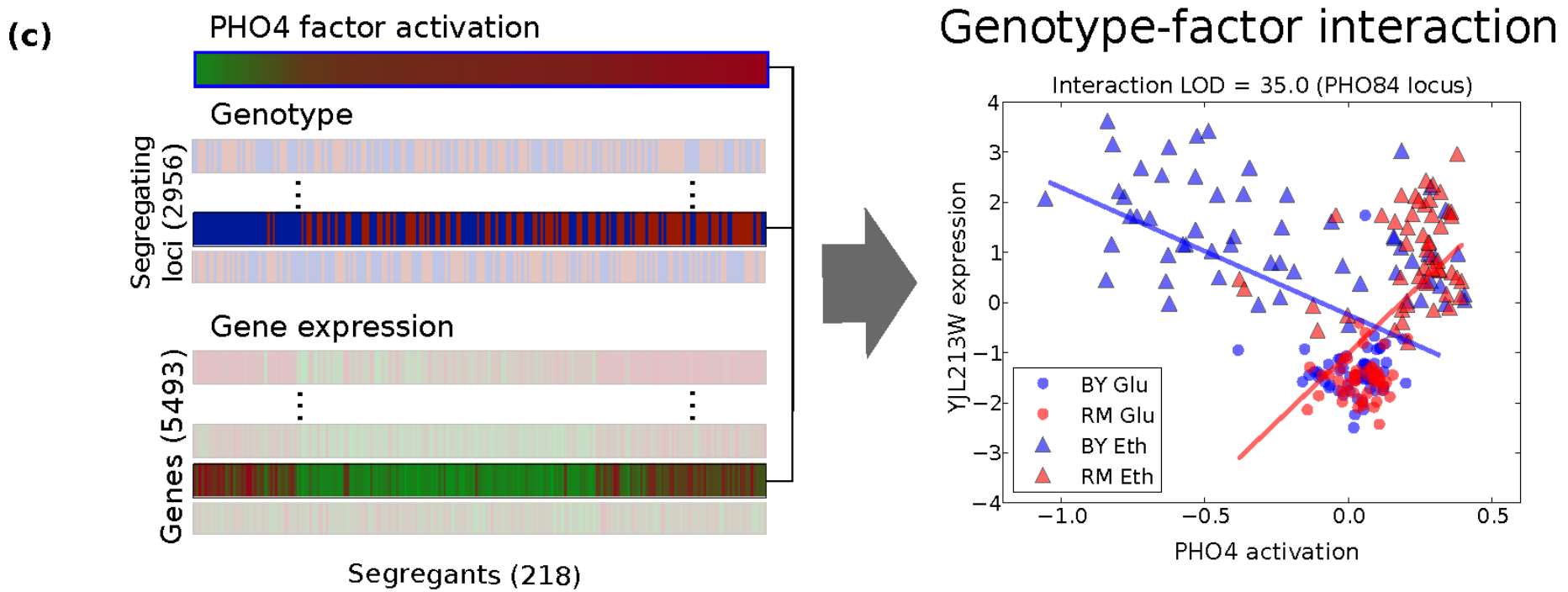
Application to yeast

Factor interactions

- Example of genotype-specific factor regulation.

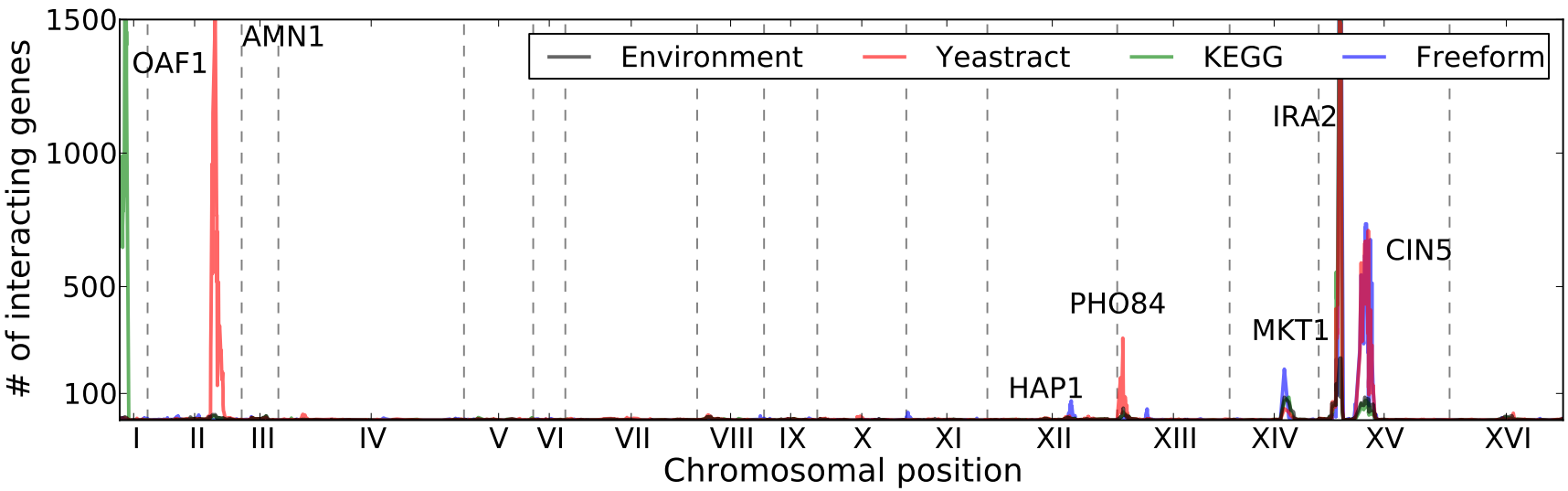


[Parts et al., 2011]

Application to yeast

Factor interactions

- Genome-wide interaction density.



[Parts et al., 2011]

Summary

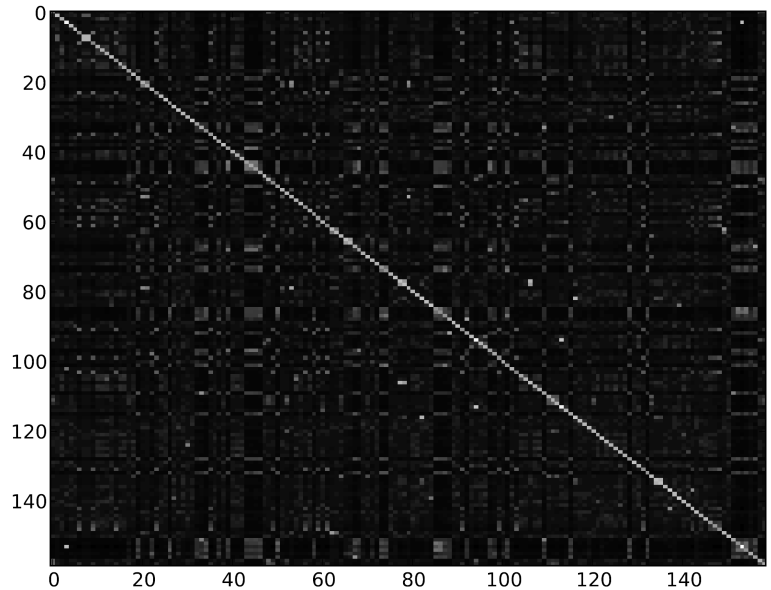
- Accounting for hidden factors can greatly increase the power and meaningfulness of analysis results.
- Joint genetic analysis of cellular features and gene expression for improved interpretability.
- Open source **PEER** software package (Python, R, C++)
  `http://github.com/PMBio/peer`

[Stegle et al., 2012]

Outline

Swedish lines

- 160 Lines, extensive population structure
- Genome sequencing
- Transcriptome sequencing
- Bisulfite sequencing
- Two environments; 10C and 16C



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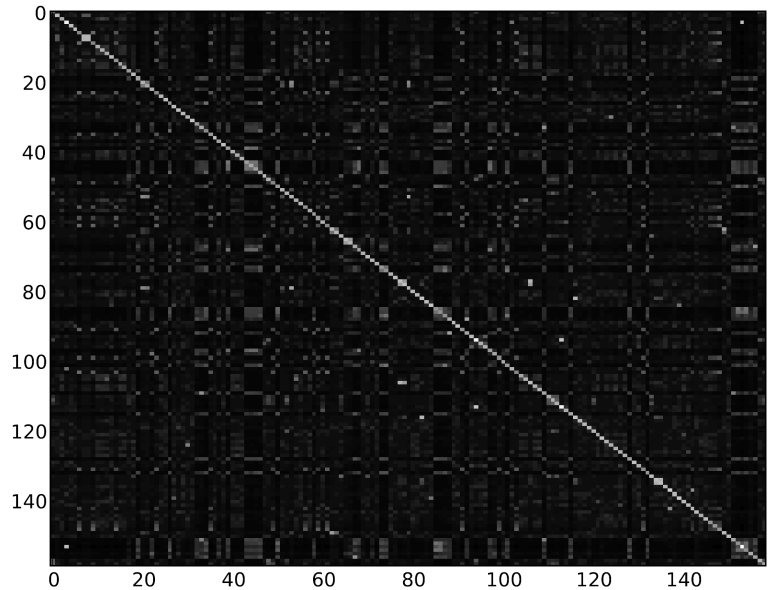

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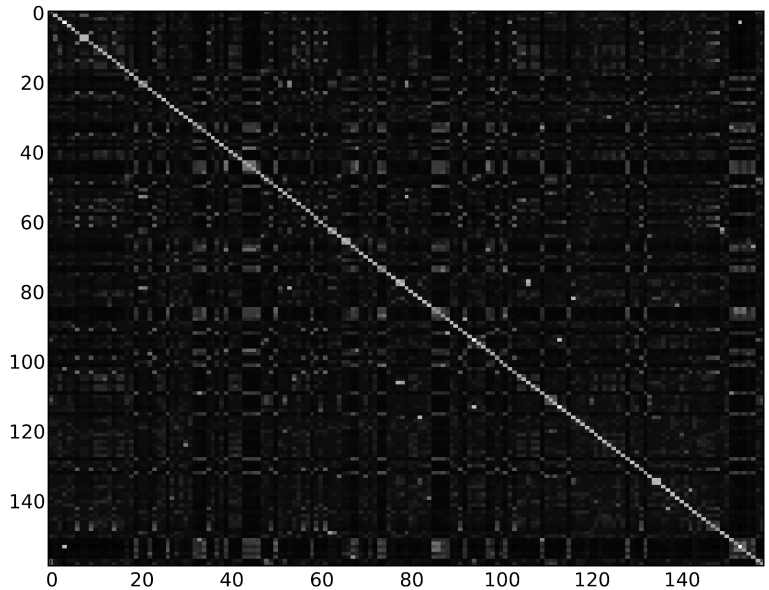

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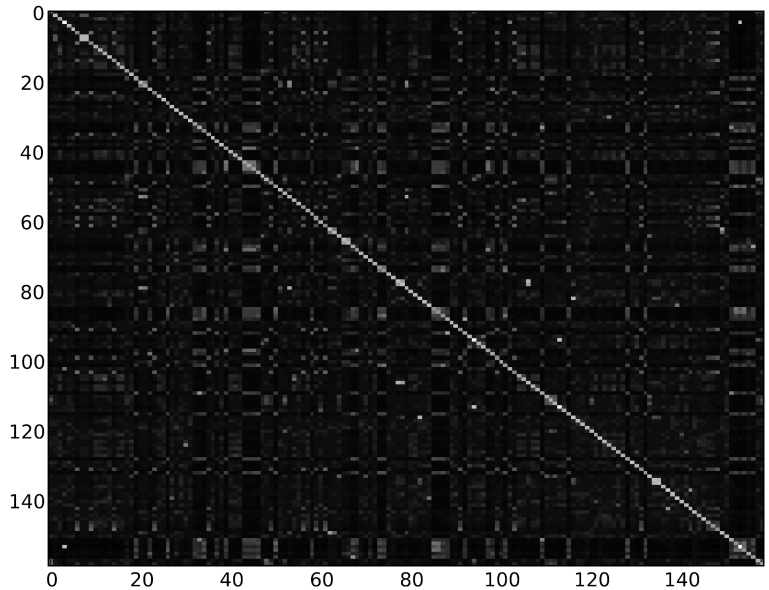

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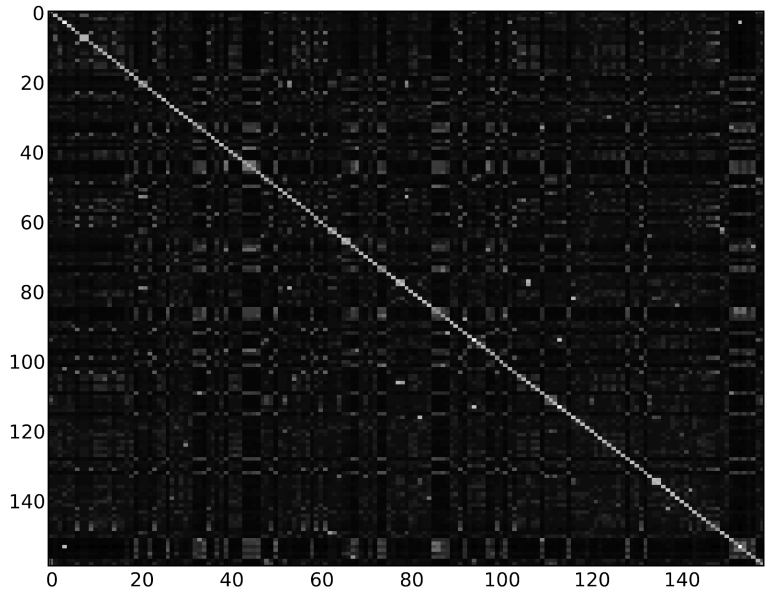

Variance component analysis

A random effect variance estimation model

- Variance dissection of expression levels of gene g in environment $e = \{0, 1\}$

$$\mathbf{y}_{g,e} = \underbrace{\mu_e}_{\text{env effect}} + \underbrace{\sum_{n=1}^{N_{\text{cis}}} b_{n,e}\mathbf{s}_n}_{\textit{cis} \text{ genetics}} + \underbrace{\sum_{l=1}^{L_{\text{trans}}} d_{l,e}\mathbf{s}_l}_{\textit{trans} \text{ genetics}} + \boldsymbol{\psi}_{g,e}.$$

- Standard multi trait correlation model
  - *cis* & *trans* genotype prior:

$$\mathbf{b}_n \sim \mathcal{N}\left(\mathbf{0}, \begin{bmatrix} \beta_0^2 & \beta_{0,1} \\ \beta_{0,1} & \beta_1^2 \end{bmatrix}\right) \quad \mathbf{d}_n \sim \mathcal{N}\left(\mathbf{0}, \begin{bmatrix} \delta_0^2 & \delta_{0,1} \\ \delta_{0,1} & \delta_1^2 \end{bmatrix}\right)$$

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Observational model needs to acknowledge count statistics

- The observed quantities are read counts $\mathbf{c}_{g,e}$ and not true expression levels
- Log-normal model on the Poisson rates
  - MCMC inference
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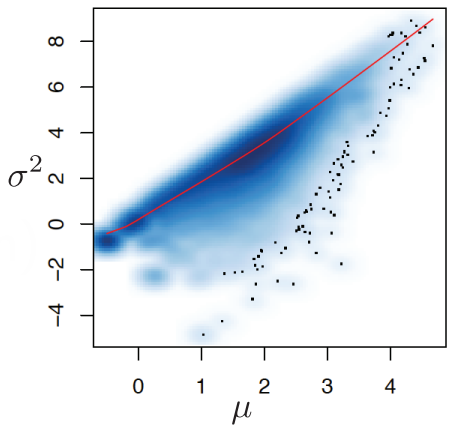
  - Variance stabilizing transform (Anscombe transform)



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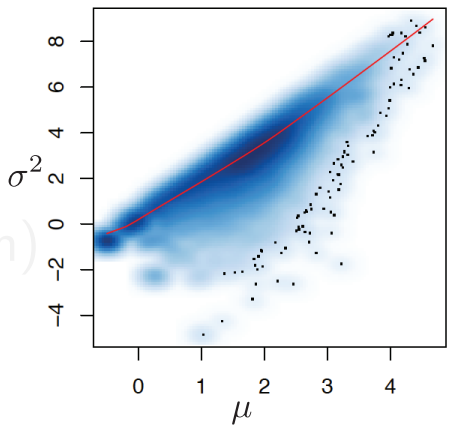

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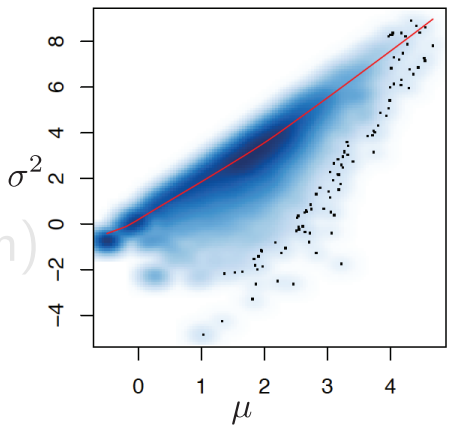

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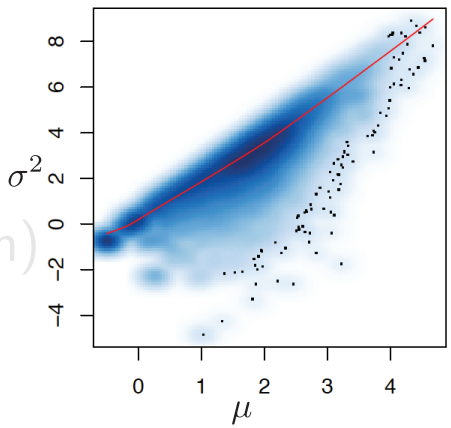

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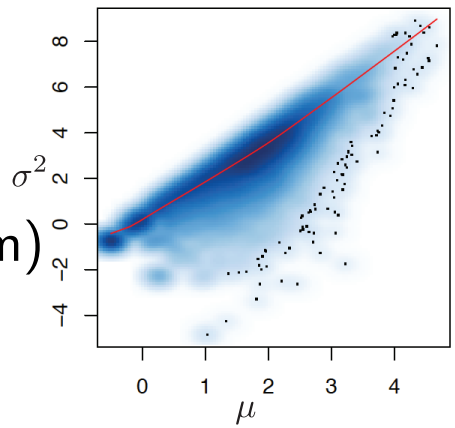

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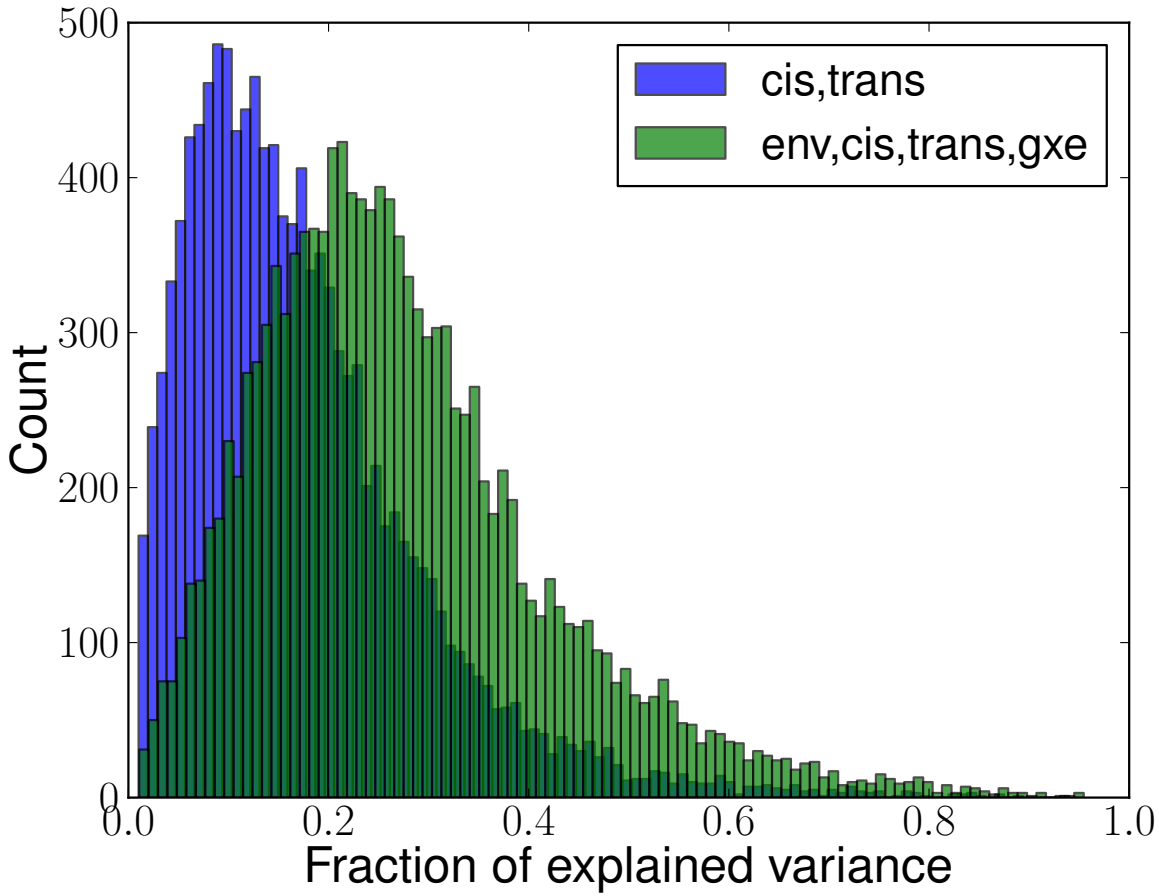
Impact of environment

- Environment greatly affects heritability
- Absolute environment contribution small



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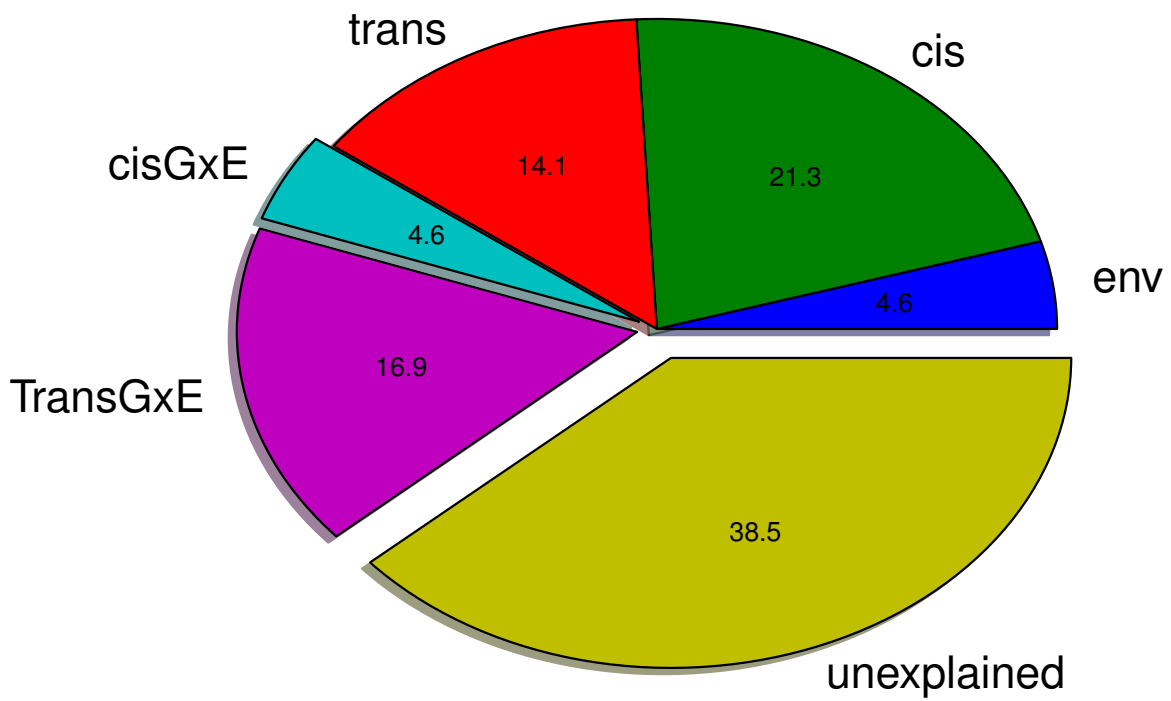
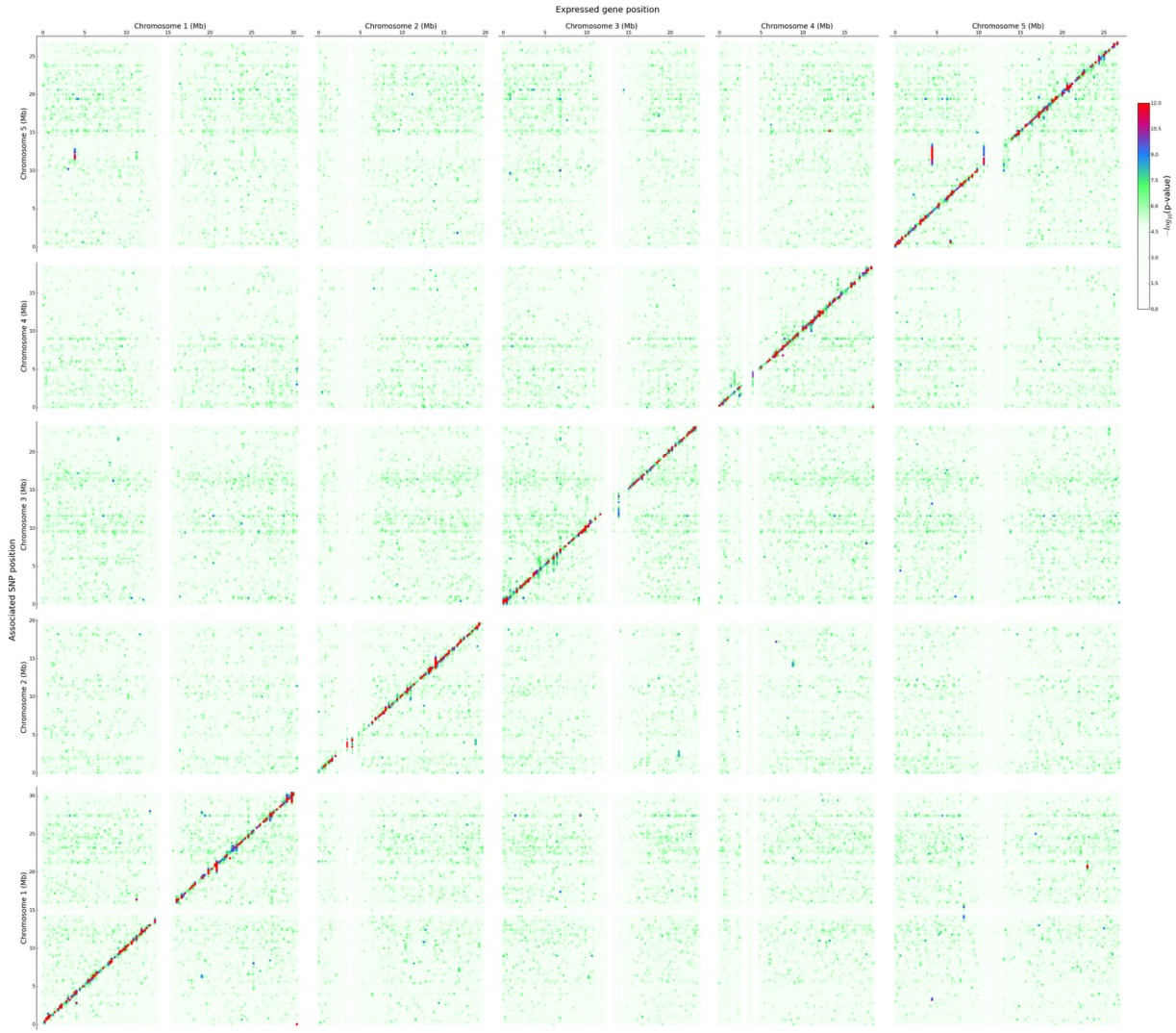


(Average across upper 50% quantile of heritable genes)

GWAS

main effects



GWAS

GxE effects

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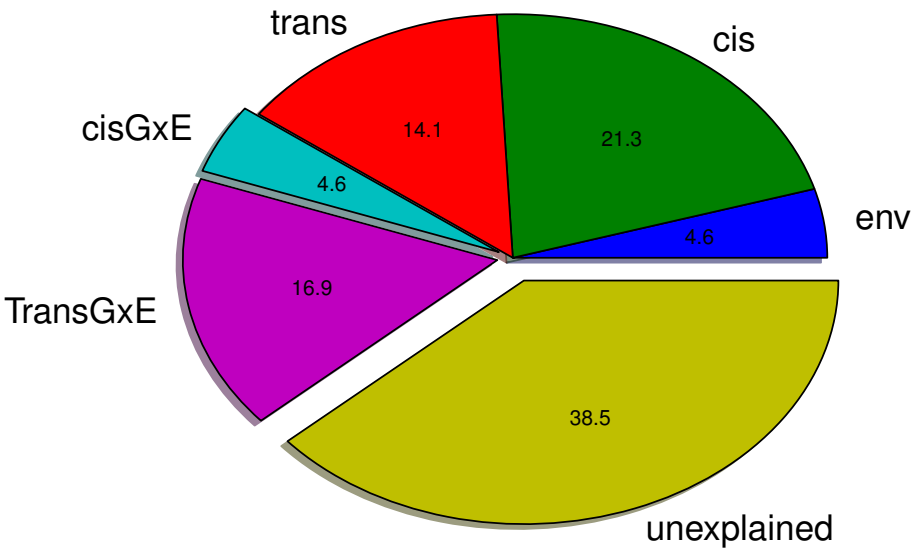

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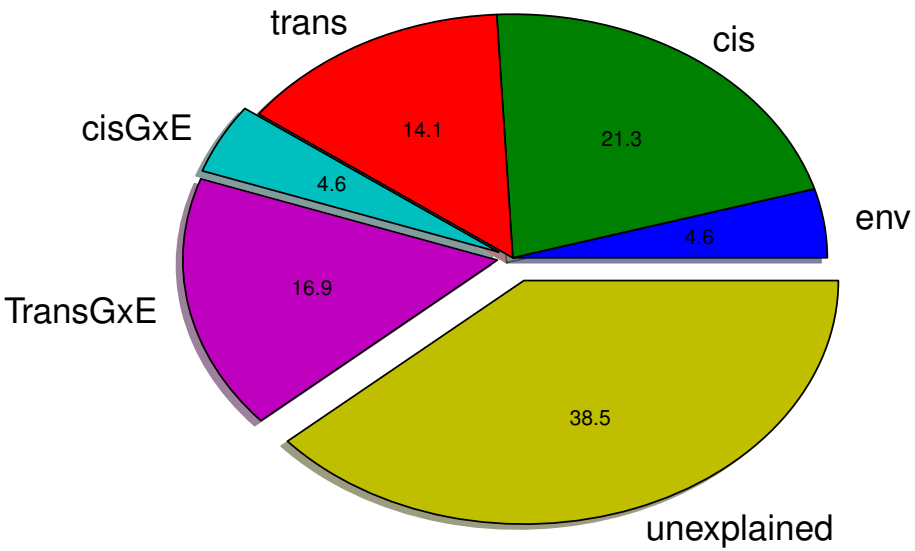

- Lack of power to detect GxE?
- GxE largely aligned with population structure?

Outline

Summary

1. eQTL mapping is sensitive to background signals
   - co-factors
   - population structure
   - "hidden confounding"
   - Leverage on high dimensionality of gene expression
2. Mechanistic models in eQTL
   - Intermediate molecular traits can be measured or learnt from data.
3. Analysis of variance is well applicable for NGS data
   - GxE explains substantial variance, however is difficult to map

Summary

1. eQTL mapping is sensitive to background signals
   - co-factors
   - population structure
   - "hidden confounding"
   - Leverage on high dimensionality of gene expression
2. Mechanistic models in eQTL
   - Intermediate molecular traits can be measured or learnt from data.
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   - GxE explains substantial variance, however is difficult to map

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Acknowledgements

- **Accounting for background variation in eQTL studies**
  L. Parts, J. Winn, Nicolo Fusi, N. Lawrence, Richard Durbin
- **Mechanistic models: Genetic analyses of cellular features**
  L. Parts, J. Winn, R. Durbin
- **The role of GxE in the A. thaliana transcriptional landscape**
  E. J. Osborne, M. Remigereau, P. Zhang,, Oliver Stegle, Philipp Drewe, Quan Long, Ümit Seren, Andre Kahles, Qiang Song, Arthur Korte, Andrew D. Smith, Gunnar Rätsch, Richard M Clark,Magnus Nordborg, Bjarni Vilhjalmsson

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