Probabilistic Modelling of Expression Variation in Modern eQTL Studies

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MAX-PLANCK-GESELLSCHAFT

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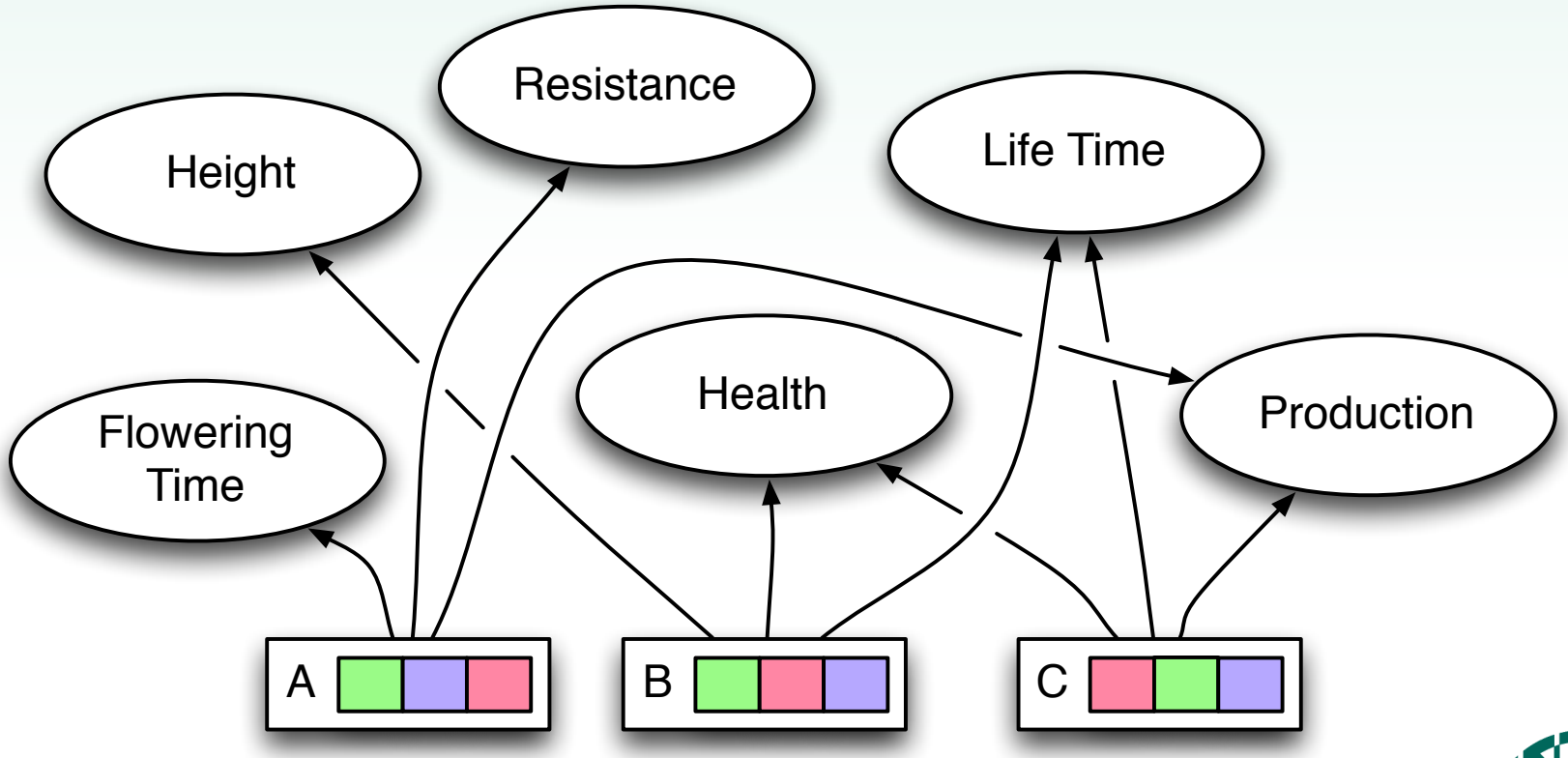
Why Genome-wide Association Studies?



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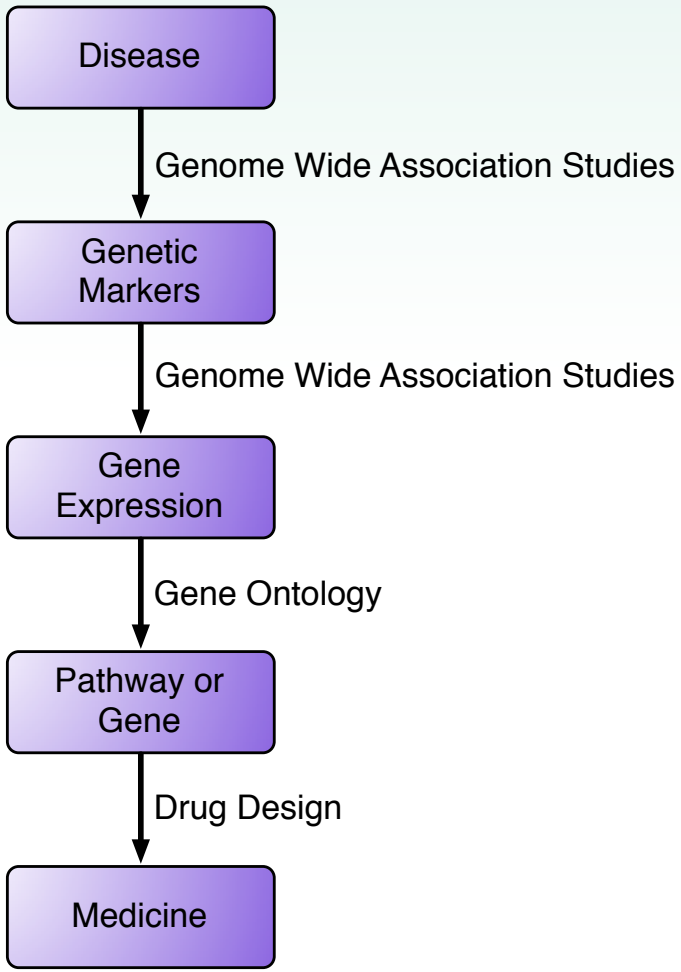
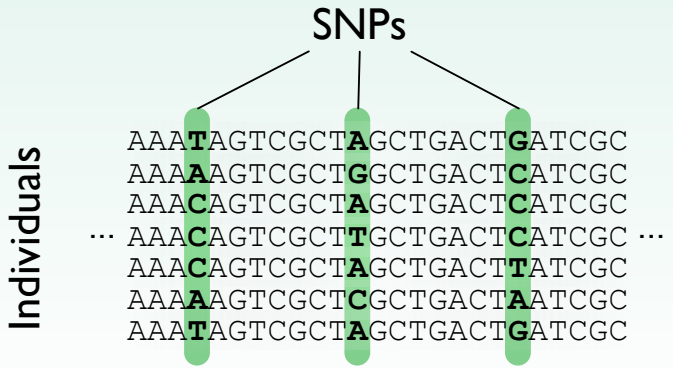


Outline

Outline

Genome-wide Association Studies



Find Function f, which maps

- Genotype Variants **S**
- Gene Expression **Y**

$\Rightarrow$ $\mathbf{Y} = f(\mathbf{S})$.

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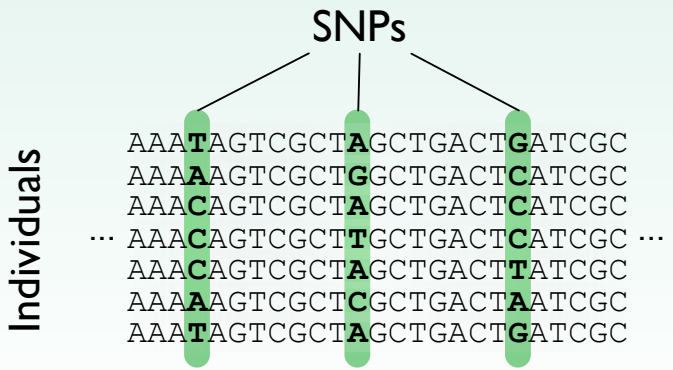

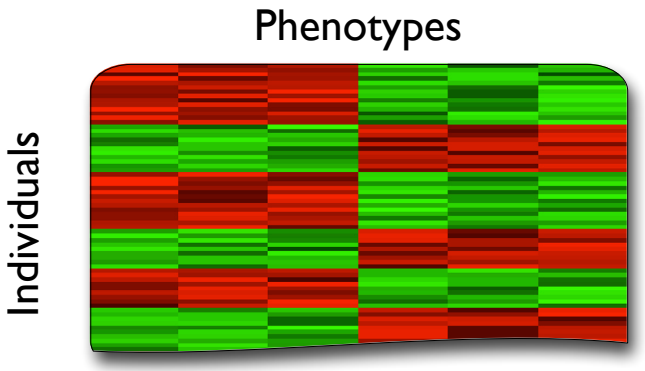

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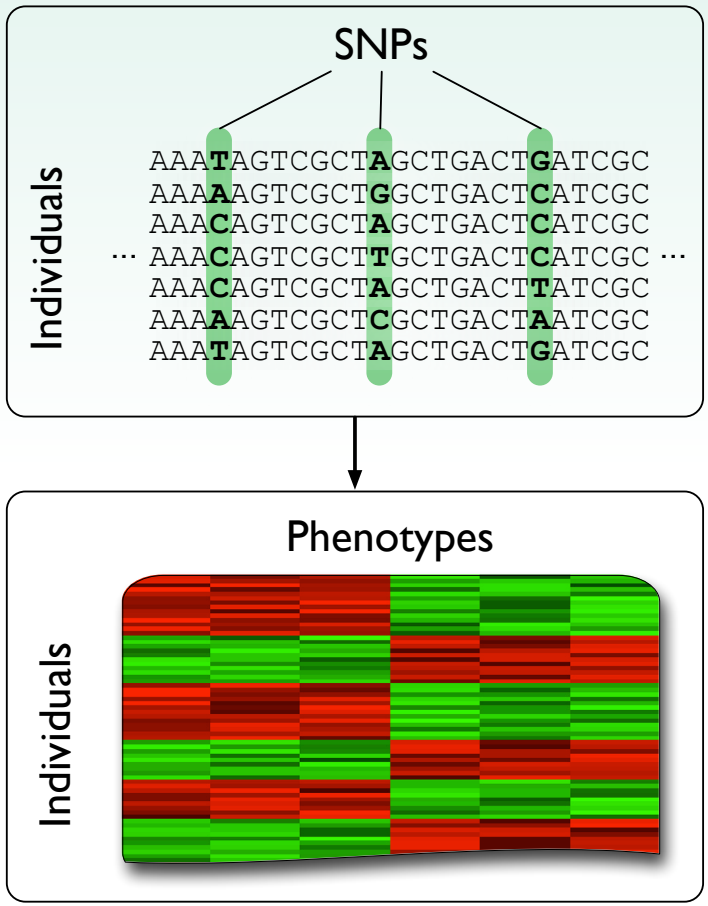

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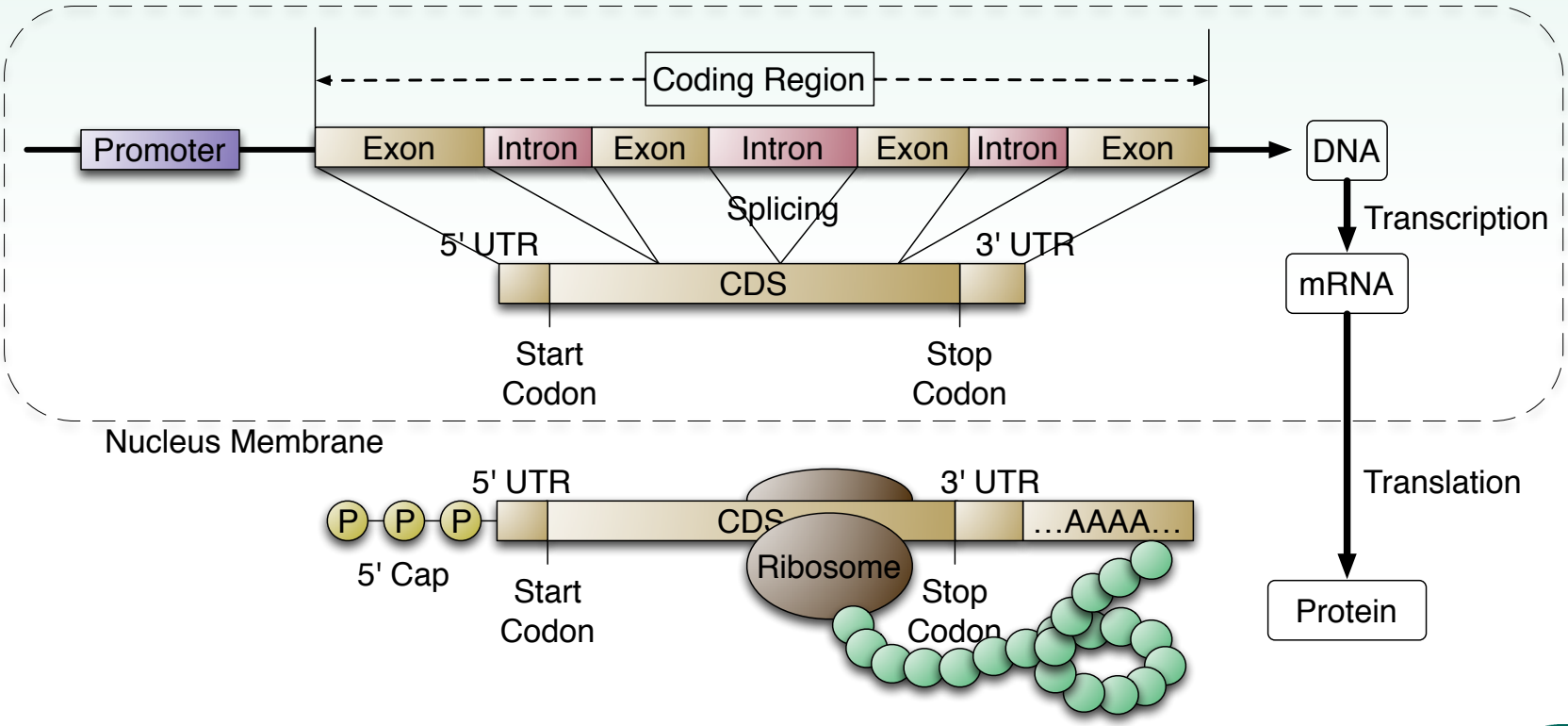
Gene Expression as quantitative Trait



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Confounding Variation (for more see [3])

Confounders:

"Non Genotype Variant Influences on Gene Expression"

Genetically driven:

- Combinatorial Effects of Expressed Genes
- Population Stratification
- Gender

Environmentally driven:

- Treatment Control Experiments
- Exposure to Stress:
  - Physical (pressure, height...)
  - Chemical
  - Human Made (Sea Water quality)

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Confounders and Probabilistic Modelling

Confounding Variation not known:

- Number Q (Dimension) of Confounders
- Abundance of Variation $\mathbf{X}$ itself
- Combinatorial Effects uncertain

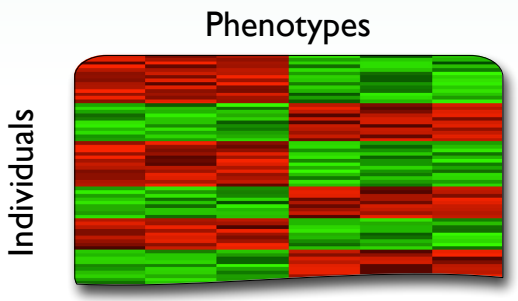
$\Rightarrow$ Bayesian Modelling of Confounders (Latent Variables)

Outline

Notation

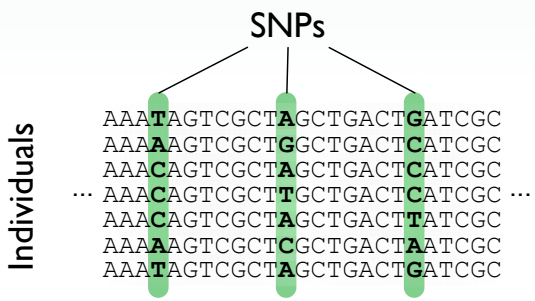
Expression Matrix:

$$\mathbf{Y} \in \mathbb{R}^{N \times D}$$



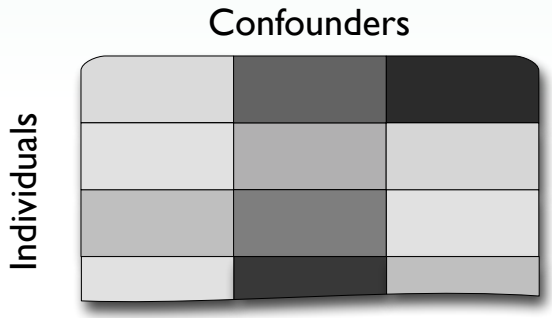
SNP Matrix:

$$\mathbf{S} \in \mathbb{R}^{N \times K}$$



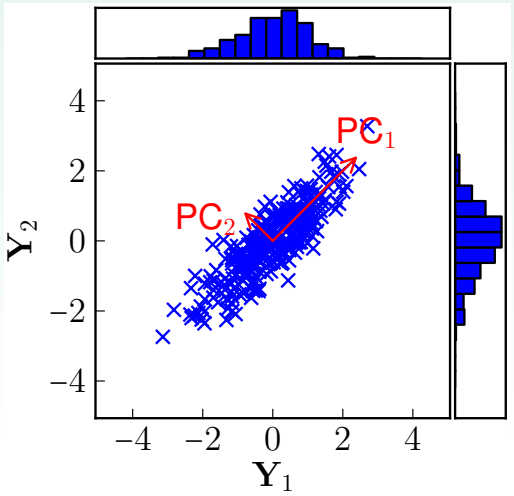
Confounder Matrix:

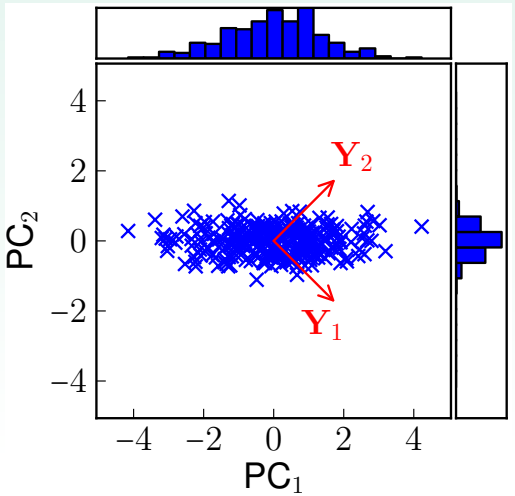
$$\mathbf{X} \in \mathbb{R}^{N \times Q}$$

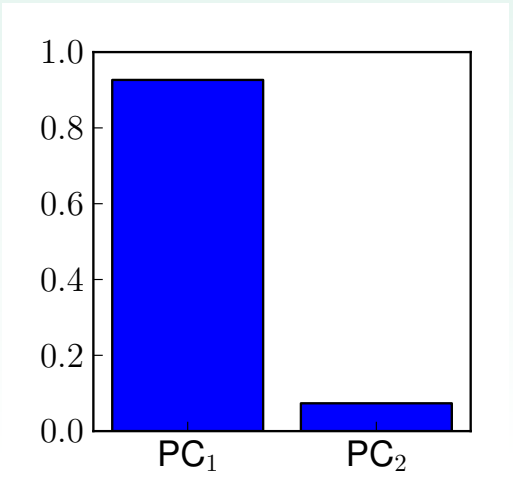


N : Samples D : Genes K : SNPs Q : Confounders

Principal Component Analysis







$$\mathbf{Y} = \mathbf{XV} \quad , \text{ where}$$

$$\mathbf{V}^{-1} = \text{eig}(\mathbf{Y}^\top \mathbf{Y})$$

$$\mathbf{X} = \mathbf{Y}\mathbf{V}_Q^{-1} \quad , \text{ where}$$

$$\mathbf{V}_Q^{-1} = \{\mathbf{v}_q : 1 \leq q \leq Q \text{ largest eigenvalues}\}$$

Gaussian Process Latent Variable Model [4, 5]

Consider Linear Generative Model:

$$\mathbf{Y} = \mathbf{X}\mathbf{V} \tag{1}$$

Prior over $\mathbf{V}$, instead of $\mathbf{X}$:

$$p(\mathbf{V}) = \prod_{d=1}^{D} \mathcal{N}(\mathbf{v}_d | \mathbf{0}, \mathbf{I}_Q) \tag{2}$$

Integrate out $\mathbf{V}$ to get:

$$p(\mathbf{Y}|\mathbf{X}) = \int p(\mathbf{Y}|\mathbf{X}, \mathbf{V}) p(\mathbf{V}|\mathbf{X})\, d\mathbf{V} \tag{3}$$

$$= \prod_{d=1}^{D} \mathcal{N}(\mathbf{y}_d | \mathbf{0}, \mathbf{K}^{\mathrm{NN}} + \beta^{-1}\mathbf{I}_N) \quad , \text{ where} \tag{4}$$

$\mathbf{K}_{ij}^{NN} = k(\mathbf{x}_i, \mathbf{x}_j)$ Covariance Function.

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Gaussian Process Latent Variable Model [4, 5]

Learn Latent Variables $\mathbf{X}$ through Maximum A Posteriori (MAP):

$$\{\hat{\mathbf{X}}, \hat{\boldsymbol{\theta}}\}_{\text{MAP}} = \arg\max_{\mathbf{X},\boldsymbol{\theta}} \ln p(\mathbf{Y}|\mathbf{X}, \boldsymbol{\theta}) \quad , \text{ where} \tag{5}$$

$$\ln p(\mathbf{Y}|\mathbf{X}) = -\frac{DN}{2}\ln(2\pi) - \frac{D}{2}\ln|\mathbf{K}| - \frac{1}{2}\text{tr}(\mathbf{K}^{-1}\mathbf{Y}\mathbf{Y}^{\mathsf{T}}) \quad , \text{ with} \tag{6}$$

$$\mathbf{K} = \mathbf{K}^{NN} + \beta^{-1}\mathbf{I}_N \tag{7}$$

But, we want Bayesian estimate

$$p(\mathbf{Y}) = \int p(\mathbf{Y}|\mathbf{X})p(\mathbf{X})\, d\mathbf{X} \tag{8}$$

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Variational Bayesian GPLVM [1]

$$p(\mathbf{Y}) = \int p(\mathbf{Y}|\mathbf{X})p(\mathbf{X})\, d\mathbf{X} \tag{9}$$

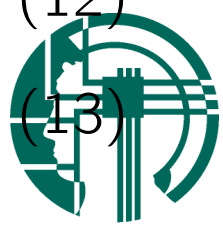
Intractable in $\mathbf{X} \Rightarrow$ Variational Approximation $q(\mathbf{X})$:

$$\ln p(\mathbf{Y}) \geq \mathcal{F}(q) = \int q(\mathbf{X}) \ln \frac{p(\mathbf{Y}|\mathbf{X})p(\mathbf{X})}{q(\mathbf{X})} d\mathbf{X} \tag{10}$$

$$= \int q(\mathbf{X}) \ln p(\mathbf{Y}|\mathbf{X}) d\mathbf{X} - \int q(\mathbf{X}) \ln \frac{p(\mathbf{X})}{q(\mathbf{X})} d\mathbf{X} \tag{11}$$

$$= \int q(\mathbf{X}) \ln p(\mathbf{Y}|\mathbf{X}) d\mathbf{X} - \mathrm{KL}(q||p) \tag{12}$$

$$= \tilde{\mathcal{F}}(q) - \mathrm{KL}(q||p) \tag{13}$$

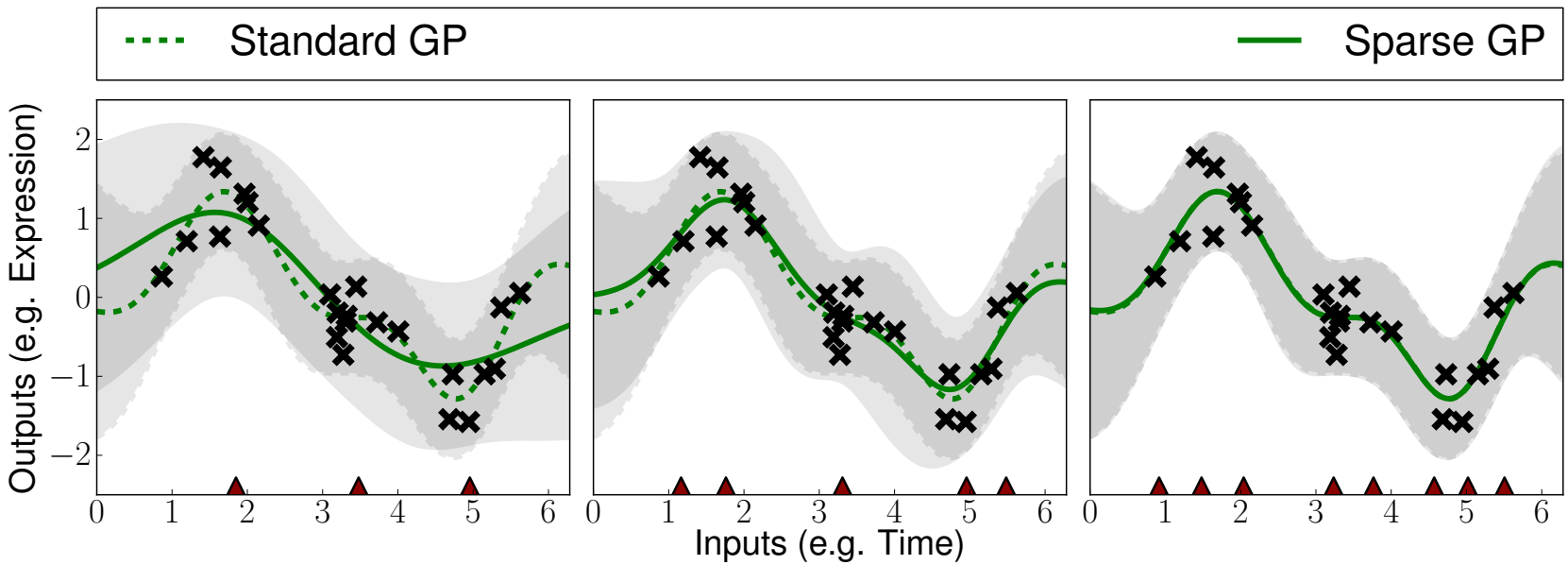


Variational Bayesian GPLVM [1]

$$\ln p(\mathbf{Y}) \geq \mathcal{F}(q) = \tilde{\mathcal{F}}(q) - \mathrm{KL}(q||p) \tag{14}$$

$$\tilde{\mathcal{F}}(q) = \int q(\mathbf{X}) \ln p(\mathbf{Y}|\mathbf{X}) d\mathbf{X} \tag{15}$$

Sparse Approximation for $p(\mathbf{Y}|\mathbf{X})$:

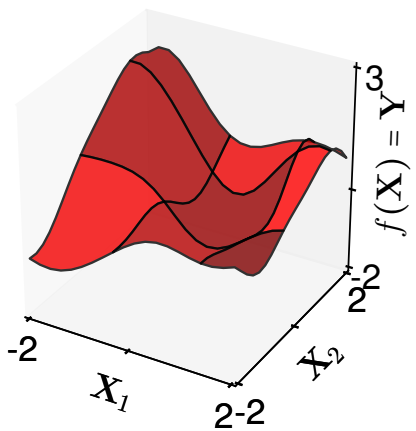


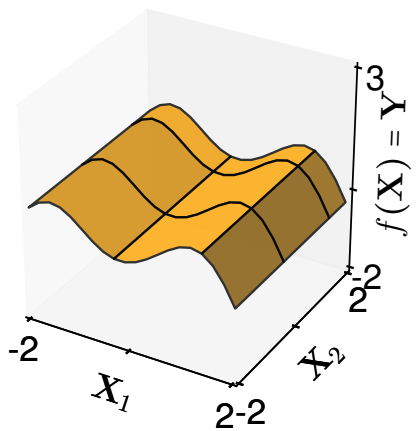
Automatic Relevance Determination [6]

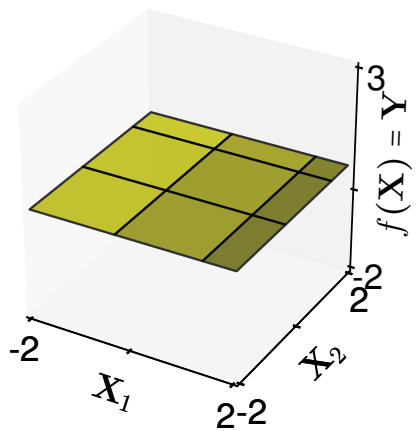
Consider Squared Exponential Covariance Function

$$k(\mathbf{x}, \mathbf{x}') = \sigma^2 \exp\left\{\frac{1}{2}\boldsymbol{\alpha}^\top ||\mathbf{x} - \mathbf{x}'||^2\right\} \tag{16}$$

$\boldsymbol{\alpha} \in \mathbb{R}^Q$ contains Relevance for each Dimension $1 \leq q \leq Q$ of $\mathbf{X}$
$\mathbf{X} \in \mathbb{R}^{N \times Q}$ with rows $\mathbf{x} \in \mathbb{R}^Q$







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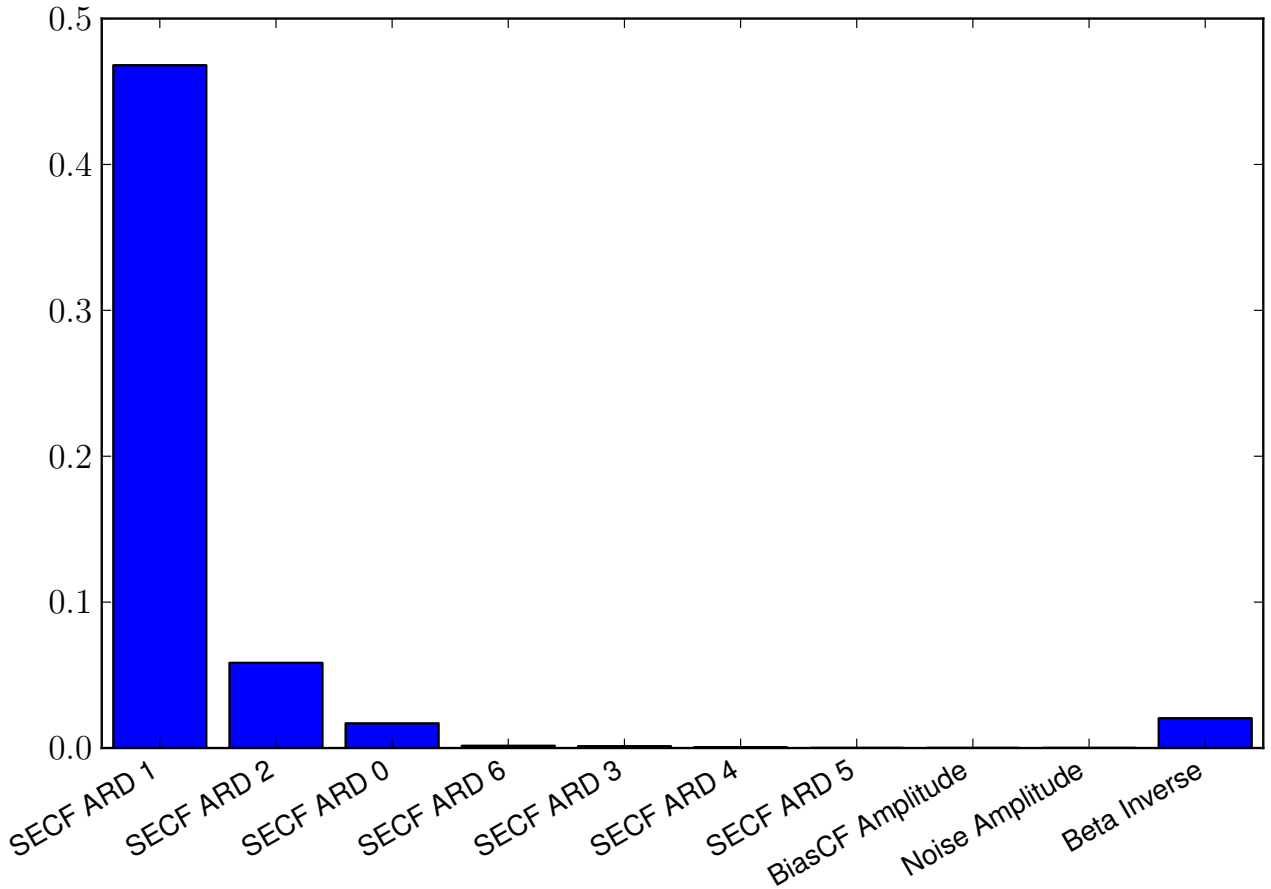
Intuition



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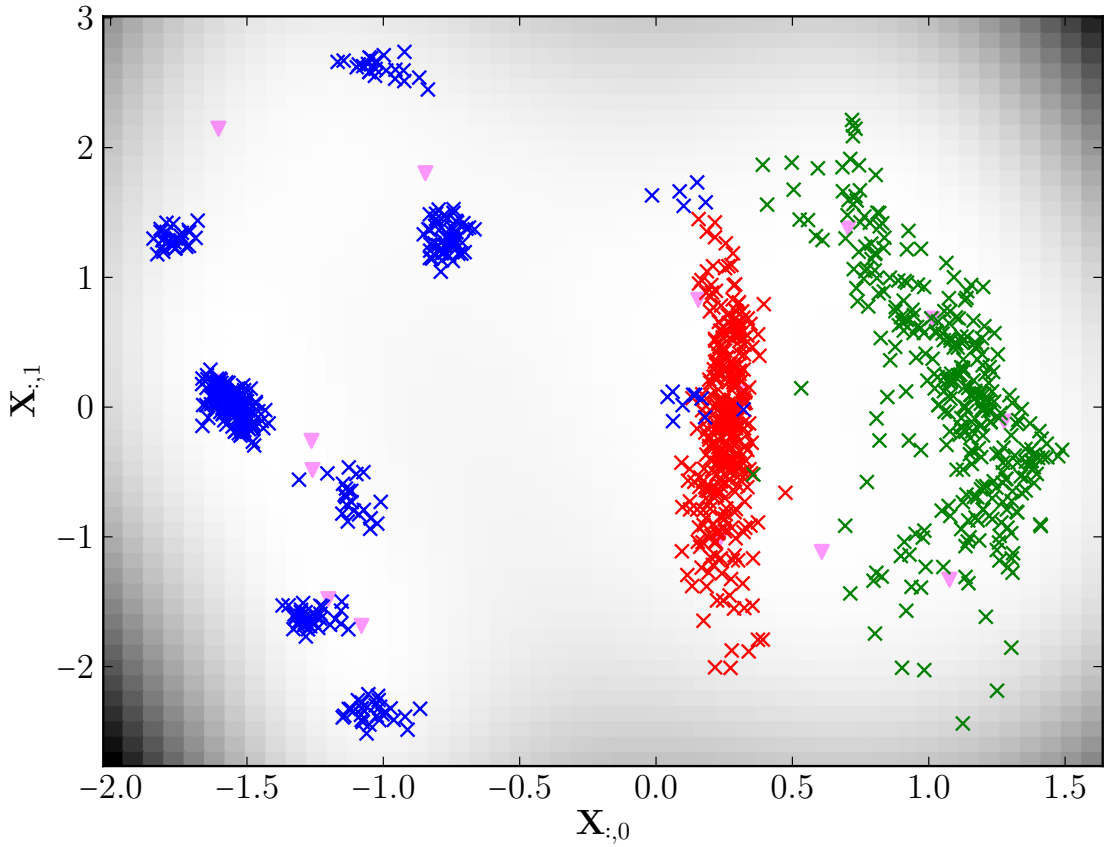

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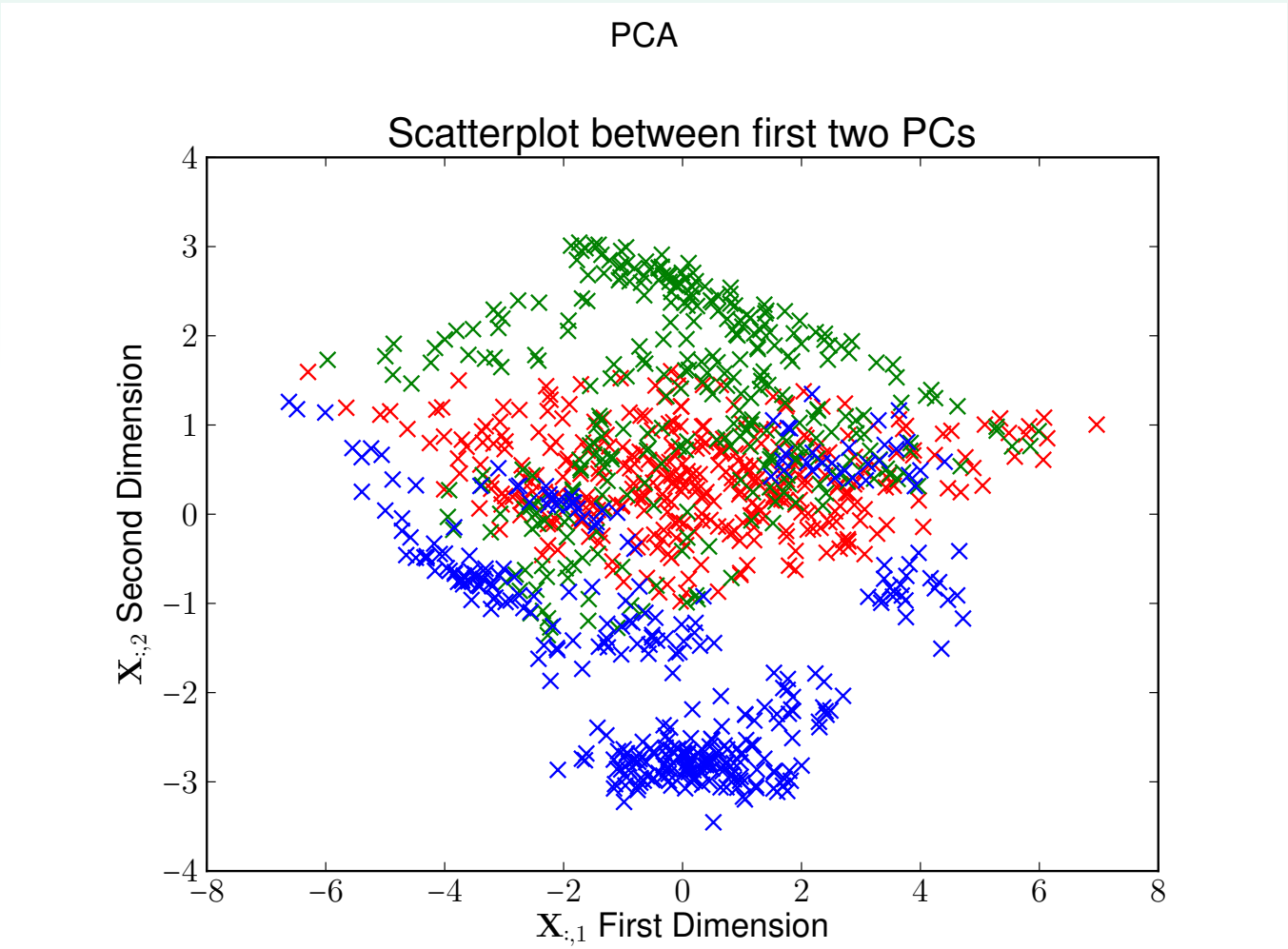
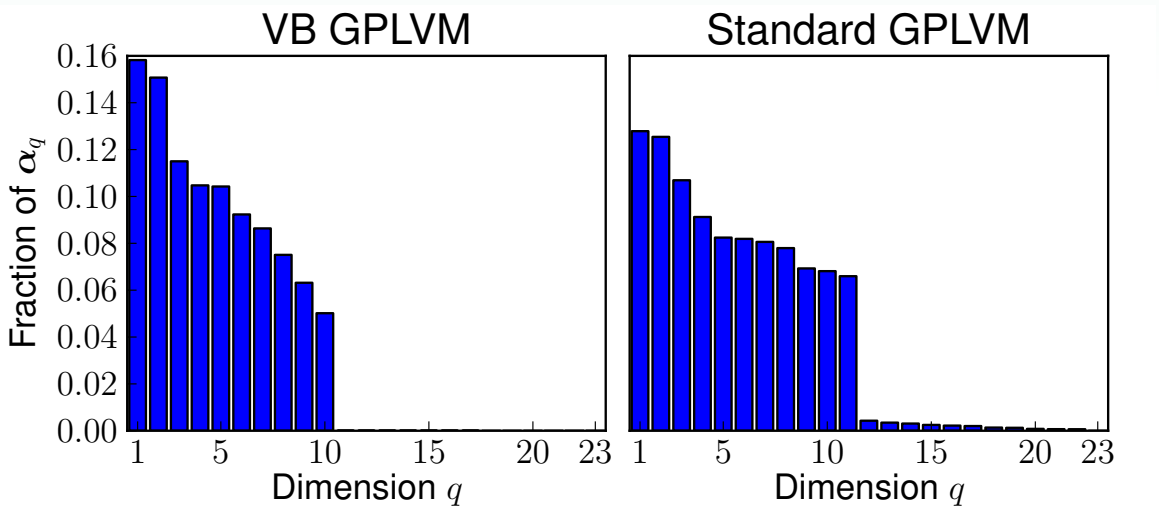

PCA
Scatterplot between first two PCs
$\mathbf{X}_{:,2}$ Second Dimension
$\mathbf{X}_{:,1}$ First Dimension
4
3
2
1
0
−1
−2
−3
−4
−8
−6
−4
−2
0
2
4
6
8

Learning the right Dimensionality

Simulated Dataset (from Linear Mixed Model) with $Q = 10$ Confounders:



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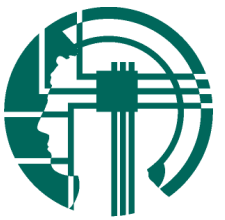

PANAMA

Linear Mixed Model Assumed:

$$\overbrace{\mathbf{Y}}^{N\times D} = \overbrace{\mathbf{S}}^{N\times K}\mathbf{W} + \overbrace{\mathbf{X}}^{N\times Q}\mathbf{V} \tag{17}$$

N : Samples D : Genes K : SNPs Q : Confounders

Iterative Approach through GPLVM:

1. Learn Confounders by GPLVM
2. Add Confounders correlated with Genotype
3. Fit the new Model
4. Continue with 1. until no Confounders are added

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Variational Bayesian GPLVM for Confounder Detection

Same Linear Mixed Model Assumed:

$$\mathbf{Y} = \mathbf{SW} + \mathbf{XV} \tag{18}$$

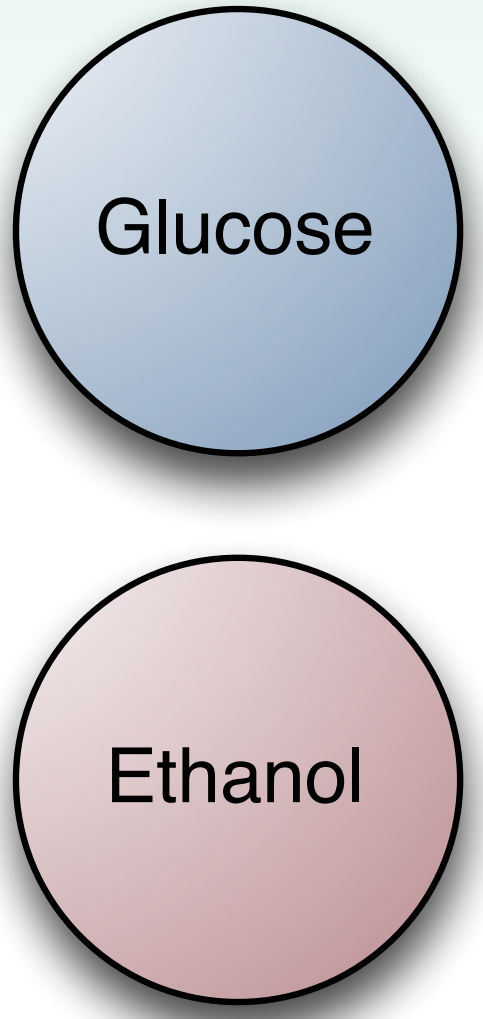
No Iterative Approach necessary
$\Rightarrow$ ARD + Bayesian Approximation

- Learn Confounders $\mathbf{X}$ through Variational Bayesian GPLVM
- Fit Linear Mixed Model with learned Confounders.

Yeast Dataset [7]

Saccharomyces Cerevisiae:

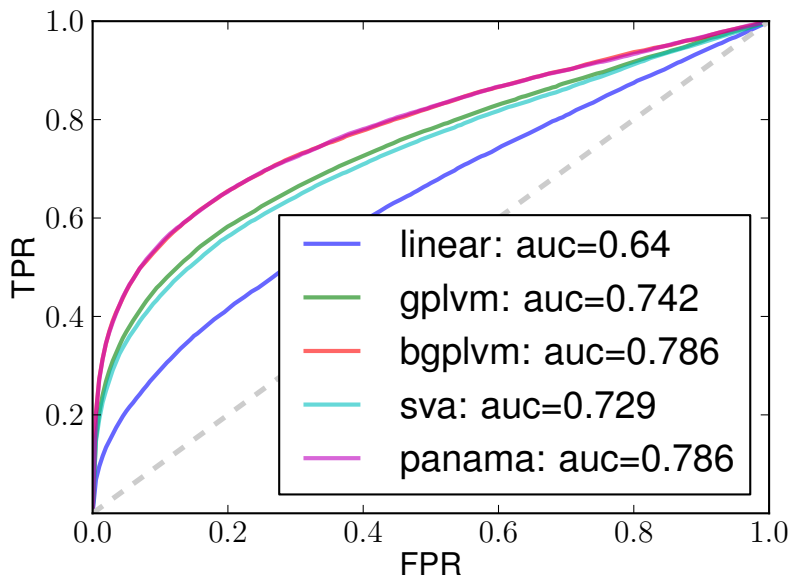
- Expression Profiled $N = 109$ Samples over $D = 5493$ Genes
- $K = 2956$ SNPs Genotyped
- 2 Environments: Glucose and Ethanol
- We only use Glucose Part.



Simulated Dataset by [2]

- Simulated Dataset founded on real Yeast [7] eQTL Experiment

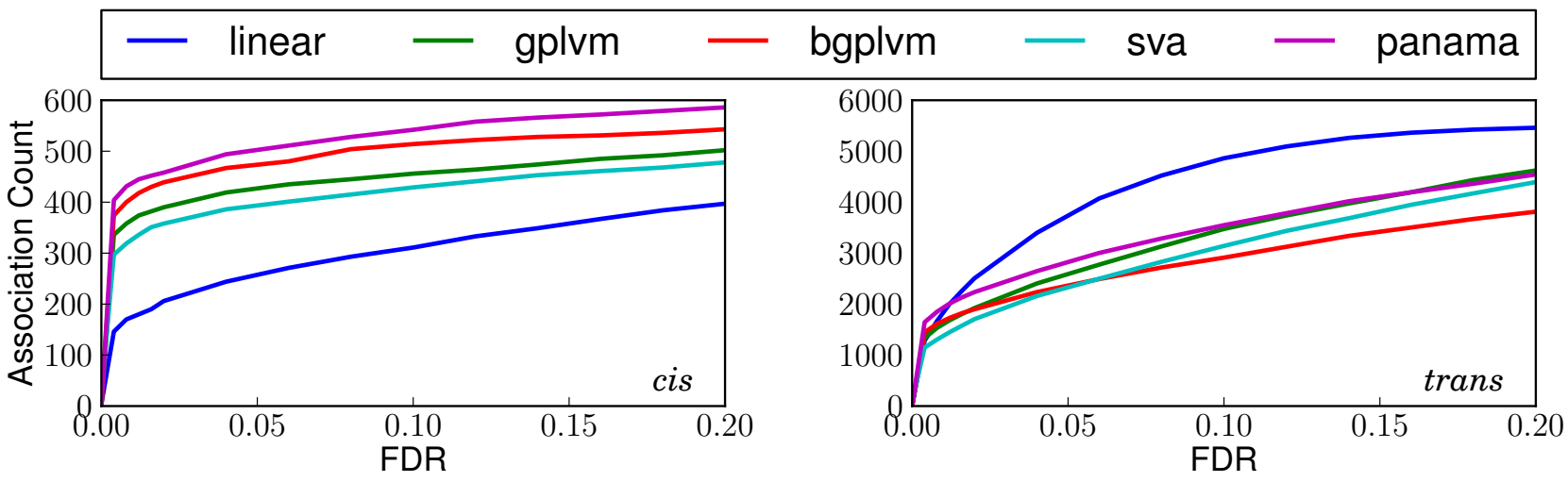
⇒ Ground Truth for Confounding Variation and Associations:



Simulated Dataset by [2]

- *cis* and *trans* Associations:

⇒ Less False Positives:



Manifold Relevance Determination for eQTL Studies

Combine Variational Bayesian GPLVMs to determine Private/Shared Information:

$$\ln p(\mathbf{Y}^{\kappa}) \geq \ln \sum_{\iota \in \kappa} \int q(\mathbf{X}) \ln p(\mathbf{Y}^{\iota}|\mathbf{X}) d\mathbf{X} \quad - \mathrm{KL}(q||p) \quad , \text{ where} \tag{19}$$

$$\mathbf{Y}^{\kappa} = \{\mathbf{Y}^{\iota} : \iota \in \kappa\} \tag{20}$$

Thus,

- One Confounder Matrix $\mathbf{X}$
- ARD Parameters $\boldsymbol{\alpha}^{\iota}$ per Experiment $\mathbf{Y}^{\iota}$

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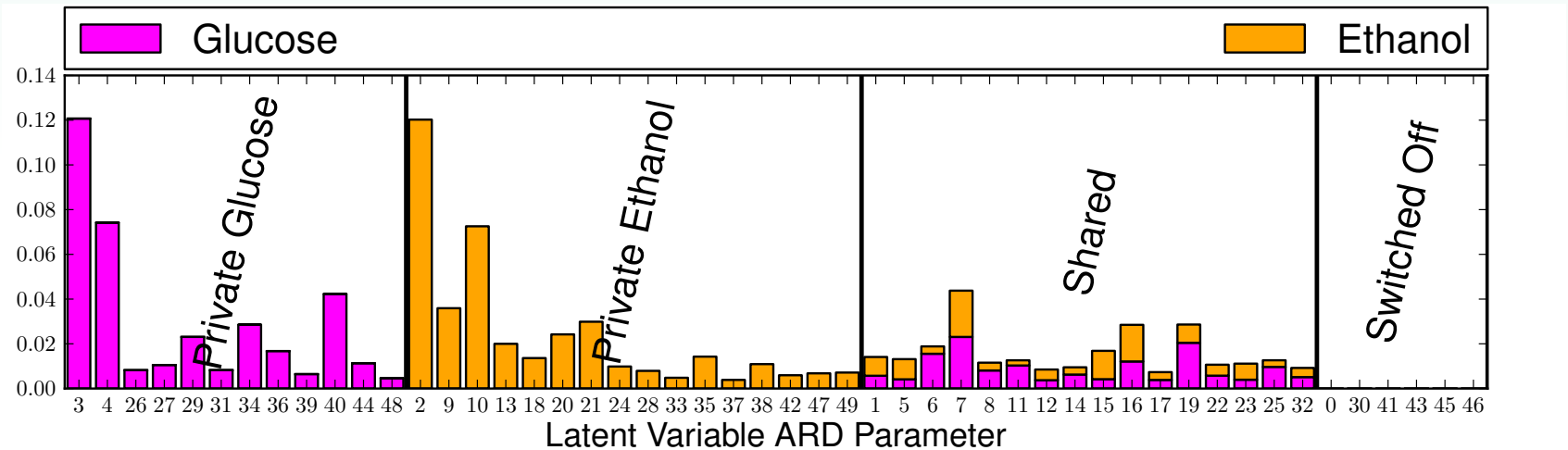
Manifold Relevance Determination for eQTL Studies

Apply to both parts of Smith [7] Experiment:



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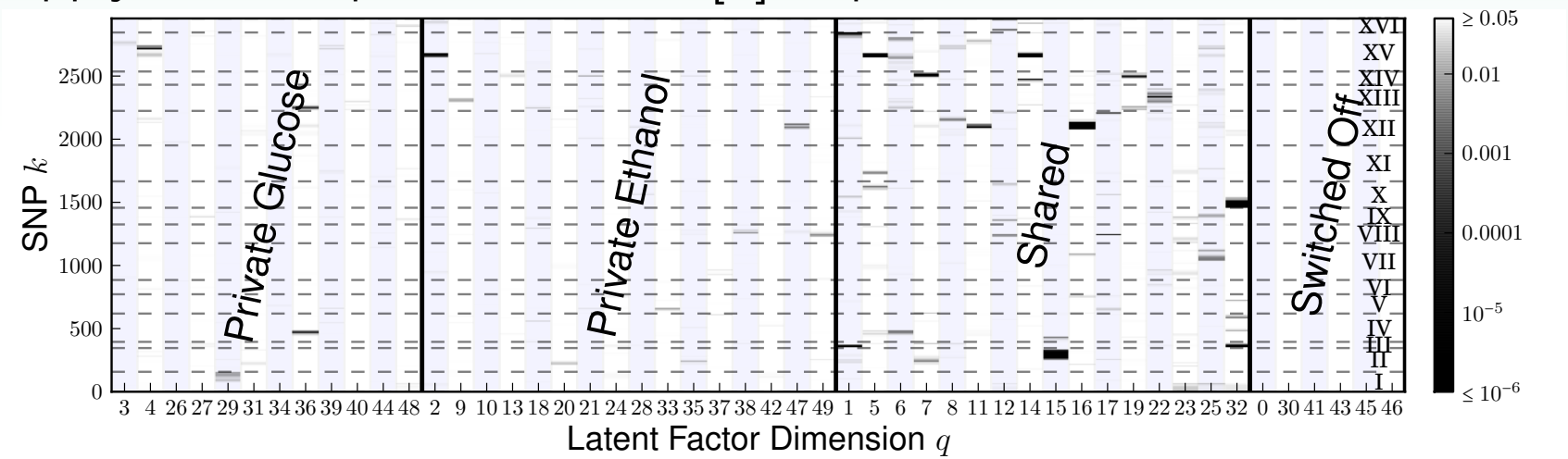
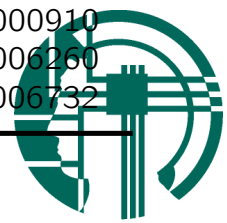


Manifold Relevance Determination for eQTL Studies

Private Glucose	#Hits	GO
cellular macromolecule catabolic process	7	0044265
macromolecule catabolic process	7	0009057
ncRNA processing	6	0034470
ncRNA metabolic process	6	0034660
tRNA metabolic process	4	0006399
Private Ethanol	**#Hits**	**GO**
response to abiotic stimulus	6	0009628
regulation of cell cycle	5	0051726
pseudohyphal growth	4	0007124
cell growth	4	0016049
growth of unicellular organism as a thread of attached cells	4	0070783
regulation of cell cycle process	4	0010564
Shared	**#Hits**	**GO**
cell cycle	42	0007049
cell cycle process	34	0022402
tRNA metabolic process	14	0006399
cytokinesis	13	0000910
DNA replication	13	0006260
coenzyme metabolic process	13	0006732



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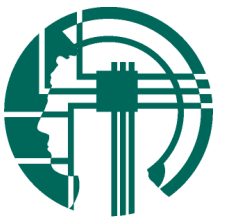
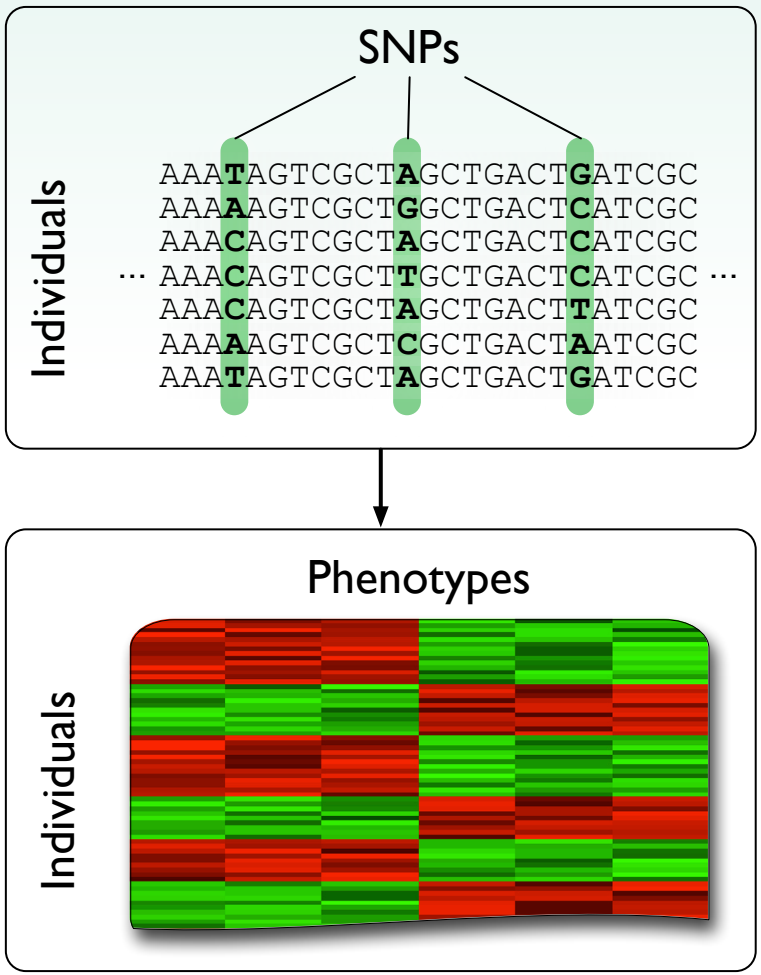
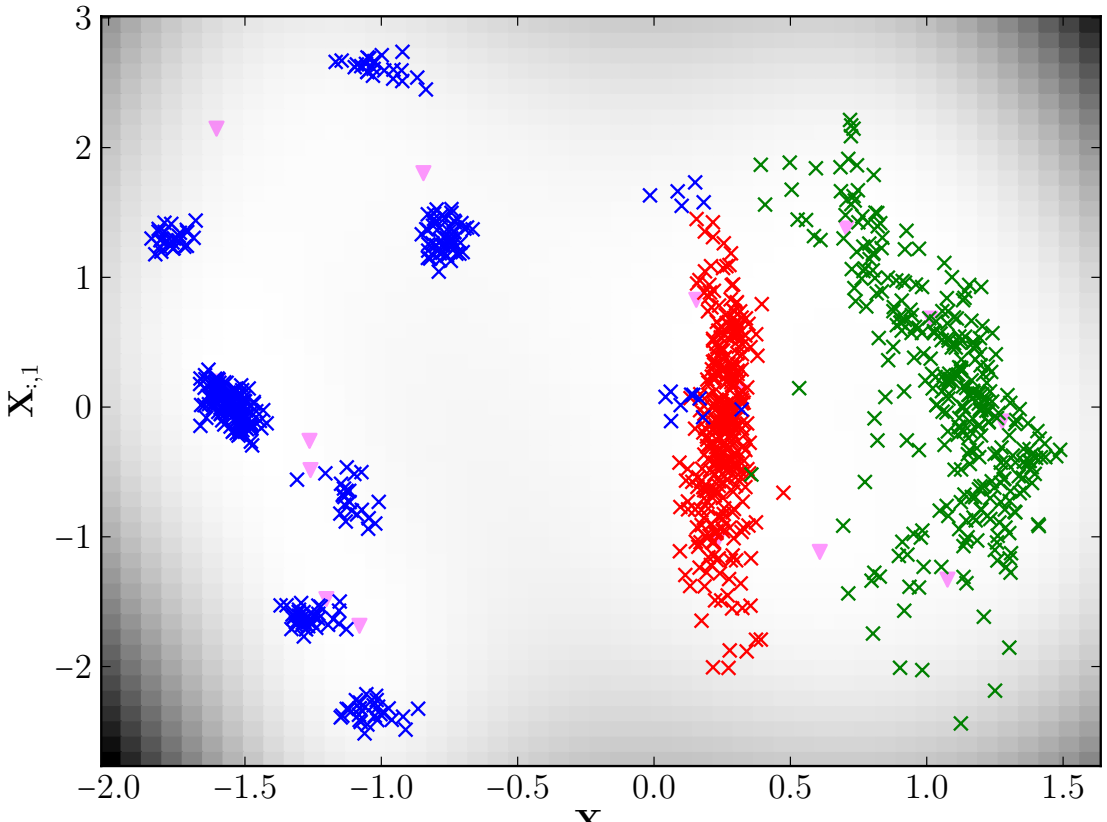


Summary

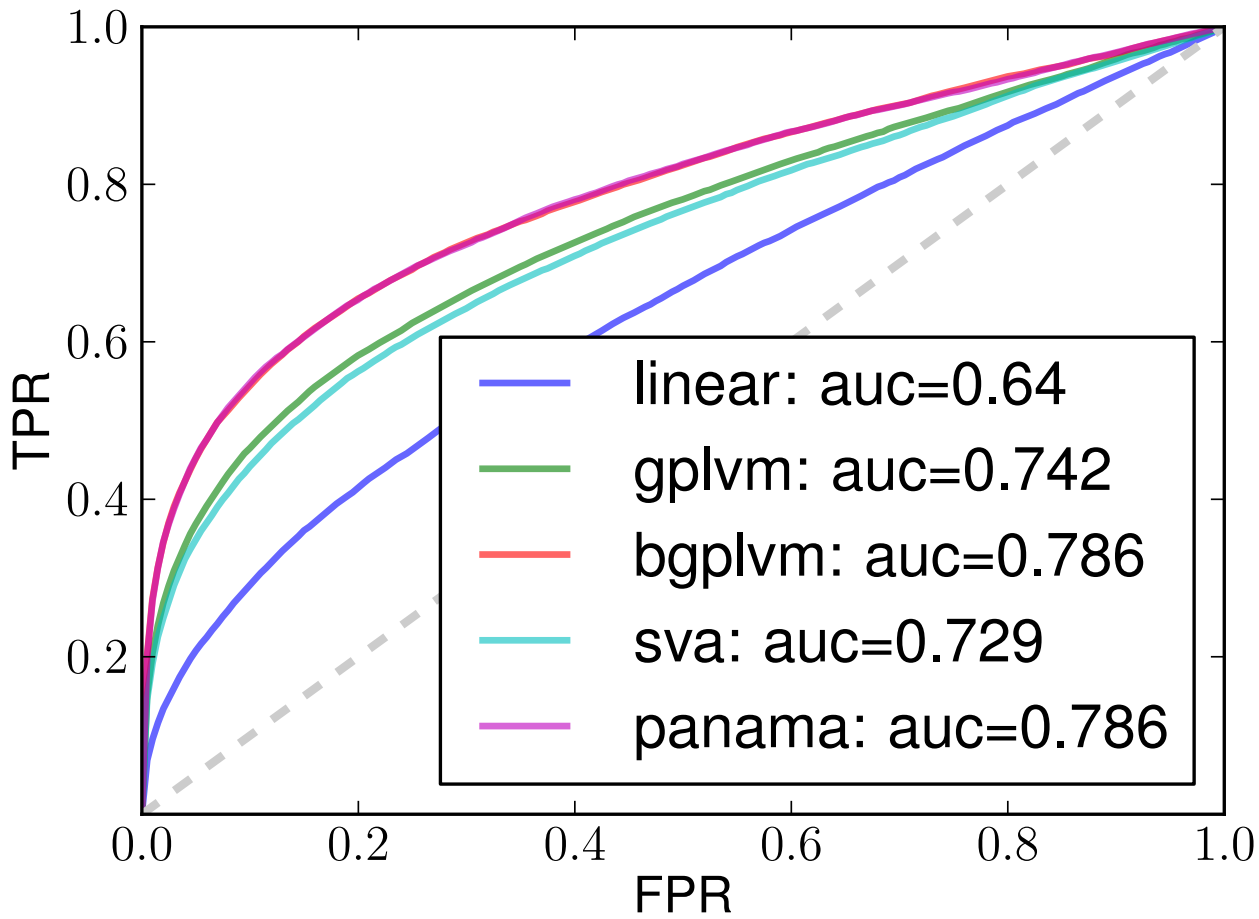

SNPs
Individuals
AAATAGTCGCTAGCTGACTGATCGC
AAAAAGTCGCTGGCTGACTCATCGC
AAACAGTCGCTAGCTGACTCATCGC
AAACAGTCGCTTGCTGACTCATCGC
AAACAGTCGCTAGCTGACTTATCGC
AAAAAGTCGCTCGCTGACTAATCGC
AAATAGTCGCTAGCTGACTGATCGC
Phenotypes
Individuals

Summary

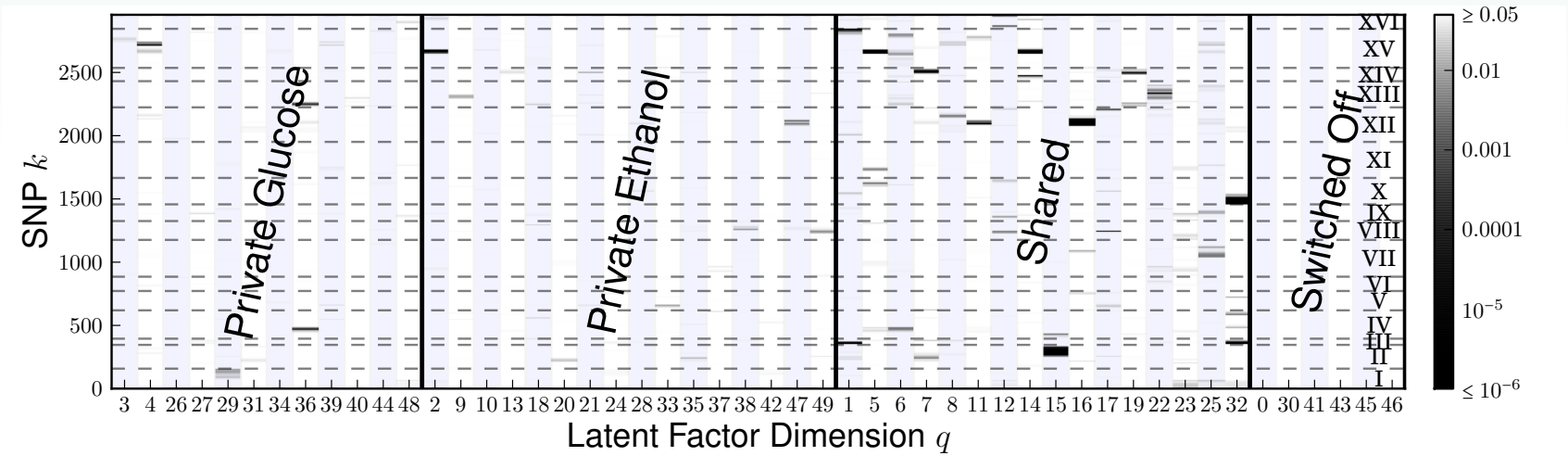
$$p(\mathbf{Y}) = \int p(\mathbf{Y}|\mathbf{X})p(\mathbf{X})\, d\mathbf{X} \tag{21}$$



Summary


1.0
0.8
0.6
0.4
0.2
TPR
0.0
0.2
0.4
0.6
0.8
1.0
FPR
linear: auc=0.64
gplvm: auc=0.742
bgplvm: auc=0.786
sva: auc=0.729
panama: auc=0.786

Summary


SNP k
Latent Factor Dimension q
Private Glucose
Private Ethanol
Shared
Switched Off
≥ 0.05
0.01
0.001
0.0001
10^{-5}
≤ 10^{-6}

Discussion

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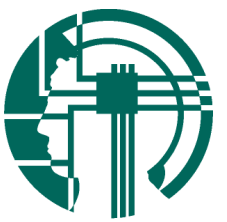

From DNA to Protein