Linear models III: Improved linear mixed models

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[2] Max-Planck-Institutes Tübingen, Germany

Basel
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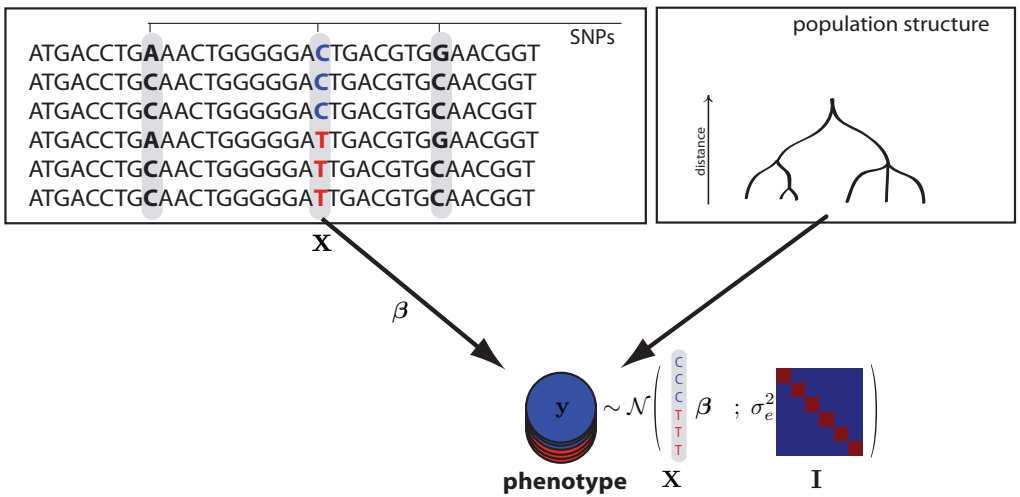
Microsoft Research

Correcting for population stratification using linear mixed models

- Confounding structure leads to false positives.
  - Population structure
  - Family structure
  - Cryptic relatedness
- Genetic similarity matrix $\mathbf{K}$
  - Estimated from SNP data
  - *models the probability that two individuals share causal SNPs*



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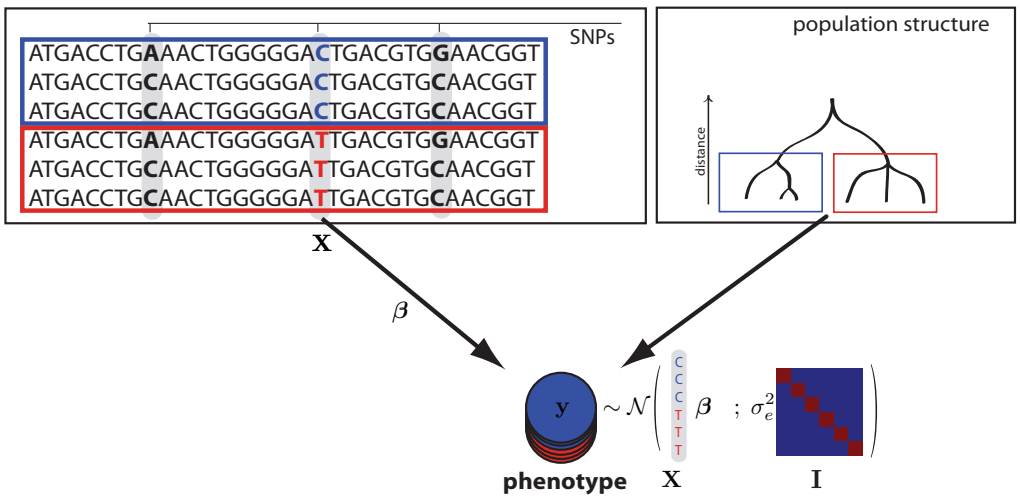

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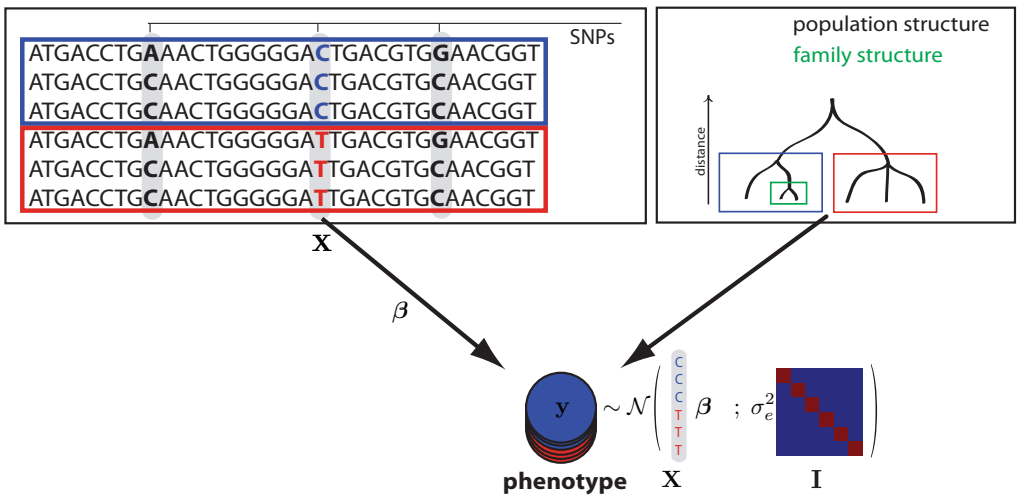

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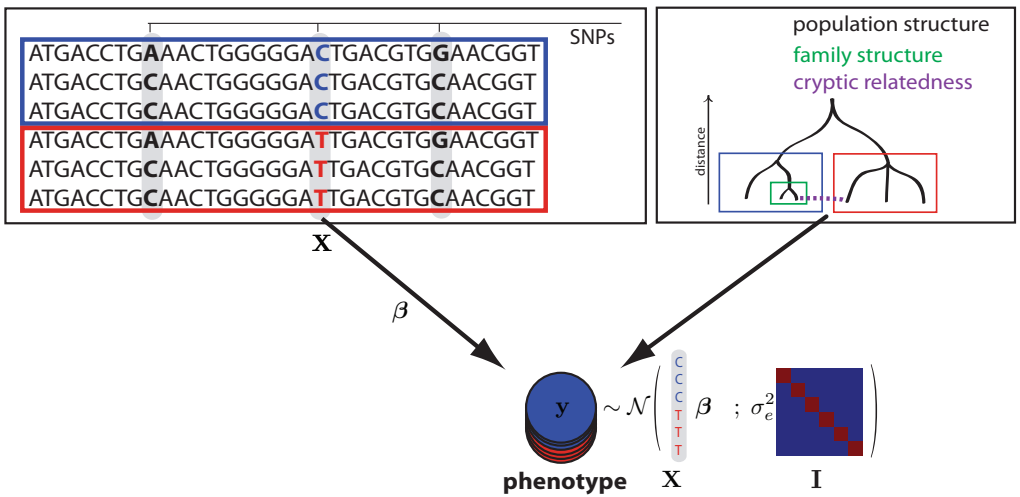

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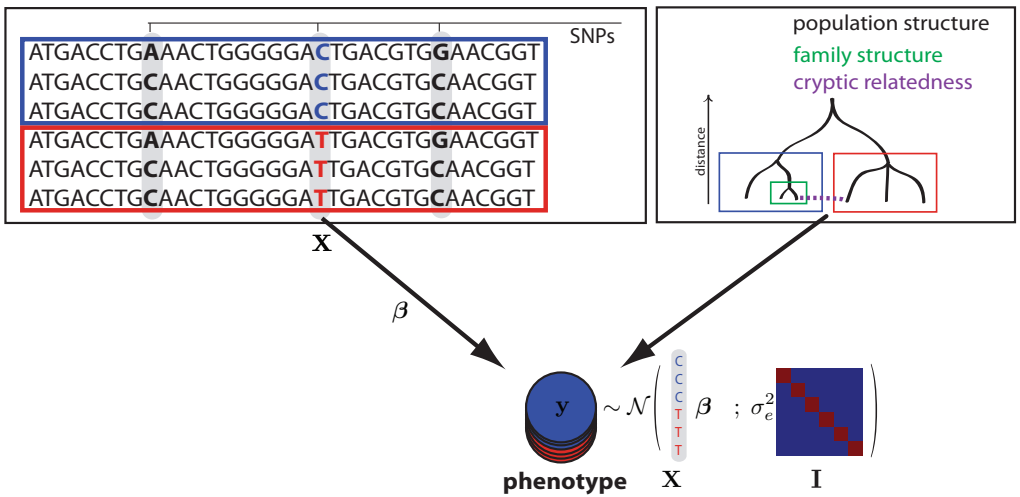

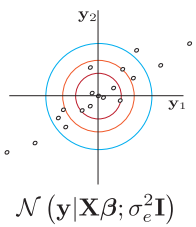

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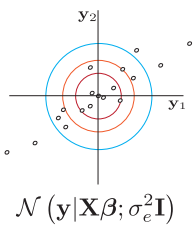

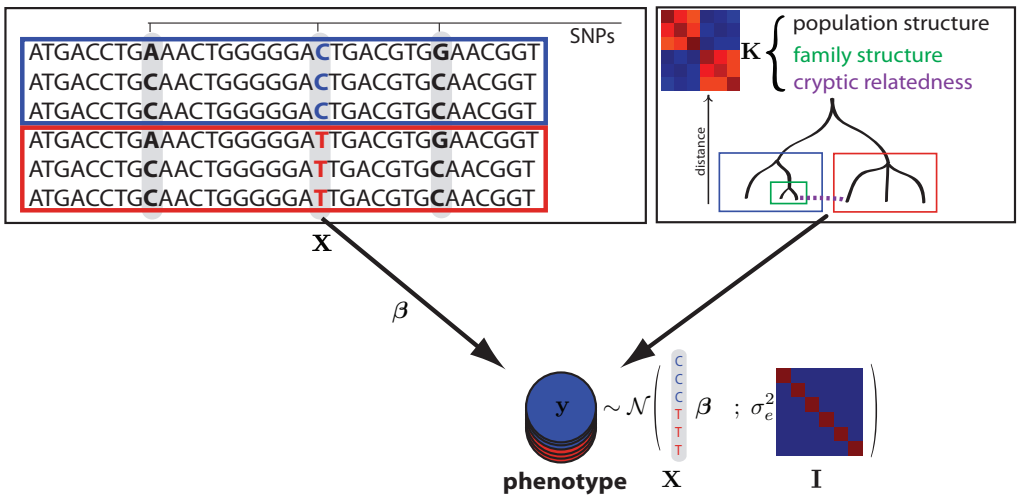

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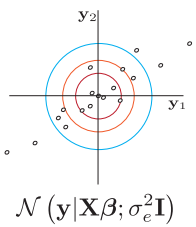

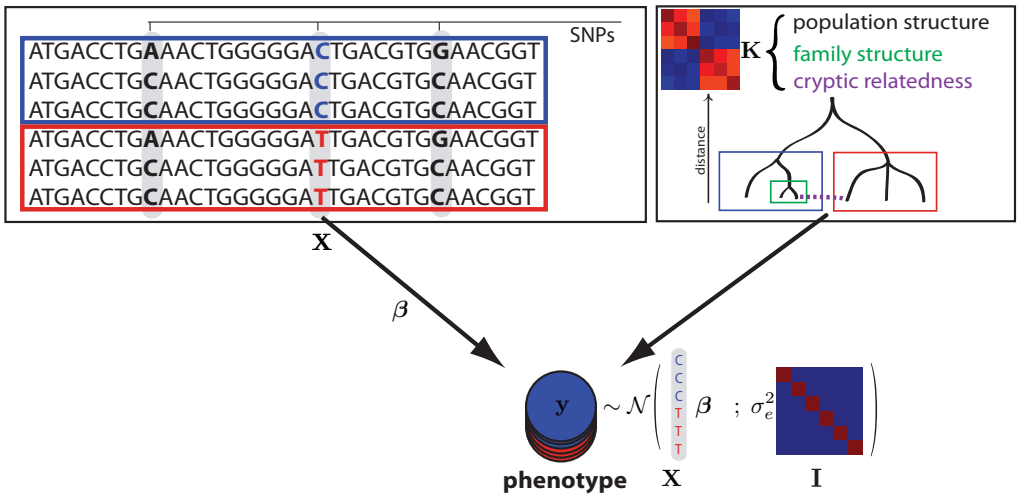

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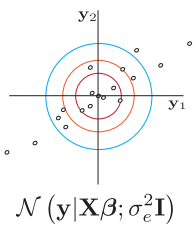

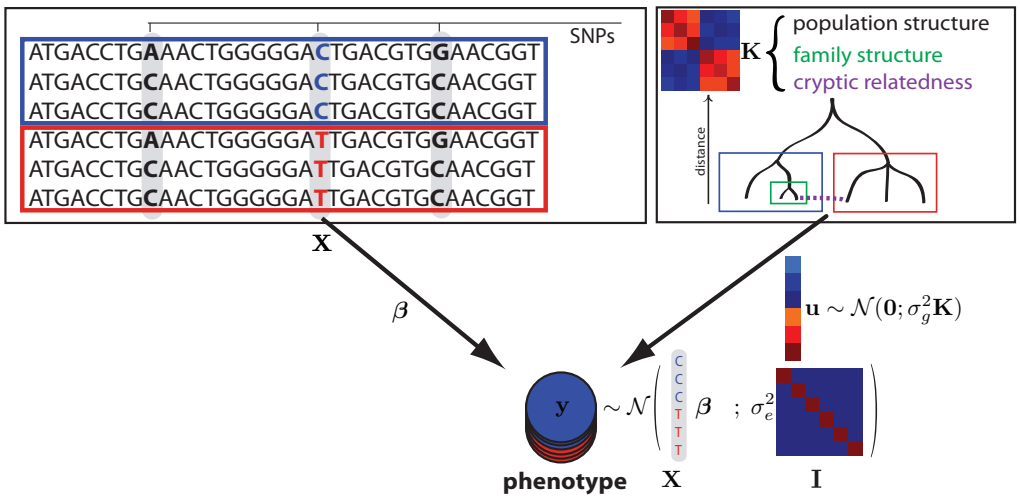

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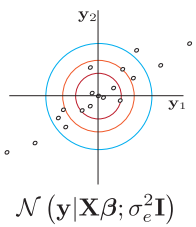

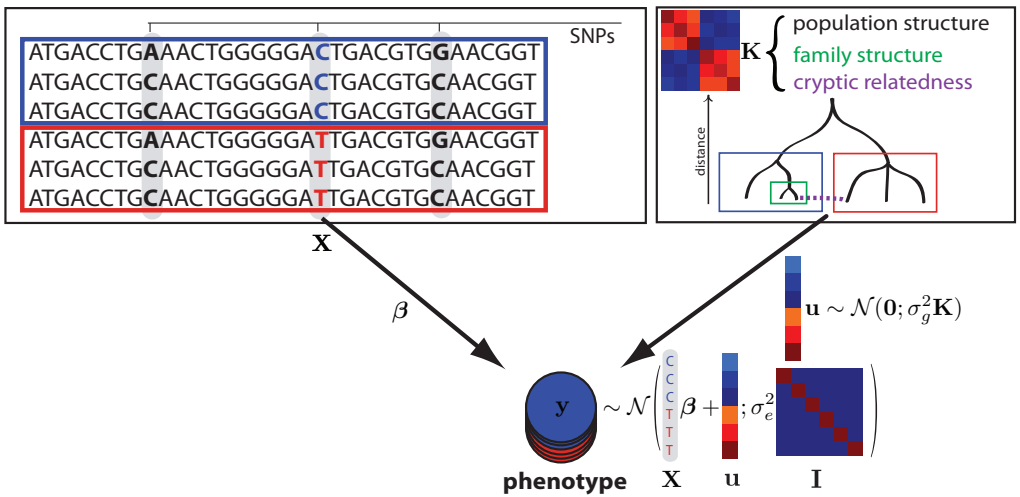

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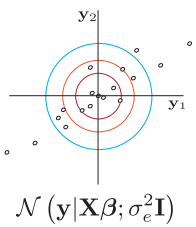

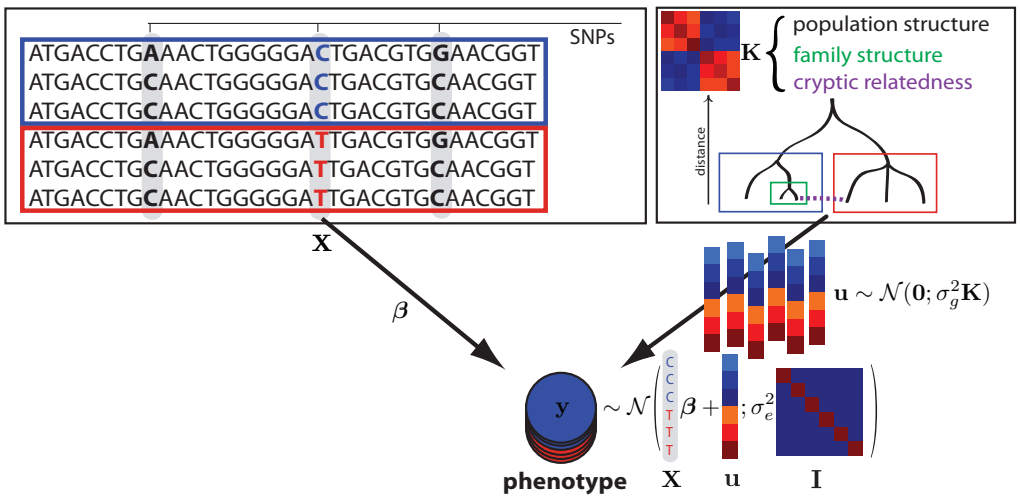

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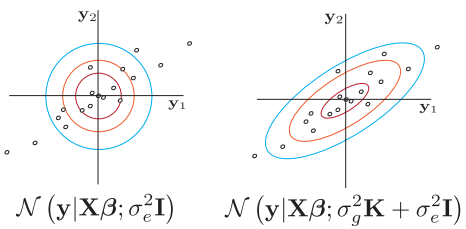

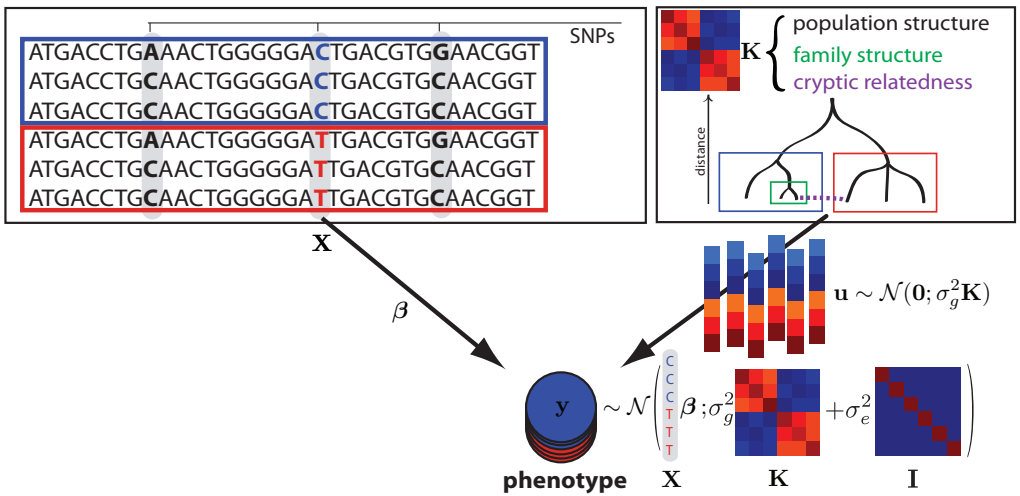

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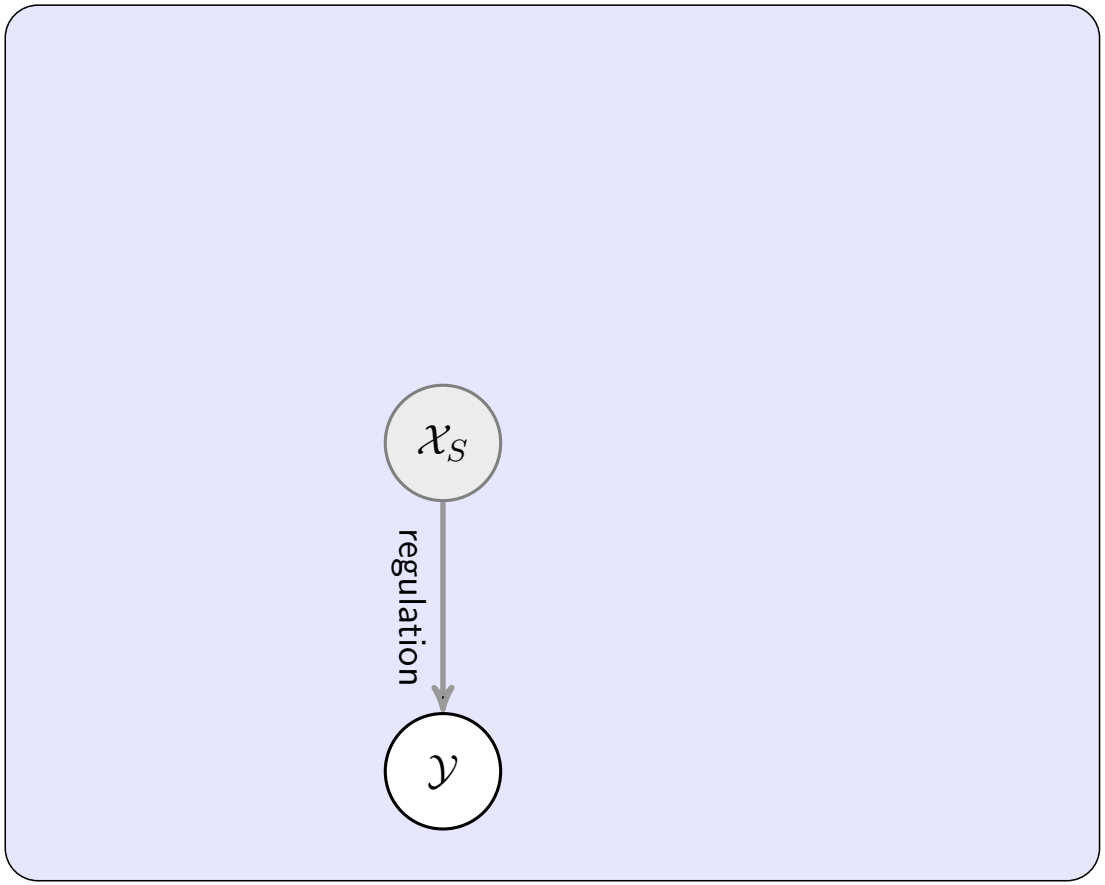
A graphical model view of GWAS

- Goal: genotype-phenotype relatioships
- Associations via linkage disequislibrium
- SNPs confounded by population structure
- Spurious associations if not taken into account
- Alternatively condition on causal SNPs



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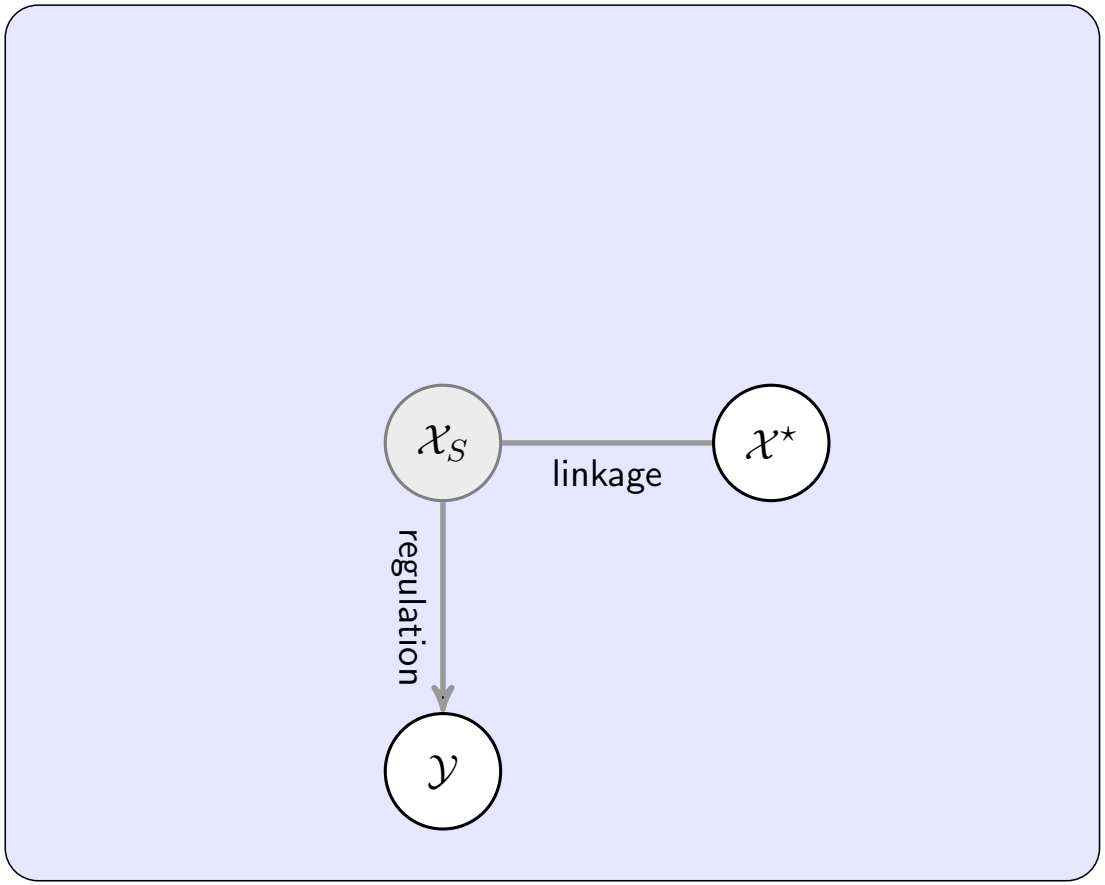

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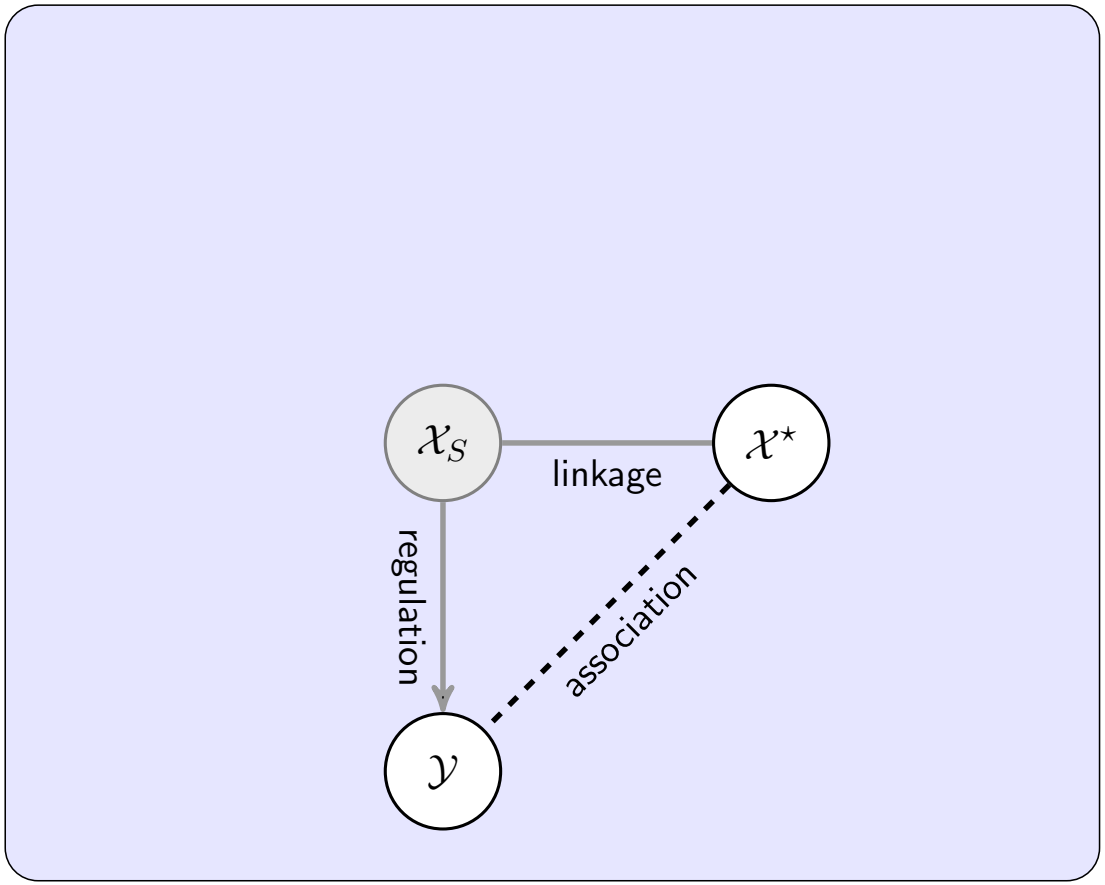

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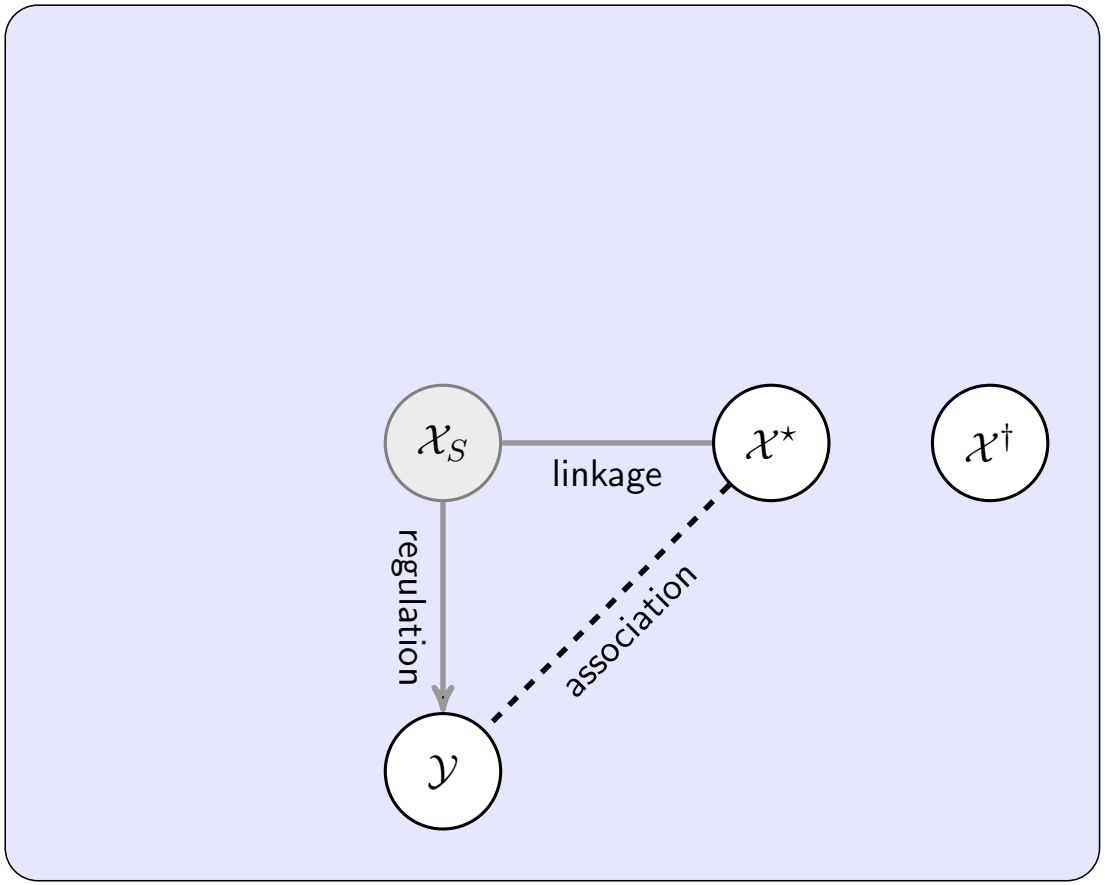

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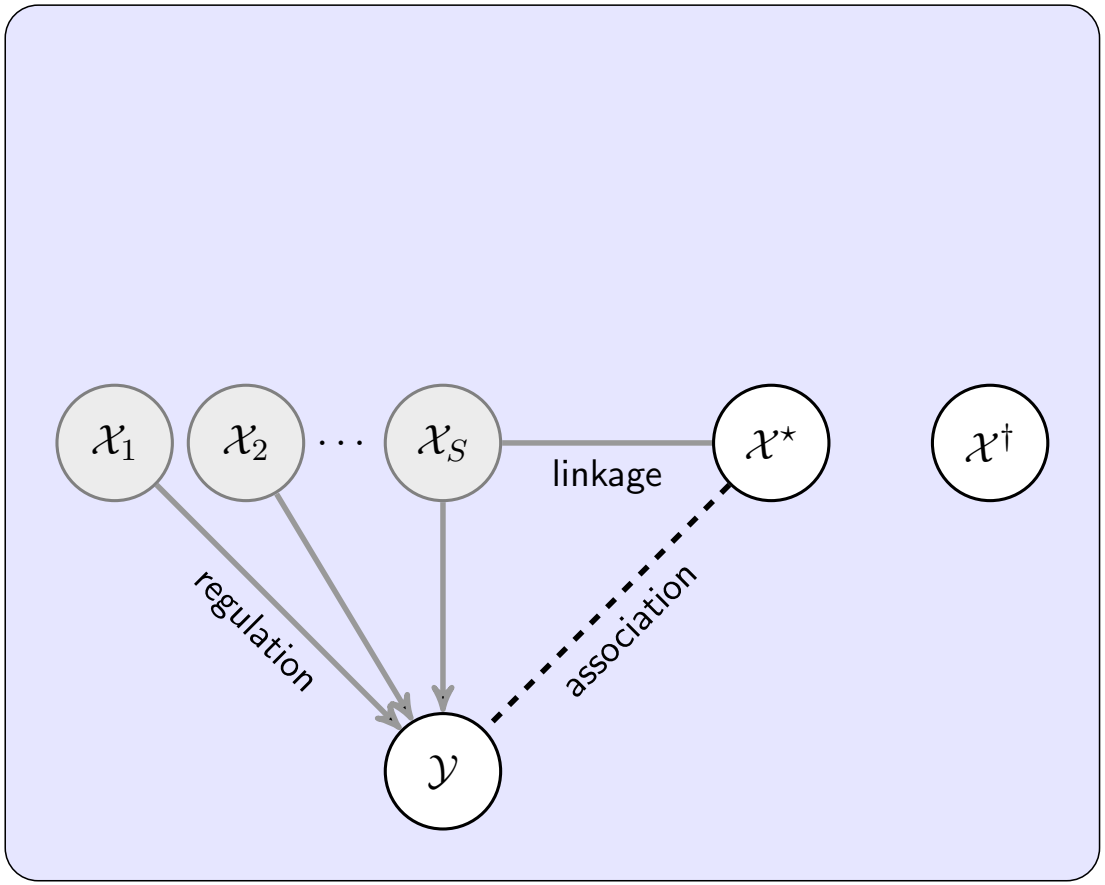

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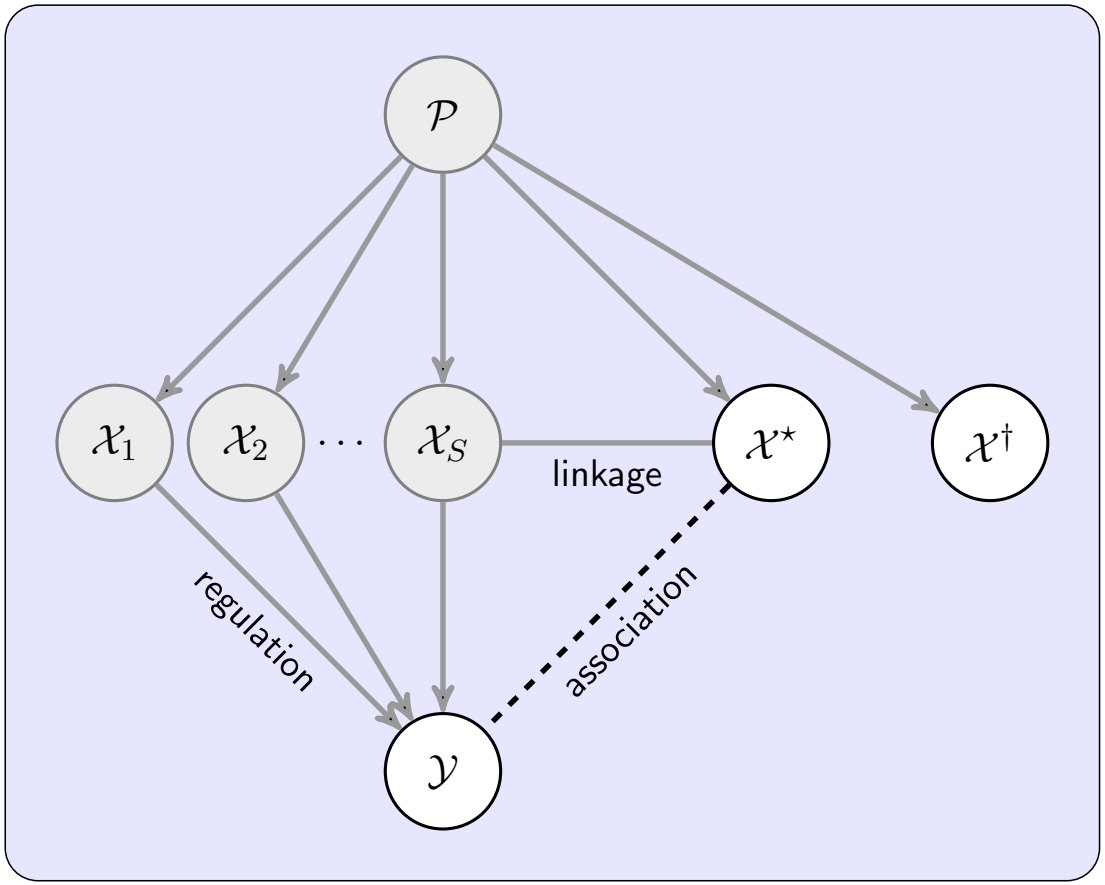

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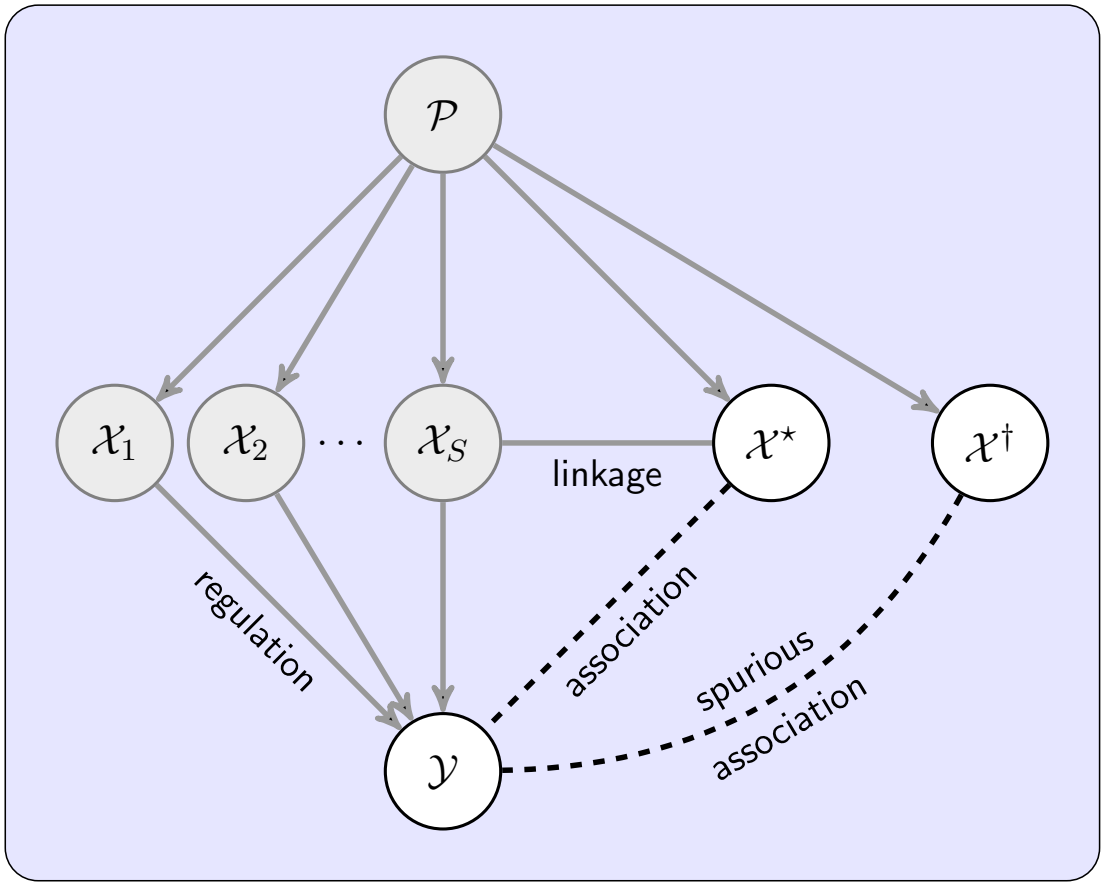

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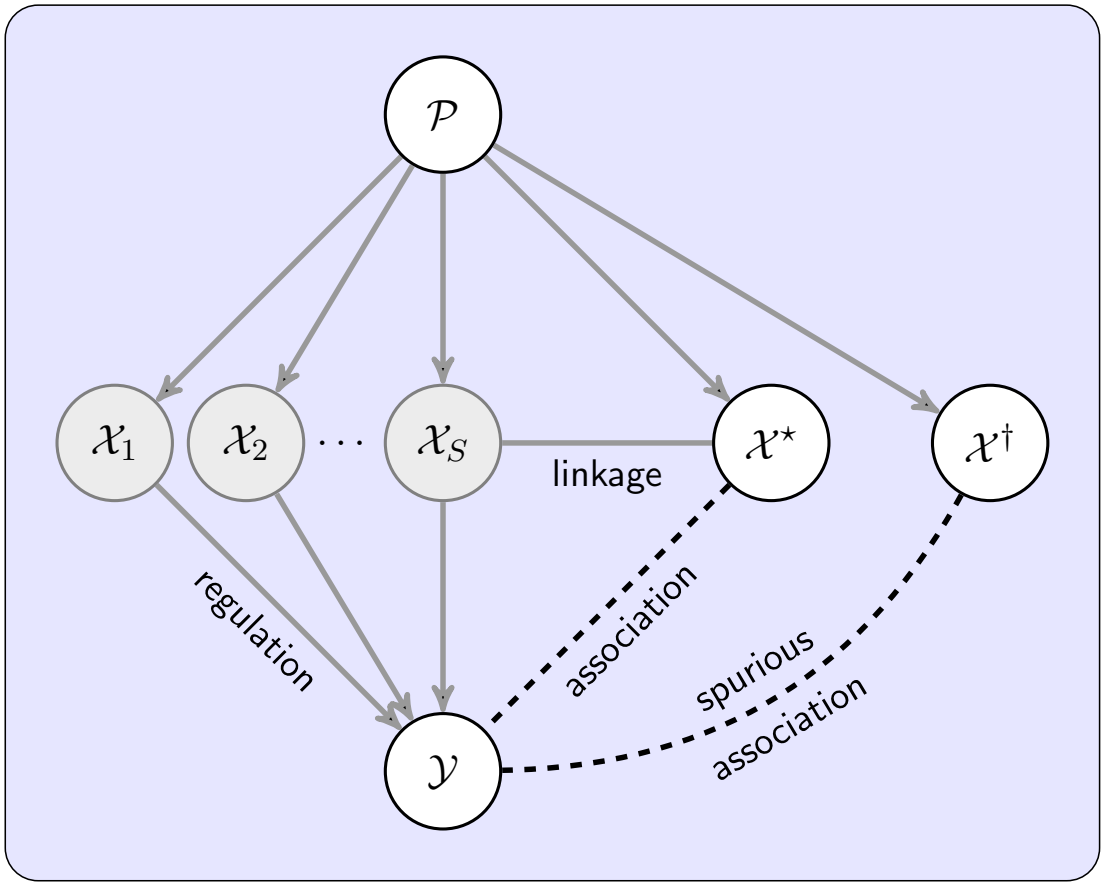

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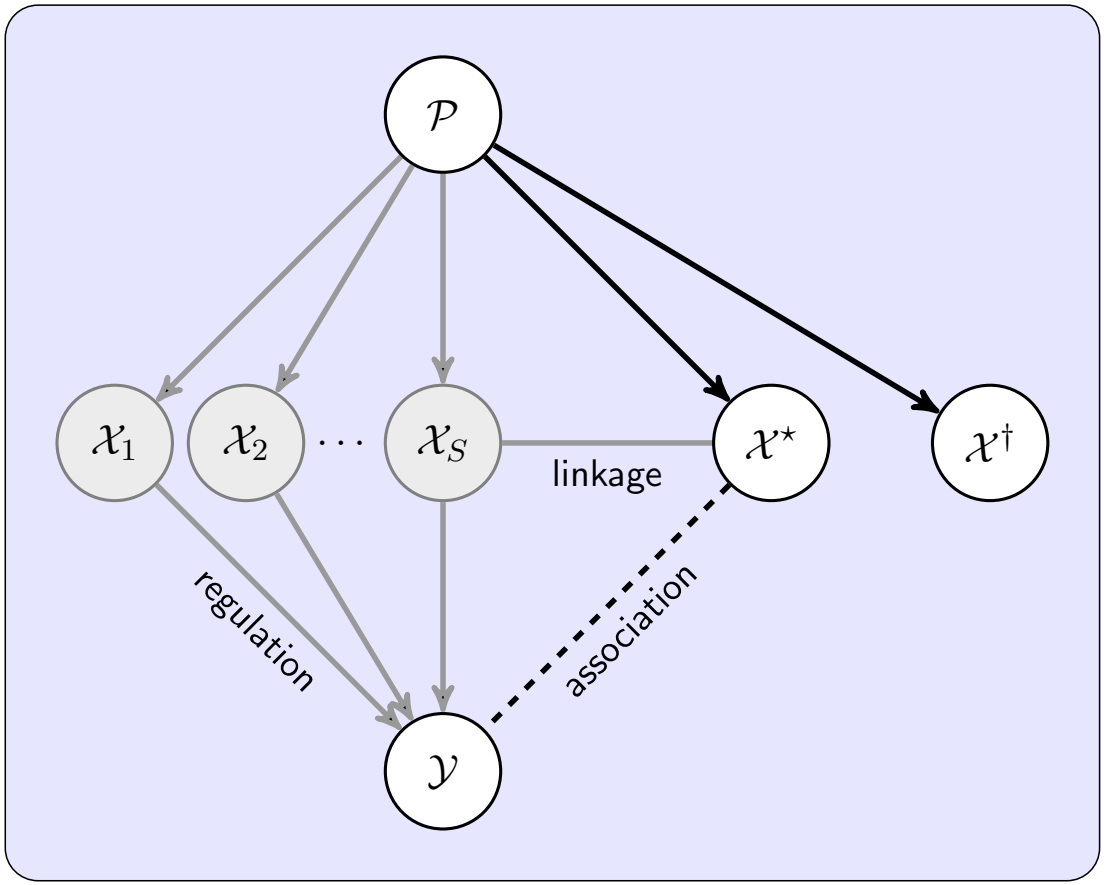

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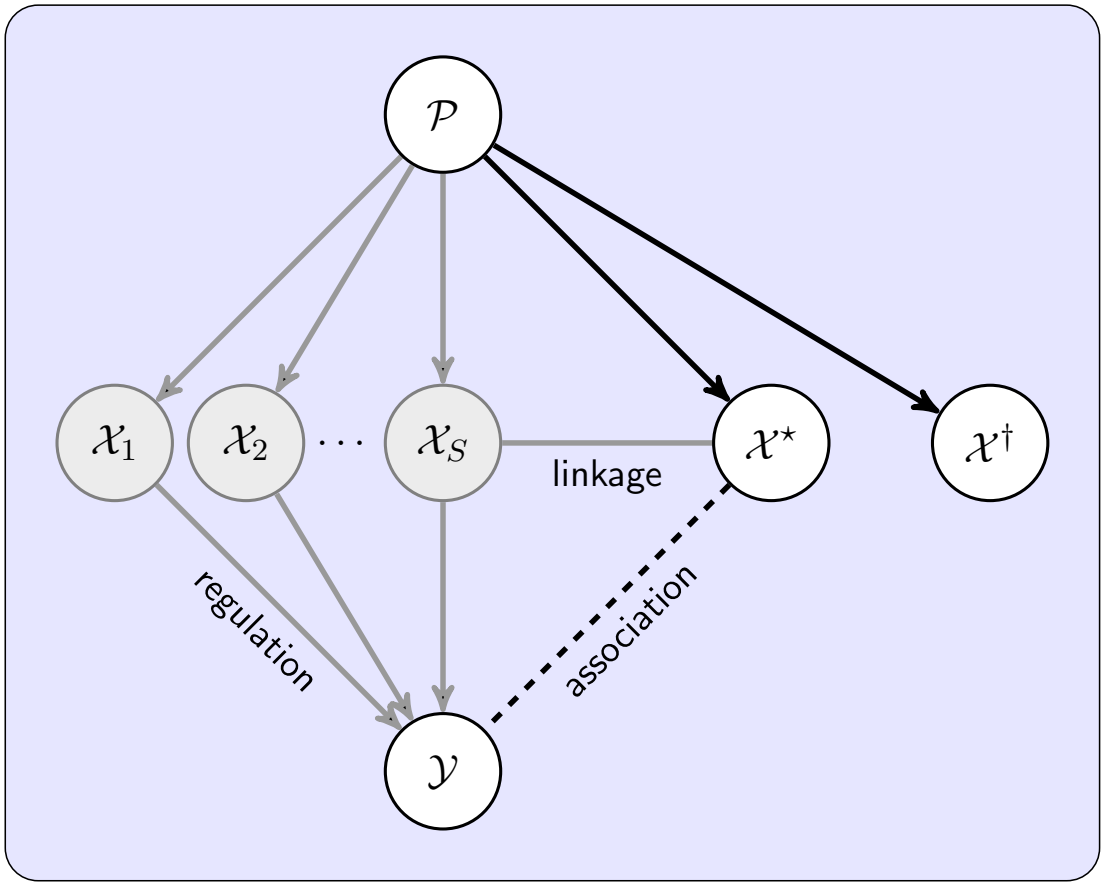

A LMM accounts for model misspecification when testing a univariate model when in reality the trait is multi-factorial.

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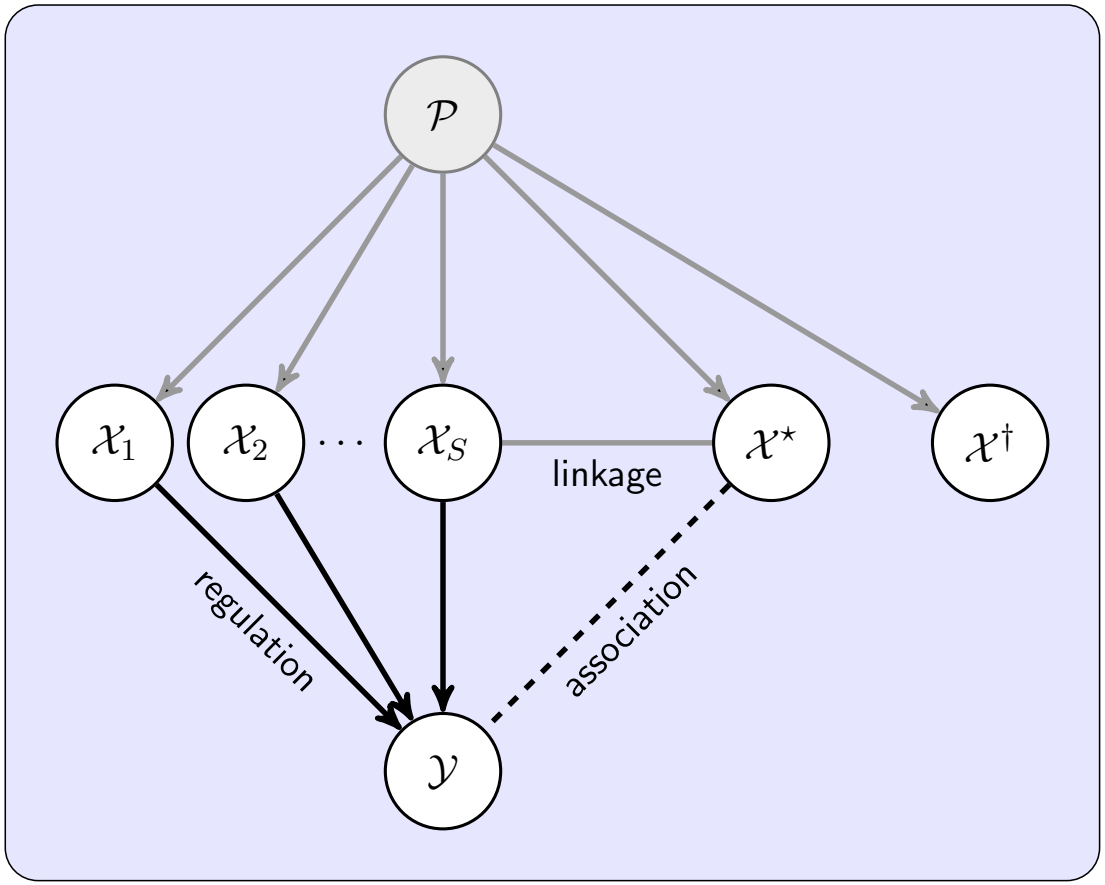

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Linear mixed models

Bayesian linear regression view

- *A LMM accounts for model misspecification when testing a univariate model when in reality the trait is multi-factorial.*
- For linear similarities, a LMM is equivalent to a *linear regression*.
- All SNPs are used as regression covariates.
- Uncertainty about identity of regulative SNPs expressed by using a Bayesian prior distribution on the regression weights.

$$\mathcal{N}\left(\mathbf{y}|\mathbf{x}\beta; \sigma_g^2\mathbf{K} + \sigma_e^2\mathbf{I}\right).$$

[Listgarten et al., 2012]

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Can we do better than using **all** SNPs for correction?

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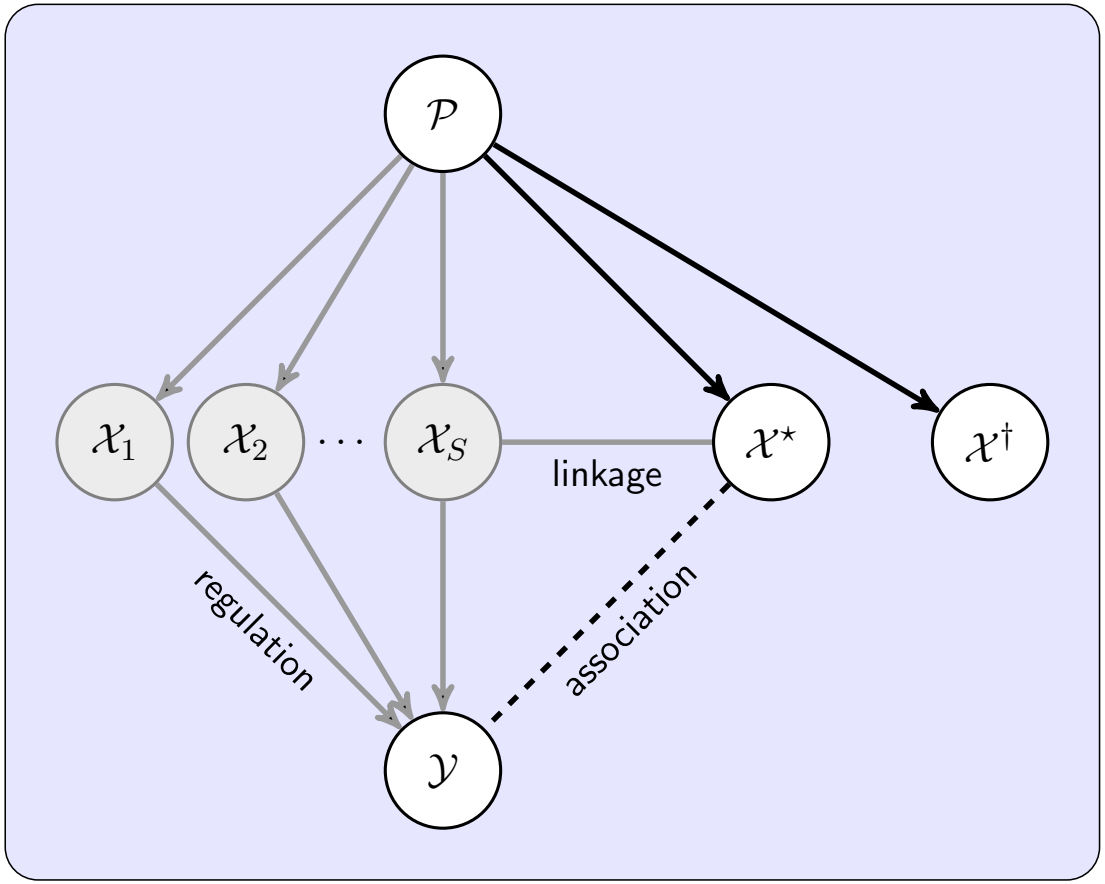
Can we do better than using **all** SNPs for correction?
$\rightarrow$ Select SNPs by their association to the phenotype.

[Listgarten et al., 2012]

FaST-LMM **select**

- Compute similarity matrix based on highly associated SNPs
- Equivalent to linear regression conditioned on these SNPs
- Conditioning on SNPs in LD blocks association.
  $\rightarrow$ False negative results!
- Remove SNPs in LD from computation of similarity matrix



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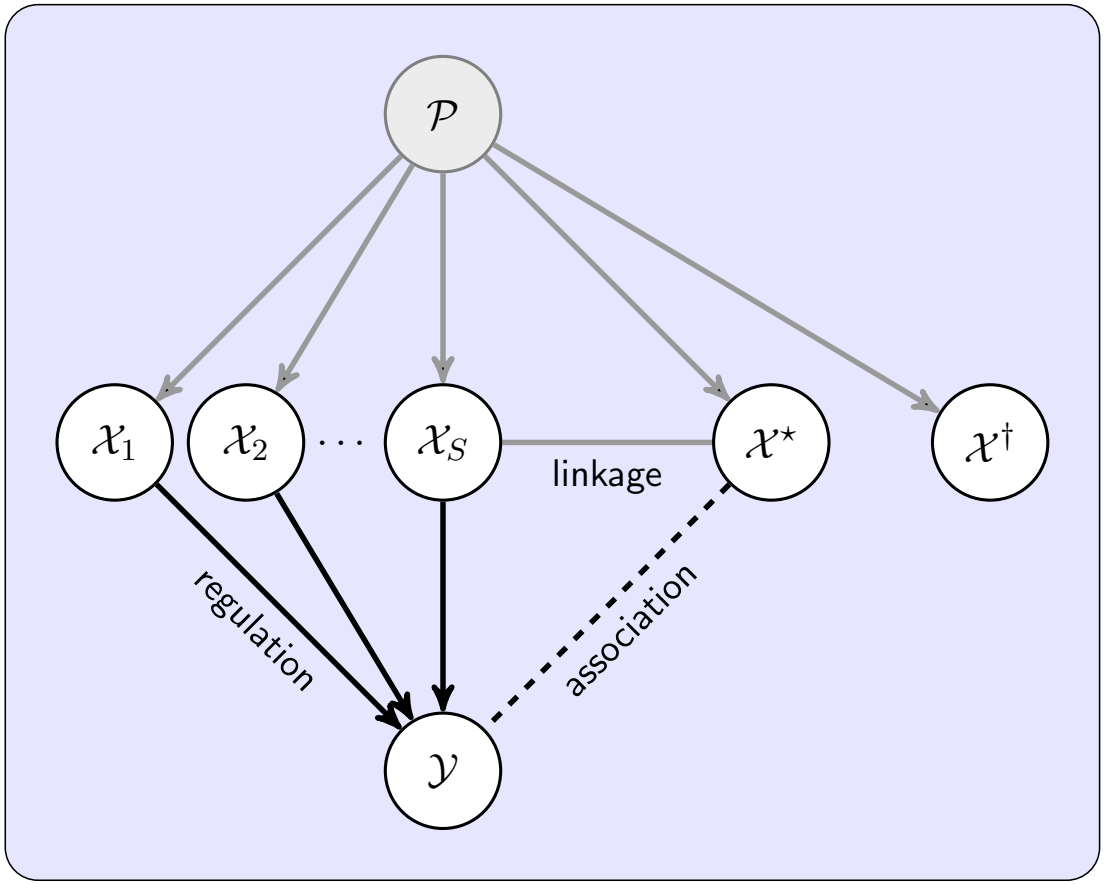

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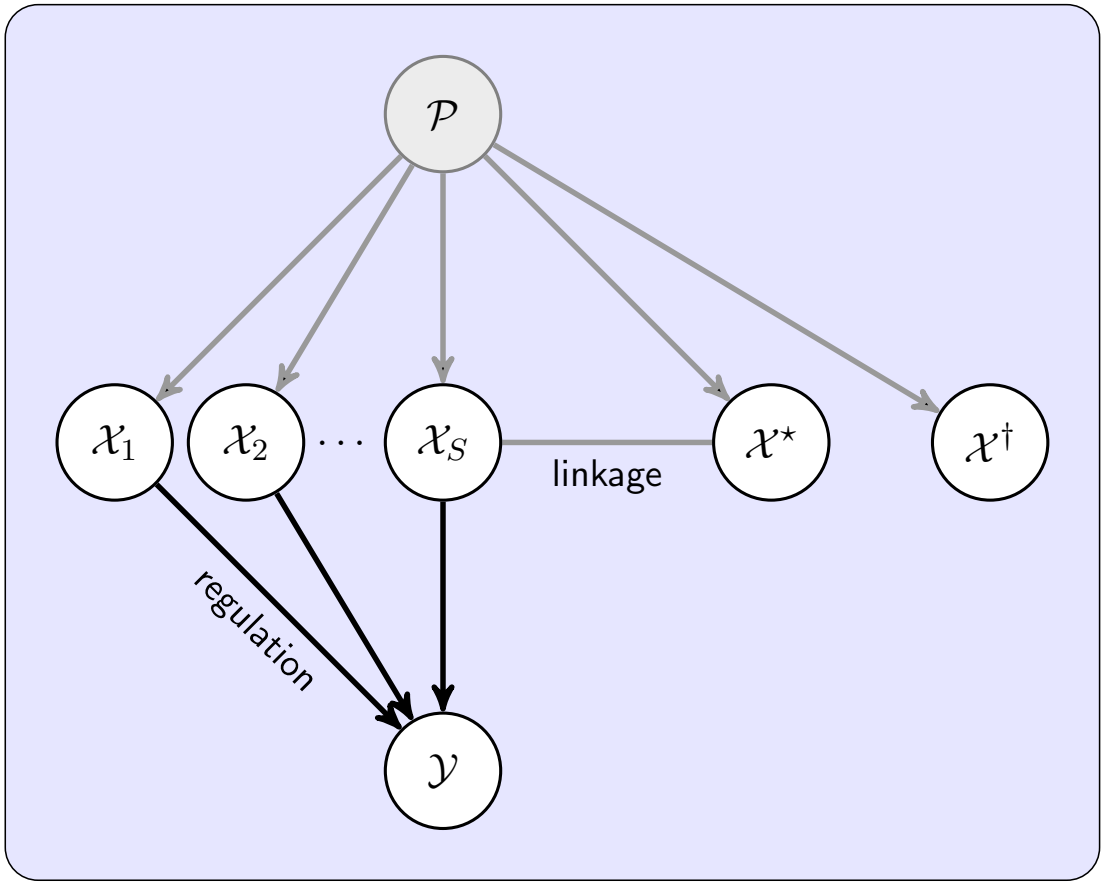

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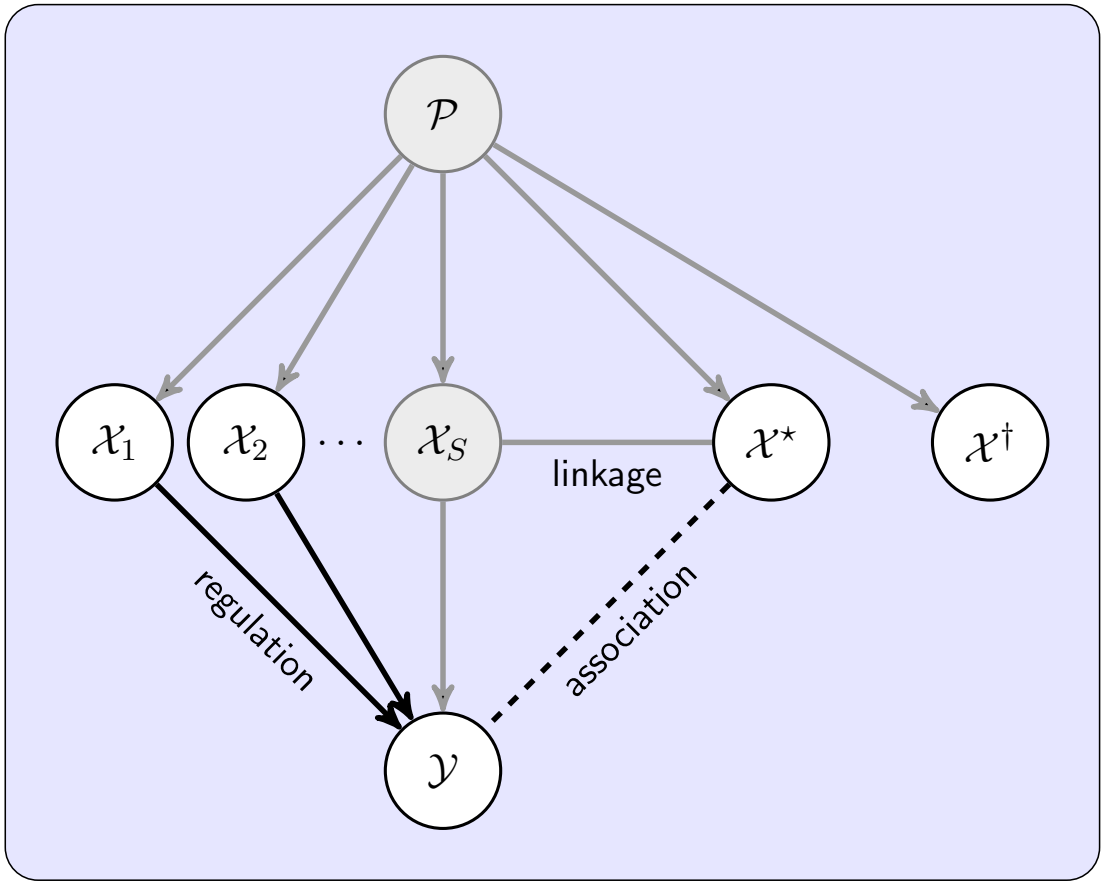

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Proximal contamination

- SNPs that are in close proximity on the chromosome are highly correlated.
- Having a SNP in the similarity matrix that is close to the SNP tested is equivalent to conditioning on this SNP in the null-model.
- Correct by removing a sliding window around test-SNP from the similarity matrix.
- Correction is computed efficiently by subtracting a low-rank term.

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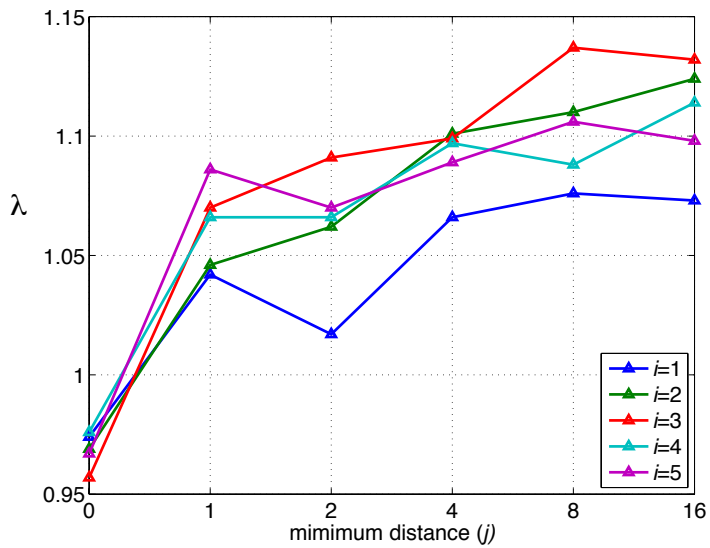

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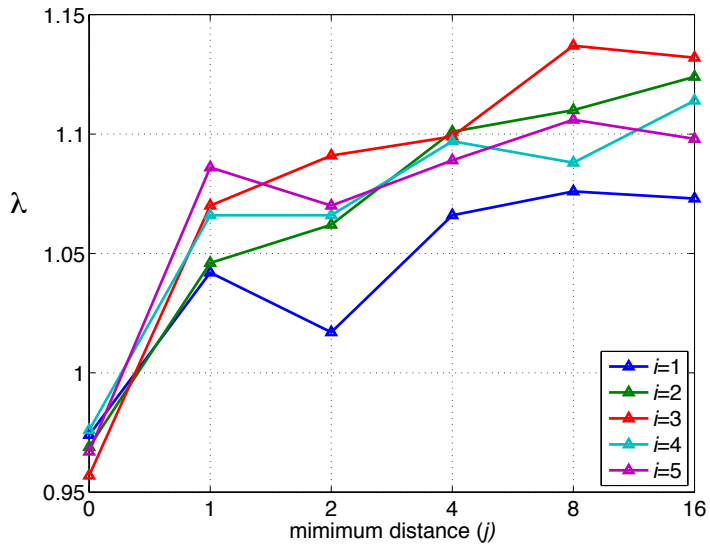

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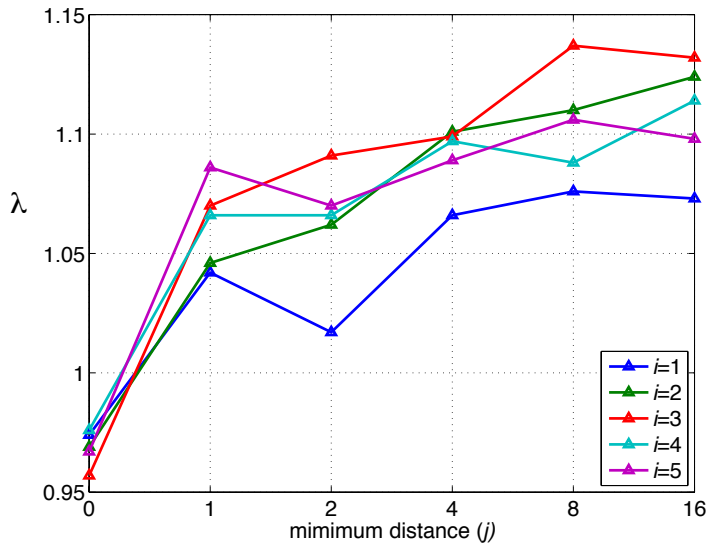

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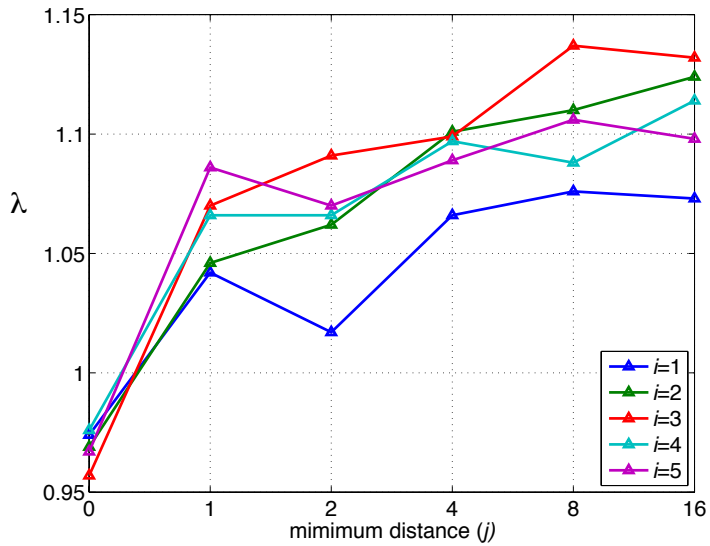

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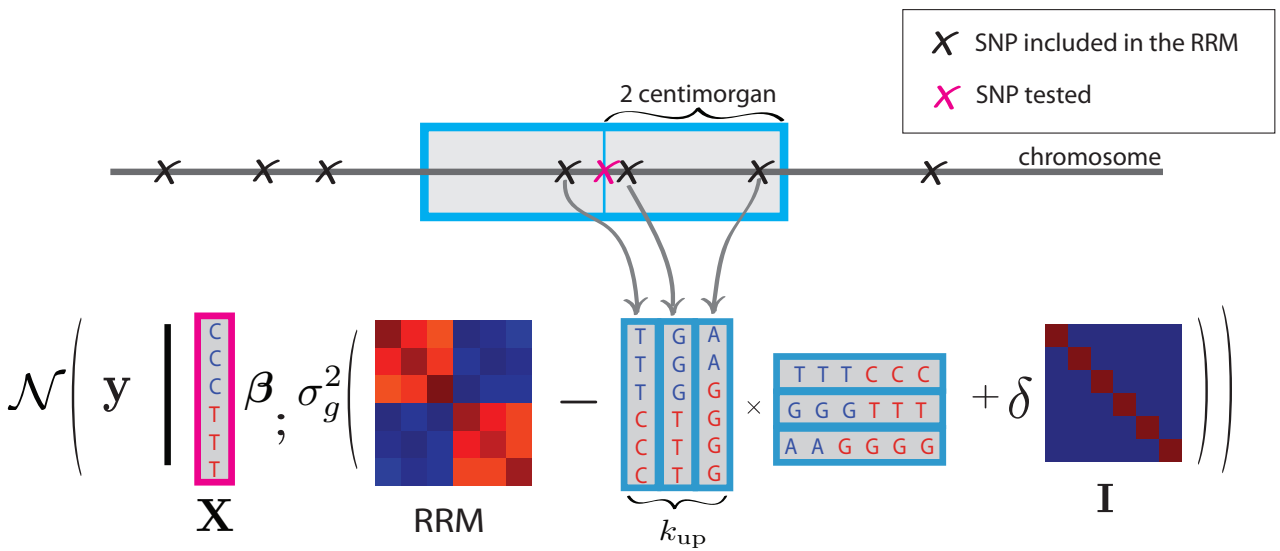

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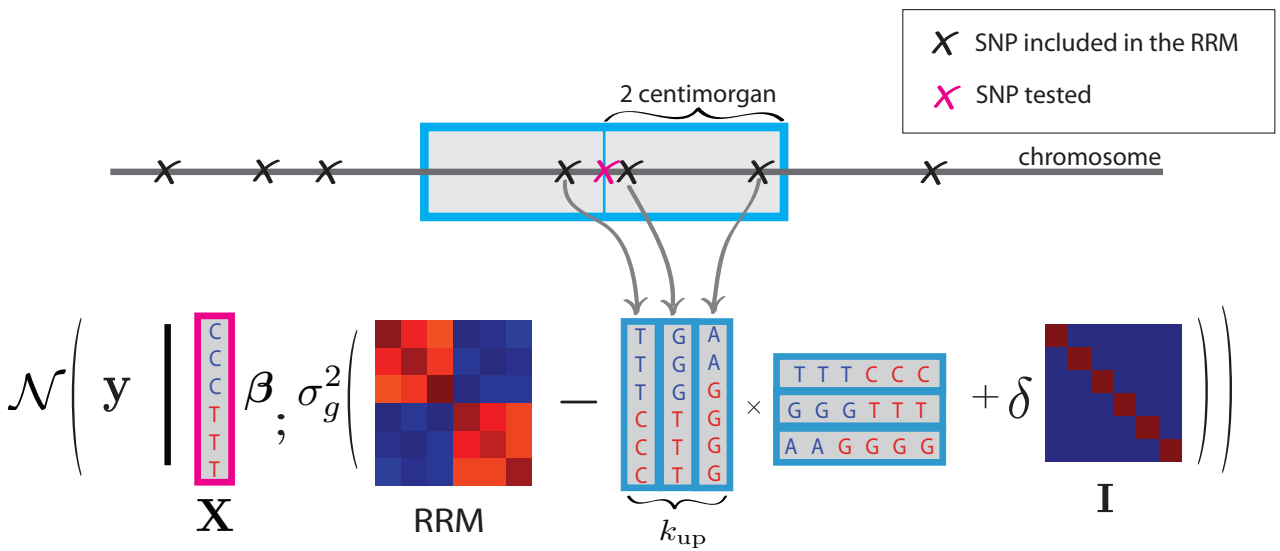

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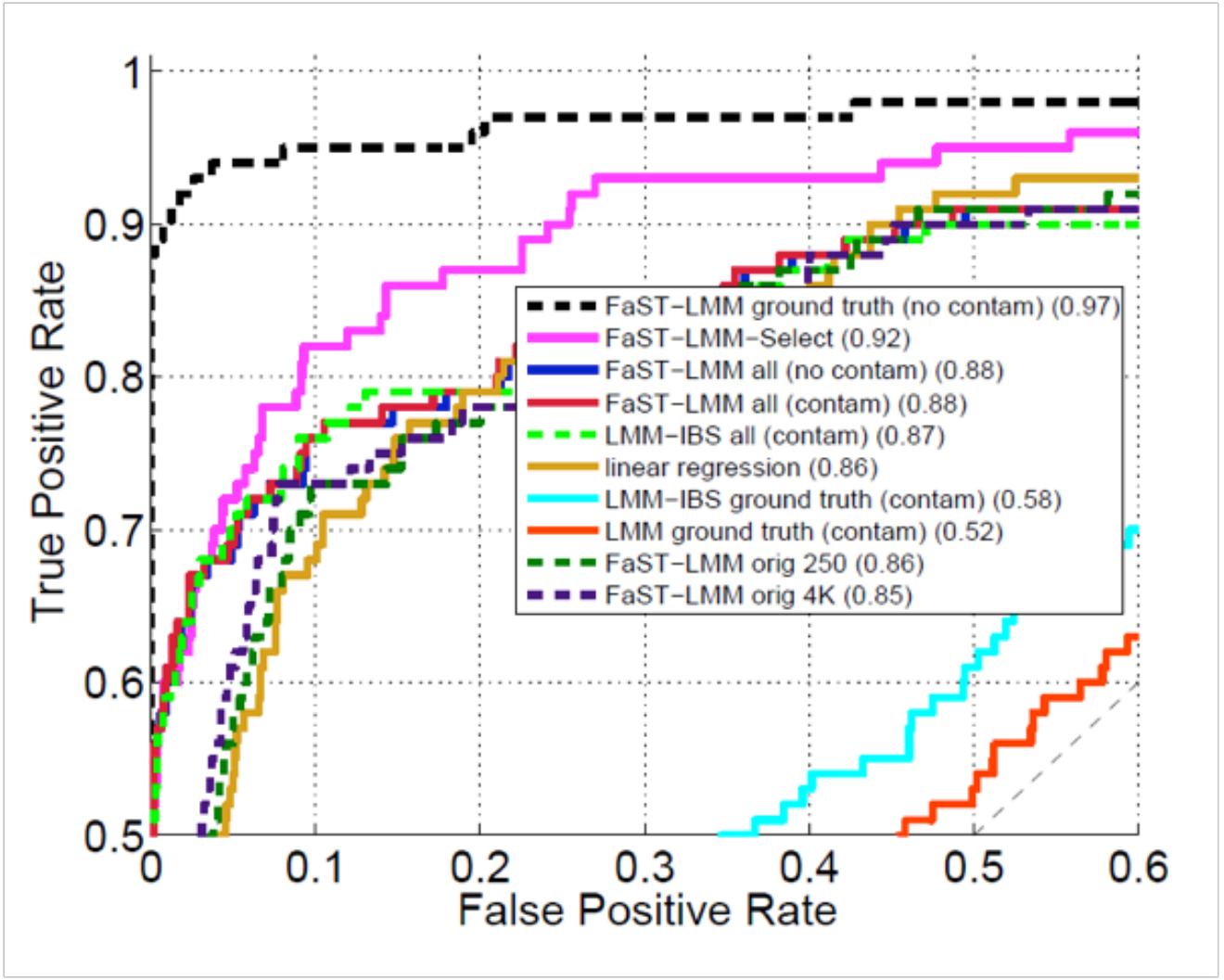
Power study

- 3000 individuals
- Two populations (6:4)
- Balding-Nichols model
- 100000 non-causal SNPs
- 100 causal SNPs ($\sigma_g^2 = \sigma_e^2 = 0.1$)
- Test-set of 5100 SNPs



[Listgarten et al., 2012]

Inflammatory bowel disease [WTCCC, Nature 2007]

Algorithm parameters				**Algorithm performance**					
Name	SNP selection method	#SNPs in matrix	Avoid prox contam	λ_{GC}	False Positives	True Positives	Runtime (min) without speedup	Runtime (min) with speedup	Memory use (GB)
FaST-LMM-Select	Select	310	yes	1.08	0	100	1.3×10^3	45	<1
FaST-LMM all	All	All	yes	1.09	2	108	4.0×10^6	4567	86
FaST-LMM orig 310	Equi-spaced	310	yes	1.26	15	128	1.1×10^3	6	<1
FaST-LMM orig 4K	Equi-spaced	4000	yes	1.17	8	114	2.1×10^5	30	2
Traditional	All	All	no	0.97	2	64	42	NA	45

SNPs considered True Positive if:

- Reported in WTCCC paper [WTCCC, Nature 2007]
- Reported in meta analysis [Franke et al., Nat Gen 2010]
- In major histocompatibility complex (MHC) region

[Burton et al., 2007]

Conclusions

- Relationship between linear mixed models and multi-variate modelling using linear regression
- Computing genetic similarities on associated SNPs improves correction *FaST-LMM* **select**
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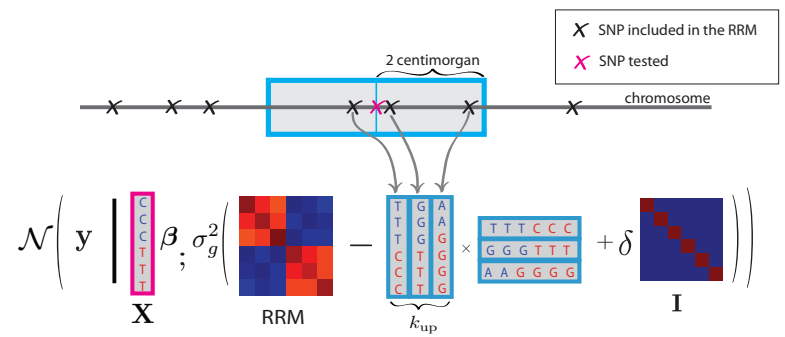

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