Probabilistic Analysis of Genetic Associations with Clinical Features in Cancer

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Motivation

Objective: Finding meaningful relationships between genetic information and clinical features.

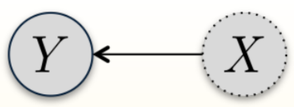
Why does it matter?

- Improved Diagnosis
- Risk Identification
- Biological Insight

Our models should be able to deal with...

- Epistasis
- Pleiotropy
- **Confounders**

Linear Mixed Model (State-of-the-art)



$$y = X\beta + u + \epsilon \quad (1)$$

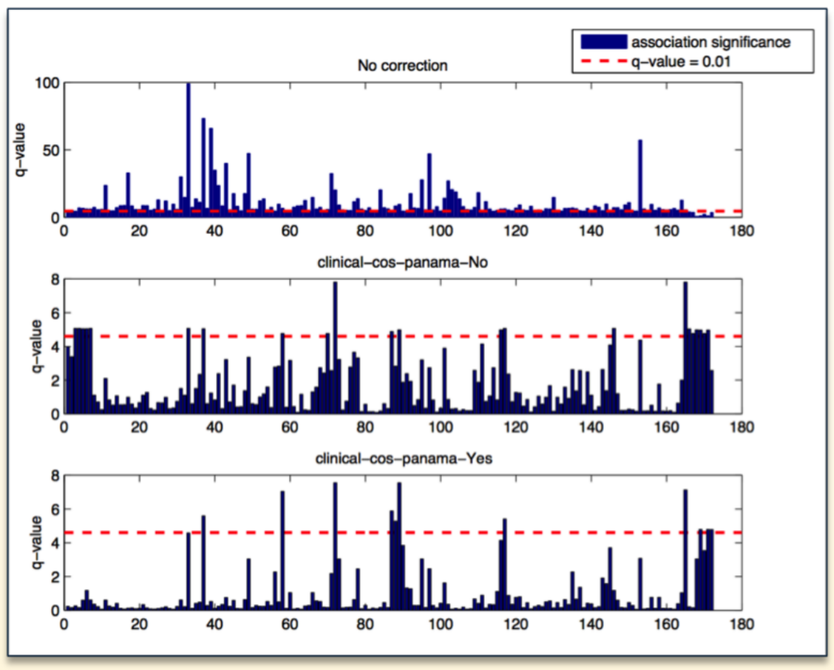
where

$$u \sim \mathcal{N}(0, K) \quad (2)$$
$$\epsilon \sim \mathcal{N}(0, \sigma_e^2 I) \quad (3)$$

- medical observation $y \in \mathbb{R}^{P\times 1}$
- genetic variation matrix $X \in \{0,1\}^{P\times G}$
- fixed effects $\beta \in \mathbb{R}^{G\times 1}$, random effects $u \in \mathbb{R}^{P\times 1}$
- K: covariance matrix (e.g. $K = CC^{\mathrm{T}}$)

- Classical model in statistical genetics [1]
- Rank Transformation to make Y observations Gaussian
- Inference of hidden confounders W using PANAMA [2], resulting in $y = X\beta + u + \epsilon + W\gamma$

Results LMM - Most Conservative



10 significant hits with clinical covariates, 165 without correction. Examples:

Gene	MAF	q-value	β	Sentence prototype
APC	112	0.0037	0.33	He underwent a colonoscopy which revealed a pedunculated polyp in the ascending colon.
ALK	40	0.0063	0.57	The patient showed a mild decrease in her blood counts.
HNF1A	13	0.0028	0.70	The patient was tearful presented with depressed affect and mood.
TRAF7	11	0.0008	0.59	He has a history of adenoid cystic carcinoma of the salivary gland.

Conclusion and Future Work

- LMM is easy to interpret and gives False Discovery Rate estimate
- PFM can deal with epistasis naturally and finds better clinical feature representation
- Sparsity of topics
- Conditional model of θ given C
- Non-parametric extension

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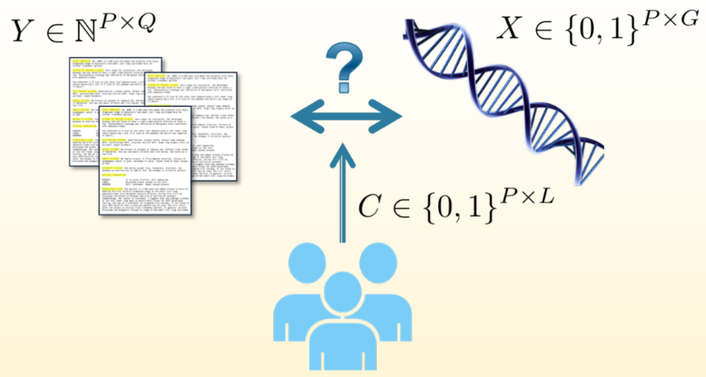
This work is based on unpublished MSKCC data.

Problem Setting

Notation

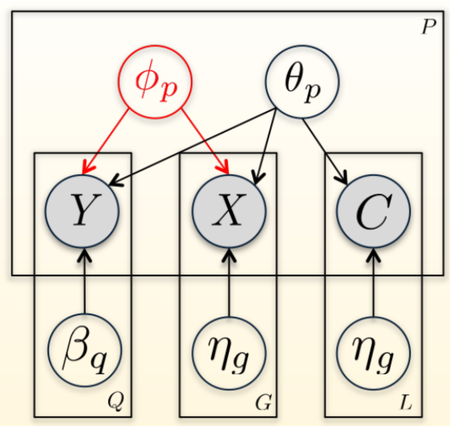
- P patients
- G genes
- Q features
- L covariates



Features are medical observations extracted from the Medical Health Records. This work considers sentence clusters and word topics.

Poisson Factorization Model

The idea is to build a joint generative model of the clinical text and genetic information.

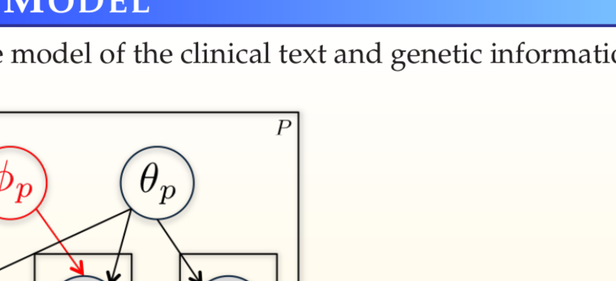


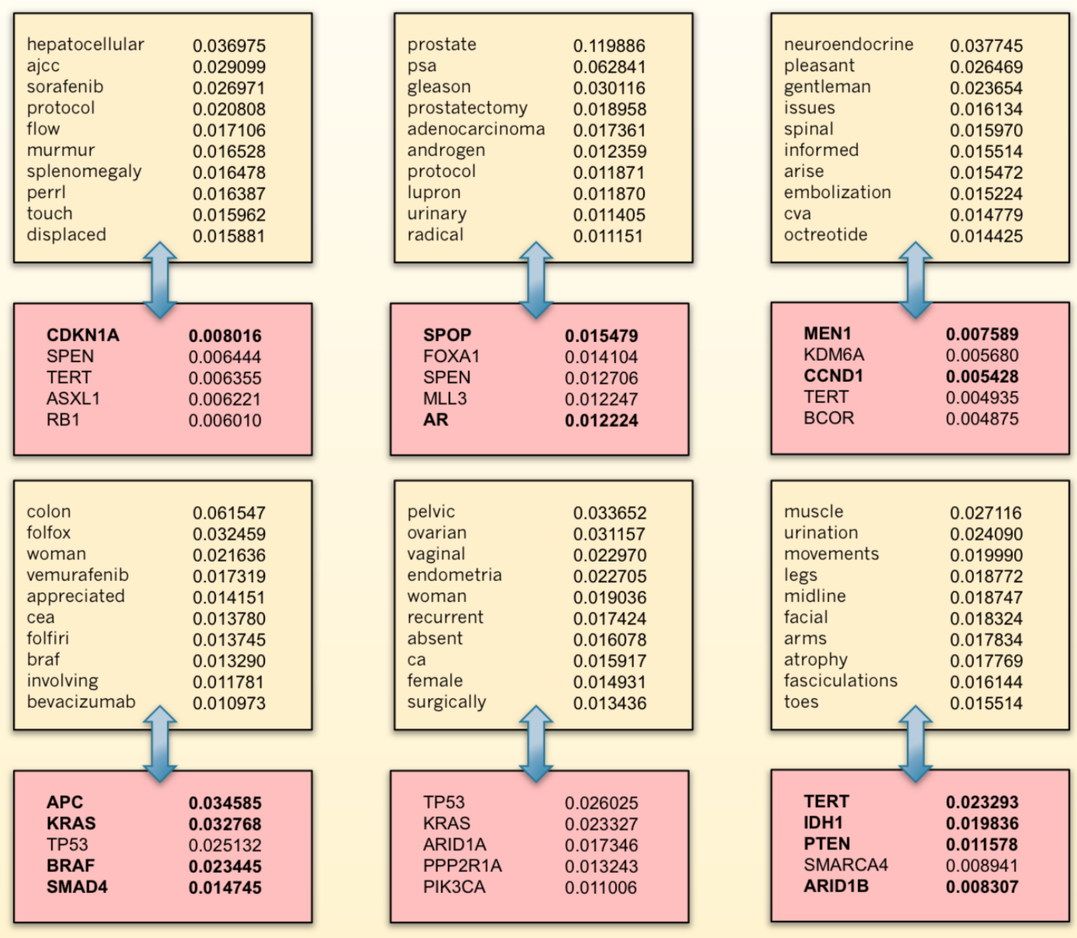
- Medical factors β_q
- Genetic factors η_g
- New interesting associations captured by ϕ, confounders by θ
- Based on [3], variational inference

$$x_{pg} \sim \text{Poisson}(\phi_p \eta_g' + \theta_p \eta_g) \quad (4)$$
$$y_{pq} \sim \text{Poisson}(\phi_p \beta_q' + \theta_p \beta_q) \quad (5)$$
$$c_{pl} \sim \text{Poisson}(\theta_p \zeta_q) \quad (6)$$
$$\text{rest} \sim \text{Gamma}(a, b) \quad (7)$$

Results PFM - Preliminary

- $P = 1265$ patients, $\sim 15k$ documents, G =343 genes, K =20 factors, $Q = 1k$ words out of $30k$ selected with highest it-idf index.
- Associations in grey generated by θ, in color by ϕ.
- Associations with genes in bold have a q-value $< 5.10^{-4}$.





- A False Discovery Rate estimate is obtained by plugging the inferred word topics to the LMM as new input matrix Y.

Basic References

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3 P. Gopalan and D. Blei, "Content-based recommendations with Poisson factorization", presented at the Advances in Neural Information Processing Systems 27, 2014.