Indian Buffet Process for Biomarker Discovery

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S. Stark, S. Hyland, J. Vogt, Gunnar Rätsch at MSKCC, New York

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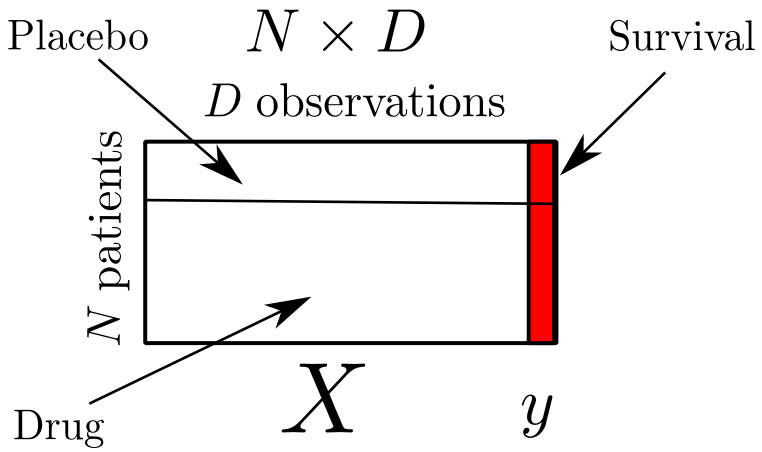
Example 1: Genetic Association Study

- Objective: Find association between genotype and phenotype.
- We would like a robust method able to deal with epistasis and pleiotropy while taking into account confounders.

Example 2: Clinical Trial



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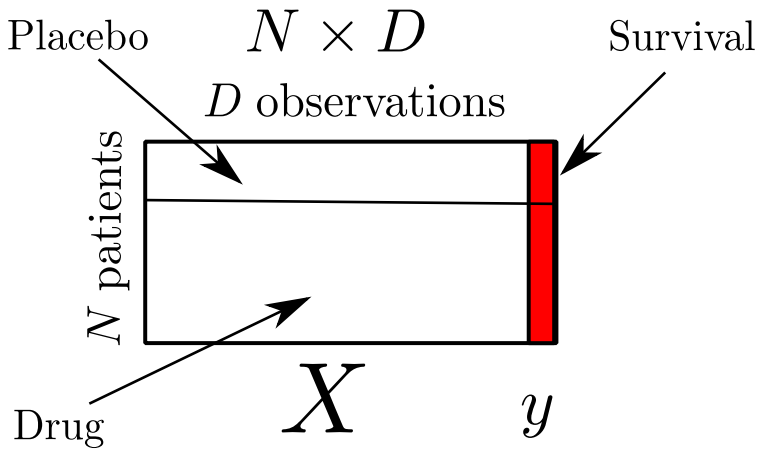

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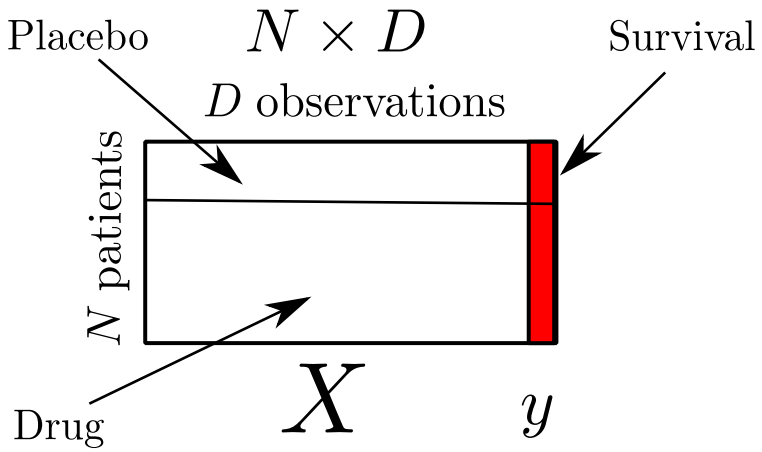

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Problem Formulation

Aim: Find interesting correlations (data exploration).

Challenges

- Noisy/missings
- Uncertainty
- Complexity
- Heterogeneity
- $N << D$

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Potential Approaches

X: observations matrix, y: survival, θ: model parameters, W: latent variables

Supervised Methods

$$y = f(X; \theta) + \epsilon \tag{1}$$

- Examples: Linear Regression, Lasso (Penalized LR), Gaussian Process, Random Forest, ...
- Problems: Not so easy to interpret, and $N << D$ makes it hard

Unsupervised Methods

$$(X, y) = f(W; \theta) + \epsilon \tag{2}$$

- Examples: Dimensionality Reduction, Clustering, **Latent Factors**, ...
- Advantages: Interpretable, flexible (suitable for data exploration)

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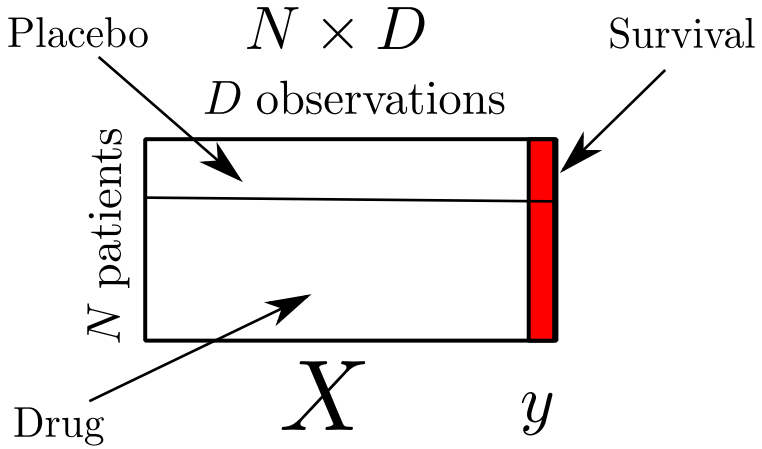
Our approach
A probabilistic perspective

- Focus on latent factor models using Bayesian non-parametrics.



$$Z \sim \text{Indian Buffet Process}(\alpha) \quad (3)$$

- Bayesian: Put a prior over assumptions
- Non-parametric: Model complexity, i.e., number of latent vars., is also infered

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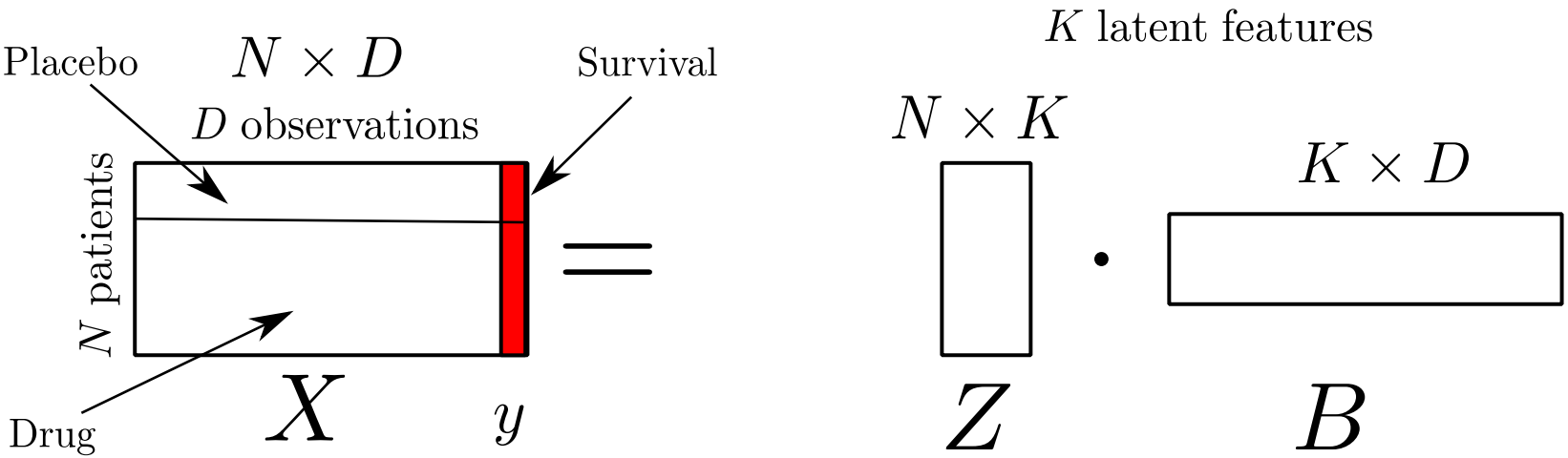

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Previous Works using the IBP

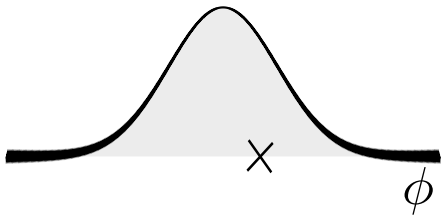
- Identify patients at risk of suicide attempts [F.J.R. Ruiz et.al, NIPS2012].
- Find out latent relationship among psyquiatric disorders [F.J.R. Ruiz et.al, JMLR2014, I. Valera et.al, NC2015].
- Analysis of gene expression data [D. Knowles, and Z. Ghahramani, 2011]
- Discovery of biological interaction networks [H. Son, B. Joseph, 2011]
- Multi-platform Genomics [Ray et. al. 2014]
- Modeling of genetic tumor variations [Chen et. al. 2013, Lee et. al. 2015]

Outline

Indian Buffet Process

- IBP: distribution over binary matrices $Z_{N \times K}$
- Model chooses number of hidden features, $K \to \infty$
- Finite N implies finite number of non-zero columns K_+.

Indian Buffet Process



$$x \sim \mathcal{N}(\mu_0, \sigma_0^2) \longrightarrow x = 0.356$$

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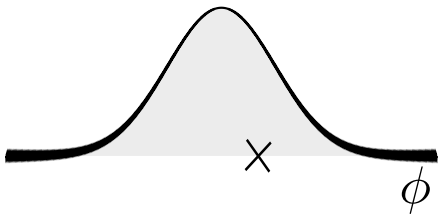

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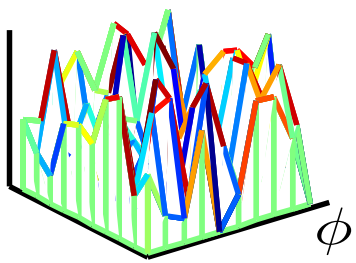

$$Z \sim \mathrm{IBP}(\alpha) \longrightarrow Z = \begin{bmatrix} 1 & 0 & 1 \\ 0 & 1 & 0 \\ 1 & 1 & 0 \\ 1 & 0 & 1 \end{bmatrix} \vdots$$

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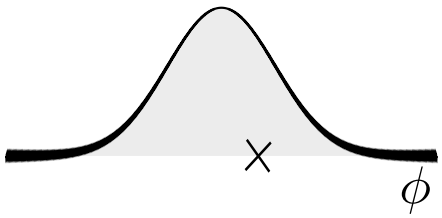

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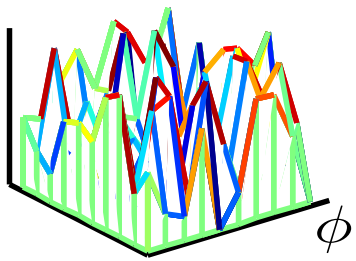

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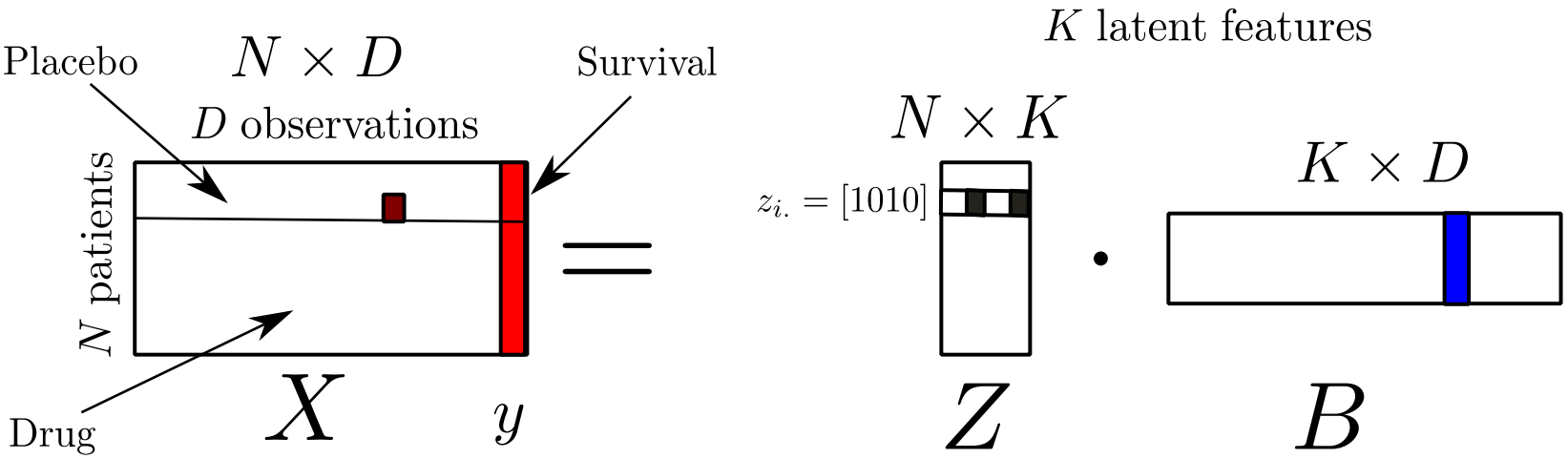
Infinite Latent Feature Model



- $x_{id} = 173\,\mathrm{ml/dL} = 73 + 0 + 100\,\mathrm{ml/dL}$

Note: Correlation does not imply causality!

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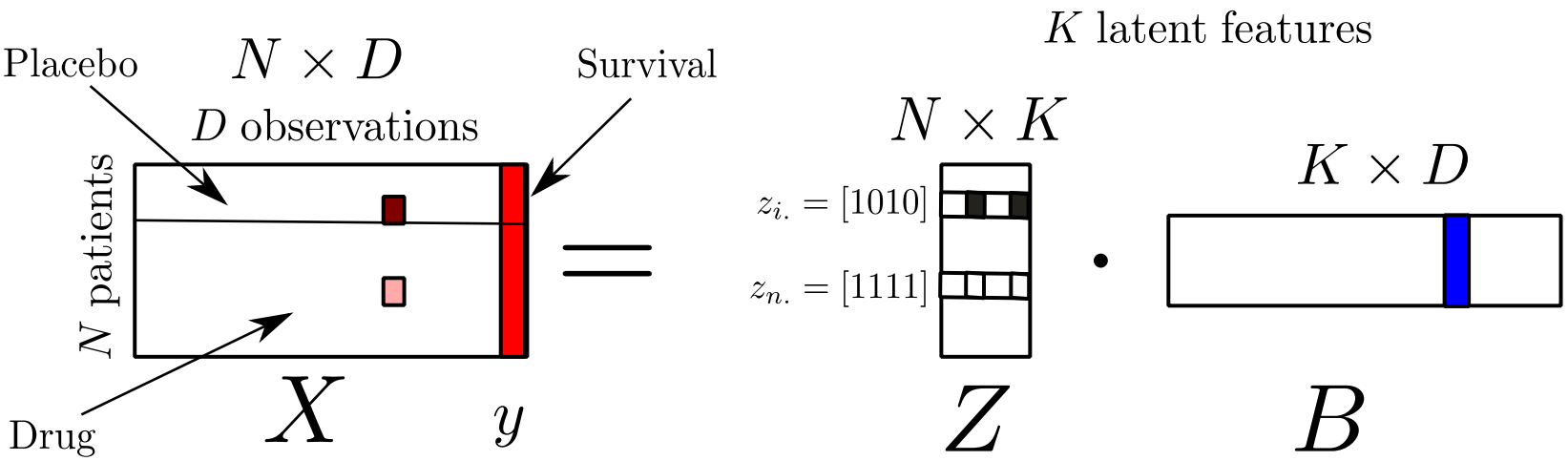

- $x_{id} = 173\,\mathrm{ml/dL} = 73 + 0 + 100\,\mathrm{ml/dL}$
- $x_{nd} = 136\,\mathrm{ml/dL} = 86 + 40 + 60 - 50\,\mathrm{ml/dL}$

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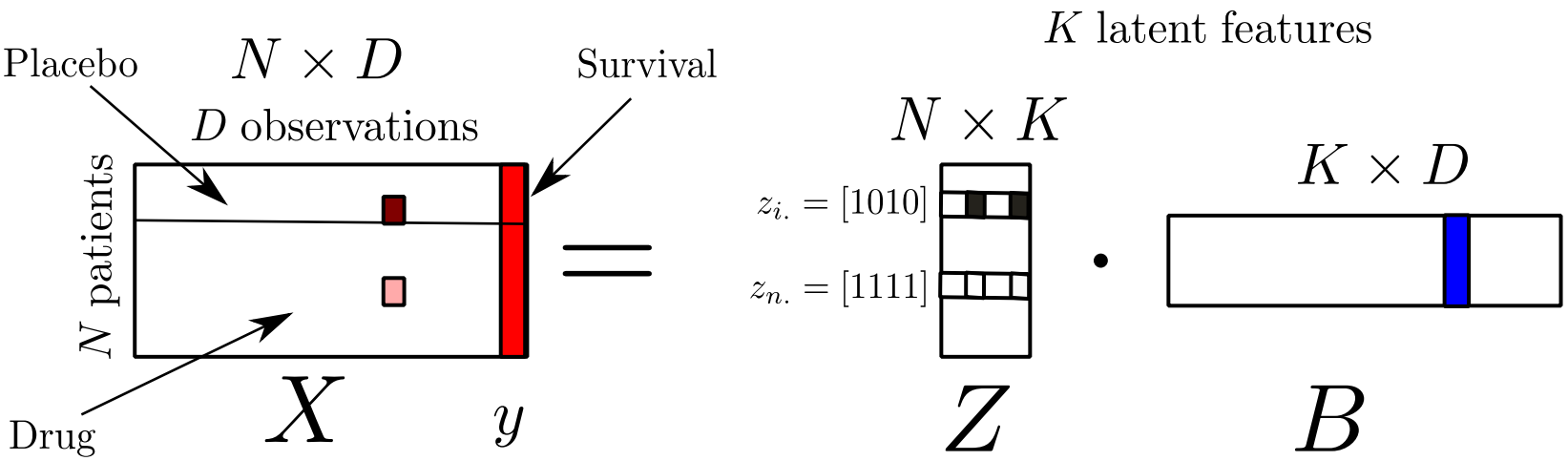

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Addressing the challenges

Challenges

- Noisy/missings
- Uncertainty
- Complexity
- Heterogeneity
- $N << D$

Our Approach

Challenges

- Noisy/missings
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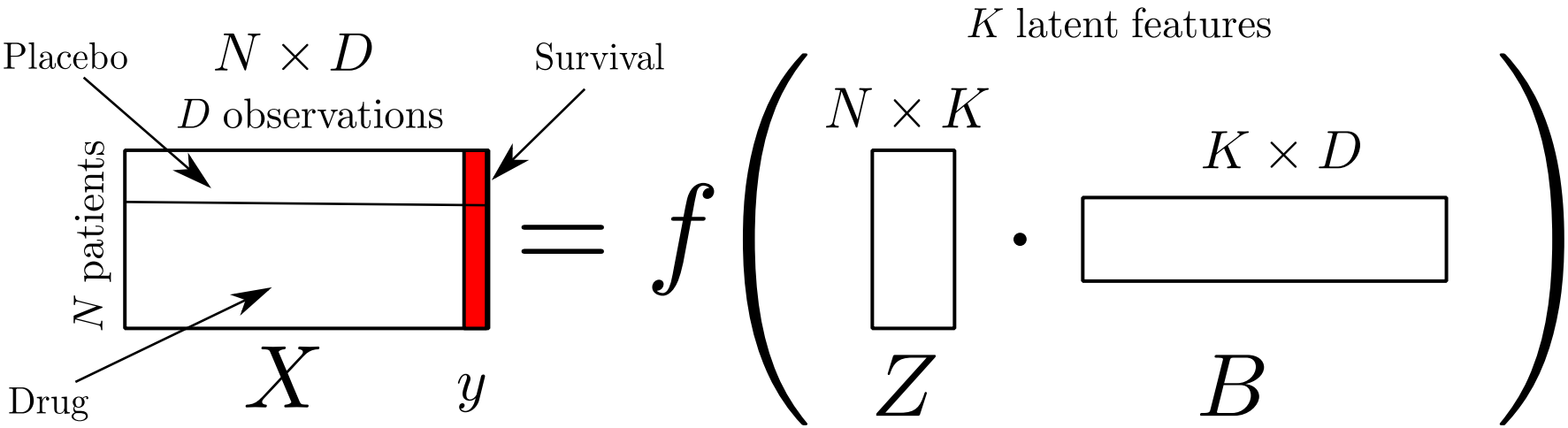
Our Approach

- Probabilistic Models
- Bayesian Approach
- Non-parametric
- Generalized
- Sharing Information

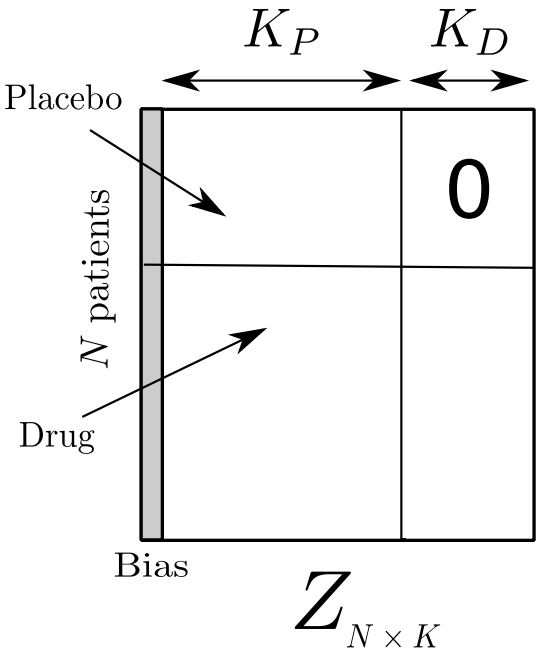
What about heterogeneous data?



- Generalized IBP [I.Valera et.al, 2015]
- Idea: assume auxiliary Gaussian latent variables, and choose link function f depending on data type

How about $N << D$ problem?

1. Shared information between all patients
   - Placebo patients define background population
   - Some extra features only for patients taking the drug
2. Robust method: bootstrapping + soft partitions



Robust Methodology

1. Sample from posterior $p(Z|\text{data})$ to identify interesting subpopulations
2. Analysis of feature effect on observations
   - Define patterns of interest G^* and reference G^B
   - Do Bootstrapping L times (to deal with low N)
   - Compute measure of effect size and significance

Outline

Database
GC33 Antibody Treatment against Liver Cancer

- Clinical trial with N =180 patients
- 60 patients take Placebo, 120 take the drug
- $D = 80$ observations (including demographics, clinical data, and survival)

- Our model uses:
  - 3 features to define whole population
  - 1 extra feature for Drug population

Partition according to Feature Patterns

Nr.	Patterns					Occur. (number patients)	Mean TFPD (months)	Median TFPD (months)
	F1	F2	F3	F4	F5			
1.	0	1	0	0	0	33.37	3.06	1.65
2.	0	1	0	1	0	4.07	2.29	2.24
3.	0	1	1	0	0	17.84	2.72	1.81
4.	0	1	1	1	0	4.72	7.05	7.18
5.	1	1	0	0	0	51.52	3.22	2.55
6.	1	1	0	0	1	16.77	4.17	3.65
7.	1	1	0	1	0	8.38	1.74	1.33
8.	1	1	0	1	1	2.07	2.69	2.65
9.	1	1	1	0	0	29.88	3.36	2.03
10.	1	1	1	0	1	4.90	4.44	4.34
11.	1	1	1	1	0	4.53	6.31	5.31
12.	1	1	1	1	1	1.94	10.04	10.01
Total	120.00	180.00	63.82	25.72	25.69	180	3.44	2.04

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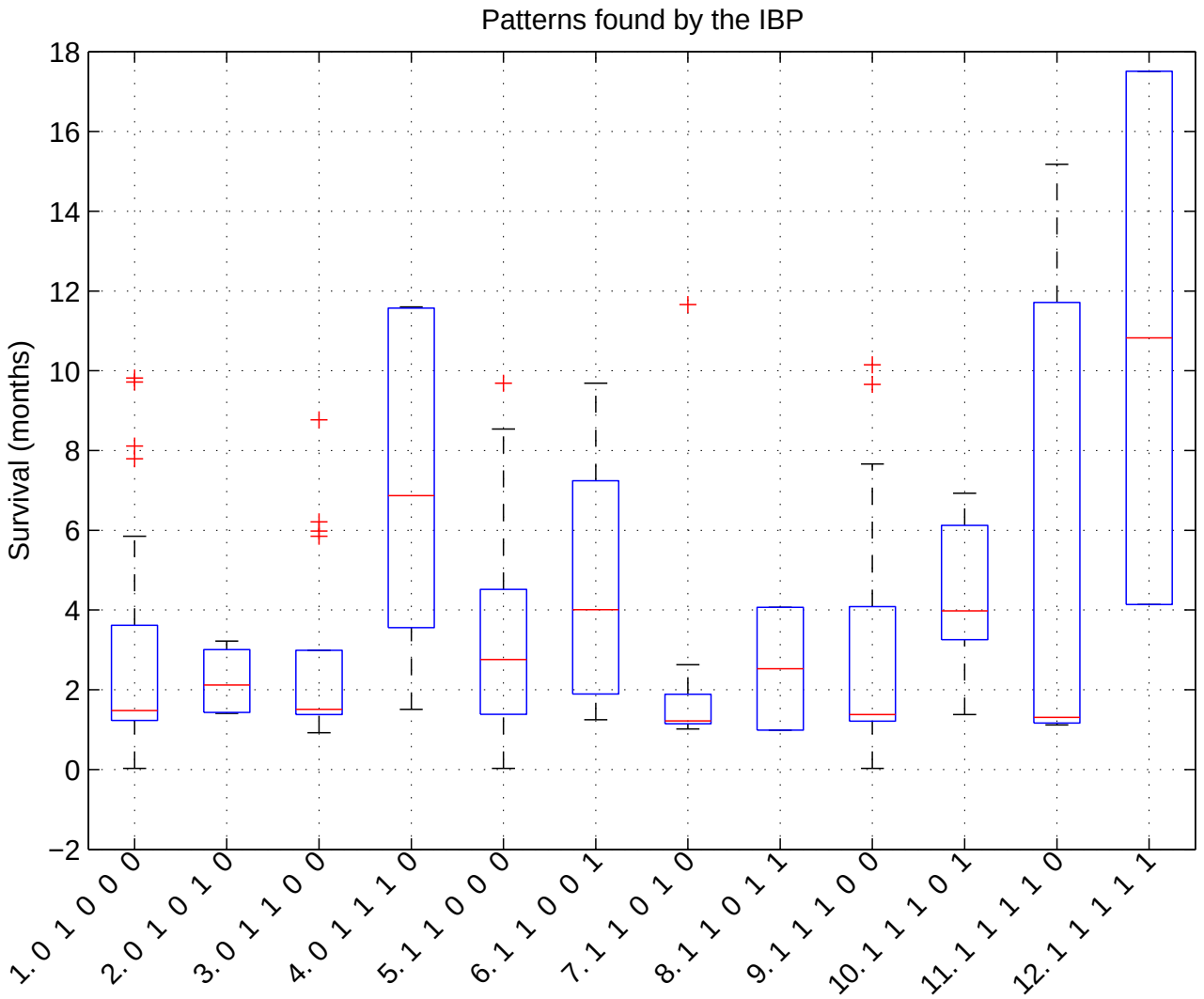

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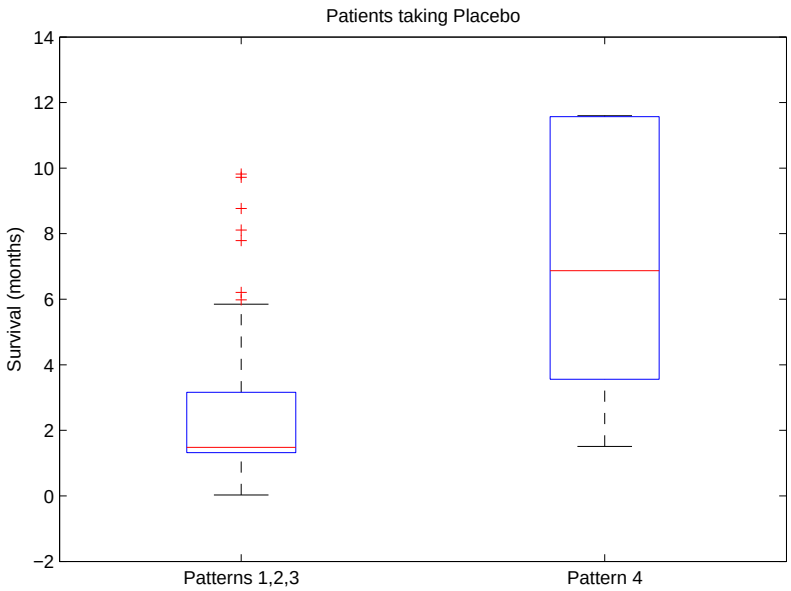
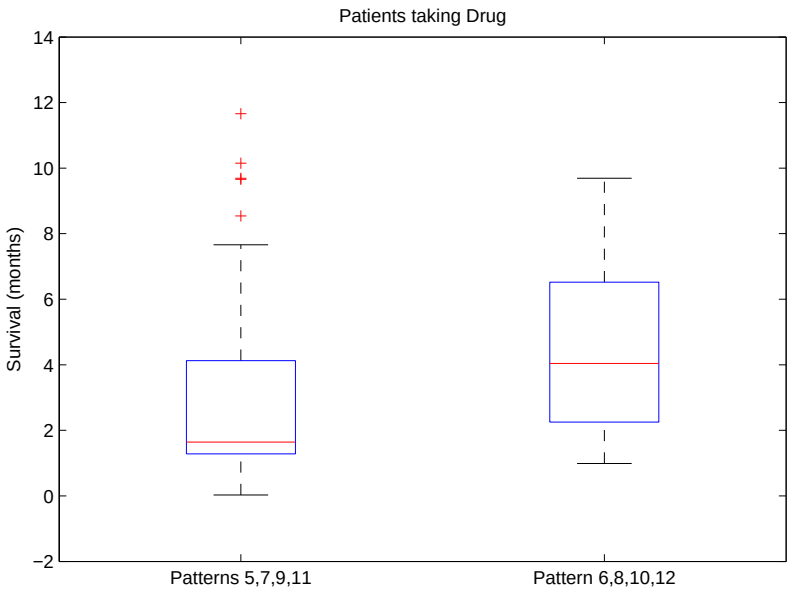
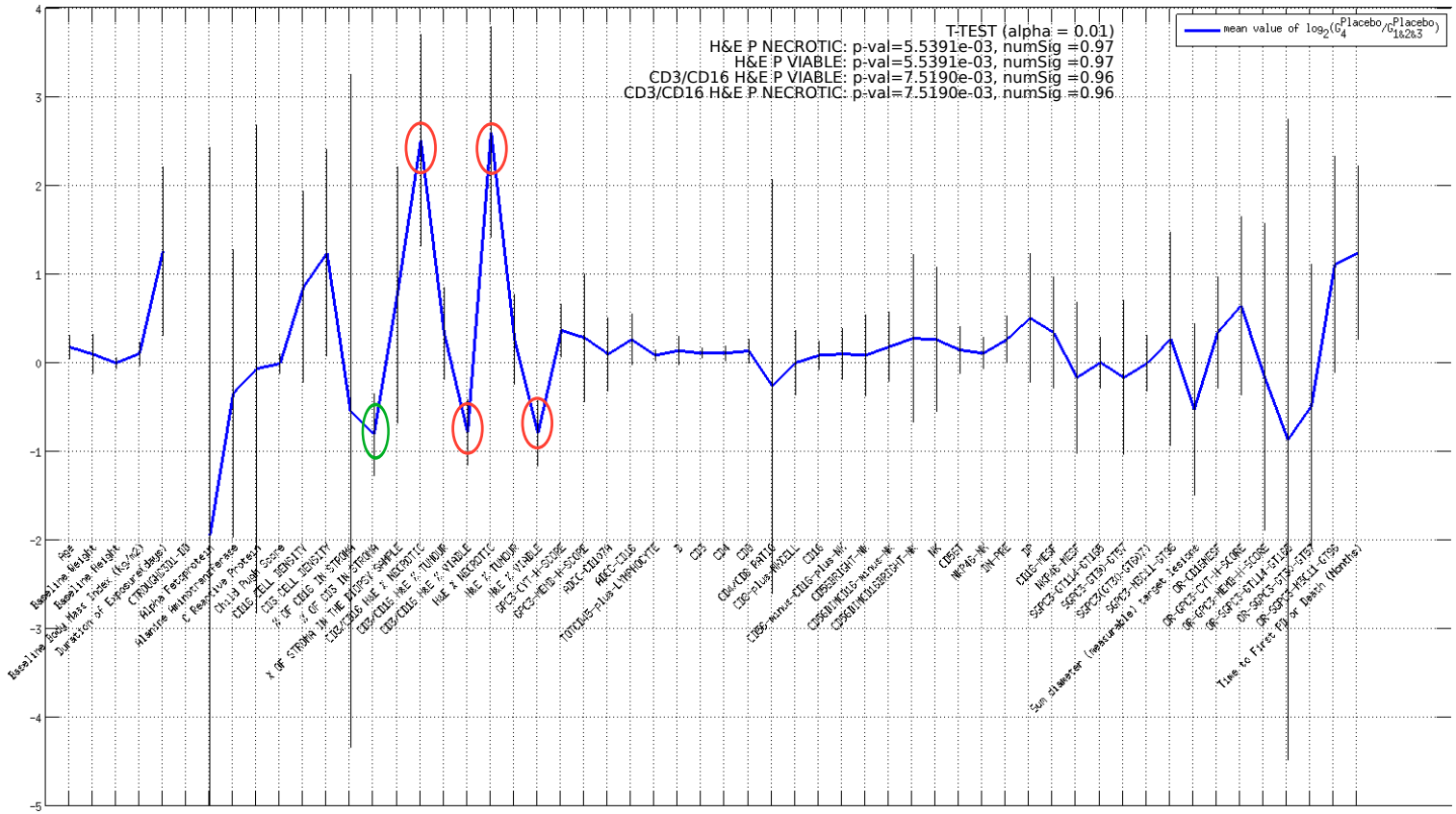




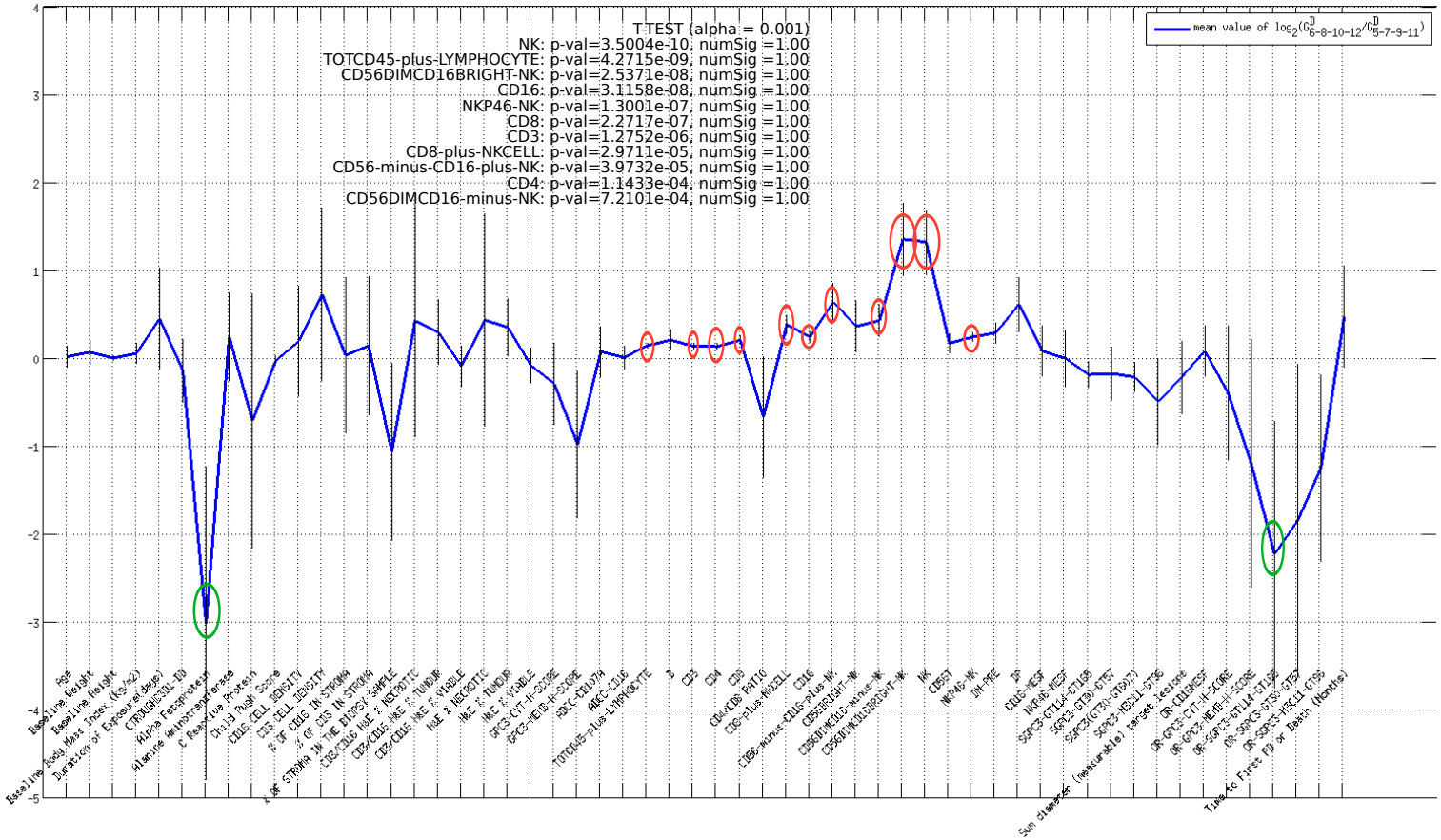
Strong Placebo Vs Normal Placebo

1. Which observations have an impact on survival?



Strong Drug Vs Normal Drug

2. Which observations make the drug work?



Outline

Conclusions

In this talk...

- Bayesian Non-parametrics for Data Exploration
- Indian Buffet Process in Latent Feature Models
- IBP Adaptation for Clinical Trial Problem

In particular...

1. Identification of subpopulations
2. Potential prognostic and predictive variables

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In particular...

1. Identification of subpopulations
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My contribution to the MLPM network

- Probabilistic models for data exploration

Challenges I address

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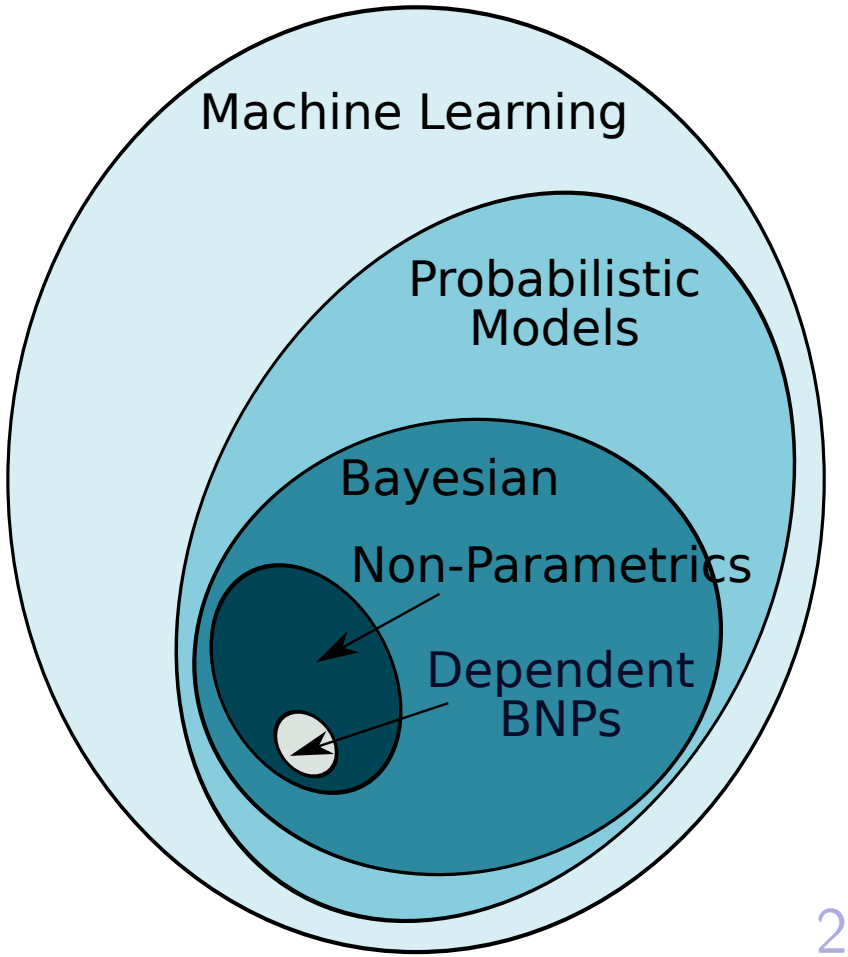
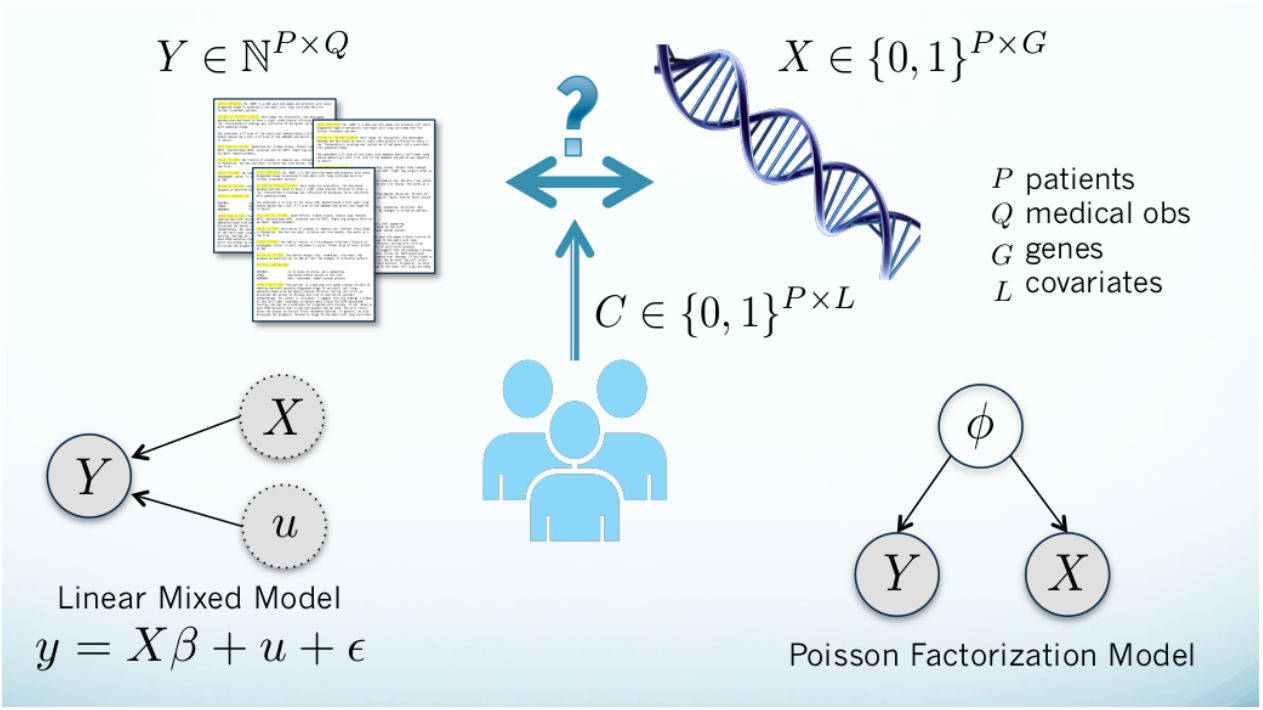
- Uncertainty
- Complexity
- Heterogeneity
- $N << D$
- Confounders



Probabilistic Modeling for Genetic Associations in Cancer

Current and future research results at: www.melaniefpradier.work

- M. F. Pradier, S. Stark, S. Hyland, J. E. Vogt, G. Rätsch and F. Perez-Cruz. **Large-Scale Sentence Clustering from Electronic Health Records for Genetic Associations in Cancer**, Paper at Machine Learning for Computational Biology Workshop (NIPS 2015).
- M. F. Pradier, F. Perez-Cruz and G. Rätsch. **Sparse Poisson Factorization Model for Genetic Associations with Clinical Features in Cancer.** Working paper. 2016.

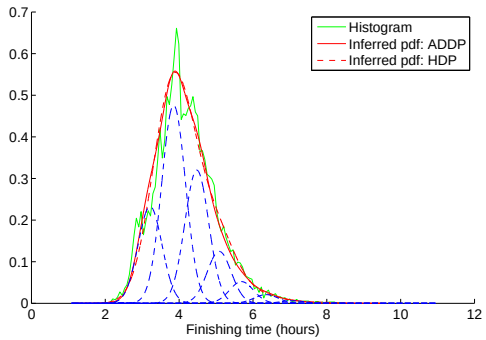


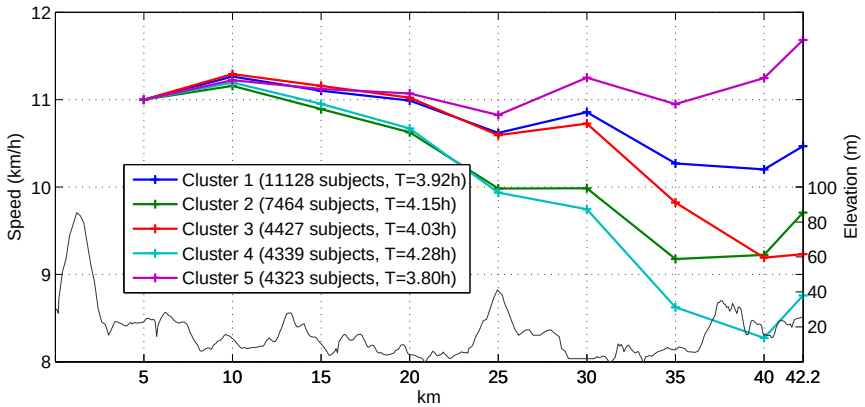
Past Projects

Current and future research results at: www.melaniefpradier.work

M. F. Pradier and F. Perez-Cruz. **Infinite Mixture of Global Gaussian Processes.** Paper at Bayesian Non-parametric: the Next Generation Workshop (NIPS 2015).

M. F. Pradier, F. J. R. Ruiz and F. Perez-Cruz. **Prior Design for Dependent Dirichlet Processes: An Application to Marathon Modeling.** Published at PlosONE. January 2016.





M. F. Pradier, P. G. Moreno, F. J.R. Ruiz, I. Valera, H. Mollina-Bulla and F. Perez-Cruz, **Map/Reduce Uncollapsed Gibbs Sampling for Bayesian Non Parametric Models.** Workshop in Software Engineering for Machine Learning (Software Workshop at NIPS). 2014.

Acknowledgments

Current and future research results at: www.melaniefpradier.work

- Fernando Perez-Cruz
- Gunnar Rätsch
- Francesca Miletti
- Oscar Puig
- Francisco J.R. Ruiz
- Isabel Valera
- CB at MSKCC
- TSC at UC3M
- Marie-Curie ITN-MLPM

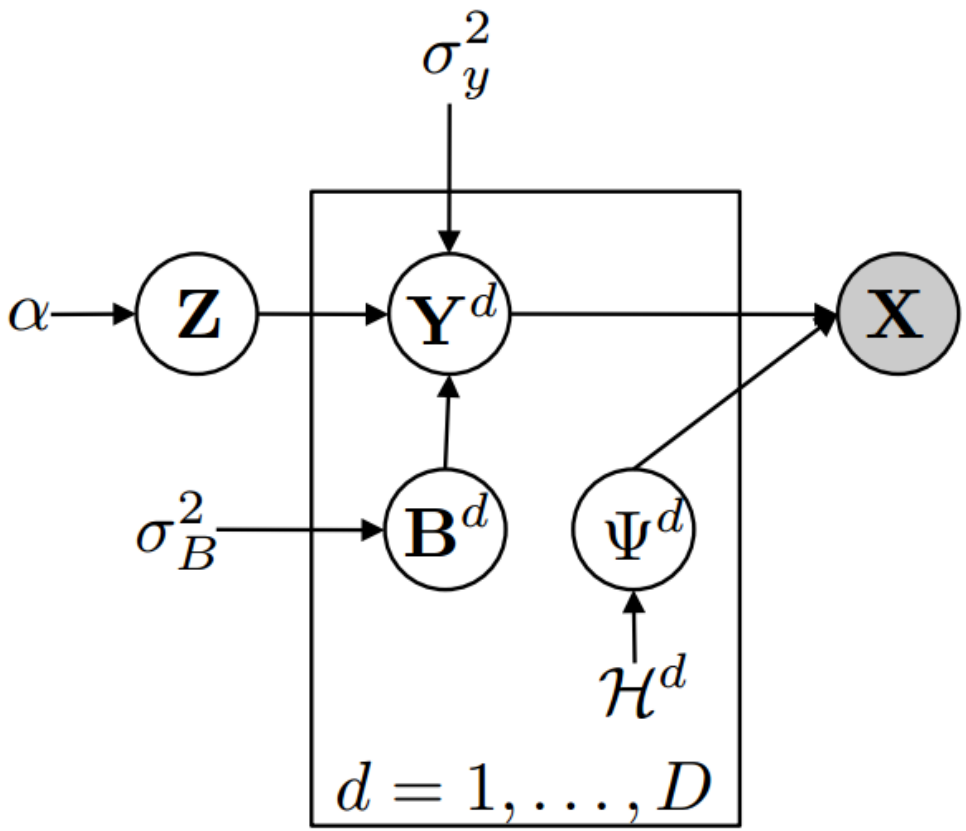
Thank you!

Appendix

Appendix

What about heterogeneous data?

- Generalized IBP [I.Valera et.al, 2015]
- Link function f depending on data type



Measures for Effect Size and Significance

Continuous variable d

- Effect Size

$$\beta_d = \frac{1}{L}\sum_{l=1}^{L} \log_2\left(\frac{\mu_d(\widetilde{G_l^*})}{\mu_d(\widetilde{G_l^B})}\right)$$

- Significance
  - Relative Deviation Metric
  - T-Test

Categorical variable r

- Effect Size

$$\beta_r = \frac{1}{L}\sum_{l=1}^{L} \left(\mu_d(\widetilde{G_l^*}) - \mu_d(\widetilde{G_l^B})\right)$$

- Significance
  - Binomial Test
  - Fisher Exact Test

Measure of Effect Size

- For continuous variable d:

$$\beta_d = \frac{1}{L} \sum_{l=1}^{L} \log_2 \left(\frac{\mu_d(\widetilde{G_l^*})}{\mu_d(\widetilde{G_l^B})} \right) \tag{4}$$

- For categorical variable r:

$$\beta_r = \frac{1}{L} \sum_{l=1}^{L} \left(\mu_d(\widetilde{G_l^*}) - \mu_d(\widetilde{G_l^B}) \right) \tag{5}$$

Measure of Significance
Continuous Variables

For continuous variables, compute:

- Deviation compared to G^* variance

$$\gamma^* = \frac{\left|\mu_d(G^*) - \mu_d(G^B)\right|}{\sigma_d(G^*)} \tag{6}$$

- Deviation compared to G^B variance

$$\gamma^B = \frac{\left|\mu_d(G^*) - \mu_d(G^B)\right|}{\sigma_d(G^B)} \tag{7}$$

- T-test: Standard statistical test to compare two groups of data.

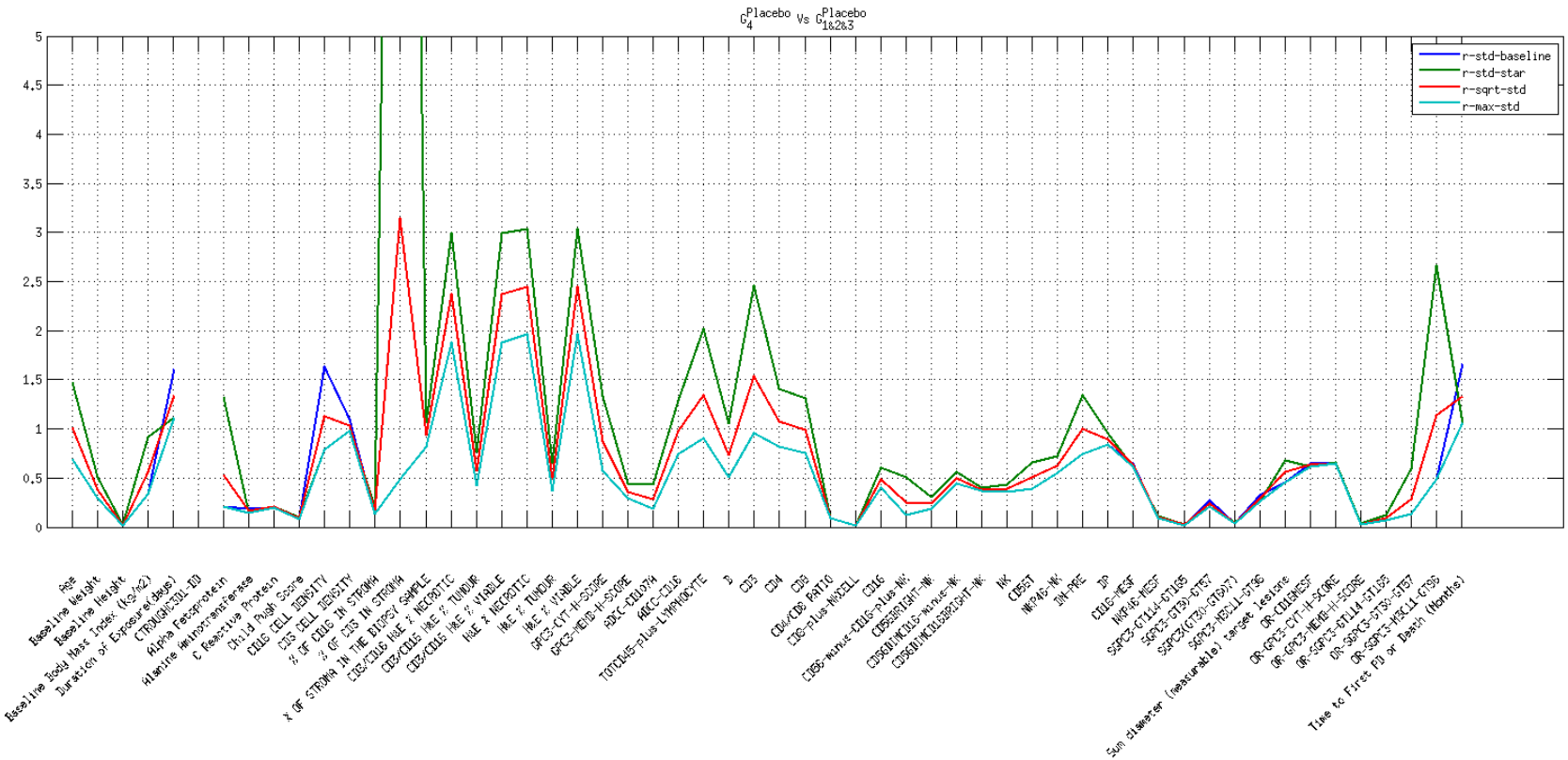
Measure of Significance
Categorical Variables

For categorical variables, compute:

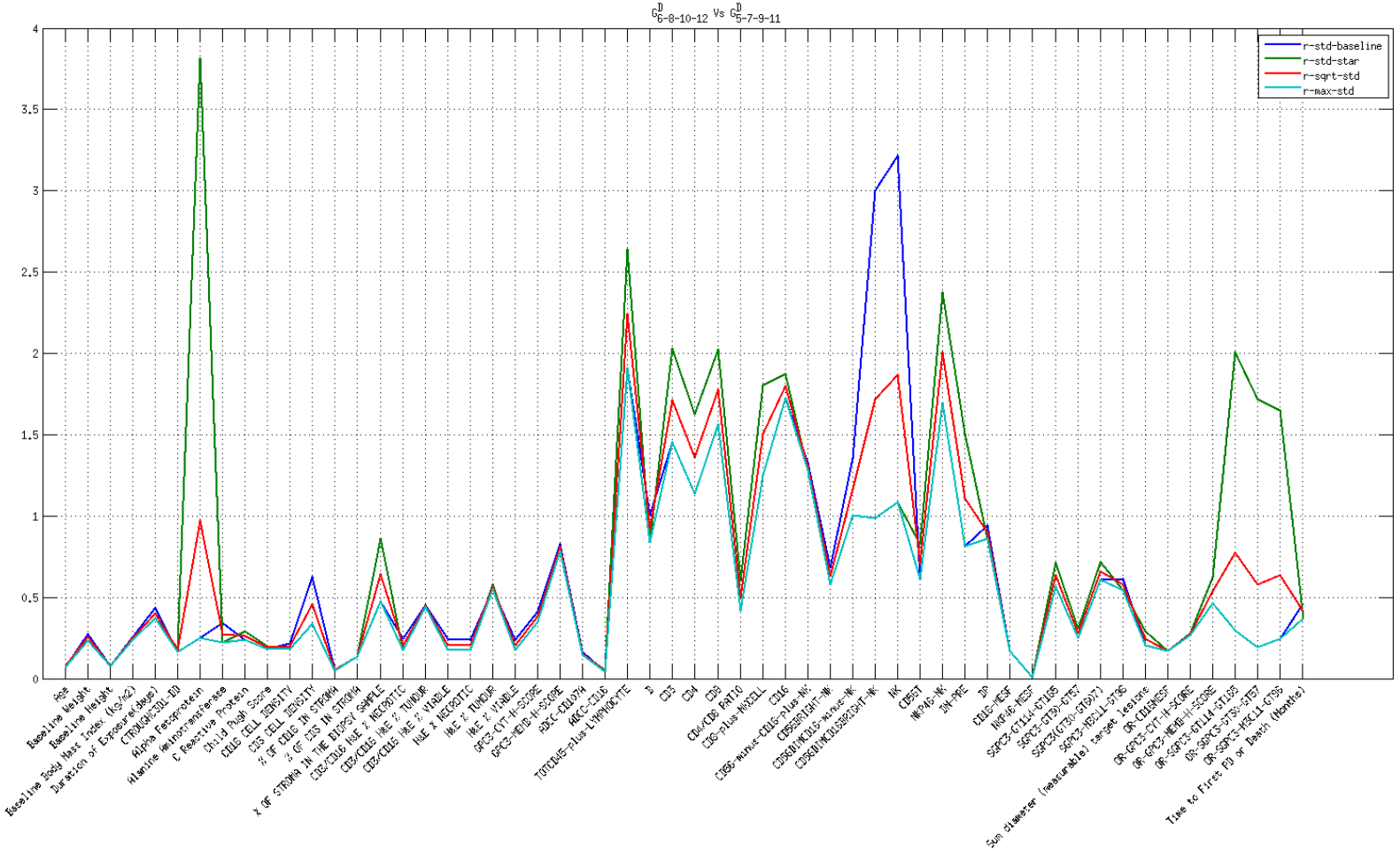
- Distance to Binomial Mean
  - Fit a Binomial distribution to G^B
  - A variable r is considered significant if $\mu_r(G^*)$ is outside confidence interval

- Fisher Exact Test: Standard statistical test for contingency tables.

Significance using mean deviation metrics: Placebo Patients



Significance using mean deviation metrics: Drug Patients



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