CASE-CONTROL INDIAN BUFFET PROCESS FOR BIOMARKER DISCOVERY IN CLINICAL TRIALS

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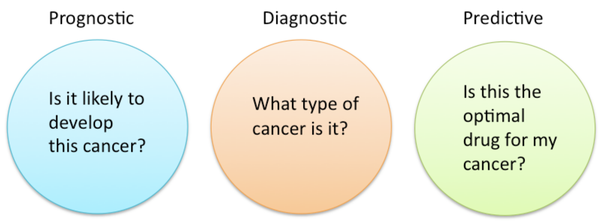
MOTIVATION

Biomarkers are used everywhere!!

- Prostate-specific antigen (PSA) to diagnose prostate cancer.
- Estrogen / progesterone to predict sensitivity to endocrine therapy in breast cancer.
- KRAS mutation to predict resistance to EGFr antibody treatment.



Cancer Drugs are ineffective for 75% of patient population (B. Spear et. al. *Clinical Trends in Molecular Medicine*, 2001).

OBJECTIVE

In a clinical trial scenario, we want to discover:

1. Indicators of disease progression: **prognostic** biomarkers
2. Indicators of (positive) drug response: **predictive** biomarkers
3. Actionable biomarkers as potential new targets for drugs

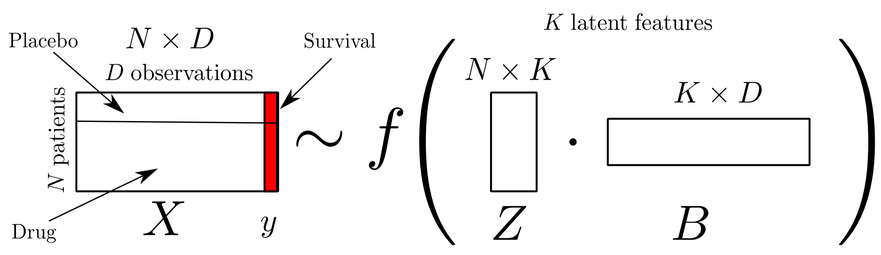
Challenges

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

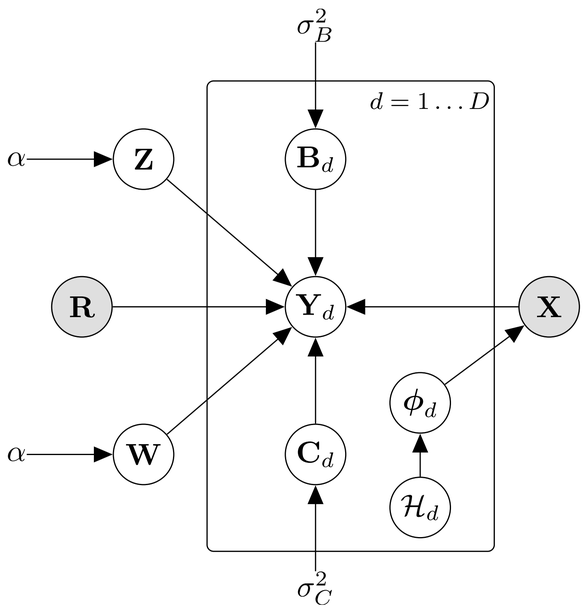
Solutions

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

CASE-CONTROL INDIAN BUFFET PROCESS (C-IBP)



- Model based on Generalized IBP for matrix completion (I. Valera, 2014)
- Let **Z** be a binary assignment matrix for **global** features
- Let **W** be a binary assignment matrix for **drug-specific** features



$$x_{nd}|y_{nd}, \phi_{\boldsymbol{d}} = T_d(y_{nd}, \phi_{\boldsymbol{d}})$$

$$y_{nd}|others \sim \mathcal{N}(z_{n\cdot}B_{\cdot d} + \mathbb{1}[\mathbf{R}_n = 1]\ w_{n\cdot}C_{\cdot d}, \sigma_y^2)$$

$$B_{kd} \sim \mathcal{N}(0, \sigma_B^2)$$

$$C_{kd} \sim \mathcal{N}(0, \sigma_C^2)$$

$$\mathbf{Z} \sim \text{IBP}(\alpha) \text{ and } \mathbf{W} \sim \text{IBP}(\alpha)$$

Nodes represent random variables, grey ones are observed. **X** is the matrix of observations and **R** is the drug indicator vector to distinguish placebo and drug patients.

INFERENCE

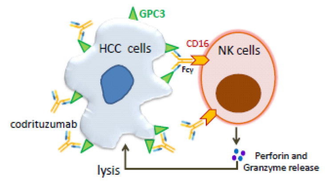
Here, let $\mathbf{Z^0}$, $\mathbf{Z^1}$ be the global feature assignment matrices for placebo and drug patients. We also distinguish the auxiliary variable matris $\mathbf{Y^0}$ and $\mathbf{Y^1}$ based on the drug indicator. Inference based on accelerated Gibbs sampling for the IBP (F. Doshi-Velez et.al. 2009).

1: **Initialize:** **Z**, **W**, and **Y**
2: **for** each iteration **do**
3: Sample $\mathbf{Z^0}$, $\mathbf{Y^0}$, and **B** given $\mathbf{X^0}$, using accelerated Gibbs sampling.
4: **for** $d = 1, \dots, D$ **do**
5: Sample $\mathbf{Z^1}$ given $\mathbf{Y^1}$, and **B** according to $p(z_{nk}^1 = 1|\mathbf{Z}_{-nk}, \mathbf{B}) \propto \frac{m_k}{N} \prod_{d=1}^{D} \mathcal{N}(y_{nd}|\sum_k z_{nk}^1 B_{kd}, \sigma_y^2)$
6: **end for**
7: Sample **W** given $\mathbf{Z^1}$ and $\mathbf{Y^1}$ using accelerated Gibbs sampling.
8: **for** $d = 1, \dots, D$ **do**
9: Sample $\mathbf{C}_d$ given **Z**, **W**, and $\mathbf{Y}_d$.
10: Sample $\mathbf{Y^1}_d$ given $\mathbf{X^1}$, **Z**, **W**, $\mathbf{B}_d$ and $\mathbf{C}_d$.
11: Sample $\phi_{\boldsymbol{d}}$ if needed. $\mathcal{H}_d$ are the hyperparameters over $\phi_{\boldsymbol{d}}$.
12: **end for**

DATABASE

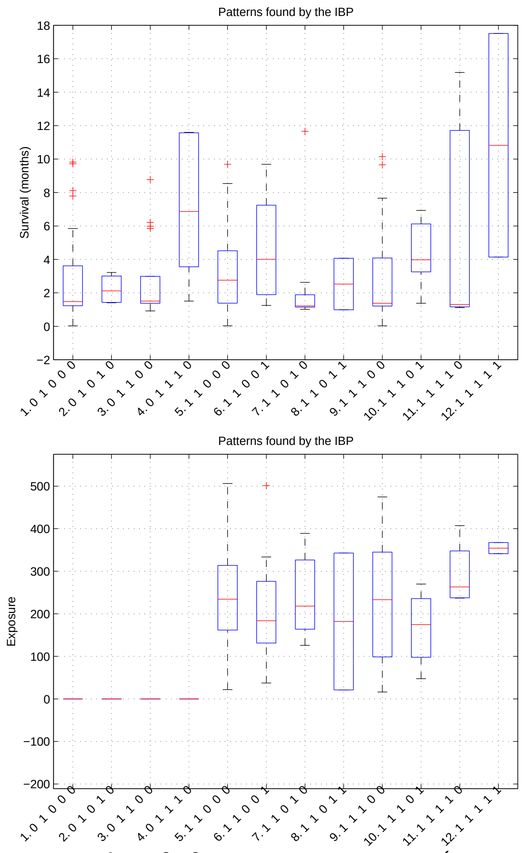
We demonstrate the utility of our approach in a **randomized phase II clinical trial** for the assessment of a cutting-edge immunotherapy treatment called Codrituzumab against **liver cancer** (J. Hepatology. 2016 Apr 13, Abou-Alfa et.al.)

- Clinical trial with 180 patients: 60 placebo, 120 drug.
- 80 obs. (demographics, clinical data, and survival).
- 48000 variables of RNA-seq data.



RESULTS

Sub-population	Drug Indicator	F1	F2	F3	Size (number of patients)	Mean TFPD (months)	Median TFPD (months)
1.	0	0	0	0	33.37	3.06	1.65
2.	0	0	1	0	4.07	2.29	2.24
3.	0	1	0	0	17.84	2.72	1.81
4.	0	1	1	0	4.72	7.05	7.18
5.	1	0	0	0	51.52	3.22	2.55
6.	1	0	0	1	16.77	4.17	3.65
7.	1	0	1	0	8.38	1.74	1.33
8.	1	0	1	1	2.07	2.69	2.65
9.	1	1	0	0	29.88	3.36	2.03
10.	1	1	0	1	4.90	4.44	4.34
11.	1	1	1	0	4.53	6.31	5.31
12.	1	1	1	1	1.94	10.04	10.01



Robustness: we combine bootstrapping techniques with soft-feature assignments (posterior averages). We assess statistical significance using T-test, Fisher test, and Wald test. We also correct for multiple hypothesis testing using the Benjamini-Hochberg procedure.

CONCLUSIONS

We propose a **general method for biomarker discovery in clinical trials**. The C-IBP can identify both prognostic and predictive variables both global or specific to subpopulations.

1. **Complex correlations**: Captured by latent features.
2. **Population Heterogeneity**: Patients have different feature assignments.
3. **Natural Vs Drug Response**: Distinction via drug-specific features.

FUTURE WORK

- Release open-source package.
- Dependency based on drug exposure.
- Discriminative model towards survival.

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