Generalized Group Lasso for Patient Subgroup Selection

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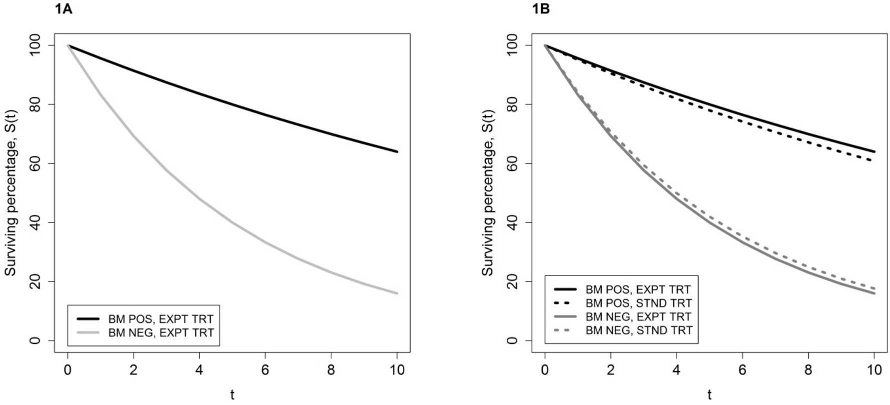
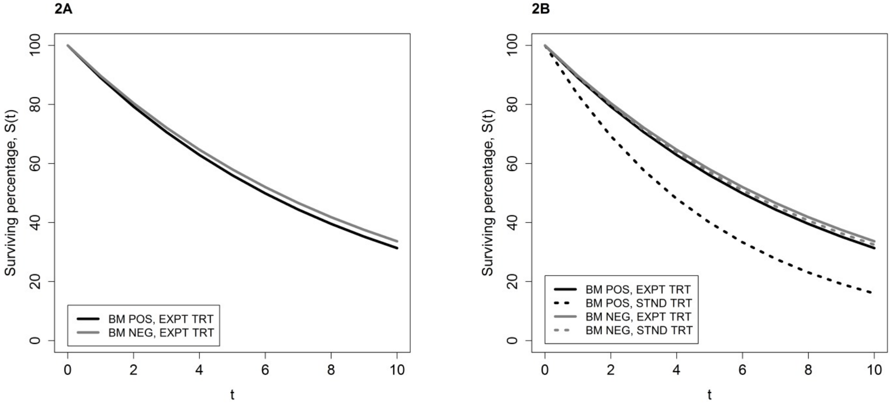
Overview

Prognostic Biomarkers



Predictive Biomarkers



Tree-based Methods

Regression trees GUIDE[Loh, 2018]:

- piecewise-linear Model
- examine residual patterns for each treatment level

Cannot repeat even the most naive simulation in GUIDE paper.

Reason: limited sample size. Even two splits will results in small sample size in each branch. The results would be highly unstable. Tree-based method is not appropriate to clinical trial dataset and identify prognostic and predictive biomarkers.

Ordinary Linear Model

$$Y = X\beta + W\tau + G\alpha + W \otimes G\gamma + \epsilon$$

- X: Baseline variables
- W: Treatment variables
- G: Main effects of genes, i.e. expression levels, SNP or mutation
- $W \otimes G$: Interaction effects of genes and treatment
- ϵ: Random errors

Group lasso

We choose group lasso for its ability to

- handle high dimensional data
- allow hierarchical structure

However, the current group lasso based methods

- penalize on all parameters
- have no efficient adaptive penalty weights
- do not specifically target on patients treatment subgroup identification

Loss Function

We assume the hierarchical relationship between prognostic biomarkers and predictive biomarkers, that is a predictive biomarker should be a prognostic biomarker.

The loss function is

$$\min_{\theta} f(\theta | Y, X, W, G) + g(\theta)$$

where

$$g(\theta) = \lambda \sum_i \phi_i^I |\gamma_i| + \lambda \sum_i \phi_i^M \sqrt{\alpha_i^2 + \gamma_i^2}$$

where $f(\theta | Y, X, W, G)$ is L-2 loss function, i.e. sum of squared errors for ordinary linear model.

$\theta = (\beta, \tau, \alpha, \gamma)$ is parameter vector.

Loss function for ordinary linear model

$$\min_{\theta} \| Y - (X\beta + W\tau + G\alpha + W \otimes G\gamma) \|^2 + \lambda \sum_i \phi_i^I |\gamma_i| + \lambda \sum_i \phi_i^M \sqrt{\alpha_i^2 + \gamma_i^2}$$

Denote $X^{(l)} = [G_l, W \otimes G_l]$ is the lth group of the main and interaction effects of gene l. Then we let

$$\phi_i^I = \| X^{(i)} \|_2$$

Optimization Stratgies

- Fast iterative shrinkage-thresholding algorithm with backtracking[Beck and Teboulle, 2009]
- Adaptive restart for rippling behavior [ODonoghuet and Candes, 2009]
- Adaptive stepsize of cyclic Barzilai-Borwein spectral approach[Wright, 2009]
- Warm start in cross validation

Proximal Operator

Definition

Let

$$Q_{\tau_i,g}(t,u) = g(t) + \frac{1}{2\tau} \parallel t - u \parallel^2$$

then the proximal operator is defined as

$$\tilde{t} = arg \min Q_{\tau_i,g}(t,u)$$

For convenience, we denote $P_{\tau_i,g}(u) = \tilde{t}$

Remark: Proximal operator is a point that compromises between minimizing g and being near to u.

Algorithm

initialization $\theta 0 = 0$ or warm start from previous run, $\tau_0 = 0.1$, stepsize $\eta = 0.5$;

while $i \leq k$ **do**

$u_i = \theta_{i-1} - \tau_i \bigtriangledown f(\theta_{i-1})$ Find the smallest nonnegative integers s_i such that with $\tau_i = \eta^{s_{i-1}} \tau_{i-1}$,

$(f + g)(P_{\tau_i,g}(u_i)) \leq Q_{\tau_i,g}(P_{\tau_i,g}(u_i), u_i)$;

Then, we compute $t_i = P_{\tau_i,g}(u_i)$ And accelarate the computation by setting **if** $f(\theta_i + g(\theta_i)) > f(\theta_{i-1}) + g(\theta_{i-1})$ **then**

$\rho_i = 1$

else

$$\rho_i = \frac{1 + \sqrt{1 + 4\rho_{i-1}^2}}{2}$$

end

$\theta_i = t_i + (\frac{\rho_{i-1} - 1}{\rho_i})(t_i - t_{i-1})$ and find τ_{i+1} that $\tau_{i+1} I$ can mimic the Hessian $\bigtriangledown^2 f(\theta_i)$

end

Algorithm 1: Patient Subgroup Identification Group Lasso Algorithm

Theorem

Because $Q_{\tau_i,g}(t,u)$ is separable, so we have

$$arg\min Q_{\tau_i,g}(t,u) = [arg\min \frac{1}{2} \parallel t^{(i)} - u^{(i)} \parallel^2 + \lambda\phi_i^I|\gamma_i| + \lambda\phi^M\sqrt{\alpha_i^2+\gamma_i^2}]_{1\leq i\leq}$$

Theorem

$E = mc^2$

Multiple Columns

Heading

1. Statement
2. Explanation
3. Example

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Table

Treatments	**Response 1**	**Response 2**
Treatment 1	0.0003262	0.562
Treatment 2	0.0015681	0.910
Treatment 3	0.0009271	0.296

Table: Table caption

Theorem

Theorem (Mass–energy equivalence)

$E = mc^2$

Verbatim

Example (Theorem Slide Code)

```
\begin{frame}
\frametitle{Theorem}
\begin{theorem}[Mass--energy equivalence]
$E = mc^2$
\end{theorem}
\end{frame}
```

References

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The End