# Generalized Group Lasso for Patient Subgroup Selection

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# Overview


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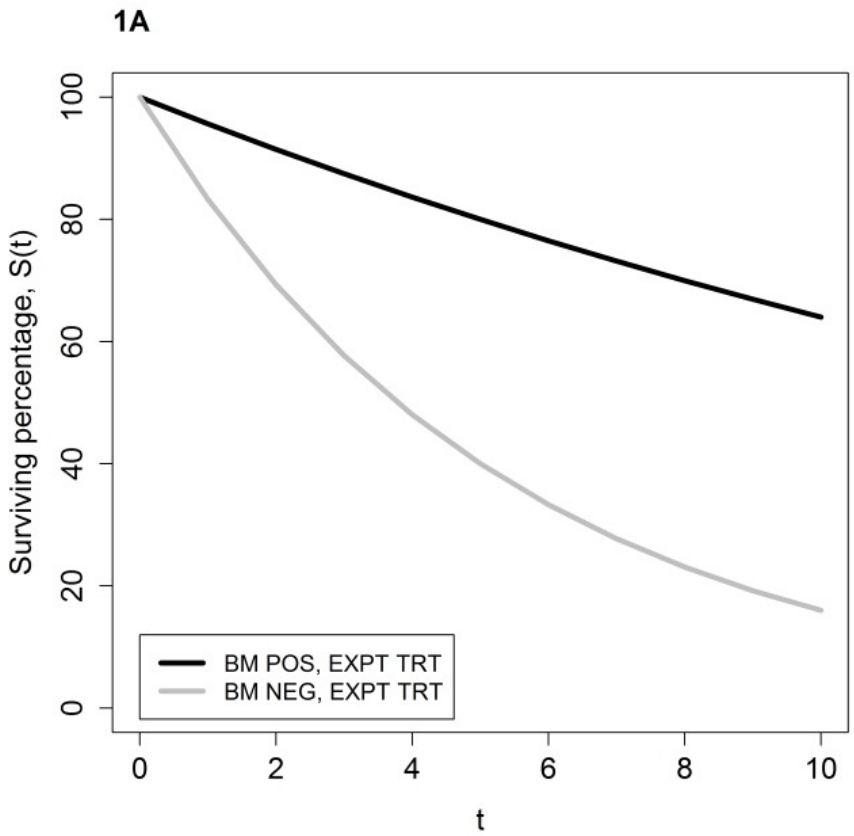
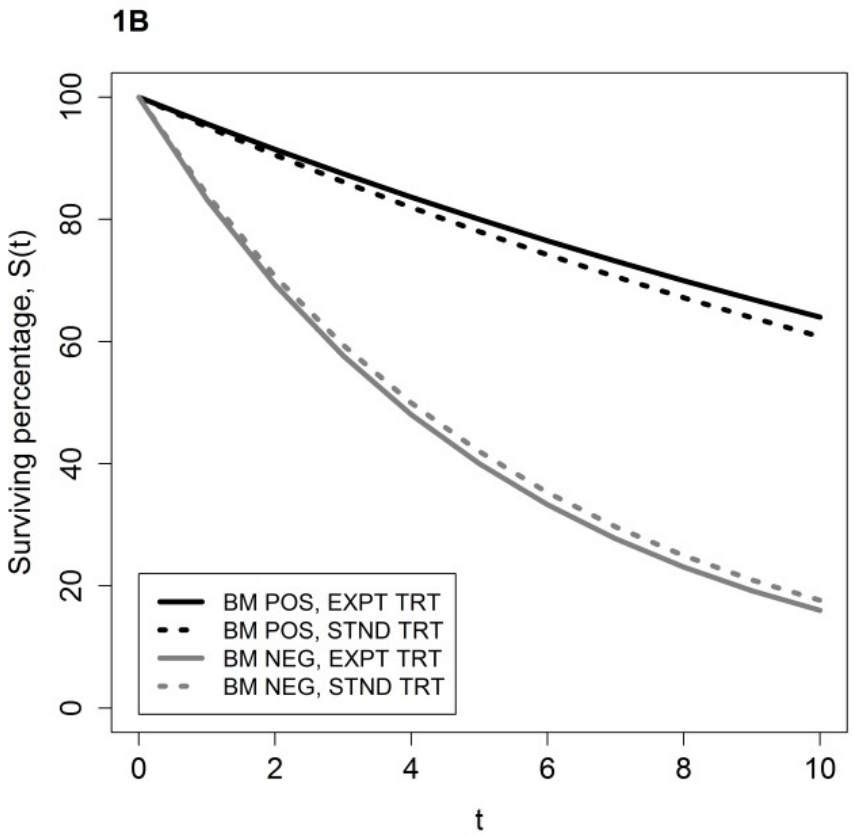
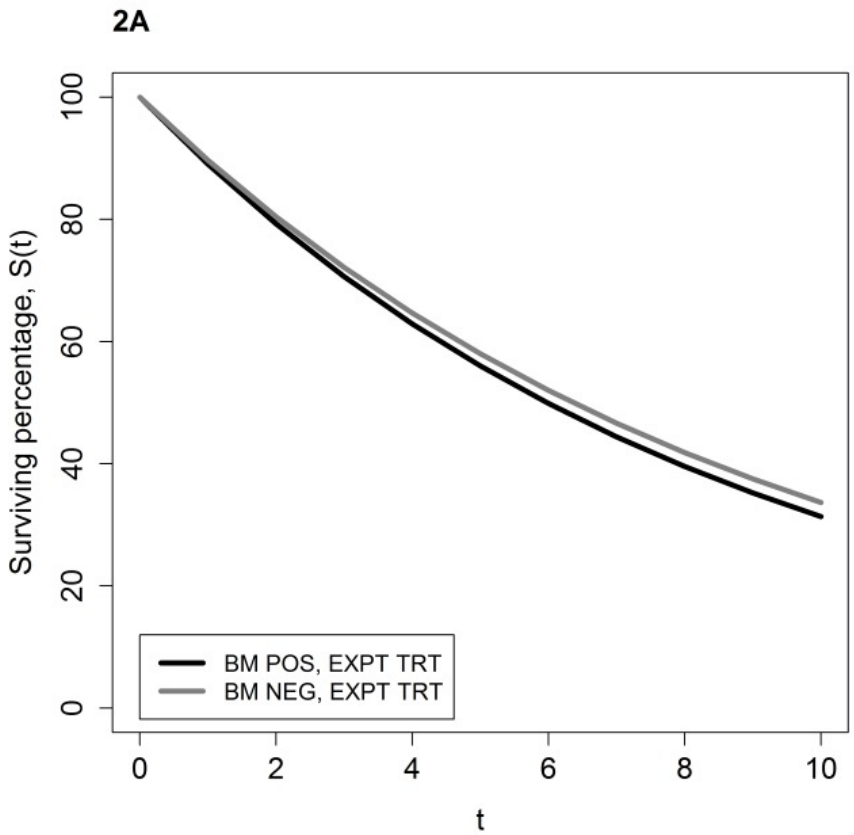
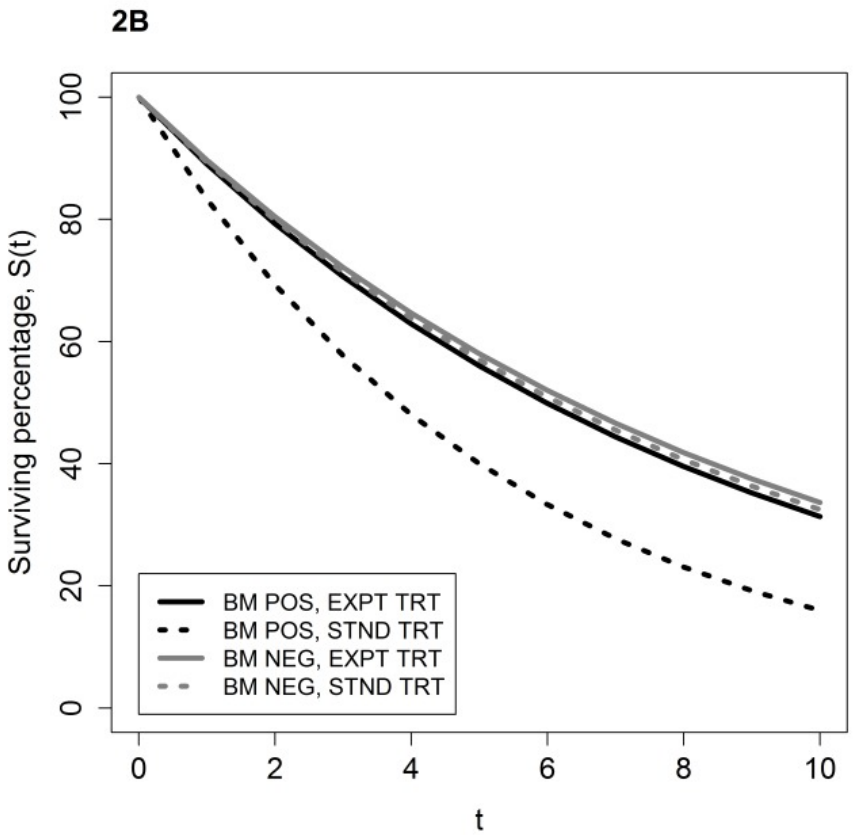
# Prognostic Biomarkers



# 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
- $\epsilon$: 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

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

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

$$\phi_i^I = \parallel X^{(i)} \parallel_2$$

$$\phi_i^M = \sqrt{\parallel G_i \parallel_2^2 +2(1-\sqrt{\frac{2}{\pi}}) \parallel W \otimes G_i \parallel_2^2}$$

# Optimization Stratgies

- Fast iterative shrinkage-thresholding algorithm with backtracking[Beck and Teboulle, 2009]
- Adaptive restart for rippling behavior [O'Donoghuet 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 $\tau_{i+1}$ that $\tau_{i+1} I$ can mimic the Hessian $\bigtriangledown^2 f(\theta_i)$

**end**

**Algorithm 1:** Patient Subgroup Identification Group Lasso Algorithm

# 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

# References

Loh, Wei-Yin, Michael Man, and Shuaicheng Wang.

"Subgroups from regression trees with adjustment for prognostic effects and postselection inference."

*Statistics in medicine* (2018).

Beck, Amir, and Marc Teboulle.

"A fast iterative shrinkage-thresholding algorithm for linear inverse problems."

*SIAM journal on imaging sciences 2.1 (2009): 183-202.* (2009).

Wright, Stephen J., Robert D. Nowak, and Mário AT Figueiredo.

"Sparse reconstruction by separable approximation."

*IEEE Transactions on Signal Processing 57.7 : 2479-2493.*(2009)

O'Donoghue, B., and E. Candes.

"Adaptive restart for accelerated gradient schemes."

*Foundations of computational mathematics 15.3: 715-732.* (2015)

# The End