Modeling Strategies for Developing Treatment Response Indices

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Abstract

To find biosignatures of treatment response, clinicians are interested in identifying patient features at baseline that predict differential response to different treatment. The treatments could be drug and placebo, or different drugs. These differential predictors may be termed "moderators of treatment effect", because the differences between the efficacies of the treatments depend on the levels of those predictors. It is common in clinical research to model the outcome as a linear function of the predictor and to test for significance of the interaction between treatment and the predictors in order to find moderators of treatment effect. Also, typically, moderators are identified either one by one, using one model for each potential predictor, or from a large model which includes all potential predictors and their 2-way interactions with treatment, but not interactions between the potential predictors. However, neither of these modeling strategies aids in the determination of combinations of patient characteristics that could be used to select patients who have high probability to respond to a given drug. In this talk we present flexible methods that extend the existing approaches for identification of differential predictors of treatment response in two directions: (1) allowing for non-linear association of the potential predictors with the outcome and (2) identifying combinations of predictors that are the "best" moderators of treatment effect, i.e. offer the largest differences between the efficacies of the treatments as a function of the combination.

1   Introduction

Directly relevant to clinical practice and personalized medicine would be the ability, at the time a patient presents for treatment, to make predictions about the extent of a patient's likelihood to improve due to nonspecific effects

of treatment. Baseline variables that *differentially* predict outcomes from drug and placebo treatments point the way to understanding the mechanisms of response to treatment and shed light on the possible pathways of the disease and its cure. The standard approach for finding such differential predictors is based on linear models that test for significance of the interaction between a baseline variable and the treatment indicators (Kraemer *et al.*, 2002). Let Y denote the outcome (e.g., symptom severity) and let T be an indicator for treatment (e.g., $T = 0$ for placebo and $T = 1$ for drug). To determine whether a scalar predictor X differentially predicts outcome in the two treatment groups, the typical *moderator analysis* tests for significance of the interaction term β_3 in the following model:

$$E(Y|T, X) = \beta_0 + \beta_1 T + \beta_2 X + \beta_3 TX. \tag{1}$$

Here we extend this model to increase its utility for identifying biosignatures for treatment response.

2   Linear models, combinations of predictors

2.1   General idea

Let $\boldsymbol{X} = (X_1, \ldots, X_p)'$ denote p predictors representing possible moderators of response; without loss of generality they can be considered standardized. The goal is to find an optimal linear combination $\boldsymbol{\alpha}'\boldsymbol{X}$ for some vector $\boldsymbol{\alpha}$ that maximizes the magnitude of the interaction term β_3 in the model

$$Y = \beta_0 + \beta_1 T + \beta_2(\boldsymbol{\alpha}'\boldsymbol{X}) + \beta_3 T(\boldsymbol{\alpha}'\boldsymbol{X}) + \epsilon. \tag{2}$$

Finding such a linear combination $\boldsymbol{\alpha}'\boldsymbol{X}$ will then define a biosignature (or moderator) for placebo response that incorporates all of the important predictors (some coefficients in $\boldsymbol{\alpha}$ may be zero or near zero).

   Let $\boldsymbol{\Psi}_x$ denote the covariance matrix for $\boldsymbol{X}$ with eigen-decomposition $\boldsymbol{HDH}'$, where $\boldsymbol{H}$ is orthogonal and $\boldsymbol{D}$ is a diagonal matrix of eigenvalues. If Y_d and Y_p denote the outcomes for the drug and placebo arms and $\boldsymbol{\Psi}_{xy_d}$ and $\boldsymbol{\Psi}_{xy_p}$ are the vector of covariances between the response and the p-predictors in each arm, then the squared interaction effect when a principal component regression is performed can be expressed as $\boldsymbol{\alpha}'\boldsymbol{A}\boldsymbol{\alpha}$, where

$$\boldsymbol{A} = \boldsymbol{D}^{-1/2}\boldsymbol{H}'(\boldsymbol{\Psi}_{xy_1} - \boldsymbol{\Psi}_{xy_2})(\boldsymbol{\Psi}_{xy_1} - \boldsymbol{\Psi}_{xy_2})'\boldsymbol{H}\boldsymbol{D}^{-1/2}. \tag{3}$$

Thus, the interaction effect is maximized by setting $\boldsymbol{\alpha}^*$ equal to the eigenvector associated with the positive eigenvalue of $\boldsymbol{A}$. Consequently, the optimal linear combination that maximizes the interaction term for the original variables is $\boldsymbol{\alpha}'\boldsymbol{X} = \boldsymbol{\alpha}^{*\prime}\boldsymbol{D}^{-1/2}\boldsymbol{H}'\boldsymbol{X}$. This method can be readily extended to more than two treatments and is very fast making it possible to use resampling techniques for inference.

2.2   Example

   A study for the treatment of Post Traumatic Stress Disorder (PTSD) compared three psychotherapies for treating the condition: two different
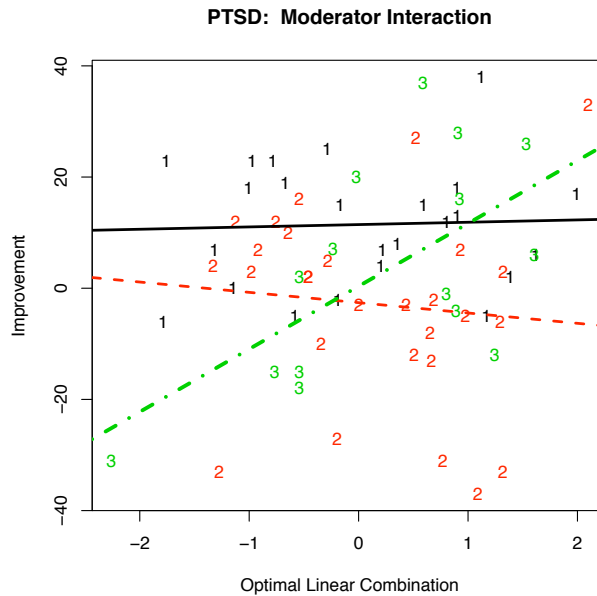
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Figure 1: *Post Traumatic Stress Disorder: Change in outcome (CAPS) from immediate post treatment to follow up.*

treatment approaches and a combination of the two, (Cloitre *et al.*, 2010). Efficacy was measured with the Clinician Administered PTSD Scale (CAPS) and patients were assessed at treatment end and at two follow up times. All interventions were efficacious in reducing PTSD symptoms immediately post-treatment. A question of clinical importance is whether different treatments worked better for different types of patients in terms of reducing symptoms and maintaining improvement during follow up. Six candidate baseline characteristics were identified as potential moderators but none of them produced significant moderating interactions in model (1) when modeling the change in outcome from immediate post-treatment to end of follow up (the smallest p-value for a treatment-by-covariate interaction term was 0.085 and all others were above 0.50). Applying the method in Section 2.1 produced a clinically meaningful linear combination (i.e., biosignature) of the predictors producing a statistically significant interaction term ($p = 0.029$) and a plot of the improvement in CAPS during follow up versus this biosignature is shown on Figure 1 here for each of the three treatments. The plot shows that the maintenance of post-treatment gains for subjects in the 1st treatment did not depend on the value of the estimated biosignature (i.e., $\hat{\boldsymbol{\alpha}}' \boldsymbol{x}$) and everyone had a small improvement; subjects in the 3rd treatment with low values of the biosignature had serious worsening and those with high values had a meaningful improvement; for subjects in the 2nd treatment, as the estimated biosignature varies from small to large, there was a small loss of post-treatment gains.

3 Generalized Additive Models

A linear model such as (1) is inadequate if the true relationship between a biosignature and an outcome is nonlinear. The flexibility needed can be gained by generalizing the traditional moderator analysis using nonparametric approaches such as *generalized additive models* (GAM) (e.g. Hastie and Tibshirani, 1990; Wood, 2006).

3.1 Generalizing the concept of moderator of treatment effect

If $X_1, \ldots, X_p$ denote baseline predictors, then the standard GAM is

$$E[Y|X_1, \ldots, X_p] = \beta_0 + \sum_{j=1}^{p} f_j(X_j), \tag{4}$$

where f_j are smooth nonparametric functions. Returning to the problem of moderator analysis, (1) can be written as

$$E(Y|T, X) = \beta_0 + \beta_1 T + \beta_2 X + \beta_3 T X = \beta_0 + \beta_1 T + f(X) + T g(X), \tag{5}$$

which is similar to a generalized additive model with a "treatment by curve" interaction (Coull *et al.*, 2001) with $f(X) = \beta_2 X$ and $g(X) = \beta_3 X$. To allow flexibility for discovering interesting moderating effects, the GAM methodology will be implemented whereby f and the interaction curve g are estimated as smooth nonparametric functions. To search simultaneously for several differential predictors for placebo response, (4) can be augmented to

$$E[Y|T, X_1, \ldots, X_p] = \beta_0 + \beta_1 T + \sum_{j=1}^{p} f_j(X_j) + \sum_{j=1}^{p} T g_j(X_j). \tag{6}$$

The significance of interaction terms in the additive model can be tested by comparing models with and without interaction terms via a deviance test. In addition to significance tests, we need to quantify potential moderators by measuring the relative strength of the interaction terms $g_j(X_j)$ that measure the deviation from $f_j(X_j)$ continuously over the range of X_j. A natural metric for this is

$$E[\{g_j(X_j)\}^2] = \int (g_j(x))^2 d\mu_j(x), \tag{7}$$

where we assume the X_j's are standardized and the integration is with respect to the distribution X_j.

3.2 Example

The effect of age on response to different antidepressant medications has been investigated in many studies and the contradictory reports are testament to the complex relationship of age and treatment outcome. We studied the effect of age on response to fluoxetine using data from 10 randomized placebo controlled clinical trials; all had similar designs and collected similar data.
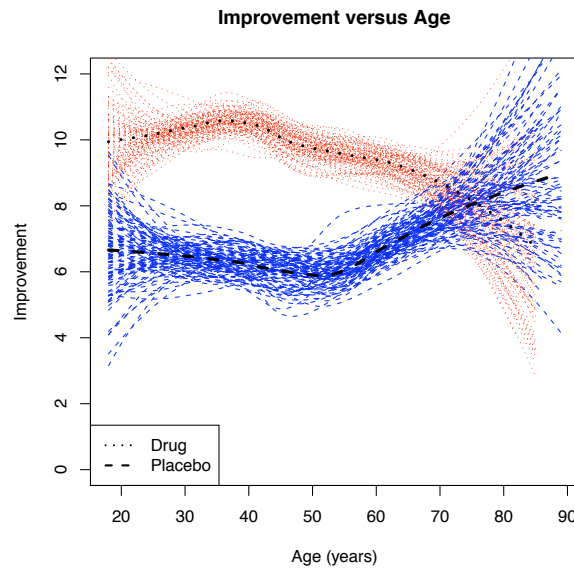
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Figure 2: *Loess curves of improvement on vs. Age across 10 studies*

The outcome Y was improvement in symptoms from baseline to the study end, as measured by the Hamilton Depression Rating Scale (HDRS), and X was subject's age. Figure 2 shows smooth nonparametric loess curves of improvement versus age for drug and placebo treated subjects along with 100 bootstrap curve estimates to indicate the degree of variability in the fitted curves. Simple inspection indicates that improvement depends on age in a nonlinear way in both arms and that the relationship of improvement with age is different for the two treatments. Here nonlinear flexibility is needed to discover this apparent moderating effect of age.

4   Conclusion

The presentation will discuss details of the algorithms for fitting those flexible models for identification of biosignatures, also called moderators of treatment effect. More examples will be shown as well as directions of future research.

Acknowledgement

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