Incorporating Longitudinal Outcomes and Baseline Covariates to Validate Surrogate Endpoints

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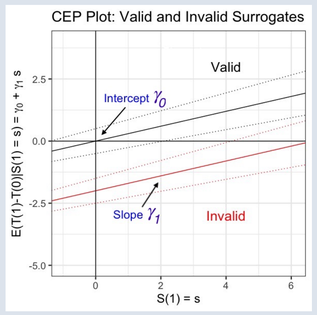
Overview

- **Valid surrogate endpoints are useful** to decrease the duration and cost of clinical trials
- **Validating a potential surrogate endpoint is challenging:** correlation between outcomes is not sufficient for validation. Determining whether the potential surrogate is causally associated with the treatment and outcome can provide assurance that the surrogate is indeed valid
- **Surrogate-dependent treatment efficacy curves** at a given time show how we can validate the surrogate, or we can integrate over time for an overall conclusion of surrogacy
- **Use of baseline covariates and longitudinal outcomes:** Because identification in causal inference settings often relies on untestable assumptions such as independence among counterfactuals, conditioning on covariates can be beneficial. Here we also incorporate repeated measurements of the trial outcome
- **Gene therapy with the surrogate biologically constrained to be zero in the placebo arm** is a special case, and the functional outcomes are measured repeatedly throughout the trial

Principal Surrogacy

- Principal surrogacy can be used to assess a surrogate endpoint S for a true outcome T where $S(z)$ and $T(z)$ refer to the endpoint values had the treatment, possibly counter-factually, been assigned to level z



- Can model the joint distribution of normally-distributed potential outcomes $S(1)$, $T(0)$, and $T(1)$ with or without repeated measurements[1,2]
- We explored how baseline measurements could be used to stratify the validation analysis[3]
- The causal effect predictiveness (CEP) curves demonstrate if the surrogate is valid, meaning small (large) causal effects on a surrogate are associated with small (large) causal effects on the outcome[4]
- The causal quantities for validation, γ_0 and γ_1 based on $E(T(1) - T(0)|S(1) = s)$ appear on the CEP curves in linear form showing $\gamma_0 + \gamma_1 s$ over values of $S(1) = s$ with $\gamma_1 = \frac{\rho_{11}\sigma_{T1} - \rho_{10}\sigma_{T0}}{\sigma_{S1}}$ and $\gamma_0 = \alpha_3 - \alpha_2 - \gamma_1\alpha_1$ from the following specified model parameters
- When the distribution of outcomes is multivariate normal, validation conditions are fulfilled if $\gamma_0 = 0$ and $\gamma_1 \neq 0$

Longitudinal Outcomes

- Using the causal association framework, we previously considered the joint distribution of three potential outcomes with covariates

$$\begin{pmatrix} S(1)_i \\ T(0)_i \\ T(1)_i \end{pmatrix} \Big| X \sim N\left(\begin{pmatrix} \alpha_1 + \eta_1 X \\ \alpha_2 + \eta_2 X \\ \alpha_3 + \eta_3 X \end{pmatrix}, \begin{pmatrix} \sigma^2_{S_1} & \rho_{10}\sigma_{S_1}\sigma_{T_0} & \rho_{11}\sigma_{S_1}\sigma_{T_1} \\ & \sigma^2_{T_0} & \rho_T\sigma_{T_1}\sigma_{T_0} \\ & & \sigma^2_{T_1} \end{pmatrix}\right)$$

- Covariates may make proposed conditional independence assumptions of outcomes more plausible and improve estimation efficiency

Random intercepts: Each individual i has multiple observed and counterfactual outcomes $S(1)_i$, $T(0)_{ij}$, $T(1)_{ij}$ at time j modeled by one random intercept for $\boldsymbol{T(0)}_i$: b_{i0}, and one for $\boldsymbol{T(1)}_i$: b_{i1}

$$T(0)_{ij} = \boldsymbol{X}_i^T\beta_2 + Z_i b_{i0} + e_{ij0} \qquad T(1)_{ij} = \boldsymbol{X}_i^T\beta_3 + Z_i b_{i1} + e_{ij1}$$

$$\begin{pmatrix} S(1)_i \\ b_{i0} \\ b_{i1} \end{pmatrix} \sim MVN\left(\begin{pmatrix} \beta_1 \\ 0 \\ 0 \end{pmatrix}, \Psi_{3\times 3} = \begin{pmatrix} \sigma^2_{S1} & \rho_{10}\sigma_{S1}\sigma_{b_0} & \rho_{11}\sigma_{S1}\sigma_{b_1} \\ & \sigma^2_{b_0} & \rho_T\sigma_{b_0}\sigma_{b_1} \\ & & \sigma^2_{b_1} \end{pmatrix}\right)$$

$\boldsymbol{X}$ could contain any number of baseline covariates

Random intercepts and slopes: We also consider $\boldsymbol{X}_i = \boldsymbol{Z}_i = (\boldsymbol{1} \ \ \boldsymbol{time}_i)$ so that the validation metrics can also vary over time

$$T(0)_{ij} = \boldsymbol{X}_i^T\begin{pmatrix}\beta_2 \\ \delta_2\end{pmatrix} + \boldsymbol{Z}_i b_{.i1} + e_{ij0} \qquad T(1)_{ij} = \boldsymbol{X}_i^T\begin{pmatrix}\beta_3 \\ \delta_3\end{pmatrix} + \boldsymbol{Z}_i b_{.i2} + e_{ij1}$$

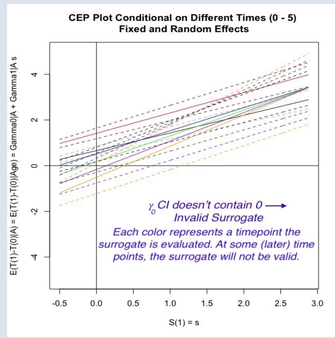
$$\begin{pmatrix} S(1)_i \\ b_{.i1} \\ b_{.i2} \end{pmatrix} = \begin{pmatrix} S(1)_i \\ \begin{pmatrix} b_{0i1} \\ b_{1i1} \end{pmatrix} \\ \begin{pmatrix} b_{0i2} \\ b_{1i2} \end{pmatrix} \end{pmatrix} \sim MVN\left(\begin{pmatrix} \beta_1 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \boldsymbol{\Psi}_{5\times 5}\right)$$

Estimation

- **Some parameters are not identifiable.** Using Bayesian methods, parameters are drawn using Markov Chain Monte Carlo (MCMC). We explore prior distributions to specify for the correlation parameters and draw them from the appropriate posterior bounds
- **Make conditional independence assumptions** on the random effects and outcomes such as $S(1) \perp b_0 | b_1 \Rightarrow \rho_T = \frac{\rho_{10}}{\rho_{11}}$ and incorporate baseline covariates to make these more plausible
- **Cross-over design** where those in the $z = 0$ placebo arm eventually receive the gene therapy permits identifiabilty in some cases. Changes in model assumptions can be made to accommodate such a study design

Surrogacy Validation Metric

- The validation metrics are based on the distribution of $S(1)$, $\boldsymbol{T(0)}$, $\boldsymbol{T(1)}$ as a function of model parameters at a certain time and integrated over random effects
- Consider the CEP evaluated at different time points where $\gamma_0 = 0$ and $\gamma_1 \neq 0$ may always hold or may only be true at certain times



- γ_1 will depend on time if there are non-zero and non-equal covariances between $S(1)$ and the random slopes b_{11}, b_{12}
- γ_0 will depend on time if there are non-zero and non-equal main effects of time for $T(0)$ and $T(1)$ outcomes
- We can look at the CEP curve as a function of time where the validity of the surrogate may increase or decrease over the trial duration
- If we want a marginal value to validate the surrogate overall, we could average these values across multiple time points

Data Example and Discussion

- Our data mimic a clinical trial of the ambulatory function of muscular dystrophy patients evaluated with an assessment scale that is repeatedly measured, and the surrogate is micro-dystophin expression
- Modeling age and time are important due to both natural disease progression and growth with age. Subgroups may also exist based on age and baseline ability measurements

References

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4. Gilbert P, Hudgens M. Evaluating candidate principal surrogate endpoints. Biometrics. 2008; 64:1146-1154.

Acknowledgements

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