Global Sensitivity Analysis of Randomized Trials with Missing Data: From the Software Development Trenches

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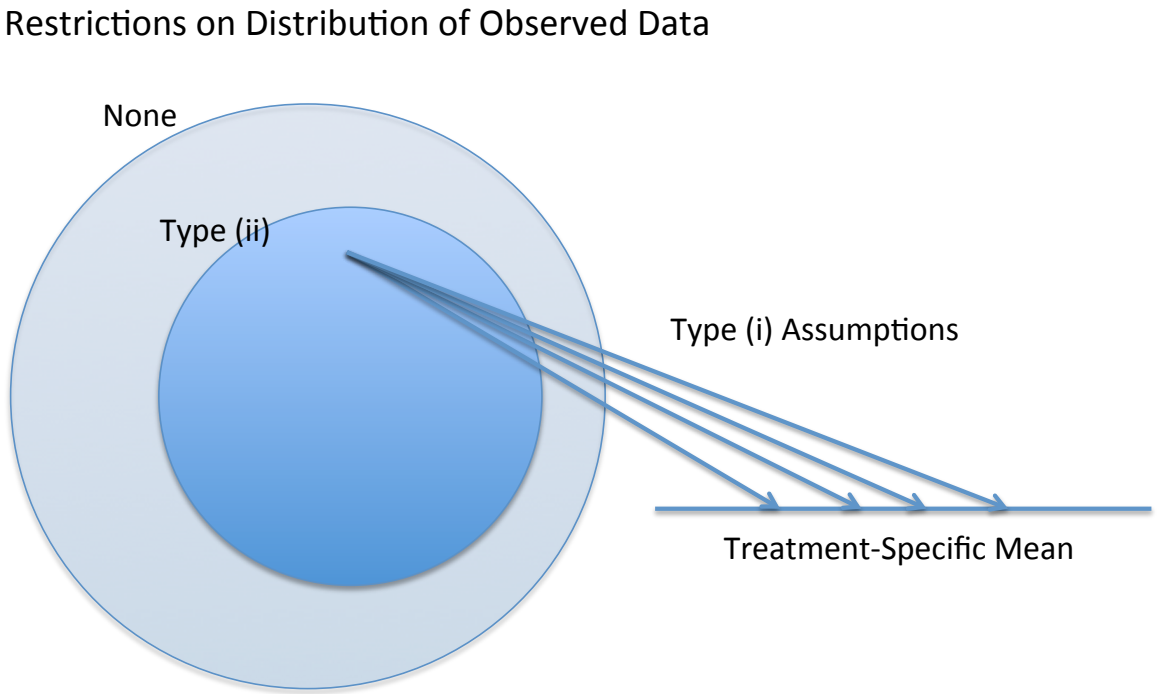
Sensitivity Analysis

- Interested in comparing treatment groups with respect to the mean outcome at the last scheduled study visit.
- Some patients prematurely drop out of the study.
- The set of possible assumptions about the drop out mechanism is very large and cannot be fully explored.
- Sensitivity analysis:
  - Ad-hoc
  - Local
  - Global - “Tipping point”

Global Sensitivity Analysis

- Inference requires two types of assumptions:
  - (i) *unverifiable* assumptions about the distribution of outcomes among those who dropped out and
  - (ii) additional testable assumptions that serve to increase the efficiency of estimation.

Global Sensitivity Analysis



Notation

- K scheduled post-baseline assessments.
- There are $(K+1)$ patterns representing each of the visits an individual might last be seen, i.e., $0, \ldots, K$.
- The $(K+1)^{st}$ pattern represents individuals who complete the study.
- Let Y_k be the outcome scheduled to be measured at visit k, with visit 0 denoting the baseline measure (assumed to be observed).
- Let $Y_k^- = (Y_0, \ldots, Y_k)$

Notation

- Let R_k be the indicator of being on study at visit k
- $R_0 = 1$; $R_k = 1$ implies that $R_{k-1} = 1$.
- Let C be the last visit that the patient is on-study.
- We focus inference separately for each treatment arm.
- The observed data for an individual is $O = (C, Y_C^-)$.
- We want to estimate $\mu^* = E[Y_K]$.

Model

$$\text{logit } P[R_{k+1} = 0 | R_k = 1, Y_{k+1}^-, Y_K] = h_{k+1}(Y_k^-) + \alpha r(Y_{k+1})$$

where

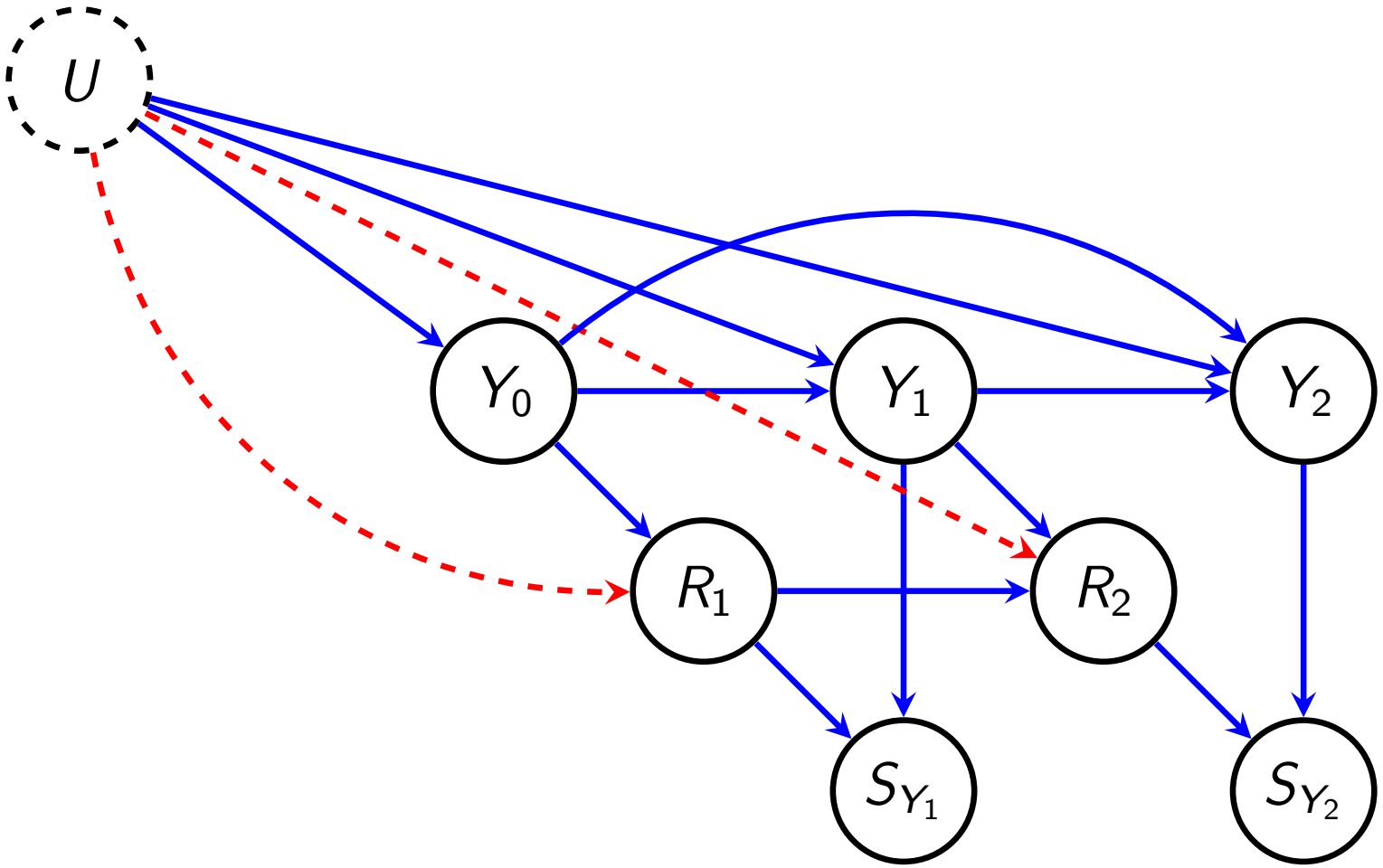
$$\begin{aligned} h_{k+1}(Y_k^-) &= \text{logit } P[R_{k+1} = 0 | R_k = 1, Y_k^-] - \\ &\quad \log\{E[\exp\{\alpha r(Y_{k+1})\} | R_{k+1} = 1, Y_k^-]\} \end{aligned}$$

- $r(Y_{k+1})$ is a specified function of Y_{k+1}
- α is a sensitivity analysis parameter
- Each α is type (i) assumption.

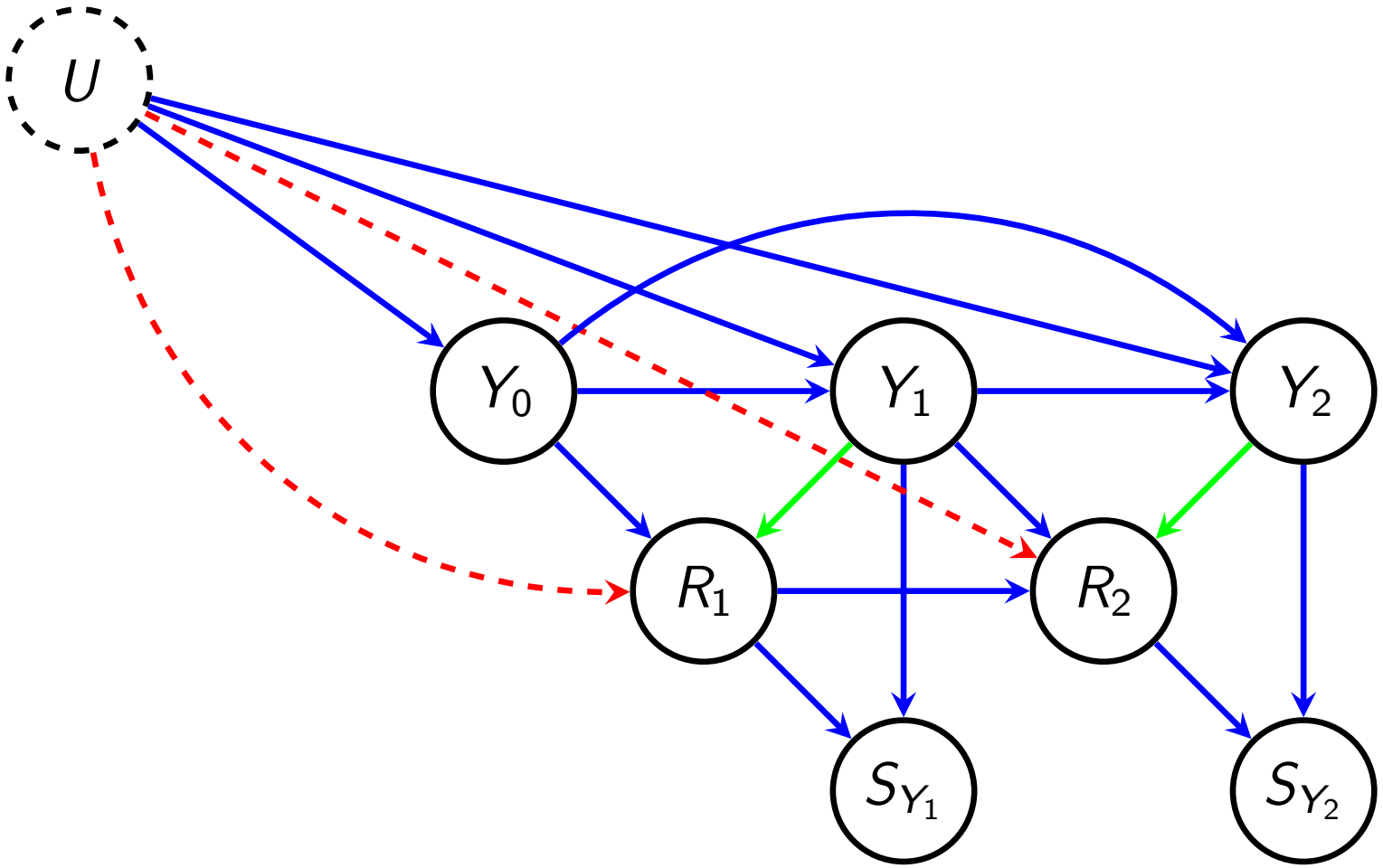
Inference

- Inference will rely on models for either
  - $f(Y_{k+1}|R_{k+1}=1, Y_k^-)$
  - $P(R_{k+1}=0 \mid R_k=1, Y_k^-)$
- Impose first-order Markov assumption (Type (ii) assumption)
- Non-parametric smoothing using cross-validation
- Corrected plug-in estimator using efficient influence function
- Confidence intervals using t-based bootstrap

DAG - MAR



DAG - NMAR



Alternative Model

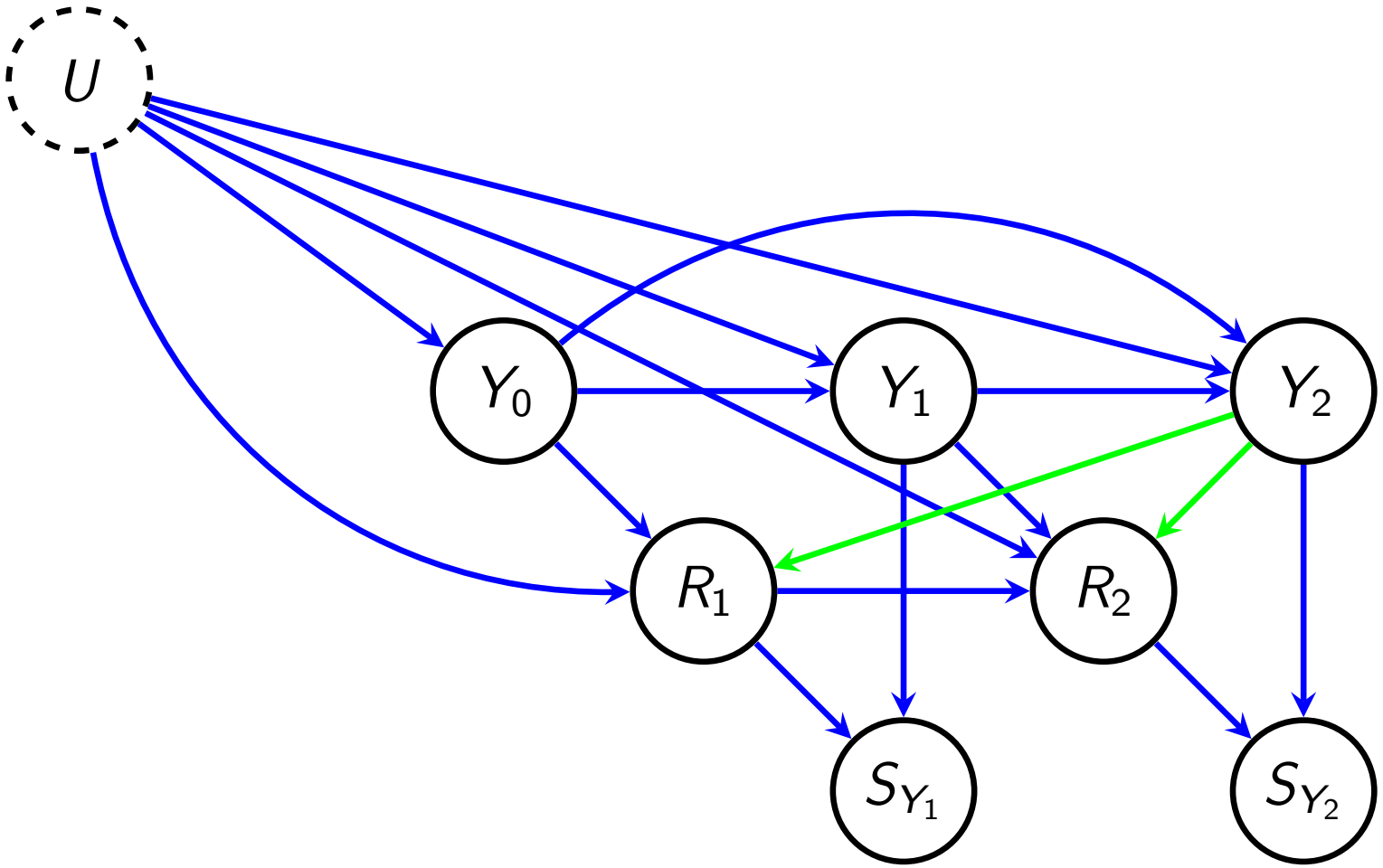
$$\text{logit } P[R_{k+1} = 0 | R_k = 1, Y_k^-, Y_K] = l_{k+1}(Y_k^-) + \alpha q(Y_K)$$

where

$$\begin{aligned} l_{k+1}(Y_k^-) &= \text{logit } P[R_{k+1} = 0 | R_k = 1, Y_k^-] - \\ &\quad \log\{E[\exp\{\alpha r(Y_K)\} | R_{k+1} = 1, Y_k^-]\} \end{aligned}$$

- $q(Y_K)$ is a specified function of Y_K
- α is a sensitivity analysis parameter
- Each α is type (i) assumption.

DAG - NMAR



Major Challenges

- Wald confidence intervals with influence function-based standard errors perform poorly in sample sizes seen in registration trials.
  - Is it our simulation procedure?
- Intermittent missing data
  - Impute to a monotone structure?

More Information

Software, Papers, Presentations

www.missingdatamatters.org

- Funded by FDA and PCORI