A visual guide to g-estimation to handle symptomatic medication at multiple timepoints in a randomized controlled trial

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The use of symptomatic/rescue therapy (ST) alongside treatments under investigation is a common issue in randomized controlled trials (RCT) and can complicate the interpretation of study results. This is particularly true if sponsors are interested in learning about the "direct" effect of their investigative treatment on the outcome variable, absent the influence of any other medications patients might want to take along the way.

A common approach in such situations has been to simply censor or omit observations taken after initiation of ST. In addition to being subject to bias, such approaches are also inefficient, potentially discarding substantial information if ST use is frequent.

G-estimation is a modeling technique developed for this type of situation. The essential idea of g-estimation is to de-mediate the effect of ST on subsequent outcomes, enabling analysis on a new vector of outcomes that are now independent of ST use. This is accomplished by estimation of so-called *structural nested mean models* (SNMM) which quantify the causal effect of ST use on the outcomes of interest. G-estimation of SNMMs uses all available data and has been found to produce precise estimates even in the presence of substantial ST use.

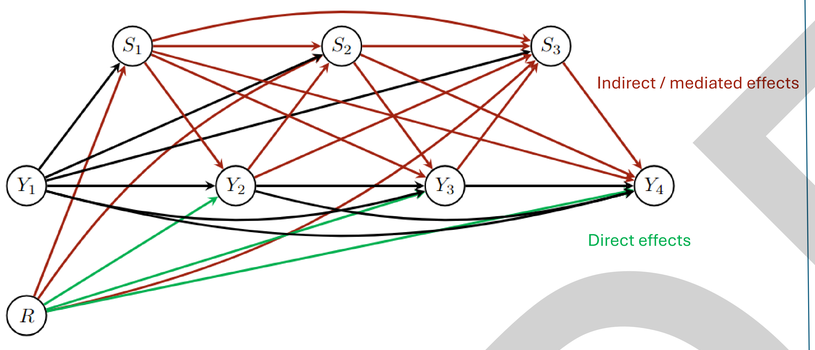
1. The Causal DAG

To introduce the model and causal relationships, we use the following notation. For time $t = 1, \dots, T$, let

- Y_t = outcome of interest at time t
- R = randomized treatment assignment
- S_t = use of ST between time t and $t+1$

In our setup, Y_1 is the baseline measurement, taken at randomization.

We use the below Directed Acyclic Graph (DAG) to encode the causal assumptions regarding the data generation mechanism. The illustration is given with $T = 4$ to keep the graph reasonably simple.



Key takeaways from the graph include 1) patients can initiate ST at any point in the study, and 2) any of the Y_i measurements (after Y_1) can be affected by prior ST use.

Although baseline is commonly indexed by $t = 0$, we use $t = 1$ here as it makes the programming steps in sections 4, 5, and 6 arguably somewhat easier to follow.

2. The estimand of interest

In our setting, we are interested in estimating the direct effects of R on $Y_2, Y_3, \dots$ in the absence of any prior ST use. In the mediation literature, these is known as controlled direct effects (CDEs).

To define the CDE, let $Y_{t+1}^{\bar{s}_t}(r)$ = the potential outcome for Y_{t+1} if investigative treatment r is taken, and symptomatic treatment history $\bar{s}_t = (s_1, \dots, s_t)$ is followed. The CDE at time $t+1$ is then defined as

$$E\left[Y_{t+1}^{\bar{s}_t=\bar{0}_t}(r=1) - Y_{t+1}^{\bar{s}_t=\bar{0}_t}(r=0)\right]$$

This corresponds to a hypothetical estimand in the context of ICH E9(R1).

3. g-estimation, the first steps

The basic idea of g-estimation is to quantify the lagged effects of ST initiation on subsequent Y_t measurements. We do this in two overarching steps:

1. Estimate the visit-wise ST initiation probabilities (propensities)
2. Quantify and "peel off" the lagged effects of ST use, for all possible lags

Assume our dataset is structured as follows:

Starting point

Imagine the data for a single patient.

- Long-format
- One row per visit

id	T	R	Y	S
1	1			0
1	2			0
1	3			1
1	4			1
1	5			1

Compute lags

Extend the dataset with all possible lags for Y and S

- Subscript $-l$ means lag l

id	T	R	Y	Y_{-1}	Y_{-2}	Y_{-3}	...	S	S_{-1}	S_{-2}	S_{-3}	...
1	1							0	0			
1	2							0	0	0		
1	3						...	1	0	0	0	...
1	4							1	1	0	0	
1	5							1	1	1	0	

1) The faint zeros in the lag columns for S are there to indicate that by design, ST was not being used prior to randomization. Hence by definition, $S_0 = 0$.
2) Although not required for g-estimation, in our example $S_t \leq S_{t'}$ for all $t < t'$. That is, if $S_t = 1$ then all subsequent $S_{t'}$ also equal 1.

4. Estimating the propensities

The first step is to estimate the propensity scores, i.e., the probability of initiating symptomatic treatment at time t, given Y_t, R, and $S_{t-1} = 0$.

$$\hat{p}_t = \text{expit}\{\text{logit}[\hat{E}(S_t \mid Y_t, R, t, S_{t-1} = 0)]\}$$

Compute propensities

- Pick out all rows with $S_{-1} = 0$
- Feed into a `glm` call

```
prop_fit <- glm( S ~ Y + R + T , family = binomial)
```

- Use `predict` to calculate $\hat{p}_t$ =

```
= p̂_t <- predict(prop_fit, type = "response")
```

Extend and lag

Add $\hat{p}_t$ = to the dataset and compute lags

id	T	R	Y	Y_{-1}	Y_{-2}	Y_{-3}	...	S	S_{-1}	S_{-2}	S_{-3}	...	$\hat{p}_t$	$\hat{p}_{-1}$	$\hat{p}_{-2}$	$\hat{p}_{-3}$	...
1	1							0	0								
1	2							0	0	0							
1	3						...	1	0	0	0	...					...
1	4							1	1	0	0						
1	5							1	1	1	0						

Rows where $S_{-1} = 1$ do not contribute to the propensity estimation. For those rows, when adding $\hat{p}_t$ to the dataset in the last step, we simply set $\hat{p}_t = 1$.

5. Quantifying the 1-lag effect ($S_t \to Y_{t+1}$)

The SNMM for the 1-lag effect of initiating ST at time t on Y_{t+1} is given as

$$E\left[Y_{t+1}^{\bar{0}_{t-1}1} - Y_{t+1}^{\bar{0}_{t-1}0} \mid \bar{S}_{t-1} = 0, R\right] = \psi_1$$

for $t = 1, \dots, T-1$. In this model ψ_1 = effect of initiating ST between t and $t+1$ (but not earlier) on Y_{t+1}. The model should condition on all potential confounders of the relationship between S_t and Y_{t+1}; in our DAG these are only R and the history of $\bar{S}_{t-1}$ but if other time-varying confounders are present, they should be included as well (see section 6).

We assume that the lag effect is the same for all t, but the model can be extended to allow effect modification to depend on other variables as well.

We estimate ψ_1 by regressing Y_{t+1} on $Y_t, S_t, \hat{p}_t$, and R. Because ψ_1 is assumed to be time-invariant, we can do this for all time points at once.

Estimate ψ_1

- Pick out all rows with $S_{-2} = 0$ and $t > 1$
- Regress Y on S_{-1}, $\hat{p}_{-1}, Y_{-1}, R$
- Set $\hat{\psi}_1$ as the coefficient of S_{-1}

```
psi1_fit <- lm( Y ~ S_-1 + R + p̂_-1 + Y_-1 )
```

```
ψ̂_1 <- coef(psi1_fit)["S_-1"]
```

Peel off the 1-lag effect

$\tilde{Y}$ <- Y - $\hat{\psi}_1$ * S_{-1}

id	T	R	Y	Y_{-1}	Y_{-2}	Y_{-3}	...	S	S_{-1}	S_{-2}	S_{-3}	...	$\hat{p}_t$	$\hat{p}_{-1}$	$\hat{p}_{-2}$	$\hat{p}_{-3}$	...	$\tilde{Y}$
1	1							0	0									
1	2							0	0	0								
1	3						...	1	0	0	0	...					...	
1	4							1	1	0	0							
1	5							1	1	1	0							

- Add $\tilde{Y}$ = to the dataset

6. Quantifying the 2-lag effect ($S_{t-1} \to Y_{t+1}$)

Now that we know the effect of S_t on Y_{t+1}, we next estimate the longer-term effect of S_{t-1} via the SNMM

$$E\left[Y_{t+1}^{\bar{0}_{t-2}10} - Y_{t+1}^{\bar{0}_{t-2}00} \mid \bar{S}_{t-2} = 0, R\right] = \psi_2$$

for $t = 2, \dots, T-1$.

Estimate ψ_2

- Pick out all rows with $S_{-3} = 0$ and $t > 2$
- Regress $\tilde{Y}$ on $S_{-2}, R, \hat{p}_{-2}, Y_{-2}$
- Set $\hat{\psi}_2$ as the coefficient of S_{-2}

```
psi2_fit <- lm( Ỹ ~ S_-2 + R + p̂_-2 + Y_-2 )
```

```
ψ̂_2 <- coef(psi2_fit)["S_-2"]
```

Peel off the 2-lag effect

$\tilde{Y}$ <- $\tilde{Y}$ - $\hat{\psi}_2$ * S_{-2}

id	T	R	Y	Y_{-1}	Y_{-2}	Y_{-3}	...	S	S_{-1}	S_{-2}	S_{-3}	...	$\hat{p}_t$	$\hat{p}_{-1}$	$\hat{p}_{-2}$	$\hat{p}_{-3}$	...	$\tilde{Y}$
1	1							0	0									
1	2							0	0	0								
1	3						...	1	0	0	0	...					...	
1	4							1	1	0	0							
1	5							1	1	1	0							

- Update $\tilde{Y}$ in the dataset

Continue in this fashion until all ψ_l, $l = 1, \dots, T-1$ have been estimated and we have a vector of de-mediated $\tilde{Y}$ for all lags.

7. Wrapping it up & additional considerations

With the vector of de-mediated observations $\tilde{Y}$ we can now perform the appropriate analysis that targets the original estimand of interest, e.g., analysis of covariance, mixed effect models, etc.

For inference, one can use non-parametric bootstrap or sandwich standard error calculations.

Our DAG could be extended in several ways, for example:

1. Time-varying covariates L_t that might influence the decision to initiate ST
2. Unobserved confounders U_t of ST use and outcome

Variables L_t could be straightforwardly added to our dataset and included in the models for propensities and lag effects. Further, g-estimation is thought to be robust to the presence of unmeasured ST-outcome confounders U_t.

References:

Vansteelandt, S., & Joffe, M. (2014). Structural nested models and G-estimation: the partially realized promise. Statistical Science, 29(4), 707-731.

Vansteelandt, S., & Sjolander, A. (2016). Revisiting g-estimation of the effect of a time-varying exposure subject to time-varying confounding. Epidemiologic Methods, 5(1), 37-56.