

# *G Estimation*

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## Outline

G Estimation

## Some Preliminaries

Structural nested models map a *conditional contrast* of potential outcomes to the treatment, within nested sub-groups of individuals defined by levels of  $A_1$ ,  $Z_1$ , and  $A_0$ . Our structural nested model can be written as

$$\begin{aligned} E(Y^{a_0, a_1} - Y^{a_0, 0} \mid A_0 = a_0, Z_1 = z_1, A_1 = a_1) &= a_1(\psi_1 + \psi_2 a_0 + \psi_3 z_1 + \psi_4 a_0 z_1) \\ E(Y^{a_0, 0} - Y^{0, 0} \mid A_0 = a_0) &= \psi_0 a_0 \end{aligned}$$

Note this model introduces two additional parameters than the marginal structural model:  $\psi_3$  for the two-way interaction between  $a_1$  and  $z_1$ , and  $\psi_4$  for the three-way interaction between  $a_1$ ,  $z_1$ , and  $a_0$ . Indeed, the ability to explicitly quantify interactions between time-varying exposures and time-varying covariates (which cannot be modeled via standard marginal structural models) is a major strength of structural nested models when effect modification is of interest (Robins and Hernán 2009). To simplify our exposition, we set  $(\psi_3, \psi_4) = (0, 0)$  in our data example, allowing us to drop the  $\psi_3 z_1$  and  $\psi_4 a_0 z_1$  terms from the model. In effect, this renders our structural nested mean model equivalent to a semi-parametric marginal structural model. (In the Supplementary Material of Ashley I Naimi, Cole, and Kennedy (2017), we explain how marginal structural and structural nested models each relate to time-varying interactions in more detail.)

We can now use g-estimation to estimate  $(\psi_0, \psi_1, \psi_2)$  in the above structural nested model. G-estimation is based on solving equations that directly result from conditional exchangeability (applied sequentially), combined with assumptions implied by the structural nested model. If, at each time point, the exposure is conditionally independent of the potential outcomes (sequential exchangeability) then the conditional covariance between the exposure and potential outcomes is zero (Vansteelandt and Joffe 2014). Formally, these conditional independence relations can be written as:

$$\begin{aligned}
0 &= \text{Cov}(Y^{a_0,0}, A_1 \mid Z_1, A_0) \\
&= \text{Cov}(Y^{0,0}, A_0)
\end{aligned}$$

where  $\text{Cov}(\cdot)$  is the well-known covariance formula (Wasserman 2006). These equalities are of little direct use for estimation, though, as they contain unobserved potential outcomes and are not yet functions of the parameters of interest. However, by counterfactual consistency and the structural nested model, we can replace these unknowns with quantities estimable from the data.

Specifically, the structural nested model, together with exchangeability and counterfactual consistency imply that we can replace the potential outcomes  $Y^{a_0,0}$  and  $Y^{0,0}$  in the above covariance formulas with their values implied by the structural nested model, yielding:

$$\begin{aligned}
0 &= \text{Cov}\{Y - A_1(\psi_1 + \psi_2 A_0), A_1 \mid Z_1, A_0\} \\
&= \text{Cov}\{Y - A_1(\psi_1 + \psi_2 A_0) - \psi_0 A_0, A_0\}.
\end{aligned}$$

We provide an intuitive explanation for this substitution in the Supplementary Material of A I Naimi (2016). We also show how these covariance relations yield three equations that can be used to solve each of the unknowns in the above structural nested model  $(\psi_0, \psi_1, \psi_2)$ .

Two of the three equations yield the following g estimators:

$$\begin{aligned}
\hat{\psi}_{1_{GE}} &= \frac{\hat{E}[(1 - A_0)Y\{A_1 - \hat{E}(A_1 \mid Z_1, A_0)\}]}{\hat{E}[(1 - A_0)A_1\{A_1 - \hat{E}(A_1 \mid Z_1, A_0)\}]} \\
\hat{\psi}_{1_{GE}} + \hat{\psi}_{2_{GE}} &= \frac{\hat{E}[A_0Y\{A_1 - \hat{E}(A_1 \mid Z_1, A_0)\}]}{\hat{E}[A_0A_1\{A_1 - \hat{E}(A_1 \mid Z_1, A_0)\}]}
\end{aligned}$$

Note that to solve these equations we need to model  $E(A_1 \mid Z_1, A_0)$ , which in practice we might assume can be correctly specified as the predicted values from a logistic model for  $A_1$ . In our simple setting, the correctness of this model is guaranteed by saturating it (i.e., conditioning the model on  $Z_1, A_0$  and their interaction).

As we show in the Supplementary Material, implementing these equations in software can be easily done using either an instrumental variables (i.e., two-stage least squares) estimator, or ordinary least squares.

Once the above parameters are estimated, the next step is to subtract the effect of  $A_1$  and  $A_1A_0$  from  $Y$  to obtain  $\tilde{Y} = Y - \hat{\psi}_{1GE}A_1 - \hat{\psi}_{2GE}A_1A_0$ . We can then solve for the last parameter using a sample version of the third g estimation equality, yielding our final estimator and completing the procedure:

$$\hat{\psi}_{0GE} = \frac{\hat{E}[\tilde{Y}\{A_0 - \hat{E}(A_0)\}]}{\hat{E}[A_0\{A_0 - \hat{E}(A_0)\}]}.$$

Again the above estimator can be implemented using an instrumental variable or ordinary least squares estimator. Here, we demonstrate how to do this using the least squares approach:

```
# arrange into wide data
a0 <- c(0, 0, 0, 0, 1, 1, 1, 1)
z1 <- c(0, 0, 1, 1, 0, 0, 1, 1)
a1 <- c(0, 1, 0, 1, 0, 1, 0, 1)
y <- c(87.29, 112.11, 119.65, 144.84, 105.28, 130.18, 137.72, 162.83)
N <- c(209271, 93779, 60654, 136293, 134781, 60789, 93903, 210530)
D <- NULL
for (i in 1:8) {
  d <- data.frame(cbind(rep(a0[i], N[i]), rep(z1[i], N[i]), rep(a1[i], N[i]), rep(y[i], N[i]))))
  D <- rbind(D, d)
}
nrow(D)

## [1] 1000000

names(D) <- c("a0", "z1", "a1", "y")

# model the exposure at the last time point and create residuals
D$rA1 <- D$a1 - glm(a1 ~ z1 + a0 + z1:a0, data = D, family = binomial("logit"))$fitted.values
D$rA1a0 <- D$rA1 * D$a0
stage1 <- coef(lm(y ~ -1 + rA1 + rA1a0, data = D))
```

```

# the effect of the second exposure is:
stage1[1]

##          rA1
## 24.96551

# transform the outcome
D$y_tilde <- D$y - stage1[1] * D$a1 - stage1[2] * D$a1 * D$a0

# model the exposure at the first time point and create residuals
D$rA0 <- D$a0 - glm(a0 ~ 1, data = D, family = binomial("logit"))$fitted.values
# estimate the second exposure effect
stage2 <- coef(lm(y_tilde ~ -1 + rA0, data = D))
# the effect of the first exposure is:
stage2

##          rA0
## 24.98026

```

Implementing this procedure in our example data, we obtain  $[\psi_{0_{GE}} = 25.0, \psi_{1_{GE}} = 25.0, \psi_{2_{GE}} = 0.0]$ , thus yielding  $\psi_{GE} = 50.0$ .

The potential outcome under no treatment can be thought of as a given subject's baseline prognosis: in our setting, individuals with poor baseline prognosis will have low CD4 levels, no matter what their treatment status may be. In the absence of confounding or selection bias, one expects this baseline prognosis to be independent of treatment status. G estimation exploits this independence by assuming no uncontrolled confounding (conditional on measured confounders), and assigning values to  $\hat{\psi}_{GE}$  that render the potential outcomes independent of the exposure. However, assigning the correct values to  $\hat{\psi}_{GE}$  depends on there being no confounding or selection bias.

## References

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Robins, James M, and Miguel Á Hernán. 2009. "Estimation of the Causal Effects of Time-Varying Exposures." In *Advances in Longitudinal Data Analysis*, edited by G Fitzmaurice, M. Davidian, G Verbeke, and G Molenberghs, 553–99. Boca Raton, FL: Chapman & Hall.

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