

eAppendix: R code to simulate example data and implement targeted maximum likelihood estimators.

```
GenerateData <- function(n, estimate.truth=FALSE) {
  rexpit <- function (x) rbinom(n=length(x), size=1,
  prob=plogis(x))

  L1 <- runif(n, min=8, max=12)
  if (estimate.truth) {
    A1 <- rep(0, n)    #estimate the true expected value of Y3
when A1 and A2 are set to zero
  } else {
    A1 <- rexpit(-5 + 0.5*L1)
  }
  Y2 <- rexpit(-4.5 + A1 + 2/(L1 - 7))
  L2 <- A2 <- Y3 <- rep(NA, n)
  alive <- Y2 == 0    #Y2==1 indicates death
  L2[alive] <- L1[alive] + A1[alive] + rnorm(n=sum(alive))
  if (estimate.truth) {
    A2[alive] <- 0    #estimate the true expected value of Y3
when A1 and A2 are set to zero
  } else {
    A2[alive] <- rexpit(-5 + 0.25*L1[alive] + A1[alive] +
0.25*L2[alive])
  }
  Y3[alive] <- rexpit(-5.5 + A1[alive] + A2[alive] +
2/(L1[alive]-7) + 2/(L2[alive]-7))
  Y3[!alive] <- 1
  if (estimate.truth) {
    return(mean(Y3))
  } else {
    return(data.frame(L1, A1, Y2, L2, A2, Y3))
  }
}

set.seed(6)
library(ltmle)
truth <- GenerateData(n=1000000, estimate.truth=TRUE) #estimate
the true expected value of Y3 when A1 and A2 are set to zero
cat("True parameter value = ", truth, "\n")
data <- GenerateData(n=200) #generate the data, letting A1 and
A2 follow the data generating process
```

```
cat("\n----- using Main Terms GLM -----\n")
result <- ltmle(data, Anodes=c("A1", "A2"), Lnodes="L2",
Ynodes=c("Y2", "Y3"), abar=c(0,0), survivalOutcome=TRUE)
print(summary(result, estimator="tmle"))

cat("\n----- using SuperLearner -----\n")
library(SuperLearner)
SL.library <- list("SL.glm", "SL.stepAIC", "SL.gam", "SL.knn",
"SL.bayesglm") #many prediction algorithms are available, this
is just a sample
result.SL <- ltmle(data, Anodes=c("A1", "A2"), Lnodes="L2",
Ynodes=c("Y2", "Y3"), abar=c(0,0), survivalOutcome=TRUE,
SL.library=SL.library)
print(summary(result.SL, estimator="tmle"))
```