Day 3, Lecture 2

Longitudinal TMLE (LTMLE)

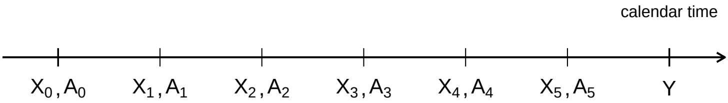
Overview

1. Targeting algorithm
   - Practical 2 (Task 1)
2. `ltmle` software package
   - Practical 2 (Task 2)
3. A note on right-censoring

Longitudinal data structure

Longitudinal data structure:

- $O = (X_0, A_0, X_1, A_1, \ldots, X_K, A_K, Y = X_{K+1}) \in (\mathbb{R}^d \times \{0,1\})^K \times \{0,1\}$
- Covariates $X = (X_0, X_1, \ldots, X_K)$ change over time
- Treatment decisions $A = (A_0, A_1, \ldots, A_K)$ are updated over time
- Covariates and treatment decisions interact in complex ways



Longitudinal targeting

(For the representation in terms of iterated conditional expectations)

Targeting algorithm

Recall —

TMLE is a two-step procedure:

Step 1 Construct initial estimator $\hat{P}_n$ for P.

Step 2 Update the estimator $\hat{P}_n \mapsto \hat{P}^*_n$ such that $\hat{P}^*_n$ solves the efficient influence curve equation.

Step 1 = "initial estimation step"

Step 2 = "targeting step"

Targeting algorithm

Recall — for the ATE:

TMLE is a two-step procedure:

Step 1 Construct initial estimators $\hat{f}_n, \hat{\pi}_n$ for f, π.

Step 2 Update the estimator $\hat{f}_n \mapsto \hat{f}_n^*$ for f such that $\hat{f}_n^*$ for the fixed $\hat{\pi}_n$ solves the efficient influence curve equation.

Step 1 = "initial estimation step"

Step 2 = "targeting step"

Targeting algorithm

The relevant part of P needed to evaluate our target parameter:

$$\mathbb{E}_P\big[\,Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*}\,\big] = \tilde{\Psi}(\bar{Q}),$$

with $\bar{Q} = (\bar{Q}_k)_{1\le k\le K+1}$.

Starting backwards from the last time-point:

$$\bar{Q}_{K+1}(\bar{x}_K, \bar{a}_K) = \mathbb{E}_P\big[\,Y \mid \bar{X}_K = \bar{x}_K, \bar{A}_K = \bar{a}_K\,\big]$$

and iteratively for $k = K, K-1, \dots, 1$,

$$\bar{Q}_k(\bar{x}_{k-1}, \bar{a}_{k-1}) = \mathbb{E}_P\big[\,\bar{Q}_{k+1}(\bar{X}_k, a_k^*, \bar{A}_{k-1}) \mid \bar{X}_{k-1} = \bar{x}_{k-1}, \bar{A}_{k-1} = \bar{a}_{k-1}\,\big]$$

so that

$$\mathbb{E}_P\big[\,Y^{A_\mathbf{0}=a_\mathbf{0}^*, A_\mathbf{1}=a_\mathbf{1}^*, \dots, A_K=a_K^*}\,\big] = \mathbb{E}_P\big[\,\bar{Q}_1(X_0, a_0^*)\big] = \tilde{\Psi}(\bar{Q}).$$

Targeting algorithm

We need the efficient influence function:

- Tells us what we need to estimate (to construct TMLE)
- Guides the construction of the targeting step

Construction of the targeting step for a given target parameter $\Psi : \mathcal{M} \to \mathbb{R}$ with efficient influence function $\phi^*(P)$ involves:

(i) A parametric submodel $\{\bar{Q}_\varepsilon : \varepsilon \in \mathbb{R}\} \subset \mathcal{M}$

(ii) A loss function $(O, \bar{Q}) \mapsto \mathscr{L}(\bar{Q})(O)$

such that: (1) $\bar{Q}_{\varepsilon=0} = \bar{Q}$, and, (2) $\frac{d}{d\varepsilon}\Big|_{\varepsilon=0} \mathscr{L}(\bar{Q}_\varepsilon)(O) = \phi^*(P)(O)$

Targeting algorithm

The efficient influence function is given by:

$$\begin{aligned}\phi^*(P)(O) &= \tilde{\phi}^*(\bar{Q},\pi)(O) \\ &= \sum_{k=1}^{K+1}\left(\prod_{l=0}^{k-1}\frac{1\{A_l = a_l^*\}}{\pi_{A_l}(a_l^* \mid \bar{x}_l, \bar{a}_{l-1}^*)}\right)\left\{\bar{Q}_{k+1}(\bar{X}_k, a_k^*, \bar{A}_{k-1}) - \bar{Q}_k(\bar{X}_{k-1}, \bar{A}_{k-1})\right\} \\ &\qquad + \bar{Q}_1(X_0, a_0^*) - \Psi(P)\end{aligned}$$

(with $\bar{Q}_{K+2} := Y$)

Targeting algorithm

The efficient influence function is given by:

$$\phi^*(P)(O) = \tilde{\phi}^*(\bar{Q}, \pi)(O)$$

$$= \sum_{k=1}^{K+1} \left(\prod_{l=0}^{k-1} \frac{1\{A_l = a_l^*\}}{\pi_{A_l}(a_l^* \mid \bar{x}_l, \bar{a}_{l-1}^*)} \right) \{ \bar{Q}_{k+1}(\bar{X}_k, a_k^*, \bar{A}_{k-1}) - \bar{Q}_k(\bar{X}_{k-1}, \bar{A}_{k-1}) \}$$

$$+ \bar{Q}_1(X_0, a_0^*) - \Psi(P)$$

(with $\bar{Q}_{K+2} := Y$)

- Need initial estimators for: $\pi = (\pi_{A_k})_{0 \le k \le K}$, $\bar{Q} = (\bar{Q}_k)_{1 \le k \le K+1}$

Targeting algorithm

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$$= \sum_{k=1}^{K+1} \left(\prod_{l=0}^{k-1} \frac{1\{A_l = a_l^*\}}{\pi_{A_l}(a_l^* \mid \bar{x}_l, \bar{a}_{l-1}^*)} \right) \left\{ \bar{Q}_{k+1}(\bar{X}_k, a_k^*, \bar{A}_{k-1}) - \bar{Q}_k(\bar{X}_{k-1}, \bar{A}_{k-1}) \right\}$$

$$+ \; \bar{Q}_1(X_0, a_0^*) - \Psi(P)$$

(with $\bar{Q}_{K+2} := Y$)

- Need initial estimators for: $\pi = (\pi_{A_k})_{0 \le k \le K}$, $\bar{Q} = (\bar{Q}_k)_{1 \le k \le K+1}$
- Submodel and loss function for each $\bar{Q}_k$ in turn *to solve the k-specific part of the efficient influence curve equation*,

$$\tilde{\phi}_k^*(\bar{Q}, \pi)(O) = \left(\prod_{l=0}^{k-1} \frac{1\{A_l = a_l^*\}}{\pi_{A_l}(a_l^* \mid \bar{X}_l, \bar{a}_{l-1}^*)} \right) \left\{ \bar{Q}_{k+1}(\bar{X}_k, a_k^*, \bar{A}_{k-1}) - \bar{Q}_k(\bar{X}_{k-1}, \bar{A}_{k-1}) \right\}$$

Targeting algorithm

We construct a submodel $\bar{Q}_{k,\varepsilon}$ through a given $\bar{Q}_k$ and a loss function $(O, \bar{Q}_k) \mapsto \mathscr{L}_{\bar{Q}_{k+\mathbf{1}}}(\bar{Q}_k)(O)$ such that

$$(1) \quad \bar{Q}_{k,\varepsilon=0} = \bar{Q}_k, \quad \text{and,} \quad (2) \quad \left.\frac{d}{d\varepsilon}\right|_{\varepsilon=0} \mathscr{L}_{\bar{Q}_{k+\mathbf{1}}}(\bar{Q}_{k,\varepsilon})(O) = \phi^*_k(\bar{Q},\pi)(O)$$

Note that the loss function is indexed by $\bar{Q}_{k+1}$.

Targeting algorithm

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Note that the loss function is indexed by $\bar{Q}_{k+1}$*.*

We define:

$$\mathscr{L}_{\bar{Q}_{k+\mathbf{1}}}(\bar{Q}_k) = -\big(\bar{Q}_{k+1} \log(\bar{Q}_k) + (1 - \bar{Q}_{k+1}) \log(1 - \bar{Q}_k)\big)$$

and,

$$\bar{Q}_{k,\varepsilon}(O) = \operatorname{expit}\big(\operatorname{logit}(\bar{Q}_k(\bar{X}_{k-1}, \bar{A}_{k-1})) + \varepsilon H_k(\pi)(O)\big)$$

with the "clever covariate": $H_k(\pi)(O) := \prod_{l=0}^{k-1} \frac{1\{A_l = a_l^*\}}{\pi_{A_l}(a_l^* \mid \bar{x}_l, \bar{a}_{l-1}^*)}$

Targeting algorithm

Another valid choice of loss function and submodel would be:

We define:

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and,

$$\bar{Q}_{k,\varepsilon}(O) = \operatorname{expit}\Big(\operatorname{logit}(\bar{Q}_k(\bar{X}_{k-1}, \bar{A}_{k-1})) + \varepsilon\Big)$$

using the "clever covariate" $H_k(\pi)(O) := \prod_{l=0}^{k-1} \frac{1\{A_l = a_l^*\}}{\pi_{A_l}(a_l^* \mid \bar{x}_l, \bar{a}_{l-1}^*)}$

as a weight.

Targeting algorithm

The targeting step becomes a targeting algorithm that proceeds iteratively along the sequence of iterated conditional expectations, *starting from the last time-point*.

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- We set $\hat{\hat{Q}}_{K+2} := Y$

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- We start by targeting an estimator $\hat{\bar{Q}}_{K+1}$
- We set $\hat{\bar{Q}}_{K+2} := Y$
- Regress Y on $\bar{X}_K, \bar{A}_K$ and obtain the predictions $\hat{\bar{Q}}_{K+1}(\bar{X}_k, \bar{A}_k)$

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- Logistic regression of $\hat{\bar{Q}}_{K+2}$ on the clever covariate $H_{K+1}(\hat{\pi})(O)$ and offset $\mathrm{logit}\{\hat{\bar{Q}}_{K+1}(\bar{X}_K, \bar{A}_K)\}$ to obtain estimate $\hat{\varepsilon}_n$ for ε

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- Update according to the submodel: $\hat{\hat{Q}}^*_{K+1}(\bar{X}_k, a^*_k, \bar{A}_{k-1}) := \mathrm{expit}\big(\mathrm{logit}\{\hat{\hat{Q}}_{K+1}(\bar{X}_k, a^*_k, \bar{A}_{k-1})\} + \hat{\varepsilon}_n H_{K+1}(\hat{\pi})(O)\big)$

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We then solve:

$$\frac{1}{n}\sum_{i=1}^{n} H_{K+1}(\hat{\pi})(O_i)\big\{\hat{\hat{Q}}^*_{K+2} - \hat{\hat{Q}}^*_{K+1}(\bar{X}_{K,i}, \bar{A}_{K,i})\big\} = 0$$

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We then solve:

$$\frac{1}{n}\sum_{i=1}^{n} H_k(\hat{\pi})(O_i)\big\{\hat{\hat{Q}}^*_{k+1}(\bar{X}_{k,i}, a^*_k, \bar{A}_{k-1,i}) - \hat{\hat{Q}}^*_k(\bar{X}_{k-1,i}, \bar{A}_{k-1,i})\big\} = 0$$

Targeting algorithm

The targeting step becomes a targeting algorithm that proceeds iteratively along the sequence of iterated conditional expectations, *starting from the last time-point*.

This procedure gives a sequence of updated estimators $\hat{\hat{Q}}^* = (\hat{\hat{Q}}^*_{K+1}, \hat{\hat{Q}}^*_K, \dots, \hat{\hat{Q}}^*_1)$ that solves the efficient influence curve equation:

$$\frac{1}{n}\sum_{i=1}^{n}\sum_{k=1}^{K+1}\left(\prod_{l=0}^{k-1}\frac{1\{A_{l,i}=a^*_l\}}{\hat{\pi}_{A_l}(a^*_l \mid \bar{X}_{l,i}, \bar{a}^*_{l-1})}\right)\Big\{\hat{\hat{Q}}^*_{k+1}(\bar{X}_{k,i}, a^*_k, \bar{A}_{k-1,i}) \\ - \hat{\hat{Q}}^*_k(\bar{X}_{k-1}, \bar{A}_{k-1})\Big\} + \hat{\hat{Q}}^*_1(X_0, a^*_0) - \Psi(\hat{\hat{Q}}^*)$$

where

$$\tilde{\Psi}(\hat{\hat{Q}}^*) = \frac{1}{n}\sum_{i=1}^{n}\hat{\hat{Q}}^*_1(X_{0,i}, a^*_0).$$

Practical 2: Implementing the targeting step (Task 1)

Read the first page of **day3_practical2.pdf** and then go through the steps of **Task 1**.

[If time permits, we will continue with **Task 2** after the next part of the lecture.]

ltmle software package

ltmle software package

See also: https://cran.r-project.org/web/packages/ltmle/ltmle.pdf

```
install.packages(ltmle)
library(ltmle)
```

ltmle software package

Some useful arguments to know:

```
ltmle(data,
      Anodes, Lnodes, Cnodes, Ynodes,
      abar, rule,
      Qform, gform,
      SL.library,
      gbounds,
      ...)
```

ltmle software package

- data: data frame

  NB the order of columns correspond to the order of variables.

- Anodes: names of treatment variables
- Lnodes: names of covariates
- Cnodes: names of censoring variables
- Ynodes: names of outcome variables

NB All variables except baseline covariates must be specified in Anodes, Lnodes, Cnodes or Ynodes.

ltmle software package

For the dataset simulated in Lecture 1:

```
        X0.1        X0.2 X0.3 A0 X1.1 X1.2 A1 Y
1:  1.2915853 -0.29726781    0  0    1    0  0 1
2:  0.8407983 -0.48032616    0  0    0    1  0 0
3:  1.8633391 -0.50152323    0  1    1    1  0 1
4: -1.6855569 -1.57948481    0  1    0    0  1 1
5: -1.7854517  0.04438914    0  0    1    1  0 1
6:  0.2999129 -1.41470763    0  1    0    1  0 0
```

```
Anodes = paste0("A",0:1)
Lnodes = c(paste0("X0.", 1:3), paste0("X1.", 1:2))
Ynodes = "Y"
```

The ordering of columns dictates the temporal ordering of variables:

$$\begin{Bmatrix} X_{0,1} \\ X_{0,2} \\ X_{0,3} \end{Bmatrix} \rightarrow A_0 \rightarrow \begin{Bmatrix} X_{1,1} \\ X_{1,2} \end{Bmatrix} \rightarrow A \rightarrow Y$$

`ltmle` software package

Specifying interventions:

- `abar`: a binary vector of treatment assignments of length = length(`Anodes`) **or** a list of two elements to contrast treatment regimes
  - to specify *static treatment regimes*
- `rule`: a function that can be applied to each row of the data to return a binary vector of treatment assignments of length = length(`Anodes`)
  - to specify *dynamic treatment regimes*

ltmle software package

For example:

```
summary(ltmle(sim.data,
          Anodes=paste0("A",0:1),
          Lnodes=c(paste0("X0.", 1:3), paste0("X1.", 1:2)),
          Ynodes="Y",
          abar=list(treatment=c(1,1), control=c(0,0))))
```

[output next slide]

ltmle software package

```
Treatment Estimate:
   Parameter Estimate:  0.3029
    Estimated Std Err:  0.086738
              p-value:  0.00047919
    95% Conf Interval: (0.1329, 0.4729)

Control Estimate:
   Parameter Estimate:  0.36688
    Estimated Std Err:  0.015419
              p-value:  <2e-16
    95% Conf Interval: (0.33666, 0.3971)

Additive Treatment Effect:
   Parameter Estimate:  -0.063978
    Estimated Std Err:  0.088095
              p-value:  0.46769
    95% Conf Interval: (-0.23664, 0.10868)
```

ltmle software package

Here note that Treatment Estimate and Control Estimate were fitted completely separately, and that they could had been obtained with separate calls:

`ltmle` software package

Here note that `Treatment Estimate` and `Control Estimate` were fitted completely separately, and that they could had been obtained with separate calls:

`Treatment Estimate`:

```
summary(ltmle(...,
           abar=c(1,1)))
```

```
Parameter Estimate:  0.3029
 Estimated Std Err:  0.086738
           p-value:  0.00047919
 95% Conf Interval: (0.1329, 0.4729)
```

`Control Estimate`:

```
summary(ltmle(...,
           abar=c(0,0)))
```

```
Parameter Estimate:  0.36688
 Estimated Std Err:  0.015419
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```

- For each parameter we get the standard error,[a] the p-value of the null hypothesis that that quantity equals zero, and confidence intervals

[a] influence curve based if the argument `variance.method="ic"` is specified, otherwise a more robust variance estimator based on TMLE is used.

ltmle software package

Effect of a dynamic regime:

```r
summary(ltmle(sim.data,
          Anodes=paste0("A",0:1),
          Lnodes=c(paste0("X0.", 1:3), paste0("X1.", 1:2)),
          Ynodes="Y",
          rule=function(row) c(1, ifelse(row["X1.1"]==1, 0,
    1))))
```

ltmle software package

Effect of a dynamic regime:

```r
summary(ltmle(sim.data,
          Anodes=paste0("A",0:1),
          Lnodes=c(paste0("X0.", 1:3), paste0("X1.", 1:2)),
          Ynodes="Y",
          rule=function(row) c(1, ifelse(row["X1.1"]==1, 0,
    1))))
```

Static regimes can also be specified as a dynamic regime:

```r
summary(ltmle(sim.data,
          Anodes=paste0("A",0:1),
          Lnodes=c(paste0("X0.", 1:3), paste0("X1.", 1:2)),
          Ynodes="Y",
          rule=list(
          treatment=function(row) c(1,1),
          control=function(row) c(0,0))))
```

`ltmle` software package

- `Qform`: character vector of regression formulas for the outcome regressions
  - `Qform` indicates what variables are included in each outcome regression
  - default is `NULL` which means that all variables from previous time-points are included
  - (does *not* mean that `GLM` is used)
- `gform`: character vector of regression formulas for the propensity scores
  - `gform` indicates what variables are included in each propensity score regression
  - default is `NULL` which means that all variables from previous time-points are included
  - (does *not* mean that `GLM` is used)

`ltmle` software package

- `SL.library`: list with names entries `Q` and `g` specifying super learner libraries to pass to `SuperLearner` for the outcome regressions and the propensities scores

You can see available models for the super learner here: `https://cran.r-project.org/web/packages/SuperLearner/vignettes/Guide-to-SuperLearner.html` (Section 4)

NB Some algorithms are really very slow

NB Some algorithms may not converge (gives error messages)

NB Think about what you know about each particular algorithm and do not just blindly include a ton of heavy algorithms

ltmle software package

We can extract the super learner weights applied to each algorithm from the ltmle object (here called fit.ltmle.sl):

```
fit.ltmle.sl$fit$Q[[1]]
```

```
$X1.1
                              Risk       Coef
SL.glm_All              0.01672344 0.96580665
SL.mean_All             0.01765778 0.03419335
SL.glm.interaction_All  0.01681181 0.00000000
SL.glmnet_All                   NA 0.00000000
SL.gam_All              0.01673172 0.00000000

$Y
                             Risk       Coef
SL.glm_All              0.2092472 0.97832296
SL.mean_All             0.2346187 0.02167704
SL.glm.interaction_All  0.2116557 0.00000000
SL.glmnet_All           0.2097088 0.00000000
SL.gam_All              0.2093541 0.00000000
```

ltmle software package

We can extract the super learner weights applied to each algorithm from the ltmle object (here called fit.ltmle.sl):

```
fit.ltmle.sl$fit$g[[1]]
```

```
$A0
                   Risk Coef
SL.glm_All    0.2508915    0
SL.mean_All   0.2502013    1
SL.glmnet_All 0.2502013    0
SL.gam_All    0.2512009    0

$A1
                    Risk     Coef
SL.glm_All    0.03332285 0.000000
SL.mean_All   0.08031019 0.000000
SL.glmnet_All 0.03330272 0.822445
SL.gam_All    0.03337456 0.177555
```

Practical 2: Implementing the targeting step (Task 2–)

In this part of the practical, we consider application of `ltmle`:

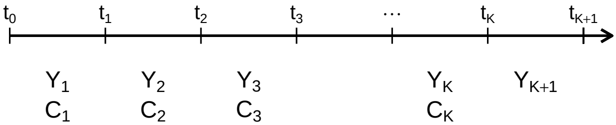
- Static and dynamic interventions
- Super learning

Proceed from **Task 2** of **day3_practical2.pdf**.

A note on: `ltmle` for right-censored data

Outcome process Y_k can jump from 0 to 1 at any time-point t_k.

Censoring process C_k can jump from 0 to 1 at any time-point t_k.



- Time to event: $\tilde{T} = k' \wedge K + 1$ where $k' = \min(k : Y_k = 1 \text{ or } C_k = 1)$
- Event indicator: $\Delta = 1\{Y_{\tilde{T}} = 1\}$

A note on: `ltmle` for right-censored data

One way that we can represent the survival data over a grid of $K = 7$ time-points (long format), e.g., for three different individuals:

```
   id k Y C
1:  2 1 0 0
2:  2 2 0 0
3:  2 3 0 0
4:  2 4 1 0
```

```
   id k Y C
1:  5 1 0 0
2:  5 2 0 0
3:  5 3 0 0
4:  5 4 0 0
5:  5 5 0 0
6:  5 6 0 0
7:  5 7 0 0
8:  5 8 0 0
```

```
   id k Y C
1:  7 1 0 0
2:  7 2 0 1
```

A note on: `ltmle` for right-censored data

One way that we can represent the survival data over a grid of $K = 7$ time-points (long format), e.g., for three different individuals:

```
   id k Y C
1:  2 1 0 0
2:  2 2 0 0
3:  2 3 0 0
4:  2 4 1 0
```

```
   id k Y C
1:  5 1 0 0
2:  5 2 0 0
3:  5 3 0 0
4:  5 4 0 0
5:  5 5 0 0
6:  5 6 0 0
7:  5 7 0 0
8:  5 8 0 0
```

```
   id k Y C
1:  7 1 0 0
2:  7 2 0 1
```

Same data may also be presented as (wide format):

```
   id Y1 C1 Y2 C2 Y3 C3 Y4 C4 Y5 C5 Y6 C6 Y7 C7 Y8
1:  2  0  0  0  0  0  0  1  0  1  0  1  0  1  0  1
2:  5  0  0  0  0  0  0  0  0  0  0  0  0  0  0  0
3:  7  0  0  0  1  0  1  0  1  0  1  0  1  0  1  0
```

A note on: `ltmle` for right-censored data

One way that we can represent the survival data over a grid of $K = 7$ time-points (long format), e.g., for three different individuals:

```
   id k Y C
1:  2 1 0 0
2:  2 2 0 0
3:  2 3 0 0
4:  2 4 1 0
```

```
   id k Y C
1:  5 1 0 0
2:  5 2 0 0
3:  5 3 0 0
4:  5 4 0 0
5:  5 5 0 0
6:  5 6 0 0
7:  5 7 0 0
8:  5 8 0 0
```

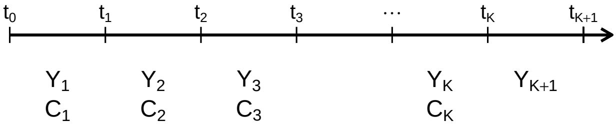
```
   id k Y C
1:  7 1 0 0
2:  7 2 0 1
```

Same data may also be presented as (wide format):

```
   id Y1 C1 Y2 C2 Y3 C3 Y4 C4 Y5 C5 Y6 C6 Y7 C7 Y8
1:  2  0  0  0  0  0  0  1  0  1  0  1  0  1  0  1
2:  5  0  0  0  0  0  0  0  0  0  0  0  0  0  0  0
3:  7  0  0  0  1  0  1  0  1  0  1  0  1  0  1  0
```

(The wide format is needed for `ltmle`).

A note on: `ltmle` for right-censored data



Example:

```
   id   X0.1   X0.2 X0.3 A0 Y1 C1 Y2 C2 Y3 C3 Y4 C4 Y5 C5 Y6 C6 Y7 C7 Y8
1:  1  0.408 -0.196    0  1  0  1  0  1  0  1  0  1  0  1  0  1  0  1  0
2:  2 -1.220  0.595    1  1  0  0  0  0  0  0  0  0  0  0  0  0  0  1  0
3:  3  1.866 -1.609    0  1  0  0  1  0  1  0  1  0  1  0  1  0  1  0  1
4:  4  0.604  0.041    0  1  0  0  0  0  0  0  0  0  0  0  0  0  0  0  0
5:  5 -0.532 -1.251    0  0  0  0  0  0  0  0  0  0  0  0  0  0  0  0  0
6:  6  1.955  0.133    1  1  0  0  0  0  0  0  0  1  0  1  0  1  0  1  0
```

- Baseline covariate vector: $X_0 = (X_{0,1}, X_{0,2}, X_{0,3})$
- Baseline treatment decision: $A_0 \in \{0, 1\}$
- Time to event: $\tilde{T} = k' \wedge K + 1$ where $k' = \min(k : Y_k = 1 \text{ or } C_k = 1)$
- Event indicator: $\Delta = 1\{Y_{\tilde{T}} = 1\}$

A note on: `ltmle` for right-censored data

Generally:

$$O = (X_0, A_0, Y_1, C_1, X_1, A_1, \dots, Y_K, C_K, X_K, A_K, Y = X_{K+1}).$$

- Covariates $X = (X_0, X_1, \dots, X_K)$ change over time.
- Treatment decisions $A = (A_0, A_1, \dots, A_K)$ are updated over time.
- Censoring status $C = (C_1, C_2, \dots, C_K)$ change over time.
- Outcome (death) status $Y = (Y_1, Y_2, \dots, Y_K)$ change over time.

[After death/censoring, all variables are deterministically set to their last observed values].

A note on: `ltmle` for right-censored data

Inferring on the uncensored event time is like imposing a simple static intervention on all right-censoring nodes to impose 'no censoring'.

Target causal parameter:

$$\Psi_{k^*}(P) = \mathbb{E}[\, Y_{k^*}^{A_{\mathbf{0}}=a_{\mathbf{0}}^*, C_{\mathbf{1}}=0, A_{\mathbf{1}}=a_k^*, \dots, C_K=0, A_K=a_K^*}] - \mathbb{E}[\, Y_{k^*}^{A_{\mathbf{0}}=0, C_{\mathbf{1}}=0, A_{\mathbf{0}}=0, \dots, C_K=0, A_K=0}]$$

I.e., the effect of the treatment *had there been no loss to follow-up*.

$=$ the absolute risk by time t_{k^*} if everyone had received treatment $(a_0^*, a_1^*, \dots, a_K^*)$ contrasted to the absolute risk if everyone had not been treated.

A note on: `ltmle` for right-censored data

The ordering of

$$O = (X_0, A_0, Y_1, C_1, X_1, A_1, \dots, Y_K, C_K, X_K, A_K, Y = X_{K+1}),$$

implies a temporal ordering:

$$X_0 \to A_0 \to \cdots \to Y_k \to C_k \to X_k \to A_k \to \cdots \to Y_{K+1}.$$

- at each time-point t_k, a patient is only at risk of dying if they did not yet die and they were not yet right-censored $(Y_{k-1} = 0, C_{k-1} = 0)$.
- at each time-point t_k, a patient is only at risk of being right-censoring if they did not yet die at this time and they were not yet right-censored $(Y_k = 0, C_{k-1} = 0)$.

A note on: `ltmle` for right-censored data

Factorization of the density p of $P \in \mathcal{M}$:

$$
\begin{aligned}
p(o) = \mu_{X_\mathbf{0}}(x_0)\pi_{A_\mathbf{0}}(a \mid x_0) \\
\prod_{k=1}^{K} \Big(\mu_{Y_k}(y_k \mid \bar{y}_{k-1}, \bar{c}_{k-1}, \bar{x}_{k-1}, \bar{a}_{k-1}) \pi_{C_k}(c_k \mid \bar{y}_k, \bar{c}_{k-1}, \bar{x}_k, \bar{a}_{k-1}) \\
\times \mu_{X_k}(x_k \mid \bar{y}_k, \bar{c}_k, \bar{x}_{k-1}, \bar{a}_{k-1}) \pi_{A_k}(a_k \mid \bar{y}_k, \bar{c}_k, \bar{x}_k, \bar{a}_{k-1}) \Big) \\
\times \ \mu_{Y_{K+\mathbf{1}}}(y_{K+1} \mid \bar{y}_K, \bar{c}_K, \bar{x}_K, \bar{a}_K)
\end{aligned}
$$

Without going into too many details, note for example that:

- $\mu_{Y_k}(1 \mid \bar{0}_{k-1}, \bar{0}_{k-1}, \bar{x}_{k-1}, \bar{a}_{k-1})$ is the risk of outcome (dying) for a subject who did not yet die nor were right-censored plus had covariate and treatment history equal to $\bar{x}_{k-1}, \bar{a}_{k-1}$.
- $\pi_{C_k}(1 \mid \bar{0}_k, \bar{0}_{k-1}, \bar{x}_{k-1}, \bar{a}_{k-1})$ is the probability of being right-censored for a subject who did not yet die nor were right-censored plus had covariate and treatment history equal to $\bar{x}_{k-1}, \bar{a}_{k-1}$.

A note on: `ltmle` for right-censored data

Identification of the target parameter as without censoring:

$$
\begin{aligned}
\bar{Q}_{K+1}(\bar{x}_K, \bar{a}_K, \bar{y}_K) &= \mathbb{E}_P[\, Y_{K+1} \mid \bar{Y}_K = \bar{y}_K, \bar{C}_K = 0, \bar{X}_K = \bar{x}_K, \bar{A}_K = \bar{a}_K \,] \\
\bar{Q}_K(\bar{x}_{K-1}, \bar{a}_{K-1}, \bar{y}_{K-1}) &= \mathbb{E}_P[\, Q_{K+1}(\bar{X}_K, a^*_K, \bar{A}_{K-1}, \bar{Y}_{K-1}) \mid \bar{Y}_{K-1} = \bar{y}_{K-1}, \bar{C}_{K-1} = 0, \\
&\vdots \\
\bar{Q}_k(\bar{x}_{k-1}, \bar{a}_{k-1}, \bar{y}_{k-1}) &= \mathbb{E}_P[\, Q_{k+1}(\bar{X}_k, a^*_k, \bar{A}_{k-1}, \bar{Y}_{k-1}) \mid \bar{Y}_{k-1} = \bar{y}_{k-1}, \bar{C}_{k-1} = 0, \bar{X}_{k-} \\
&\vdots \\
\bar{Q}_2(\bar{x}_1, \bar{a}_1, \bar{y}_1) &= \mathbb{E}_P[\, Q_3(\bar{X}_2, a^*_2, A_1, Y_1) \mid \bar{Y}_1 = y_1, \bar{C}_1 = 0, \bar{X}_1 = \bar{x}_1, A_1 = a_1 \,] \\
\bar{Q}_1(x_0, a_0) &= \mathbb{E}_P[\, Q_2(\bar{X}_1, a^*_1) \mid X_0 = x_0, A_0 = a_0 \,]
\end{aligned}
$$

+ note that $\bar{Q}_k(\bar{x}_{k-1}, \bar{a}_{k-1}, \bar{y}_{k-1}) = 1$ if $y_{k'-1} = 1$ for $k' \leq k$.

A note on: `ltmle` for right-censored data

The efficient influence function is given by:

$$\begin{aligned}
&\tilde{\phi}^*(\bar{Q},\pi)(O) \\
&= \sum_{k=1}^{K+1} 1\{Y_k = 0\}\left(\prod_{l=0}^{k-1} \frac{1\{A_l = a_l^*\}1\{C_l = 0\}}{\pi_{A_l}(0,0,a_l^* \mid \bar{x}_l, \bar{a}_{l-1}^*)\pi_{C_l}(0 \mid 0,0,\bar{x}_l,\bar{a}_{l-1}^*)} \right) \\
&\qquad \times \left\{ \bar{Q}_{k+1}(\bar{X}_k, a_k^*, \bar{A}_{k-1}, 0) - \bar{Q}_k(\bar{X}_{k-1}, \bar{A}_{k-1}, 0) \right\} + \bar{Q}_0(X_0) - \Psi(P).
\end{aligned}$$

A note on: ltmle for right-censored data

```
ltmle(data,
      Anodes, Lnodes, Cnodes, Ynodes,
      abar, rule,
      Qform, gform,
      SL.library,
      gbounds,
      survivalOutcome=TRUE,
      ...)
```

- Right-censoring nodes are specified in the Cnodes argument.
- The formatting of Cnodes is a bit peculiar — it should be a factor variable with the values 0 and 1 and the labels "uncensored" and "censored".
- Note that we further specify survivalOutcome=TRUE, so that Ynodes are treated as indicators of a terminating event.

A note on: `ltmle` for right-censored data

- `Qform`: character vector of regression formulas for the outcome regressions
  - `Qform` indicates what variables are included in each outcome regression
  - default is `NULL` which means that all variables from previous time-points are included
  - (does *not* mean that `GLM` is used)
- `gform`: character vector of regression formulas for the propensity scores and the hazards of censoring
  - `gform` indicates what variables are included in each propensity score regression and the hazards of censoring
  - default is `NULL` which means that all variables from previous time-points are included
  - (does *not* mean that `GLM` is used)

A note on: ltmle for right-censored data

For the example:

```
   id   X0.1   X0.2 X0.3 A0 Y1 C1 Y2 C2 Y3 C3 Y4 C4 Y5 C5 Y6 C6 Y7 C7 Y8
1:  1  0.408 -0.196    0  1  0  1  0  1  0  1  0  1  0  1  0  1  0  1  0
2:  2 -1.220  0.595    1  1  0  0  0  0  0  0  0  0  0  0  0  0  0  1  0
3:  3  1.866 -1.609    0  1  0  0  1  0  1  0  1  0  1  0  1  0  1  0  1
4:  4  0.604  0.041    0  1  0  0  0  0  0  0  0  0  0  0  0  0  0  0  0
5:  5 -0.532 -1.251    0  0  0  0  0  0  0  0  0  0  0  0  0  0  0  0  0
6:  6  1.955  0.133    1  1  0  0  0  0  0  0  0  1  0  1  0  1  0  1  0
```

```r
for (k in 1:7)
    sim.data[, (paste0("C", k)):=BinaryToCensoring(is.censored=get(
    paste0("C", k)))]
```

```r
ltmle.fit <- ltmle(sim.data[, -"id"],
           Anodes="A0", Lnodes=paste0("X0.", 1:3),
           Cnodes=paste0("C", 1:7), Ynodes=paste0("Y", 1:8),
           abar=list(treatment=1, control=0),
           SL.library=list(Q=c("SL.glm", "SL.mean"),
                   g=c("SL.glm", "SL.mean")),
           survivalOutcome=TRUE)
```

A note on: ltmle for right-censored data

```
Treatment Estimate:
   Parameter Estimate:  0.40391
    Estimated Std Err:  0.031247
              p-value:  <2e-16
    95% Conf Interval: (0.34267, 0.46515)

Control Estimate:
   Parameter Estimate:  0.49545
    Estimated Std Err:  0.029052
              p-value:  <2e-16
    95% Conf Interval: (0.43851, 0.55239)

Additive Treatment Effect:
   Parameter Estimate:  -0.091539
    Estimated Std Err:  0.041653
              p-value:  0.027973
    95% Conf Interval: (-0.17318, -0.0099008)

Relative Risk:
   Parameter Estimate:  0.81524
  Est Std Err log(RR):  0.095263
              p-value:  0.032009
    95% Conf Interval: (0.67639, 0.98259)
```

A note on: ltmle for right-censored data

```
ltmle.fit$fit$g[[1]]
```

```
$A0
                Risk      Coef
SL.glm_All  0.2502361 0.4568067
SL.mean_All 0.2501919 0.5431933

$C1
                Risk       Coef
SL.glm_All  0.1533290 0.98494501
SL.mean_All 0.1667804 0.01505499

$C2
                Risk     Coef
SL.glm_All  0.1365783 0.956276
SL.mean_All 0.1428211 0.043724

$C3
                Risk       Coef
SL.glm_All  0.1373765 0.92097765
SL.mean_All 0.1440681 0.07902235

$C4
```