Missing data and composite endpoints

Efficient estimation of the distribution of time to composite endpoint when one of the endpoints is incompletely observed

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CSM Seminar, 25th January 2013

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

This talk is based on:

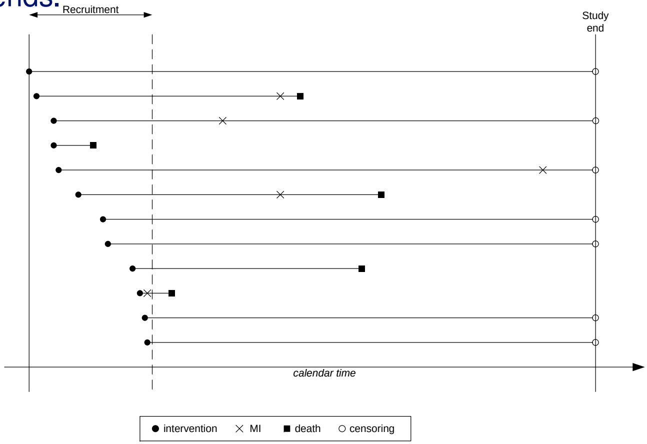
- Daniel RM, Tsiatis AA
  Efficient estimation of the distribution of time to composite endpoint when some endpoints are only partially observed.
  Lifetime Data Analysis, under revision.

Work carried out while I visited Prof Butch Tsiatis in Raleigh NC, January–April 2012.

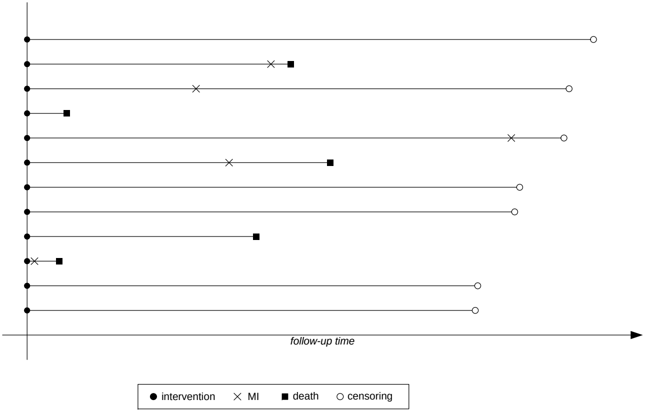
Funded by MRC Career Development Award in Biostatistics G1002283.

Setting (1)

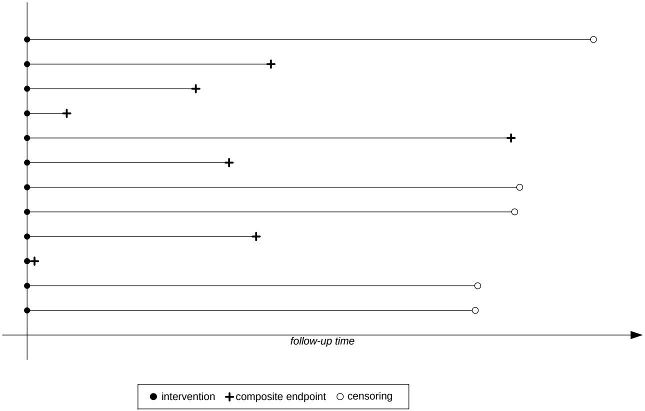
Consider a study in which patients are recruited (and given an intervention) and then followed up until MI or death, or until the study ends.



Typically we would analyse such a study on the follow-up timescale.

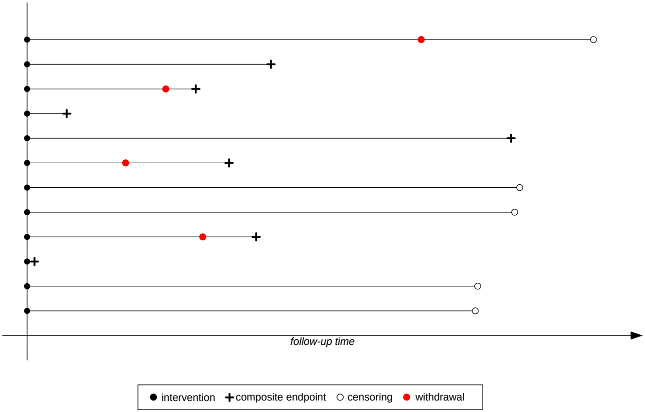


And often we look only at time to **composite endpoint**: MI *or* death.

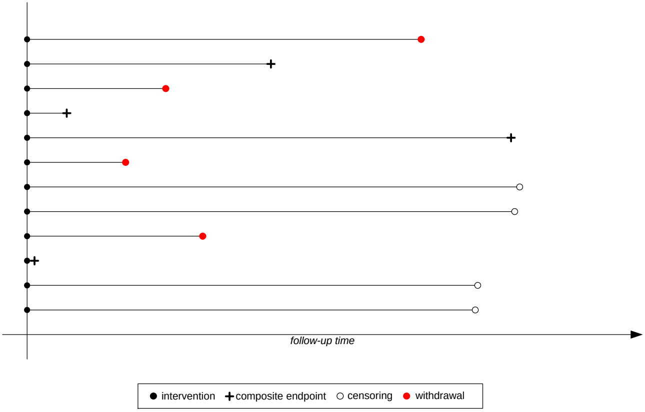


Setting (4)

Suppose some subjects withdraw before the end of the study.

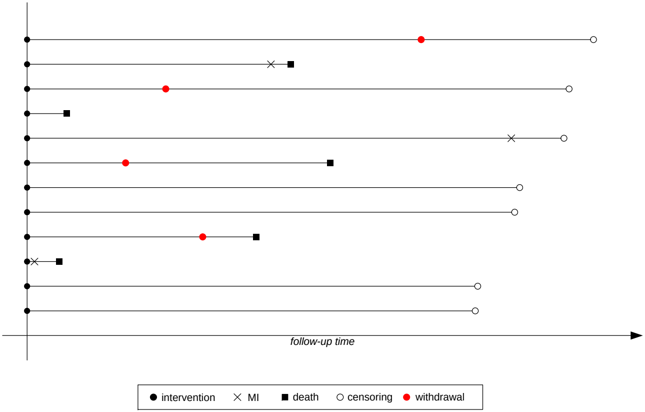


Often we know nothing about what happens to these subjects subsequently.



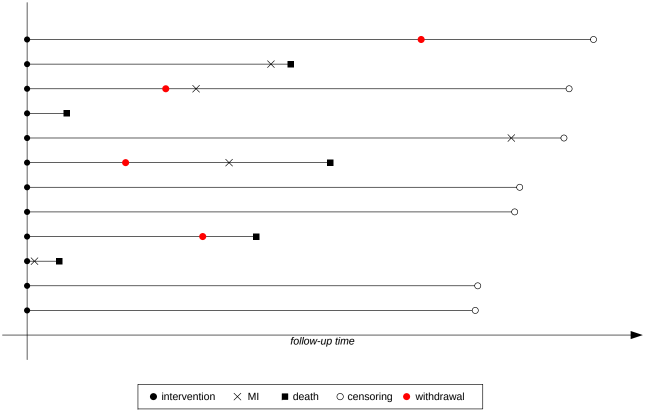
Setting (6)

But in our setting, we DO have data on whether or not death occurred before the end of the study, even for those who withdrew — from a national death index.

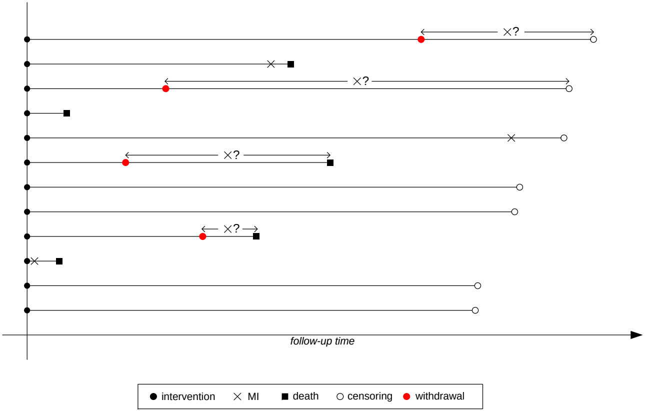


Setting (7)

But for those who in fact had an MI, we don't know this. And for those who did not, we don't know this either.



So here is a depiction of our data:



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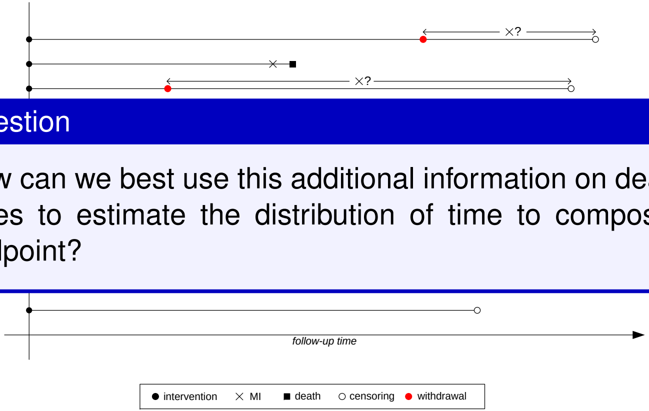

Question

How can we best use this additional information on death times to estimate the distribution of time to composite endpoint?

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Suggestions

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– Ideally want a principled, efficient alternative, not too dependent on extra parametric models *–we will achieve this using the semiparametric theory of augmented inverse probability weighted estimating equations*

Outline

- Setting
- Notation
- Counting processes
- Semiparametric theory
- Estimators for the distribution of time to composite endpoint
  full data $\rightarrow$ complete cases $\rightarrow$ inverse probability weighted CC $\rightarrow$ augmented IPWCC
- Double robustness and semiparametric efficiency
- Variance estimation
- Simulation study
- Summary and further issues

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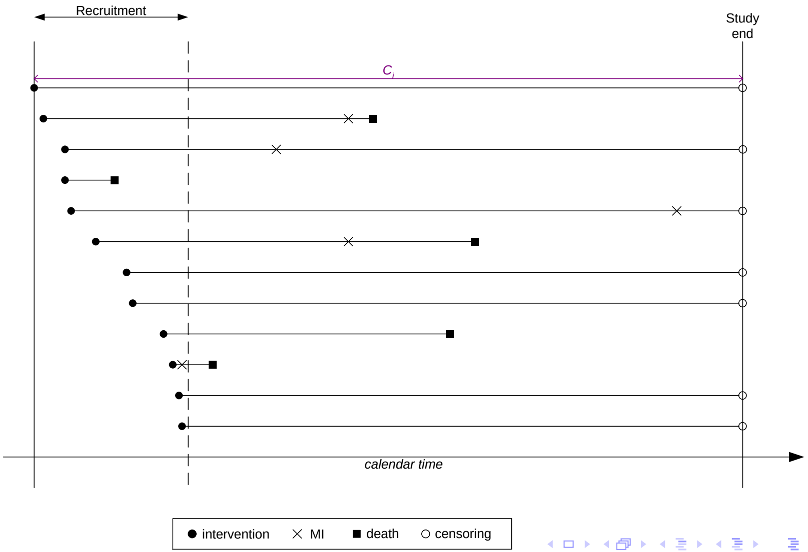

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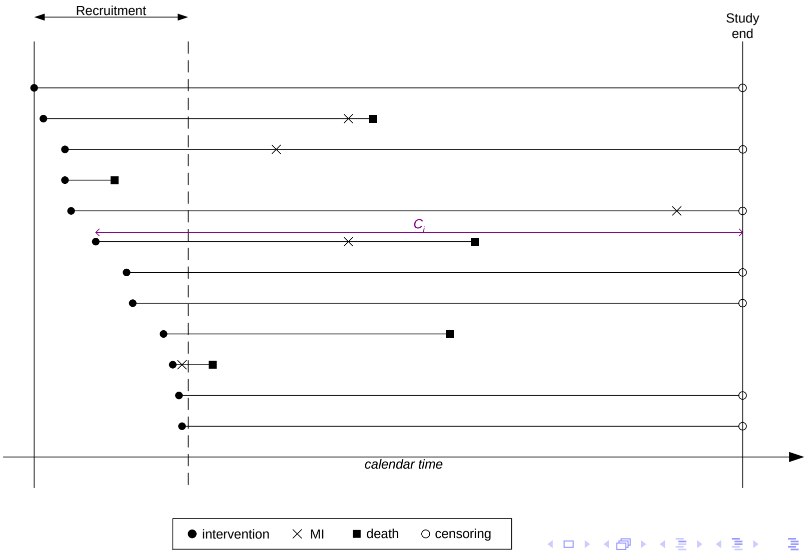

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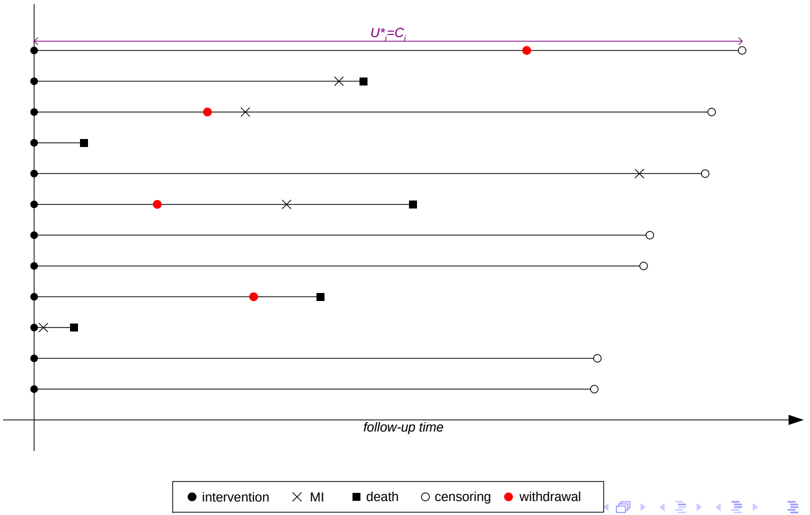

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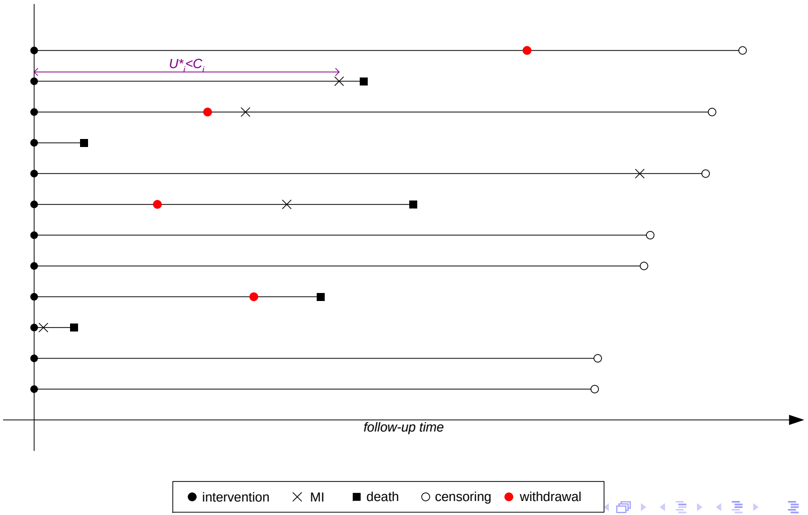

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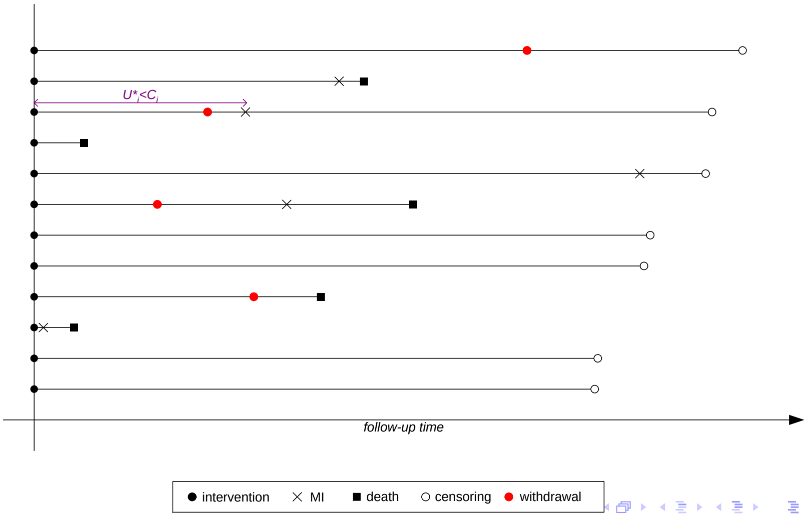
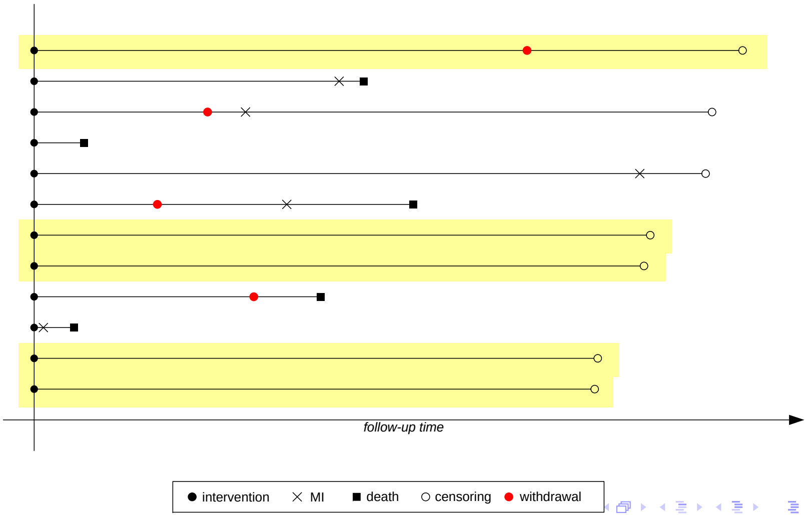
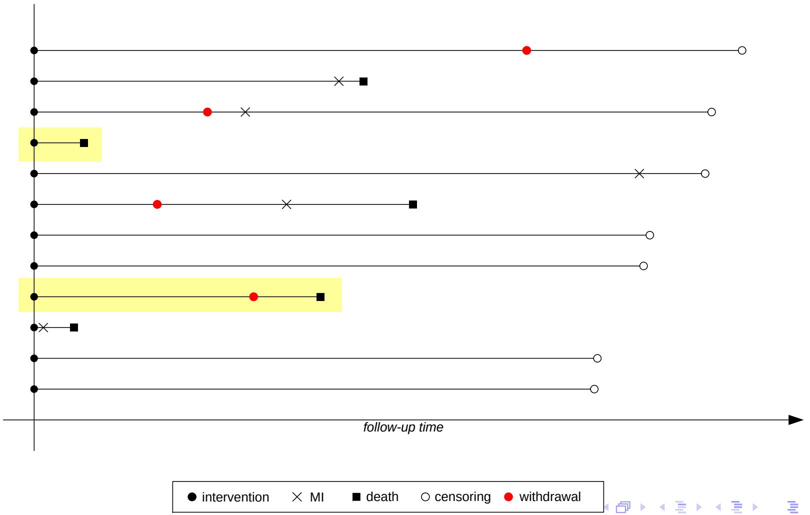


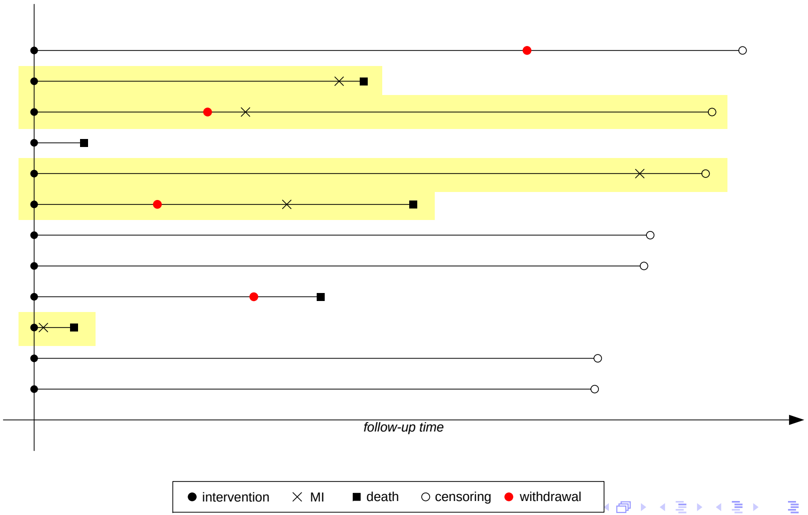
$\Delta_i^* = 0$: U_i^* is a censoring time



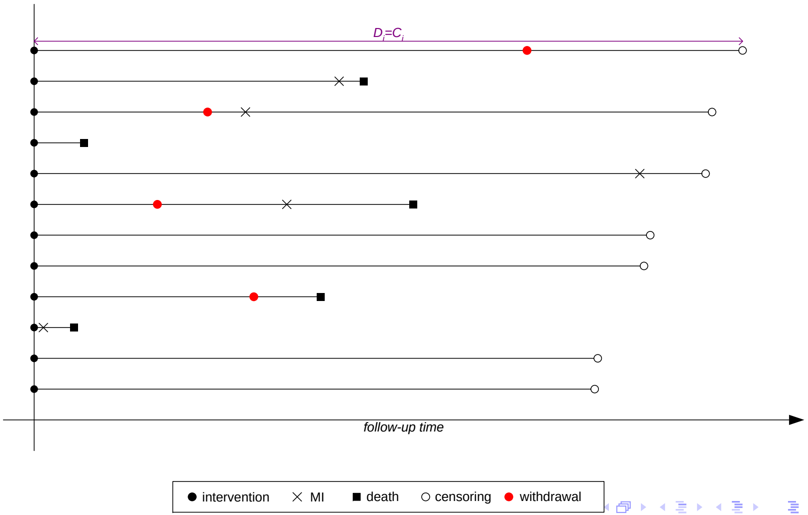
$\Delta_i^* = 1$: U_i^* is a death time



$\Delta_i^* = 2$: U_i^* is a time to MI



D_i: time to death or censoring



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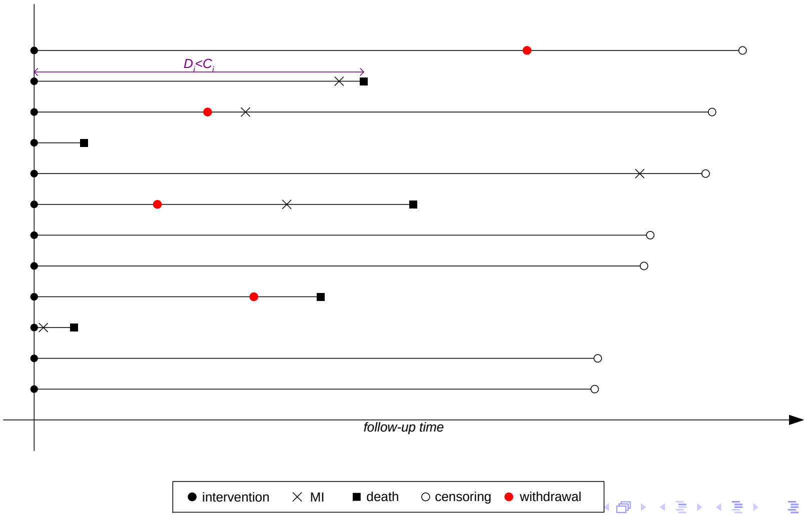

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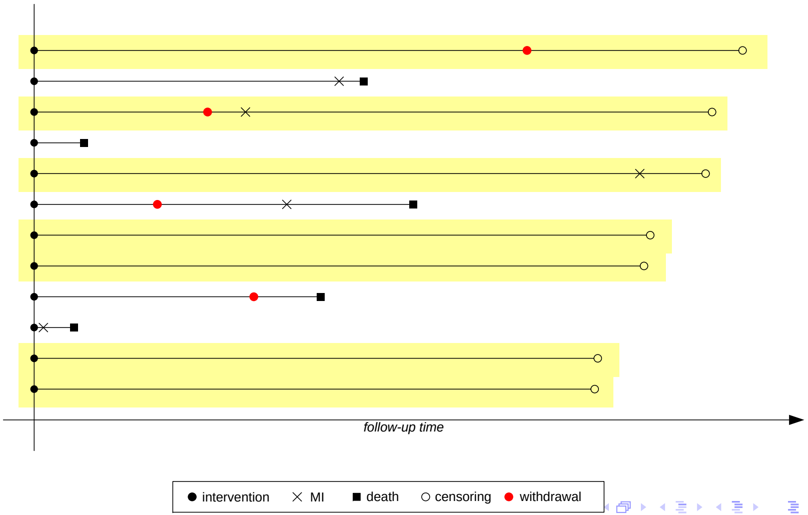

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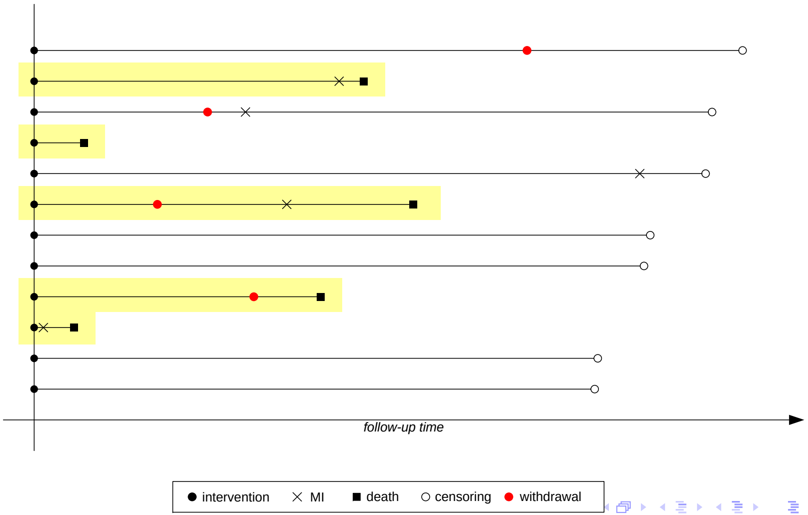
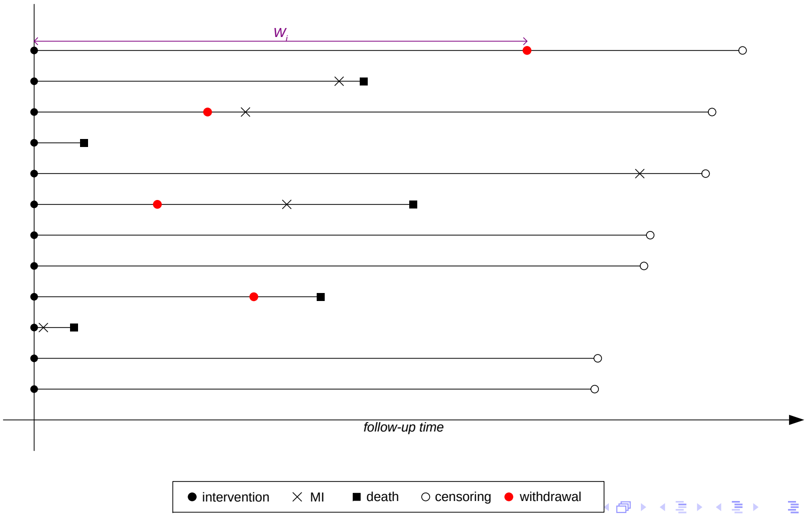


W_i: time to withdrawal



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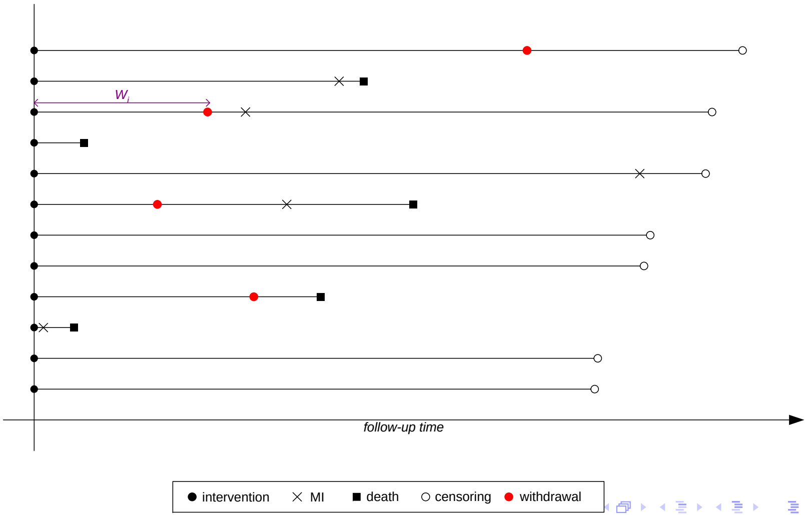
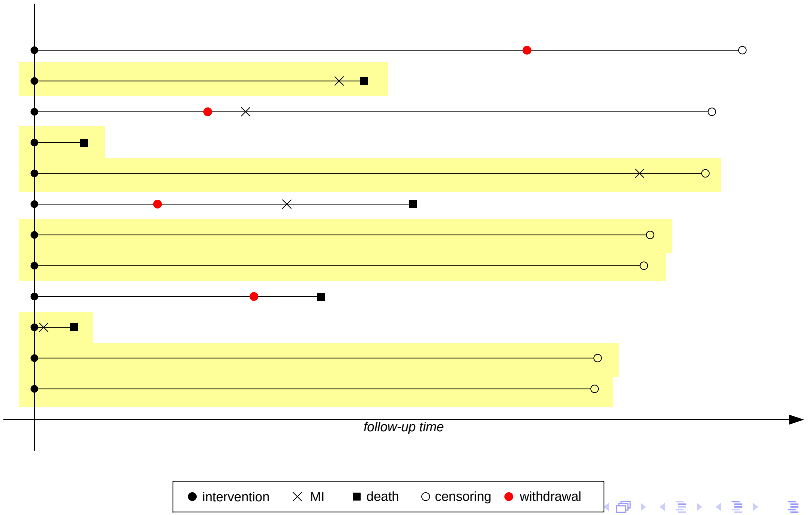
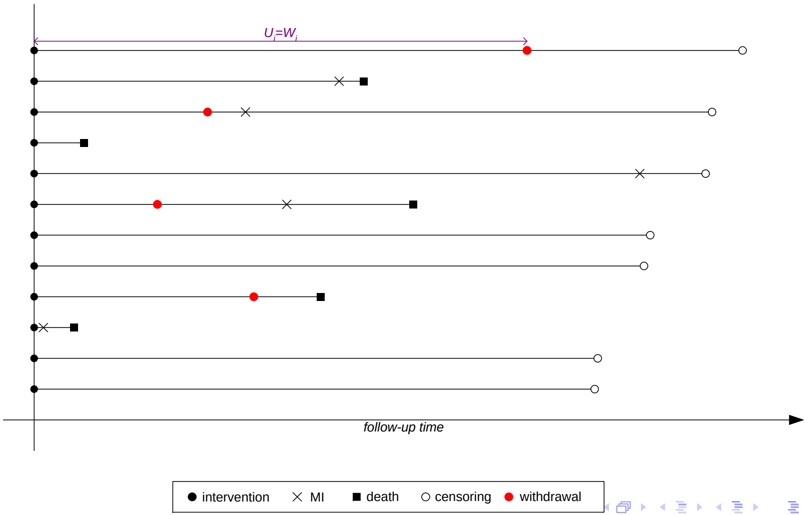


$W_i = \infty$: for those who don't withdraw



U_i: time to first event or censoring or withdrawal



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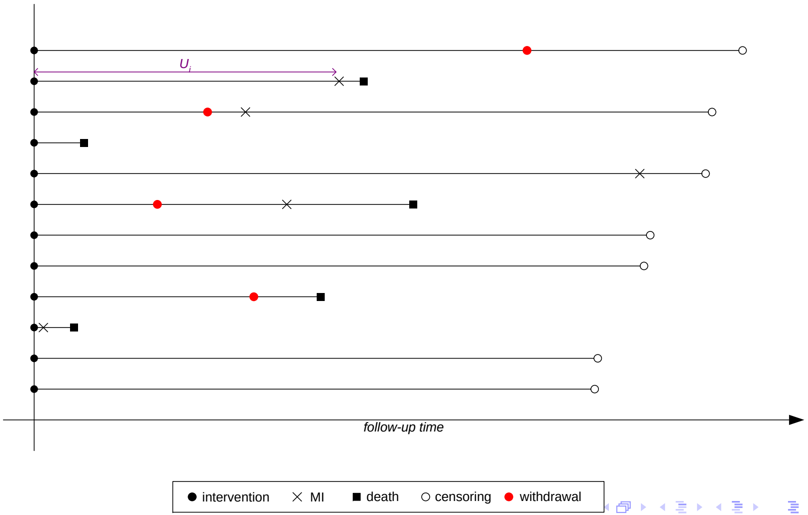

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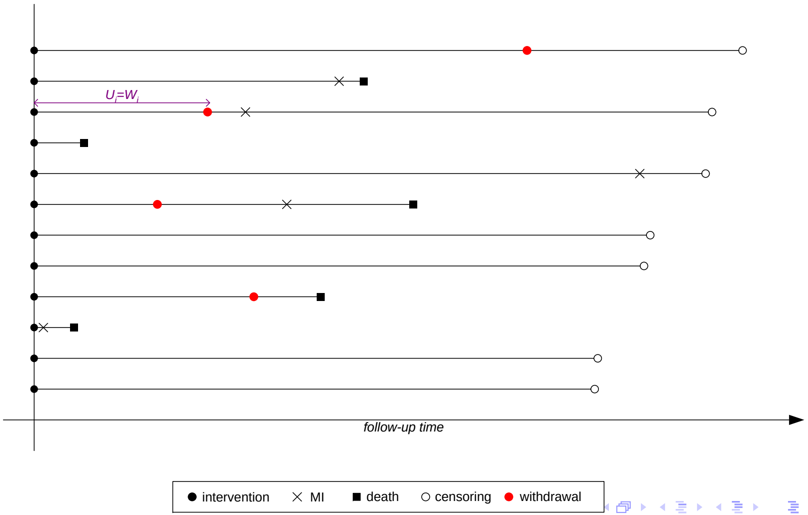

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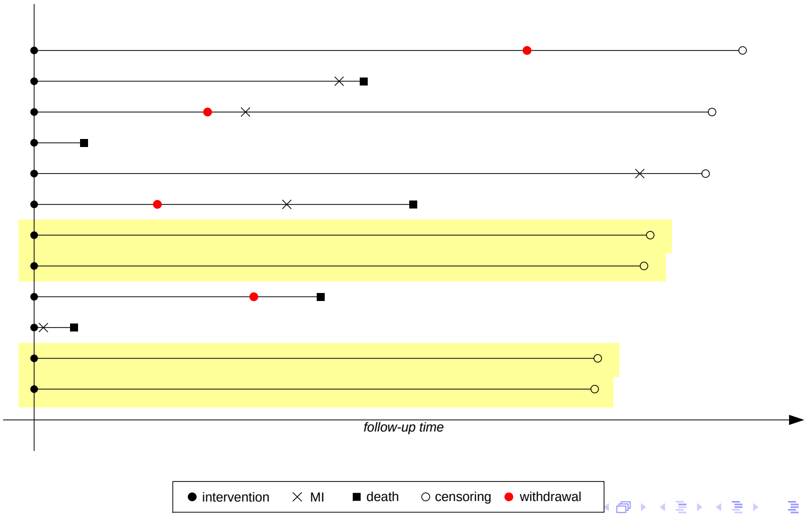

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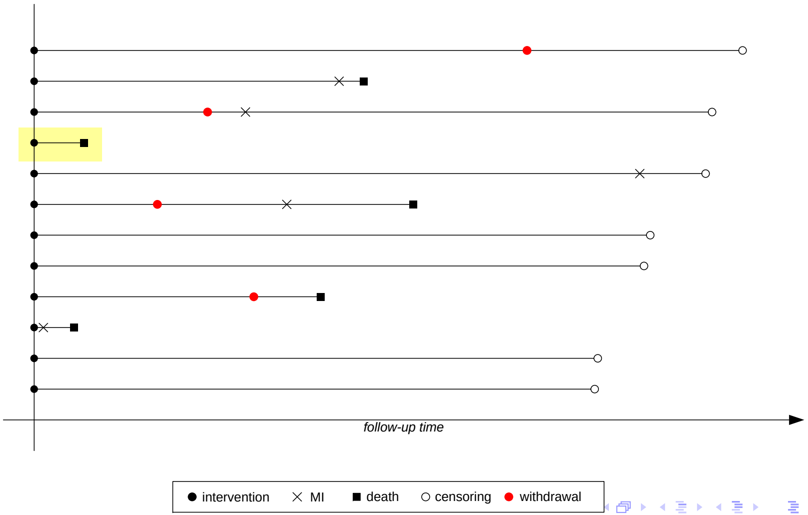
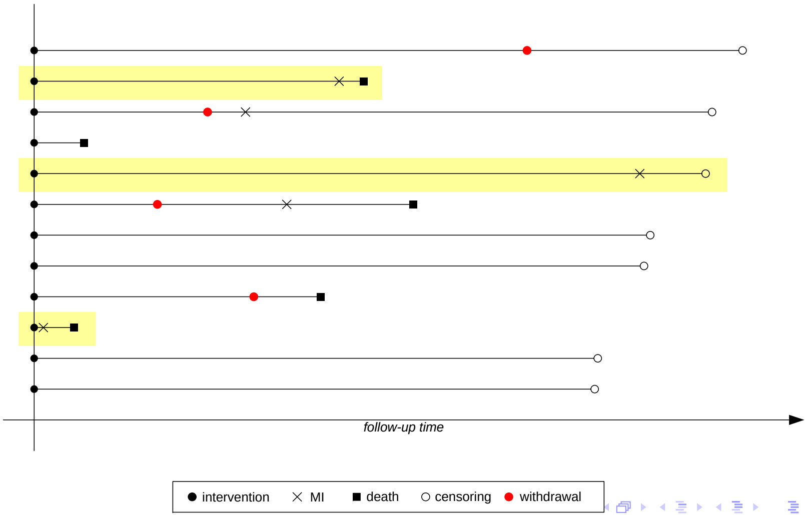
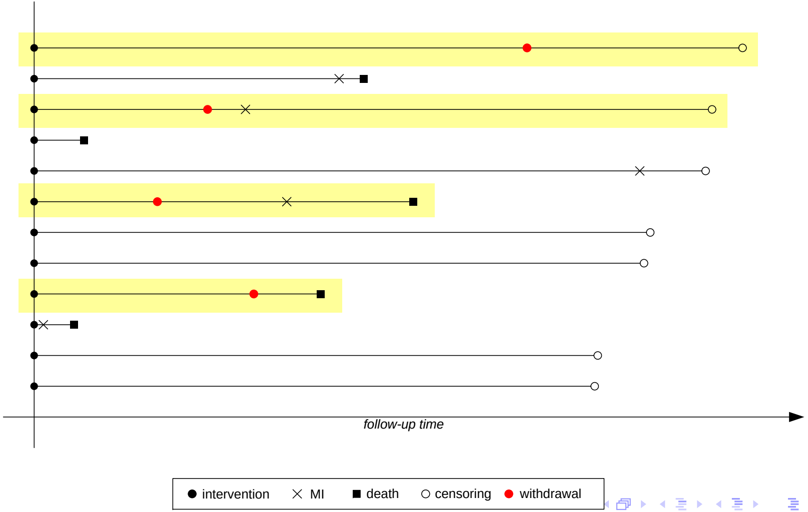


$\Delta_i = 2$: U_i is a time to MI



$\Delta_i = -1$: U_i is a withdrawal time



Notation summary (1)

- C_i: time to censoring
- U_i^*: time to MI or death or censoring
- Δ_i^*: event 'indicator' for U_i^*,

$$\Delta_i^* = \begin{cases} 0 \text{ if } U_i^* = C_i \\ 1 \text{ if } U_i^* \text{ is time to death} \\ 2 \text{ if } U_i^* \text{ is time to MI} \end{cases}$$

- D_i: time to death or censoring
- Γ_i: event indicator for D_i,

$$\Gamma_i = \begin{cases} 0 \text{ if } D_i = C_i \\ 1 \text{ if } D_i \text{ is time to death} \end{cases}$$

- $W_i \in (0, U_i^*) \cup \{\infty\}$: time to withdrawal
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Note: starred quantities are not fully-observed

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$$G_r(\mathcal{F}_i) =$$
$$\left\{C_i, I(U_i^* < r), I(U_i^* < r)U_i^*, I(U_i^* < r)\Delta_i^*, \bar{\mathbf{X}}_i\{\min(r, U_i^*)\}, D_i, \Gamma_i\right\}.$$

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(think of this as the information we would see on subject i were s/he to withdraw at time r)

Notation summary (3)

— Writing T_i for the uncensored time to composite endpoint, we are interested in estimating the usual related survival estimands:

– the survivor function

$$S(t) = Pr(T_i > t),$$

– the hazard function

$$\lambda(t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} Pr(t \leq T_i < t + \Delta t \,|\, T_i \geq t)$$

– and the cumulative hazard function:

$$\Lambda(t) = \int_0^t \lambda(u)\, du,$$

with

$$S(t) = \exp\{-\Lambda(t)\} = \exp\left\{-\int_0^t \lambda(u)\, du\right\}.$$

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$N_i^*(t)$: counting process for the composite endpoint
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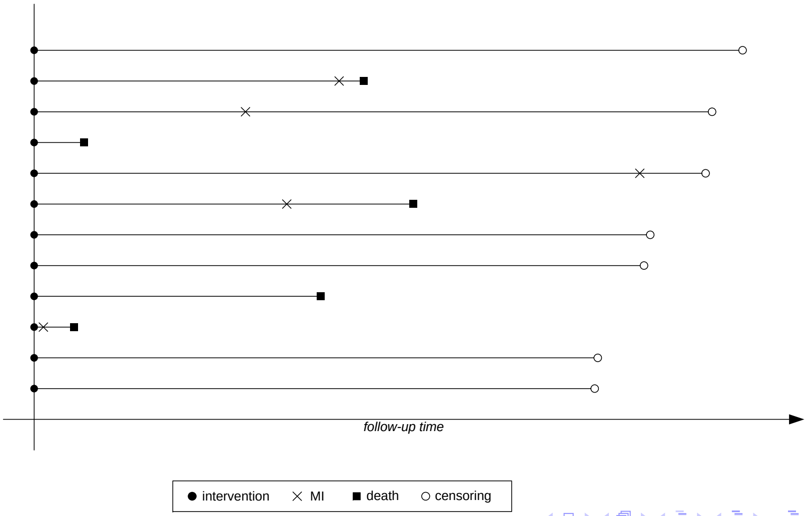

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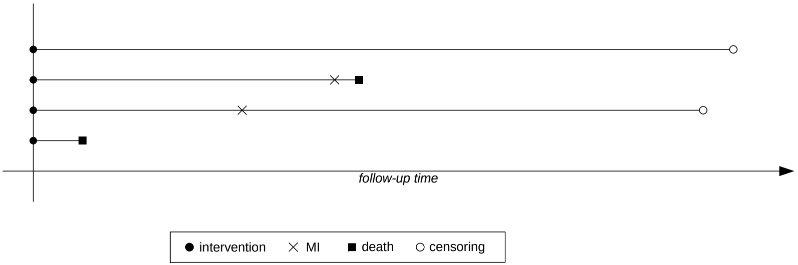

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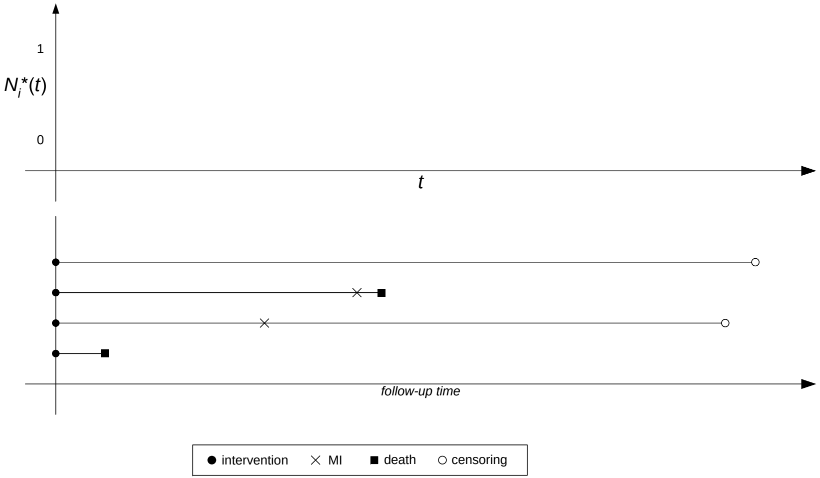

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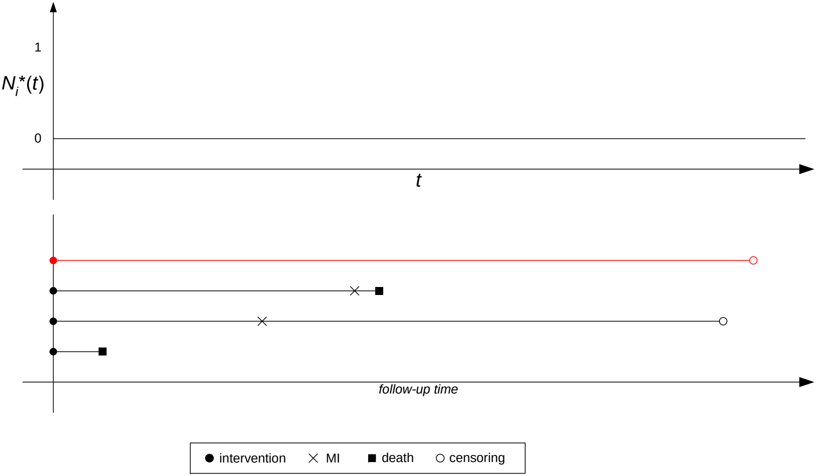

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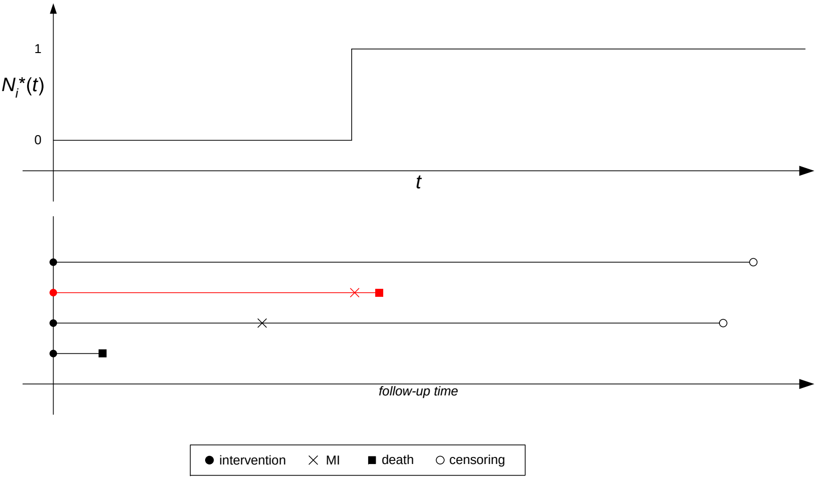

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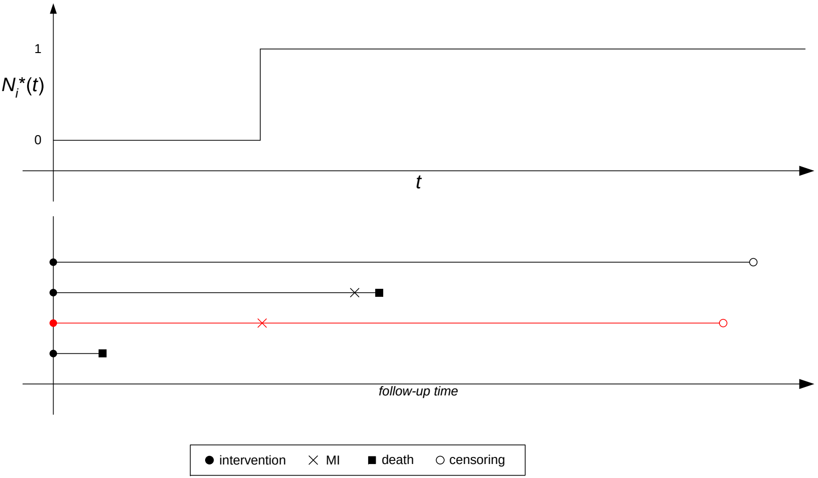

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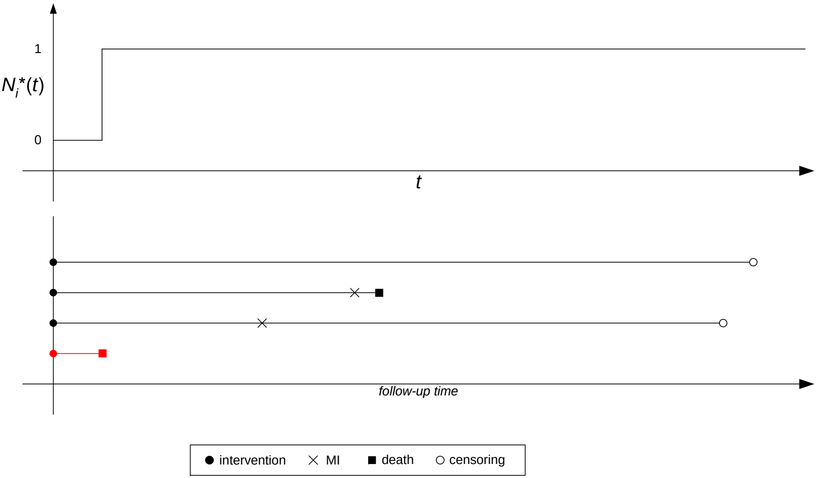

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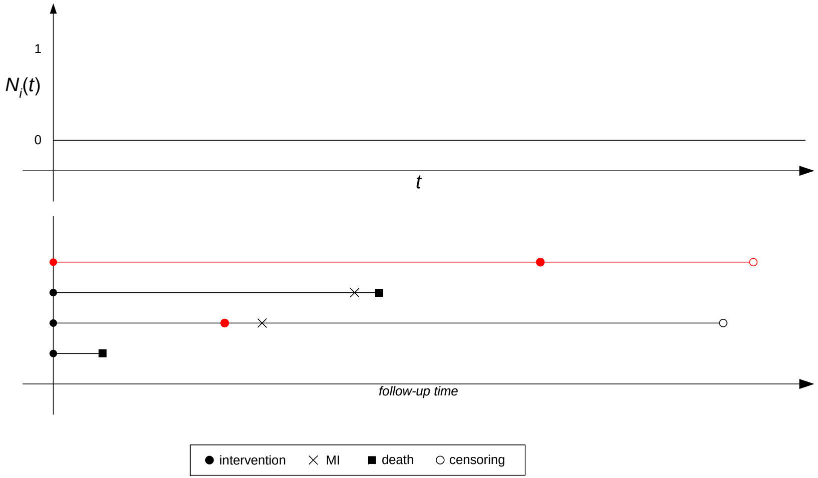

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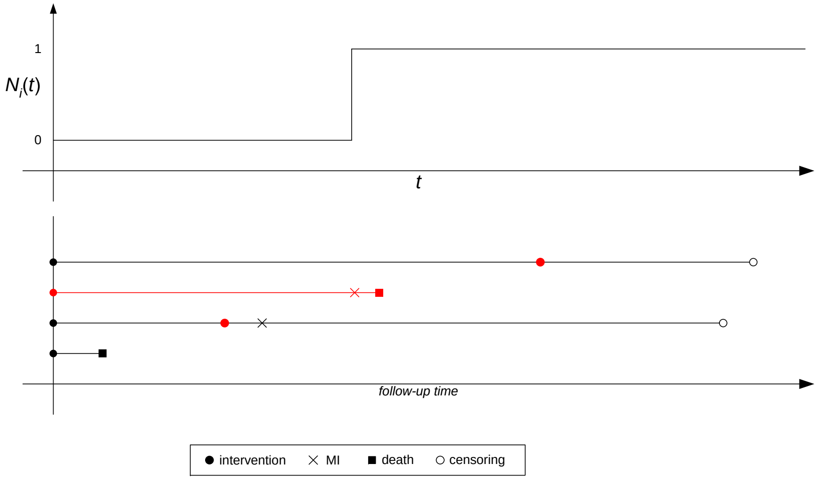

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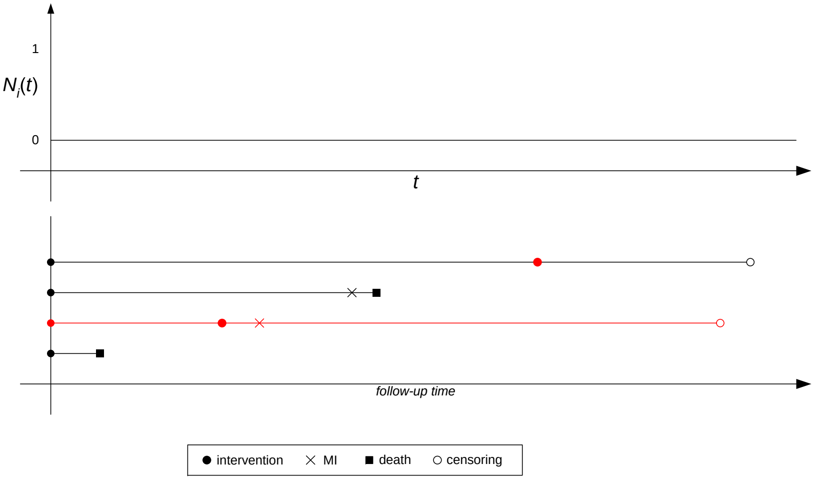

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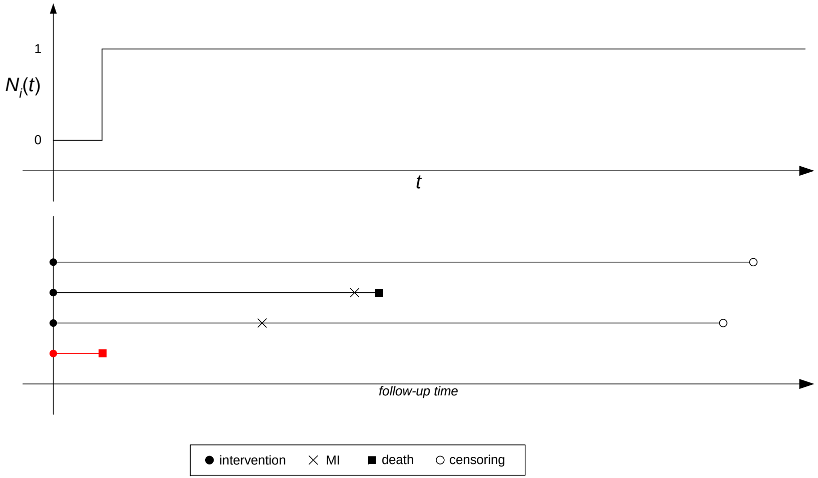

$Y_i^*(t)$: risk set for the composite endpoint
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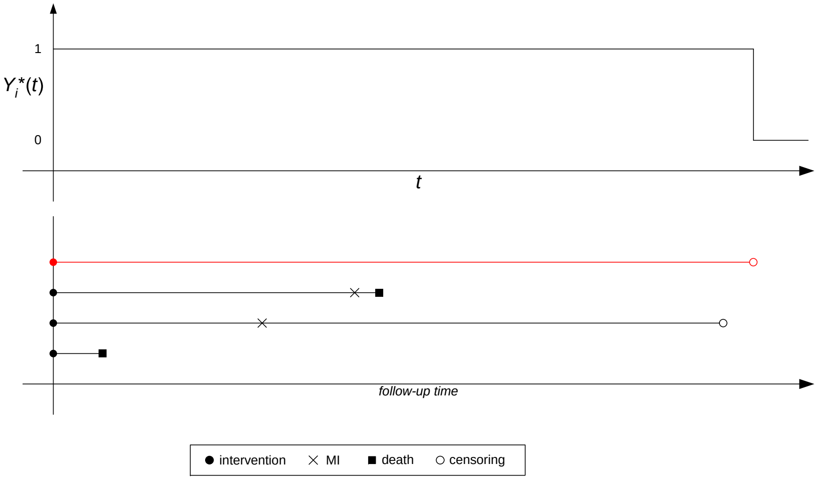

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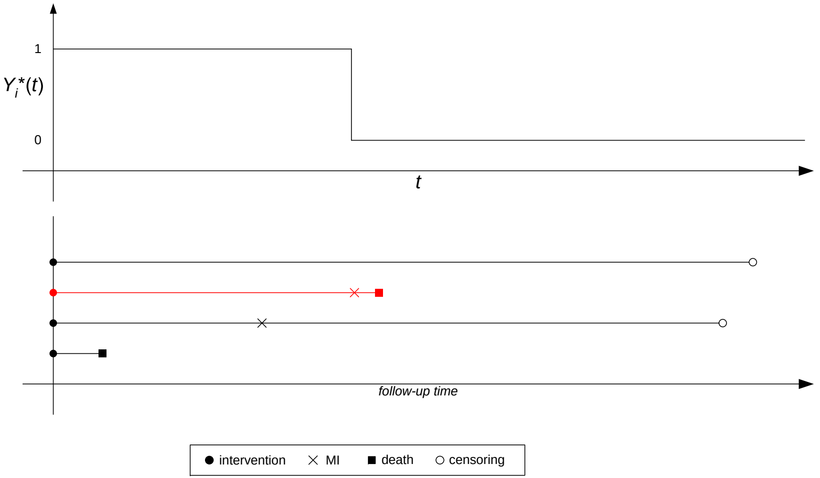

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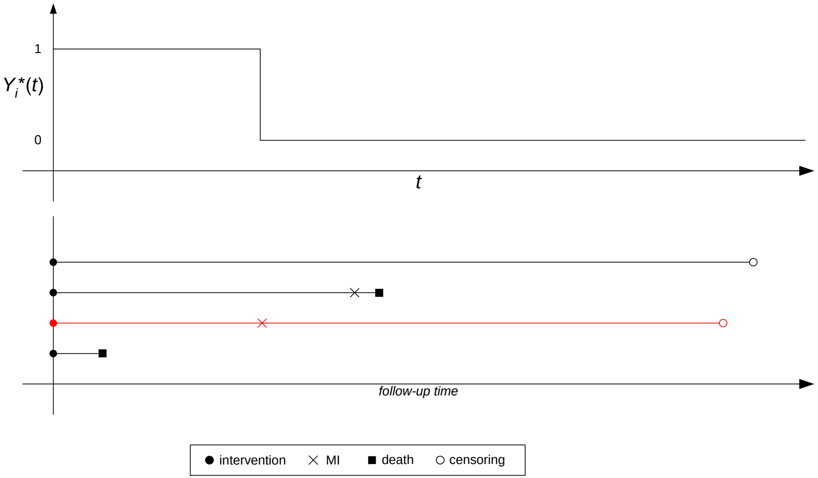

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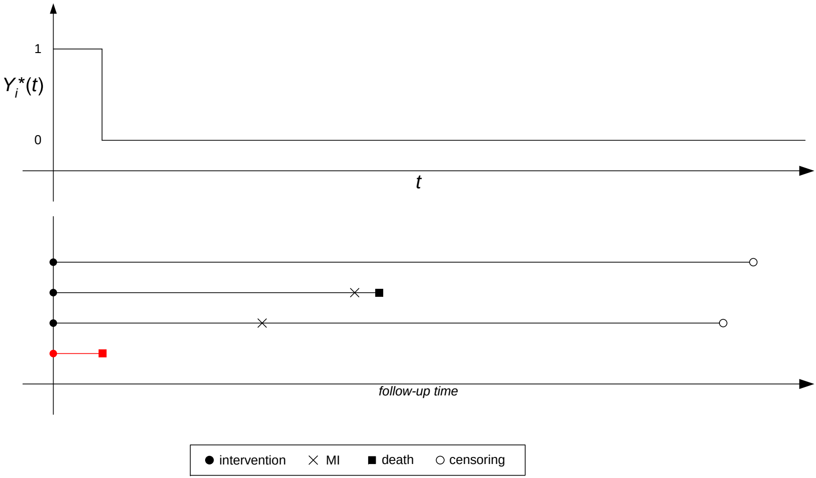

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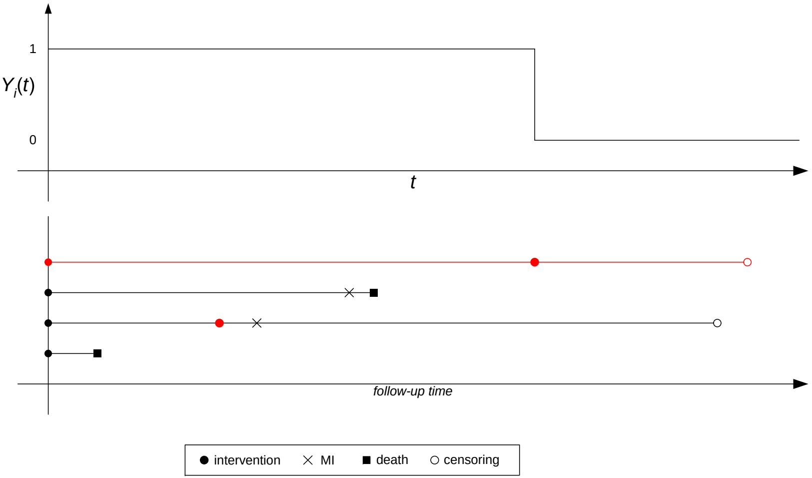

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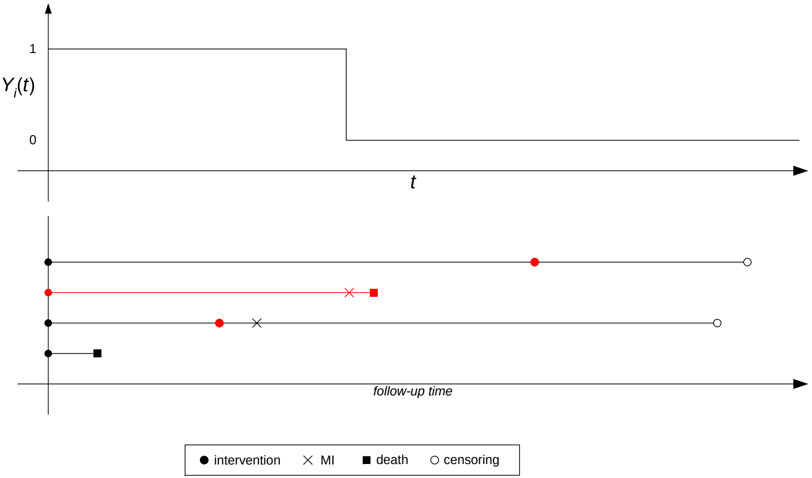

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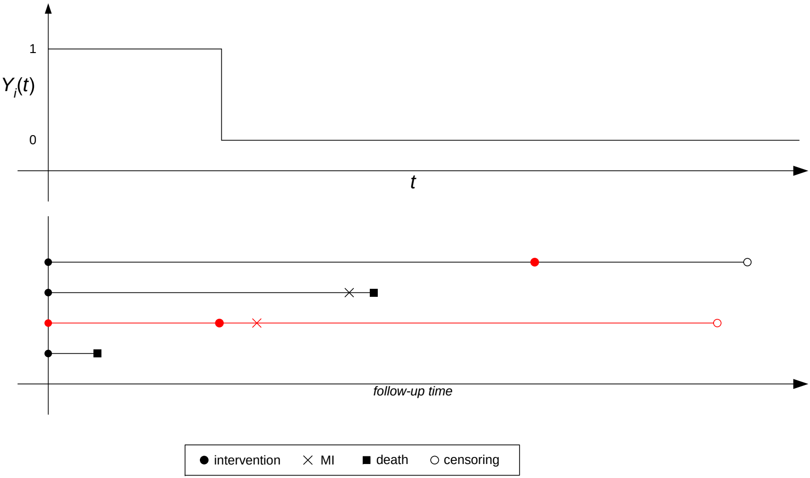

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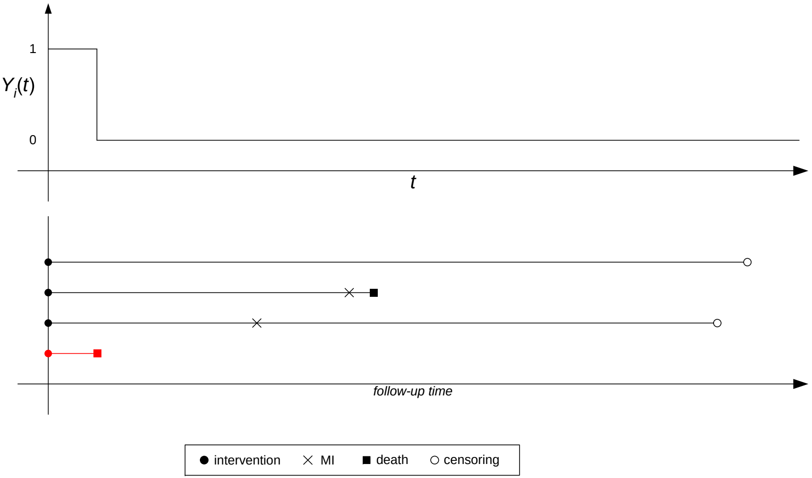

Why is this notation useful?

— It allows us to express the process in this form:

$$\underbrace{dN_i^*(t)}_{\text{`outcome'}} = \underbrace{\overbrace{d\Lambda(t)}^{\lambda(t)\cdot dt}\, Y_i^*(t)}_{\text{`fixed part'}} + \underbrace{d\ \overbrace{\zeta_i(t)}^{\text{martingale}}}_{\text{`error'}}$$

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Statistical models

— A model $\mathcal{M}$ for a set of i.i.d. observations $Z_1, Z_2, \ldots, Z_n$ is a set of densities

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— If $\mathcal{M}$ contains all possible densities for Z then it is nonparametric.

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— The more variables we have, the more difficult it gets to specify a correct parametric model for their joint distribution (or whatever aspects of that joint distribution we require).
— In these 'non-ideal' settings, semiparametric models that leave some of these additional modelling aspects unspecified, are particularly appealing.

Semiparametric estimator

— Given a semiparametric model $\mathcal{M}$, a semiparametric estimator $\hat{\beta}$ of q-dimensional β must be consistent

$$\hat{\beta} - \beta \xrightarrow{\mathcal{P}\{\beta,\eta(\cdot)\}} 0$$

and asymptotically normal

$$n^{\frac{1}{2}}\left(\hat{\beta} - \beta\right) \xrightarrow{\mathcal{D}\{\beta,\eta(\cdot)\}} N\left(0, \Sigma^{q\times q}\left\{\beta, \eta\left(\cdot\right)\right\}\right)$$

for all $p\left\{z, \beta, \eta\left(\cdot\right)\right\} \in \mathcal{M}$.

$*$ $\xrightarrow{\mathcal{P}\{\beta,\eta(\cdot)\}}$: convergence in probability, $\xrightarrow{\mathcal{D}\{\beta,\eta(\cdot)\}}$: convergence in distribution, for density $p\left\{z, \beta, \eta\left(\cdot\right)\right\}$.

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Asymptotically linear estimators and influence functions

— An estimator $\hat{\beta}$ is asymptotically linear if it can be written as

$$n^{\frac{1}{2}}\left(\hat{\beta}-\beta_0\right)=n^{-\frac{1}{2}}\sum_{i=1}^{n}\varphi\left(Z_i\right)+o_p\left(1\right)$$

where β_0 is the true value of β, $o_p\left(1\right)$ converges in probability to zero, and $\varphi\left(Z_i\right)$ is a $(q \times 1)$ random vector, $E_{\theta_0}\left\{\varphi\left(Z_i\right)\right\}=0$, $E_{\theta_0}\left\{\varphi\left(Z_i\right)\varphi\left(Z_i\right)^T\right\}<\infty$, det $\left[E_{\theta_0}\left\{\varphi\left(Z_i\right)\varphi\left(Z_i\right)^T\right\}\right]\neq 0$.

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— $\varphi\left(Z_i\right)$ is the i^{th} **influence function** of $\hat{\beta}$.
— Note that

$$n^{\frac{1}{2}}\left(\hat{\beta}-\beta_0\right)\xrightarrow{\mathcal{D}\left\{\beta_0,\eta_0(\cdot)\right\}}N\left(0,E_{\theta_0}\left\{\varphi\left(Z_i\right)\varphi\left(Z_i\right)^T\right\}\right).$$

Thus the asymptotic properties of an asymptotically linear estimator are governed by its influence function.

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Key reference

Tsiatis (2006) *Semiparametric Theory and Missing Data*.

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— $\hat{\Lambda}^{\text{full}} (t)$ is the *only* semiparametric estimator of $\Lambda (t)$ for $\mathcal{M}_{\text{full}}$, and thus it is (trivially) semiparametric efficient (see Tsiatis (2006) for precise definition).

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— Then withdrawal is 'just another form of censoring' and so the Nelson–Aalen estimator for the observed data is consistent.

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— To proceed we must assume something about the withdrawal mechanism.

— Suppose we assume that **withdrawal is independent**:

$$\lim_{\Delta t \to 0} \frac{1}{\Delta t} Pr(t \leq W_i < t + \Delta t \,|\, W_i \geq t, U_i^*, \Delta_i^*) = I(U_i^* \geq t)\kappa(t).$$

— Call this model (independent withdrawal, together with independent censoring, but nothing else) $\mathcal{M}_{\text{ind}}$.

— Then withdrawal is 'just another form of censoring' and so the Nelson–Aalen estimator for the observed data is consistent.

— That is, we solve:

$$\sum_{i=1}^{n} \{dN_i(t) - d\Lambda(t) Y_i(t)\} = 0.$$

Complete case estimator (2)

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— and thus

$$\begin{aligned} E\left\{dN_i(t) - \right. & \left. d\Lambda(t)\, Y_i(t)\right\} \\ &= E\left[I(W_i > t)\left\{dN_i^*(t) - d\Lambda(t)\, Y_i^*(t)\right\}\right] \\ &= E\left(E\left[I(W_i > t)\left\{dN_i^*(t) - d\Lambda(t)\, Y_i^*(t)\right\} \middle| U_i^*, \Delta_i^*\right]\right) \\ &= E\left[Pr\left(W_i > t \,|\, U_i^*, \Delta_i^*\right)\left\{dN_i^*(t) - d\Lambda(t)\, Y_i^*(t)\right\}\right]. \end{aligned}$$

— Independent withdrawal implies:

$$
\begin{aligned}
Pr\left(W_i > t \,|\, U_i^*, \Delta_i^*\right) &= \exp\left\{-\int_0^t I\left(U_i^* \geq u\right)\kappa\left(u\right)du\right\} \\
&= \exp\left\{-\int_0^{\min(t,U_i^*)} \kappa\left(u\right)du\right\} \\
&= I\left(U_i^* \geq t\right)\exp\left\{-\int_0^t \kappa\left(u\right)du\right\} \\
&\quad + I\left(U_i^* < t\right)\exp\left\{-\int_0^{U_i^*} \kappa\left(u\right)du\right\}.
\end{aligned}
$$

Complete case estimator (4)

— Thus,

$$E\left\{dN_i(t) - d\Lambda(t)\,Y_i(t)\right\} = E\left(\left[I\left(U_i^* \geq t\right)\exp\left\{-\int_0^t \kappa(u)\,du\right\} + I\left(U_i^* < t\right)\exp\left\{-\int_0^{U_i^*} \kappa(u)\,du\right\}\right]\left\{dN_i^*(t) - d\Lambda(t)\,Y_i^*(t)\right\}\right).$$

Complete case estimator (5)

— But

$$I\left(U_i^* \geq t\right)\left\{dN_i^*\left(t\right) - d\Lambda\left(t\right)Y_i^*\left(t\right)\right\} = dN_i^*\left(t\right) - d\Lambda\left(t\right)Y_i^*\left(t\right)$$

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— So this simplifies to give:

$$\begin{aligned}
E\left\{dN_i\left(t\right)\right. & \left. - d\Lambda\left(t\right)Y_i\left(t\right)\right\} \\
& = E\left[\exp\left\{-\int_0^t \kappa\left(u\right)du\right\}\left\{dN_i^*\left(t\right) - d\Lambda\left(t\right)Y_i^*\left(t\right)\right\}\right] \\
& = \exp\left\{-\int_0^t \kappa\left(u\right)du\right\}\underbrace{E\left\{dN_i^*\left(t\right) - d\Lambda\left(t\right)Y_i^*\left(t\right)\right\}}_{=0} \\
& = 0
\end{aligned}$$

as required.

Complete case estimator (6)

— This leads to:

$$\hat{\Lambda}^{CC}(t) = \int_0^t \frac{\sum_{i=1}^n dN_i(u)}{\sum_{i=1}^n Y_i(u)}.$$

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— First, however, we consider relaxing the assumption of independent withdrawal.

Outline

- Setting
- Notation
- Counting processes
- Semiparametric theory
- Estimators for the distribution of time to composite endpoint
  full data → complete cases → inverse probability weighted CC →
  augmented IPWCC
- Double robustness and semiparametric efficiency
- Variance estimation
- Simulation study
- Summary and further issues

Inverse probability weighted CC estimator (1)

— Independent withdrawal often implausible.

— We may wish to relax this to an assumption of **covariate-driven withdrawal at random**:

$$\lim_{\Delta t \to 0} \frac{1}{\Delta t} Pr\left(t \leq W_i < t + \Delta t \,|\, W_i \geq t, \mathcal{F}_i\right) = I\left(U_i^* \geq t\right) \lambda\left\{t, \bar{\mathbf{X}}_i(t)\right\}$$

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— This will not hold, when $Pr\left(W_i > t \,|\, \mathcal{F}_i\right)$ depends on $\bar{\mathbf{X}}_i\left(t\right)$, and $\bar{\mathbf{X}}_i\left(t\right)$ is associated with U_i^*, Δ_i^*.

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$$\hat{\Lambda}^{\mathrm{IPWCC}}(t) = \int_0^t \frac{\sum_{i=1}^n \frac{dN_i(u)}{Pr\left\{W_i > t \middle| U_i^* \geq t, \bar{\mathbf{X}}_i(t)\right\}}}{\sum_{i=1}^n \frac{Y_i(u)}{Pr\left\{W_i > t \middle| U_i^* \geq t, \bar{\mathbf{X}}_i(t)\right\}}}.$$

Inverse probability weighted CC estimator (3)

— To see that this estimator is consistent, note that:

$$
\begin{aligned}
E\left\{\frac{dN_i(t) - d\Lambda(t)\,Y_i(t)}{Pr\left\{W_i > t \,\middle|\, U_i^* \geq t, \bar{\mathbf{X}}_i(t)\right\}}\right\}
&= E\left\{\frac{I(W_i > t)\left\{dN_i^*(t) - d\Lambda(t)\,Y_i^*(t)\right\}}{Pr\left\{W_i > t \,\middle|\, U_i^* \geq t, \bar{\mathbf{X}}_i(t)\right\}}\right\} \\
&= E\left[E\left\{\left.\frac{I(W_i > t)\left\{dN_i^*(t) - d\Lambda(t)\,Y_i^*(t)\right\}}{Pr\left\{W_i > t \,\middle|\, U_i^* \geq t, \bar{\mathbf{X}}_i(t)\right\}}\right| \mathcal{F}_i\right\}\right] \\
&= E\left[\frac{Pr\left(W_i > t \mid \mathcal{F}_i\right)\left\{dN_i^*(t) - d\Lambda(t)\,Y_i^*(t)\right\}}{Pr\left\{W_i > t \,\middle|\, U_i^* \geq t, \bar{\mathbf{X}}_i(t)\right\}}\right] \\
&= E\left\{dN_i^*(t) - d\Lambda(t)\,Y_i^*(t)\right\} = 0
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under covariate-driven withdrawal at random.

Inverse probability weighted CC estimator (4)

— $\hat{\Lambda}^{\text{IPWCC}}(t)$ is a semiparametric estimator of $\Lambda(t)$ under model $\mathcal{M}_{\text{CDW}}$, but again it is not the only one, and is not semiparametric efficient: it ignores data on (D_i, Γ_i) for those who withdraw.

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— Let $\mathcal{M}_{\text{CM}}$ (for 'coarsening model') be the set of densities for which this holds.
— The feasible IPWCC estimator is then:

$$\hat{\Lambda}^{\text{f-IPWCC}}(t) = \int_0^t \frac{\sum_{i=1}^n \frac{dN_i(u)}{K\left\{t, \bar{\mathbf{X}}_i(t); \hat{\gamma}\right\}}}{\sum_{i=1}^n \frac{Y_i(u)}{K\left\{t, \bar{\mathbf{X}}_i(t); \hat{\gamma}\right\}}}$$

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— $\hat{\Lambda}^{\text{f-IPWCC}}(t)$ is a semiparametric estimator under $\mathcal{M}_{\text{CDW}} \cap \mathcal{M}_{\text{CM}}$. Also, provided that γ are estimated sufficiently efficiently by $\hat{\gamma}$, $\hat{\Lambda}^{\text{f-IPWCC}}(t)$ is more efficient than $\hat{\Lambda}^{\text{IPWCC}}(t)$. (Why?)

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— This has the advantage of being consistent under **covariate-and-death-time-driven withdrawal at random** $(\mathcal{M}_{\text{CDDW}})$:

$$\lim_{\Delta t \to 0} \frac{1}{\Delta t} Pr\left(t \leq W_i < t + \Delta t \,|\, W_i \geq t, \mathcal{F}_i\right) = I\left(U_i^* \geq t\right) \nu\left\{t, \bar{\mathbf{X}}_i(t), D_i, \Gamma_i\right\}$$

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— And is also more efficient than $\hat{\Lambda}^{\text{f-IPWCC}}(t)$ even under $\mathcal{M}_{\text{CDW}} \cap \mathcal{M}_{\text{CM}}$. (Why?)

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— So far made no use of data on (D_i, Γ_i) for those who withdraw.
— The simplest way to incorporate this additional information is to extend the weights model to $\mathcal{M}_{\text{ECM}}$:

$$Pr\left\{W_i > t \,\middle|\, U_i^* \geq t, \bar{\mathbf{X}}_i(t), D_i, \Gamma_i\right\} = \tilde{K}\left\{t, \bar{\mathbf{X}}_i(t), D_i, \Gamma_i; \tilde{\gamma}\right\}$$

— The feasible extended IPWCC estimator is:

$$\hat{\Lambda}^{\text{f-IPWCC-ext}}(t) = \int_0^t \frac{\sum_{i=1}^n \frac{dN_i(u)}{\tilde{K}\left\{t, \bar{\mathbf{X}}_i, D_i, \Gamma_i(t); \hat{\tilde{\gamma}}\right\}}}{\sum_{i=1}^n \frac{Y_i(u)}{\tilde{K}\left\{t, \bar{\mathbf{X}}_i, D_i, \Gamma_i(t); \hat{\tilde{\gamma}}\right\}}}$$

— This has the advantage of being consistent under **covariate-and-death-time-driven withdrawal at random** $(\mathcal{M}_{\text{CDDW}})$:

$$\lim_{\Delta t \to 0} \frac{1}{\Delta t} Pr\left(t \leq W_i < t + \Delta t \,|\, W_i \geq t, \mathcal{F}_i\right) = I\left(U_i^* \geq t\right) \nu\left\{t, \bar{\mathbf{X}}_i(t), D_i, \Gamma_i\right\}$$

— And is also more efficient than $\hat{\Lambda}^{\text{f-IPWCC}}(t)$ even under $\mathcal{M}_{\text{CDW}} \cap \mathcal{M}_{\text{CM}}$. (Why?)
— But it's not semiparametric efficient. We can do better…

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Augmented IPWCC (1)

— Consider augmenting the IPWCC estimating equation to:

$$\sum_{i=1}^{n}\left[\frac{dN_i(t)-d\Lambda(t)\,Y_i(t)}{Pr\left\{W_i>t\,\middle|\,U_i^*\geq t,\bar{\mathbf{X}}_i(t)\right\}}\right.$$
$$\left.+\int_0^t \frac{dM_i(u)}{Pr\left\{W_i>u\,\middle|\,U_i^*\geq u,\bar{\mathbf{X}}_i(u)\right\}}h\left\{u,G_u\left(\mathcal{F}_i\right)\right\}\right]=0$$

where

$$dM_i(u)=\lim_{\Delta u\to 0}\left[I\left(u\leq W_i<u+\Delta u\right)-\lambda\left\{u,\bar{\mathbf{X}}_i(u)\right\}I\left(W_i\geq u\right)\right]I\left(U_i^*\geq u\right)$$

and $h\left\{u,G_u\left(\mathcal{F}_i\right)\right\}$ is an arbitrary function at time u of $G_u\left(\mathcal{F}_i\right)$.

Augmented IPWCC (2)

— Under covariate-driven withdrawal at random

$$E\left\{dM_i\left(u\right)\middle|G_u\left(\mathcal{F}_i\right)\right\} = 0.$$

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— Thus the augmented estimator is consistent under $\mathcal{M}_{\text{CDW}}$ for any choice of $h\{u, G_u(\mathcal{F}_i)\}$.
— Semiparametric theory shows that the optimal (most efficient) choice of $h\{u, G_u(\mathcal{F}_i)\}$ is

$$h_{\text{opt}}\{u, G_u(\mathcal{F}_i)\} = E\left\{ dN_i^*(t) - d\Lambda(t)\, Y_i^*(t) \middle|\, G_u(\mathcal{F}_i)\right\}$$

— This conditional expectation is equal to:

$$\frac{I(C_i > t)\, I(U_i^* > u)}{H\left\{u, \bar{\mathbf{X}}_i(u), D_i, \Gamma_i\right\}} \Big(I(D_i = t)\, H\left\{t, \bar{\mathbf{X}}_i(u), D_i, \Gamma_i\right\} + \left\{ I(C_i \leq D_i) + I(C_i > D_i)\, I(D_i > t) \right\} \cdot \left[dH\left\{t, \bar{\mathbf{X}}_i(u), D_i, \Gamma_i\right\} - d\Lambda(t)\, H\left\{t, \bar{\mathbf{X}}_i(u), D_i, \Gamma_i\right\} \right] \Big)$$

where $I(D_i = t)$ is used as shorthand for $\lim_{\Delta t \to 0} I(t \leq D_i < t + \Delta t)$, $\mu\left(u, \bar{\mathbf{X}}_i(u), D_i, \Gamma_i\right)$ is the cause-specific conditional hazard of MI given $\bar{\mathbf{X}}_i(u)$, D_i, and Γ_i,

Augmented IPWCC (3)

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$$+ \{I(C_i \leq D_i) + I(C_i > D_i)\, I(D_i > t)\} \cdot$$
$$\left[dH\left\{t, \bar{\mathbf{X}}_i(u), D_i, \Gamma_i\right\} - d\Lambda(t)\, H\left\{t, \bar{\mathbf{X}}_i(u), D_i, \Gamma_i\right\}\right]\Big)$$

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Augmented IPWCC (4)

$$H\left\{u, \bar{\mathbf{X}}_i(u), D_i, \Gamma_i\right\} = \exp\left\{-\int_0^u \mu\left(r, \bar{\mathbf{X}}_i(r), D_i, \Gamma_i\right) dr\right\},$$

$$H\left\{t, \bar{\mathbf{X}}_i(u), D_i, \Gamma_i\right\} = \int_{\bar{\mathbf{x}} \in \bar{\mathcal{X}}(t)} H\left\{t, \bar{\mathbf{X}}_i(t) = \bar{\mathbf{x}}, D_i, \Gamma_i\right\} f_{\bar{\mathbf{X}}(t)|\bar{\mathbf{X}}(u),D,\Gamma}\left\{\bar{\mathbf{x}}, \bar{\mathbf{X}}(u), D_i, \Gamma_i\right\} d\bar{\mathbf{x}}$$

and

$$dH\left\{t, \bar{\mathbf{X}}_i(u), D_i, \Gamma_i\right\} = \lim_{\Delta t \to 0}\left[H\left\{t + \Delta t, \bar{\mathbf{X}}_i(u), D_i, \Gamma_i\right\} - H\left\{t, \bar{\mathbf{X}}_i(u), D_i, \Gamma_i\right\}\right].$$

Augmented IPWCC (5)

— These are substituted into the estimating equation, which can then be solved for $d\Lambda(t)$, leading to the AIPW estimator $\hat{\Lambda}^{\text{AIPW}}(t)$ (further ugly details omitted!).

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— To make it feasible ($\hat{\Lambda}^{\text{f-AIPW}}(t)$) we need a coarsening model ($\mathcal{M}_{\text{CM}}$), but also a model ($\mathcal{M}_{\text{CSM}}$) for $\mu\left(u, \bar{\mathbf{X}}_i(u), D_i, \Gamma_i\right)$, the cause-specific conditional hazard of MI, and for the conditional density of the time-updated covariates $f_{\bar{\mathbf{x}}(t)|\bar{\mathbf{x}}(u),D,\Gamma}\left\{\bar{\mathbf{x}}, \bar{\mathbf{X}}(u), D_i, \Gamma_i\right\}$, $\mathcal{M}_{\text{TUCM}}$.

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— We can also extend it ($\hat{\Lambda}^{\text{f-AIPW-ext}}(t)$), by including (D_i, Γ_i) in the coarsening model ($\mathcal{M}_{\text{ECM}}$).

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Double robustness and semiparametric efficiency (1)

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— This property is known as double robustness.

— Double robustness is especially important in our setting, where it is probably unrealistic to hope that the cause-specific and time-updated covariates models are correctly specified.

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— Under only the assumption that the coarsening model is correctly specified, the f-AIPW estimator is consistent.
— Furthermore, if we correctly specify all three models, then the f-AIPW estimator is optimally efficient.
— In practice, when the cause-specific and time-updated covariates models are not correctly specified, experience suggests that augmentation will lead to efficiency gains as long as model misspecification is not too severe.

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— See paper for details.

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— Conditional on X, withdrawal is exponential with hazard $\exp(-0.5 + X)$.

We compare five estimators of the survivor distribution:

1. the full data estimator, $\hat{S}^{\text{full}}(t)$.
2. the complete case estimator, $\hat{S}^{\text{CC}}(t)$.
3. the IPWCC estimator, $\hat{S}^{\text{f-IPWCC}}(t)$, with only X used to predict the weights using Cox PH model. This coarsening model is correctly specified.
4. the IPWCC estimator, $\hat{S}^{\text{f-IPWCC-ext}}(t)$, with X and (D, Γ) used to predict the weights using a Cox PH model. Correctly specified but more elaborate than necessary.
5. the AIPW estimator, $\hat{S}^{\text{f-AIPW-ext}}(t)$. X and (D, Γ) used in the model for the weights, and for the cause-specific MI model in a Cox PH model. This CS model is not correctly specified.

Simulation study

Results: $S(0.5)$

Estimator of survivor function	Mean	SE	% increase in SE compared with full data	Coverage of 95% CI
full	0.622	0.0464		
CC	0.631	0.0479	3.3%	
f-IPWCC	0.622	0.0486	4.9%	
f-IPWCC-ext	0.622	0.0482	4.0%	
f-AIPW-ext	0.622	0.0475	2.3%	94.7%

Estimator of survivor function	Mean	SE	% increase in SE compared with full data	Coverage of 95% CI
full	0.430	0.0485		
CC	0.463	0.0536	10.4%	
f-IPWCC	0.432	0.0535	10.2%	
f-IPWCC-ext	0.432	0.0524	7.9%	
f-AIPW-ext	0.430	0.0513	5.6%	95.9%

Simulation study
Results: $S(2.5)$

Estimator of survivor function	Mean	SE	% increase in SE compared with full data	Coverage of 95% CI
full	0.359	0.0483		
CC	0.401	0.0564	16.7%	
f-IPWCC	0.363	0.0548	13.3%	
f-IPWCC-ext	0.363	0.0541	11.9%	
f-AIPW-ext	0.360	0.0512	6.0%	96.7%

Estimator of survivor function	Mean	SE	% increase in SE compared with full data	Coverage of 95% CI
full	0.318	0.0480		
CC	0.362	0.0596	24.3%	
f-IPWCC	0.324	0.0569	18.6%	
f-IPWCC-ext	0.326	0.0556	16.0%	
f-AIPW-ext	0.320	0.0522	8.9%	95.6%

Estimator of survivor function	Mean	SE	% increase in SE compared with full data	Coverage of 95% CI
full	0.288	0.0495		
CC	0.332	0.0689	39.1%	
f-IPWCC	0.297	0.0640	30.0%	
f-IPWCC-ext	0.301	0.0619	25.0%	
f-AIPW-ext	0.289	0.0573	15.8%	93.8%

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— An appeal of this approach is that, although further models are required (for the cause-specific hazard of the incompletely-observed event, and for the evolution of the time-updated covariate process, if this is to be modelled), the consistency of our estimator does not rely on having correctly specified these models.

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— Efficiency gains are guaranteed if the additional models are correctly specified, and typically will be seen even if this is not the case.
— In simulations, AIPW seen to recover up to 50% of the efficiency lost through withdrawal in standard approaches.

Further issues

— Although the approach can deal in theory with time-updated covariates, in practice incorporating these into the cause-specific model for the incompletely-observed event will be problematic, since further models are required, along with the calculation of a typically intractable integral.

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— Future work: the comparison of the distributions of time to composite endpoint in two independent groups, via a weighted log-rank test.