Statistical Approaches for Component-Wise Censored Composite Endpoints

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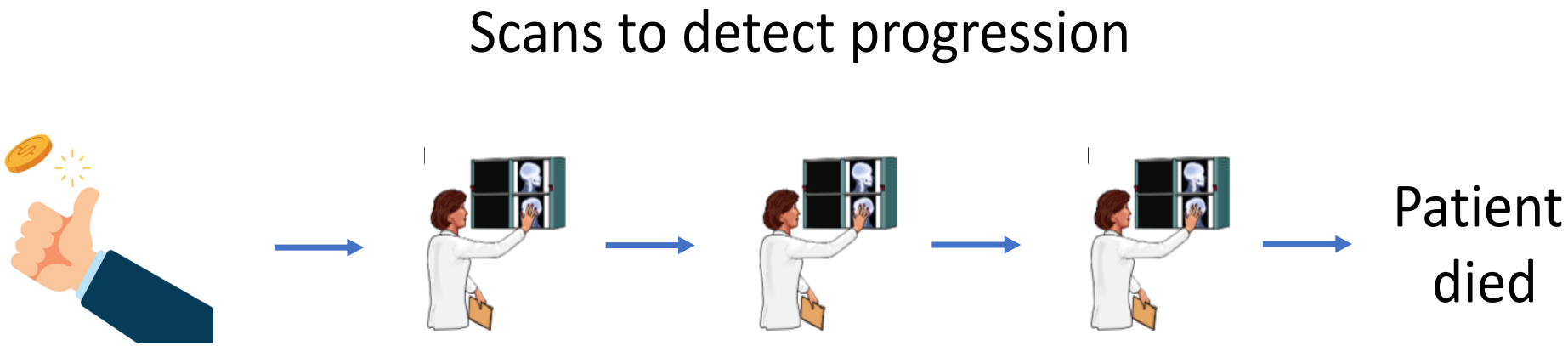
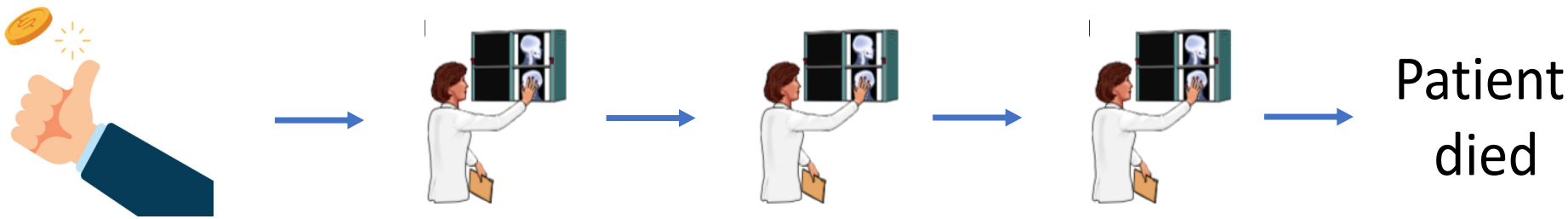
Component-Wise Censoring of Progression-Free Survival



Component-Wise Censoring of Progression-Free Survival

Scans to detect progression



Interval censored + **Right censored** = **Component-wise censored**

progression death progression-free survival

Defining "Component-Wise Censoring"

1. **Right censored death** and an **interval censored non-fatal event**: the **focus of this talk**
2. Different right censoring times by event

   Diao G., Zeng D., Ke C., Ma H., Jiang Q. and Joseph G Ibrahim. Semiparametric regression analysis for composite endpoints subject to componentwise censoring. Biometrika, 105(2): 403–418.
3. Multiple interval censored components with different censoring intervals (i.e., events assessed on different schedules)

- The term "dual censoring" has been used to refer to 1 and 2

  Boruvka A. and R. Cook 2016. Sieve estimation in a Markov illness-death process under dual censoring. Biostatistics, 17(2),: 350–363.

Handling Component-Wise Censoring: 3 Approaches

How to handle uncertainty in the progression status between visits?

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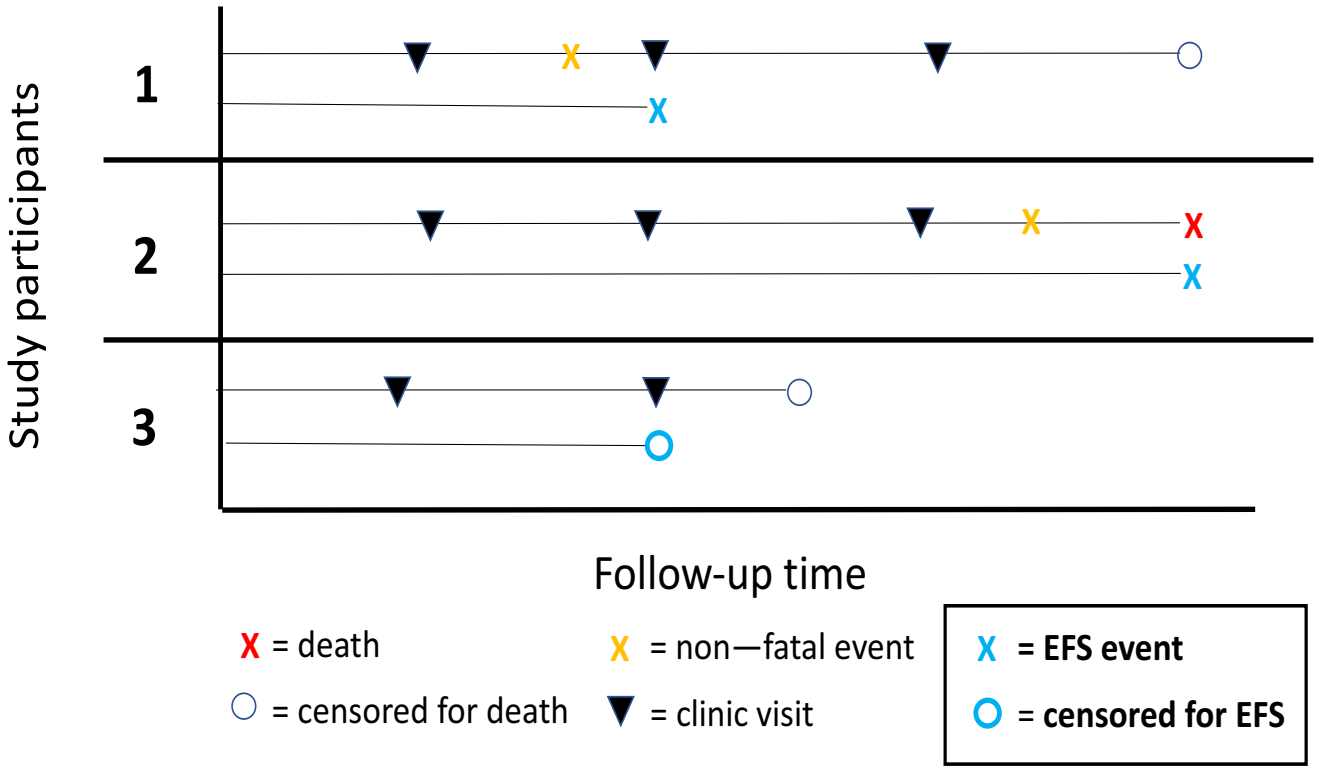
How to handle uncertainty in the progression status between visits?

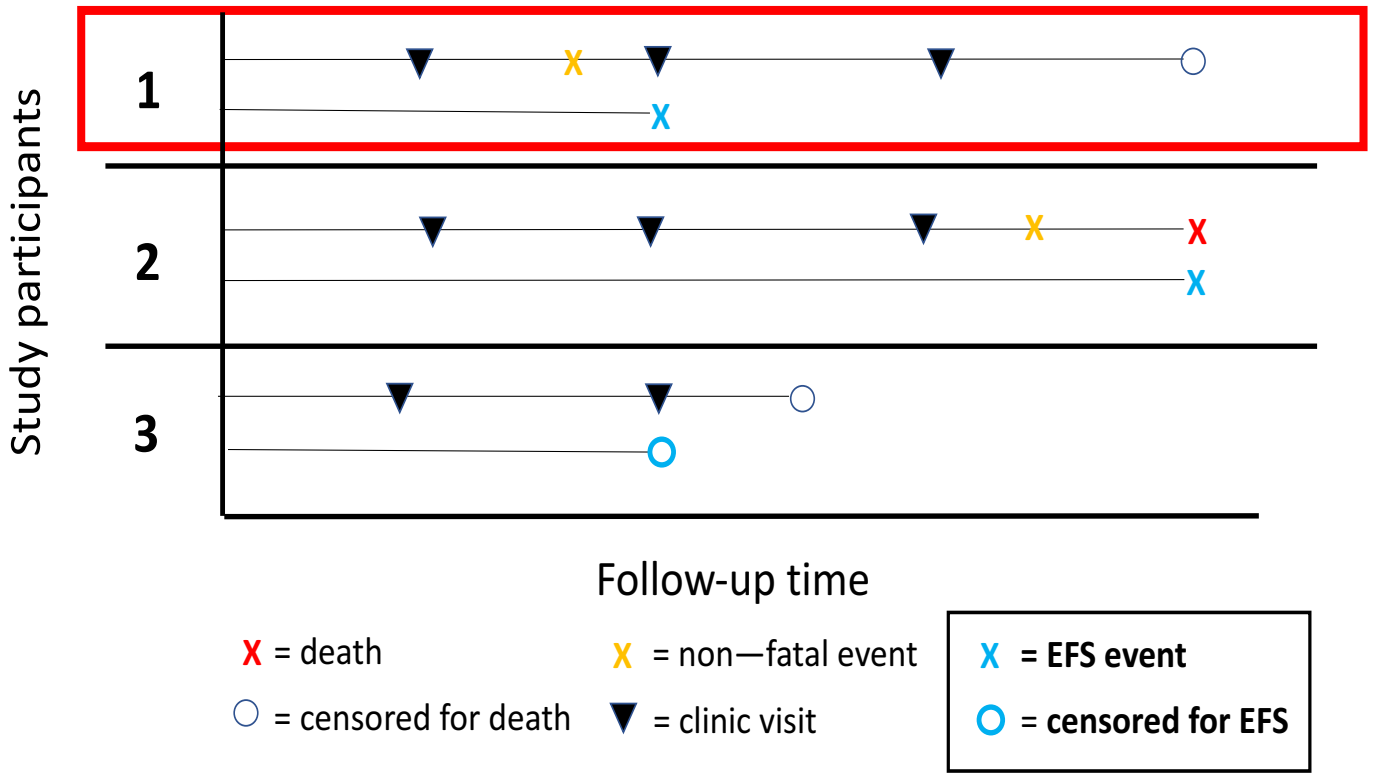
1. Fill in the individual missing data, similar to last observation carried forward
2. Characterize the progression pattern in the population by smoothing across patients/visits with a kernel estimator
3. Likelihood-based methods

Modifying Data to Apply the Kaplan-Meier Estimator



FDA recommended approach for estimating progression-free survival when progression is detected at visits:

Modifying Data to Apply the Kaplan-Meier Estimator



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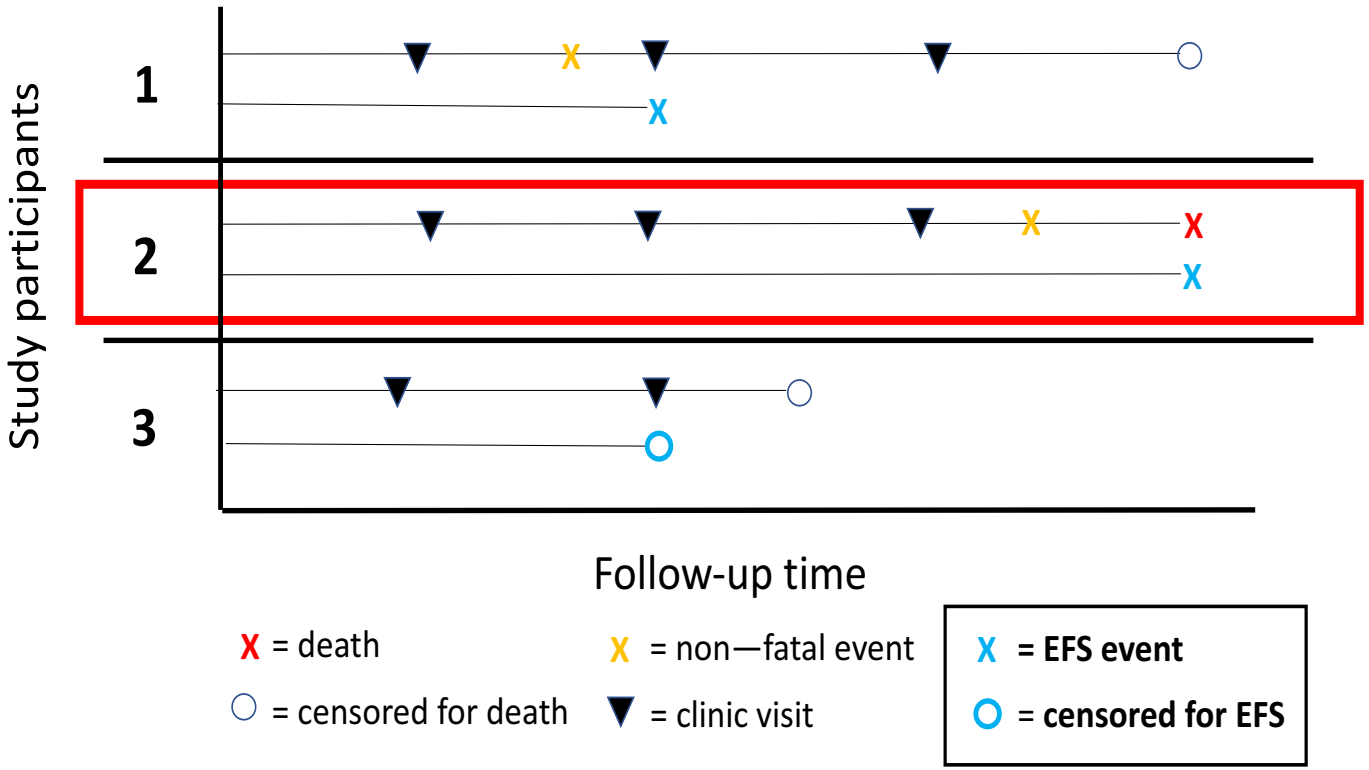

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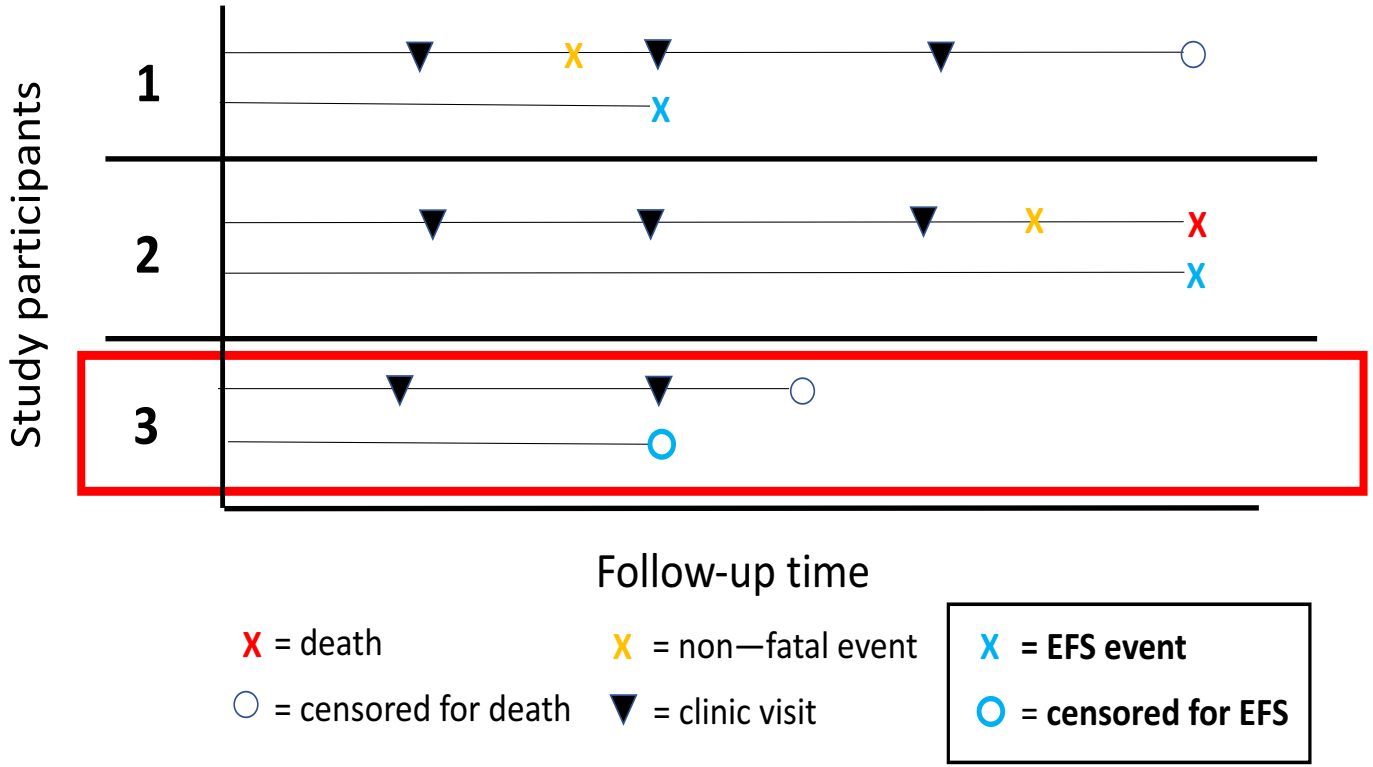
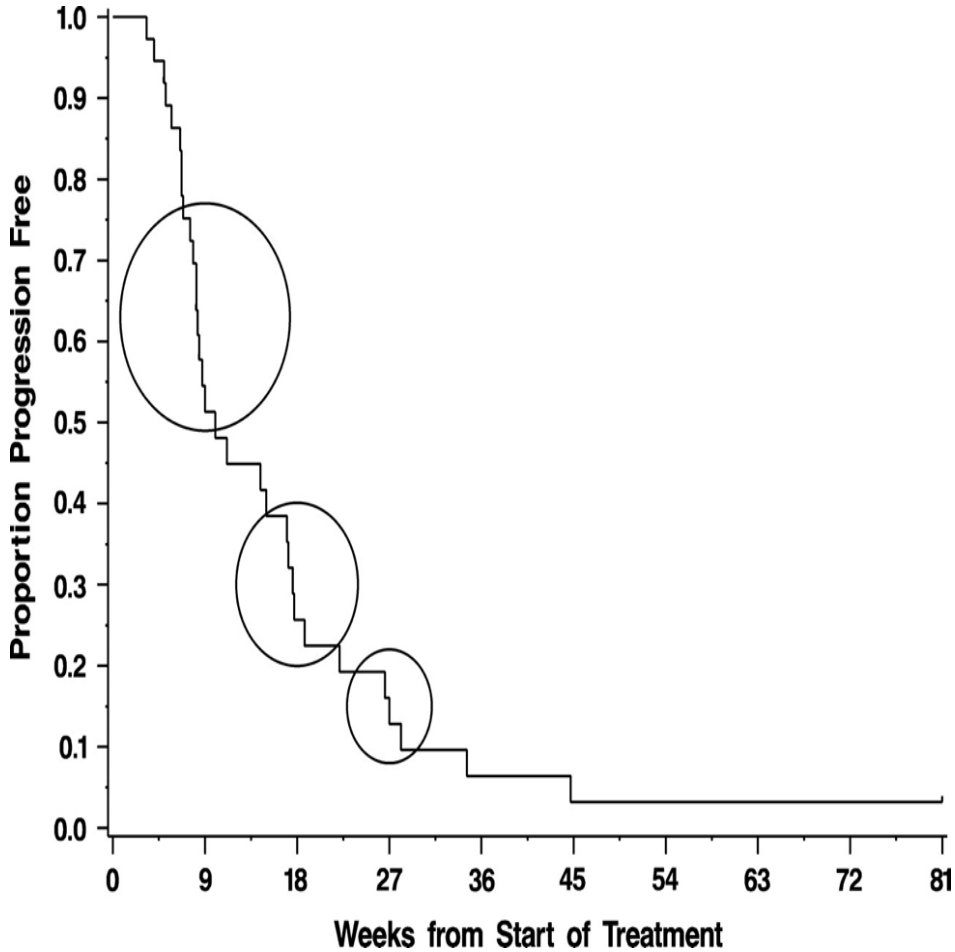


FDA recommended approach for estimating progression-free survival when progression is detected at visits:

- Treat progression as happening on the day it was observed
- Assume no progression between last visit and death
- Censor patients without observed death or progression at last visit

When You Look Matters!



Panageas K., Ben-Porat L., Dickler M., Chapman P. and D. Shrag 2007. When You Look Matters: The Effect of Assessment Schedule on Progression-Free Survival. J Natl Can Inst, 99(6): 428-432.

Kernel Estimator for Event-Free Survival

We developed an intuitive **non-parametric** estimator of event-free survival probability, analogous to the **Kaplan-Meier estimator**

> Eaton A., Y. Sun, J. Neaton and X. Luo 2022. Nonparametric estimation in an illness-death model with component-wise censoring. Biometrics, 78(3):1168-1180.

Notation

- Let D denote death time, subject to right censoring at time C

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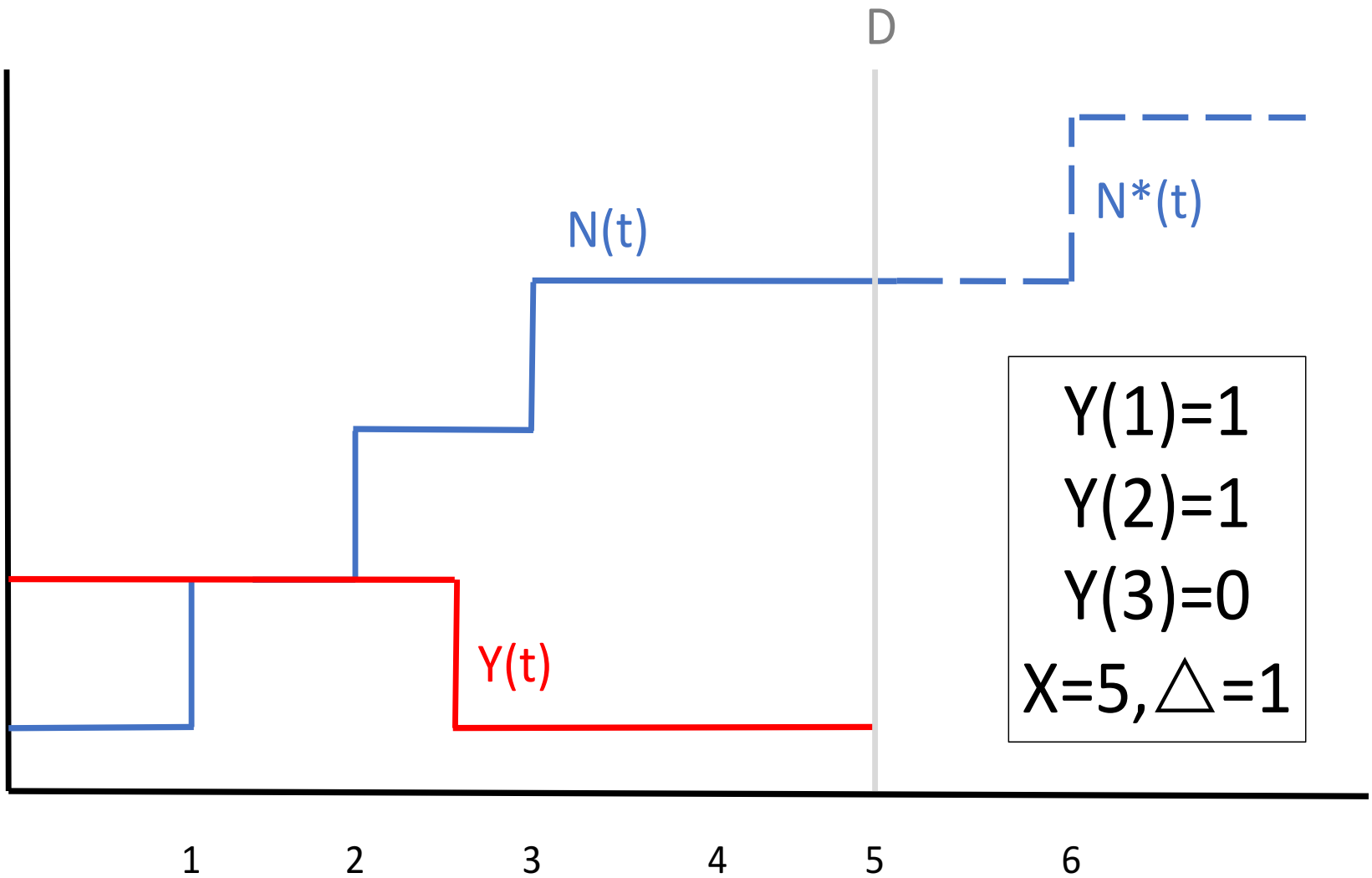
- Let $N(\cdot)$ be the visit counting process; $Y(\cdot)$ will be **intermittently observed** at times that $N(\cdot)$ jumps
- Assume C is independent of $\{Y(\cdot), D\}$ and that the potential visit process is independent of $\{Y(\cdot), D, C\}$

Observed Data



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  - $P(D \geq t)$ can be estimated using the **Kaplan-Meier estimator**
  - Think of $Y(\cdot)$ as intermittently observed; estimate $P(Y(t) = 1 | D \geq t)$ using a **kernel estimator**

Proposed Estimator

Estimate $r(t) = E\{Y(t)|D \geq t\} = P(Y(t) = 1|D \geq t)$ with

$$\hat{r}_h(t) = \frac{\sum_{i=1}^{n} \int_0^\tau K_h(t-s) Y_i(s) dN_i(s)}{\sum_{i=1}^{n} \int_0^\tau K_h(t-s) dN_i(s)}, \qquad t \in [h, \tau - h]$$

where $K_h(x) = h^{-1} K(x/h)$ is a kernel function with bandwidth h

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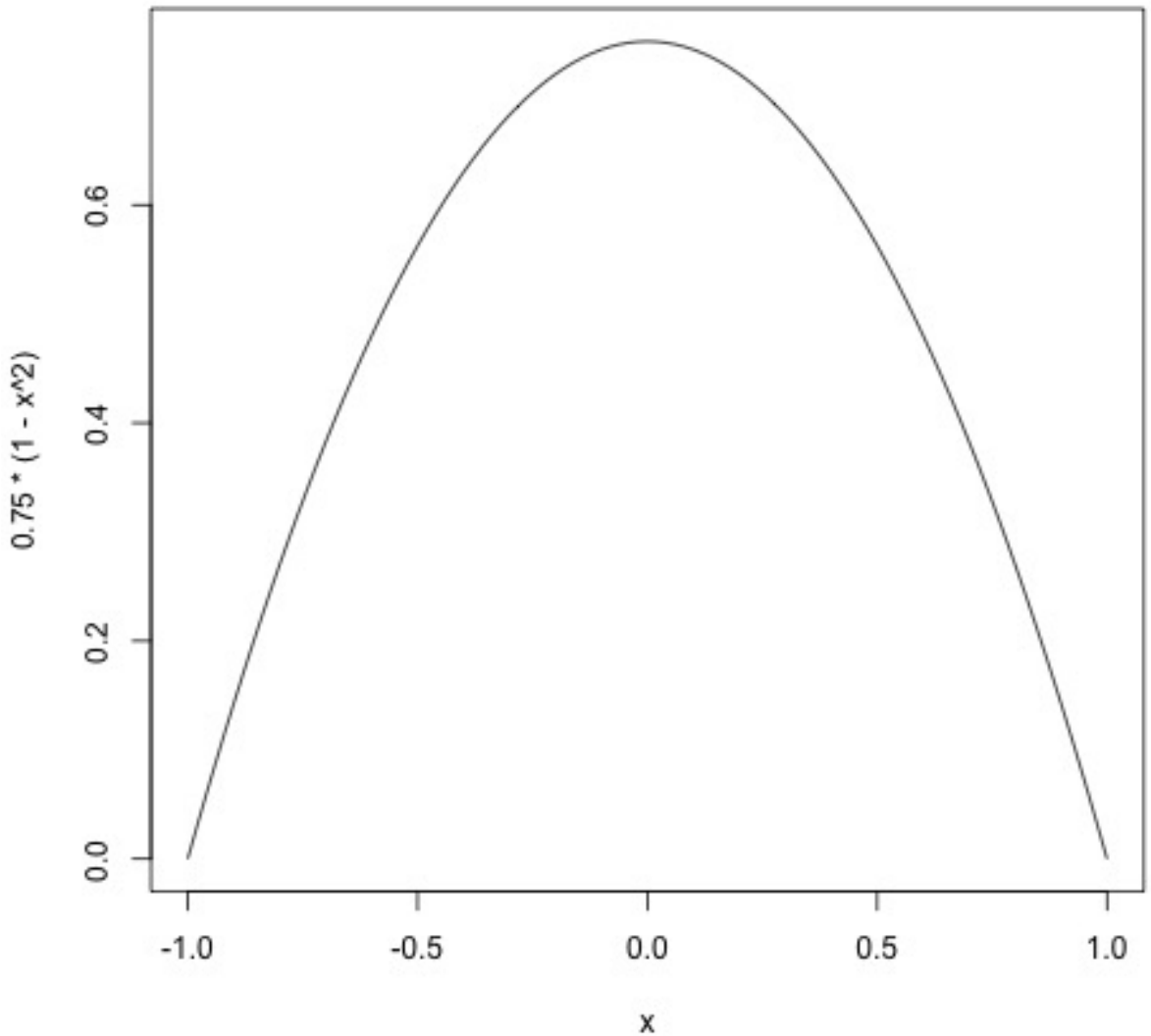
Epanechnikov Kernel



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Proposed Estimator

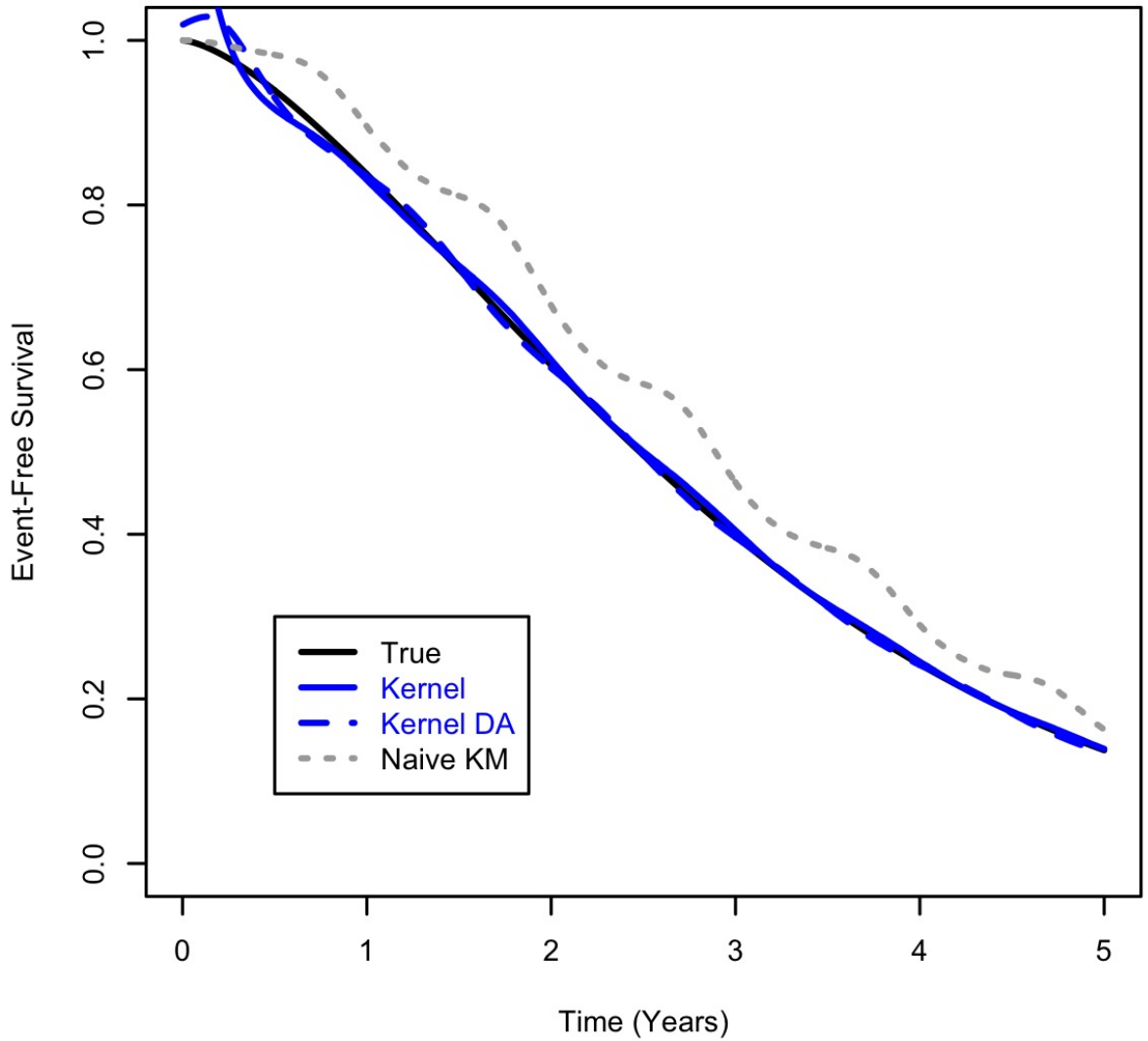
$$\hat{P}\{D \geq t, Y(t) = 1\} = \hat{S}_D(t) \times \hat{r}_h(t)$$

- We avoided the component-wise censoring problem by breaking the estimand into parts that can be estimated with established methods

$$P(D \geq t, Y(t) = 1) = P(D \geq t) \times P(Y(t) = 1 | D \geq t)$$

- $\hat{S}_D(t)$ is the **Kaplan-Meier estimator**
- $\hat{r}_h(t)$ is a **kernel estimator** of $r(t) = P(Y(t) = 1 | D \geq t)$

Simulation Results



Likelihood-Based Estimation

- Likelihood reflects the information we have (and lack) under component-wise censoring
- Estimation via maximum likelihood

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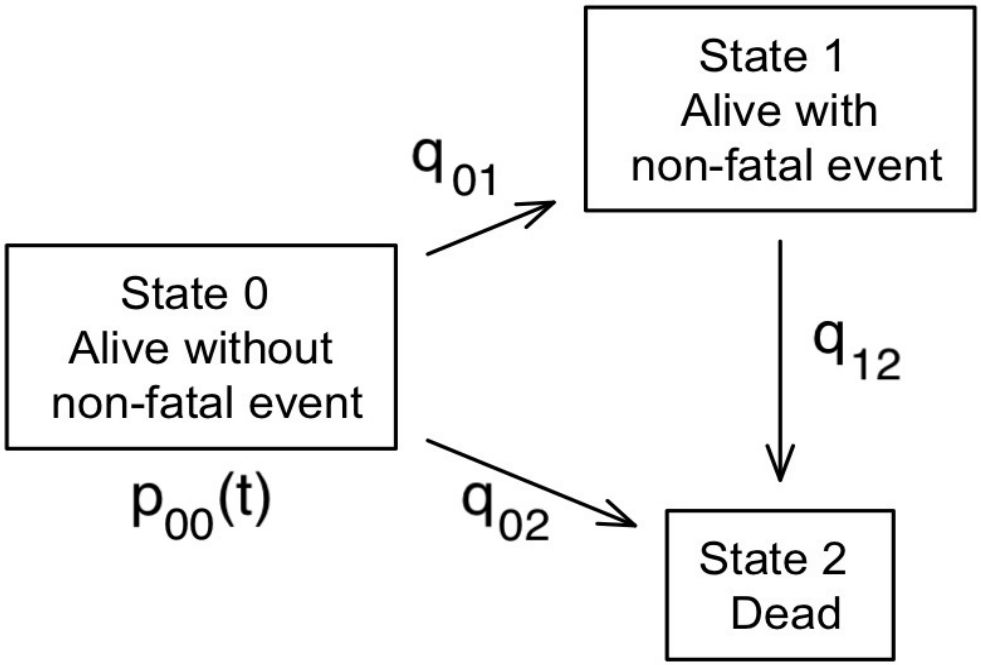
- Likelihood reflects the information we have (and lack) under component-wise censoring
- Estimation via maximum likelihood
- Parametric assumption: constant transition intensities over time
- Implemented in the msm R package

Kalbfleisch J. D. and J. F. Lawless 1985. The analysis of panel data under a Markov assumption. Journal of the American Statistical Association, 80(392):863-871.

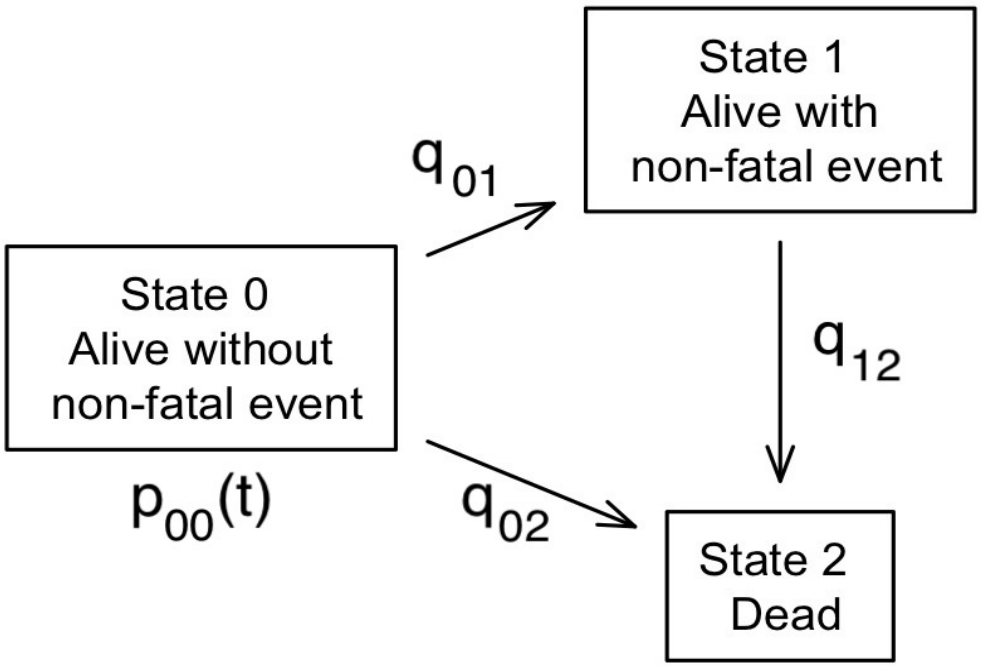
Jackson C. H. 2011. Multi-state models for panel data: The msm package for R. Journal of Statistical Software, 38(8).

Model + Parameters



- Let q_{rs} be the intensity or instantaneous risk of moving from state r to state s
- Let $p_{rs}(t)$ be the probability of being in state s at time $u + t$, given one was in state r at time u

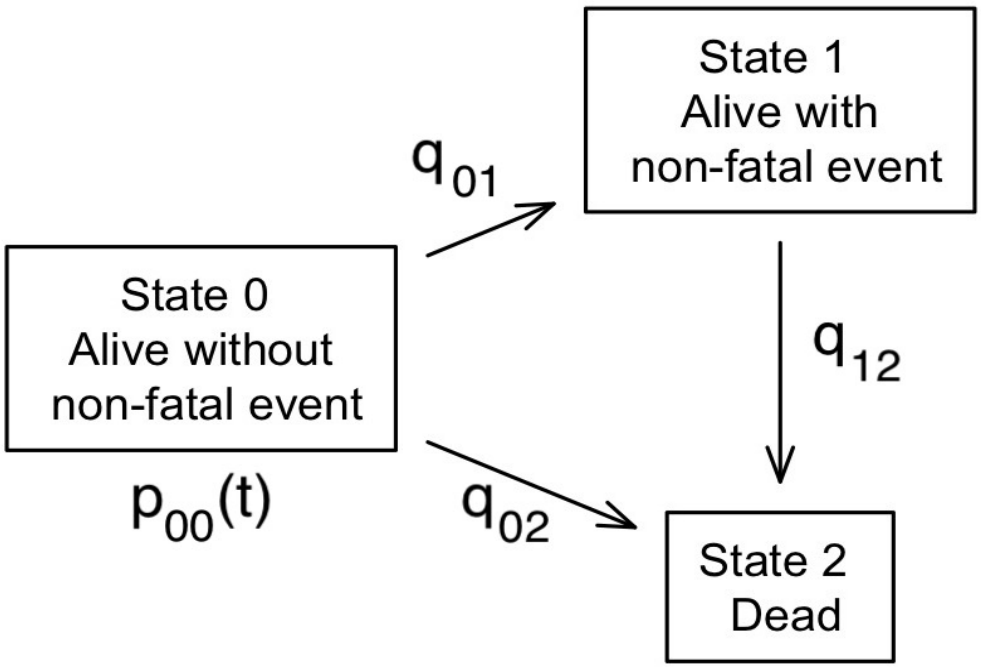
Likelihood Formulation



Likelihood contribution for a participant in state 0 at time t_1 and state 1 at time t_2

$$p_{00}(t_1)p_{01}(t_2 - t_1)$$

Likelihood Formulation

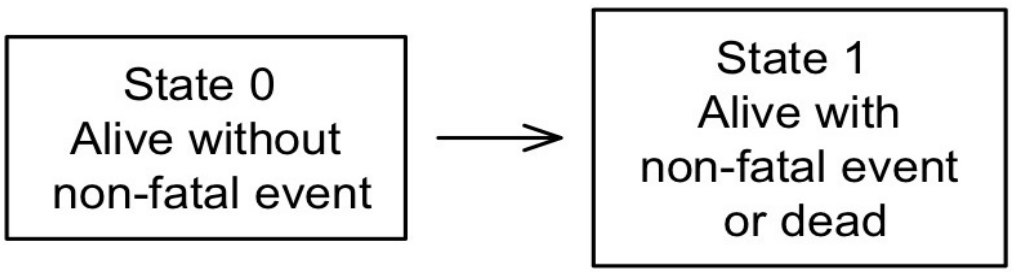


Likelihood contribution for a person who died at time t_1 with no visits to assess the non-fatal event

$$\sum_{m \in \{0,1\}} p_{0,m}(t_1) q_{m,2}$$

Defining States

Likelihood contribution is not clear if components that are censored differently share a state



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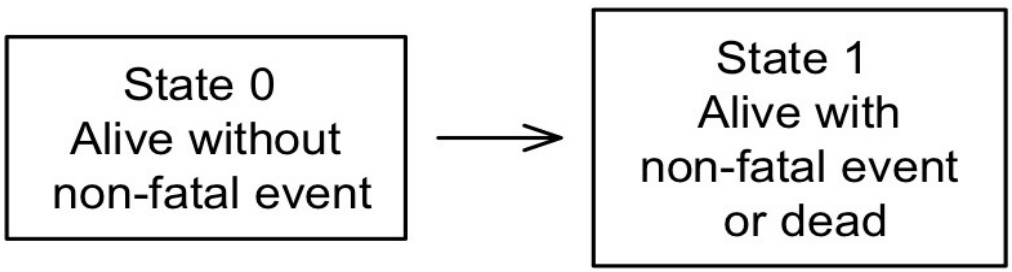

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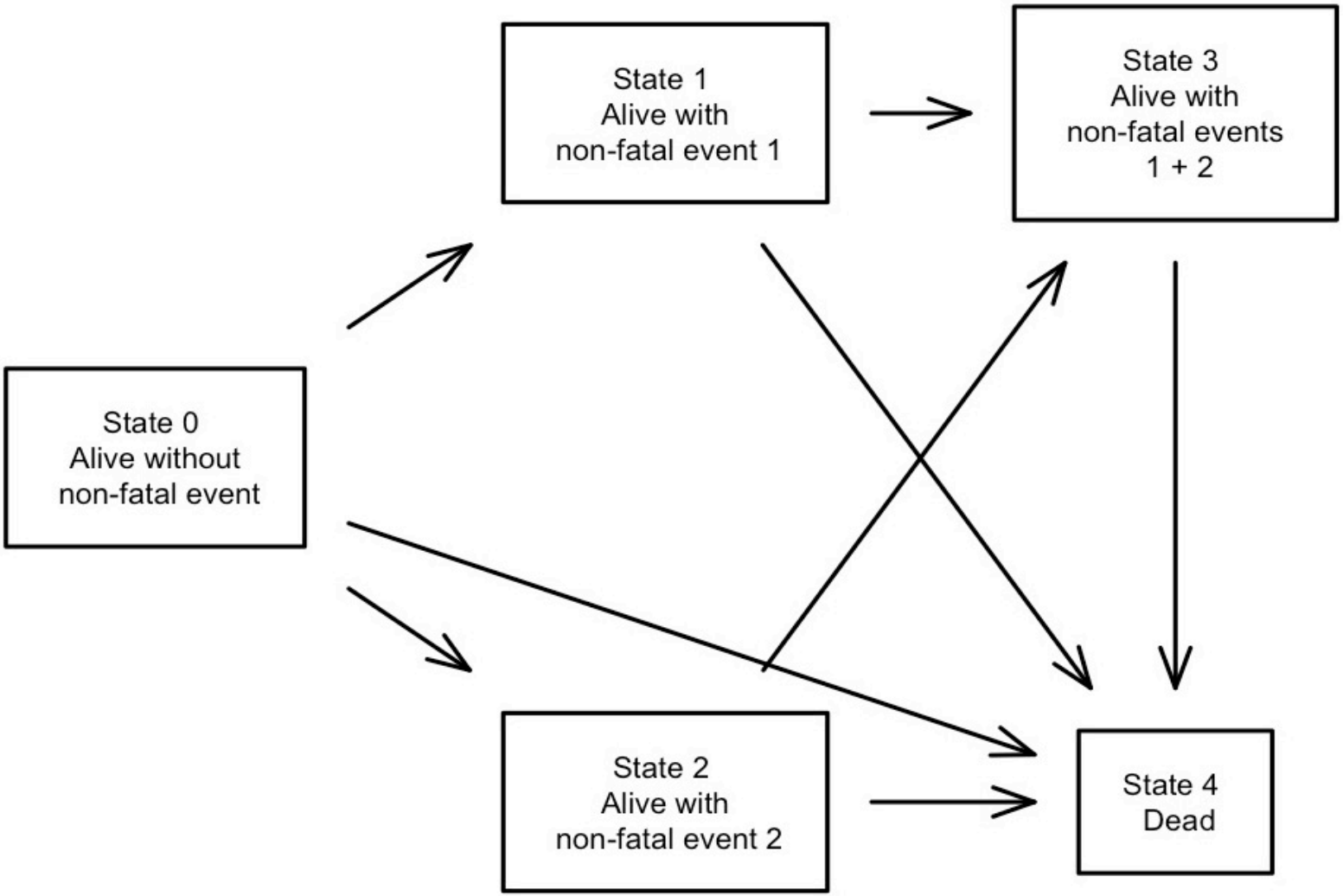
Events Assessed on Different Schedules



Loosening Parametric Assumptions

- Can allow $q(t)$ to be piecewise constant with fixed changepoints
- Non-parametric MLE has been established by Frydman and Szarek

  Frydman H. and M. Szarek 2009. Nonparametric estimation in a Markov "illness-death" process from interval censored observations with missing intermediate transition status. Biometrics, 65(1): 143-51.
- Boruvka and Cook use a sieve, i.e. a finite-dimensional approximation for the cumulative transition intensity whose size increases with n

  Boruvka A. and R. Cook 2016. Sieve estimation in a Markov illness-death process under dual censoring. Biostatistics, 17(2),: 350–363.

Data Application: the MRFIT Trial

- RCT aiming to reduce the risk of **coronary heart disease** in high-risk men using a **multifactor intervention** (smoking cessation, treatment for hypertension, dietary advice)
- Followed 12866 men (6438 control, 6428 treatment) for $\geq$ 6 years

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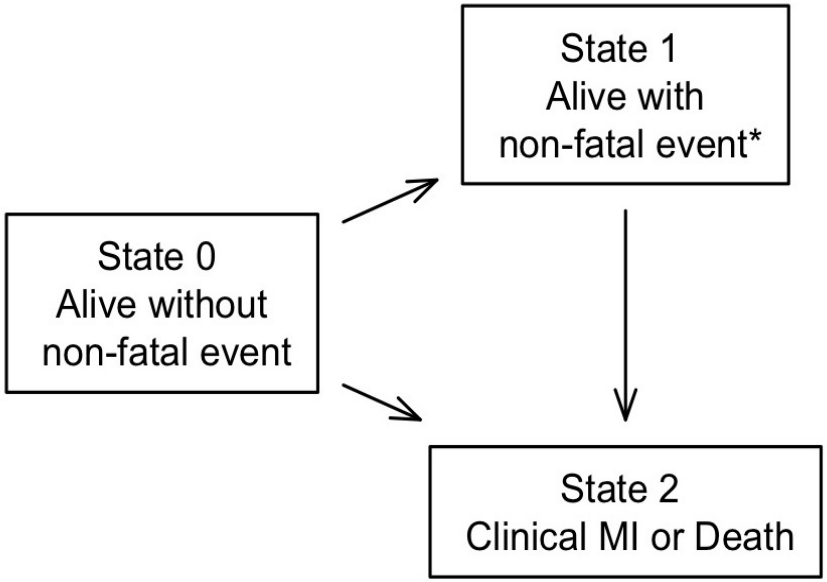
- Death and CMI are right censored
- Information on other non-fatal cardiovascular events was collected at **annual visits**, and exact dates were not ascertained, leading to **component-wise censoring**

Data Application: the MRFIT Trial



* Impaired renal function, congestive heart failure, myocardial infarction by serial ECG change, surgery for coronary artery disease or stroke

Multiple Risk Factor Intervention Trial Research Group 1982. Multiple Risk Factor Intervention Trial: Risk factor changes and mortality results. JAMA, 248(12):1465-1477.

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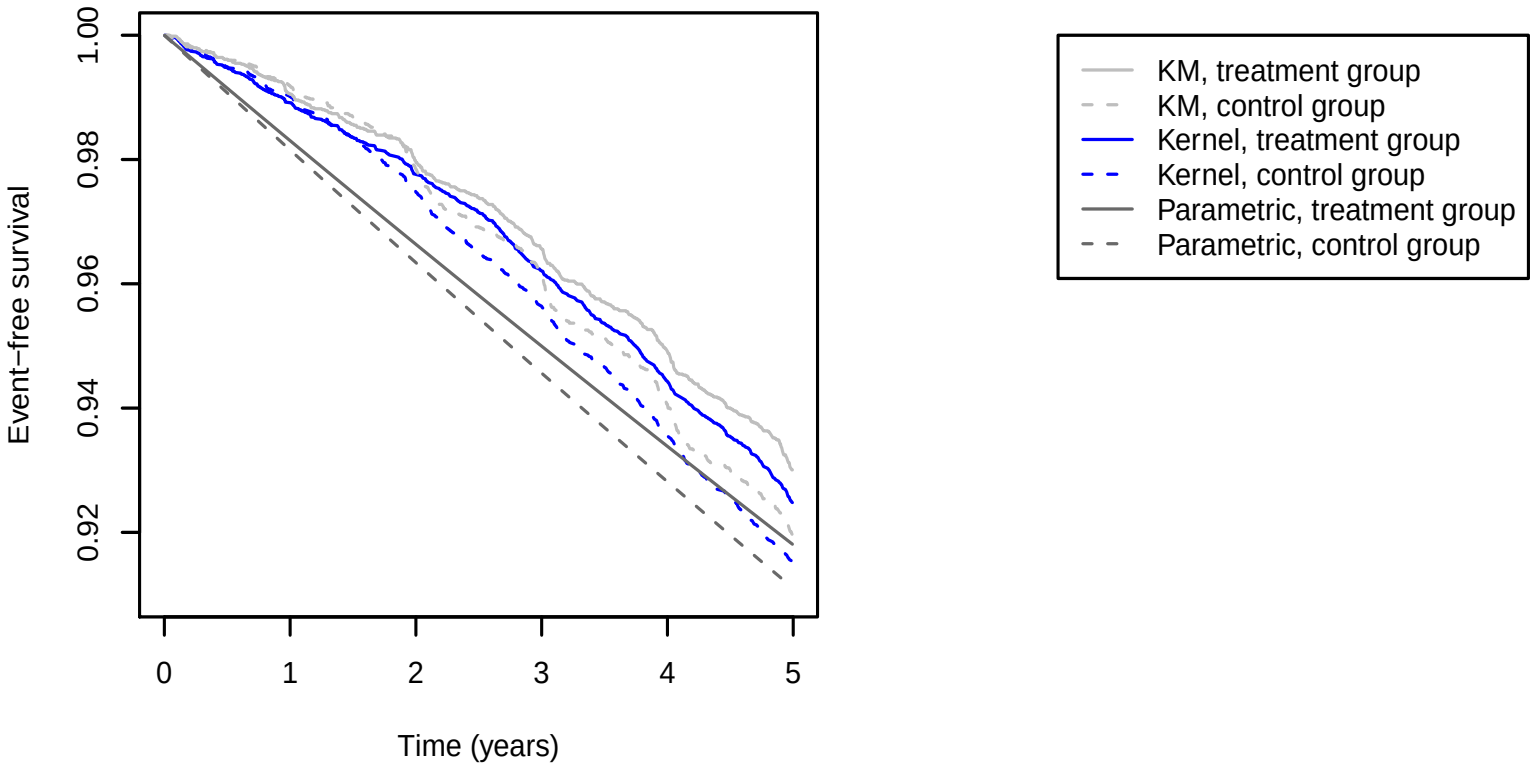

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    Eaton A. and E. Zabor 2022. Analysis of composite endpoints with component-wise censoring in the presence of differential visit schedules. Statistics in Medicine, 41(9): 1599-1612.
- Likelihood-based approaches: constrain the treatment effect on $0 \rightarrow 1$ and $0 \rightarrow 2$ transition intensities to be equal

Data Application: the MRFIT Trial

Table: Hazard ratio estimates and 95% CIs

Event	Naive Cox model	Parametric model	Parametric model with constraint
Composite (death/CMI + other cardiovascular events)	0.93 (0.84, 1.03)		0.92 (0.83, 1.02)
Death/CMI		0.99 (0.87, 1.13)	
Other cardiovascular events		0.82 (0.69, 0.97)	

Results from the sieve estimator were very similar to the parametric model

Key Takeaways

- Component-wise censored data is common in clinical trials and routinely analyzed with naive methods
- Analysis methods differ in how they deal with uncertainty in non-fatal event status between visits
  - Naive approach fills in data, similar to last observation carried forward
  - The proposed kernel estimator smooths over visits close to time t to estimate $P(Y(t) = 1 | D \geq t)$
  - Multistate models allow us to express the likelihood for a wide variety of observation schemes, including component-wise censoring, and estimate quantities of interest via maximum likelihood