Evaluating Survival Prognosis in the Presence of Immortal Time Bias

for *a meeting of the research group of Prof. Sandrine Dudoit*,
given Friday 2nd March, 2018

Kevin Benac and Nima Hejazi

Group in Biostatistics
University of California, Berkeley

slides: goo.gl/Cqd9ex

Data and Motivation

- Consider a data analysis scenario in which we are given survival times for patients recruited based on a first primary melanoma.
- Over the course of the observational study, an *a priori* unknown number of the patients (n_2) develop a second primary melanoma prior to death.
- **Question of interest:** *How does the occurrence of a second primary melanoma change the survival prognosis of a patient?*

Preview: Summary

- Nonparametric estimators of survival (even the NP-MLE) displays bias under this data-generating mechanism.
- The Cox proportional hazards model provides a way to mitigate this bias but comes with assumptions that are difficult to verify in practice.
- Youlden provides an approach that appears intuitive but fails to approach the parameter of interest.
- Jewell provides a correction for employing the Kaplan–Meier estimator in this setting.

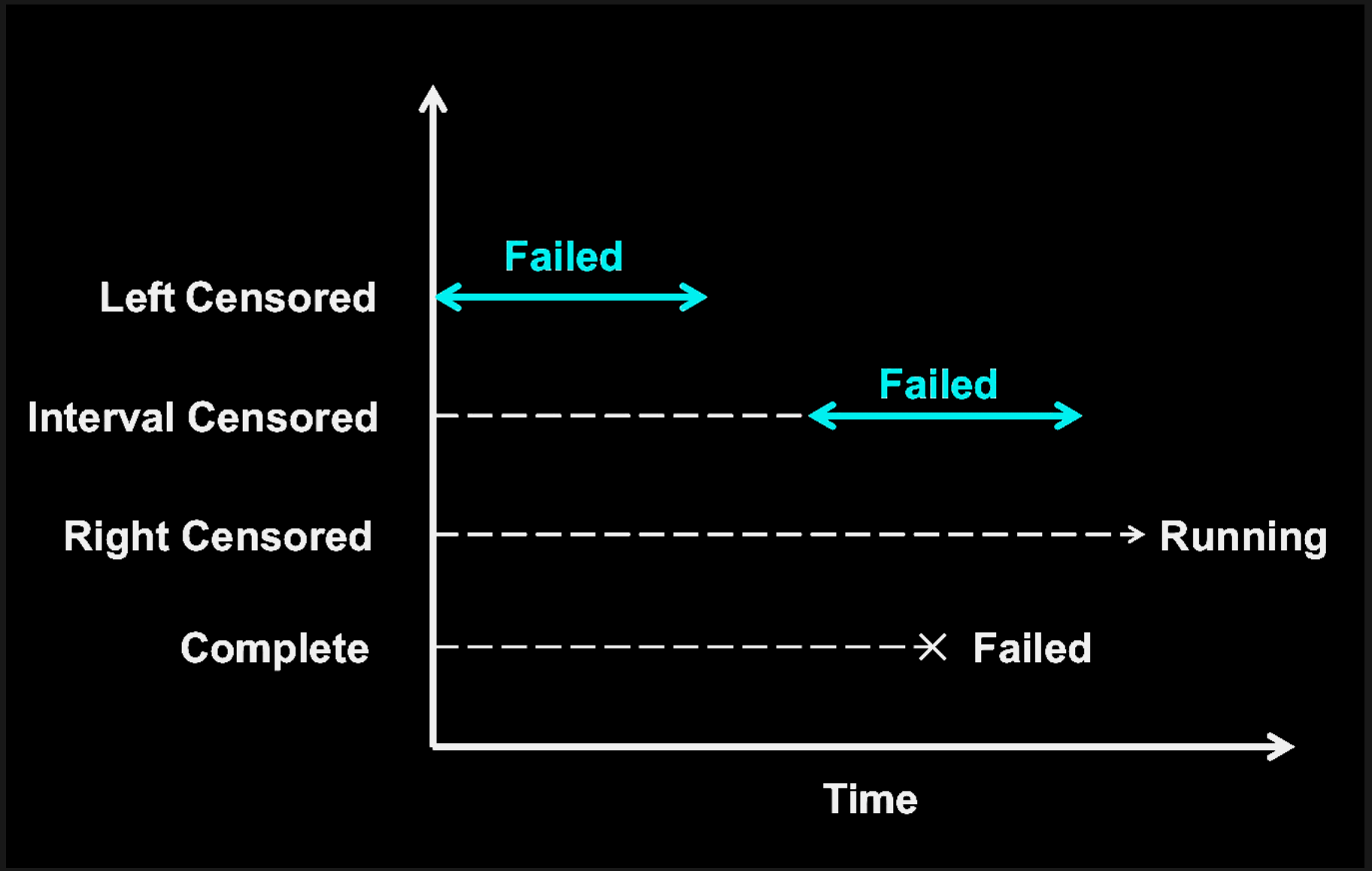
Survival Analysis

- Study of the distribution of a lifetime T, corresponding to the time from a **well-defined origin** until the occurrence of a **well-defined event** or **endpoint**.
- For historical reasons, the event is often referred to as a **failure**.
- An individual for whom an event has not occurred at time t is said to be **at risk** at time t.
- Although the term *failure* is usually associated with *death*, especially in medical research, it has to be taken in the broad sense of a well-defined event.

Survival Analysis

- T is a non-negative random variable.
- If $T_1, \ldots, T_n \overset{iid}{\sim} T$ are observed, then we know that the empirical cumulative distribution function (eCDF) is the NP-MLE of $F_T(\cdot)$.
- *Problem:* In practice, we always have to deal with missing data (i.e., **censored observations**) in the context of survival data. Most of the time, this is merely **right-censoring**.

Survival Analysis



The Kaplan–Meier Estimator

- Kaplan and Meier (1958) extensively studied the case where right-censored data are present in survival analysis.
- Let us denote the distinct ordered times of observed failures by

$$t^{(1)} < \ldots < t^{(m)},$$

Time	$t^{(1)}$	$t^{(2)}$	$\ldots$	$t^{(m)}$
Failures	d_1	d_2	$\ldots$	d_m
At risk	$n_1 = n$	n_2	$\ldots$	n_m

The Kaplan–Meier Estimator

If $t > 0$, $t^{(i)} < t \leq t^{(i+1)}$ then we can decompose $S(t^{(i)})$ as

$$P\left\{T > t^{(1)}\right\} P\left\{T > t^{(2)} \mid T > t^{(1)}\right\} \cdots P\left\{T > t^{(i)} \mid T > t^{(i-1)}\right\}.$$

The Kaplan–Meier estimator is defined as

$$\widehat{S}(t) = \prod_{i:t(i)<t} \left(1 - \frac{d_i}{n_i}\right), \quad t \geq 0.$$

The Kaplan–Meier Estimator

- In the case of data including possible right-censoring, the Kaplan–Meier estimator is the NP-MLE for $S(t)$.
- When there is no censoring, the Kaplan–Meier estimator coincides with $1 -$ eCDF$(\cdot)$.
- The Kaplan–Meier estimator relies on a central assumption that T and C (censoring variable) are independent, which is non-testable in practice.

Hazard Function

The *hazard function* at time t is defined by

$$\lambda(t) = \lim_{h \to 0} \frac{P\left(T < t + h \mid T \geq t\right)}{h} = \frac{f(t)}{S(t)}, \quad t > 0.$$

The hazard and the survival functions are related by

$$S(t) = \exp\left\{-\Lambda(t)\right\}, \quad t > 0,$$

where

$$\Lambda(t) = \int_0^t \lambda(s) ds, \quad t > 0$$

and is known as the **cumulative hazard function**.

The Cox Proportional Hazards Model

- The most widely used regression model in survival analysis is Cox's *proportional hazards* model (of the hazard function):

$$\lambda\left(t; Z = z\right) = \lambda_0(t) \exp\left(\beta^T z\right), \quad t \geq 0.$$

- This is a *semiparametric* model: nonparametric in $\lambda_0(\cdot)$ but parametric in β.

Data and Motivation

- *Problem:* Efficiently estimate survival prognosis for a data structure exhibiting immortal time bias.
- *Why?* Efficient estimation under a time-dependent risks bias presents a novel challenge that has received meager attention in the literature.
- We employ and compare
  1. semiparametric estimators of survival: the Cox proportional hazards model (with time-varying covariates),
  2. Nonparametric estimators of survival: variations of the the Kaplan–Meier estimator.

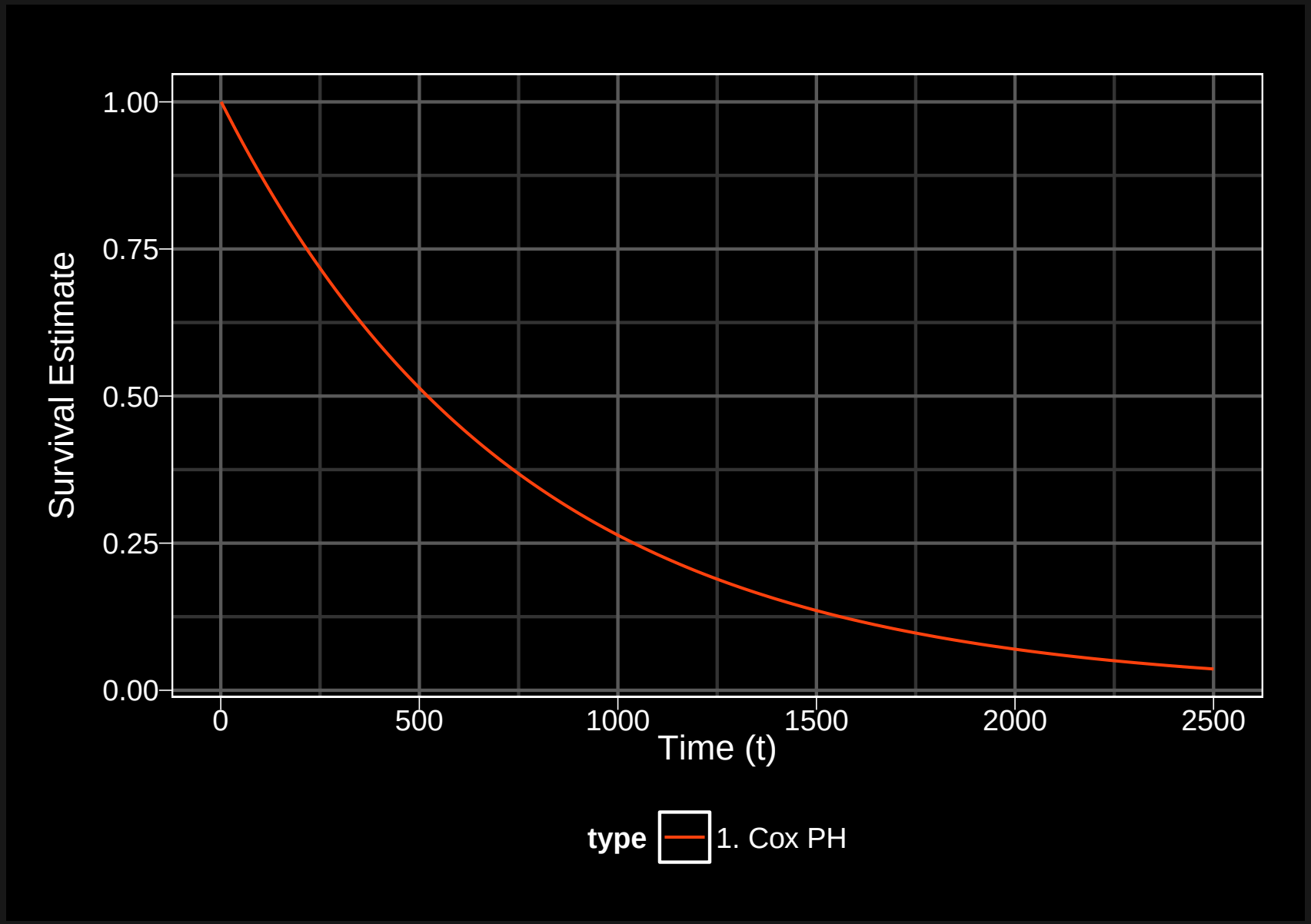
The Cox Proportional Hazards Model

- In the case we consider for motivation, let U be the time where a second event occurs, then define $Z(t) = I(t > U), \quad t \geq 0.$
- Fitting the Cox model with $Z(t)$ as a covariate enables us to estimate how the risk for the patient changes after the appearance of the second melanoma.

Methodology — Cox Regression

- We simulate observed data under the assumptions of the Cox model a total of $10,000$ times, averaging the estimated survival across all observed time points for each fit of the Cox proportional hazards regression.
- Recall that Cox regression estimates the hazard at a given time, assuming a simplistic relationship between hazards for events of interest.
- This borrows information across the two groups to estimate survival — that is, groups experiencing a single primary melanoma and those with two both inform estimation of survival.
- We account for transitions between the two groups by way of a *time-varying covariate*.

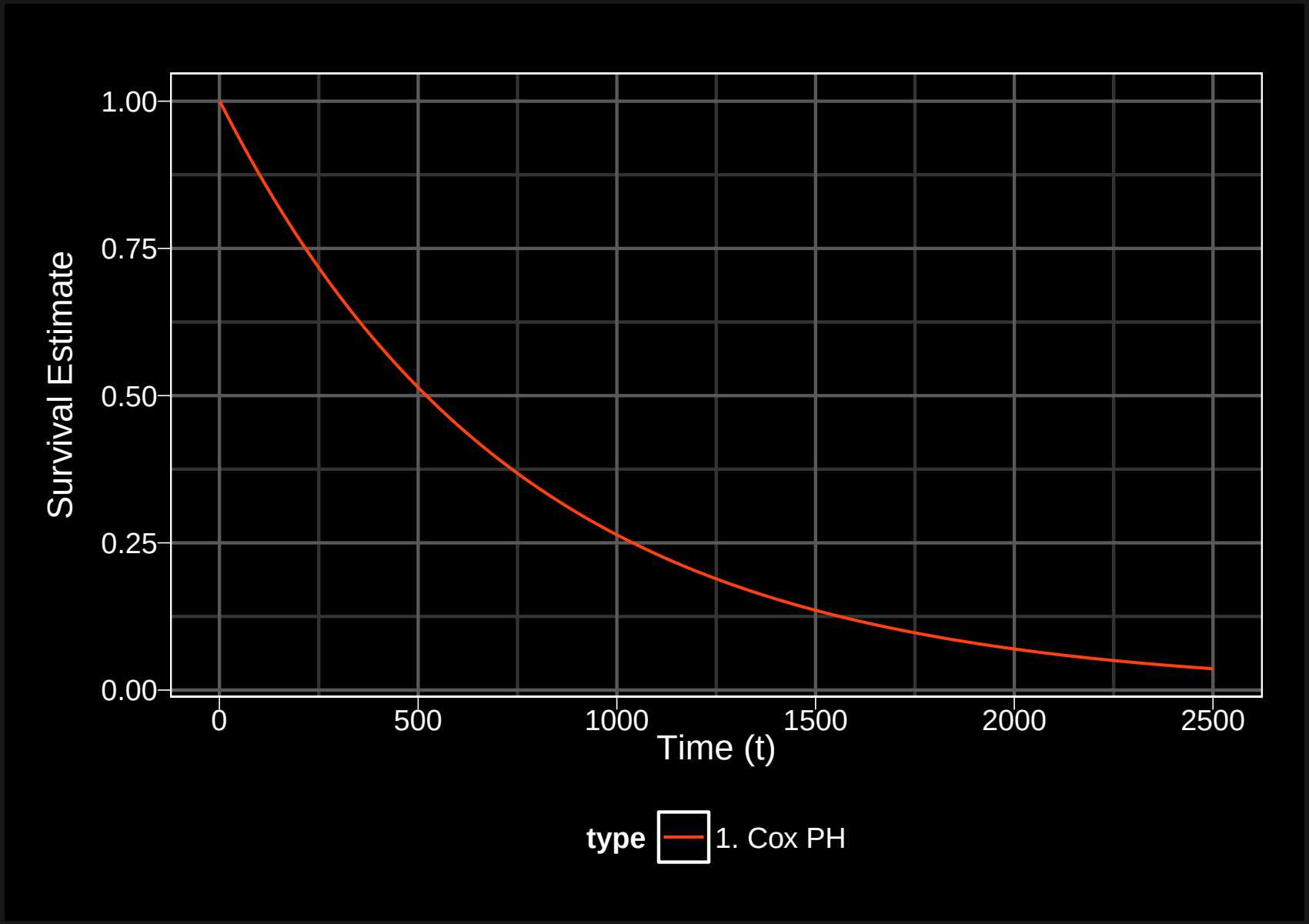
Results — Cox Proportional Hazards



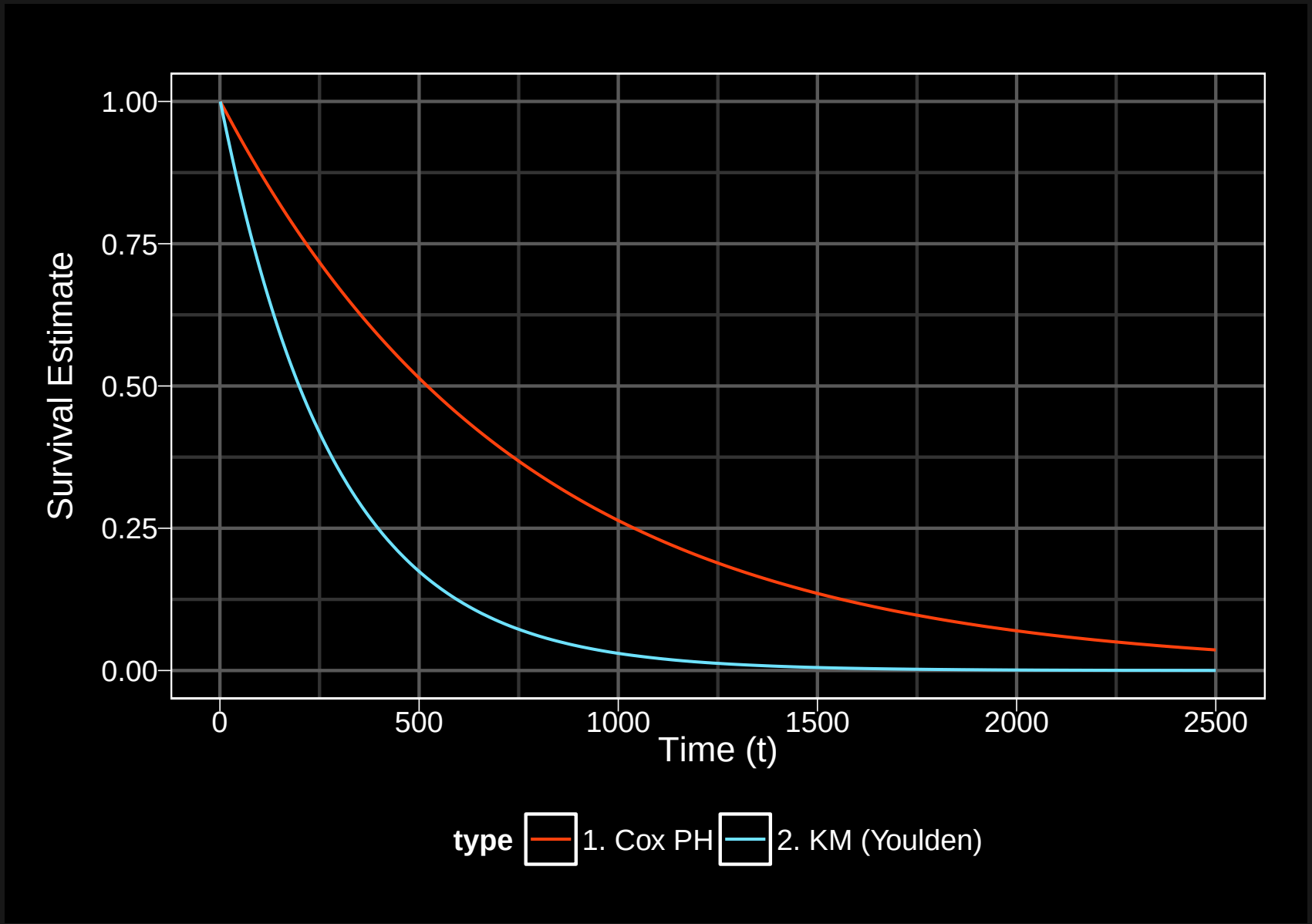
Methdology — Kaplan–Meier (Youlden)

- In pratice it's impossible to know if assumptions of the Cox model hold for a given data-generating process we encounter "in the wild."
- This makes the use of a nonparametric approach highly desirable, so, *how might we formulate a Kaplan–Meier estimator for this setting*?
- Recall that we cannot provide covariate information when fitting Kaplan–Meier estimators, let alone time-varying disease status.
- *Proposal:* Fit a Kaplan–Meier estimator for patients that experience only a single primary melanoma.

Results — Kaplan–Meier (Youlden)



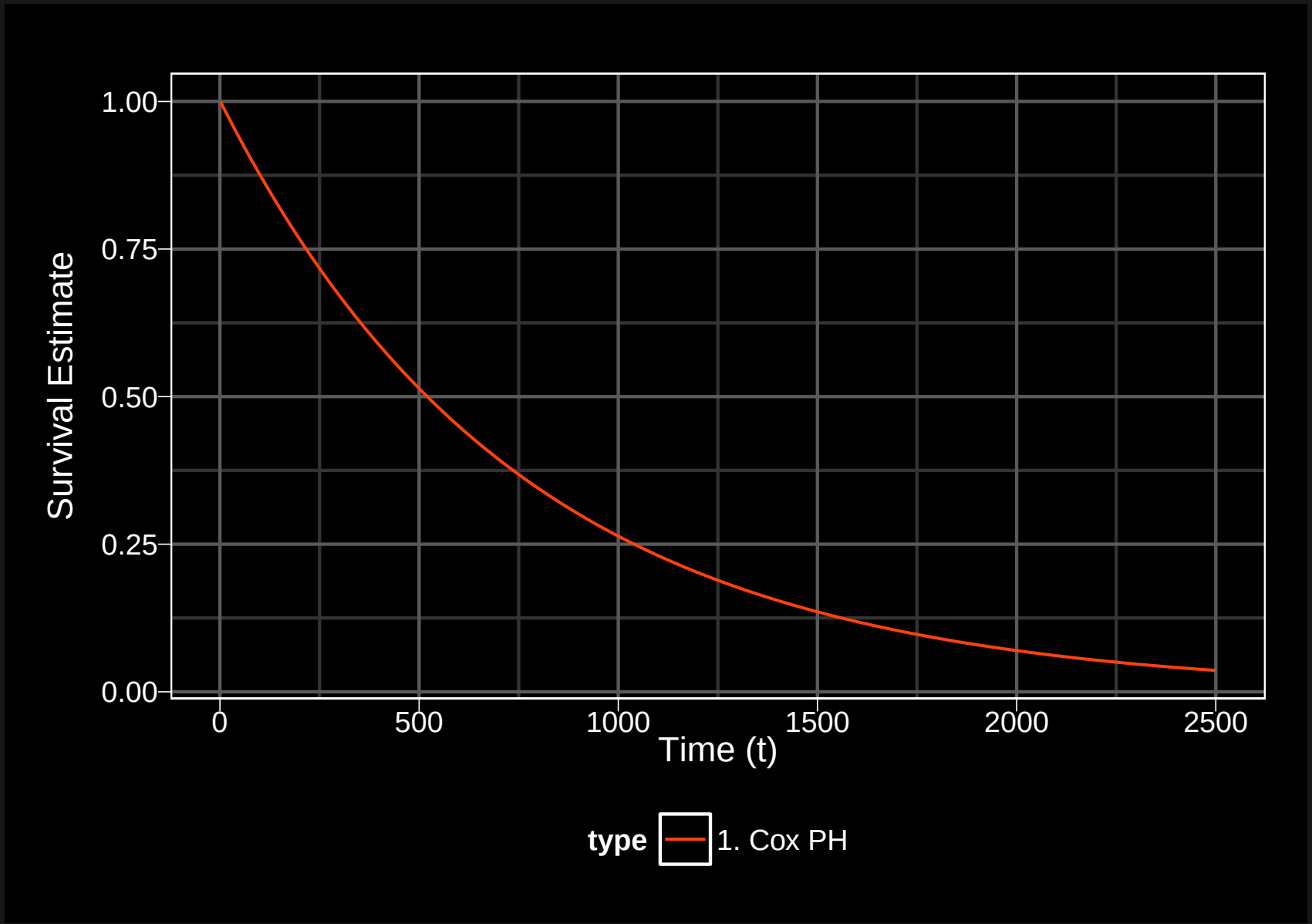
Results — Kaplan–Meier (Youlden)



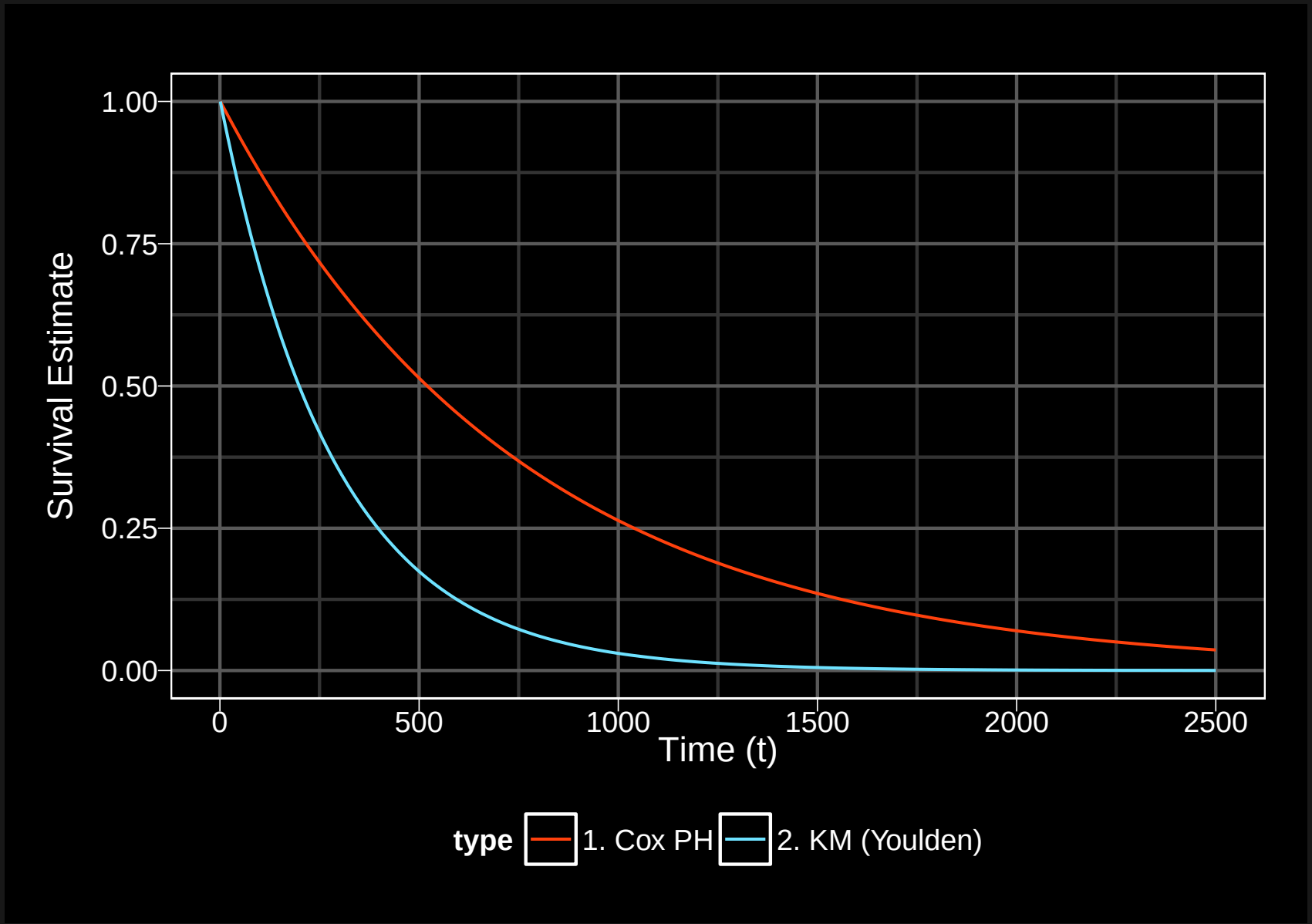
Methdology — Kaplan–Meier (Jewell)

- The difference between the Kaplan–Meier and Cox regression estimates of survival is quite striking.
- Given that the assumptions of the Cox model hold, we can evaluate Kaplan–Meier relative to Cox — why is KM so strongly biased?
- Recall that we *chose* to discard the second group when fitting our chosen KM estimator.
- Including such observations when fitting our KM estimator should *de-bias* the early (in time) estimates.

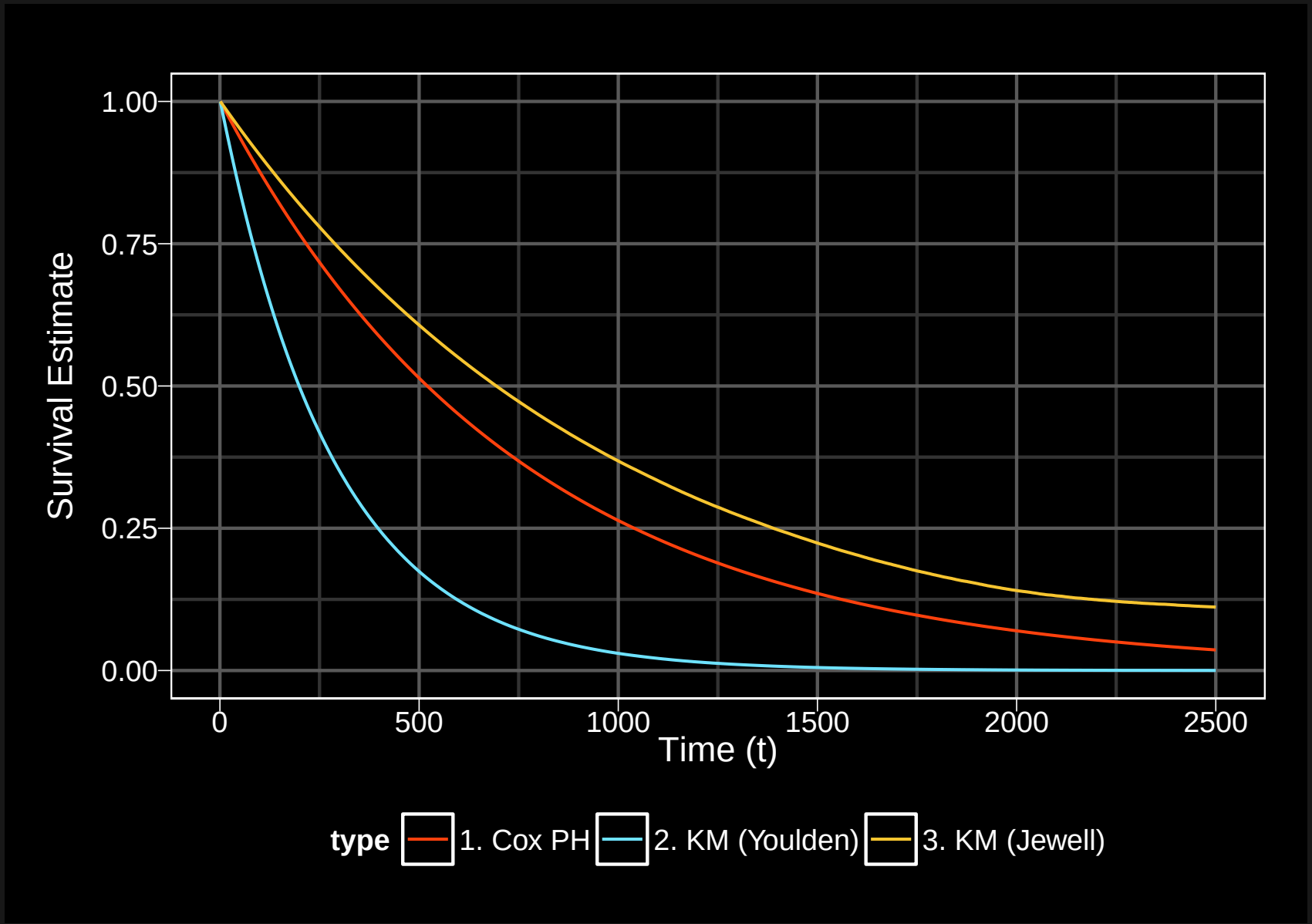
Results — Kaplan–Meier (Jewell)



Results — Kaplan–Meier (Jewell)



Results — Kaplan–Meier (Jewell)



Discussion

- Each of three estimators provides strikingly different estimates of survival across the observed times.
- Since the assumptions of the Cox model hold in our simulation, we can evaluate results from each of the nonparametric KM estimators relative to those from Cox PH.
- Further/ongoing investigation: *How does the relative performance of these estimators differ when the assumptions of the Cox model do not hold?*

Discussion

- Our initial KM proposal exhibited strong bias, underestimating survival at all observed times, with a particularly noticeable bias early on.
- The corrected KM estimator, which draws on information from both groups, provides better estimates early in time, but displays a stronger positive bias at later times (overestimating survival).

Review: Summary

- Nonparametric estimators of survival (even the NP-MLE) displays bias under this data-generating mechanism.
- The Cox proportional hazards model provides a way to mitigate this bias but comes with assumptions that are difficult to verify in practice.
- Youlden provides an approach that appears intuitive but fails to approach the parameter of interest.
- Jewell provides a correction for employing the Kaplan–Meier estimator in this setting.

References I

Snapinn, S. M., Jiang, Q., and Iglewicz, B. (2005). Illustrating the impact of a time-varying covariate with an extended kaplan-meier estimator. *The American Statistician*, 59(4):301–307.

Tsai, W.-Y., Jewell, N. P., and Wang, M.-C. (1987). A note on the product-limit estimator under right censoring and left truncation. *Biometrika*, 74(4):883–886.

Youlden, D. R., Baade, P. D., Soyer, H. P., Youl, P. H., Kimlin, M. G., Aitken, J. F., Green, A. C., and Khosrotehrani, K. (2016). Ten-year survival after multiple invasive melanomas is worse than after a single melanoma: a population-based study. *Journal of Investigative Dermatology*, 136(11):2270–2276.

Acknowledgments

Nicholas P. Jewell University of California, Berkeley

Thank you. Questions?

- Nonparametric estimators of survival (even the NP-MLE) displays bias under this data-generating mechanism.
- The Cox proportional hazards model provides a way to mitigate this bias but comes with assumptions that are difficult to verify in practice.
- Youlden provides an approach that appears intuitive but fails to approach the parameter of interest.
- Jewell provides a correction for employing the Kaplan–Meier estimator in this setting.