Nonparametric Reinforcement Learning for Survival Outcomes

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Precision Medicine

- (Statistical) precision medicine
  - Data-driven decision support for treating patients in the presence of heterogeneity (dynamic treatment regimes or DTRs)
  - Treatment can include drug choice, administrative actions, dosing, timing, potentially modifiable risk factors, and/or other potentially beneficial actions to the patients
  - Must be reproducible and generalizable (empirically and inferentially valid)

Operating Principles

- Observable Constituents:
  - Tailoring variables (X)
  - Choice of treatments and/or potentially modifiable risk factors (A)
  - Vector of outcomes or utilities (R)
  - Could be multiple (X, A, R) triples over time for each patient
- Dynamic Treatment Regime (DTR):
  - Single decision: make a single recommendation for treatment
  - Multiple decision: make a series of interdependent recommendations
  - Continual monitoring: for diabetes, mHealth

Heterogeneity

- Role of Heterogeneity in the data:
  - Heterogeneity of patients is beneficial (essential) for good precision medicine analysis so that estimated treatment rules are broadly applicable
  - Need heterogeneity of treatment assignment (either naturally or by design) in the data so we can determine best treatment under a variety of situations

Outline of Overall Pipeline

- Dynamic Treatment Regime:
  - $\pi(X)$ gives recommended A to maximize R in future patients
  - Regression: model R as a function of X and A ($Q(X, A) = E[R|X, A]$ is the "value"), with interaction between X and A being most important
  - Policy estimation: directly estimate $\pi(X)$ without necessarily needing $Q(X, A)$ (e.g., outcome weighted learning)
  - Prediction versus prescriptive decision support:
    - Suppose $R = f(X) + Ag(X) + e$, where bigger R is better and $A = \{0 \text{ or } 1\}$
    - We only care about $g(x)$, since rule $\pi(X) = \{1 \text{ if } g(X) > 0, \text{ 0 otherwise}\}$ yields optimal decision
    - A focus on prediction may yield information inefficiency through focus on $f(X)$ instead of $g(X)$

The Multi-Decision Setting

- The multi-decision setting:
  - Two or more opportunities for treatment decisions (i.e., cancer treatment involving multiple lines of chemotherapy, other chronic diseases, etc.).
  - Interventions can affect patients in multiple ways
    - Immediate effects (proximal)
    - Delayed effects (distal): sometimes the best treatment is initially harmful but sets the patient up for a better response to certain future treatments

Multi-Decision Setting, cont.

- The basic ingredients:
  - The data: $(X_1, A_1, R_1, \ldots, X_K, A_K, R_K)$, where
    - $X_1 \in \mathcal{X}_1$ denotes baseline information
    - $X_k \in \mathcal{X}_k$ denotes interim information collected during treatment stages $k = 2, \ldots, K$
    - $A_k \in \mathcal{A}_k$ denotes treatment and
    - R_k denotes proximal outcome measured after treatment at stage k,
    - for $k = 1, \ldots, K$.
  - Define $H_1 = X_1$ and $H_k = (H_{k-1}, A_{k-1}, R_{k-1}, X_k)$ so that H_k is the available patient history at time k before new action.
  - The data used for analysis is now $(H_1, A_1, R_1, \ldots, H_K, A_K, R_K)$.

DTR Estimation for the Multi-Decision Setting

The Bellman equation and Q-learning

- $Q_k^{\pi}(h,a) =$
  $E[R_k + Q_{k+1}^{\pi}(H_{k+1}, A_{k+1} = \pi_{k+1}(H_{k+1})) \mid H_k = h, A_k = a],$
  $k = K-1, K-2, ..., 1,$

  where π is a certain policy that maps
  $\mathcal{H} \equiv (\mathcal{H}_1, ..., \mathcal{H}_k) \mapsto \mathcal{A} \equiv (\mathcal{A}_1, ..., \mathcal{A}_k)$.

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  $\mathcal{H} \equiv (\mathcal{H}_1, ..., \mathcal{H}_k) \mapsto \mathcal{A} \equiv (\mathcal{A}_1, ..., \mathcal{A}_k)$.

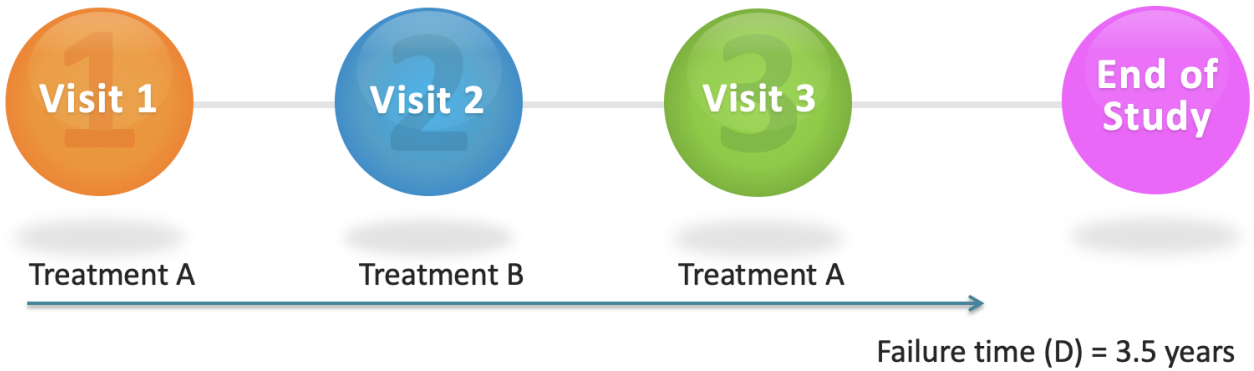
- Q-learning recursively finds the optimal policy as
  $\pi_k^*(h) = \arg\max_{a \in \mathcal{A}_k} Q_k^{\pi^*}(h,a), \quad k = K, K-1, ..., 1.$

Q-learning for the Multi-Decision Setting

- Regress R_K onto (H_K, A_K) to obtain an estimate of $E[R_K|H_K = h, A_K = a]$, denoted $\hat{Q}_K(h, a)$.
- For each individual, compute $\hat{R}_K = \sup_{a \in \mathcal{A}_K} \hat{Q}_K(H_K, a)$.
- Proceeding backwards from $k = K - 1$ to $k = 1$, do the following:
  - Regress $R_k + \hat{R}_{k+1}$ onto (H_k, A_k) to obtain an estimate of $E[R_k + \hat{R}_{k+1}|H_k = h, A_k = a]$, denoted $\hat{Q}_k(h, a)$.
  - For each individual, compute $\hat{R}_k = \sup_{a \in \mathcal{A}_k} \hat{Q}_k(H_k, a)$.

  The estimated optimal dynamic treatment regime is then $\hat{\pi}_k(h_k) = \arg\max_{a \in \mathcal{A}_k} \hat{Q}_k(h_k, a)$, for $k = 1, \ldots, K$.

Dynamic treatment regimes (DTR) for survival outcomes



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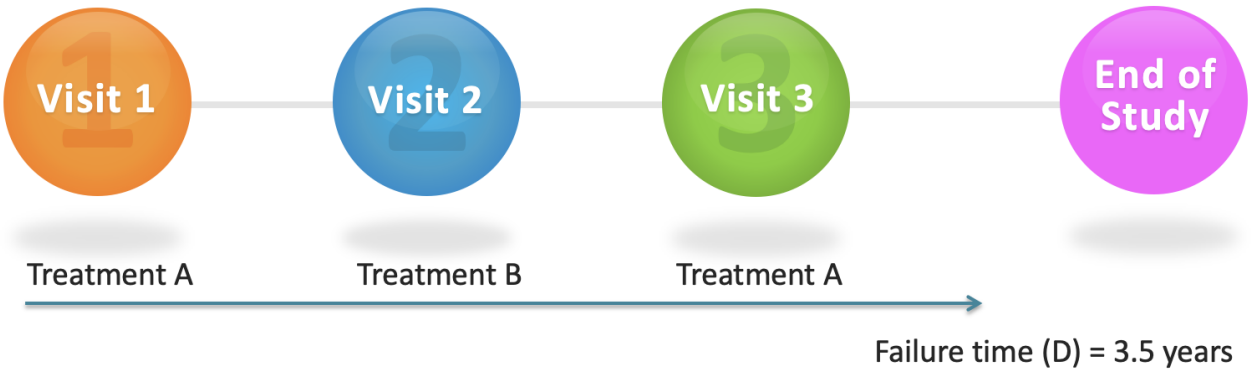

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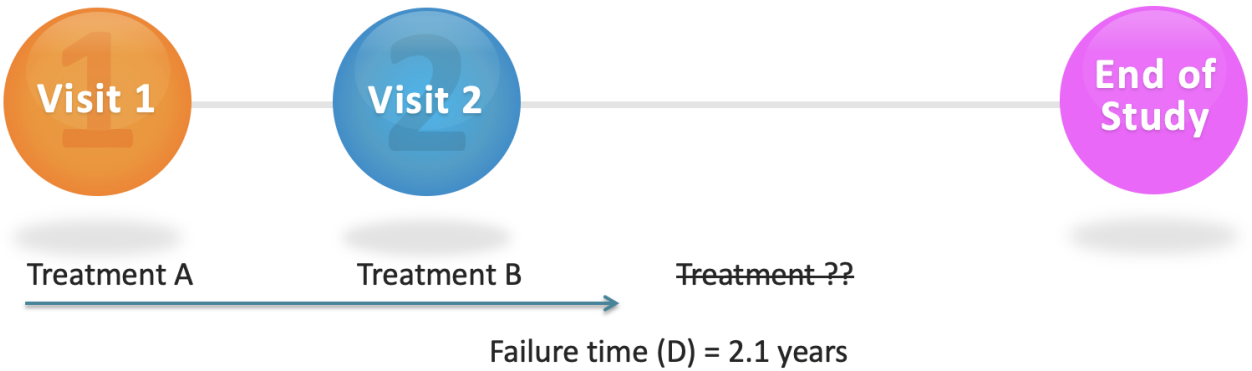

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Challenges:

- Number of stages differ (failure or dropout before all planned visits).
- How to do backward recursion for survival data?

DTR for survival outcomes – Literature

How was censoring handled in the literature?
Goldberg and Kosorok (2012)

- modified data without loss or addition of information
  - The time increments ($R_k = T_k$) after censoring/failure are left as zero
  - The history after censoring/failure is set as $H_k = \emptyset$
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However, *independent censoring* was assumed.

DTR for survival outcomes – Literature, continued

Several other relevant methods.

method	$\lvert\mathcal{A}_k\rvert$	failure time	policy class	censoring	criterion
Goldberg et al (2012)	finite	nonparametric	flexible	$C \perp T_k$	$E[T]$
Huang et al (2014)	finite	AFT	linear	CI	$E[T]$
Simoneau et al (2019)	2	AFT	linear	CI	$E[T]$
Jiang et al (2017)	2	PH	linear	CI	$S(t)$

- $|\mathcal{A}_k|$, the number of treatment arms at stage k.
- criterion, the target value being optimized.
- AFT, accelerated failure time; PH, proportional hazards; CI, conditional independence.
- $E[T]$, mean (truncated) survival time; $S(t)$, survival probability at time t.

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DTR for survival outcomes – the proposed method

The proposed method.

- Nonparametric Q-function estimation (random forest).
- Censoring mechanism: covariate-conditionally independent.
- The outcome of interest $= \phi(S)$, some function of the survival probability;
  $\phi(S)$ can be the (truncated) mean survival time ($E[T \wedge \tau]$) or survival probability at a certain time t ($S(t)$).

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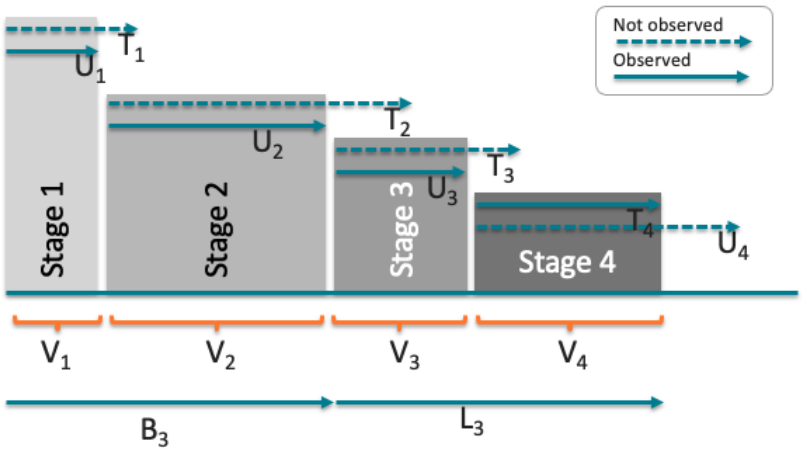
  $\phi(S)$ can be the (truncated) mean survival time ($E[T \wedge \tau]$) or survival probability at a certain time t ($S(t)$).
- Backward recursion $\Rightarrow$ Slightly more general than Q-learning

DTR for survival outcomes - Notation



- K treatment stages $(A_k \in \mathcal{A}_k,\ k = 1, 2, ..., K)$.
- (T_k, U_k) are the times to failure and the next treatment at Stage k.
- $V_k = T_k \wedge U_k$.
- $\gamma_k = 1(T_k \leq U_k)$.
- L_k = "the remaining life" after start of Stage k.
- B_k = time elapsed before k.

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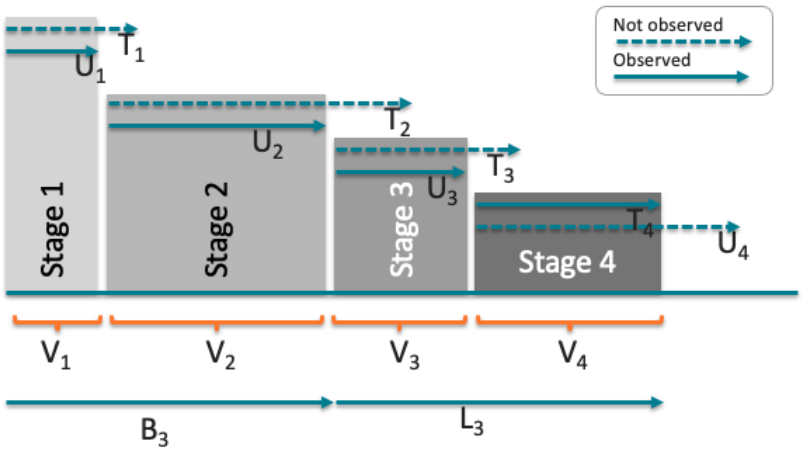

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$$L_k = V_k + (1 - \gamma_k)L_{k+1} \qquad \text{for } k < K - 1.$$

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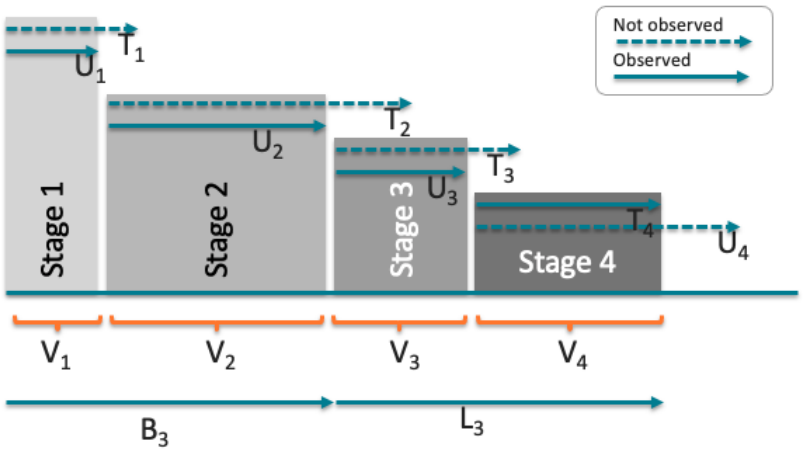

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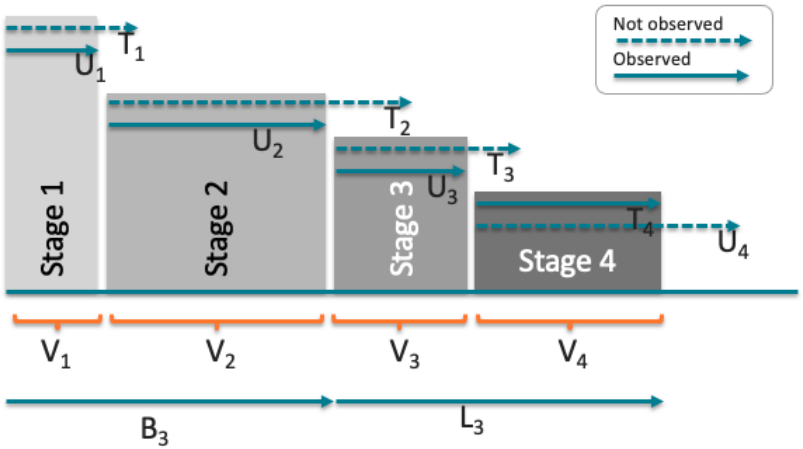
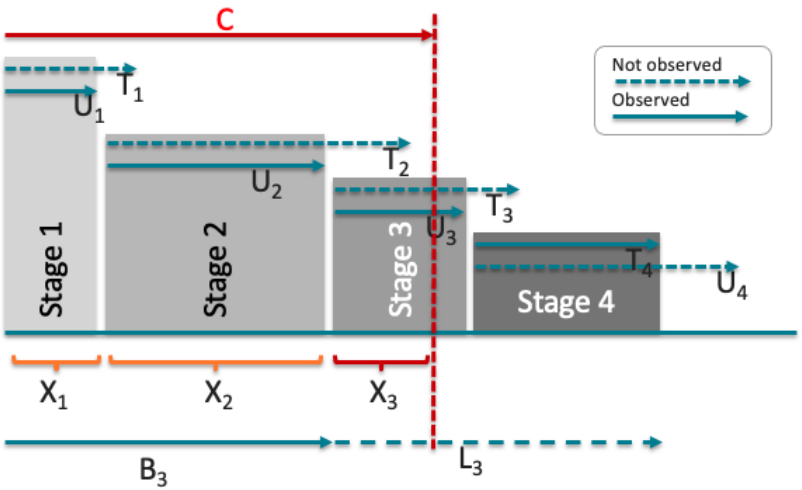
- L_k^* = the remaining life, were the optimal treatments given in later stages $(k' > k)$.

DTR for survival outcomes - Notation, continued



- $X_k = \min(\underbrace{T_k, U_k}_{\wedge = V_k}, C - B_k)$
  is the observed stage length.
- $\delta_k = 1(V_k \leq X_k)$.

DTR for survival outcomes - Notation, continued



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DTR for survival outcomes - Overview of the estimator

- Backward recursion: Start from stage $K, K-1, ..., 1$.
- For stage k,
  - Estimate S_k (the "*cumulative*" survival curves): $\hat{S}_k(t \mid H_k, A_k = a)$
  - Find $\hat{\pi}_k$ (the stage k decision rule):
    $\hat{\pi}_k(h) = \arg\max_a \phi(\hat{S}_k(...|H_k = h, a))$
  - Augmentation: Add the previous stage length to the optimized curve when $\gamma_{k-1} = 0$. $X_{k-1} + L_k^*$ where $L_k^* \sim \hat{S}_k^{\hat{\pi}_k}$.
- The final rule: $\hat{\boldsymbol{\pi}} = (\hat{\pi}_1, \hat{\pi}_2, ..., \hat{\pi}_K)^\top$.

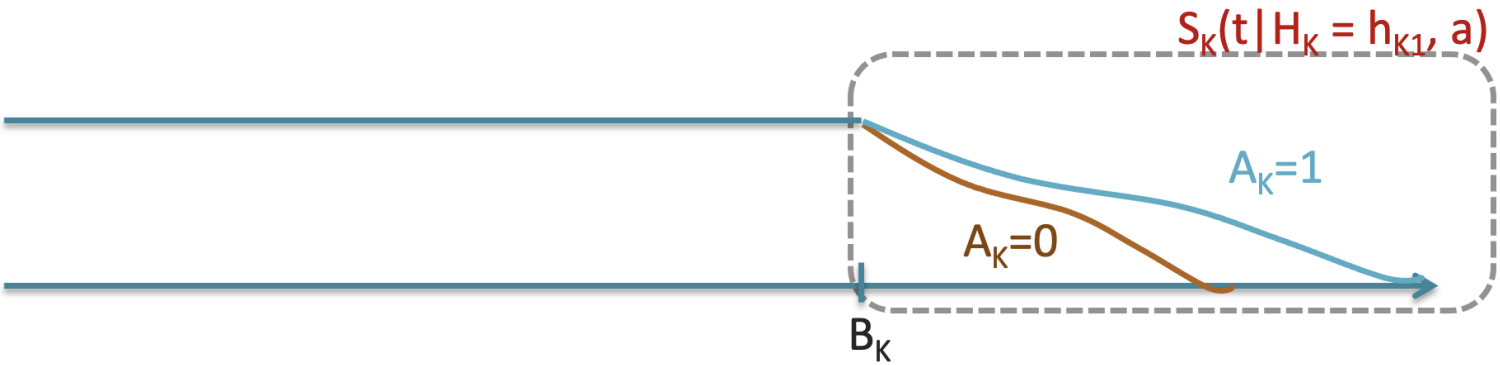
DTR for survival outcomes - some details

The terminal stage estimator ($k = K$)

- $S_K(t|H_K, A_K)$: the 'terminal stage' survivor function of $L_K(= T_K)$.
- Estimated using random survival forest.
- The optimal ITR estimator for stage K is,

$$\hat{\pi}_K(h_K) = \arg\max_{a \in \mathcal{A}_K} \phi(\hat{S}_k(t - B_k|H_K = h_K, A_K = a)).$$

DTR for survival outcomes - illustration



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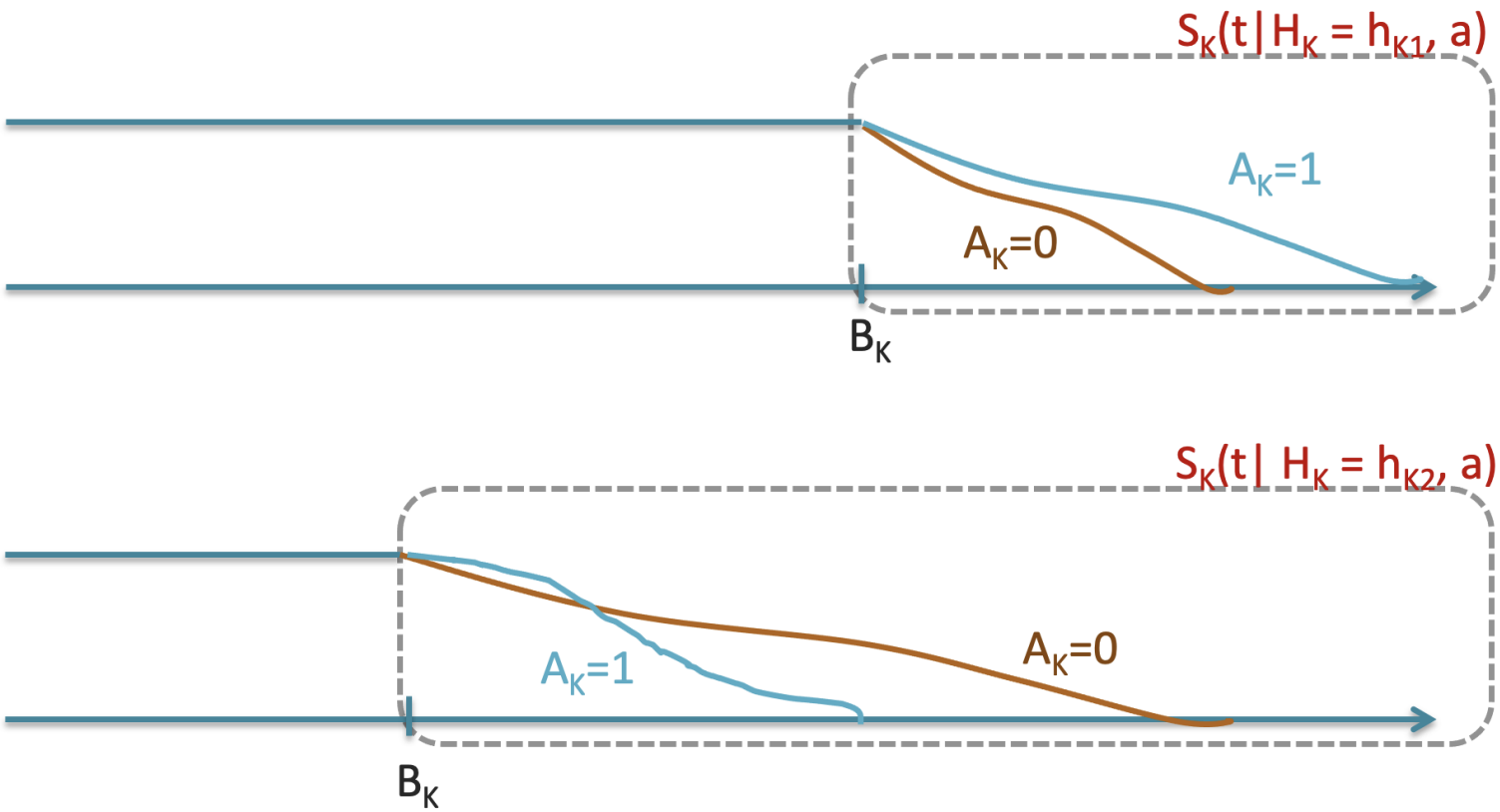

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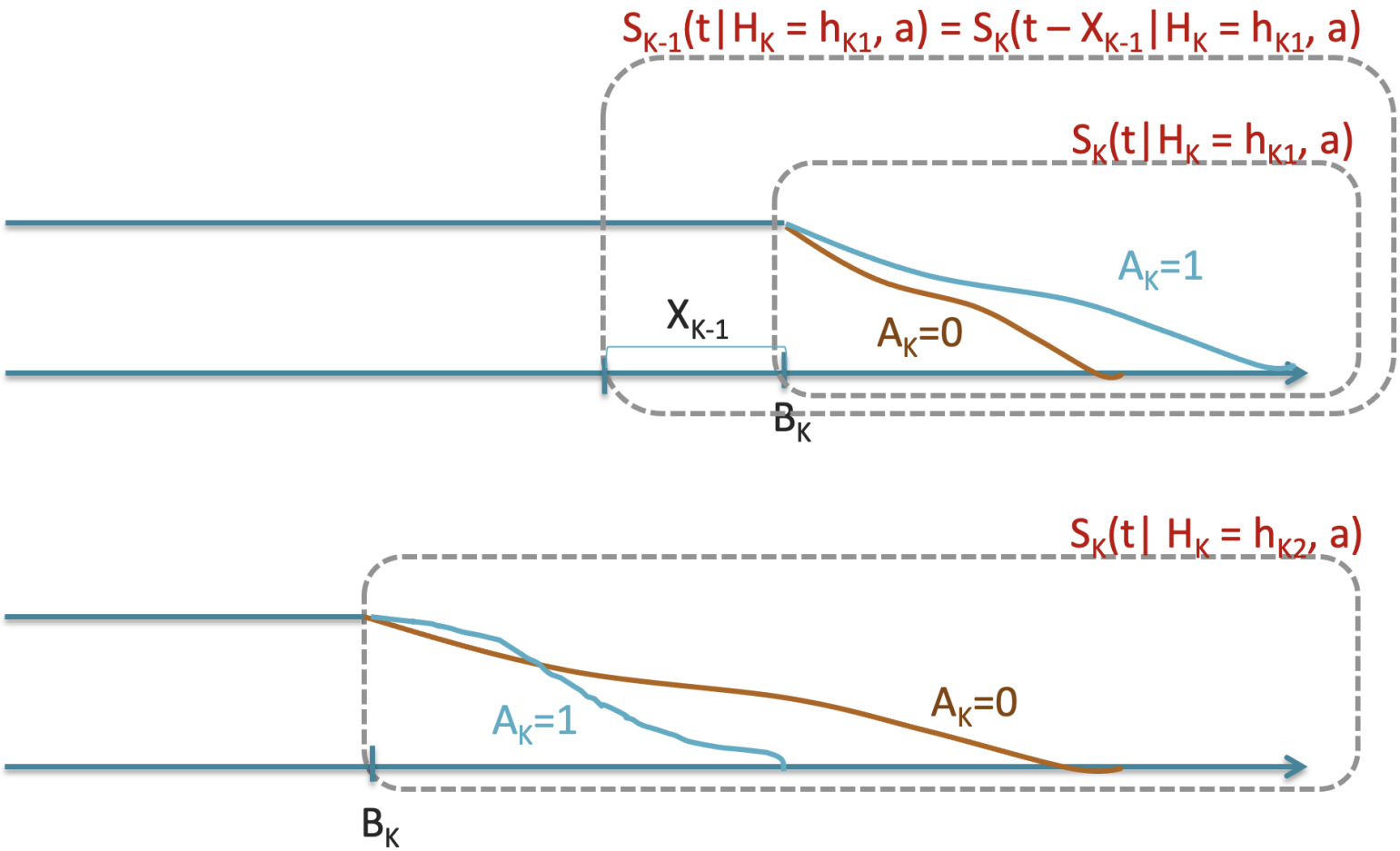

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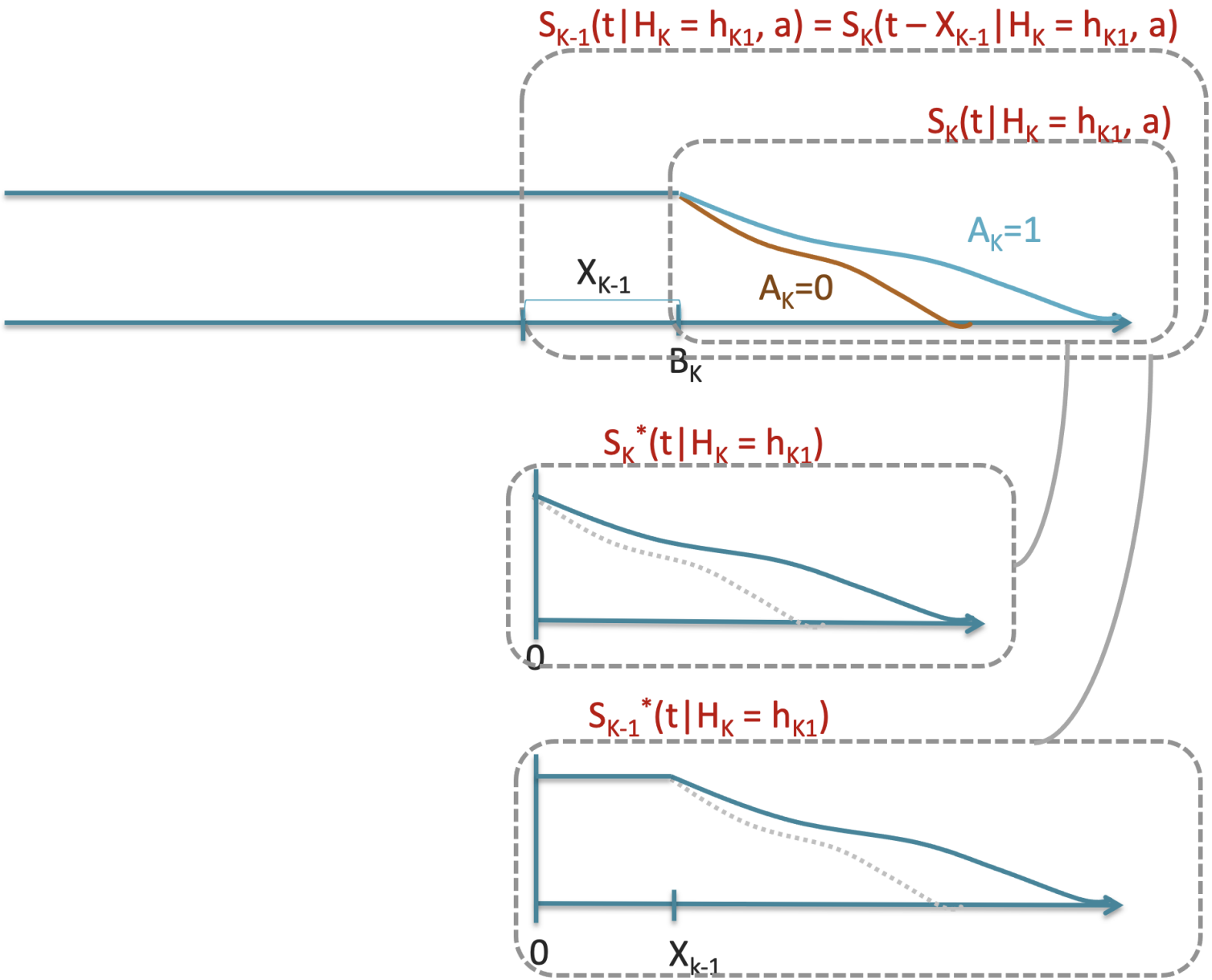


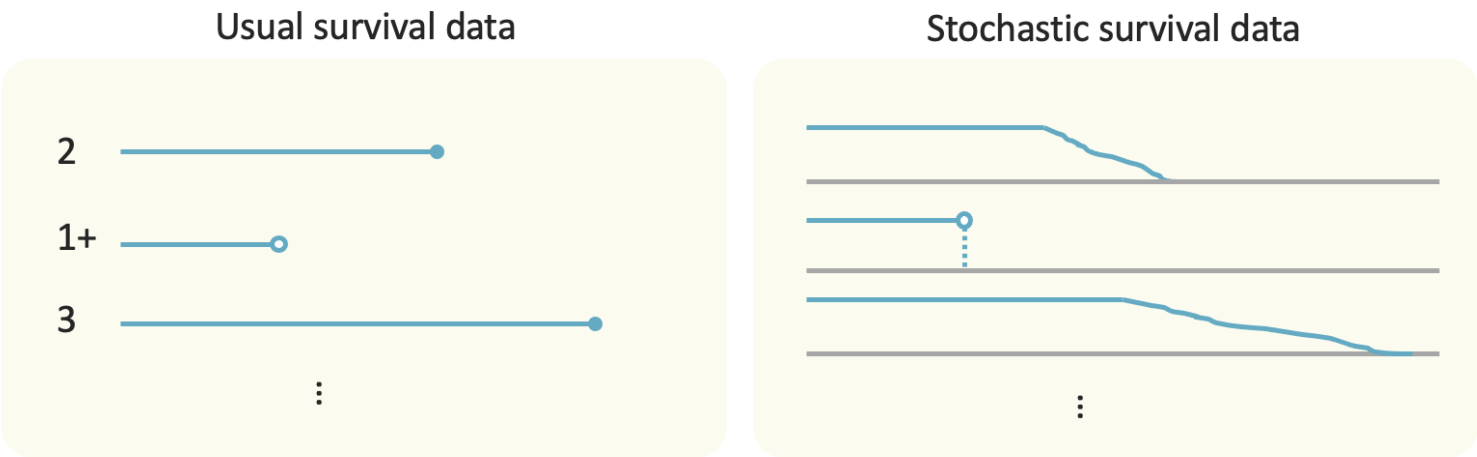
DTR for survival outcomes - The estimator, continued

For earlier stages. Consider stage $k < K$.

- stage length X_k at k is augmented by $\hat{S}^*_{k+1}$.
  This is done by using $\hat{S}^*_{k+1}(t - X_k | H_k, A_k)$ for each individual.
  (For those censored during stage k, no augmentation is needed.)

- Now the survival distribution of L_k is estimated using the stochastically augmented intervals $\{\hat{S}^*_{k+1}(t - X_{k,i} | H_{k,i}, A_{k,i})\}_i$.

DTR for survival outcomes - Generalized random forests



- Generalized random survival forests are used.
  Modified splitting rules, Modified Kaplan-Meier at terminal nodes
- Properties: uniform consistency under certain regularity conditions.
- Simulations validate theory, is effective in example application.

DTR for survival outcomes - Theoretical results

Theorem

Assuming the conditions that follow, the value $\mathcal{V}$ of the estimated optimal dynamic treatment regime, $\hat{\boldsymbol{\pi}}$, is consistent for the truth. I.e.,

$$|\mathcal{V}(\hat{\boldsymbol{\pi}}) - \mathcal{V}(\boldsymbol{\pi}_*)| \to_P 0,$$

as $n \to \infty$, where the value ($\mathcal{V}(\boldsymbol{\pi})$) is either the restricted mean survival time ($E[T^{\boldsymbol{\pi}} \wedge \tau]$) or the survival probability at a certain time ($S^{\boldsymbol{\pi}}(t_0)$).

DTR for survival outcomes - Theoretical results, assumptions

Assumptions for each stage k:

1. Stable unit treatment value assumption — SUTVA
2. $A_k \perp T_k^a \mid H_k, \forall a \in \mathcal{A}_k$ — sequential ignorability
3. $\Pr(A_k = a \mid H_k = h) > L_1 \quad \forall a, h, \exists L_1 > 0.$ — positivity
4. $\Pr(U_k < T_k \wedge C_k | \boldsymbol{h}) > M, \quad \forall \boldsymbol{h} \in \mathcal{H}_k, \exists M > 0.$ — completion
5. $|S_k(t \mid \boldsymbol{h}_1) - S_k(t \mid \boldsymbol{h}_1)| \leq L_S \|\boldsymbol{h}_1 - \boldsymbol{h}_2\|,$ $|G_k(t \mid \boldsymbol{h}_1) - G_k(t \mid \boldsymbol{h}_1)| \leq L_G \|\boldsymbol{h}_1 - \boldsymbol{h}_2\|,$ $\forall \boldsymbol{h}_1, \boldsymbol{h}_2, \exists 0 < L_S, L_G < \infty.$ — Lipschitz continuity
6. $1/\zeta \leq f_{H_k}(h) \leq \zeta$ — weak dependence
7. $n_{\text{min}} \to \infty$ with $\frac{\log n \log\log n}{n_{\text{min}}} \to \infty$ — terminal node size
8. Regular and random-split trees — less greedy splitting

DTR outline of proof

- We use error bounding methods given in Murphy (2005) and Goldberg and Kosorok (2012) to bound the DTR error by the uniform accuracy of the nonparametric survival estimator at each $1 \leq k \leq K$.
- Specifically, we show that

$$\mathcal{V}(\pi_*) - \mathcal{V}(\hat{\pi}) \leq \sum_{k=1}^{K} c_k(\phi) \times \sqrt{\sup_{h_k, a_k, t \in [0,\tau]} \left| \hat{S}_k\left(t \,|h_k, a_k\right) - S_k\left(t \,|h_k, a_k\right) \right|},$$

  where $c_k(\phi)$ are constants that depend on the reward function ϕ.
- We then establish the needed uniform consistency and convergence rates.

Uniform consistency of survival estimators - Theoretical results

Theorem

Suppose the assumptions hold. Let $\hat{\boldsymbol{S}} = (\hat{S}_1, ..., \hat{S}_2, ..., \hat{S}_K)$ *be the sequence of the generalized random survival forest estimators of* $\boldsymbol{S} = (S_1, ..., S_k, ..., S_K)$ *such that the* k*th stage random survival forest is built based on* $\hat{S}_{k+1}$ *for* $k = 1, 2, ..., K-1$*. Then,*

$$\sup_{t \in [0,\tau], \boldsymbol{h} \in \mathcal{H}_k, k \in \{1,2,...,K\}} |\hat{S}_k(t \mid \boldsymbol{h}) - S_k(t \mid \boldsymbol{h})| \to 0,$$

in probability as $n \to \infty$.

Survival consistency outline of proof

- Results follow from uniform consistency of each $\hat{S}_k$, beginning with $k = K$ and going backwards to $k = 1$.
- We use Z-estimator consistency based on identifiably of the estimating equation (i.e., showing that if the expected Z-function, evaluated at θ_n, goes to zero uniformly over the index, then this forces $\|\theta_n - \theta_0\| \to 0$) combined with uniform consistency of the empirical Z-function (see, e.g., Theorem 2.10 of Kosorok, 2008).
- We use VC-dimension bounded kernel representations of the random forests based on axis-aligned rectangles to obtain consistency of the empirical Z-function.

Uniform convergence rate of survival estimators - Theoretical results

Theorem

Suppose the assumptions hold plus a few additional assumptions. Then, for any $k = 1, 2, ..., K$*, there exists an* $1 \leq n_0 < \infty$ *such that for all* $n > n_0$ *the following holds with probability* $\geq 1 - \frac{3(K-k+1)}{\sqrt{n}}$*:*

$$\begin{aligned}
&\sup_{t \leq \tau, \boldsymbol{h}_k} |\hat{S}_k(t; \boldsymbol{h}_k) - S_k(t; \boldsymbol{h}_k)| \\
&\leq \sum_{l=k}^{K} \frac{11}{c_1} \sqrt{\frac{\log(\frac{n}{n_{\min}})\{\log(d_l n_{\min}) + 3\log\log(n)\}}{n_{\min} \log((1-\alpha)^{-1})}} \\
&\quad + \zeta L_S \left\{ \frac{2n_{\min}}{n} \right\}^{\frac{\log((1-\alpha)^{-1})}{\log(\alpha^{-1})} \frac{0.991\varphi}{d_l}},
\end{aligned}$$

where the constants come from the assumptions.

Uniform convergence rate of survival estimators - Theoretical results, cont.

Theorem

In the context of the previous theorem, $n_{\min}$ and the the other tuning parameters can be chosen so that, for some $\eta > 0$,

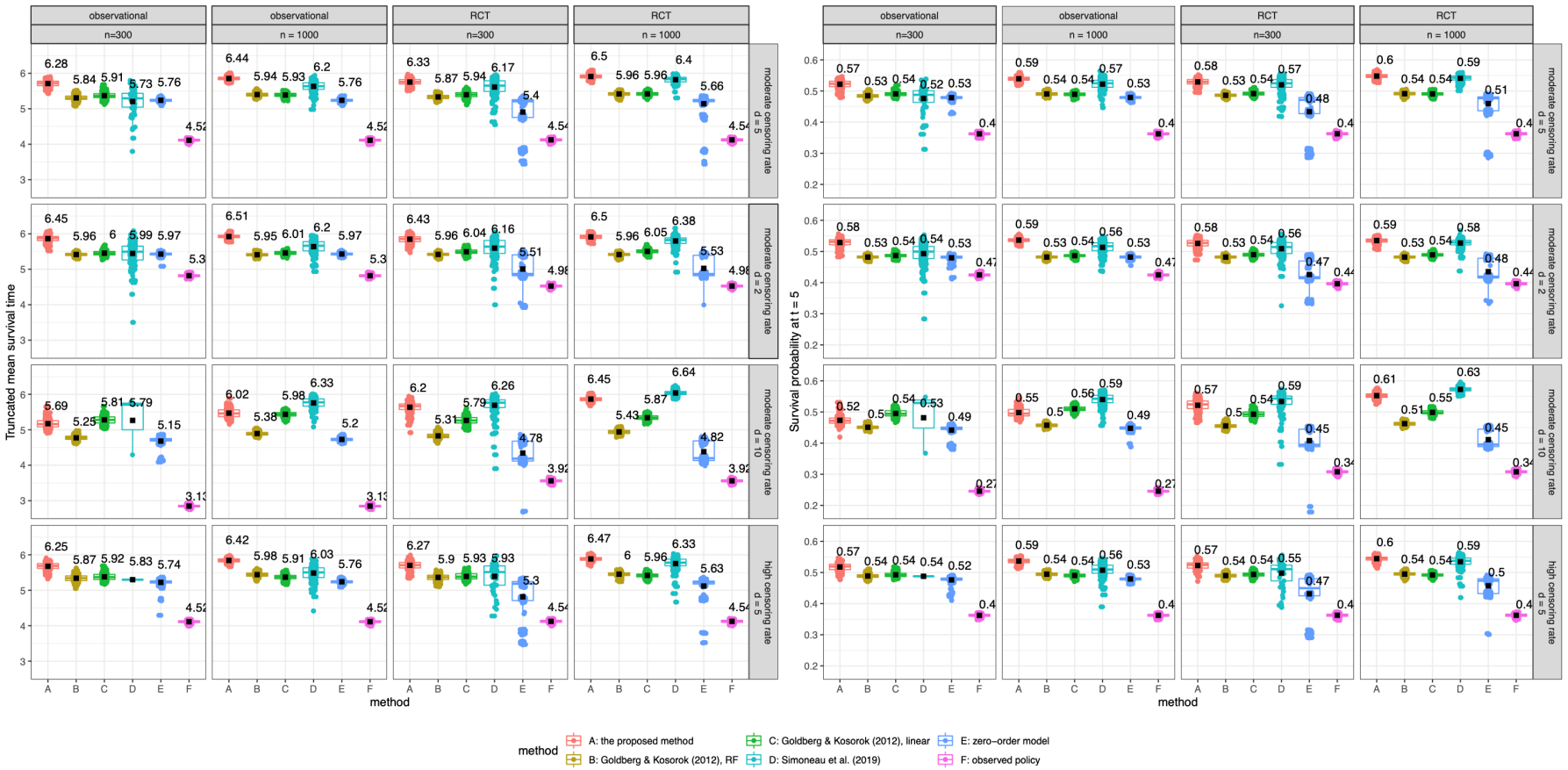
$$\sup_{t \leq \tau, \boldsymbol{h}_k} |\hat{S}_k(t; \boldsymbol{h}_k) - S_k(t; \boldsymbol{h}_k)| = O_P(n^{-\eta}),$$

and

$$\mathcal{V}(\pi_*) - \mathcal{V}(\hat{\pi}) \leq O_P(n^{-\eta/2}).$$

Thus the convergences rates are polynomial in n.

Simulation results

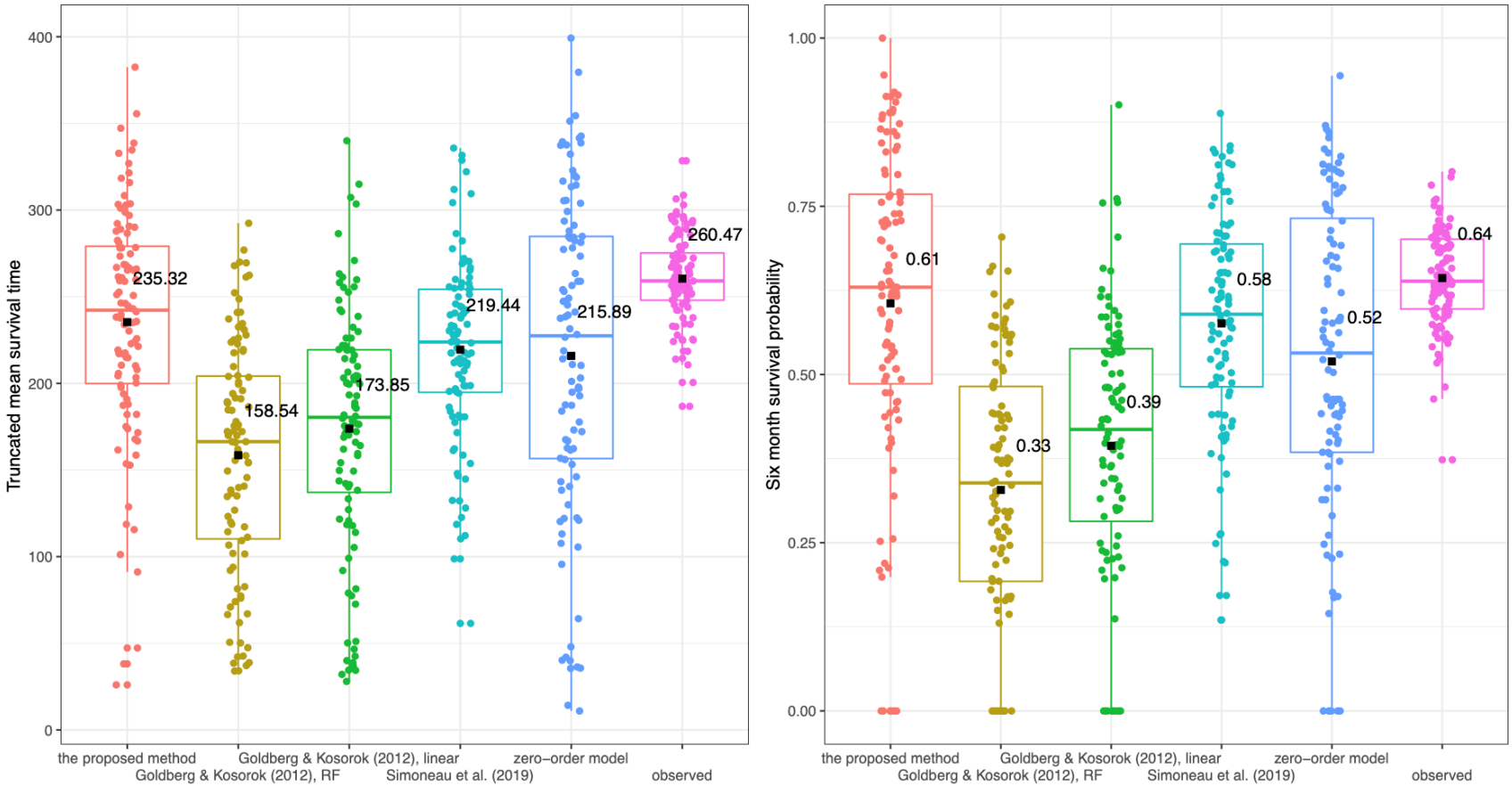


from Cho, Holloway and Kosorok (2020)

Leukemia clinical trial results

- We applied these methods to an acute myeloid leukemia clinical trial with survival as an outcome (Wahed & Thall, 2013; Xu et al, 2016).
- 210 patients were randomized to frontline treatment (4 possibilities) followed by salvage treatment (2 classes) adaptively chosen by clinicians based on patient status.

Leukemia clinical trial results, cont.



from Cho, Holloway and Kosorok (2020)

DTR for survival outcomes - Discussion

- Clinicians appear to be making treatment selection effectively.
- Composite criterion
  - Optimize $S(t)$ first and, if tied, use $E(T)$ as the second criterion.
- Non-Markov assumption: History matters.
  However, the disease dynamics need to be stationary within a treatment stage.

DTR for survival outcomes–Collaboration, status, and Acknowledgement

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- Invited revision for *Biometrika*. Available on arXiv.
- R package `dtrSurv` on CRAN.