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 $\pi(X) = \{1 \text{ if } g(X) > 0, 0 \text{ otherwise}\}$ 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: $(X_1, A_1, R_1, \ldots, X_T, A_T, R_T)$, where
    - $X_1 \in \mathcal{X}_1$ denotes baseline information
    - $X_t \in \mathcal{X}_t$ denotes interim information collected during treatment stages $t = 2, \ldots, T$
    - $A_t \in \mathcal{A}_t$ denotes treatment and
    - R_t denotes proximal outcome measured after treatment at stage t,
    - for $t = 1, \ldots, T$.
  - Define $H_1 = X_1$ and $H_t = (H_{t-1}, A_{t-1}, R_{t-1}, X_t)$ so that H_t is the available patient history at time t before new action.
  - The data used for analysis is now $(H_1, A_1, R_1, \ldots, H_T, A_T, R_T)$.

DTR Estimation for the Multi-Decision Setting

The Bellman equation and Q-learning

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

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

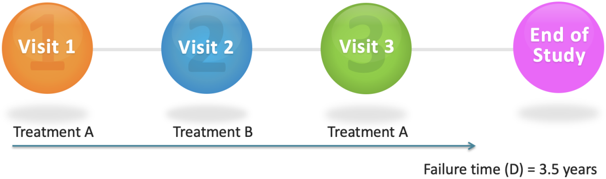
- Q-learning recursively finds the optimal policy as
  $\pi_k^*(h) = \arg\max_{a \in \mathcal{A}_k} Q_k^{\pi^*}(h,a), \qquad k = K, K-1, ..., 1.$

Q-learning for the Multi-Decision Setting

- Regress R_T onto (H_T, A_T) to obtain an estimate of $E[R_T|H_T = h, A_T = a]$, denoted $\hat{Q}_T(h, a)$.
- For each individual, compute $\hat{R}_T = \sup_{a \in \mathcal{A}_T} \hat{Q}_T(H_T, a)$.
- Proceeding backwards from $t = T - 1$ to $t = 1$, do the following:
  - Regress $R_t + \hat{R}_{t+1}$ onto (H_t, A_t) to obtain an estimate of $E[R_t + \hat{R}_{t+1}|H_t = h, A_t = a]$, denoted $\hat{Q}_t(h, a)$.
  - For each individual, compute $\hat{R}_t = \sup_{a \in \mathcal{A}_t} \hat{Q}_t(H_t, a)$.

  The estimated optimal dynamic treatment regime is then $\hat{\pi}_t(h_t) = \arg\max_{a \in \mathcal{A}_t} \hat{Q}_t(h_t, a)$, for $t = 1, \ldots, T$.

Dynamic treatment regimes (DTR) for survival outcomes



Question: Can we find a set of dynamic rules that maximizes the survival outcomes?

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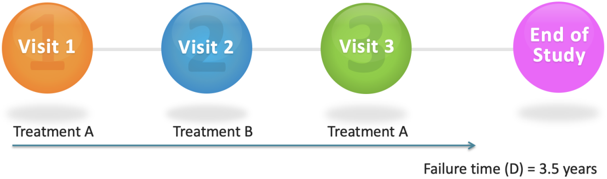

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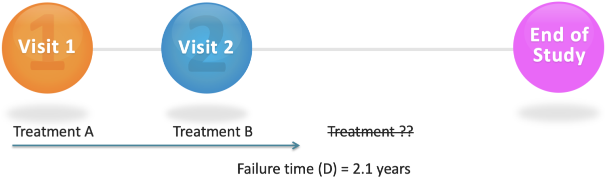

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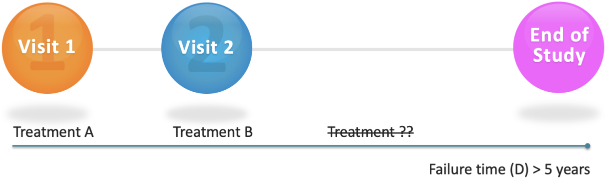

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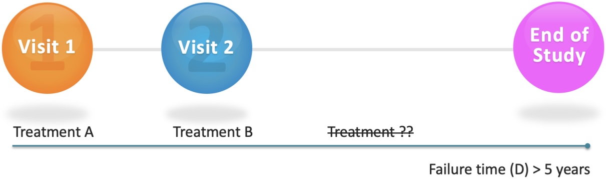

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A potential solution: Q-learning.

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	$S(t)$

- $\lvert\mathcal{A}_k\rvert$, 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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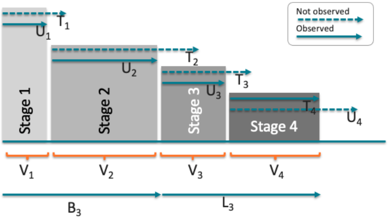
  $\phi(S)$ can be the (truncated) mean survival time ($E[T \wedge \tau]$) or survival probability at a certain time t ($S(t)$).
- Backward recursion ⇒ Slightly more general than Q-learning

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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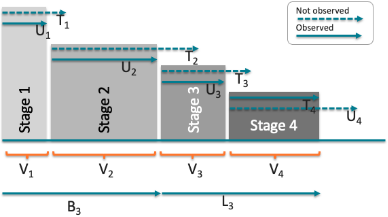

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- L_k can be recursively written as,

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

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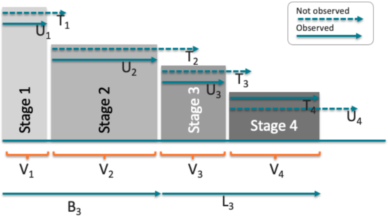

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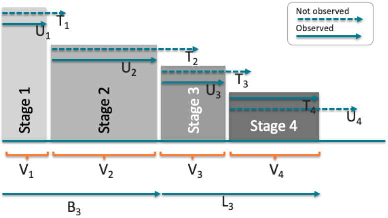
$$L_k = V_k + (1 - \gamma_k)L_{k+1} \qquad \text{for } k < K - 1.$$

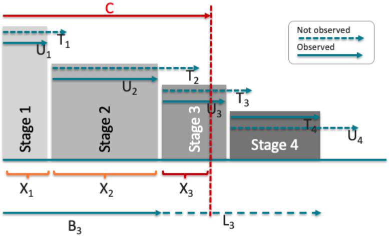
- L_k^* = the remaining life, were the optimal treatments given in later stages $(k' > k)$.

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 $L^*_k \ \sim \hat{S}^{\hat{\pi}_k}_k$.
- The final rule: $\hat{\boldsymbol{\pi}} = (\hat{\pi}_1, \hat{\pi}_2, ..., \hat{\pi}_K)^\top$.

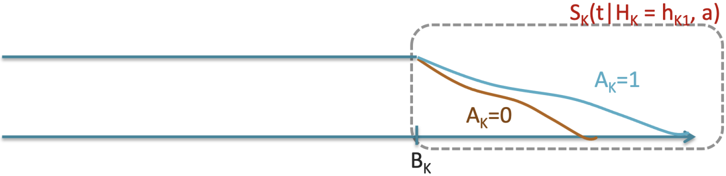
DTR for survival outcomes - some details

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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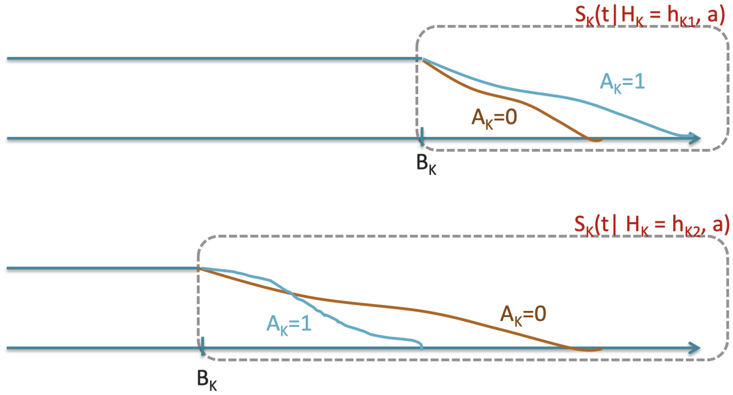

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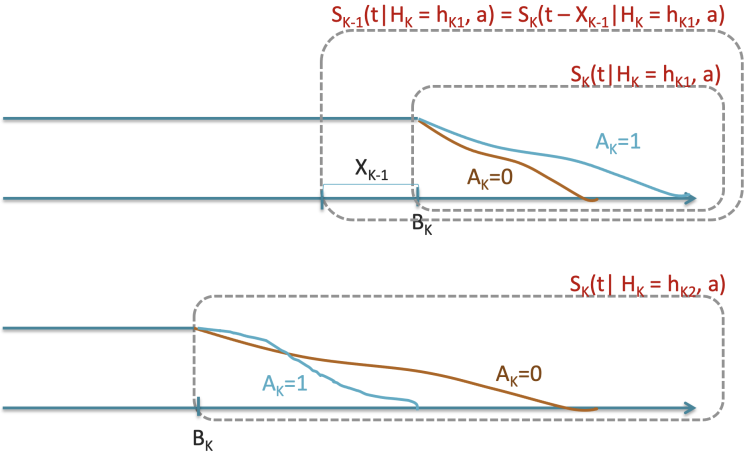
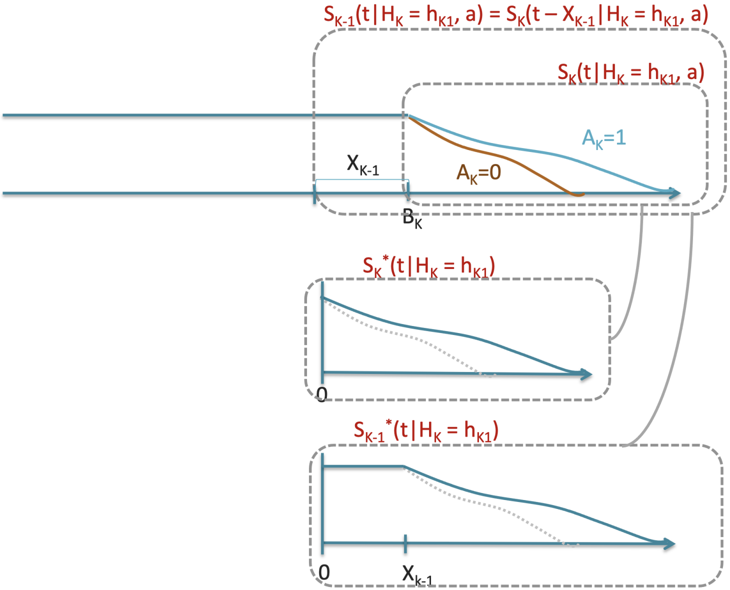

$S_{K-1}(t|H_K = h_{K1}, a) = S_K(t - X_{K-1}|H_K = h_{K1}, a)$
$S_K(t|H_K = h_{K1}, a)$
A_K=1
X_{K-1}
A_K=0
B_K
$S_K(t| H_K = h_{K2}, a)$
A_K=1
A_K=0
B_K

DTR for survival outcomes - illustration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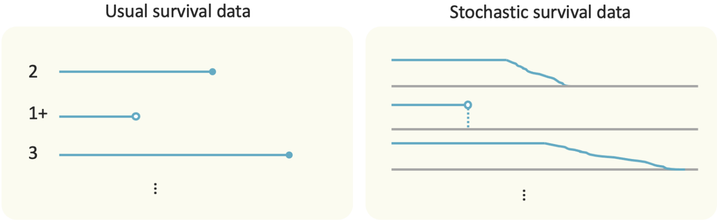
$S_K(t|H_K = h_{K1}, a)$
A_K=1
X_{K-1}
A_K=0
B_K
$S_K^*(t|H_K = h_{K1})$
0
$S_{K-1}^*(t|H_K = h_{K1})$
0
X_{k-1}

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. $|S_k(t \mid \boldsymbol{h}_1) - S_k(t \mid \boldsymbol{h}_1)| \leq L_S \|\boldsymbol{h}_1 - \boldsymbol{h}_2\|,$ Lipschitz continuity
   $|G_k(t \mid \boldsymbol{h}_1) - G_k(t \mid \boldsymbol{h}_1)| \leq L_G \|\boldsymbol{h}_1 - \boldsymbol{h}_2\|,$
   $\forall \boldsymbol{h}_1, \boldsymbol{h}_2, \exists 0 < L_S, L_G < \infty.$
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

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

  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* $\geq 1 - \frac{3(K-k+1)}{\sqrt{n}}$*:*

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

$$\leq \sum_{l=k}^{K} \frac{11}{c_1} \sqrt{\frac{\log(\frac{n}{n_{\min}})\{\log(d_l n_{\min}) + 3 \log\log(n)\}}{n_{\min} \log((1-\alpha)^{-1})}}$$

$$+ \zeta L_S \left\{ \frac{2 n_{\min}}{n} \right\}^{\frac{\log((1-\alpha)^{-1})}{\log(\alpha^{-1})} \frac{0.991\varphi}{d_l}},$$

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 $\eta > 0$,

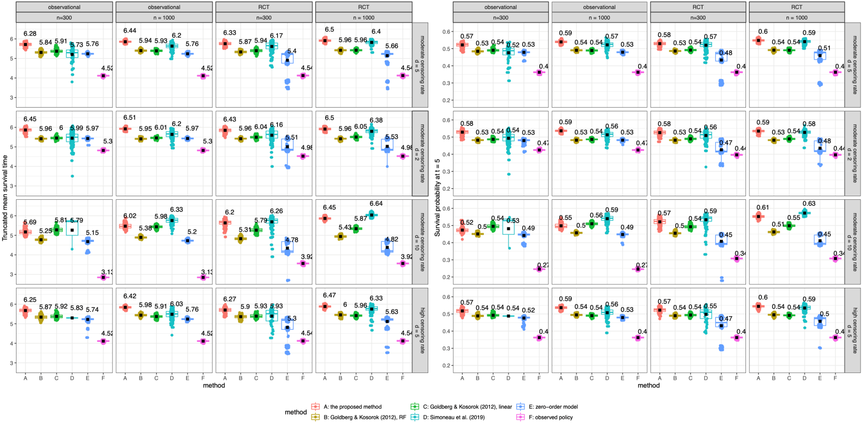
$$\sup_{t \leq \tau, \boldsymbol{h}_k} |\hat{S}_k(t; \boldsymbol{h}_k) - S_k(t; \boldsymbol{h}_k)| = O_P(n^{-\eta}),$$

and

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

Thus the convergences rates are polynomial in n.

Simulation results

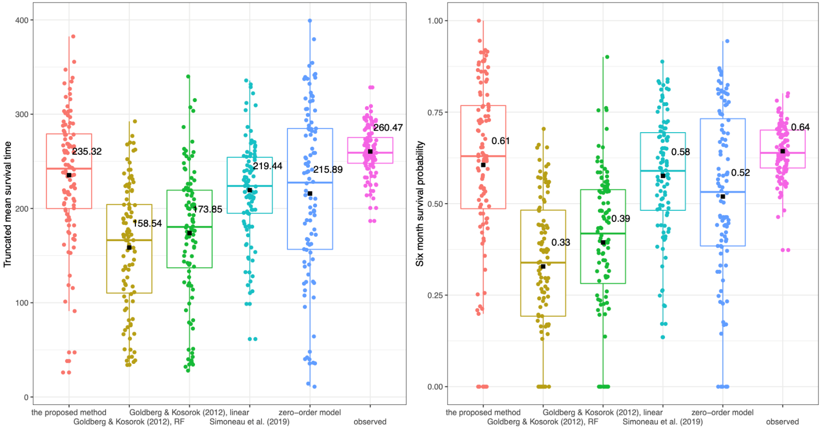


from Cho, Holloway and Kosorok (2020)

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.



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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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