Applications with BART in causal inference part II

Rodney Sparapani
Associate Professor of Biostatistics
Medical College of Wisconsin

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Single-arm phase II trial

Harun, Sparapani et al. 2025 *Head & Neck*

- Head and Neck Squamous Cell Carcinoma (HNSCC) is the sixth most common cancer worldwide
- Treating locally recurrent HNSCC is challenging resulting in high morbidity and poor outcomes
- The standard of care for patients is salvage surgery
- But surgery achieves durable control in $<50\%$ of patients
- Immune checkpoint blockade with PD-1 inhibitors was approved by the US FDA in 2019 (around the time the study ended)
- PD-1 inhibitors have a favorable toxicity profile
- Enrolled a single-arm after 6 months of adjuvant nivolumab following surgery
- A historical control group with surgery alone was identified from electronic medical records for comparison
- 39 treated patients and 66 controls satisfied our study criteria
- disease-free survival (DFS): time from salvage resection to the first evidence of a tumor or all-cause mortality

Rubin's causal model: Potential outcomes framework

Rubin 1974 *Journal of Educational Psychology*
Neyman 1923 *Annals of Agricultural Sciences*

- Suppose we have a dichotomous treatment
  $Z_i = 1$ is treated vs. $Z_i = 0$ is control
- The potential outcome is denoted $Y_i(Z)$, but only one is observed
- $Y_i(Z_i)$ is the observed *actual/factual* outcome
  while $Y_i(1 - Z_i)$ is the unobserved *counter-factual*
- $Y_i = Z_i Y_i(1) + (1 - Z_i) Y_i(0)$

Treatment effects and randomized trials

- For the moment, suppose that we have a randomized clinical trial
- And assume that the types of outcomes considered like mortality or relapse are not appropriate for a cross-over trial
- The Individual Treatment Effect (ITE) is $\boldsymbol{Y_i(1) - Y_i(0)}$
- But obviously only one of these outcomes is observed
- Yet we can calculate the Average Treatment Effect (ATE) like so $\mathbf{E}\left[\boldsymbol{Y_i(1) - Y_i(0)}\right]$

Rubin's causal model: Potential outcomes framework

i. *Stable unit treatment value assumption* (SUTVA). The potential outcome of any patient is unaffected by any other; also known as the assumption of no interference.
ii. *Consistency*. The values of the intervention are well-defined such that a patient's potential outcome under the observed treatment corresponds to their observed outcome.
iii. *Conditional exchangeability*. The conditional probability of receiving a given treatment depends only on the observed baseline covariates, $\boldsymbol{X_i}$, that we denote $\boldsymbol{(Y_i(0), Y_i(1)) \perp Z_i | X_i}$.
iv. *Positivity*. There is a positive probability of receiving treatment given the covariates: $\mathbf{P}[\boldsymbol{Z_i = 1 | X_i}] > \mathbf{0}$.

Treatment effects and potential outcomes

- Suppose we have a Single Arm study with Historical Controls
- For a randomized trial we had: $\mathbf{ITE}_i = Y_i(1) - Y_i(0)$
- And then $\mathbf{ATE} = \mathbf{E}[Y_i(1) - Y_i(0)]$
- But here we get $\mathbf{ITE}_i = \mathbf{E}[Y_i(1) - Y_i(0) | X_i]$
- With $\mathbf{ATE} = \mathbf{E}_X[\mathbf{E}[Y_i(1) - Y_i(0) | X_i]]$

	Randomization	Causal Inference
ITE	$Y_i(1) - Y_i(0)$	$\mathbf{E}[Y_i(1) - Y_i(0) \| X_i]$
ATE	$\mathbf{E}[Y_i(1) - Y_i(0)]$	$\mathbf{E}_X[\mathbf{E}[Y_i(1) - Y_i(0) \| X_i]]$

Survival analysis and potential outcomes

- Here we are interested in time to DFS denoted by Y_i
- The maximum length of follow-up in this study is $L = 36$ months
- And some patients were censored earlier: $C_i \leq 36$
- Therefore, we cannot observe Y_i for everyone
- We can only ascertain $T_i = \delta_i Y_i + (1 - \delta_i)C_i$
  where $\delta_i = \mathbf{I}(Y_i < C_i)$ is the event indicator
- Nevertheless, our interest is for the survival probability:
  $S(t) = \mathbf{P}[Y_i > t]$.
- Define a success (failure) as 1 (0) for no DFS (DFS) at time t
  by the dichotomous temporal process $A_i(t, Z_i) = \mathbf{I}(Y_i(Z_i) > t)$
  where $\mathbf{P}[A_i(t, Z_i) = 1|X_i, Z_i] = S(t|X_i, Z_i)$
- This process is random yielding $\mathbf{1}$ at each success time t:
  $(t \leq T_i, \delta_i = 0)$ or $(t < T_i, \delta_i = 1)$
- Then deterministically $\mathbf{0}$ at/after failure time: $(t \geq T_i, \delta_i = 1)$

Survival analysis and potential outcomes: Consistency

- However, our process $\boldsymbol{A_i(t, Z_i)}$ has to abide by causal *Consistency* (Assumption ii.)
- The potential outcome due to the treatment actually assigned, $\boldsymbol{Z_i}$, must correspond to the observed outcome.

For the factual outcome process, $\boldsymbol{A_i(t, Z_i)}$, we have two cases

Observed $\boldsymbol{\delta_i = 1}$: the process yields successes (1) for times $\boldsymbol{t \in (0, T_i)}$ and failures (0) for times $\boldsymbol{t \in [T_i, L]}$

Censored $\boldsymbol{\delta_i = 0}$: the process yields successes (1) for times $\boldsymbol{t \in (0, T_i]}$ while unobserved for times $\boldsymbol{t \in (T_i, L]}$

Survival analysis and potential outcomes: the individual treatment effect

- The ITE is now defined by $\mathbf{ITE}_i(t) = \mathbf{E}\left[Y_i(1) - Y_i(0) | t, X_i\right]$

If $\delta_i = 1$ or $(\delta_i = 0, t \leq T_i)$, then
$\mathbf{ITE}_i(t) = Z_i(A_i(t,1) - S(t|X_i,0)) + (1 - Z_i)(S(t|X_i,1) - A_i(t,0))$
Else: $\mathbf{ITE}_i(t) = S(t|X_i,1) - S(t|X_i,0)$

- However, notice that each $\mathbf{ITE}_i(t)$ naturally depends on X_i
- Rather, we want the *marginal* that is free of X_i
- Frequentist methods rely on *G-computation* for inference
- These *marginal structural models* employ linear regression
- Linearity is a precarious restrictive assumption we want to avoid

Survival analysis and potential outcomes: the value function marginal

- A marginal technique from optimal treatment rules
- Very similar to Friedman's partial dependence function
- Originally, not a Bayesian idea, but easily adapted
- And here, we extend it to survival analysis
- In this study, t, the time-point of interest is 2 years

$$
\begin{aligned}
\textbf{value}(t, Z^*) &= \mathbf{E}_X \left[\mathbf{E} \left[Y_i(Z) | t, X_i, Z = Z^*(X_i) \right] | t \right] \\
Z^{\textbf{opt}}(t, X_i) &= \arg\max_{Z^*} \mathbf{E} \left[Y_i(Z) | t, X_i, Z = Z^*(X_i) \right] \\
\textbf{value}(t, Z^{\textbf{opt}}) &= \mathbf{E}_{\mathbf{X}} \left[\mathbf{E} \left[Y_i(Z) | t, X_i, Z = Z^{\textbf{opt}}(X_i) \right] | t \right] \\
&\equiv N^{-1} \sum_i \mathbf{E} \left[Y_i(Z) | t, X_i, Z = Z^{\textbf{opt}}(X_i) \right]
\end{aligned}
$$

Qian & Murphy 2011 *Annals of Statistics*
Logan, Sparapani, et al. 2019 *SMMR*

Survival analysis and potential outcomes: the value function and the average treatment effect

Harun, Sparapani et al. 2025 *Head & Neck*

- We chose discrete time BART to estimate $S(t|X_i, Z_i)$
- The value function marginal at the mth MCMC draw $N^{-1}\sum_i \mathrm{ITE}_{im}(t)$ is now free of X_i
- Leading directly to the ATE now defined by
  $\mathrm{ATE}(t) = \mathrm{E}_X\left[\mathrm{E}\left[Y_i(1) - Y_i(0)|t, X_i\right]|t\right]$
  $\widehat{\mathrm{ATE}}(t) = M^{-1}N^{-1}\sum_m \sum_i \mathrm{ITE}_{im}(t)$
- The inner sum above is the value function approach
- And its corresponding $1-\alpha$ level credible interval $\left(\sum_i \mathrm{ITE}_{im_{\alpha/2}}(t), \sum_i \mathrm{ITE}_{im_{1-\alpha/2}}(t)\right)$
- Our R programs are included in the **BART3** package
- `R> system.file("HNSCC", package = "BART3")`
- And the data too: `R> ?hnscc`

Frequentist G-computation

Robins, Hernan and Brumback 2000 *Epidemiology*

- Here is a description of G-computation for comparison
- Admittedly clever, but it feels very contrived
- Conversely, the Bayesian approach seems more elegant
- The first step is a predictive model called a *Q-model*
- Here let $Q(t|X_i, Z) = S(t|X_i, Z)$ to be comparable
- The second step is a *marginal structural model* (MSM)
- To estimate the ATE by linear regression with $2 \times N$ observations

$$\widehat{Y}_i(t,0) = \begin{cases} (1 - z_i)A_i(t,0) + z_i S(t|X_i, Z_i = 0) & \text{if } (\delta_i = 1) \cup (t \le T_i) \\ S(t|X_i, Z_i = 0) & \text{otherwise} \end{cases}$$

$$\widehat{Y}_i(t,1) = \begin{cases} z_i A_i(t,1) + (1 - z_i)S(t|X_i, Z_i = 1) & \text{if } (\delta_i = 1) \cup (t \le T_i) \\ S(t|X_i, Z_i = 1) & \text{otherwise} \end{cases}$$

$$\widehat{Y}_i(t, Z_i) = \beta_0 + Z_i \mathrm{ATE}(t) + \epsilon_i \text{ where } \epsilon_i \overset{\text{iid}}{\sim} \mathrm{N}\left(0,\ \sigma^2\right)$$

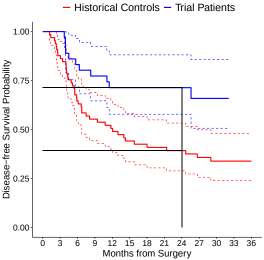
Baseline Characteristics

Total	Single Arm 39		Historical Controls 66	
Age:mean(SD)	66	(9)	61	(11)
Male	27	69%	43	65%
Caucasian	34	87%	59	89%
10+ pack-years	24	62%	51	77%
5+ drinks/week	8	21%	24	36%
Prior chemotherapy	22	56%	39	59%
Larynx	17	44%	23	35%
Oral cavity	14	36%	27	41%
Oropharynx	8	21%	16	24%
ECS	11	28%	17	26%
Positive margins	9	23%	14	21%
PNI	13	33%	28	42%
LVI	10	26%	14	21%
3+ Lymph nodes	3	8%	10	15%
High risk	18	46%	29	44%
Diagnosis year 2011-19 vs. 2002-10	36	92%	49	74%

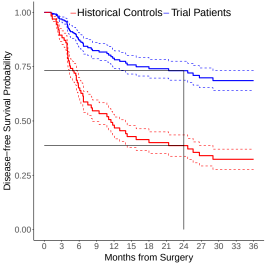
Pocock's Acceptability Criteria of Historical Controls

Pocock's Criteria (paraphrased for brevity on this slide)	Met?
1. Must have received a precisely defined standard treatment the same as the treatment for the randomized controls.	Yes
2. The group must have been part of a recent clinical study which contained the same requirements for patient eligibility.	Yes
3. The methods of treatment evaluation must be the same.	Yes
4. The distributions of important patient characteristics in the group should be comparable with those in the new trial.	Mostly yes
5. The previous study must have been performed in the same organization with largely the same clinical investigators.	Mostly yes
6. There must be no other indications to expect differing results between the randomized and historical controls.	Uncertain

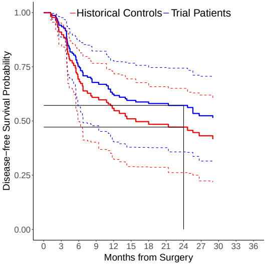
Disease-Free Survival Marginal Effects and ATE



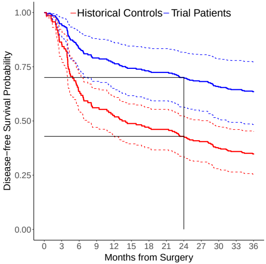
(a) Unadjusted



(b) CPH



(c) RSF



(d) BART

Estimates of 2-year Disease-Free Survival

DFS	Single Arm			Historical Controls		
Unadjusted	0.714	(0.578,	0.881)	0.392	(0.289,	0.533)
CPH	0.731	(0.688,	0.775)	0.387	(0.337,	0.436)
RSF	0.571	(0.357,	0.744)	0.472	(0.262,	0.651)
BART*	0.701	(0.595,	0.807)	0.432	(0.340,	0.535)
DFS differential	Marginal Effect			ATE		
Unadjusted	0.321	(0.129,	0.514)	NA		
CPH	0.345	(0.279,	0.411)	0.202	(0.098,	0.306)
RSF	0.096	(0.068,	0.124)	0.159	(0.070,	0.248)
BART*	0.273	(0.130,	0.412)	0.268	(0.126,	0.406)

* 95% Bayesian credible intervals