Debiased Brier score estimation using TMLE

Anders Munch (with Thomas G., Helene, and Paul)

September 22, 2021

Disclaimer – unfinished work

Mostly theory and not so much implementation and “results”.

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You have the opportunity to influence the project!

Validating risk prediction models

Full data

$X \in \mathbb{R}^p$	Static covariates measured at baseline ($t = 0$).
$T \in \mathbb{R}_+$	Time of event
$t \in \mathbb{R}_+$	Fixed time horizon
$r(t \mid X) \in [0, 1]$	Risk prediction at time t given baseline covariates

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We assume the risk prediction model r is fixed (i.e., non-random); for instance, it could have been fitted on a separate data set. We want to use the data (X_i, T_i), $i = 1, \ldots, n$ to evaluate the performance of r.

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Example

Is a particular bio-marker relevant for predicting the risk of developing some disease within the next two years? Is it relevant when other risk factors are measured?

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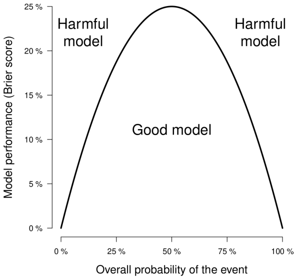
Benchmark prediction	Brier score
50% always	25%
Overall event prob.	See figure
Coin toss	50%
Uniform[0,1]	33%



[Gerds and Kattan, 2021]

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$\Delta \in \{0, 1\}$ Event indicator ($\Delta := \mathbb{1}\{\tilde{T} = T\}$)

Let $(X, T) \sim Q$ and $O := (X, \tilde{T}, \Delta) \sim P$.

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Inverse probability of censoring weights (IPCW)

When $T \perp\!\!\!\perp C \mid X$ the Brier score is identifiable from the observed data[1]:

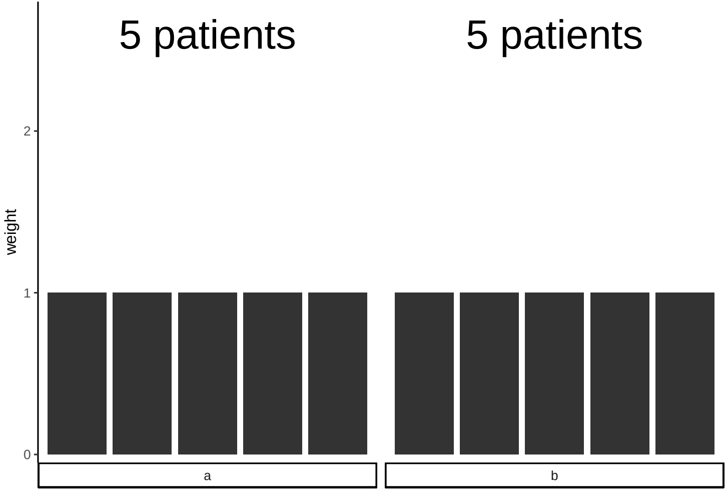
$$\mathbb{E}_Q\left[\{Y(t) - r(r \mid X)\}^2\right] = \mathbb{E}_P\left[W(t)\{Y(t) - r(r \mid X)\}^2\right],$$

with

$$W(t) = \frac{\mathbb{1}(\tilde{T} > t)}{G(t \mid X)} + \frac{\mathbb{1}(\tilde{T} \leq t)\Delta}{G(\tilde{T} \mid X)}.$$

[1] Note that $W(t)\{Y(t) - r(t \mid X)\}^2$ is a function of the observed data, as $Y(t)$ is observed whenever $W(t)$ is non-zero.

Visualizing the reweighting



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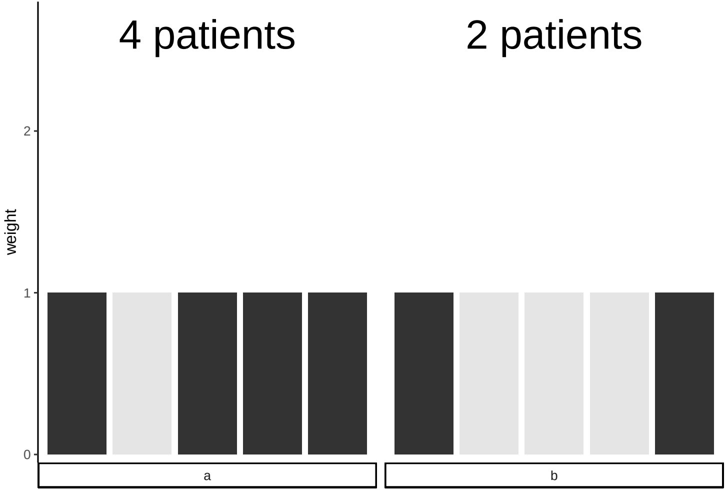

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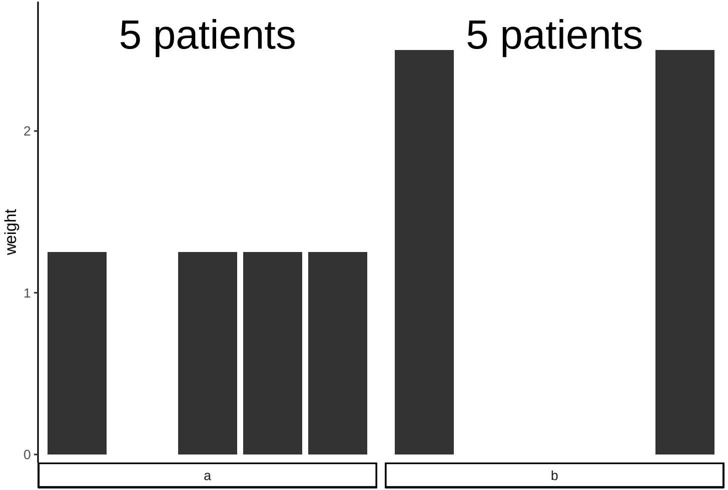

Estimating the Brier score from censored data

By estimating the censoring distribution G we obtain the IPCW estimator

$$\widehat{W}_i(t) = \frac{\mathbb{1}(\tilde{T}_i > t)}{\hat{G}(t \mid X_i)} + \frac{\mathbb{1}(\tilde{T}_i \leq t)\Delta_i}{\hat{G}(\tilde{T}_i \mid X_i)}, \quad \hat{\theta}_n^t = \hat{\mathbb{P}}_n[\widehat{W}_i(t)\,\{Y_i(t) - r(t \mid X_i)\}^2]$$

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- The parametric ($n^{-1/2}$) rate of convergence of $\hat{G}_n$ is obtainable under suitable assumptions on the censoring distribution (for instance random censoring or a Cox model), giving also $n^{-1/2}$ convergence and asymptotic normality of $\hat{\theta}_n^t$.

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- When modeling G with flexible, data-adaptive methods we cannot expect $n^{-1/2}$-rate convergence, and hence the simple plug-in estimator $\hat{\theta}_n^t$ cannot be expected to be $n^{-1/2}$ consistent and asymptotically normal in this setting.

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Can we construct an IPCW estimator using "flexible/data-adaptive" estimation of G?

Brier score estimation with "flexible" censoring modeling

By "flexible" we mean estimators of the censoring distribution not converging at parametric ($n^{-1/2}$) rate. The problem with the plug-in estimation using such nuisance parameter estimators is bias.

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Undersmoothing

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TMLE [van der Laan and Rose, 2011, van der Laan and Rubin, 2006]

TMLE constructs a plug-in estimator that solves the efficient score equation. Typically based on the G-formula, but theoretically this should not be important.

Different ways to the target

The target parameter (average Brier score) can be identified from the observed data using either the censoring or the survival distribution as nuisance parameter:

$$\mathbb{E}_Q\left[\{Y(t) - r(t \mid X)\}^2\right] = \mathbb{E}_P\left[\varphi^t_{\mathrm{IPCW}}(O; G)\right] = \mathbb{E}_P\left[\varphi^t_{\mathrm{alt}}(O; S)\right],$$

with

$$\varphi^t_{\mathrm{IPCW}}(O; G) = \left(\frac{\mathbb{1}(\tilde{T}_i > t)}{G(t \mid X_i)} + \frac{\mathbb{1}(\tilde{T}_i \le t)\Delta_i}{G(\tilde{T}_i \mid X_i)}\right)\{Y(t) - r(t \mid X)\}^2,$$

and

$$\varphi^t_{\mathrm{alt}}(O; S) = (1 - S(t \mid X))\{1 - 2r(t \mid X)\} + r(t \mid X)^2.$$

Representations of the efficient influence function

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$$\varphi^t = \varphi^t_{\mathrm{IPCW}} - \Pi\left[\varphi^t_{\mathrm{IPCW}} \mid \mathcal{T}_G\right],$$

or

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where $\mathcal{T}_G$ and $\mathcal{T}_S$ are the orthogonal components of the tangent space corresponding to the parameters G and S, i.e., $\mathcal{T} = \mathcal{T}_G \oplus \mathcal{T}_S$.

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Both representation can be useful; and starting from one, it might not be complete straightforward to derive the alternative one.

The efficient influence function

The two representations give

$$\begin{aligned}\varphi^t(O; S, G) =& \varphi^t_{\mathrm{IPCW}}(O; G) \\ &+ \{1 - r(t \mid X)\}^2 \int_0^t \frac{M^C(\mathrm{d}s \mid X; G)}{G(s \mid X)} \\ &- \{1 - 2r(t \mid X)\} S(t \mid X) \int_0^t \frac{M^C(\mathrm{d}s \mid X; G)}{G(s \mid X) S(s \mid X)},\end{aligned}$$

and

$$\begin{aligned}\varphi^t(O; S, G) =& \varphi^t_{\mathrm{alt}}(O; S) \\ &+ \left[\int_0^t \frac{M(\mathrm{d}s \mid X; S)}{S(s \mid X) G(s \mid X)}\right] S(t \mid X)(1 - 2r(t \mid X)).\end{aligned}$$

Decomposition

We want to pick the nuisance estimator $\hat{G}_n$ such that the estimator

$$\hat{\theta}_n^t = \tilde{\Psi}^t(\hat{G}_n, \hat{\mathbb{P}}_n) = \hat{\mathbb{P}}_n \left[\varphi^t_{\mathrm{IPCW}}(O; \hat{G}_n)\right]$$

is asymptotically linear (and efficient), i.e., such that

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Let $f^t := -\Pi(\varphi^t_{\mathrm{IPWC}} \mid \mathcal{T}_G)$ and consider the decomposition

$$\begin{aligned}
&\tilde{\Psi}^t(\hat{G}_n, \hat{\mathbb{P}}_n) - \tilde{\Psi}^t(G_P, P) \\
&= \hat{\mathbb{P}}_n \left[\varphi^t_{\mathrm{IPCW}}(O; \hat{G}_n)\right] - \tilde{\Psi}^t(G_P, P) \pm \hat{\mathbb{P}}_n \left[f^t(O; \hat{G}_n, \hat{S}_n)\right] \\
&= \hat{\mathbb{P}}_n \left[\varphi^t(O; \hat{G}_n, \hat{S}_n)\right] - \tilde{\Psi}^t(G_P, P) - \hat{\mathbb{P}}_n \left[f^t(O; \hat{G}_n, \hat{S}_n)\right] \\
&= (\hat{\mathbb{P}}_n - P) \left[\varphi^t(O; \hat{G}_n, \hat{S}_n)\right] + \mathrm{Rem}(\hat{G}_n, \hat{S}_n, P) - \hat{\mathbb{P}}_n \left[f^t(O; \hat{G}_n, \hat{S}_n)\right], \\
&=: (A) + (B) + (C)
\end{aligned}$$

with

$$\mathrm{Rem}(G, S, P) := P[\varphi^t(O; G, S)] - \tilde{\Psi}^t(G_P, P).$$

Donsker condition and remainder term

Donsker class conditions (or sample splitting) gives

$$(A) = (\hat{\mathbb{P}}_n - P)\left[\varphi^t(O; \hat{G}_n, \hat{S}_n)\right] = (\hat{\mathbb{P}}_n - P)\left[\varphi^t(O; G, S)\right] + o_P(n^{-1/2}).$$

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As $\mathrm{Rem}(P, \hat{G}_n, \hat{S}_n) = \tilde{\Psi}^t(\hat{G}_n, P) - \tilde{\Psi}^t(G_P, P) + P[f^t(O; \hat{G}_n, \hat{S}_n)]$ and $f^t(O; \hat{G}_n, \hat{S}_n)$ acts like the derivative of $G \mapsto \tilde{\Psi}^t(G, P)$, a functional Taylor expansion would suggest that

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TMLE focuses on constructing $\hat{G}_n$ such that $(C) = \hat{\mathbb{P}}_n\left[f^t(O; \hat{G}_n, \hat{S}_n)\right] \approx 0.$[2]

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[2] Note that the exact same arguments would hold if we replaced $\varphi^t_{\mathrm{IPCW}}$ with φ^t_{alt} and used $f^t = -\Pi(\varphi^t_{\mathrm{alt}} \mid \mathcal{T}_S)$ instead of $f^t = -\Pi(\varphi^t_{\mathrm{IPWC}} \mid \mathcal{T}_G)$.

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We construct the estimator $\hat{G}$ of G as $\hat{G} = e^{-\hat{\Lambda}_C}$ where $\hat{\Lambda}_C$ is the cumulative hazard of censoring.

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$$\mathcal{F}^k := \left\{ \hat{\Lambda}_C^k(\cdot; \varepsilon) \,:\, \varepsilon \in \mathbb{R} \right\} \subset \mathcal{F}, \quad k = 1, 2, \ldots,$$

and let ε_k^* denote the MLE of the fluctuation model $\mathcal{F}^k$, and $\hat{\Lambda}_C^k := \hat{\Lambda}_C^k(\cdot; \varepsilon_k^*)$ the model corresponding to the MLE.

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1. At $\varepsilon = 0$, $\hat{\Lambda}_C^1(\cdot\,; 0) = \hat{\Lambda}_C^0$ and $\hat{\Lambda}_C^{k+1}(\cdot\,; 0) = \hat{\Lambda}_C^k = \hat{\Lambda}_C^k(\cdot\,; \varepsilon_k^*)$.

The TMLE strategy for controlling the remaining component

We construct the estimator $\hat{G}$ of G as $\hat{G} = e^{-\hat{\Lambda}_C}$ where $\hat{\Lambda}_C$ is the cumulative hazard of censoring. We assume available (initial estimators) $\hat{\Lambda}_C^0$ and $\hat{\Lambda}$, where $\hat{\Lambda}$ is the cumulative hazard of the event of interest. To construct $\hat{\Lambda}_C$ in the right way, we recursively construct fluctuation models

$$\mathcal{F}^k := \left\{ \hat{\Lambda}_C^k(\cdot\,; \varepsilon) \,:\, \varepsilon \in \mathbb{R} \right\} \subset \mathcal{F}, \quad k = 1, 2, \ldots,$$

and let ε_k^* denote the MLE of the fluctuation model $\mathcal{F}^k$, and $\hat{\Lambda}_C^k := \hat{\Lambda}_C^k(\cdot\,; \varepsilon_k^*)$ the model corresponding to the MLE. These should be constructed such that

1. At $\varepsilon = 0$, $\hat{\Lambda}_C^1(\cdot\,; 0) = \hat{\Lambda}_C^0$ and $\hat{\Lambda}_C^{k+1}(\cdot\,; 0) = \hat{\Lambda}_C^k = \hat{\Lambda}_C^k(\cdot\,; \varepsilon_k^*)$.
2. The score function of the model $\hat{P}_n^{k+1}(\cdot\,; \varepsilon)$ equals f^t, i.e.,

$$\frac{\partial}{\partial \varepsilon}\bigg|_{\varepsilon = 0} \log \mathrm{d}\hat{P}_n^{k+1}(\cdot\,; \varepsilon) = f^t(\cdot\,; e^{-\hat{\Lambda}_C^k}, e^{-\hat{\Lambda}}).$$

The obtained estimator works

If the procedure converges after some K, we set $\hat{\Lambda}_C = \hat{\Lambda}_C(\cdot\ ; \varepsilon_K^*)$; then

$$\begin{aligned}
\hat{\mathbb{P}}_n[f^t(O; e^{-\hat{\Lambda}_C}, e^{-\hat{\Lambda}})] &\approx \hat{\mathbb{P}}_n[f^t(O; e^{-\hat{\Lambda}_C^{K-1}}, e^{-\hat{\Lambda}})] \\
&= \frac{\partial}{\partial \varepsilon}\Big|_{\varepsilon=0} \hat{\mathbb{P}}_n \left[\log \mathrm{d}\hat{P}_n^K(\cdot; \varepsilon)\right] \\
&\approx \frac{\partial}{\partial \varepsilon}\Big|_{\varepsilon=\varepsilon_K^*} \hat{\mathbb{P}}_n \left[\log \mathrm{d}\hat{P}_n^K(\cdot; \varepsilon)\right] = 0,
\end{aligned}$$

as $\varepsilon_K^* \approx 0$ because the procedure is converging.

Fluctuation model

We can choose a multiplicative update step to get the fluctuation model

$$\mathcal{F}^{k+1} := \left\{ \hat{\Lambda}_C^{k+1}(\cdot\,;\varepsilon) \;\middle|\; \hat{\Lambda}_C^{k+1}(\mathrm{d}s \mid x;\varepsilon) := e^{\varepsilon g(s,x;\hat{\Lambda}_C^k,\hat{\Lambda})}\hat{\Lambda}_C^k(\mathrm{d}s \mid x), \varepsilon \in \mathbb{R} \right\},$$

where

$$g(s,x;\Lambda_C,\Lambda) := \mathbb{1}(s \leq t)\left\{ \frac{\{1 - r(t \mid x)\}^2}{e^{-\Lambda_C(s|x)}} - \frac{\{1 - 2r(t \mid x)\}e^{-\Lambda(t|x)}}{e^{-\Lambda_C(s|x) - \Lambda(s|x)}} \right\}.$$

Fluctuation model

We can choose a multiplicative update step to get the fluctuation model

$$\mathcal{F}^{k+1} := \left\{ \hat{\Lambda}_C^{k+1}(\cdot\,; \varepsilon) \;\middle|\; \hat{\Lambda}_C^{k+1}(\mathrm{d}s \mid x; \varepsilon) := e^{\varepsilon g(s,x;\hat{\Lambda}_C^k,\hat{\Lambda})} \hat{\Lambda}_C^k(\mathrm{d}s \mid x), \varepsilon \in \mathbb{R} \right\},$$

where

$$g(s,x;\Lambda_C,\Lambda) := \mathbb{1}(s \leq t) \left\{ \frac{\{1 - r(t \mid x)\}^2}{e^{-\Lambda_C(s|x)}} - \frac{\{1 - 2r(t \mid x)\} e^{-\Lambda(t|x)}}{e^{-\Lambda_C(s|x) - \Lambda(s|x)}} \right\}.$$

One can then verify that $\hat{\Lambda}_C^{k+1}(\cdot\,; 0) = \hat{\Lambda}_C^k$ and

$$\begin{aligned} \frac{\partial}{\partial \varepsilon}\bigg|_{\varepsilon=0} \log \mathrm{d}\hat{P}_n^{k+1}(O; \varepsilon) &= \int g(s, X; \hat{\Lambda}_C^k, \hat{\Lambda}) M_C(\mathrm{d}s \mid X; \hat{\Lambda}_C) \\ &= f^t(O; e^{-\hat{\Lambda}_C^k}, e^{-\hat{\Lambda}}). \end{aligned}$$

Final algorithm

Algorithm 1: TMLE-based IPCW estimator of the average Brier score.

Input : Data O_i, $i = 1, \ldots, n$, risk prediction model r, and estimates $\hat{\Lambda}_C^0$ and $\hat{\Lambda}$

Output: Estimate of the average Brier score

$\varepsilon^* \leftarrow \infty$

$\hat{\Lambda}_C \leftarrow \hat{\Lambda}_C^0$

while $\varepsilon^* \not\approx 0$ **do**

$\quad g(s, x; \hat{\Lambda}_C, \hat{\Lambda}) \leftarrow \mathbb{1}(s \leq t) \left\{ \frac{\{1-r(t|x)\}^2}{e^{-\hat{\Lambda}_C(s|x)}} - \frac{\{1-2r(t|x)\}e^{-\hat{\Lambda}(t|x)}}{e^{-\hat{\Lambda}_C(s|x)-\hat{\Lambda}(s|x)}} \right\}$

$\quad \hat{\Lambda}_C^\dagger(\mathrm{d}s \mid x; \varepsilon) \leftarrow e^{\varepsilon g(s,x;\hat{\Lambda}_C,\hat{\Lambda})} \hat{\Lambda}_C(\mathrm{d}s \mid x)$

$\quad \varepsilon^* \leftarrow \mathrm{argsmax}_\varepsilon \sum_{i=1}^n \left\{ (1 - \Delta_i) \log(\mathrm{d}\hat{\Lambda}_C^\dagger(\tilde{T}_i \mid X_i; \varepsilon)) - \hat{\Lambda}_C^\dagger(\tilde{T}_i \mid X_i; \varepsilon) \right\}$

$\quad \hat{\Lambda}_C \leftarrow \hat{\Lambda}_C(\cdot; \varepsilon^*)$

$\hat{G}(s \mid x) \leftarrow e^{-\hat{\Lambda}_C(s|x)}$

$\widehat{W}_i \leftarrow \frac{\mathbb{1}(\tilde{T}_i > t)}{\hat{G}(t|X_i)} + \frac{\mathbb{1}(\tilde{T}_i \leq t)\Delta_i}{\hat{G}(\tilde{T}_i|X_i)}$, for $i = 1, \ldots, n$

$\hat{\theta}_n^t \leftarrow \frac{1}{n} \sum_{i=1}^n \widehat{W}_i \{r(t \mid X_i) - Y_i\}^2$

return $\hat{\theta}_n^t$

Next steps and discussion

- Implement the estimator...
- Construct both type of TMLE plug-in estimators – is the are finite sample difference, and are they more or sensitive to mis-specification of which nuisance model?
- Compare with undersmoothing – should be quite similar, and maybe they don't have to construct a fluctuation model?
- Extend to time-dependent covariates.
- General discussion about cross validation in the presence of censoring.

Thank you!

Thought and comments?

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