

# Loss functions and cross-validation with censored survival data

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# Outline

Setting and data structure

Loss functions and hold-out samples for survival data

Double robustness and fluctuation risk

# Data structure and target of inference

## Survival setting

$O = (\tilde{T}, \Delta, X) \sim P \in \mathcal{P}$  Observed data with  $\mathcal{O} = \mathbb{R}_+ \times \{0, 1\} \times \mathbb{R}^p$ .

$Z = (T, X) \sim Q \in \mathcal{Q}$  The distribution  $Q$  (or a feature of it) is of interest.

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## Parameters of interest

Low-dimensional feature of  $Q$ , e.g., the marginal survival probability  $Q(T > t)$  for a fixed time horizon  $t \in \mathbb{R}_+$ .

## Estimation of the nuisance parameter $S$

The distribution  $Q$  is identifiable from the observed data distribution  $P$  under coarsening at random. Without further assumptions we would typically need to estimate the conditional survival function  $S(t | x) = Q(T > t | X = x)$  (and/or the conditional censoring distribution).

# Cross-validation and super learning for $S$

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Most machine learning methods depend on one or more hyperparameters which are typically chosen using **cross-validation**.

More generally, to build robust estimators we can use **stacked regression** / **super learning** [Breiman, 1996, van der Laan et al., 2007] to select from or combine a collection candidate estimators/algorithms.

A central component for both cross-validation and super learning is the partitioning of data into training and test folds. A suitable loss function is then used to evaluate the performance of an estimator in hold-out samples.

# Evaluate performance in hold-out samples

$D$  data set  $(O_1, \dots, O_n)$

$\mathcal{A}$  collection of algorithms for estimating  $S \in \mathcal{S}$

$\nu \in \mathcal{A}$  mapping  $D \mapsto \nu(D) = \hat{S} \in \mathcal{S}$

$L$  loss function,  $L: \mathcal{S} \times \mathcal{O} \rightarrow \mathbb{R}_+$

To evaluate the performance of  $\nu \in \mathcal{A}$  let

$D_1, \dots, D_K$  partition of the data set  $D$

$D_{-k}$  the  $k$ 'th training sample,  $D_{-k} = D \setminus D_k$ ,  $k = 1, \dots, K$

and evaluate for all  $i = 1, \dots, n$ ,

$$L(\nu(D_{-k}), O_i), \quad \text{where } O_i \in D_k.$$

Averaging these values gives us an estimate of the expected loss of the algorithm  $\nu \in \mathcal{A}$ , and we can then pick the one with lowest expected loss. Alternatively, we can use these value to combine all algorithms into a super learner.

# The partial likelihood and hold-out samples

A popular choice for training survival models is the negative partial log-likelihood loss. Assuming conditional independence between the outcome and the censoring given the covariates, the observed data factorizes as

$$\ell(P, O) = \ell_t(S, O) \cdot \ell_c(G, O) \cdot \ell_0(h, O),$$

where  $G \in \mathcal{G}$  denotes the censoring mechanism and  $h$  the marginal distribution of the baseline covariates. The negative partial log-likelihood for the component  $S$  is

$$-\log \ell_t(S, O) = -\left\{ (1 - \Delta) \log S(\tilde{T} \mid X) + \Delta \log f_S(\tilde{T} \mid X) \right\},$$

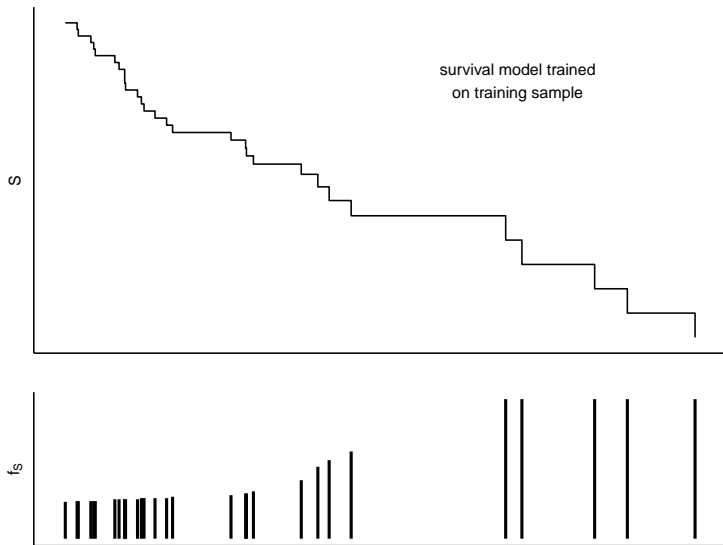
where  $f_S$  is the conditional density corresponding to  $S$ .

However, in continuous time this loss function is unsuitable for evaluating performance of most common survival estimators in hold-out samples, because (a.s.)

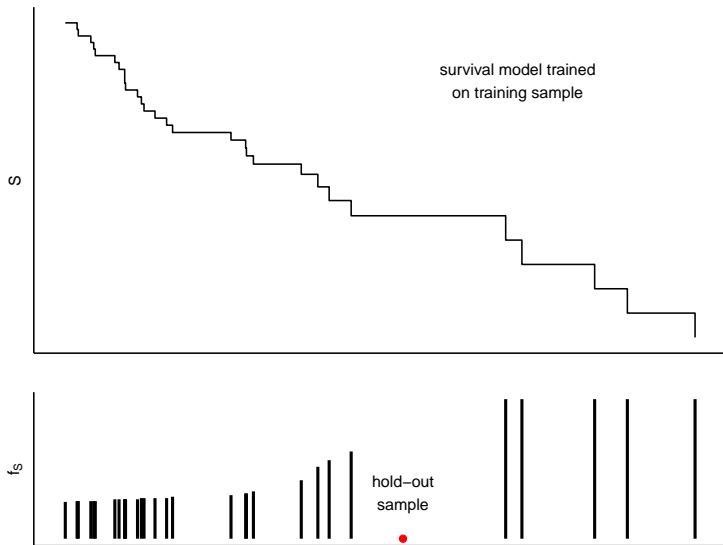
$$f_{\hat{S}}(\tilde{T}_i \mid X_i) = 0 \quad \text{when} \quad \hat{S} = \nu(D_{-k}) \quad \text{and} \quad (\tilde{T}_i, \Delta_i, X_i) \in D_k.$$



# Illustration



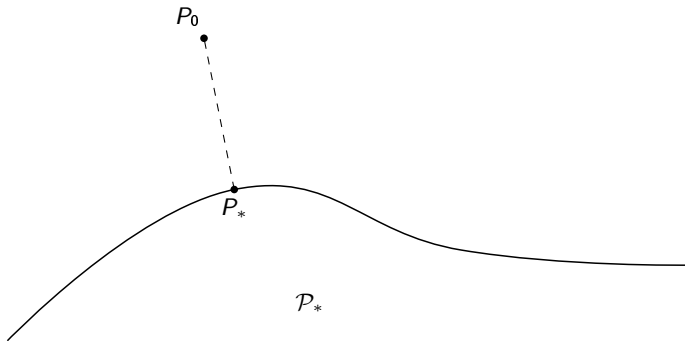
# Illustration



# Kullback-Leibler divergence and partial likelihoods

Maximum likelihood estimation is connected to minimizing the Kullback-Leibler divergence and gives an interpretation of the MLE under misspecified models.

$$D_{\text{KL}}(P_0 \parallel P) := P_0 \left[ \log \frac{p_0}{p} \right], \quad \text{where} \quad P_0 = p_0 \cdot \mu, P = p \cdot \mu.$$



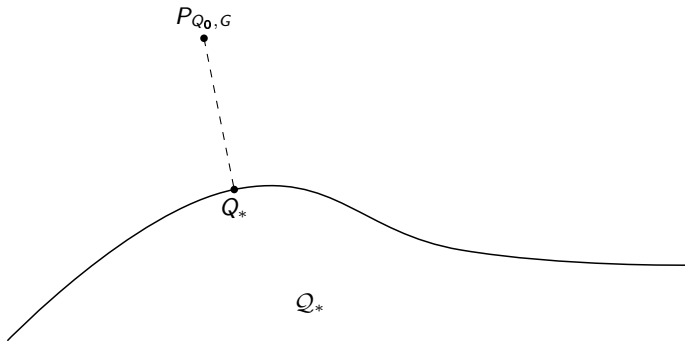
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$$Q \mapsto D_{\text{KL}}(P_{Q_0, G} \parallel P_{Q, G}), \quad \text{with} \quad Q \in \mathcal{Q}_*.$$



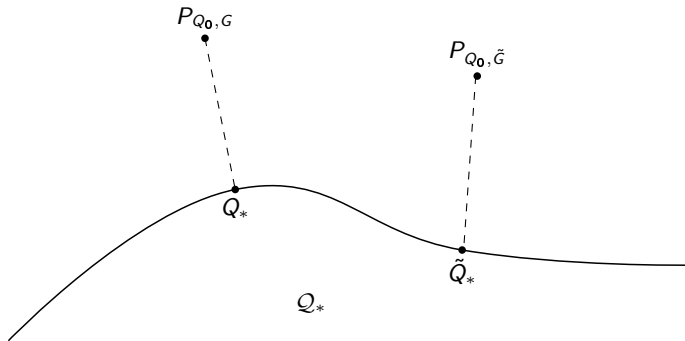
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# Inverse probability of censoring weighted loss functions

A conceptually more attractive strategy is to use loss functions that are

- (i) suited for evaluating the performance of estimating the *survival function*
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A conceptually more attractive strategy is to use loss functions that are

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- (ii) defined in terms of the *distribution  $Q$  of interest*

We can do this using inverse probability of censoring weighted (IPCW) loss functions. For instance, with the Brier score

$$L_{\text{Brier}}(S, Z) = (S(t | X) - \mathbb{1}\{T > t\})^2, \quad Z = (T, X) \sim Q,$$

the expected loss is identifiable through

$$\mathbb{E}_Q [L_{\text{Brier}}(S, Z)] = \mathbb{E}_P [W_G \cdot L_{\text{Brier}}(S, Z)],$$

with

$$W_G = \frac{\mathbb{1}\{\tilde{T} > t\} + \mathbb{1}\{\tilde{T} \leq t\}\Delta}{G(\tilde{T} \wedge t | X)},$$

where  $G$  is the conditional “survivor” function for the censoring distribution [Graf et al., 1999, Gerds and Schumacher, 2006, van der Laan and Dudoit, 2003].

## Estimation of the IPC weights

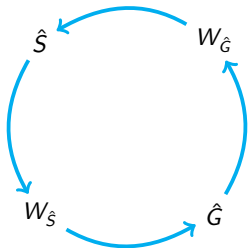
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$\Rightarrow$  The exact same challenges face us when attacking this problem.



Recently, Han et al. [2021] and Westling et al. [2021] have suggested to iterate between estimation of  $\hat{S}$  and  $\hat{G}$  until convergence.

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### Exploit double robustness

Cui and Tchetgen [2020], building on ideas from Robins et al. [2007], proposed to exploit double robustness as a model selection criteria.

## Fluctuation risk

Let  $\psi$  be the efficient influence for the parameter  $\Psi$ , and assume we can write  $\psi(O, P) = \varphi(O, S_P, G_P) - \Psi(P)$  such that

$$\mathbb{E}_P [\varphi(O, S_P, G_*)] = \mathbb{E}_P [\varphi(O, S_*, G_P)] = \Psi(P),$$

for any  $S_*$  and  $G_*$ , where  $S_P$  and  $G_P$  are the conditional survivor functions corresponding to the data generating distribution.

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Let  $\mathcal{G}$  be a (finite) collection of models for  $G$ . The double robustness property implies that  $\mathbb{E}_P [\varphi(O, S_P, G)] = \mathbb{E}_P [\varphi(O, S_P, G')]$  for any  $G, G' \in \mathcal{G}$ . In particular,

$$\max_{G, G' \in \mathcal{G}} |\mathbb{E}_P [\varphi(O, S_P, G)] - \mathbb{E}_P [\varphi(O, S_P, G')]| = 0.$$

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This motivates the “fluctuation risk”,<sup>1</sup>

$$R(S) = \max_{G, G' \in \mathcal{G}} |\mathbb{E}_P [\varphi(O, S, G)] - \mathbb{E}_P [\varphi(O, S, G')]|.$$

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<sup>1</sup>or pseudo-risk because it depends  $\mathcal{G}$  which is suppressed in the notation.



## Estimating the fluctuation risk

Let  $\mathcal{A}_c$  be a collection of algorithms for estimating  $G$ . For any  $\nu \in \mathcal{A}$ ,  $\gamma \in \mathcal{A}_c$ , and  $k = 1, \dots, K$  define

$$\hat{\Psi}_{\nu, \gamma}^k = \frac{1}{|D_k|} \sum_{O \in D_k} \varphi(O, \nu(D_{-k}), \gamma(D_{-k})).$$

For any  $\nu \in \mathcal{A}$  we approximate the fluctuation risk with

$$\hat{R}(\nu) = \frac{1}{K} \sum_{k=1}^K \max_{\gamma, \gamma' \in \mathcal{A}_c} |\hat{\Psi}_{\nu, \gamma}^k - \hat{\Psi}_{\nu, \gamma'}^k|.$$

Recall

$\mathcal{A}$  collection of algorithms for estimating  $S \in \mathcal{S}$

$D_1, \dots, D_K$  partition of the data set  $D$

$D_{-k}$  the  $k$ 'th training sample,  $D_{-k} = D \setminus D_k$ ,  $k = 1, \dots, K$

# Illustration of the method

Consider the following simple setting where  $X = (A_1, A_2, A_3)^T$  with  $A_j \in \{0, 1\}$  for all  $j$  and our parameter of interest is the marginal survival probability  $Q(T > t)$  at some fixed time  $t > 0$ . We consider using Kaplan-Meier estimators stratified on each of  $A_j$ .<sup>2</sup>

## outcome algorithms

```
S1 <- function(d) prodlim(Surv(time,event) ~ A1, data = d)
S2 <- function(d) prodlim(Surv(time,event) ~ A2, data = d)
S3 <- function(d) prodlim(Surv(time,event) ~ A3, data = d)
```

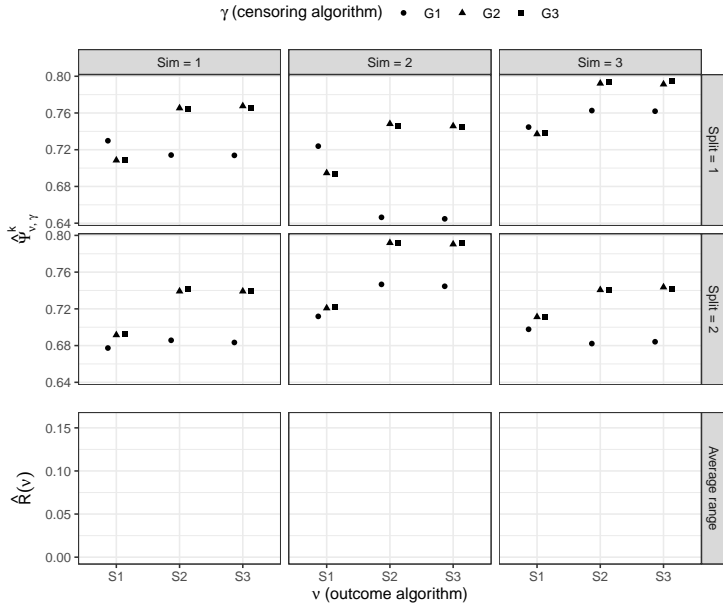
## censoring algorithms

```
G1 <- function(d) prodlim(Surv(time,event) ~ A1, rev = T, data = d)
G2 <- function(d) prodlim(Surv(time,event) ~ A2, rev = T, data = d)
G3 <- function(d) prodlim(Surv(time,event) ~ A3, rev = T, data = d)
```

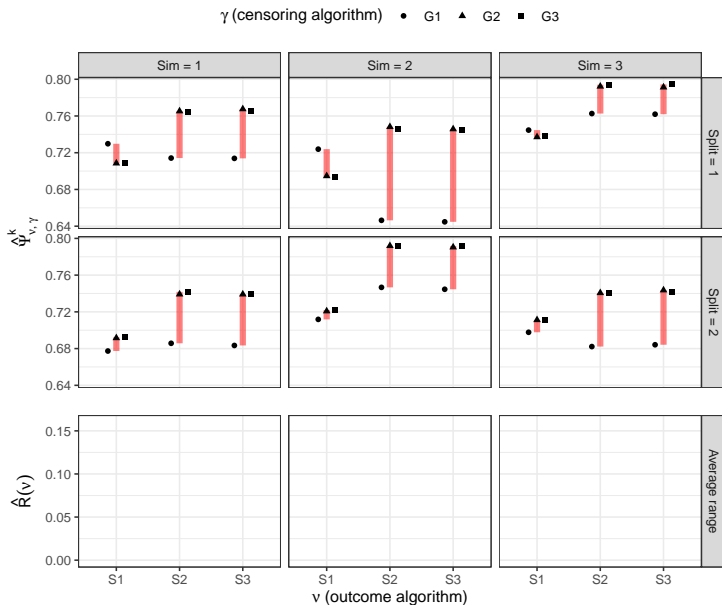
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<sup>2</sup>In this simulation, only  $A_1$  influences survival and censoring.

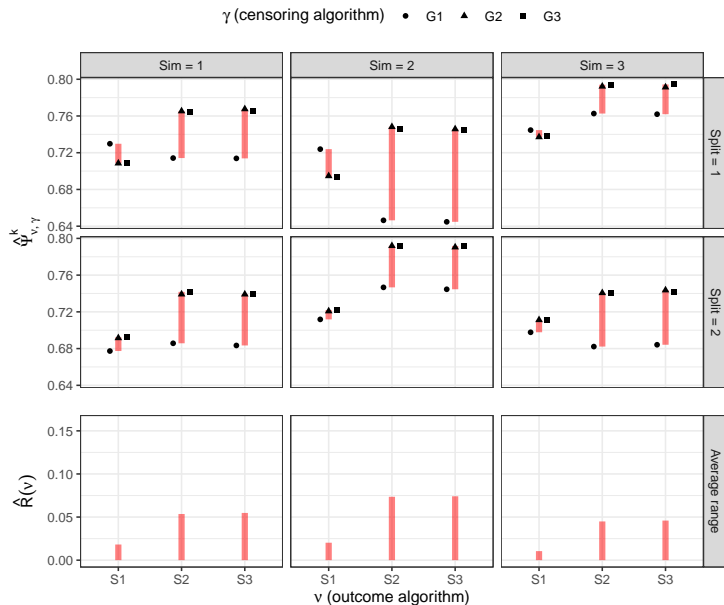
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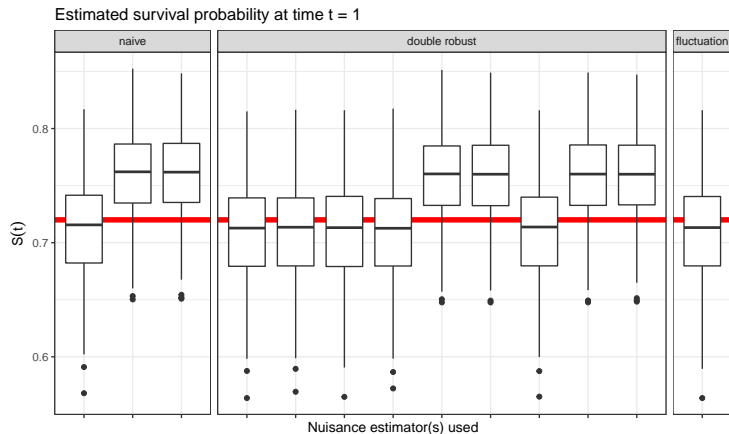
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# Some simulation results

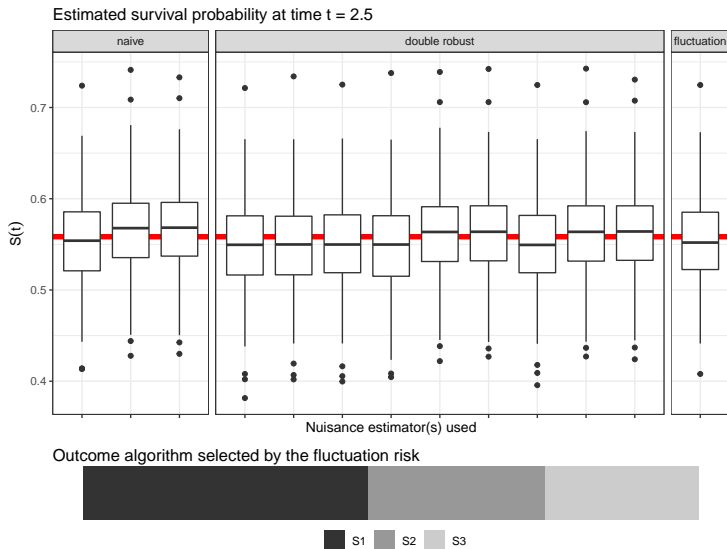


Outcome algorithm selected by the fluctuation risk



■ S1 ■ S2 ■ S3

# Some simulation results



# Conclusion

- It is not obvious what loss function to use for estimating the conditional survivor function with censored data observed in continuous time.
- If the parameter of interest is a low-dimension feature of the full data distribution we could exploit this and evaluate the performance of the nuisance parameter estimators in terms of their effect on the estimator of the target parameter.



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# If the conditional survivor function was the target parameter

Consider now the situation where the conditional survival function  $S(t | x)$  is the actual parameter of interest for fixed  $t$ . Assume that our goal is to build a prediction model minimizing the average Brier score. Given a model  $S$  we can consider the average Brier score of  $S$  as a low dimensional target parameter

$$\Psi_S(P) = \mathbb{E}_P [W_G \cdot L_{\text{Brier}}(S, Z)] \quad \text{with} \quad G = G_P,$$

and proceed as above.

- With a finite *collection* of models  $\mathcal{S}^* \subset \mathcal{S}$  we get a different target parameter  $\Psi_S$  for each  $S \in \mathcal{S}^*$ .
- With an infinite collection of models  $\mathcal{S}^*$  (e.g., indexed by  $\beta \in \mathbb{R}^p$ ) the previous approach is problematic.

$\implies$  It is desirable to fit the weights *once* so that they are “universally” applicable for estimating the performance of all  $S \in \mathcal{S}$ .

One idea is to use undersmoothed HAL to do this.

## Double robustness

Many estimators based on the efficient influence function has a double robustness property. For instance, the efficient influence function for  $\Psi$  is  $\psi(O, P) = \varphi(O, S_P, G_P) - \Psi(P)$ , with

$$\varphi(O, S, G) = S(t | X) \left( 1 - \int_0^t \frac{N(du) - \mathbb{1}\{\tilde{T} \geq u\} \Lambda_S(du | X)}{G(u | X) S(u | X)} \right),$$

where  $N(u) = \mathbb{1}\{\tilde{T} \leq u, \Delta = 1\}$  is the counting process and  $\Lambda_S$  is the conditional cumulative hazard corresponding to  $S$ . It holds that

$$\mathbb{E}_P [\varphi(O, S_P, G_*)] = \mathbb{E}_P [\varphi(O, S_*, G_P)] = \Psi(P),$$

for any  $S_*$  and  $G_*$ , where  $S_P$  and  $G_P$  are the conditional survivor functions of the data generating distribution.

This motivates estimating  $\Psi(P)$  with

$$\hat{\Psi} = \frac{1}{n} \sum_{i=1}^n \varphi(O_i, \hat{S}, \hat{G}),$$

which is consistent if either  $\hat{S}$  or  $\hat{G}$  is consistent.