Semi-supervised Algorithms for Risk Assessment with Noisy EHR Data

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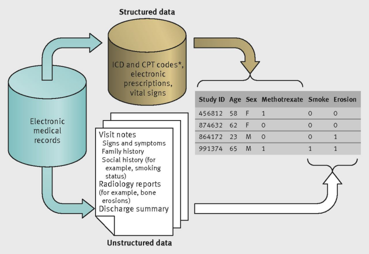
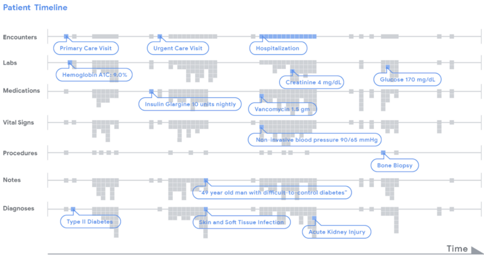
EHR Structure



(Figure from Liao et al. 2015)



(Figure from ai.googleblog.com)

- **Structured data**: ICD billing codes; lab results etc
- **Unstructured text data**: extracted via natural language processing (NLP)
- **Detailed longitudinal patient level data**

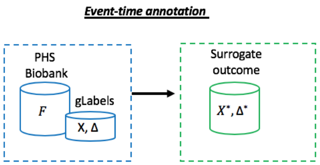
Challenges in EHR-linked Survival Analysis

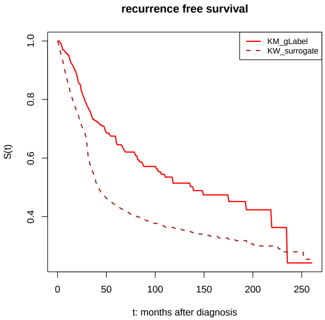
Disease status and event time information is not readily available.

- Annotating **event time** requires labor extensive chart review
- Time to first ICD codes **inaccurate**
- **Surrogate event time**: derived from label+codes+NLP
- $\rightsquigarrow$ power loss, biased estimates

Motivating Example: PHS Lung Cancer Study

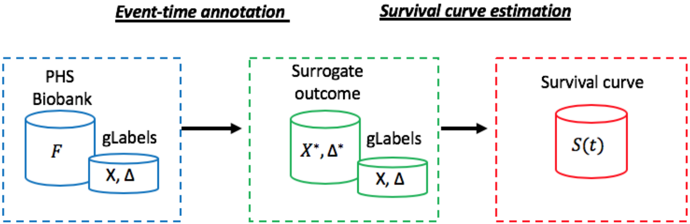
- PHS: Partners Healthcare contains both a wealth of clinical and also biological measurements.





- Aim to estimate recurrence free survival for lung cancer patients.
- Lung cancer data mart
- 70K patients from PHS biobank EMR
- 40K patients identified as lung cancer
- 5K early stage patients
- 300 gLabels for event time manually annotated by domain experts
- Surrogate outcomes derived by using Uno et al. 2018

Motivating Example: PHS Lung Cancer Study



Solution: Develop a calibrated survival curve that combines imperfect sources of information on event time in EHR, together with the exact event time.

Sources of information on event times in EHRs

- T_i: failure time, the time that the patient developed the event
- C_i: censoring time

Labeled data: $i = 1, \cdots, n$

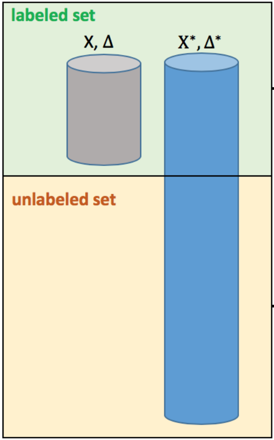
- $X_i = \min(T_i, C_i)$: observed event time:
- $\Delta_i = \mathbb{1}(T_i \leq C_i)$: the censoring indicator (whether the patient developed the event prior to the last visit)

Unlabeled data: $i = 1, \cdots, n + N$

- X^*: imperfect estimates of event times
  – time to the first ICD code related to the event
  – time to the first NLP mention of the event
  – algorithm annotated event time
- $\Delta_i^* = \mathbb{1}(T_i^* \leq C_i)$

Goal: estimate the survival function $S(t)$.

Conditional Nelson-Aalen Estimator



$$\hat{S}(t|X_i^* = x, \Delta_i^* = d) = \exp\{-\widehat{\Lambda}(t;x,d)\},$$

$$where, \widehat{\Lambda}(t;x,d) = \int_0^t \frac{\sum_{i;\Delta_i^*=d} K_h(X_i^* - x)dN_i(z)}{\sum_{i;\Delta_i^*=d} K_h(X_i^* - x)Y_i(z)}$$

$$with\ N_i(t) = I(X_i \leq t)\Delta_i, and\ \ Y_i(t) = I(X_i \geq t)$$

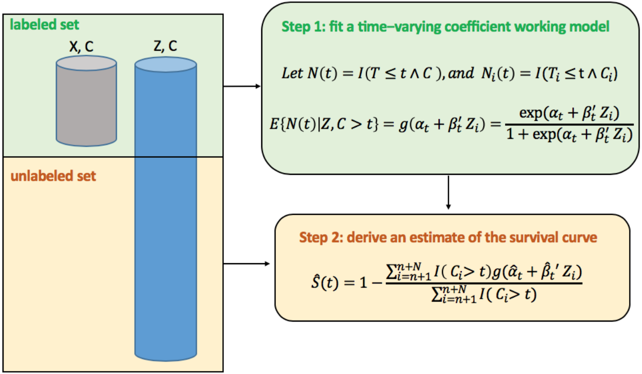
$$\hat{S}(t) = N^{-1} \sum_{i=n+1}^{n+N} \hat{S}(t|X_i^*, \Delta_i^*)$$

- Parast et al. 2014: baseline covariates
- In our case, T and C may no longer be independent conditional on X^* and Δ^* if there is no restriction on X^* and Δ^*.
- As a result, the Nelson-Aalen type estimator defined above may not be consistent.

Semiparametric Estimator

Let $\mathbf{Z}$ denote a variable related to both T and C.
As $T \perp\!\!\!\perp C$, we have

$$
\begin{aligned}
\pi_t &= E\{\mathbb{1}(T \le t)\} = E\{\mathbb{1}(T \le t) \mid C > t\} = E\{\mathbb{1}(T \le t)\Delta \mid C > t\} \\
&= E[E\{N(t) \mid \mathbf{Z}, C > t\} \mid C > t].
\end{aligned}
$$



Combined Estimator

To improve the efficiency, we combine proposed semiparametric estimator with the KM.

Let $\widehat{\boldsymbol{\mu}} = (\widehat{S}_{\mathrm{Semi}}, \widehat{S}_{\mathrm{KM}})^{\mathsf{T}}$, and $\boldsymbol{\Sigma}$ denote their covariance matrix, then the combined estimator is constructed as

$$(\mathbf{1}^{\mathsf{T}}\boldsymbol{\Sigma}^{-1}\mathbf{1})^{-1}\mathbf{1}^{\mathsf{T}}\boldsymbol{\Sigma}^{-1}\widehat{\boldsymbol{\mu}}$$

- unbiased
- smallest possible variance among all linear combinations

Asymptotic Properties of Proposed Estimator

Let $\mathbf{W}_i = (1, \mathbf{Z}_i^{\mathsf{T}})^{\mathsf{T}}$.

Step 1.

$$\sqrt{n}(\widehat{\boldsymbol{\theta}}_t - \boldsymbol{\theta}_t) \to \text{Normal}\{\mathbf{0}, \mathbf{A}^{-1}\mathbf{B}(\mathbf{A}^{-1})^{\mathsf{T}}\},$$

where

$$\begin{aligned} \mathbf{A} &= -E\{\mathbb{1}(C > t) g'(\boldsymbol{\theta}_t^{\mathsf{T}}\mathbf{W})\mathbf{W}\mathbf{W}^{\mathsf{T}}\}; \\ \mathbf{B} &= \text{cov}[\mathbb{1}(C > t)\{N(t) - g(\boldsymbol{\theta}_t^{\mathsf{T}}\mathbf{W})\}\mathbf{W}]; \\ g'(x) &= \exp(x)/\{1 + \exp(x)\}^2. \end{aligned}$$

Step 2.

$$\sqrt{n}(\widehat{\pi}_t - \pi_t) = G(t)^{-1} E\{\mathbb{1}(C > t) g'(\boldsymbol{\theta}_t^{\mathsf{T}}\mathbf{W})\mathbf{W}\}^{\mathsf{T}} \sqrt{n}(\widehat{\boldsymbol{\theta}}_t - \boldsymbol{\theta}_t) + o_p(1),$$

where $G(t) = P(C > t)$.

Asymptotic Properties of Kaplan Meier Estimator

We have

$$\sqrt{n}(\widehat{\pi}_t^{\mathrm{KM}} - \pi_t) \quad = \quad \frac{1}{\sqrt{n}} \sum_{i=1}^{n} (1 - \pi_t) \int_0^t \frac{dM_i(u)}{P(X \geq u)} + o_p(1).$$

In practice, we have to replace all the unknown quantities in the above influence function with their estimations. This leads to

$$(1 - \widehat{\pi}_t^{\mathrm{KM}}) \int_0^t \frac{d\widehat{M}_i(u)}{\overline{Y}(u)} \quad = \quad (1 - \widehat{\pi}_t^{\mathrm{KM}}) \left\{ \frac{\Delta_i \mathbb{1}(X_i \leq t)}{\overline{Y}(X_i)} - \sum_j \frac{\Delta_j \mathbb{1}(X_j \leq t \wedge X_i)}{n\overline{Y}^2(X_j)} \right\},$$

where $\overline{Y}(u) = n^{-1} \sum Y_i(u)$ and $Y_i(u) = \mathbb{1}(X_i \geq u)$.

Combined Estimator

To improve the efficiency, we combine proposed semiparametric estimator with the KM.

Let $\widehat{\boldsymbol{\mu}} = (\widehat{S}_{\mathrm{Semi}}, \widehat{S}_{\mathrm{KM}})^{\mathsf{T}}$, and $\boldsymbol{\Sigma}$ denote their covariance matrix, then the combined estimator is constructed as

$$(\mathbf{1}^{\mathsf{T}}\boldsymbol{\Sigma}^{-1}\mathbf{1})^{-1}\mathbf{1}^{\mathsf{T}}\boldsymbol{\Sigma}^{-1}\widehat{\boldsymbol{\mu}}$$

where

$$\begin{aligned}
\Sigma_{1,1} &= \mathbf{C}^{\mathsf{T}} E[\mathbb{1}(C_j > t)\{N_j(t) - g(\boldsymbol{\theta}_t^{\mathsf{T}}\mathbf{W}_j)\}^2 \mathbf{W}_j \mathbf{W}_j^{\mathsf{T}}]\mathbf{C}. \\
\Sigma_{2,2} &= E[\mathbb{1}(T_i \wedge t \le C_i)\{\pi_t^{\mathrm{KM}} - \mathbb{1}(X_i < t)\}^2 / G^2(X_i \wedge t)]. \\
\Sigma_{1,2} &= -\mathbf{C}^{\mathsf{T}} E[\mathbb{1}(C_i > t)\{N_i(t) - g(\boldsymbol{\theta}_t^{\mathsf{T}}\mathbf{W}_i)\}\mathbf{W}_i w_i(t)\{\pi_t^{\mathrm{KM}} - \mathbb{1}(X_i < t)\}]
\end{aligned}$$

- unbiased
- smallest possible variance among all linear combinations

Simulation Setup

- 400 datasets, each has 200 labeled subjects and 2000 unlabeled subjects
- For each dataset, generate
  - $T_i \sim$ Exponential(1)
  - $C_i \sim$ Exponential(1) or $C_i \sim$ Uniform(3)
  - $Z_i = h(\lambda, T_i, C_i) + e_i$, with $e_i \sim$ Normal$(0, \sigma)$
  - λ large vs. small

Settings

1. $T_i \sim \text{Exponential}(1)$, $C_i \sim \text{Exponential}(1)$,
   $Z_i = \log(T_i) + \lambda \log(C_i) + e_i$, with $e_i \sim \text{Normal}(0, 1)$;
   $\lambda = 1$ and $\lambda = 0.1$.
2. $T_i \sim \text{Exponential}(1)$, $C_i \sim \text{Exponential}(1)$,
   $Z_i = \lambda \log(T_i) + (1 - \lambda) \log(C_i) + e_i$, with $e_i \sim \text{Normal}(0, 1)$;
   $\lambda = 1/2$ versus $\lambda = 0.9$.
3. $T_i \sim \text{Exponential}(1)$, $C_i \sim \text{Exponential}(1)$,
   $Z_i = \lambda \log(T_i) + (1 - \lambda) \log(C_i) + e_i$, with $e_i \sim \text{Normal}(0, 0.25)$;
   $\lambda = 1/2$ versus $\lambda = 0.9$.
4. $T_i \sim \text{Exponential}(1)$, $C_i \sim \text{Uniform}(0, 3)$,
   $Z_i = \lambda \log(T_i) + (1 - \lambda) \log(C_i) + e_i$, with $e_i \sim \text{Normal}(0, 0.25)$;
   $\lambda = 1/2$ versus $\lambda = 0.9$.
5. $T_i \sim \text{Exponential}(1)$, $C_i \sim \text{Uniform}(0, 3)$,
   $Z_i = \log\{\min(T_i^*, C_i)\}$, with $T_i^* = T_i + e_i$ and $e_i \sim \text{Exponential}(\lambda)$;
   $\lambda = 2$ versus $\lambda = 5$.

Simulation Results

$T_i \sim \text{Exponential}(1),\ C_i \sim \text{Uniform}(0,3),$
$Z_i = \lambda \log(T_i) + (1-\lambda)\log(C_i) + e_i$, with $e_i \sim \text{Normal}(0, 0.25)$;
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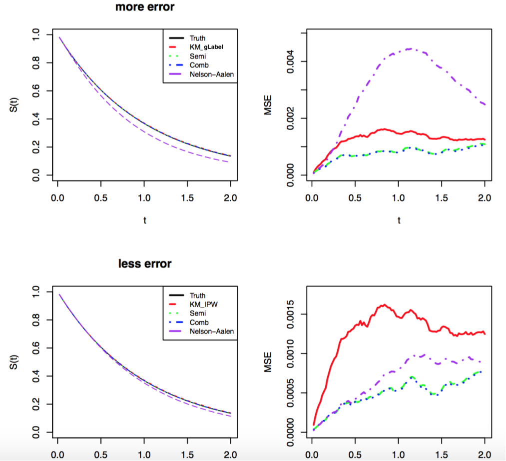
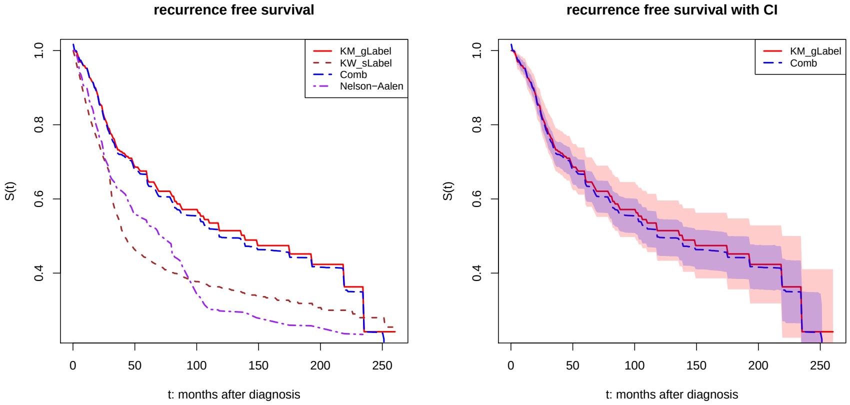


Real data example

- Goal: estimate the recurrence-free survival curve of lung cancer patients
- Dataset
  - 37,021 total lung cancer patients
  - 5K early stage patients
  - 340 had recurrence status and observed time to recurrence labels from chart review (Δ_i, X_i)
  - Surrogate outcomes (Δ_i^*, Z_i) are available for each patient obtained by Uno's two-step estimator
    –binary recurrence status
    –predict event times using peaks of specific features
  - Accuracy of Δ_i^* is only 0.79;

Results - Survival Curve Comparisons



Remarks

- a semi-supervised calibrated survival curve
- fully utilize both labeled and unlabeled data
- next step: estimate the survival function among different risk groups (e.g., different treatment group), and test for difference.

Thank you!

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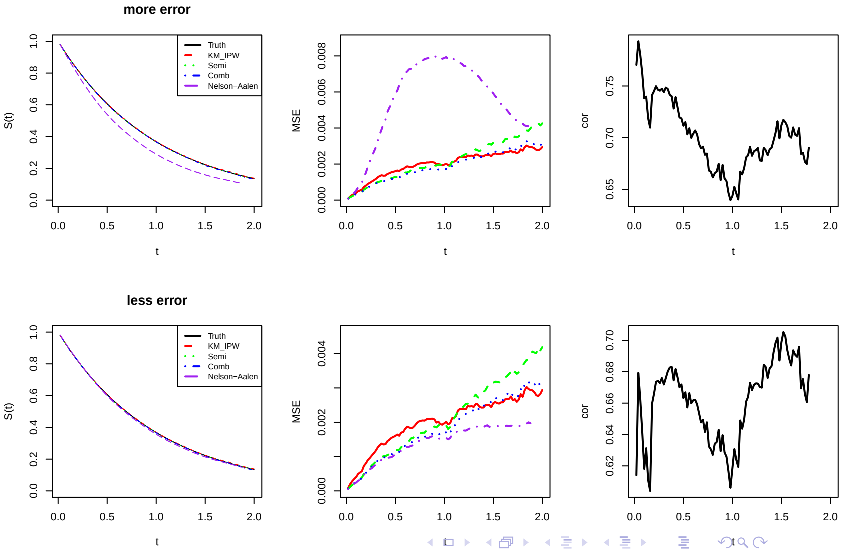

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$T_i \sim \text{Exponential}(1),\ C_i \sim \text{Exponential}(1),$
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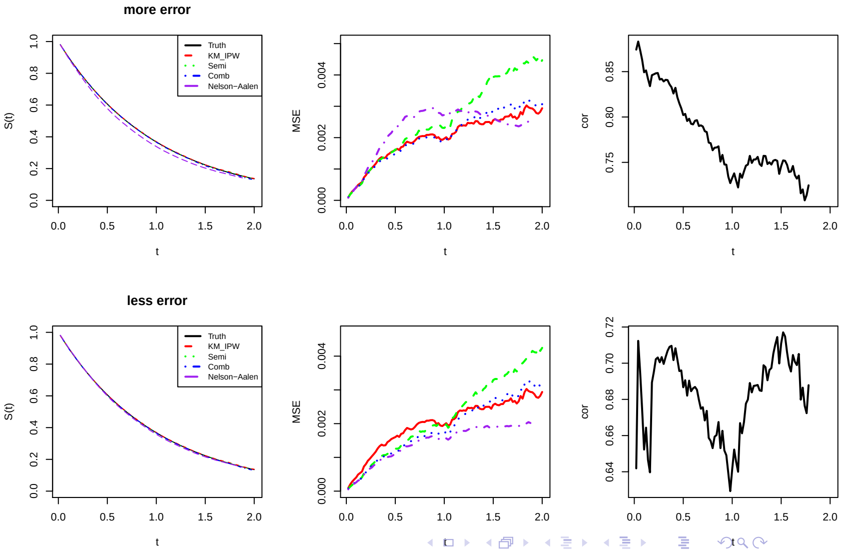

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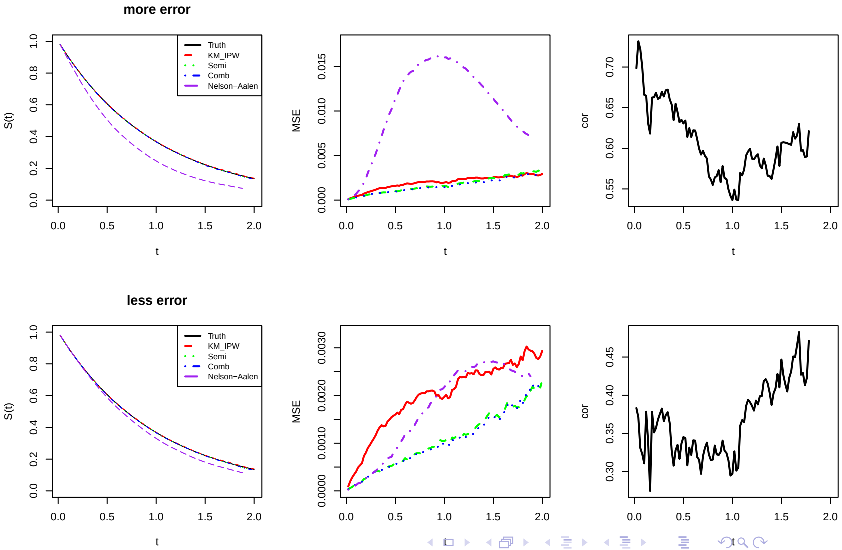

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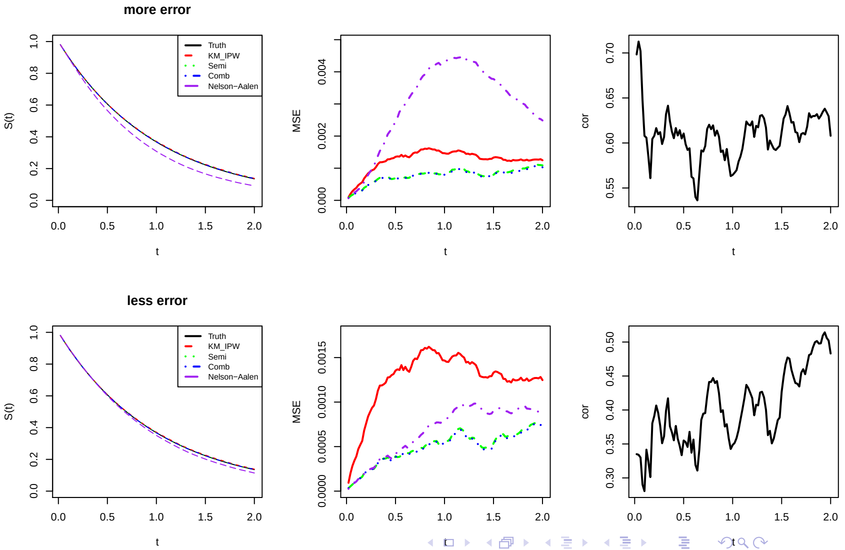

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