

# **Deep Learning of Semi-Competing Risk Data**

## **via a Neural Expectation-Maximization Algorithm**

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## 1 Background

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- Motivation
- Notation

## 2 Neural Expectation-Maximization Algorithm

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- Illness-Death Model
- Method
- Bivariate Brier Score

## 3 Simulations

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## 4 Boston Lung Cancer Study

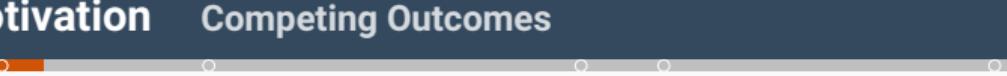
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- 5-year survival rate of **1 in 5** [Bade and Cruz, 2020]
- Prognosis depends on **individualized risk factors** [Ashworth et al., 2014]
- **Progression, metastasis prior to death** [Inamura and Ishikawa, 2010]

Approximately **1 in 5** cancer deaths  
are attributed to **lung cancer**.



Source: World Health Organization, International Agency for Research on Cancer, Latest global cancer data: Cancer burden rises to 18.1 million new cases and 9.6 million cancer deaths in 2018.



Many studies report on ***lung cancer outcomes***, however:

- Mortality is often studied without considering ***competing events***
- Or ***composite endpoints*** such as ***progression-free survival*** are used [Jazić et al., 2016]



When progression and death ***do not correlate well***, the effects of certain risk factors may differ across ***states*** of a patient's disease trajectory [Amir et al., 2012, Chakravarty and Sridhara, 2008]<sup>1</sup>

<sup>1</sup><https://www.aacr.org/blog/2016/01/04/advancing-lung-cancer-research/>



Our data come from the **Boston Lung Cancer Study**, one of the largest **cancer epidemiology cohorts** investigating lung cancer. Our **scientific questions** are:

1. What are the **complex mechanisms** governing the relationship between risk factors for lung cancer?
2. Do these relationships differ across **states** in a patient's **clinical course**?
3. Can we use this information to more **accurately predict** patient **survival**?



- In **survival analysis**, the outcome is the time until a specific event, such as cancer **progression** or **death**, which may be **censored**
- Many survival processes involve **non-terminal** (e.g., progression) and **terminal** (e.g., death) events, which form **semi-competing** relationships [Fine et al., 2001]

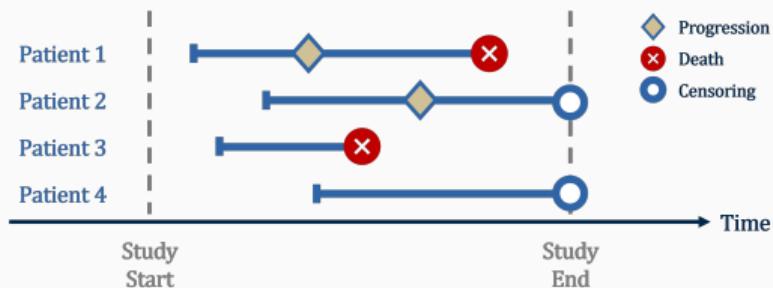


Figure: Schematic of four example patients with semi-competing risks

Let  $T_{i1}$ ,  $T_{i2}$ , and  $C_i$  denote the time to *progression*, *death*, and *censoring* for the  $i$ th individual in our study. In practice, we can only *observe*:

$$\mathcal{D} = \{(Y_{i1}, \delta_{i1}, Y_{i2}, \delta_{i2}, x_i); i = 1, \dots, n\}$$

### Observed Data Definitions

$$\begin{aligned}Y_{i2} &= \min(T_{i2}, C_i) \\ \delta_{i2} &= I(T_{i2} \leq C_i) \\ Y_{i1} &= \min(T_{i1}, Y_{i2}) \\ \delta_{i1} &= I(T_{i1} \leq Y_{i2}) \\ x_i &= \text{Covariates}\end{aligned}$$

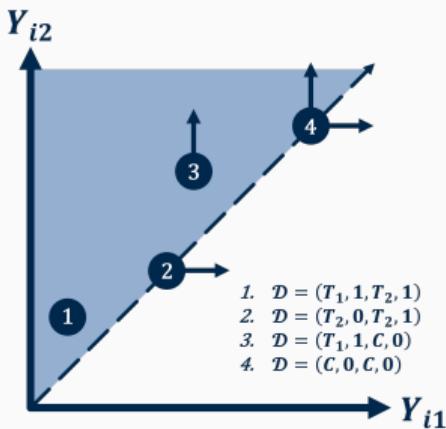


Figure: Observable data

We base our approach on the ***illness-death model***, a compartment-type model for the ***hazards/transition rates*** between event states:

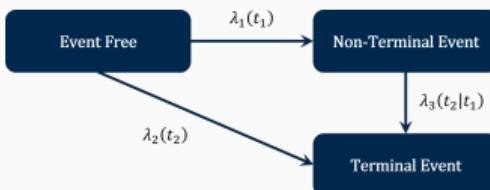


Figure: Illness-death model framework

$$\lambda_1(t_1) = \lim_{\Delta \rightarrow 0} \Pr [T_1 \in [t_1, t_1 + \Delta) \mid T_1 \geq t_1, T_2 \geq t_1] / \Delta; \quad t_1 > 0$$

$$\lambda_2(t_2) = \lim_{\Delta \rightarrow 0} \Pr [T_2 \in [t_2, t_2 + \Delta) \mid T_1 \geq t_2, T_2 \geq t_2] / \Delta; \quad t_2 > 0$$

$$\lambda_3(t_2 \mid t_1) = \lim_{\Delta \rightarrow 0} \Pr [T_2 \in [t_2, t_2 + \Delta) \mid T_1 = t_1, T_2 \geq t_2] / \Delta; \quad t_2 > t_1 > 0$$

# Parameterizing the Hazard Functions

$$\lambda_1(t_1 | \gamma_i, x_i) = \gamma_i \times \lambda_{01}(t_1) \times \exp\{h_1(x_i)\}; \quad t_1 > 0$$

$$\lambda_2(t_2 | \gamma_i, x_i) = \gamma_i \times \lambda_{02}(t_2) \times \exp\{h_2(x_i)\}; \quad t_2 > 0$$

$$\underbrace{\lambda_3(t_2 | t_1, \gamma_i, x_i)}_{\text{Hazard Function}} = \underbrace{\gamma_i}_{\text{Frailty}} \times \underbrace{\lambda_{03}(t_2 - t_1)}_{\text{Baseline Hazard}} \times \underbrace{\exp\{h_3(x_i)\}}_{\text{Risk Function}}; \quad t_2 > t_1 > 0$$

- $\gamma_i \stackrel{i.i.d}{\sim} \text{Gamma}(1/\theta, 1/\theta)$  is a patient-specific **frailty**
- Model is **semi-Markov** w.r.t.  $\lambda_3$  as a function of the **sojourn time** ( $t_2 - t_1$ )  
[Haneuse and Lee, 2016, Li et al., 2020]
- $x_i$  is a  $p$ -vector of **clinically relevant predictors**



The likelihood for the observed data  $\mathcal{D}$ :

$$\begin{aligned} L(\psi; \mathcal{D}) = & \prod_{i=1}^n \int_0^\infty \frac{\theta^{-\frac{1}{\theta}}}{\Gamma(\frac{1}{\theta})} \times \gamma_i^{\frac{1}{\theta}-1} \times e^{-\frac{\gamma_i}{\theta}} \times \gamma_i^{\delta_{i1}+\delta_{i2}} \times \left[ \lambda_{01}(Y_{i1}) e^{h_1(x_i)} \right]^{\delta_{i1}} \\ & \times \left[ \lambda_{02}(Y_{i2}) e^{h_2(x_i)} \right]^{(1-\delta_{i1})\delta_{i2}} \times \left[ \lambda_{03}(Y_{i2} - Y_{i1}) e^{h_3(x_i)} \right]^{\delta_{i1}\delta_{i2}} \\ & \times \exp \left\{ -\gamma_i \left[ \Lambda_{01}(Y_{i1}) e^{h_1(x_i)} + \Lambda_{02}(Y_{i1}) e^{h_2(x_i)} + \delta_{i1} \Lambda_{03}(Y_{i2} - Y_{i1}) e^{h_3(x_i)} \right] \right\} d\gamma_i \end{aligned}$$

- We want a **non-parametric** model for **both** the baseline hazards and covariate risk functions to achieve greater **flexibility** and **accuracy**
- Direct maximization of the likelihood function is challenging
- We resort to the EM algorithm which provides a numerically stable approach for optimization

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Treating frailties  $\gamma$  as the (unobserved) data, we form the **complete data likelihood** as follows:

$$\begin{aligned} L(\psi; \mathcal{D}, \gamma) = & \prod_{i=1}^n \frac{\theta^{-\frac{1}{\theta}}}{\Gamma\left(\frac{1}{\theta}\right)} \times \gamma_i^{\frac{1}{\theta}-1} \times e^{-\frac{\gamma_i}{\theta}} \times \gamma_i^{\delta_{i1}+\delta_{i2}} \times \left[ \lambda_{01}(Y_{i1}) e^{h_1(x_i)} \right]^{\delta_{i1}} \\ & \times \left[ \lambda_{02}(Y_{i2}) e^{h_2(x_i)} \right]^{(1-\delta_{i1})\delta_{i2}} \times \left[ \lambda_{03}(Y_{i2} - Y_{i1}) e^{h_3(x_i)} \right]^{\delta_{i1}\delta_{i2}} \\ & \times \exp \left\{ -\gamma_i \left[ \Lambda_{01}(Y_{i1}) e^{h_1(x_i)} + \Lambda_{02}(Y_{i1}) e^{h_2(x_i)} + \delta_{i1} \Lambda_{03}(Y_{i2} - Y_{i1}) e^{h_3(x_i)} \right] \right\} \end{aligned}$$

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The **expected log-complete data likelihood**, or our 'Q' function, can be written as:

$$Q(\psi | \mathcal{D}, \psi^{(m)}) = Q_1 + Q_2 + Q_3 + Q_4,$$

where  $Q_1, Q_2, Q_3$ , and  $Q_4$  are the **additive pieces** that are **separable** with respect to the model parameters:

$$Q_1 = \sum_{i=1}^n \delta_{i1} \mathbb{E}[\log(\gamma_i) | \mathcal{D}, \psi^{(m)}] + \delta_{i1} \{\log [\lambda_{01}(Y_{i1})] + h_1(\mathbf{x}_i)\} - \mathbb{E}[\gamma_i | \mathcal{D}, \psi^{(m)}] \Lambda_{01}(Y_{i1}) e^{h_1(\mathbf{x}_i)}$$

$$Q_2 = \sum_{i=1}^n \delta_{i2} \mathbb{E}[\log(\gamma_i) | \mathcal{D}, \psi^{(m)}] + (1 - \delta_{i1}) \delta_{i2} \{\log [\lambda_{02}(Y_{i2})] + h_2(\mathbf{x}_i)\} - \mathbb{E}[\gamma_i | \mathcal{D}, \psi^{(m)}] \Lambda_{02}(Y_{i1}) e^{h_2(\mathbf{x}_i)}$$

$$Q_3 = \sum_{i=1}^n \delta_{i1} \delta_{i2} \{\log [\lambda_{03}(Y_{i2})] + h_3(\mathbf{x}_i)\} - \mathbb{E}[\gamma_i | \mathcal{D}, \psi^{(m)}] \delta_{i1} (\Lambda_{03}(Y_{i2} - Y_{i1})) e^{h_3(\mathbf{x}_i)}$$

$$Q_4 = \sum_{i=1}^n -\frac{1}{\theta} \log(\theta) + \left(\frac{1}{\theta} - 1\right) \mathbb{E}[\log(\gamma_i) | \mathcal{D}, \psi^{(m)}] - \frac{1}{\theta} \mathbb{E}[\gamma_i | \mathcal{D}, \psi^{(m)}] - \log \Gamma\left(\frac{1}{\theta}\right)$$

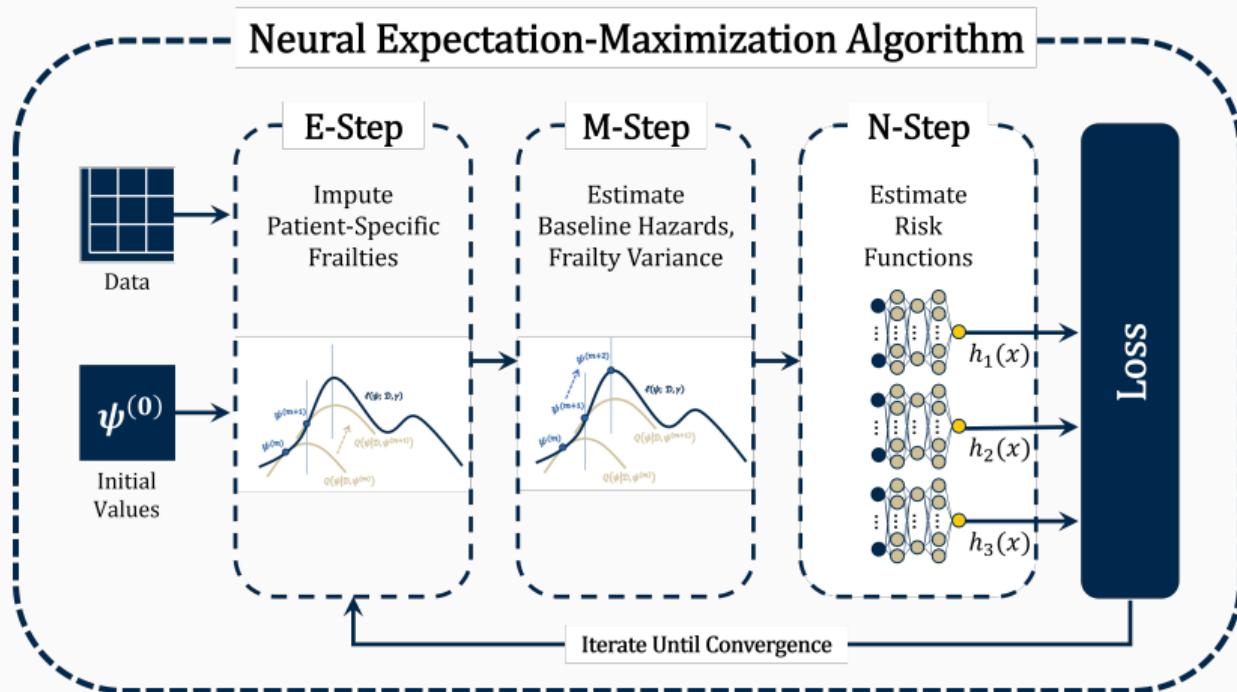


Figure: Overview of our proposed neural expectation-maximization algorithm

## Risk Prediction: A Deep Learning Approach

We extend the **EM algorithm** to a hybrid **multi-task deep learning** approach for semi-competing risk prediction. Our proposed **neural EM algorithm** consists of

- **E-Step:** *Frailities* estimated given data, current baseline hazard values, and current risk function estimates
- **M-Step:** Estimate fully **non-parametric cumulative baseline hazard** by non-decreasing **step functions** (i.e., jumps at unique failure times); estimate frailty **variance**
- **N-Step:** Maximize the expectation of the complete data likelihood given the data and the estimates of frailty and baseline hazard with respect to deep neural network parameters for each **risk function**,  $h_g(x_i); g = 1, 2, 3$

- Sub-network predictions are based on an  $L$ -fold **composite function**

$$F_L(\cdot) = f_L \circ f_{L-1} \circ \cdots \circ f_1(\cdot) \text{ where } (g \circ f)(\cdot) = g(f(\cdot))$$

$$f_l(x) = \sigma_l(\mathbf{W}_l x + \mathbf{b}_l) \in \mathbb{R}^{k_{l+1}}$$

- where  $\sigma_l$  is an activation function,  $\mathbf{W}_l$  are weights, and  $\mathbf{b}_l$  are biases
- For **identifiability**, we require  $h_g(\mathbf{0}) = 0$ , where  $\mathbf{0}$  is a  $p$ -vector of 0's
- Hyperparameters** (e.g., hidden layers, dropout fraction, learning rate) are **optimized** over a grid of values based on **predictive performance**

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No metrics tailored to semi-competing risks exist to assess ***predictive accuracy***. We propose a bivariate extension to the ***Brier Score*** [Brier et al., 1950]

$$\begin{aligned} BBS_c(t) = & \frac{\pi_i(t)^2 \cdot \mathbb{I}\{Y_{i1} \leq t, \delta_{i1} = 1, Y_{i1} \leq Y_{i2}\}}{\hat{G}_i(Y_{i1})} \\ & + \frac{\pi_i(t)^2 \cdot \mathbb{I}\{Y_{i1} \leq t, Y_{i2} \leq t, \delta_{i1} = 0, \delta_{i2} = 1, Y_{i1} \leq Y_{i2}\}}{\hat{G}_i(Y_{i2})} \\ & + \frac{[1 - \pi_i(t)]^2 \cdot \mathbb{I}\{Y_{i1} > t, Y_{i2} > t\}}{\hat{G}_i(t)} \end{aligned}$$

- $\pi_i(t)$  is an ***estimate*** of  $S_i(t) = \Pr(T_{i1} > t, T_{i2} > t)$
- $\hat{G}_i(t)$  is an ***estimate*** of  $G_i(t) = \Pr(C_i > t) > 0$
- In ***expectation***, we have  $\mathbb{E}[BBS_c(t)]$  equal to the ***MSE*** of  $\pi_i(t)$ , plus a ***constant piece*** w.r.t.  $\pi_i(t)$

## Simulations

We generated 500 **independent datasets**,  $x_i \sim N_2(0, I_2)$ ,  $\beta_g = [1, 1]^T$ ,  $g = 1, 2, 3$ ,  $\phi_{11} = \phi_{21} = 2$ ,  $\phi_{31} = 0.75$ ,  $\phi_{12} = \phi_{22} = 2.25$ , and  $\phi_{32} = 2$ , and **we varied**:

- **Sample Sizes ( $n$ )**: 1,000 and 10,000      **Frailty Variances ( $\theta$ )**: 0.5 and 2
- **Censoring Rates**: 0%, 25%, and 50%
- **Log-Risk Functions**:
  - **Linear**:  $h_g(\mathbf{X}_i) = \mathbf{X}'_i \beta_g$ ;  $\beta_g = \mathbf{1}_p = (1, 1, \dots, 1)$ ;  $g = 1, 2, 3$
  - **Non-Linear**:  $h_g(\mathbf{X}_i) = \sum_{j=1}^p x_{ij}^3 \beta_{gj}$ ;  $\beta_{gj} = 1$ ;  $g = 1, 2, 3$ ;  $j = 1, \dots, p$
  - **Non-Monotonic**:  $h_g(\mathbf{X}_i) = \log(|\mathbf{X}'_i \beta_g| + 1)$ ;  $\beta_g = \mathbf{1}_p = (1, 1, \dots, 1)$ ;  $g = 1, 2, 3$

Performance was assessed via the **bivariate Brier score** integrated up to  $t = 1$  year and the **MISE for the log-risk surfaces**, separately

Table: Average (SD) mean integrated squared errors (MISE) for the simulated log-risk surfaces,  $h_g(\mathbf{X}_i)$ , for each state transition hazard (50% censoring)

Simulation Settings			Parametric Approach			Neural EM Algorithm		
$n$	$\theta$	Risk	$h_1(x_i)$	$h_2(x_i)$	$h_3(x_i)$	$h_1(x_i)$	$h_2(x_i)$	$h_3(x_i)$
1,000	0.5	Linear	0.02 (0.02)	0.03 (0.02)	0.05 (0.03)	0.10 (0.07)	0.10 (0.09)	0.18 (0.17)
10,000	0.5	Linear	0.00 (0.00)	0.00 (0.00)	0.00 (0.01)	0.10 (0.07)	0.11 (0.08)	0.17 (0.16)
1,000	2.0	Linear	0.03 (0.03)	0.03 (0.02)	0.03 (0.05)	0.22 (0.13)	0.19 (0.13)	0.22 (0.17)
10,000	2.0	Linear	0.00 (0.00)	0.00 (0.00)	0.01 (0.00)	0.14 (0.09)	0.14 (0.10)	0.16 (0.14)
1,000	0.5	Non-Linear	0.16 (0.11)	0.20 (0.12)	0.43 (0.42)	0.11 (0.05)	0.09 (0.06)	0.08 (0.02)
10,000	0.5	Non-Linear	0.19 (0.03)	0.22 (0.05)	0.22 (0.06)	0.08 (0.03)	0.08 (0.03)	0.11 (0.05)
1,000	2.0	Non-Linear	0.30 (0.27)	0.31 (0.20)	0.37 (0.30)	0.14 (0.11)	0.12 (0.06)	0.13 (0.06)
10,000	2.0	Non-Linear	0.22 (0.05)	0.20 (0.04)	0.19 (0.06)	0.16 (0.08)	0.14 (0.07)	0.14 (0.08)
1,000	0.5	Non-Monotonic	2.04 (0.51)	2.00 (0.66)	2.57 (1.01)	0.11 (0.12)	0.13 (0.13)	0.18 (0.14)
10,000	0.5	Non-Monotonic	2.04 (0.20)	2.05 (0.19)	2.33 (0.25)	0.06 (0.03)	0.09 (0.09)	0.14 (0.09)
1,000	2.0	Non-Monotonic	2.13 (0.69)	2.00 (0.68)	2.43 (0.88)	0.18 (0.10)	0.18 (0.09)	0.16 (0.11)
10,000	2.0	Non-Monotonic	1.94 (0.22)	1.95 (0.24)	2.25 (0.30)	0.10 (0.05)	0.11 (0.08)	0.15 (0.10)

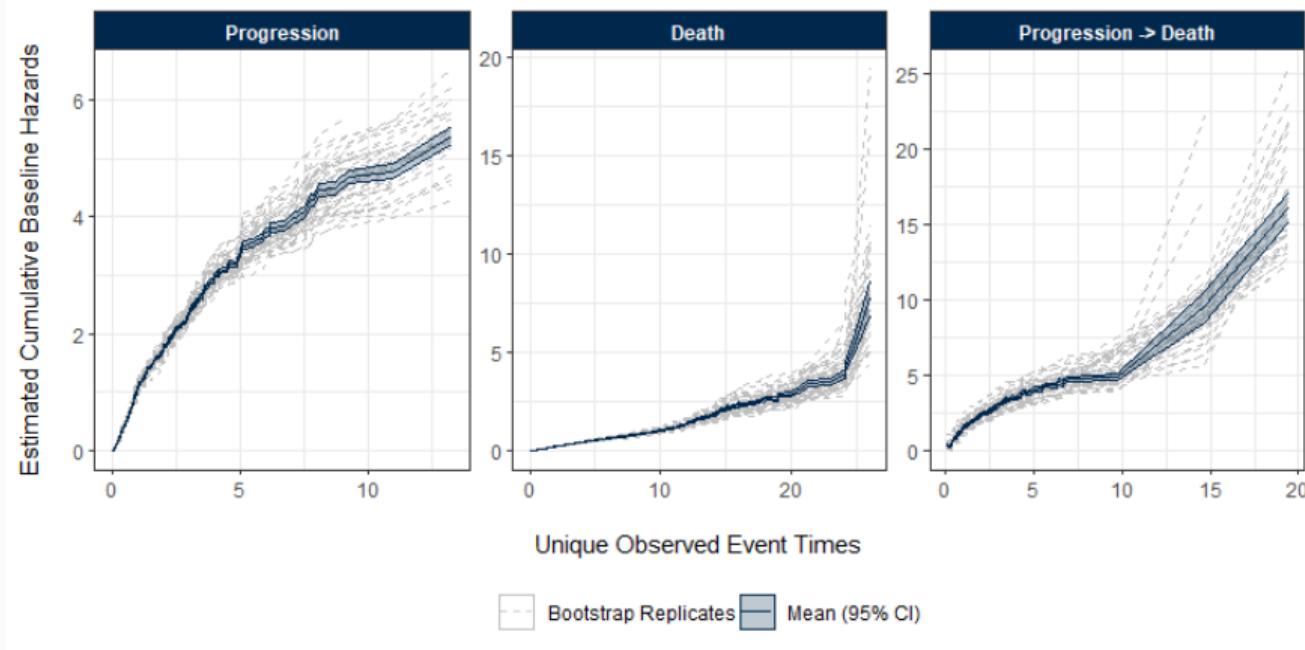
This study subset includes **7,460 patients** with non-small cell lung cancer, diagnosed between June 1983 and October 2021 [Christiani, 2017]

We investigate ***time to disease progression and death***, where progression might be censored by death or the study endpoint

Table: Semi-competing event rates among  $n = 7,460$  patients in our analytic sample.

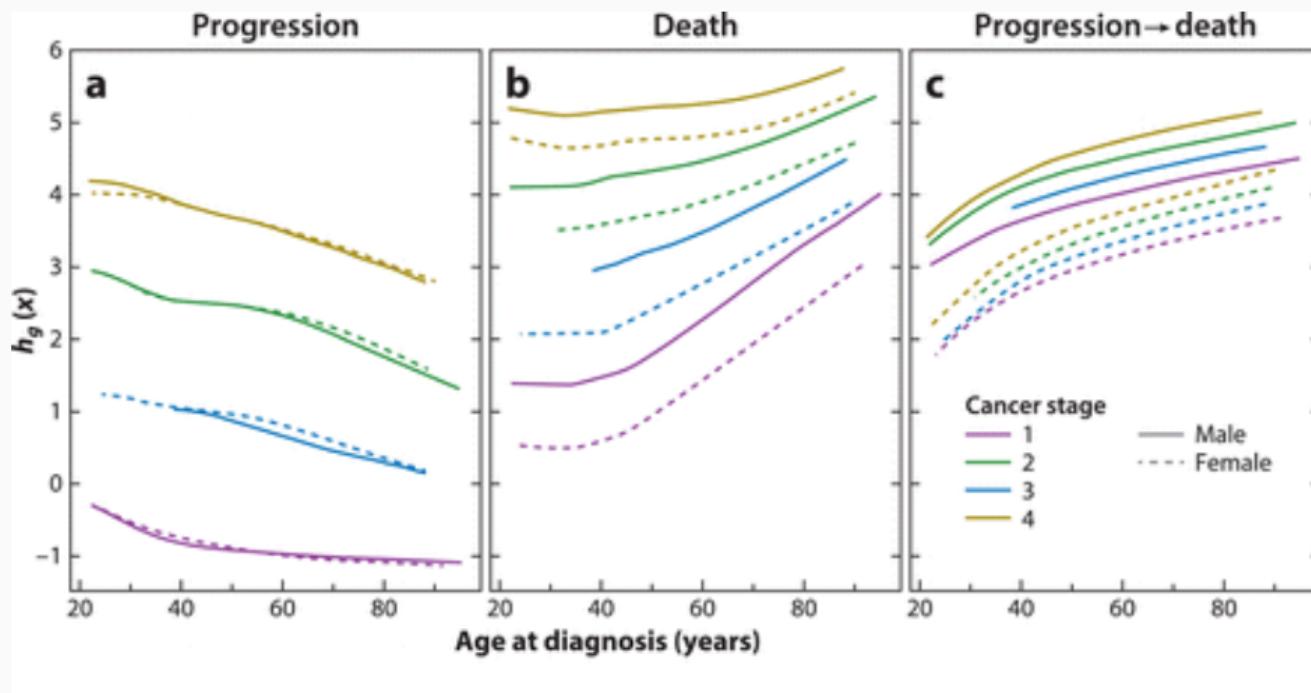
Progression Observed / Death Observed	Yes	No
Yes	143 (1.9%)	295 (4.0%)
No	2,720 (36.5%)	4,302 (57.7%)

Figure: Average estimated cumulative baseline hazard functions and 95% bootstrap confidence intervals for each state transition based on 50 bootstrap samples of our data.



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Figure: Example log-risk functions of age at diagnosis on each state transition, stratified by cancer stage (line color) and sex (solid versus dashed lines).



- Baseline hazards highest in ***sojourn time*** between progression and death
- Non-linear relationship between ***age*** and hazards, which ***differs by transition***
- Stage at diagnosis appears to have a strong effect on the ***risk of progression or death*** from diagnosis, and to a lesser extent death following progression
- ***Males*** have a ***higher risk*** of mortality than females
- ***5-year iBBS*** for our method was 0.32 vs. 0.68 from a traditional model, suggesting that a linear model is not predictive
- We estimate the ***frailty variance***,  $\theta$ , to be 3.15 (bootstrapped 95% confidence interval: 3.02–3.29), which suggests that progression is indeed correlated with death.

# Conclusions

- Assuming a ***linear relationship*** between risk factors may be an oversimplification in settings of complex cancers
- Deep learning allows for ***non-parametric*** estimation of risk functions
- Neural networks circumvent the ***curse of dimensionality*** by projecting data into a lower relevant representational space through weighting [Bauer and Kohler, 2019, Poggio et al., 2017]

## Conclusions cont.

- We proposed a ***neural expectation-maximization algorithm*** to predict time-to-event outcomes arising from semi-competing risks
- In simulation, our results show ***high accuracy*** in estimating the relationship predictors and the transition hazards in increasingly complex settings
- Our approach had a much greater ***predictive accuracy*** than traditional semi-competing regression approaches when applied to the ***BLCS***
- We detected potential ***non-linear effects*** and ***interactions*** between commonly-studied risk factors such as age, sex, and stage at diagnosis

# Questions?

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<https://arxiv.org/abs/2212.12028>



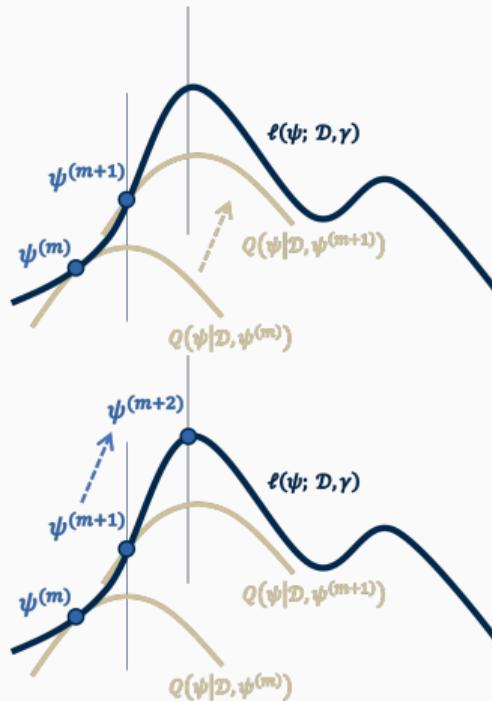
## Some Thanks

- My advisor: Yi Li
- My committee
- My lab mates
- David Christiani and the Christiani lab, Xianan Wang, and Jui Kothari
- My co-workers at KECC
- STATCOM

## Appendix

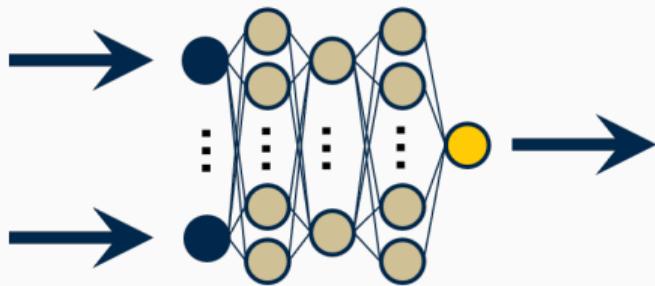
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- **E Step:** Frailties **estimated** given data and current baseline hazard values
- **M Step:** Baseline hazards and frailty variance **estimated** given current frailty estimates
- But how do we estimate the complex relationships between **risk factors**?



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**Deep learning** has emerged as a powerful tool for **survival prediction**, but limited work has been done on multi-state outcomes, let alone **semi-competing**



In artificial neural networks, **nodes** are connected as a weighted sum of inputs **affine transformations** and **nonlinear activations** [Bauer and Kohler, 2019]

We propose the use of **deep learning** to estimate the **risk functions** for each hazard (i.e, state transition)

# Expectation (E) Step

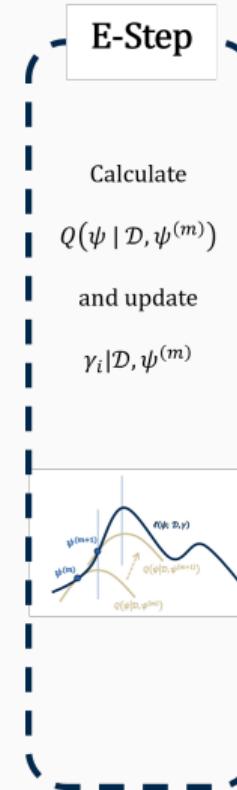
With  $\gamma_i \sim \text{Gamma}(\frac{1}{\theta}, \frac{1}{\theta})$ , calculate expected log-complete data likelihood given the observed data

$$Q(\psi | \mathcal{D}, \psi^{(m)}) = \mathbb{E}_{\gamma} [\ell(\psi; \mathcal{D}, \gamma) | \mathcal{D}, \psi^{(m)}]$$

where  $\ell(\psi; \mathcal{D}, \gamma) = \log L(\psi; \mathcal{D}, \gamma)$

As a useful quantity, we have

$$\begin{aligned} & \mathbb{E}[\gamma_i | \mathcal{D}, \psi^{(m)}] \\ &= \frac{1/\tilde{\theta} + \delta_{i1}}{1/\tilde{\theta} + \tilde{\Lambda}_{01}(y_{i1})e^{\tilde{h}_1(x_i)} + \tilde{\Lambda}_{02}(y_{i1})e^{\tilde{h}_2(x_i)} + \delta_{i1}\tilde{\Lambda}_{03}(y_{i1}, y_{i2})e^{\tilde{h}_3(x_i)}} \end{aligned}$$



# Maximization (M) Step

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Update estimates of the **baseline hazards**, which resemble Nelson-Aalen type estimators

$$\Delta\Lambda_{01}^{(m+1)}(t) = \frac{\sum_{i=1}^n \delta_{i1} I[Y_{i1} = t]}{\sum_{i=1}^n \mathbb{E}[\gamma_i | \mathcal{D}, \psi^{(m)}] I[Y_{i1} \geq t] \exp \left\{ h_1^{(m)}(\mathbf{x}_i) \right\}}$$

$$\Delta\Lambda_{02}^{(m+1)}(t) = \frac{\sum_{i=1}^n (1 - \delta_{i1}) \delta_{i2} I[Y_{i2} = t]}{\sum_{i=1}^n \mathbb{E}[\gamma_i | \mathcal{D}, \psi^{(m)}] I[Y_{i2} \geq t] \exp \left\{ h_2^{(m)}(\mathbf{x}_i) \right\}}$$

$$\Delta\Lambda_{03}^{(m+1)}(t) = \frac{\sum_{i=1}^n \delta_{i1} \delta_{i2} I[Y_{i2} - Y_{i1} = t]}{\sum_{i=1}^n \mathbb{E}[\gamma_i | \mathcal{D}, \psi^{(m)}] \delta_{i1} I[Y_{i2} - Y_{i1} \geq t] \exp \left\{ h_3^{(m)}(\mathbf{x}_i) \right\}}$$

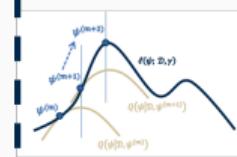
M-Step

Maximize

$\psi^{(m+1)}$

with respect to

$Q(\psi | \mathcal{D}, \psi^{(m)})$

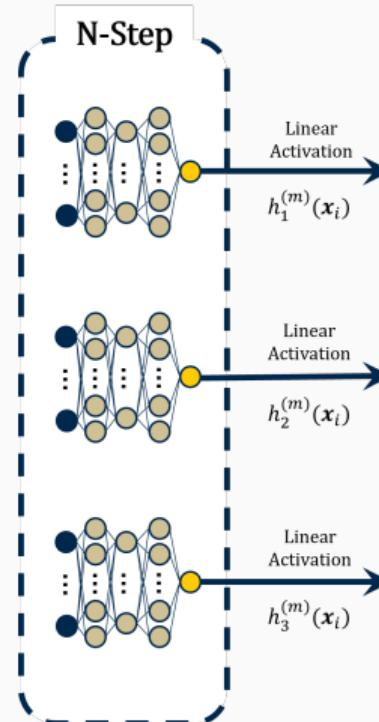


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Update the **risk functions** with outputs from three **network sub-architectures**

Sub-networks are **fully-connected feed-forward networks** with linear activations in the final layer

Each sub-network is made up of  $L$  layers, with  $k_l$  neurons in the  $l$ th layer



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In **expectation**, we have that the Bivariate Brier Score is equal to

$$\mathbb{E}[BBS_c(t)] = \text{MSE}(t) + \frac{1}{n} \sum_{i=1}^n S_i(t) \cdot [1 - S_i(t)]$$

- This is the **MSE** of  $\pi_i(t)$ , plus a **constant piece** with respect to  $\pi_i(t)$
  - Constant is **irreducible error** incurred by approximating  $S_i(t)$

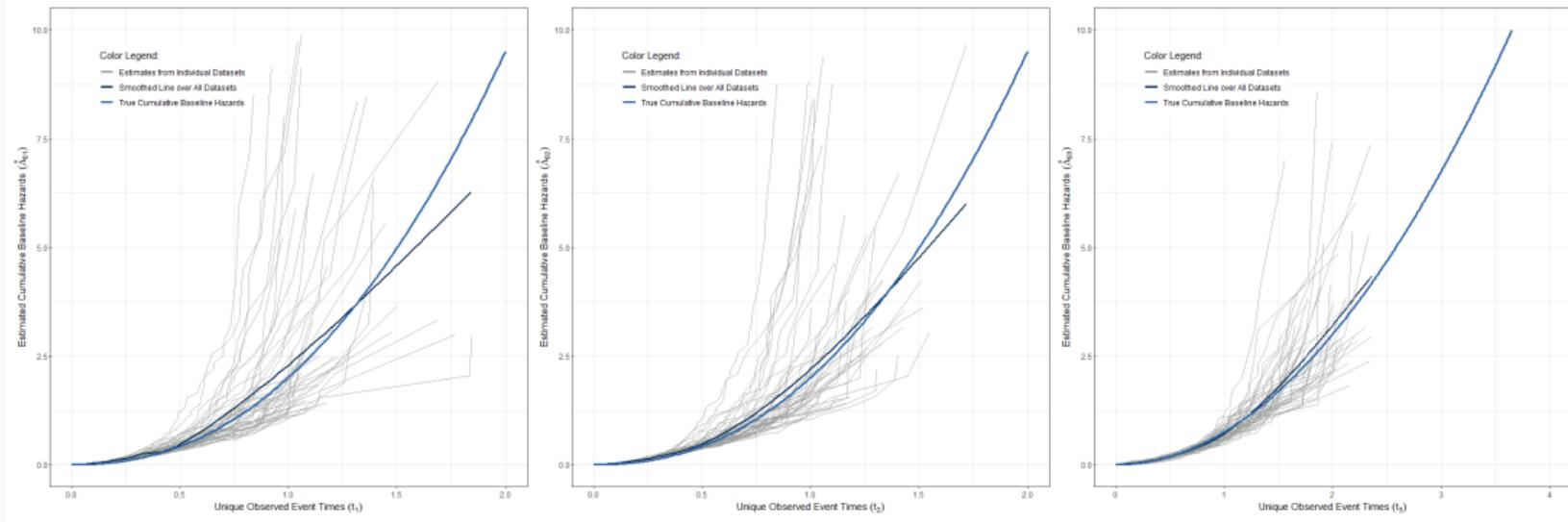


Figure: Estimated cumulative baseline hazard functions based on an example 50 generated datasets with  $n = 1,000$ ,  $\theta = 0.5$ , log-risk function = non-monotonic, and 50% censoring rates

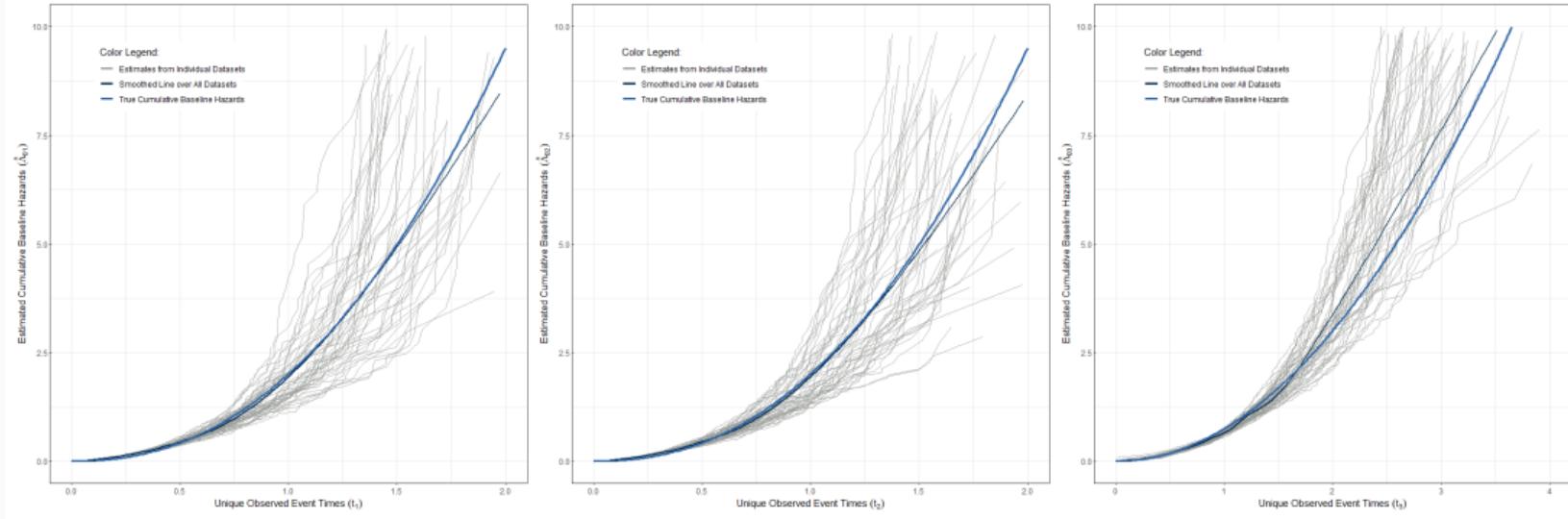


Figure: Estimated cumulative baseline hazard functions based on an example 50 generated datasets with  $n = 1,000$ ,  $\theta = 0.5$ , log-risk function = non-monotonic, and censoring rate = 0%

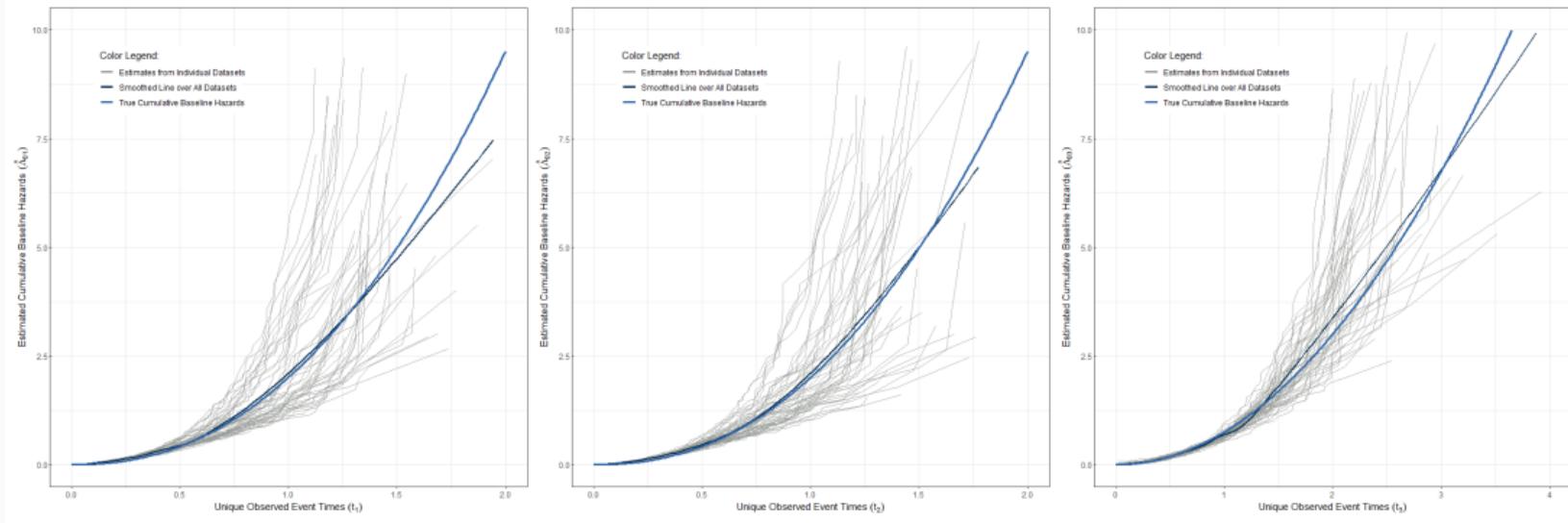


Figure: Estimated cumulative baseline hazard functions based on an example 50 generated datasets with  $n = 1,000$ ,  $\theta = 0.5$ , log-risk function = non-monotonic, and censoring rate = 25%

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Table: Estimated frailty variance and one year integrated bivariate Brier score under various simulation settings (50% censoring rate)

Simulation Settings			Integrated Bivariate Brier Score	
$n$	Risk	$\theta$	Truth	Neural EM
1,000	Linear	0.5	0.1853 (0.0060)	0.1866 (0.0075)
10,000	Linear	0.5	0.1912 (0.0042)	0.1934 (0.0044)
1,000	Linear	2.0	0.3081 (0.0323)	0.3129 (0.0355)
10,000	Linear	2.0	0.3050 (0.0133)	0.3090 (0.0142)
1,000	Non-Linear	0.5	0.1794 (0.0037)	0.1830 (0.0056)
10,000	Non-Linear	0.5	0.1819 (0.0022)	0.1853 (0.0072)
1,000	Non-Linear	2.0	0.3074 (0.0211)	0.3127 (0.0264)
10,000	Non-Linear	2.0	0.3076 (0.0065)	0.3179 (0.0146)
1,000	Non-Monotonic	0.5	0.1794 (0.0037)	0.1830 (0.0056)
10,000	Non-Monotonic	0.5	0.1819 (0.0022)	0.1853 (0.0072)
1,000	Non-Monotonic	2.0	0.3074 (0.0211)	0.3127 (0.0264)
10,000	Non-Monotonic	2.0	0.3076 (0.0065)	0.3179 (0.0146)

Table: Estimated frailty variance and one year integrated bivariate Brier score under various simulation settings (50% censoring rate)

Simulation Settings		Frailty Variance Estimation			Integrated Bivariate Brier Score		
n	Risk	Truth	Parametric	Neural EM	Truth	Parametric	Neural EM
1,000	Linear	0.5	0.47 (0.17)	0.47 (0.12)	0.1853 (0.0060)	0.1858 (0.0066)	0.1866 (0.0075)
10,000	Linear	0.5	0.51 (0.05)	0.50 (0.05)	0.1912 (0.0042)	0.1912 (0.0046)	0.1934 (0.0044)
1,000	Linear	2.0	1.96 (0.48)	1.87 (0.31)	0.3081 (0.0323)	0.3092 (0.0387)	0.3129 (0.0355)
10,000	Linear	2.0	2.00 (0.16)	1.95 (0.06)	0.3050 (0.0133)	0.3050 (0.0129)	0.3090 (0.0142)
1,000	Non-Linear	0.5	0.47 (0.20)	0.49 (0.12)	0.1794 (0.0037)	0.1808 (0.0032)	0.1830 (0.0056)
10,000	Non-Linear	0.5	0.51 (0.06)	0.49 (0.03)	0.1819 (0.0022)	0.1833 (0.0026)	0.1853 (0.0072)
1,000	Non-Linear	2.0	1.93 (0.28)	1.87 (0.21)	0.3074 (0.0211)	0.3090 (0.0239)	0.3127 (0.0264)
10,000	Non-Linear	2.0	2.06 (0.11)	1.94 (0.09)	0.3076 (0.0065)	0.3092 (0.0077)	0.3179 (0.0146)
1,000	Non-Monotonic	0.5	0.47 (0.20)	0.49 (0.13)	0.1794 (0.0037)	0.1808 (0.0032)	0.1830 (0.0056)
10,000	Non-Monotonic	0.5	0.51 (0.06)	0.49 (0.04)	0.1819 (0.0022)	0.1833 (0.0026)	0.1853 (0.0072)
1,000	Non-Monotonic	2.0	1.93 (0.28)	1.96 (0.21)	0.3074 (0.0211)	0.3090 (0.0239)	0.3127 (0.0264)
10,000	Non-Monotonic	2.0	2.06 (0.11)	1.94 (0.09)	0.3076 (0.0065)	0.3092 (0.0077)	0.3179 (0.0146)

Table: Estimated frailty variance and one year integrated bivariate Brier score under various simulation settings

Simulation Settings			Frailty Variance Estimation			Integrated Bivariate Brier Score		
n	Risk	Cens.	Truth	Parametric	Neural EM	Truth	Parametric	Neural EM
1,000	Linear	0%	0.5	0.49 (0.04)	0.49 (0.07)	0.1600 (0.0035)	0.1605 (0.0035)	0.1618 (0.0035)
10,000	Linear	0%	0.5	0.50 (0.01)	0.49 (0.03)	0.1584 (0.0013)	0.1585 (0.0013)	0.1594 (0.0014)
1,000	Linear	0%	2.0	1.96 (0.11)	1.92 (0.08)	0.1915 (0.0047)	0.1917 (0.0047)	0.1925 (0.0049)
10,000	Linear	0%	2.0	2.01 (0.03)	1.98 (0.04)	0.1911 (0.0016)	0.1911 (0.0016)	0.1921 (0.0015)
1,000	Non-Linear	0%	0.5	0.49 (0.05)	0.50 (0.08)	0.1822 (0.0038)	0.1841 (0.0036)	0.1855 (0.0036)
10,000	Non-Linear	0%	0.5	0.51 (0.01)	0.51 (0.02)	0.1821 (0.0011)	0.1836 (0.0011)	0.1858 (0.0014)
1,000	Non-Linear	0%	2.0	1.97 (0.11)	1.92 (0.07)	0.2244 (0.0022)	0.2258 (0.0022)	0.2271 (0.0024)
10,000	Non-Linear	0%	2.0	2.01 (0.03)	1.95 (0.03)	0.2245 (0.0009)	0.2251 (0.0009)	0.2276 (0.0015)
1,000	Non-Monotonic	0%	0.5	0.49 (0.05)	0.50 (0.08)	0.1822 (0.0038)	0.1841 (0.0036)	0.1855 (0.0036)
10,000	Non-Monotonic	0%	0.5	0.51 (0.01)	0.51 (0.02)	0.1821 (0.0011)	0.1836 (0.0011)	0.1858 (0.0014)
1,000	Non-Monotonic	0%	2.0	1.97 (0.11)	1.95 (0.07)	0.2244 (0.0022)	0.2258 (0.0022)	0.2271 (0.0024)
10,000	Non-Monotonic	0%	2.0	2.01 (0.03)	1.95 (0.03)	0.2245 (0.0009)	0.2251 (0.0009)	0.2276 (0.0015)
1,000	Linear	25%	0.5	0.47 (0.10)	0.47 (0.11)	0.1880 (0.0046)	0.1886 (0.0050)	0.1892 (0.0053)
10,000	Linear	25%	0.5	0.50 (0.05)	0.48 (0.02)	0.1899 (0.0030)	0.1900 (0.0029)	0.1914 (0.0029)
1,000	Linear	25%	2.0	2.00 (0.35)	1.95 (0.20)	0.2967 (0.0200)	0.2970 (0.0228)	0.2999 (0.0224)
10,000	Linear	25%	2.0	2.02 (0.12)	1.96 (0.08)	0.2979 (0.0074)	0.2979 (0.0069)	0.3030 (0.0079)
1,000	Non-Linear	25%	0.5	0.47 (0.14)	0.48 (0.12)	0.1851 (0.0045)	0.1866 (0.0040)	0.1879 (0.0048)
10,000	Non-Linear	25%	0.5	0.52 (0.05)	0.50 (0.04)	0.1858 (0.0010)	0.1874 (0.0012)	0.1893 (0.0025)
1,000	Non-Linear	25%	2.0	2.01 (0.23)	1.89 (0.21)	0.3042 (0.0176)	0.3065 (0.0220)	0.3088 (0.0201)
10,000	Non-Linear	25%	2.0	2.04 (0.10)	1.96 (0.10)	0.3032 (0.0034)	0.3044 (0.0048)	0.3113 (0.0093)
1,000	Non-Monotonic	25%	0.5	0.47 (0.14)	0.47 (0.12)	0.1851 (0.0045)	0.1866 (0.0040)	0.1879 (0.0048)
10,000	Non-Monotonic	25%	0.5	0.52 (0.05)	0.50 (0.04)	0.1858 (0.0010)	0.1874 (0.0012)	0.1893 (0.0025)
1,000	Non-Monotonic	25%	2.0	2.01 (0.23)	1.90 (0.21)	0.3042 (0.0176)	0.3065 (0.0220)	0.3088 (0.0201)
10,000	Non-Monotonic	25%	2.0	2.04 (0.10)	1.91 (0.10)	0.3032 (0.0034)	0.3044 (0.0048)	0.3113 (0.0093)

Table: Average (SD) mean integrated squared errors (MISE) for the simulated log-risk surfaces,  $h_g(\mathbf{X}_i)$ , for each state transition hazard

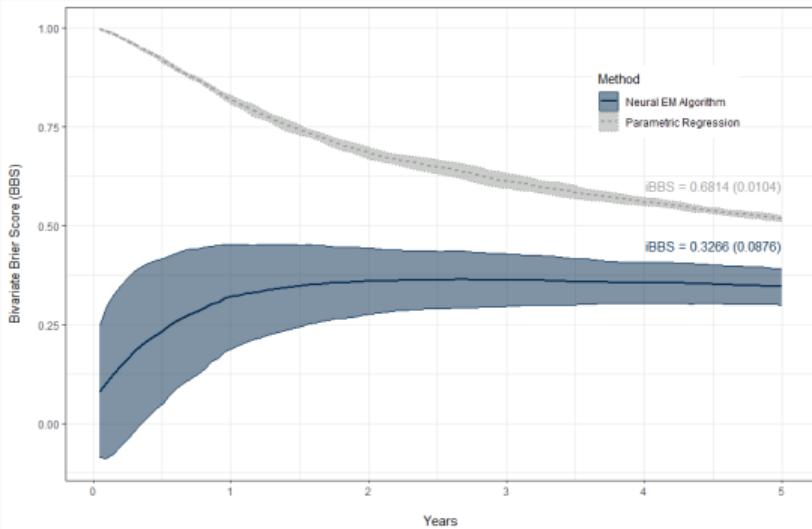
Simulation Settings			Parametric Approach			Neural EM Algorithm			
$n$	$\theta$	Risk	Cens.	$h_1(x_i)$	$h_2(x_i)$	$h_3(x_i)$	$h_1(x_i)$	$h_2(x_i)$	$h_3(x_i)$
1,000	0.5	Linear	0%	0.01 (0.01)	0.01 (0.01)	0.01 (0.01)	0.07 (0.07)	0.08 (0.08)	0.07 (0.05)
10,000	0.5	Linear	0%	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.08 (0.06)	0.07 (0.05)	0.07 (0.04)
1,000	2.0	Linear	0%	0.02 (0.01)	0.01 (0.01)	0.01 (0.01)	0.12 (0.07)	0.11 (0.08)	0.12 (0.09)
10,000	2.0	Linear	0%	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.11 (0.06)	0.11 (0.06)	0.13 (0.09)
1,000	0.5	Non-Linear	0%	0.17 (0.07)	0.15 (0.06)	0.19 (0.08)	0.07 (0.04)	0.09 (0.03)	0.07 (0.01)
10,000	0.5	Non-Linear	0%	0.17 (0.02)	0.19 (0.04)	0.18 (0.02)	0.08 (0.01)	0.08 (0.03)	0.08 (0.03)
1,000	2.0	Non-Linear	0%	0.22 (0.15)	0.27 (0.15)	0.22 (0.18)	0.15 (0.01)	0.10 (0.05)	0.11 (0.04)
10,000	2.0	Non-Linear	0%	0.20 (0.04)	0.19 (0.03)	0.20 (0.06)	0.14 (0.07)	0.14 (0.08)	0.12 (0.05)
1,000	0.5	Non-Monotonic	0%	1.79 (0.32)	1.79 (0.38)	1.83 (0.35)	0.09 (0.05)	0.09 (0.04)	0.09 (0.06)
10,000	0.5	Non-Monotonic	0%	1.82 (0.11)	1.81 (0.14)	1.76 (0.12)	0.07 (0.03)	0.08 (0.03)	0.08 (0.05)
1,000	2.0	Non-Monotonic	0%	1.89 (0.49)	1.86 (0.53)	1.97 (0.52)	0.15 (0.05)	0.13 (0.06)	0.14 (0.07)
10,000	2.0	Non-Monotonic	0%	1.82 (0.18)	1.80 (0.18)	1.85 (0.17)	0.14 (0.04)	0.12 (0.03)	0.14 (0.06)
1,000	0.5	Linear	25%	0.01 (0.02)	0.01 (0.01)	0.01 (0.02)	0.11 (0.10)	0.10 (0.07)	0.13 (0.12)
10,000	0.5	Linear	25%	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.12 (0.08)	0.12 (0.05)	0.12 (0.10)
1,000	2.0	Linear	25%	0.03 (0.02)	0.02 (0.02)	0.03 (0.03)	0.15 (0.10)	0.13 (0.08)	0.16 (0.11)
10,000	2.0	Linear	25%	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.14 (0.09)	0.12 (0.06)	0.14 (0.10)
1,000	0.5	Non-Linear	25%	0.18 (0.12)	0.15 (0.06)	0.32 (0.30)	0.10 (0.04)	0.08 (0.02)	0.07 (0.02)
10,000	0.5	Non-Linear	25%	0.19 (0.03)	0.21 (0.05)	0.21 (0.06)	0.08 (0.03)	0.08 (0.04)	0.09 (0.04)
1,000	2.0	Non-Linear	25%	0.29 (0.24)	0.31 (0.20)	0.38 (0.29)	0.14 (0.05)	0.11 (0.05)	0.12 (0.04)
10,000	2.0	Non-Linear	25%	0.21 (0.04)	0.20 (0.03)	0.19 (0.06)	0.12 (0.04)	0.14 (0.06)	0.19 (0.19)
1,000	0.5	Non-Monotonic	25%	1.97 (0.47)	2.02 (0.51)	2.18 (0.60)	0.10 (0.08)	0.10 (0.08)	0.12 (0.08)
10,000	0.5	Non-Monotonic	25%	1.92 (0.16)	1.91 (0.16)	2.16 (0.17)	0.09 (0.04)	0.09 (0.05)	0.11 (0.06)
1,000	2.0	Non-Monotonic	25%	2.00 (0.62)	1.97 (0.69)	2.25 (0.75)	0.13 (0.07)	0.15 (0.08)	0.13 (0.06)
10,000	2.0	Non-Monotonic	25%	1.85 (0.20)	1.85 (0.21)	2.12 (0.27)	0.10 (0.05)	0.11 (0.06)	0.11 (0.05)

- Generated 1,000 **independent datasets** of size  $n = 1,000$
- Assumed **Weibull** baseline hazards with  $\phi_{g1} = 1.5$ ,  $\phi_{g2} = 0.2$ , and  $\theta = 0.5$
- Varied whether **covariate** generated and **censoring rate** of 0% vs. 50%

Table: Mean (SD) integrated Bivariate Brier Score under various data generation settings

Simulation Settings		1-Year iBBS	
Covariate	Censoring	True	Estimated
No	No	0.0187 (0.0068)	0.0199 (0.0073)
Yes	No	0.0181 (0.0067)	0.0205 (0.0077)
No	Yes	0.0206 (0.0067)	0.0219 (0.0072)
Yes	Yes	0.0195 (0.0066)	0.0221 (0.0075)

Figure: Average (SD) Bivariate Brier score (BBS) for our Neural EM Algorithm (blue, solid line) versus a semi-competing regression model (gray, dashed line), with 5-fold cross-validation. Integrated (BBS) was taken over 100 evenly spaced time points from time zero to five years post-diagnosis.



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