Toward a Well-Calibrated Discrimination through Survival Outcome-Aware Contrastive Learning

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Outline

- Introduction to Survival Analysis
- Consideration
- Objective
- Challenges and Motivation
- Proposed Method
- Experiments

What is survival analysis?

- A very common outcome in medical studies is the time until an event occurs:
	- The time until a patient dies
	- The time until a patient suffers a heart attack
	- The time until a liver transplant patient needs a new liver
	- The time until the recurrence of cancer following treatment

○ Data involving such an outcome is often called "time-to-event" data or "failure-time data" or "survival" data, and the branch of statistics that deals with analyzing these data is called survival analysis

Survival data

○ Survival (a.k.a. time-to-event) data

$$
\mathcal{D} = \{(\mathbf{x}_i, \tau_i, \delta_i)\}_{i=1}^N
$$

- x: Observed features (covariates)
- τ : Time-to-event or time-to-censoring elapsed since the baseline (e.g., the entry to a clinical trial)
- δ : Label indicating whether event the event or the censoring occurred

Figure. An illustration of survival data

Survival data

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○ Distinct Characteristics: **Right-censoring**

Survival data

○ Notations

- $T \in \mathbb{R}_+$ be the random variable for time-to-event
- $-C \in \mathbb{R}_+$ be the random variables for time-to-censoring
- Right-censoring indicates when censoring occurs before the event of interest is observed. Denoting t and c be the realizations of r.v.s T and C , we have

$$
\delta = \mathbb{I}(t \leq c) \qquad \tau = \min(t, c)
$$

Often assume "independent censoring", i.e., $P(T, C | X = x) = P(T | X = x) P(C | X = x)$

Solution: Survival Analysis

○ **Our goal**

- Provides the probability an event occurring as a function of time and patient features
- Provides understanding of interactions between features and the time-to-event outcomes

- We want to use partial information from the right-censored samples:
	- Censoring implies that the event will occur after the censoring time

Important quantities : Survival / Risk function

 \circ Formally, we want to estimate the survival function given x

$$
S(t|\mathbf{x}) = \mathbb{P}(T > t|\mathbf{x})
$$

probability an event occurring after time t

- $T \in \mathbb{R}_+$: Random variable for the time-to-event
- $-$ x: Patient input feature
- o Or equivalently, we want to estimate the risk function given x

$$
R(t|\mathbf{x}) = 1 - S(t|\mathbf{x}) = \mathbb{P}(T \le t|\mathbf{x})
$$

probability an event occurring before time t

Consideration

○ Discriminate patients' risks of having an event of interest

Objective : Negative log-likelihood loss

- \circ The log-likelihood of the time-to-events for survival dataset \rightarrow unbiased
	- Event is observed (i.e., $\delta_i = 1$), knowing that the event occurred at time τ_i
	- Event is not observed (i.e., $\delta_i = 0$), knowing that the event will occur after time τ_i

$$
\mathcal{L}_{NLL} = -\log \prod_{i=1}^{N} \left[\hat{p}(\tau_i | \mathbf{x}_i)^{\delta_i} \cdot \hat{S}(\tau_i | \mathbf{x}_i)^{(1-\delta_i)} \right]
$$

$$
= -\sum_{i=1}^{N} \left[\underbrace{\delta_i \log \hat{p}(\tau_i | \mathbf{x}_i)}_{\text{for uncensored}} + \underbrace{(1-\delta_i) \log \hat{S}(\tau_i | \mathbf{x}_i)}_{\text{for censored}} \right]
$$

- Often augmented with the NLL loss to enhance the discriminative power
- Aim to maximize a relaxed proxy of the concordance index
	- Well-established metric for evaluating the quality of patient rankings based on the risk predictions of survival model

$$
\mathcal{L}_{Rank} = \sum_{i \neq j} A_{i,j} \cdot \eta \left(\hat{R}(\tau_i | \mathbf{x}_i), \hat{R}(\tau_i | \mathbf{x}_j) \right)
$$

Objective : Ranking loss

$$
\mathcal{L}_{Rank} = \sum_{i \neq j} A_{i,j} \cdot \eta \left(\hat{R}(\tau_i | \mathbf{x}_i), \hat{R}(\tau_i | \mathbf{x}_j) \right) \quad \text{where}
$$

Case 1: Correctly ordered pairs Case 2: Wrongly ordered pairs

- $\hat{R}(\tau_i|\mathbf{x}_i) > \hat{R}(\tau_i|\mathbf{x}_i)$ (O)
- Rewards the estimated Risk Function $\hat{R}(\tau_i|\mathbf{x}_i)$ $\hat{R}(\tau_i|\mathbf{x}_i)$

$$
A_{i,j} = \mathbb{I}(\delta_i = 1, \tau_i < \tau_j)
$$
\n
$$
\text{and } \eta(x, y) = \exp\left(\frac{-(x - y)}{\sigma}\right)
$$

- $\hat{R}(\tau_i|\mathbf{x}_i) < \hat{R}(\tau_i|\mathbf{x}_i)$ (X)
- Penalizes the estimated Risk Function

Challenges

- Combining NLL with ranking loss enhances discrimination but compromises calibration, harming the clinical utility of predicted survival outcomes.
- Ranking loss directly modifies model outputs, potentially leading to misalignment with the actual risk distribution.
	- Typically based on exponential, log-sigmoid, or linear functions

Motivation

- Propose a novel contrastive learning approach for deep survival model
	- Differentiate each sample by their survival outcome, leveraging contrastive learning framework
	- Overcomes ranking loss limitations from directly comparing model outcome in the form of risk/survival function.

 \circ **The encoder**, $f_{\theta}: \mathcal{X} \to \mathcal{H}$, takes features $\mathbf{x} \in \mathcal{X}$ as input and outputs latent representation, i.e., $\mathbf{h} = f_{\theta}(\mathbf{x})$.

○ The projection head., $g_{\psi}: \mathcal{H} \to \mathbb{R}^d$, maps latent representation **h** to the embedding space where contrastive learning is applied, i.e., $z = f_{\theta}$ (h).

○ **Contrastive Learning Network**

By passing the original, positive, and negative samples through $f = g_{\psi} \circ f_{\theta}$, computing our survival outcome-based contrastive learning loss function \mathcal{L}_{SNCE}

- Goal : Aligns with our inductive bias that patients with similar survival outcomes should share similar clinical status, which manifests through similar representations.
- Noise Contrastive Estimation (NCE)
	- To learn mapping $f = g_{\psi} \circ f_{\theta}$ utilizing a positive sample \mathbf{x}^+ ∼ p_{X^+} , and negative samples $\mathbf{x}^- \sim q$

$$
\mathbb{E}_{\mathbf{x}^+ \sim p_X} \left[-\log \frac{e^{s(\mathbf{x}, \mathbf{x}^+)} }{M \cdot \mathbb{E}_{\mathbf{x}^- \sim q} [e^{s(\mathbf{x}, \mathbf{x}^-)}]} \right]
$$

 $-$ *M* : scaling term which is set to the batch size, $s(\mathbf{x}, \mathbf{x}') = \frac{f(\mathbf{x})^T f(\mathbf{x}')}{\prod f(\mathbf{x}) \prod f(\mathbf{x}')},$ $f(\mathbf{x})||\cdot||f(\mathbf{x}')||$

– omit the corresponding temperature v and write $e^{s(\mathbf{x}, \mathbf{x}^-)}$ to denote $e^{s(\mathbf{x}, \mathbf{x}^-)/v}$

- Key aspect of NCE : selecting negative samples to differentiate the anchor sample
- To reflect the difference in the time-to-events in the embedding space, we design a novel distribution q by utilizing the available information from survival outcomes.

- To accurately distinguish patients based on their time-to-event outcomes, we fully utilize the time-to-event information
- \circ Hence, given an anchor (x, τ) and a negative $(x^-; \tau^-)$, we define the weight function, $\sigma > 0$ is a temperature coefficient.
	- This function is a variant of the Laplacian Kernel, which assigns larger weights to samples with large differences in time-to-event outcomes, and smaller weights to samples with small differences

$$
w(\tau^-;\tau)=1-e^{\vert\tau-\tau^-\vert/\sigma}
$$

- \circ Designing q based on the following inductive bias : similar patients are more likely to experience the event at similar time points than the ones who are not.
- \circ We will slightly abuse the notation $w(\mathbf{x}^-; \mathbf{x})$ to denote $w(\tau^-; \tau)$

$$
q(\mathbf{x}^-;\mathbf{x}) = \frac{1}{Z}w(\mathbf{x}^-;\mathbf{x})p(\mathbf{x}^-)
$$

normalizing constant $Z = \frac{1}{M} \sum_{j=1}^{M} w(x_j^{-})$; x

○ Importance sampling using survival outcomes

$$
E_{x \sim q}[e^{s(x,x^{-})}] = E_{x \sim p}\left[\left(\frac{q(x^{-};x)}{p(x^{-})}\right) \cdot e^{s(x,x^{-})}\right]
$$

$$
= E_{x^- \sim p} \left[\left(\frac{w(x^-;x)}{z} \right) \cdot e^{s(x,x^-)} \right]
$$

$$
\approx \frac{1}{Z \cdot M} \sum_{j=1}^{M} w(x_j^-; x) \cdot e^{s(x, x_j^-)}
$$

normalizing constant $Z = \frac{1}{M} \sum_{j=1}^{M} w(x_j^-; x_j)$

○ Survival outcome-aware NCE (SNCE) loss

$$
\mathcal{L}_{SNCE} = \sum_{i=1}^{N} \left[-\log \left(\frac{e^{s(x_i, x_i^+)} }{\frac{1}{Z} \sum_{j=1}^{M} w(x_j^-; x_i) \cdot e^{s(x_i, x_j^-)}} \right) \right]
$$

○ case 1 : Both samples are uncensored(i.e., have observed events)

- o case 2 : Both samples are censored
- o case 3 : One is uncensored and the other is censored.

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○ case 3 : One is uncensored and the other is censored.

○ Redefine the weight function considering the right-censoring as

○ **The hazard network.**, f_{ϕ} : $\mathcal{H} \times \mathcal{T}$ → [0,1], predicts the hazard rate at each time point $t \in \mathcal{T}$ given input latent representation **h**, i.e., $\hat{\lambda}(t|\mathbf{x}) = f_{\phi}(\mathbf{h}, t) = f_{\phi}(f_{\theta}(\mathbf{x}), t)$

Important quantities : Hazard function

 \circ The hazard function, $\lambda(t)$, is the instantaneous rate of failure at time t, given that an individual has survived until at least time t :

$$
\lambda(t|\mathbf{x}) = P(T = t | T \geq t, \mathbf{x} \text{ for } t \in \{1, 2, \dots\}
$$

○ There is an important relationship between the survival and hazard functions:

$$
S(t|\mathbf{x}) = P(T > t | \mathbf{x})
$$

= P(T \neq 1 | \mathbf{x}) \cdot P(T \neq 2 | T > 1, \mathbf{x}) \cdots P(T = t | T > t - 1, \mathbf{x})
= P(1 - \lambda(1 | \mathbf{x})) \cdot P(1 - \lambda(2 | \mathbf{x})) \cdots \cdots P(1 - \lambda(t | \mathbf{x}))
= \prod_{t' \le t} (1 - \lambda(t'|\mathbf{x}))

○ **Negative Log-likelihood**

– Hazard estimate is defined as a function of time given an input feature, we can naturally model the time-varying effect of input features on risk/survival functions.

○ **Negative Log-likelihood**

 $-$ Then, compute ${\cal L}_{NLL}^{\theta,\phi}$ by plugging in $f_{\bm{\phi}}(f_{\bm{\theta}}({\bf x}),t)$ into \hat{p} and \hat{S}

 $-\hat{p}(\tau|\mathbf{x}) = f_{\boldsymbol{\phi}}(f_{\boldsymbol{\theta}}(\mathbf{x}), \tau) \prod_{t' \leq \tau-1} (1 - f_{\boldsymbol{\phi}}(f_{\boldsymbol{\theta}}(\mathbf{x}), t'))$, $\hat{S}(\tau|\mathbf{x}) = \prod_{t' \leq \tau} (1 - f_{\boldsymbol{\phi}}(f_{\boldsymbol{\theta}}(\mathbf{x}), t')$

○ Overall, we can estimate the hazard function by training ConSurv with a loss function that combines the NLL loss and the SNCE loss, where β is a balancing coefficient

$$
\mathcal{L}_{Total}^{\theta,\phi,\psi} = \mathcal{L}_{NLL}^{\theta,\phi} + \beta \mathcal{L}_{SNCE}^{\theta,\psi}
$$

Experiments Setup : Datasets & Benchmarks & Metrics

○ **Datasets** ○ **Benchmarks**

○ **Metrics**

- Effect of Contrastive Learning
	- \mathcal{L}_{NLL} only, \mathcal{L}_{SNCE} only, and ConSurv (i.e., \mathcal{L}_{NLL} & \mathcal{L}_{SNCE})
	- significantly improves the alignment of representations with event time information

- o Comparing calibration plot of ConSurv with the DL-based survival models
	- The x=y line represents the ideal state where predicted probabilities perfectly match the observed outcome

○ **Subgroup Analysis**

- To confirm the calibration performance of survival models, compare their survival plots with the Kaplan-Meier (KM) curve
- KM curve provides a non-parametric estimate of survival function at population level
- Examine three binary hormone receptor status in the METABRIC dataset: estrogen receptor (ER) ,human epidermal growth factor receptor 2 (HER2), and progesterone receptor (PR)

○ **Subgroup Analysis**

○ **Subgroup Analysis**

– To quantitatively assess calibration performance, compare the survival predictions of each model with the KM curves for each subgroup using the Wasserstein distance

Discussion & Future works

- Survival data often lacks clear event times complicating learning due to censored data.
	- Potential avenues include modifying models to account for uncertainties or developing alternative learning approaches
	- Need for new evaluation metrics that consider the characteristics
- Limited augmentation techniques in tabular data reduce model robustness
	- Explore augmentation methods suitable for survival datasets to enhance contrastive learning performance

Thank you