Deep conditional transformation models for survival analysis

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Abstract

An every increasing number of clinical trials features a time-to-event outcome and records non-tabular patient data, such as magnetic resonance imaging or text data in the form of electronic health records. Recently, several neural-network based solutions have been proposed, some of which are binary classifiers. Parametric, distribution-free approaches which make full use of survival time and censoring status have not received much attention. We present deep conditional transformation models (DCTMs) for survival outcomes as a unifying approach to parametric and semiparametric survival analysis. DCTMs allow the specification of non-linear and non-proportional hazards for both tabular and non-tabular data and extend to all types of censoring and truncation. On real and semi-synthetic data, we show that DCTMs compete with state-of-the-art DL approaches to survival analysis.

1 Introduction

Arguably one of the most important aspects of health and medical research is being able to understand and predict patient outcome in order to improve patient management and ultimately extend their life span or time in remission (Hosny et al., 2018). Survival analysis is used for these purposes to study time-to-event information relating to for example death, response to treatment, adverse treatment effects, disease relapse, and the development of new disease

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Traditional approaches, such as Cox Proportional Hazards (cf. Section 3), relied on tabular features and are not amenable to analyze high-dimensional non-tabular data such as medical images. With recent advances in computer vision and deep leaning, there has been increasingly more interest in performing survival analysis directly from high-dimensional data in order to automatically learn patterns that stratify patients based on their outcome without the need for feature engineering.

In this paper we present DCTM, a framework for parametric and semiparametric survival analysis rooted in statistical modeling. DCTMs allow the specification of non-linear and non-proportional hazards for both tabular and non-tabular (image or text) data. We will describe in detail the formalization of our proposed models and apply them to a real dataset of medical images. Additionally, we describe how DCTMs can be used as generative models for the generation of semi-synthetic data. To the best of our knowledge, this paper is the first to cover deep survival regression from the DCTM point of view.

2 Deep transformation models for survival outcomes

In the following, we introduce deep conditional transformation models (DCTMs) for survival outcomes. We briefly recap survival analysis and conditional transformation models. Then we describe how to setup, fit, evaluate and sample from our proposed models. Fig. 1 is an overview of the proposed class of models.

Survival analysis  Survival analysis characterizes the distribution of the positive real-valued event time $T$ conditional on covariates $X$, usually on the scale of the survivor function, $S_{T|X=x}(t) = 1 - F_{T|X=x}(t)$, where $F_{T|X=x}$ denotes the cumulative distribution function (CDF) of $T | X = x$. One of the most popular choices is the Cox proportional hazards (Cox PH) model (Cox 1972)

$$F_{T|X=x}(t) = 1 - \exp(-\Lambda(t | x)) = 1 - \exp(-\Lambda_0(t) \exp(x^\top \beta)),$$

where $\Lambda(t | x)$ denotes the positive, monotone increasing cumulative hazard function. The hazard function is assumed to be decomposable into a baseline hazard $\Lambda_0$, independent of the covariates, and a hazard ratio $\exp(x^\top \beta)$. The hazard ratio models the influence of the covariates on the survivor function. The hazard function $\lambda(t | x) = \frac{d}{dt} \Lambda(t | x)$ measures the instantaneous risk of an event after time $t$ conditional on the covariates $x$ and having survived until $t$ (Collett 2015).

The Cox PH model is commonly estimated using the maximum partial likelihood obtained from profiling out $\Lambda_0$ (Cox 1975). The connection to transformation models for distributional regression is drawn next.
Conditional transformation models

CTMs are parametric distributional regression models of the form (Hothorn et al., 2014)
\[ F_{T|X=x}(t) = F_Z(h(t \mid x)), \] (2)
where the conditional distribution of the response \( T \mid X = x \) is decomposed into an \textit{a priori} chosen and parameter-free target distribution \( F_Z \) and a conditional transformation function \( h \), which depends on the input data \( x \). In order for \( F_T \) to be a valid CDF, \( h \) needs to be monotonically increasing in \( t \) (Hothorn et al., 2018).

CTMs can be estimated via maximum likelihood and allow various kinds of responses and uninformative censoring. The model in (2) suggests a close connection to the Cox PH model in (1), namely for \( F_Z(z) = 1 - \exp(-\exp(z)) \) (the minimum extreme value distribution) and \( h(t \mid x) = \log \Lambda(t \mid x) \), the two models coincide.

DCTMs for survival analysis

In DCTMs, the transformation function is parameterized via (deep) neural networks. For instance, let \( \phi: \mathcal{X} \to \mathbb{R}^d \) denote a feature extractor, which maps the input \( x \) to a feature vector of dimension \( d \). We can then choose different parameterizations for the transformation function, depending on the desired complexity of the model. For example,
\[ h(t \mid x; \phi) = \alpha + \beta \log(t) + \phi(x)^\top w, \quad \beta > 0, \] (3)
together with \( F_Z(z) = 1 - \exp(-\exp(z)) \) is a Weibull proportional hazards model with non-linear log hazard-ratios depending on the input \( x \) (for instance, medical images). However, also non-proportional (time-varying) hazards can be realized in DCTMs, via
\[ h(t \mid x; \phi) = \alpha + g(\phi(x)^\top w) \log(t), \] (4)
where \( g: \mathbb{R} \to \mathbb{R}_+ \), \textit{e.g.}, the soft-plus function, ensures a valid CDF. In Section 4.1, we describe the parameterization of the DCTMs used in this paper. An overview of the proposed method is given in Figure 1.

A parametric version of the Cox PH model can be estimated in the DCTM framework. Here, the log cumulative baseline hazard function is estimated as a smooth basis expansion \( a(t)^\top \vartheta \), instead of using the non-parametric estimate. A common choice are Bernstein polynomials, which are easily constrained to be monotonically increasing (see Section 4).

Fitting DCTMs

DCTMs are fitted by optimizing the empirical negative log-likelihood (NLL) via stochastic gradient descent (SGD). The likelihood contribution of a single obser-
Figure 1: Proposed DCTM model architecture. The inputs to the model consist of tabular or non-tabular explanatory variables associated with survival data in terms of exact or right-censored times to event. The explanatory variables can be mapped to a latent feature space via a feature extractor. In the case of non-tabular data such as images, the feature extractor will consist of a non linear mapping such as a convolutional neural network. The extracted features are then fed to the transformation layer. The network is optimized by minimizing the negative log-likelihood (NLL). In the figure we show the transformation function along with the cumulative density function (CDF), probability density function (PDF) and NLL for an exact event and a right-censored example.

The evaluation \((t, x)\) can be expressed in terms of the general transformation model

\[
L(h; t, x) = \begin{cases} 
  f_Z(h(t \mid x))h'(t \mid x) & t \text{ exact event,} \\
  1 - F_Z(h(t \mid x)) & t \text{ right censored.}
\end{cases}
\]  

\(\text{(5)}\)

However, also interval- and left-censored observations can be handled with the proposed method (see e.g., Hothorn et al. 2018). For a general choice of the transformation function \(h(t \mid x)\) and error distribution \(F = \sigma\), we have the following likelihood function

\[
L(h; t, x) = \begin{cases} 
  \sigma(h(t \mid x))(1 - \sigma(h(t \mid x)))h'(t \mid x) & t \text{ exact event,} \\
  1 - \sigma(h(t \mid x)) & t \text{ right censored.}
\end{cases}
\]  

\(\text{(6)}\)

Lastly, the NLL

\[
\text{NLL} = -\sum_{i=1}^{n_t} \log L(h; t_i, x_i),
\]

\(\text{(7)}\)

is minimized via SGD, where \(n_t\) denotes the training sample size.
Evaluating DCTMs  After fitting a DCTM, the conditional survivor function of a test observation can be computed from the estimated parameters via \( \hat{F}_{T\mid X=x}(t) = F_Z(\hat{h}(t \mid x)) \). Now, all evaluation metrics can be computed from (some form of) the predicted conditional distribution.

Evaluating models that predict conditional distribution of survival times are not straightforward to evaluate, due to censoring and their probabilistic nature (Collett, 2015). For instance, mean squared error or median absolute deviation are insensible for a right-censored observation \((t, +\infty), x\) and prediction \(\hat{t}\), for instance the conditional median survival time.

The c-index (Harrell, 1982)

\[
c = \sum_{i,j} \mathbb{1}_{T_j < T_i \cdot \mathbb{1}_{Y_j > Y_i}} \cdot \delta_j, \quad (8)
\]

overcomes at least the issue of censoring. However, the c-index does not encourage faithful probabilistic predictions, because it is not a proper scoring rule (Blanche et al., 2018).

Proper scoring rules (Gneiting and Raftery, 2005, 2007) are explicitly designed to evaluate probabilistic predictions and can inherently deal with censoring. A score is proper, if its average w.r.t. the data-generating distribution is minimized when predicting exactly this distribution, i.e., if \(T \sim \mathbb{P}_{T\mid X=x}\),

\[
\mathbb{E}_{\mathbb{P}_{T\mid X=x}}[S(p; T)] \leq \mathbb{E}_{\mathbb{P}_{T\mid X=x}}[S(q; T)]. \quad (9)
\]

Here, \(\mathbb{P}_{T\mid X=x}\) denotes the data-generating probability distribution with density \(p\) and \(q\) is another predicted density. A score is called strictly proper, when the above inequality holds if and only if \(p = q\).

The c-index does not fulfill (9), whereas the negative log-likelihood

\[
S_{\text{NLL}}(\hat{F}, t) = -\delta \log \hat{f}(t) - (1 - \delta) \log \hat{S}(t) \quad (10)
\]

does (Good, 1952). Here, \(\delta \in \{0, 1\}\) denotes an exact \((\delta = 1)\) or a censored \((\delta = 0)\) survival time. In fact, the NLL is the only strictly proper local scoring rule (up to affine transformations, Bröcker and Smith, 2007). However, since DCTMs are fitted by minimizing the empirical NLL, a comparison based solely on this score could be deemed unfair, if the competing method optimizes a different score, say the c-index. For this reason, we also compute the continuous ranked probability score (see e.g., Avati et al, 2020)

\[
S_{\text{CRPS}}(\hat{F}, t, \delta) = \int_0^t \hat{F}^2(u) \, du + \delta \int_t^\infty (1 - \hat{F}(u))^2 \, du. \quad (11)
\]

DCTMs as generative models  DCTMs model the entire conditional distribution of \(T \mid X = x\). Consequently, one can sample from the estimated distribution \(\hat{F}_{T\mid X=x}(t)\), e.g., via
inversion sampling (see Figure 2). In more detail, given a real sample and a fitted DCTM, the sample’s CDF can be generated. Next, random uniform probability values can be drawn and mapped back to time via the inverse CDF (Figure 2b). The usefulness of sampling from DCTMs is illustrated in our semi-synthetic experiments in Section 5.

Figure 2: Generation of semi-synthetic data via inversion sampling for DCTMs. a) Fitting of real data with three DCTM parametrizations of increasing complexity. The more flexible models reach a lower NLL. b) Example of a patient’s fitted CDF and one sampled synthetic time. c) Distribution of 1,000 sampled times for the previous CDF. d) Generated semi-synthetic datasets based on the three DCTM parametrizations compared to the real data.

3 Related work

We summarize the concurrent literature on deep learning for survival analysis and transformation models.

Deep learning for survival analysis We distinguish Bayesian and frequentist approaches and the loss function involved in fitting the models.

Several DL approaches to survival analysis are inspired by the Cox PH model. One of the earliest approaches using (shallow) neural networks for survival analysis is Liestbl et al. (1994). The authors use the partial likelihood as a loss function and even describe extensions to piece-wise constant, or non-proportional hazards and non-linear effects. A direct extension to deep Cox PH models is “DeepSurv” (Katzman et al. 2018), which optimizes the $\ell_2$-regularized log partial-likelihood. Also, Nagpal et al. (2021) proposes a mixture of Cox models together.
with an expectation maximization (EM) algorithm to optimize the partial likelihood and the evidence lower bound (ELBO) of a variational auto-encoder for the features.

In contrast to the semi-parametric approaches derived from the Cox PH model, a fully parametric framework for survival analysis was given in Nagpal et al. (2020). The authors model the survivor function as a mixture distribution and fit the model using an ELBO for exact and censored responses. Ranganath et al. (2016) present a generative (Bayesian) Weibull model for survival times. Some approaches based on pseudo-values exist (Zhao and Feng, 2020; Rahman et al., 2020). Fornili et al. (2014) employ piece-wise exponential hazard functions in a penalized likelihood loss.

“DeepHazard” proposed by Rava and Bradic (2020), uses a squared error loss based on the underlying counting process, which takes into account censoring. The model allows for time-varying covariates and non-linear effects, as well as non-proportional hazards.

A different branch of literature treats survival regression as a classification problem. Fotso (2018) introduce “neural multi-task logistic regression” (N-MTLR), which splits the positive real line into $K$ sub-intervals and fits a softmax last-layer model to the event indicators. The authors evaluate their model using proper scoring rules, namely the weighted and integrated Brier score (which is equivalent to the CRPS). Lee et al. (2019) propose “dynamic DeepHit”, which is based on “DeepHit” (Lee et al., 2018) and again uses a softmax last-layer activation. (Dynamic) DeepHit is able to deal with competing risks and non-linear effects.

DL for survival analysis has been shown to be useful in medical applications. For instance, Lao et al. (2017) use DL together with radiomics features for prediction of glioblastoma multiforme survival. A comparison between a deep learning and the classical Cox PH can be found in Matsuo et al. (2019). DeepSurv has been applied and compared against the Cox PH model and survival random forests for oral cancer (Kim et al., 2019) and non-metastatic clear cell renal cell carcinoma (Byun et al., 2021) survival prediction.

Deep conditional transformation models  Our proposed class of models belongs to the family of DCTMs. DCTMs extend the flexible class of CTMs Hothorn et al. (2014, 2018) with deep neural networks and SGD to handle non-tabular data, such as images. TMs are distributional regression models, which capture the entire conditional distribution instead of a single or few moments thereof (Kneib et al., 2021). More detail on TMs in given in Section 2.

DCTMs were first introduced by Sick et al. (2021), where the authors used a series of nested functions to model the transformation function and the standard normal CDF as the target distribution. Baumann et al. (2021) extended the work on DCTMs for continuous distributions with exact observations. Kook et al. (2022) treated ordinal regression from the DCTM point of view. The authors view the ordinal response as an interval censored version of a latent logistic distribution. By imposing structural assumptions on the transformation function, such as additivity, DCTMs retain interpretability of certain parts of the models, e.g., parameters for a single data modality. DCTMs were also developed for time series,
i.e., serially correlated data (Rügamer et al., 2021). DCTMs are all fitted by minimizing the empirical NLL via some form of SGD.

4 Experimental setup

In the following, we describe the details of the experimental setup including parameterization of the DCTMs and the use of ensemble estimates for improving prediction performance.

4.1 Model parametrizations

We employ different parameterizations of the transformation function, namely a linear shift, a linear scale, and general shift and scale models with a non-linear function in \( t \) using Bernstein polynomials. For all experiments, we choose the standard logistic CDF \( \sigma(z) = (1 + \exp(-z))^{-1} \) or the standard minimum extreme value CDF (also called Gompertz) \( F_{\text{MEV}}(z) = 1 - \exp(-\exp(z)) \) as the target distribution. Consequently, the transformation function can be interpreted on the log-odds or log-hazard scale, respectively.

For the linear shift parameterization, the transformation function is parameterized as

\[
\begin{align*}
    h(t | x; \phi) &= a + b \log t + \phi(x) \top w, \\
    \phi : X &\rightarrow \mathbb{R}^P, a \in \mathbb{R}, b \in \mathbb{R}, w \in \mathbb{R}^P,
\end{align*}
\]

where \( h \) denotes the transformation function, with a linear basis in \( t \) parameterized via \( a \) and \( b \), and a feature extractor \( \phi \) representing a neural network with linear last-layer activation and weights \( w \). Here, the extracted features enter linearly on the scale of the transformation function. In turn, the conditional distribution function changes only in terms of location, but not in terms of scale or any higher moments. That is, \( F_{T|X=x} \) is restricted to the same family of distributions as the target distribution \( F \). Hence, this model is not distribution-free. For \( F_Z = F_{\text{MEV}} \), the linear shift model is equivalent to a Weibull model. Similarly, \( F_Z = \expit \), yields a log-logistic model.

For the linear scale model, we have

\[
\begin{align*}
    h(t | x; \phi) &= a + \text{softplus}(\phi(x) \top w) \cdot \log t, \\
    \phi : X &\rightarrow \mathbb{R}^P, a \in \mathbb{R}, w \in \mathbb{R}^P,
\end{align*}
\]

in which the neural network models the scale of \( F_{T|X=x} \), which allows for linear non-proportional hazards. Still, the model is not distribution-free, the resulting distributions are again Weibull or log-logistic.

The general shift transformation model parameterizes the transformation function using
Bernstein polynomials,

\[ h(t \mid x; \phi) = b(\log t)^\top \vartheta + \phi(x)^\top w, \text{ where,} \]
\[ \phi : \mathcal{X} \to \mathbb{R}^P, b : [0, 1] \to \mathbb{R}^{K+1}, \]

(14)

which requires \( \vartheta \) to be increasing, i.e., \( \vartheta_{k+1} > \vartheta_k, k = 1, \ldots, K \), for all \( x \) to ensure monotonicity of \( h(t \mid x; \phi) \) in \( t \) (Hothorn et al., 2014). Monotonicity can be ensured by transforming

\[ \vartheta = g(\gamma) = \left( \gamma_1, \gamma_1 + \text{softplus}(\gamma_2), \ldots, \gamma_1 + \sum_{k=2}^{K+1} \text{softplus}(\gamma_k) \right). \]

The general shift transformation model allows a flexible baseline hazard function. The transformation function influences all higher moments of \( F_{T \mid X = x} \) and the model is distribution-free. Thus, the general shift model can be viewed as a parametric version of the Cox proportional hazards model.

The shift-scale transformation model,

\[ h(t \mid x; \phi) = \text{softplus}(\phi(x)^\top \beta) \cdot b(\log t)^\top \vartheta + \phi(x)^\top w, \text{ where} \]
\[ \phi : \mathcal{X} \to \mathbb{R}^P, b : [0, 1] \to \mathbb{R}^{K+1}, \]

(15)

allows for non-proportional hazards, explicitly modelling the scale of \( F_{T \mid X = x} \). The model is distribution-free (Siegfried et al., 2022).

Allowing the parameters of the Bernstein polynomials to fully flexibly depend on \( x \), we arrive at the most flexible transformation model

\[ h(t \mid x; \vartheta) = b(\log t)^\top \vartheta(x), \text{ where} \]
\[ \phi : \mathcal{X} \to \mathbb{R}^P, b : [0, 1] \to \mathbb{R}^{K+1} \]

(16)

It is important to note that for all of the above \( u = \log t \) is scaled to \( \tilde{u} = \frac{u-a}{b-a} \) where \( a, b \) are chosen appropriately, e.g., min and max.

### 4.2 Ensemble predictions

The linear shift and linear scale parameterizations induce strong distributional assumptions on \( T \mid X = x \). Nevertheless, these distributional assumptions can help prevent overfitting and lead to more stable predictions. Using the Bernstein polynomial basis loosens assumptions, but is prone to overfitting. However, deep ensembles have been shown to improve prediction performance in both cases (Lakshminarayanan et al., 2017).

Let \( \hat{F}_1, \ldots, \hat{F}_M \) be \( M \) estimates of the conditional distribution of \( T \mid X = x \), e.g., obtained by optimizing \( M \) instances of the same DCTM via SGD and early stopping on different bootstrapped data samples. The ensemble estimate is the point-wise average of those \( M \)
estimates, and denoted by $\bar{F}_M$,

$$\bar{F}_M = M^{-1} \sum_{m=1}^{M} \hat{F}_m. \quad (17)$$

The ensemble distribution is then used for evaluation. When having access to $B > M$ estimates and selecting $M$ based on their validation loss, we refer to $\bar{F}_M$ as the top-$M$ ensemble estimate.

4.3 Data

4.3.1 Real data

The real data used in this study comprised 959 stage 4 lung cancer patients from Memorial Sloan Kettering Cancer Center (MSKCC) diagnosed from Oct 2010 through Mar 2018. The data used included pre-treatment PET/CT images of the subjects, overall survival time and censoring information. 768 of the patients (80%) experienced a terminal event, while 191 (20%), were right-censored. The patients comprise a real-world, clinical grade cohort collected over many years on a wide selection of scanners, with cases reviewed by many different clinicians, and patients prescribed varying treatment regimens. The retrospective data use was approved by the local ethics committee at MSKCC, and informed consent was waived since the study was deemed minimum risk.

4.3.2 Semi-synthetic data

The DCTM architecture was used to model the conditional time to event distribution of the real data described above. Three different DCTM parametrizations were used of increasing complexity: linear shift, linear scale, and fully flexible Bernstein. The entire real data dataset was used to train each DCTM model for a predetermined number of epochs. The fitted models were then used to generate new semi-synthetic time-to-event data. If a time was predicted beyond the real data’s range, it was right-censored to the maximum value. For each patient we sampled 10 new data points, resulting in datasets 10 times larger than the original (see Figure 2d).

4.4 Computational details

All experiments were performed on the high-performance computing (HPC) cluster at MSKCC. Training scripts were written in python using PyTorch (Paszke et al. 2017) for model definition and optimization. Model optimization was performed with SGD and training learning rates were chosen via a hyperparameter grid search on a single data training/validation partition. For the DCTM models, different learning rates were used for the CNN feature extractor
and the DCTM survival layer. The full list of learning rates used for all experiments is presented in Table 1:

Table 1: List of learning rates used to train models for all experiments in this study.

| Parametrization     | CDF   | lr CNN | lr DCTM |
|---------------------|-------|--------|---------|
| Deepsurv            | 0.0005| 0.001  | 0.1     |
| Baseline            | Sigmoid| 0.1    |         |
| Linear shift        | Sigmoid| 0.001  | 0.01    |
| Linear scale        | Sigmoid| 0.001  | 0.1     |
| Bernstein shift     | Sigmoid| 0.001  | 0.1     |
| Bernstein shift/scale| Sigmoid| 0.001  | 0.01    |
| Bernstein           | Sigmoid| 0.001  | 0.1     |
| Baseline            | Gompertz| 0.01   |         |
| Linear shift        | Gompertz| 0.001  | 0.01    |
| Linear scale        | Gompertz| 0.001  | 0.01    |
| Bernstein shift     | Gompertz| 0.001  | 0.01    |
| Bernstein shift/scale| Gompertz| 0.001  | 0.01    |

5 Results

5.1 Real Data

Experiments were carried out to test the performance of DCTM models of increasing complexity. As a baseline a Bernstein non conditional model, where the same output is associated to every sample, was used. DCTM results were also compared with DeepSurv. Since DeepSurv does not compute the full likelihood, only the c-index can be compared in this case. Figure 3a reports the distributions of validation NLL for each experimental condition in order of complexity, starting with the baseline at the top and finishing with the fully flexible Bernstein model at the bottom. It can be observed that, for both CDF functions, the NLL decreases with model complexity, as expected. In addition, it is apparent that the Gompertz experiments resulted in wider NLL distributions, highlighting the underlying training instability we observed for this subset of experiments. Figure 3b reports the c-index results. The baseline results are by definition 0.5, since all patients are assigned the same output time-to-event. It is interesting to note that while the NLL decreased with model complexity, a slight trend of decreasing c-index can be observed. Compared to DeepSurv, the DCTM models perform on par or better, except in one condition. Finally, Figure 3c reports the results in terms of CRPS. In concordance with the NLL results, a slight trend of decreasing CRPS with model complexity can be noted.
Figure 3: Experimental results for the real data. The performance of different parametrizations of DCTM are shown compared to DeepSurv where possible. For DCTM, the sigmoid and Gompertz functions were tested. a) Distribution of validation NLL. b) Distribution of validation c-index. c) Distribution of validation CRPS.

5.2 Simulated Data

To analyze the behavior of DCTMs when the interaction between inputs and survival comes from different distributions, three semi-synthetic datasets of increasing complexity were generated as described earlier. In Figure 4 are shown the results of the experiments performed on the semi-synthetic data. Figure 4a shows the distribution of validation results in terms of NLL for the three datasets fitted with various DCTM parametrizations. In all the experiments, the sigmoid function was used as CDF. While it is expected that data of lower complexity would be easier to fit, the opposite effect can be observed, where the linear shift generated data resulted in a higher NLL, while the flexible bernstein generated data resulted in lower NLLs. Additionally, unlike our results on the real data, the simplest DCTM parametrization resulted in the lowest NLL in each of the three datasets. Figures 4b, c show similar trends in terms of c-index and CRPS respectively. In figure 4b it can be noted that DCTM achieves similar performance as DeepSurv on the three datasets.
6 Discussion

In this work we have introduced DCTMs as a novel framework for parametric and semi-parametric survival analysis that can leverage the power of deep learning to learn patient stratification strategies directly from high-dimensional non-tabular data. Techniques such as this are necessary in the medical domain to advance the understanding of disease generation and progression. Modelling time-to-event outcomes directly from non-tabular medical data such as radiology images, as presented here, has the potential to shed light in the biological processes underlying complex diseases such as cancer, and change how patients are treated ultimately improving patient outcomes. Extensions to time-varying covariates and competing risks exist for transformation models with tabular data (Fokas et al., 2017) and can be carried over to DCTMs, which we leave for future work.
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A Notation

\( T \mid X = x \) denotes a positive real-valued random variable conditional on covariates \( X \in \mathcal{X} \). By \( \phi_\theta : \mathcal{X} \rightarrow \mathbb{R}^d \), we denote a feature extractor, e.g., a convolutional neural network. We write \( \phi \) and suppress the dependency of \( \phi_\theta \) on network parameters \( \theta \). \( F_{T \mid X = x} \) denotes the conditional cumulative distribution function of \( T \mid X = x \), and \( F_Z \) the target distribution in a transformation model. \( F_{T \mid X = x}(t) = F(h(t \mid x)) \) then denotes a general transformation model with transformation function \( h \). For \( F_Z \) we commonly chose the standard logistic distribution, \( \sigma(z) = (1 - \exp(-z))^{-1} \), or the standard minimum extreme value distribution \( F_{\text{MEV}}(z) = 1 - \exp(-\exp(z)) \). For hazard functions we reserve \( \lambda(t \mid x) \), and \( \Lambda(t \mid x) = \int_0^t \lambda(u \mid x) \, du \) for cumulative hazard functions.

We denote \( n \) observations by \( \{(t_i, x_i, \delta_i)\}_{i=1}^n \), where \( t_i \) are i.i.d. realizations of \( T \mid X = x_i \), with event indicator \( \delta_i \in \{0, 1\} \), where 0 represents a right-censored and 1 an exact event time. The likelihood function is denoted by \( \mathcal{L}(h; t, x, \delta) \), and the log-likelihood by \( \ell(h; t, x, \delta) \). Depending on the parameterization of the transformation \( h \), we substitute the parameters of \( h \) as the argument of the (log-)likelihood function, e.g., \( \ell(a, b, w, \phi; t, x, \delta) \) for \( h(t \mid x) = a + bt + \phi(x)^\top w \).

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