A new harmonium for pattern recognition in survival data

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Abstract
Survival analysis concerns the study of timeline data where the event of interest may remain unobserved (i.e., censored). Studies commonly record more than one type of event, but conventional survival techniques focus on a single event type. We set out to integrate both multiple independently censored time-to-event variables as well as missing observations. An energy-based approach is taken with a bi-partite structure between latent and visible states, commonly known as harmoniums (or restricted Boltzmann machines). The present harmonium is shown, both theoretically and experimentally, to capture non-linear patterns between distinct time recordings. We illustrate on real world data that, for a single time-to-event variable, our model is on par with established methods. In addition, we demonstrate that discriminative predictions improve by leveraging an extra time-to-event variable. In conclusion, multiple time-to-event variables can be successfully captured within the harmonium paradigm.

Keywords: survival analysis, machine learning, harmonium, restricted Boltzmann machine

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1. Introduction

Survival analysis considers the timing of dichotomous events, and can be used to analyse, for example, time to death, breakdown of a machine, graduating university or worsening of the disease. What distinguishes time-to-event measurements from other random variables is that they are partially observed. That is to say, not all events have occurred during the interval in which they were monitored (we have lower bounds) because, e.g., subjects may be lost during follow-up, or the experiment may be too short to observe all the events. These incomplete measurements, where the event time remains unknown, are

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said to be censored. Nevertheless, the time interval in which subjects were observed prior to dropout still provides valuable information. In fact, failure to take into account censoring leads to serious underestimation of the survival, as has been repeatedly emphasised [1, 2, 3, 4].

A wide range of statistical tools have been developed to deal with censored data, which rely on modelling the survival distribution \( S(t) = \int_{t}^{\infty} d\tau p(\tau) \) where \( p(t) \) is the probability density for observing the event at time \( t \) [2]. Perhaps the most widely adopted model is Cox regression [5] which fits the so-called hazard function \( h(t) \equiv p(t)/S(t) \) via a simple (log-) linear function on top of a baseline hazard \( h_0(t) \) as \( h(t) = h_0(t) \exp[\beta \cdot x] \) with weights \( \beta \).

In addition, there are also efforts to combine machine learning techniques with survival analysis. For instance, staying within Cox's [5] proportional hazards (PH) [i.e., \( h(t) \propto \exp(\beta \cdot x) \)] setting, one can use boosting [6] to learn the parameters, or extend the linear function using a neural network architecture, as done in Refs. [7, 8, 9]. Neural network structures that go beyond the PH assumption usually rely on the binning of the time-to-event variables [10, 11, 12]. Apart from neural networks, other models such as random forests [13] and support vector machines [14, 15, 16, 17] have been developed as well.

While these models focus on one survival variable, joint analysis of multiple unordered and distinct time recordings has received comparatively little attention. A more traditional statistical approach, such as the Wei-Lin-Weissfeld model [18] (see also Ref. [19] for a related review), solves a Cox model for each individual time-to-event variable and subsequently performs joint inference on the parameters to determine their significance. MEPSUM [20] is a more recent mixture model where each mixing component fits a discrete time hazard function.

In this work, a different approach is taken by (unsupervised) training an energy based model on the multiple time-to-event variable likelihood function [21]. Specifically, we consider a neural network inspired model called a harmonium [22] (or restricted Boltzmann machine [23], as it is synonymously called), and adapt it to the approach of survival analysis.

This paper is organised as follows: first, the theory behind the model, together with a training procedure, is laid out in the section. Next, we illustrate that a harmonium can capture non-linear survival patterns. We subsequently benchmark the harmonium to established off-the-shelf survival models in the section. Finally, we discuss the relevance and scope of our findings in the section.

2. Theory

Before building a new harmonium for survival data, let us first briefly review some of its quintessential properties.

2.1. Harmoniums

The textbook harmonium [24] consists of binary input states \( x \) (\( x_i \in \{0, 1\} \) where \( i = 1 \ldots n_x \)), binary activations \( h \) (\( h_j \in \{0, 1\} \) where \( j = 1 \ldots n_h \)), and
an energy function $E$ that linearly couples $x$ and $h$ through a receptive field $W$ as

$$E(x, h) = x^T Wh.$$  \hspace{1cm} (1)

The energy function encodes the preference for specific assignments of $x$ and $h$ (with low $E$) over other assignments for which $E$ is higher.

The probability distribution is parametrised by the energy $E$ as

$$p(x, h) = \frac{1}{Z} e^{-E(x, h)},$$  \hspace{1cm} (2)

and a normalisation constant $Z$, called the partition function, which only depends on the adjustable parameters (in this case $W$). The latent states themselves are not observed but enrich $p(x)$'s capacity to capture higher-order (i.e., beyond pair-wise) statistics in the data \[25\]. Unfortunately, since the partition function $Z$ is intractable \[26\] so is $p(x)$. Sampling from $p(x|\mathbf{h})$ and $p(h|x)$ is nevertheless easy thanks to the bipartite structure of $E(x, h)$. The interpretation of $W$ as a receptive field derives from the activation function of $h_j$ given the visible states $x$, i.e., $p(h_j = 1|x) = \sigma(-\sum_{i=1}^{n_x} x_i W_{ij})$ with sigmoid activation function $\sigma(x) = 1/(1 + \exp(-x))$, which is structurally akin to a neural network. Likewise, the latent states activate the visible binary states $x$ through $p(x_i = 1|h) = \sigma(-\sum_{j=1}^{n_h} W_{ij} h_j)$.

Given a set of $m$ samples $\{x^{(i)}\}_{i=1}^{m}$, training proceeds by adjusting the free parameters $\Theta$ in $E(x, h)$—which in this case consists of $W$—to maximise the log-likelihood function

$$\mathcal{L}(\{x^{(i)}\}_{i=1}^{m}) = \frac{1}{m} \sum_{i=1}^{m} \ln p(x^{(i)}),$$  \hspace{1cm} (3)

by approximating its gradient using Gibbs samples. The contrastive divergence algorithm relies on the decomposition of the free parameter $\Theta$ gradient of the likelihood

$$\nabla_\Theta \mathcal{L} = -\left(\nabla_\Theta E\right)_{p(h|x)p_{data}(x)} - \left(\nabla_\Theta E\right)_{p(x,h)},$$  \hspace{1cm} (4)

into an expectation over the empirical data [first term on the right hand side (rhs), $p_{data}(x) = \frac{1}{m} \sum_{i=1}^{m} \delta_{x,x^{(i)}}$] called the positive phase and an expectation over the model itself ($\nabla_\Theta \ln Z = -\left(\nabla_\Theta E\right)_{p(x,h)}$, second term rhs) referred to as the negative phase \[24\].

While the positive phase can be evaluated in closed form, the negative phase (i.e., the partition function gradient $\left[24\right] - \left(\nabla_\Theta E(x, h)\right)_{p(x,h)}$) is to be approximated by Gibbs sampling between $p(x|h)$ and $p(h|x)$. The key empirical observation behind the contrastive divergence algorithm \[23, 27\] is that, when initialising the chain with the data distribution, a single chain step usually suffices to estimate the negative phase.
2.2. Model

Having reviewed the basic structure of harmoniums, lets now turn to the survival data. To accommodate survival data we need to: (i) design an energy function capturing both survival, categorical and other numerically valued variables (Sec. 2.2.1), (ii) adapt the objective (i.e., likelihood) function to account for censoring and completely missing data (Sec. 2.2.2), and (iii) layout a corresponding training algorithm (Sec. 2.2.3). Let us first focus on the energy function.

2.2.1. Energy function

To reiterate, the energy function $E(\mathbf{x}, h)$ codifies preferences for specific assignments of the variables. Since the event times are numerically valued (instead of binary, like in Sec. 2.1), we adjust the energy function accordingly. Beside the the survival events, we set out to capture binary variables (e.g., smoking status) and numeric factors (like body mass index). Let us therefore distinguish between three sets of input variables (denoted by $A$, $B$, and $C$):

- Categorical variables $\mathbf{x}^A = \{x_i : i \in A\}$ that are encoded as binary variables $x_{i \in A} \in \{0, 1\}$.
- Time-to-event variables $\mathbf{x}^B = \{x_i : i \in B\}$ that are appropriately scaled to the unit interval $(0, 1]$.
- Other numerical factors $\mathbf{x}^C = \{x_i : i \in C\}$ that can take on arbitrary values on the real line $x_{i \in C} \in \mathbb{R}$.

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Figure 1: Graphical representation of the energy function $E(\mathbf{x}, h)$. Four types of variables (nodes) can be distinguished: binary states $\mathbf{x}^A$, time-to-event variables $\mathbf{x}^B$, continuous variables $\mathbf{x}^C$, and (unobserved) binary latent states $h$. Edges between $\mathbf{x}$ and $h$, indicating the receptive fields, form a bipartite graph.
Both the binary variables (in $A$) and the numeric factors (in $C$) are assumed to be independent of time. (The interval on which the time-to-event variables are defined is discussed in more detail in Appendix A.) In addition, a single set of latent variables $\{h_i\}_{i \in H}$ is used (like in Sec. 2.1) to coherently model the three sets of input variables. The latent code will be restricted to binary values $h_i \in \{0, 1\}$ in view of its regularising effect [27].

Assigning an energy term to each variable type gives rise to the overall energy function

$$E(x, h) = E_A(x^A, h) + E_B(x^B, h) + E_C(x^C, h) + E_H(h).$$

Observe that the energy function’s bi-partite structure between $x$ and $h$ determines the form of $p(x|h)$. Decomposing $p(x)$ as $\sum_h p(x|h)p(h)$ reveals that the conditional distributions $p(x|h)$ are the building blocks of the model, weighted by the (\(\Theta\) dependent) latent priors $p(h)$. So the choice of the energy term controls the building blocks of the model.

For the categoric $x^A$ and numeric factors $x^C$ we rely on established energy functions: (i) $E_A$ is modelled as a binary-binary harmonium [27], similar to the energy function Sec. 2.1 but supplemented with a bias term, (ii) $E_C$ represents a Gaussian-binary harmonium [28, 27, 29].

For the time-to-event variables a new function $E_B$ is proposed (detailed in Appendix A) for which $p(x_i|h)$ is a (truncated) gamma distribution and use $E_H$ to bias the latent states $h$. In summary, we take the following forms for the individual energy functions

$$E_A = \sum_{i \in A, j \in H} x_i W^A_{ij} h_j + \sum_{i \in A} x_i a^A_i,$$

$$E_B = \sum_{i \in B, j \in H} x_i W^B_{ij} h_j - \ln(x_i)\|V_i\|h_j + \sum_{i \in B} x_i a^B_i - \ln(x_i)\|c_i\|,$$

$$E_C = \sum_{i \in C, j \in H} \frac{x_i W^C_{ij} h_j}{\sigma_i} + \sum_{i \in C} \frac{(x_i - a^C_i)^2}{2\sigma^2_i},$$

$$E_H = \sum_{j \in H} b_j h_j.$$

The weights $\{W^A, W^B, W^C\}$ can be interpreted as the receptive fields of $x$ to activate the latent states $h$, while $\{a^A, a^B, a^C\}$ and $b$ are their respective biases. The $V$ and $c$ terms in $E_B$ are additional receptive fields and biases that help modulate the survival distribution. The receptive fields of $E(x, h)$, coupling $x$ and $h$, are illustrated in Fig. 1 by corresponding edges. The form of $E(x, h)$ fixes the distribution over $x$ given $h$, and it is not difficult to show that

$$p(x_i|h) = \begin{cases} \sigma[(1 - 2x_i)z_i] & i \in A, \\ p_F(x_i|\alpha_i, \beta_i) & i \in B, \\ N(x_i|\mu_i, \sigma^2_i) & i \in C. \end{cases}$$
where \( \sigma[(1-2x_i)z_i] \) is the sigmoid function with latent state activation \( z_i = \alpha_i^A + \sum_{j \in H} W_{ij}^A h_j, \) \( \Pr(x_i|\alpha_i, \beta_i) \) the right truncated Gamma distribution [Eq. (A.2)] with shape \( \alpha_i = \sum_{j \in H} ||V_j||h_j + ||c_i|| + 1 \) and rate \( \beta_i = \sum_{j \in H} W_{ij}^B h_j + a_i^B, \) and finally \( \mathcal{N}(x_i|\mu_i, \sigma_i^2) \) a Gaussian with mean \( \mu_i = a_i^C - \sigma_i \sum_{j \in H} W_{ij}^C h_j \) and standard deviation \( \sigma_i. \) In a similar way, the activations of the latent variables

\[
p(h_j|x) = \sigma[(1-2h_j)\phi_j],
\]

depend on the contributions of all variable types, which are jointly captured by

\[
\phi_j = b_j + \sum_{i \in A} x_i W_{ij}^A + \sum_{i \in B} x_i W_{ij}^B + \sum_{i \in C} x_i \frac{W_{ij}^C}{\sigma_i} - \sum_{i \in B} \ln(x_i) ||V_{ij||}||.
\]

As explained in Sec. 2.2.1 a key observation that is central to the training of harmoniums is that Gibbs samples from \( p(x, h) \) can be obtained by alternating between Eq. (10) and Eq. (11). In this way, an entire block of states can be updated in parallel, thanks to its conditional independence.

2.2.2. Cost objective

With the energy function in place, let us now adapt the likelihood function (our cost objective) to incorporate partially and completely missing values. We will assume uninformative censoring and that missing values are missing at random. To simplify the exposition we shall henceforth focus on right censored data (or censored, for short). That is, observations for which there is a lower bound on the failure time (e.g., a participant that was lost to follow-up after time \( t \)). The standard likelihood approach for modelling a single time-to-event variable is as follows. In the presence of censoring, the likelihood is modified by replacing \( p(t) \) by its survival function \( S(t) \) when it is censored at time \( t. \) Writing \( S(t) = \int_0^\infty d\tau \Theta(\tau - t)p(\tau) \) with the Heaviside step function

\[
\Theta(x) = \begin{cases} 1 & x \geq 0 \\ 0 & x < 0 \end{cases},
\]

reveals that, in fact, we are integrating out the unobserved region. Both cases, censored and observed events, can be succinctly codified as an integration over the domain of event times \( \int_0^\infty d\tau p(\tau) \chi(t, \tau, e) \) constrained by \( \chi(t, \tau, e) = \delta(\tau - t)^e \Theta(\tau - t)^{1-e} \) with \( \delta(x) \) the Dirac delta function and \( e = 1 \) \((e = 0)\) indicating observation (censoring) at time \( t. \) Note the analogy with completely missing data where the entire domain (instead of subset of the domain) is marginalised, e.g., \( p(t_1) = \int_{-\infty}^\infty dt_2 p(t_1, t_2) \) when \( t_2 \in \mathcal{R} \) is missing. We can therefore apply a similar codification scheme to missing values to obtain \( \chi(t, \tau, e) = \delta(\tau - t)^e. \) A consistent generalisation from one to multiple censored variables is straightforward: integrate out the entire unobserved region [21]. To make this more precise, let \( e_a = 1 \) indicate the occurrence and \( e_a = 0 \) the absence of observation \( x_a. \) That is, \( e_a = 0 \) indicates that \( x_a \) is censored when \( a \) refers to a time-to-event variable \((a \in B)\), or completely missing otherwise \((a \in A \cup C)\). In addition, let \( \xi_a \) be the corresponding observed value when \( e_a = 1, \) its lower bound (i.e., censoring time) for the survival variables \((i.e., a \in B)\) or a placeholder \( \xi_a =? \) otherwise \((a \in A \cup C)\) when \( e_a = 0. \) As
a shorthand, denote $o_a = (\xi_a, e_a)$ and a superscript $o_a^{(i)}$ to refer to a specific sample $i$. First, group the marginalisation constraints that are imposed by the observations

$$\chi(x, o) = \prod_{i \in A \cup B \cup C} \delta(x_i - \xi_i)^{e_i} \prod_{j \in B} \Theta(x_j - \xi_j)^{1-e_j},$$

with $\Theta(x)$ the Heaviside step function and $\delta(x)$ the Dirac delta function (Kronecker delta function) for the continuous variables in $B \cup C$ (binary variables in $A$). Equation (13) is a symbolic way to represent that we should either pick the observed values (the delta function) or marginalise the unobserved region (which, for the survival variables, is the interval starting from the censor time, or the entire domain otherwise). In this way, the likelihood can be expressed as

$$L(\{o^{(i)}\}_{i=1}^m) = \prod_{i=1}^m \int dx \chi(x, o^{(i)}),$$

using the shorthand $\int dx \equiv \int_{-\infty}^{\infty} dx_c \int_{0}^{1} dx_B \sum_{x_A \in \{0,1\}^{|A|}}$. In summary, to train the model that takes into account censored and missing data should strive to optimise the likelihood function Eq. (13) or, equivalently, the log-likelihood function $L(\{o^{(i)}\}_{i=1}^m) = \ln(L)/m$.

Having spelled out the likelihood function in fair generality, next we apply it to the energy parameterisation $p(x) \propto \sum_h \exp[-E(x, h)]$. To keep the bipartite structure of the model for sampling [which would be destroyed by directly carrying out the integration in Eq. (14)] we turn to a trick from Ref. [30] to reformulate the model in terms of $p(o, x, h)$ [30], where

$$p(o, x, h) \propto e^{-E(x, h)} \chi(x, o).$$

With the help of Eq. (15) the gradient of the log-likelihood (details are in Appendix B) can be expressed as

$$\nabla_o L = - \left( \frac{1}{m} \sum_{i=1}^m \langle \nabla_o E(x, h) \rangle_{p(x, h|o^{(i)})} - \langle \nabla_o E(x, h) \rangle_{p(x, h)} \right).$$

Heuristically speaking, Eq. (16) indicates that the gradient contrasts the the empirical statistics of $\nabla_o E(x, h)$ [through $p(x, h|o^{(i)})$, first term, rhs] with the models own perception [generated by $p(x, h)$] of $\nabla_o E(x, h)$ (second term, rhs).

### 2.2.3. Training

Next, we discuss how to approximate the gradient [Eq. (16)] in order to maximise the likelihood with gradient ascent. In the standard contrastive divergence [23] approach, the negative phase is approximated using Gibbs samples while the positive phase can be evaluated exactly. Incorporating missing and censored values has modified the positive phase [first term, rhs Eq. (16)] in a way that evades a closed form solution. Instead, Eq. (16) will be estimated by Gibbs sampling both phases.
clamp the observed events and sample the censored events from the unobserved set, and carry out Gibbs chain, initialise the placeholder \( ? \) by the median value over the training.

To generate fantasy states, pick the the mini batch as the initial state of the all the states are updated (none are clamped) from the entire interval \([Eq. (10)](10)\). The negative phase \([second term r.h.s Eq. (16)](16)\) is calculated similarly, but now in interval and sample the missing values from the entire distribution \([Eq. (17)](17)\).

Phase difference and repeat the entire process until some predefi ned stopping.

Analogous to the sampling of \( p(x,h) \) for the negative phase, we alternate between \( p(x,o,h) \) and \( p(h,o,x) \) to generate \( p(x,h|o) \) samples for the positive phase where

\[
p(x_i|o,h) = \begin{cases} 
\delta(x_i - \xi_i) & \forall i \quad e_i = 1, \\
p(x_i|h) & i \in A \cup C \quad e_i = 0, \\
p_{[\xi_i,1]}(x_i|\alpha_i(h),\beta_i(h)) & i \in B \quad e_i = 0,
\end{cases} \tag{17}
\]

with \( p_{[\xi_i,1]}(x_i|\alpha_i(h),\beta_i(h)) \) the gamma distribution normalised to the \([\xi_i, 1] \) interval \([Eq. (D.2)](D.2)\) and

\[
p(h|o,x) = p(h|x). \tag{18}
\]

Physically, \( Eq. (17) \) indicates that samples \( x_i \) should adhere to the bounds imposed by the observation (which is the lower-bound censor time for the censored variables).

In summary, the training procedure is as follows: For the positive phase [first term r.h.s Eq. \( (16) \)] replace the censored and missing values with “fantasy states” and calculate the \( \nabla_o E(x,h) \) statistic. To replace the censored data, clamp the observed events and sample the censored events from the unobserved interval and sample the missing values from the entire distribution [Eq. \( (17) \)].

The negative phase [second term r.h.s Eq. \( (16) \)] is calculated similarly, but now all the states are updated (none are clamped) from the entire interval [Eq. \( (10) \)]. To generate fantasy states, pick the the mini batch as the initial state of the Gibbs chain, initialise the placeholder “?” by the median value over the training set, and carry out \( k \) Gibbs chain steps. Finally, update the weights using the phase difference and repeat the entire process until some predefined stopping.
criterion. In pseudocode, the algorithm is outlined in Algorithm 1. Reassuringly, the original contrastive divergence algorithm is recovered as a special case when all the data is observed (i.e., $e^{(i)}_a = 1$ for all $i$ and $a$).

3. Example: a non-linear two-dimensional survival distribution

![Figure 2: A harmonium captures non-linear related time recordings. (a) A synthetic time-to-event distribution where the timing of two separate events, $t_1$ and $t_2$, are non-linearly related through colour. The density is composed of two red ($v^{(1)}$ and $v^{(2)}$, dashed contours) and two blue ($v^{(3)}$ and $v^{(4)}$, solid contours) gamma distributed blobs. Side panels show the marginal probability density by colour, illustrating the multivariate nature of the problem. (b) Model fit (contours) of observed (dots) and censored recordings (crosses) sampled from (a). The contours, indicating constant probability density of the harmonium, shows that all four colour-mode combinations are recapitulated.]

The limitations of uni-survival variate (i.e., conventional survival) models is best illustrated with an intrinsically two-dimensional problem. Consider a data generating distribution yielding two event recordings $x^B = [t_1, t_2]^T$ and a colour, red ($x^A = 0$, we’ve dropped the index for convenience) or blue ($x^A = 1$). Let the probability density be confined to the unit square $[0, 1] \times [0, 1]$ symmetrically tiled with four equally weighted bell-shaped blobs: blue generating recordings along the diagonal, and red on the off-diagonal quadrants (see Fig. 2a). Specifically, blobs are two-dimensional, independent (i.e., $t_1 \perp t_2$), unit-interval truncated Gamma distributions [Eq. (A.2)] with modes placed at $v^{(1)} = \left(\frac{1}{4}, \frac{1}{4}\right)$, $v^{(2)} = \left(\frac{3}{4}, \frac{3}{4}\right)$ corresponding to red ($x^A = 0$) and $v^{(3)} = \left(\frac{1}{4}, \frac{1}{4}\right)$, $v^{(4)} = \left(\frac{3}{4}, \frac{3}{4}\right)$ for blue ($x^A = 1$). Modes are sufficiently squeezed (shape and rate $\alpha = 8.1, \beta = 58$ or $\alpha = 29, \beta = 76$) so as to form a Gaussian-like shape and sampled with equal probability.

Looking at the projections (i.e., marginals) along the axes (side panels Fig. 2a), shows how the red and blue modes collapse onto each other. Viewed from either $t_1$ or $t_2$ alone, one would therefore be inclined to (falsely) conclude there is no relation between colour and survival.

On the other hand, we can derive an approximate, not necessarily unique, but nevertheless closed-form, solution for a harmonium with $n_h = 4$ hidden
states. The harmonium approximates a mixture of Gaussians in survival space (parametrised by $x^B$) with $x^A$ clamped to mode $j$'s colour $\tilde{x}_j^A$ (see Appendix C for a derivation). The probability density can be approximated as

$$p(x^A, x^B) = \frac{1}{Z} \sum_{h_1, \ldots, h_4} \exp[-E(x^A, x^B, h)] \approx \frac{1}{4} \sum_{j=1}^{4} \delta_{x^A, \tilde{x}_j^A} N(x^B | v^{(j)}, \Sigma_j),$$

where the mean $v^{(j)}$ and the (diagonal) covariance matrix $\Sigma_j$ are determined through the rows of the receptive fields $v^{(j)} = \frac{V_j}{W_j}$ and $\Sigma_j = \frac{V_j}{(W_j)^2}$, with all other visible biases zero (all other weights are described Appendix C).

Knowing that the problem is (approximately) solvable in theory, lets illustrate training when some of the time recordings are censored. We used the aforementioned distribution to generate 1000 samples and censored each event time $t_i > \frac{3}{4}$ with 75% probability. For clarity, half of the points are shown in Fig. 2b coloured by $x^A$, and marked by a cross where censored. The harmonium was trained for $3 \cdot 10^5$ epochs with a learning rate $r_{\text{learn}} = 0.375$, 10% momentum, and 3 persistent [31] contrastive divergence sampling steps.

While a model that doesn’t account for censoring would underestimate survival, we find that the harmonium correctly identifies all four modes. We do observe that the modes are less sharply peaked (more smeared) compared to the original distribution. This is attributed to the approximate and stochastic nature of the contrastive divergence algorithm, which sometimes hinders convergence. Overall, the harmonium satisfactory captures the non-linear relationship in the survival data. As a reference, we trained a Cox model [3] on either $t_1$ or $t_2$ with $x^A$ as a covariate. In both cases we found that its regression coefficient is zero (null hypothesis) under a p-value threshold of 0.05. That is, the Cox model finds no relation between $x^A$ and survival.

4. Experiments

To illustrate performance on real world datasets, the harmonium is compared to (i) Cox regression [3] from the lifelines package [32] with both $L_1$ and $L_2$ regularisation, (ii) random survival forest [13] and (iii) the fast support vector machine (SVM) [17], where the latter two are both from the scikit-survival package.

4.1. Datasets

Our benchmark is comprised of four lifelines datasets [32], namely:

- The recidivism of convicts released from the Maryland state prisons ($m=432$ convicts) [33]—denoted as arrest—to study the effect of financial aid. All features were used for training, but we grouped the number of prior convictions $> 5$ before one-hot encoding categories as dummies.
• The duration of democratic and dictatorial political regimes \((m=1808\) countries) \([34]\) —denoted as democracy—with the continent name and type of regimes as features.

• The survival of women with breast cancer \((m=686\) patients) \([35]\) (denoted as gbsg2) to measure the effect of hormonal therapy, using all features.

• The survival of advanced lung cancer patients \((m=288\) patients) \([36]\)—denoted as ncctg—where the prognostic value of a patient’s questionnaire was examined. We used all features except for the institute code and the columns weight loss and meal calorie intake. After one-hot encoding categories as dummies, the low variance features that were on/off in more than 95% of the samples were dropped to prevent collinearity.

In addition, our benchmark comprises two additional lung cancer datasets containing two time-to-event variables (bundled with the code, but not part of lifelines):

• A Dutch study, nvalt11, considered the effect of prophylactic brain radiation versus observation in \((m=174)\) patients with advanced non-small cell lung cancer \([37]\). The nvalt11 dataset contained time recordings for overall survival (OS) and symptomatic brain metastasis-free survival (SBMFS). We modelled the categoric variables gender, control arm, performance status, and smoking status plus the numeric feature age. The categorical features histology, prior medical conditions, prior malignancies, and stage and numeric variable BMI contained missing values, and were therefore dropped in all models except the harmonium.

• Another Dutch study, called nvalt8 \((m=200\) participants), that examined if nadroparin combined with chemotherapy could reduce cancer relapse after surgical removal of a non-small cell lung tumour \([38]\). The dataset contained failure times for both OS and recurrence free survival (RFS). All models used the numeric feature age and the categories: performance status, histology, smoking status, stage of the disease, control arm and the T, N, and M tumour classification categories. After one-hot-encoding, the low variance features that were on/off in more than 95% of the samples were dropped. The harmonium also incorporated the metabolic activity measured as FDG-PET SUV\(_{\text{max}}\) ≥10 and the numeric variable BMI that both contained missing values.

Apart from the time-to-event variables, all numeric features were standardised and categorical variables were dummy encoded prior to training.

4.2. Results

To reiterate, the primary difference between the harmonium, and the implementations of Cox model, random survival forest, and SVM considered here, is that the harmonium can incorporate missing values and multiple (potentially
since the harmonium captures both survival recordings of the \textit{nvalt} datasets and computes the metrics based on the survival distribution (see Sec.~\ref{app:metrics}), we can compute it in two ways. Firstly, by factoring in the additional survival variable \(S(x_{\text{OS}}|o_{-\text{OS}})\) where \(o_{-\text{OS}}\) denotes observation \(o\) with the element OS removed (but still containing the other survival variable). Alternatively, the dependence of the other survival variable (SBMFS and RFS) can be marginalised out giving \(S(x_{\text{OS}}|o_{-\{\text{OS,SBMFS}\}})\) and \(S(x_{\text{OS}}|o_{-\{\text{OS,RFS}\}})\) for \textit{nvalt11} and \textit{nvalt8}, respectively.

The benchmark results, summarised in Fig.~\ref{fig:benchmark}, shows comparable performance across all models for the first four datasets. For the \textit{nvalt} datasets, notice that when we factor in the additional survival information (indicated by a * in the legend) we observe a substantial improvement in the model’s predictions, especially in terms of the concordance index. For the \textit{nvalt8} dataset, we find that the harmonium does slightly worse in terms of the calibration (Fig.~\ref{fig:benchmark}), but overall scores comparable over the range of datasets. These results are in line with common sense, that a disease relapse or finding a brain tumour decreases one’s expected life expectancy. Conversely, when marginalising out the extra time-to-event variable for the \textit{nvalt} datasets (without a *) the performance reduces to that of the other models. This performance reduction
upon marginalisation is illustrative for the information content captured by the complementary endpoint. Including variables with missing values, as we did for the \textit{nvalt} datasets, showed no noticeable improvement for the harmonium compared to the other models (where this could not be taken into account).

5. Discussion & Conclusion

Healthcare data follows an inherent timeline where new information, such as a lab result or a diagnosis, comes in continuously. At the same time, both statistical and machine learning models require data in tabular format. This poses a challenge, where one should strike a balance between a format that accommodates the model and simultaneously does justice to the time ordering of the data. Our work is a step towards a consolidation of these two representations of the data, by modelling both missing values and multiple time-to-event variables in one coherent framework.

One important disadvantage of the present unsupervised model is that, like many neural networks, there is a myriad of hyperparameters to tune. Choosing appropriate parameters for the learning rate, batch size, number of latent states, how many epochs to train, and regularisation can be challenging. In addition, while some quantities, e.g., the latent states, can be computed efficiently (i.e., linear in the number of input variables), others such as the survival distribution [Eq. (D.1) in Appendix D] can be computationally more demanding.

A second limitation of this work, unrelated to our model, is that Harrell’s concordance index and Brier loss — both intrinsically uni-survival variate metrics — may not be the most appropriate measures to comprehensively interrogate a model’s capacity to capture multiple time recordings. We could only indirectly probe its performance by conditioning on, and marginalising out, the second survival variable. Alas, as far as we know, no higher dimensional generalisations of, e.g., Harrell’s concordance index or the Brier loss exist. In this regard, we believe that the two-dimensional survival distribution in Sec. 3 can serve as a useful example, helping future researchers test their models on multi-dimensional non-linear survival data.

In summary, a new harmonium was proposed for partially and completely missing data. Multiple distinct failure times can be jointly modelled without imposing \textit{a priori} ordering or relation amongst the events, in contrast to conventional survival techniques. In addition, time-independent categorical and numerical features with missing values can be straightforwardly incorporated thanks to its generative structure. Our work shows that the harmonium can capture non-linear survival patterns and illustrates the information embodied in complementary survival endpoints while accounting for the uncertainty in the failure time. We have eliminated the need for selecting a single endpoint and pave the way towards a unified timeline view of the data.
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Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

Code, data, and examples are publicly available under the open source Apache License 2.0 at https://gitlab.com/hylkedonker/harmonium-models.

Appendix A. Energy function survival variables

All survival variables are assumed to be offset against a fixed landmark (e.g., the date when a participant entered the study) so that all values are > 0 and we focus on right censored events. Our goal is to construct an energy function for the survival variables where the building blocks are composed of gamma distributions. To this end, we make the following ansatz for the energy function

$$E_B(x^B, h) = \sum_{i \in B} \sum_{j \in H} x_i W^B_{ij} h_j - \ln(x_i) ||V_j|| h_j + \sum_{i \in B} x_i a^B_i - \ln(x_i) ||c_i||. \quad (A.1)$$

Henceforth $x_i$ are assumed to be scaled to the unit interval $x_i \in (0, 1]$ for all $i \in B$ by normalising $x_i \rightarrow x_i/\tau_i$ with a suitably chosen time horizon $\tau_i$. Our motivation is two fold. The first is technical: $x_i \in (0, 1]$ ensures that the probability density functions [Eq. (A.2), below] can be normalised without imposing the constraint $\beta_i > 0$ for $\beta_i = \sum_{j \in H} W^B_{ij} h_j + a^B_i$ (to prevent diverging integrals near infinity). The second is physical: normalising the data reflects one’s believe about the possible values the data can take since censoring at $\xi_i$ means: the actual event is supposed to occur somewhere in the interval $[\xi_i, 1]$. For example, it may be unrealistic to assume that a person becomes over 120 years old, and the time horizon $\tau_i$ is a way to factor in these physical constraints.

Invoking the definition of the model $p(x^B, h) \propto \exp[-E_B(x^B, h)]$ yields the right truncated gamma distribution

$$p_{\Gamma}(x_i|h) = \frac{x_i^{\alpha_i-1}e^{-\beta_i x_i}}{\Gamma(\alpha_i) \gamma^*(\alpha_i, \beta_i)}, \quad (A.2)$$

as the conditional probability distribution, where $\alpha_i = \sum_{j \in H} ||V_{ij}|| h_j + ||c_i|| + 1$, $\Gamma(x)$ the Gamma function, and

$$\gamma^*(a, z) = \frac{1}{\Gamma(a)} \int_0^1 t^{a-1} e^{-zt}dt, \quad (A.3)$$
the incomplete gamma function [40]. Note that we haven’t exhausted the entire parameter space by choosing the coupling strength $\|V_{ij}\|$ and bias $\|c_i\|$ to be positive, whence $\alpha_i \geq 1$. Technically, $\alpha_i$ must be larger than 0 to prevent poles from emerging. By introducing a term $\|c_i\| \rightarrow \|c_i\| + d_i$ with $d_i > -1$ (e.g., $d_i = \lim_{A \uparrow 1} A \cos \varphi_i$) we can cover the entire domain of $\alpha_i$. But to simplify the generation of samples from Eq. (A.2) we focus on the form laid out in Eq. (A.1). Observe that the bias $c$ can in principle be captured by $V$ at the expense of introducing additional latent states that are always turned on $h_i = 1$. To reduce the amount of parameters as much as possible, we choose instead to model the bias $c$ separate from $V$.

Appendix B. Derivation log-likelihood gradient

The derivation presented here parallels Ref. [30] with the appropriate changes to the notation, and is provided here for completeness. Our goal is to calculate the gradient of the log likelihood

$$L(\{o^{(i)}\}_{i=1}^{m}) = \frac{1}{m} \sum_{i=1}^{m} \ln \int dx p(x) \chi(x, o^{(i)}),$$

(abbreviated using $\int dx \equiv \int_{-\infty}^{\infty} dx \int_{0}^{1} dx^B \sum_{x^A \in \{0,1\} \otimes \{A\}}$) w.r.t. the expanded model

$$p(o, x, h) = \frac{\exp[-E(x, h)] \chi(x, o)}{\Xi},$$

where $\Xi$ is an unimportant normalisation constant which differs from the partition function $Z = \sum_h \int dx \exp[-E(x, h)]$. To this end, write $Z(o) \equiv \sum_h \int dx \exp[-E(x, h)] \chi(x, o)$ to further simplify the log likelihood to

$$L(\{o^{(i)}\}_{i=1}^{m}) = \frac{1}{m} \sum_{i=1}^{m} \ln \frac{Z(o^{(i)})}{Z}. \quad (B.3)$$

To calculate $\nabla_o L$ let us first compute $\nabla_o \ln Z(o)$. Working out the derivative of the first term

$$\nabla_o \ln Z(o) = \frac{1}{Z(o)} \sum_h \int dx \left[-\nabla_o E(x, h)\right] e^{-E(x, h)} \chi(x, o). \quad (B.4)$$

Substituting Eq. (B.2) with $p(o) \equiv \sum_h \int dx p(o, x, h)$ in Eq. (B.4)

$$\frac{e^{-E(x, h)} \chi(x, o)}{Z(o)} = \frac{p(o, x, h)}{p(o)} = p(x, h|o), \quad (B.5)$$

shows that the normalisation constant $\Xi$ of Eq. (B.2) cancels out exactly, and therefore

$$\nabla_o \ln Z(o) = -\langle \nabla_o E(x, h)\rangle_{p(x, h|o)}. \quad (B.6)$$
For the data-independent term $Z = \sum_h \int dx \exp[-E(x, h)]$, we obtain the standard result \[ \nabla_{\Theta} \ln Z = - (\nabla_{\Theta} E(x, h))_{p(x, h)}. \] (B.7)

Putting the two terms together, we arrive at the desired result \[ \nabla_{\Theta} \mathcal{L} = - \left( \frac{1}{m} \sum_{i=1}^{m} (\nabla_{\Theta} E(x, h))_{p(x, h|\alpha^{(i)})} - (\nabla_{\Theta} E(x, h))_{p(x, h)} \right). \] (B.8)

Appendix C. Derivation harmonium as a mixture of Gaussians

On a high level, the event time density has four temporal modes located at $v^{(1)}, \ldots, v^{(4)}$: two corresponding to binary colour $x^A_1 = 0$ ($v^{(1)}$ and $v^{(2)}$) and two for colour $x^A_1 = 1$ ($v^{(3)}$ and $v^{(4)}$). Since there are no numerical factors $x^C$ we disregard corresponding terms in $E$, so that our goal will be to compute $p(x^A, x^B) = \sum_h \exp[-E(x^A, x^B, h)]/Z$ with weights that fit the distribution. We therefore allocate one hidden unit $h_i$ for each mode $v^{(i)}$. For convenience, write $x^A = x^A_1$ since there is only one binary variable (colour). Simplifying, by setting the visible biases to zero ($c = a^A = a^B = 0$), we can evaluate $p(x^A, x^B)$ up to a normalisation constant $Z$ by marginalising out $h$:

\[ p(x^A, x^B) = \sum_h p(x^A, x^B, h) \propto \sum_h \exp[-E(x^A, x^B, h)] = 1 + e^{-\phi_j(x^A, x^B)}, \] (C.1)

where $\phi_j(x^A, x^B)$ [Eq. (12)] groups energy terms proportional to latent state $h_j$. Simplifying further, we substitute receptive fields $V$ and $W^B$ in terms of its shape $\alpha = |V| + 1$ and rate $\beta = W^B$, and replace $W^B_{ij}$ by $w^B_{ij}$ for notational convenience. In this notation, we have \[ \phi_j = - \ln(x^B_j) \cdot (\alpha_j - 1) + x^B_j \cdot \beta_j + w^B_{ij} x^A_i + b_j, \] (C.2)

where we used $\alpha_j$ to denote column $j$ of matrix $\alpha$, and similarly for $\beta$. To pin $x^A$ to its corresponding value $\tilde{x}^A_j$ of mode $j$, let $w^A_j = -q(\tilde{x}^A_j - \frac{1}{2})$ and recall the Le Roux-Bengio Kronecker delta identity \[ \lim_{q \to \infty} \exp \left[ - (w^A_j x^A_i - w^A_j \tilde{x}^A_j) \right] = \delta_{x^A_i, \tilde{x}^A_j}, \] (C.3)

when both $x^A$ and $\tilde{x}^A_j$ are binary valued. Next, observe that most of the temporal mode’s weight are concentrated around its maximum $v^{(j)}_i = (\alpha_{ij} - 1)/\beta_{ij}$, justifying a Taylor expansion around it:

\[ (\alpha_{ij} - 1) \ln x^B_i - \beta_{ij} x^B_i \approx (\alpha_{ij} - 1) \left[ \ln v^{(j)}_i - 1 \right] - \frac{\beta_{ij}}{v^{(j)}_i} \frac{(x^B_i - v^{(j)}_i)^2}{2} + O[(x^B_i - v^{(j)}_i)^3]. \] (C.4)
With both identities [Eqs. (C.3) and (C.4)] in hand, sweep the constants in the bias term:
\[ b_j = -w_j^A x_j^A + \sum_{i=1}^{2} (\alpha_{ij} - 1) \left\{ \ln v_i^{(j)} - 1 \right\} + \Lambda, \] (C.5)
together with a convergence factor \( \Lambda \). Substituting Eqs. (C.4) and (C.5) in (C.2), and using identity (C.3) we have:
\[ e^{-\phi_j} \approx \delta_{x^A, \tilde{x}_A} e^{-\Lambda} \exp \left[ -\frac{1}{2} (x^B - v^{(j)})^T \Sigma_j^{-1} (x^B - v^{(j)}) \right], \] (C.6)
with \( \Sigma_j = \text{diag} \left[ \alpha_{1j} - 1, \alpha_{2j} - 1 \right] \) a diagonal covariance matrix. Assuming that there is little overlap between the modes, i.e., \( e^{-\phi_j} e^{-\phi_k} \approx 0 \) for \( j \neq k \), we have
\[ \tilde{p}(x^A, x^B) = \prod_{j=1}^{4} \left( 1 + e^{-\phi_j} \right) \approx 1 + \sum_{j=1}^{4} e^{-\phi_j} = 1 + 2 \pi e^{-\Lambda} \sum_{j=1}^{4} \delta_{x^A, \tilde{x}_A} \sqrt{\Sigma_j} |N(v^{(j)}, \Sigma_j)|, \] (C.7)
where \( |\Sigma_j| \) is used to denote the determinant of covariance matrix \( \Sigma_j \). Finally, assume that each Gaussian \( N(v^{(j)}, \Sigma_j) \) is sufficiently localised on the \([0,1] \times [0,1] \) unit square so that
\[ \int_0^1 dx_1^B \int_0^1 dx_2^B N(v^{(j)}, \Sigma_j) \approx \int_{-\infty}^{\infty} dx_1^B \int_{-\infty}^{\infty} dx_2^B N(v^{(j)}, \Sigma_j) = 1. \] (C.8)
This integral identity allows us to normalise \( \tilde{p}(x^A, x^B) \)
\[ \sum_{x^A \in \{0,1\}} \int_0^1 dx_1^B \int_0^1 dx_2^B \tilde{p}(x^A, x^B) \approx 2 + 2 \pi e^{-\Lambda} \sum_{j=1}^{4} \sqrt{|\Sigma_j|}, \] (C.9)
giving rise to the overall solution as a mixture of Gaussians:
\[ p(x^A, x^B) \approx 4 \sum_{j=1}^{4} \pi_j \delta_{x^A, \tilde{x}_A} N(v^{(j)}, \Sigma_j), \] (C.10)
with weights \( \pi_j = \frac{\sqrt{|\Sigma_j|}}{\sum_{k=1}^{4} \sqrt{|\Sigma_k|}} \) after choosing a sufficiently large negative convergence factor \( \Lambda \). Finally, substituting \( W^B \) and \( V \) back into \( v^{(j)} \) and \( \Sigma_j \) we arrive at the mean and the (diagonal) covariance matrix in terms of the receptive fields:
\[ v_i^{(j)} = \frac{\|V_{ij}\|}{W_{ij}^B}, \quad (\Sigma_{ii})_j = \left( \frac{\|V_{ij}\|}{W_{ij}^B} \right)^2. \] (C.11)

Appendix D. Experimental aspects

Appendix D.1. Metrics

The concordance index \([1]\) orders the data according to the event time, and measures the amount of data pairs in which the model’s risk prediction is ordered...
concordantly. The concordance index is thus independent of the exact risk scores but only measures their relative ranking. We therefore chose a fixed time point \( t \), and defined the risk score as the predicted survival at that time point i.e.,

\[
r_i = S(x_i = t | o_{-i}) = \frac{p(x_i > t, o_{-i})}{p(o_{-i})},
\]

(D.1)

where \( o_{-i} \) denotes observation \( o \) with element \( i \) removed. In addition, we used \( r_i \) to compute the Brier loss \([39]\) to measure the calibration at time point \( t \). Notice that Eq. (D.1) factors in the survival information from all other survival variables, when there is more than one time-to-event variable. The risk score \( r_i \) when marginalised over survival variable \( j \) is obtained by censoring at time zero [i.e., \( o_j = (\xi_j = 0, e_j = 0) \)] so that \( r_i = S(x_i = t | o_{-(i,j)}) \). Observe, moreover, that the right hand side of Eq. (D.1) can be evaluated in terms of its unnormalised probabilities since the partition function cancels out.

There are at least two ways to compute \( r_i \) via the unnormalised probability density \( \tilde{p}(o, x, h) = e^{-E(x, h)} \chi(x, o) \):

(i) integrate out \( x \) analytically and then sum over \( h \) numerically or

(ii) carry out the \( h \) sum analytically and numerically marginalise over \( x \). While the computational complexity of the former method is linear in the number of visible units \( n_v \) and exponential in the number of latent states \( n_h \), the latter scales linearly in \( n_h \) and roughly exponentially in the number variables with censored/missing values. We therefore used, for the datasets presented here, method (i) when \( n_h < 10 \) and method (ii) otherwise.

Appendix D.2. Generation of samples

To sample from Eqs. (10), (11), and (17) requires samples from the sigmoid function, Gaussian distribution, right truncated Gamma distribution and the interval truncated Gamma distribution. Gaussian samples can be generated using the SciPy routine and binary states can be sampled by picking 1 when the sigmoid activation function exceeds a \([0, 1]\) uniformly sampled threshold, and 0 otherwise. To sample from the \([t<, 1]\) interval truncated Gamma distribution

\[
p_{\Gamma \left[ t<, 1 \right]}(x|\alpha, \beta) = \int_{t<}^{1} dt t^{\alpha-1}e^{-\beta t} = \frac{x^{\alpha-1}e^{-\beta x}}{\frac{\theta(x-t<)}{1 - \gamma^*_{\alpha, t<} \beta}} p_{\Gamma}(x|\alpha, \beta),
\]

(D.2)

and the right truncated Gamma distributions \( p_{\Gamma}(x|\alpha, \beta) \) [Eq. (A.2)], observe that the samples from the latter can be obtained from the former with \( t_\leq = 0 \). Unfortunately, we are not aware of any existing algorithms that can generate samples from intervals for \( \alpha > 0 \) and both \( \beta \geq 0 \) and \( \beta < 0 \). By noticing that

\[
x^{\alpha-1}e^{-\beta x} \leq e^{(\alpha-1)\beta x} \frac{1}{\exp(\alpha - 1)},
\]

(D.3)

for \( \alpha > 1 \), we propose the following rejection algorithm \( \forall \beta \) and \( \alpha > 1 \):
Algorithm 2 Sampling method for the \([-t_c, 1]\) interval truncated gamma distribution for \(\alpha > 1\).

1: while True do
2:     sample \(u \sim U[0, 1]\) and \(y \sim c_{[0,1-t_c]}(y|\alpha-1 - \beta)\)
3:     compute \(p_{\text{accept}}(x)\) with \(x = 1 - y\).
4:     if \(u \leq p_{\text{accept}}\) then
5:         return \(x\)
6:     end if
7: end while

with

\[
p_{\text{accept}}(x) = \left( \frac{x}{\exp(x - 1)} \right)^{\alpha-1}, \tag{D.4}
\]

\(U[0,1]\) the uniform distribution on the unit interval, and \(c_{[0,t]}(x|\lambda)\) the exponential decaying distribution

\[
c_{[0,t]}(x|\lambda) = \frac{\lambda e^{-\lambda x}}{1 - e^{-t\lambda}}, \tag{D.5}
\]

normalised on the interval \([0, t]\). Samples from Eq. (D.5) can be generated by inverting its cumulative distribution \(C(x|\lambda, t) = (1 - \exp[-\lambda x])/(1 - \exp[-t\lambda])\).

Appendix D.3. Initialisation of parameters

For the categorical weights (in \(E_A\)), \(W^A\) was drawn from the Gaussian \(\mathcal{N}(0, 0.01)\) and the bias \(a^A_i\) was initialised to \(\ln[(1 - p_i)/p_i]\) where \(p_i\) is the corresponding average value of the categorical variable in the training set (ignoring any missing values), as suggested in Ref. [27]. Initialisation of the parameters in \(E_C\) followed Ref. [29] by using Glorot-Bengio samples

\[
W^C \sim \left[-\sqrt{\frac{6}{|H| + |C|}}, \sqrt{\frac{6}{|H| + |C|}}\right]
\]

and \(\sigma\) was treated as an adjustable parameter with initial value 1. The bias \(a^C\) was set to zero since the input features can be standardised prior to training. Similarly, for the time-to-event parameters (in \(E_B\)) we used

\[
W^B \sim \left[-\sqrt{\frac{6}{|H| + |B|}}, \sqrt{\frac{6}{|H| + |B|}}\right]
\]

and sampled both \(V\) and \(c\) uniformly from \(\left[0, 2\sqrt{\frac{6}{|H| + |B|}}\right]\) to ensure unit variance [42], and picked \(a^B = 0\). Finally, hidden biases were set to \(b = 0\) as recommended in [27].

Appendix D.4. Settings of benchmark real world datasets

The concordance index [1] and the Brier loss [39] (which was not available for the SVM) were measured using 5×5 nested cross-validation [43] where the inner loop was used to hyperparameter tune the model with the random search algorithm [44] from Scikit-learn [45] using 50 samples. Since both \(n\text{valt}\) datasets consists of two time-to-event variables while the Cox model, SVM, and random forest can only consider a single time-to-event variable, we chose to train and evaluate these models on the OS while the harmonium was trained
on both survival variables and was evaluated on the OS. The Brier loss was computed at $\frac{1}{2}\tau_{\text{max}}$ with $\tau_{\text{max}}$ the maximum survival in the entire dataset. For the harmonium, the same time point were used for computing risk scores (see Appendix D.1), and we set time horizon to $\tau_{\text{max}}$. Hyperparameters were tuned to optimise the concordance index, where the harmonium factored in the RFS and SBMFS variable to predict OS in the nvalt8 and nvalt11 dataset, respectively.

For the Cox model from lifelines [32], the regularisation term $R(\beta)$ is parametrised as

$$R = \frac{\lambda_C}{2} \left[ (1 - \ell_1\|\beta\|^2 + \ell_1\|\beta\|) \right], \tag{D.6}$$

where $\beta$ are the coefficients of the model. Parameters $\lambda_C$ and $\ell_1$ were sampled log-uniformly from the intervals $[10^{-5}, 10^3]$ and $[10^{-5}, 1]$, respectively.

For the survival SVM, the hyperparameter of the squared Hinge loss $\alpha$ was sampled log uniformly from $[2^{-12}, 2^{12}]$ while the ranking ratio $r$ was uniformly sampled from $[0, 1]$ in steps of 0.05, as suggested in Ref. [17].

For the random survival forest, we selected a maximum tree depth of 7 (instead of unbounded) to reduce the memory footprint, and varied (i) the number of estimators as $2^j$ uniformly from $j = 0, \ldots, 10$, (ii) the minimum of samples required for a split as $2^k$ uniformly from $k = 1, \ldots, 5$, (iii) the minimum number of samples per leaf as $2^l$ uniformly from $l = 0, \ldots, 5$ and, (iv) maximum number of features to consider per split by randomly selecting any of $\sqrt{n}$, $\log_2 n$, or $n$ with equal probability, with $n$ the number of features.

Finally, for the harmonium (i) the number of hidden units, (ii) learning rate, (iii) number of epochs to train, (iv) mini batch size, and (v) $L_2$ penalty $R(\Theta) = \lambda_H/2\Theta^2$ were all sampled log uniformly from $[1, 128]$, $[10^{-5}, 5 \cdot 10^{-2}]$, $[500, 10^5]$, $[25, 10^5]$, and $[10^{-5}, 10^{-1}]$, respectively. In each gradient step, a part of the previous update was retained using a momentum fraction $1 - f$, where $f$ was chosen uniformly from $[0, 0.9]$. And lastly, we allowed the Gibbs chain of the negative phase to persist [31] instead of re-initialising it each step as in Algorithm 4. We considered this as an hyperparameter as well, and chose either options with 50% chance, and fixed the number of contrastive divergence steps to 1. The following exceptions were made to these settings: (i) for the democracy and ncctg dataset the number of epochs was capped to $5 \cdot 10^4$ to reduce the computation time, (ii) and we lowered the maximum learning rate for the nvalt8 dataset to 0.0125 to prevent numerical instability.

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