ABSTRACT

Background  Study individuals may face repeated events overtime. However, there is no consensus around learning approaches to use in a high-dimensional framework for survival data (when the number of variables exceeds the number of individuals, i.e., $p > n$). This study aimed at identifying learning algorithms for analyzing/predicting recurrent events and at comparing them to standard statistical models in various data simulation settings. 

Methods  A literature review (LR) was conducted to provide state-of-the-art methodology. Data were then simulated including variations of the number of variables, the proportion of active variables, and the number of events. Learning algorithms from the LR were compared to standard methods in such simulation scheme. Evaluation measures were Harrell’s concordance index, Kim’s C-index and error rate for active variables.

Results  Seven publications were identified, consisting in four methodological studies, one application paper and two reviews. The broken adaptive ridge penalization and the RankDeepSurv deep neural network were used for comparison. On simulated data, the standard models failed when $p > n$. Penalized Andersen-Gill and frailty models outperformed, whereas RandkDeepSurv reported lower performances.

Conclusion  As no guidelines support a specific approach, this study helps to better understand mechanisms and limits of investigated methods in such context.

Keywords  Recurrent Events · Survival Analysis · High-Dimensional Data · Machine Learning
1 Introduction

Study individuals may face repeated events over time, such as hospitalizations or cancer relapses. In either clinical trials or real-world set, survival analysis usually focuses on modeling the time to the first occurrence of the event. Nonetheless, variables may have a varying impact on the first event and on subsequent occurrences. When dealing with multiple occurrences of an event, it becomes a matter of modeling recurrent events (Figure 1).

Two main challenges arise when analyzing recurrent events. First, interindividual heterogeneity emerges as some subjects may be more likely than others to experience the event. Second, events for an individual are not independent, raising intraindividual heterogeneity. These issues have been statistically addressed through two approaches, marginal and conditional models. Marginal models involve implicitly averaging over the history of previous recurrent events. Conditional models can condition on the history of the events.

Moreover, modern technologies enable data to be generated on thousands of variables or observations, as per genomics, medico-administrative databases, disease monitoring by intelligent medical devices, etc. While massive data describe large numbers of observations, high-dimensional data are characterized when the number of variables studied $p$ is greater than the number of individuals $n$. It is precisely the context of high dimension that will be of particular interest in this paper. Standard statistical models may no longer be applied in this case, as they tend to face convergence problems and non-clinically relevant significance of the variables can arise. To help solve high dimension problems, many machine learning methods have emerged.

Literature reviews have previously been conducted on recurrent events, but none has dealt with a high-dimensional framework [Rogers et al., 2014; Twisk et al., 2005; Amorim and Cai, 2015]. The objectives of this study were to identify innovative methodology for the analysis and the prediction recurrent events in high-dimensional survival data and to compare them to standard methods using simulated data.

The literature review for the identification of innovative approaches is first detailed. Methodology components used for the comparison are then developed and results are outlined. Last sections finally summarize main points of discussion and provide the key messages from this paper.
2 Literature review

A literature review was conducted on PubMed based on Cochrane recommendations [Tacconelli, 2010; Higgins et al., 2019]. Hand searches were then carried out via relevant search engines and conferences [noa, 2013]. Inclusion criteria were either methodological or observational studies that analyzed any recurrent outcome. Reviews and/or surveys were also eligible. Methods were considered if the publication mentioned that data in a high-dimensional framework were used or if machine learning techniques were employed. Exclusion criteria were any Bayesian approach and clinical trial design. Research equation included (but was not limited to) the following key terms (and associated MeSH Terms): ‘recurrence’, ‘survival analysis’, ‘high-dimension’ and ‘machine learning’. Two reviewers assessed the eligibility of publications independently and any discrepancies were discussed. Data were summarized descriptively based on the following categories: publication and study characteristics, statistical/machine learning approaches used, and application of data.

Extraction was performed in November 2021 and led to the identification of 176 hits through electronic research on PubMed (Figure 2). Overall, after confirming the outcome of interest dealt with recurrence, the primary reason for exclusion was the non-consideration of recurrent events as time-to-event for each occurrence. Recurrence was considered as a classifier (19/176), as a recurrence-free survival outcome (23/176), or as a time-to-first event (29/176). This may be the illustration of authors’ caution when dealing with recurrent events in high dimensions, as no published guidelines or recommendations exist to date. In addition, three full-text articles could not be reviewed as they were not available. After title, abstract and full-text thorough review, four publications were included from the electronic database search. Three additional papers from the hand searches were identified.

Figure 2: Flowchart of Included Publications via Pubmed
A total of seven relevant publications were selected, consisting in four methodological studies, one application paper and two literature reviews (Table 1). Two articles describing learning algorithms for variable selection strategies were identified. First, focused on accelerating coefficient estimation with a coordinated descent algorithm and penalizing partial likelihood. Zhao et al. [2018] provided an extension of Ridge penalization for estimating and selecting variables simultaneously. Gupta et al. [2019] and Jing et al. [2019] developed deep neural networks extensions for the analysis of recurrence, respectively. In addition, Kim et al. [2021] proposed an application paper aiming at estimating time between two breast cancer recurrences. However, the methodology used in the latter was an extension of a recurrent neural network which was unfortunately not published in any peer-reviewed journal. Finally, two literature reviews mentioned learning algorithms for recurrent event data analysis, even though none of them provided guidelines [Wang et al., 2019, Bull et al., 2020].

Findings from this literature review demonstrated the current gap in the literature and vast differences in the context and methods of interest. In particular, not all developed models were based on simulated data, such as Jing et al. [2019]. Also, none of the included publications compared their performance one to another. For instance, variable selection approaches were compared to standard statistical model only, while neural networks were compared to other neural networks or random forests. No head-to-head comparison across standard methods, learning algorithms and deep neural network seemed to have been performed.
Table 1: Papers Identified from the Literature Review

| #  | Year | Author            | Title                                                                 | Type                      | Description                                                                                     | Data used for application | Evaluation measure | Code availability / reproducibility |
|----|------|-------------------|----------------------------------------------------------------------|---------------------------|------------------------------------------------------------------------------------------------|---------------------------|-------------------|------------------------------------|
| #1 | 2013 | Wu, et al.       | Lasso penalized semiparametric regression on high-dimensional recurrent event data via coordinate descent | Variable selection       | Regularization method with penalization and use of the coordinated descent algorithm, which computes the deviations of the optimization problem and updates the parameter value iteratively | Chronic septic granulomatosis | Number of selected predictor variables and regression coefficients | No                   |
| #2 | 2018 | Zhao, et al.     | Variable selection for recurrent event data with broken adaptive ridge regression | Variable selection       | Extension of the broken adaptive ridge method to recurrent events, involves repetition and reweighting of penalized $L_2$ models Simultaneous variable selection and parameter estimation, accounts for clustering effects | Chronic septic granulomatosis | MSE               | Number of predictor variables selected correctly, and number of predictor variables selected incorrectly | Yes                  |
| #3 | 2019 | Wang, et al.     | Machine Learning for Survival Analysis: A Survey                     | Literature review         | Introduction to survival analysis, overview of classical methods and of learning methods Recurrent events are mentioned, but ML methods are not developed | /                          | /                 | /                    |
| #4 | 2019 | Gupta, et al.    | CRESA: A Deep Learning Approach to Competing Risks, Recurrent Event Survival Analysis | Deep neural networks    | LSTM neural networks with the introduction of the cumulative incidence curve to take into account competitive and/or recurrent events | MIMIC III Machine failure data | Harrell's C-index | No                   |
| #5 | 2019 | Jing, et al.     | A deep survival analysis method based on ranking                     | Deep neural networks     | Extension of the DeepSurv model (neural networks for competitive events) with the use of ranking in the loss function on the differences between observed and predicted values | Myocardial infarction Breast cancer omic data | Harrell's C-index | Yes                  |
| #6 | 2020 | Bull, et al.     | Harnessing repeated measurements of predictor variables for clinical risk prediction: a review of existing methods | Literature review        | Summary of existing methodology to provide clinical prediction depending on the nature on input data Both statistical and learning approaches are described, but no ML methods for recurrent events highlighted | /                          | /                 | /                    |
| #7 | 2021 | Kim, et al.      | Deep Learning-Based Prediction Model for Breast Cancer Recurrence Using Adjuvant Breast Cancer Cohort in Tertiary Cancer Center Registry | Deep neural networks    | Use of Weibull Time To Event Recurrent Neural Network, an extension of recurrent neural network to sequentially estimate time to next event | Breast cancer registry in Korea | Harrell's C-index | MAE                  | Yes                  |

LSTM = long short-term memory; MAE = mean absolute error; ML = machine learning. Articles were sorted by publication year. #1 to #3 were identified via hand searches and #4 to #7 via Pubmed.
3 Materials and method

Standard statistical models were not designed to handle high dimension. The most commonly used ones were described and compared to approaches identified in the literature review. The latter were detailed in the coming sections. Only published approaches with available code were considered (Table 1). Measures of performance for evaluation and comparison were described and were selected in order to stick to survival framework, to specificities inherent to recurrent event data and to machine learning stakes. Finally, the simulation scheme was developed.

3.1 Notations

Let \( X_i \) be a \( p \)-dimensional vector of covariates, \( \beta \) the associated regression coefficients, \( \lambda_0(t) \) the baseline hazard function, \( Y_i(t) \) an indicator of whether subject \( i \) is at risk at time \( t \), \( \delta_i = 1 \) when the subject experienced the event (else \( 0 \)). Let \( E_i \) and \( C_i \) be the time to event or censoring, \( T_i = E_i \wedge C_i \) for the patient \( i \), with \( a \wedge b = \min(a, b) \). \( N_i^*(t) \) denoted the number of events over the interval \([0, t]\). Of note, \( i = 1, \ldots, n \), with \( n \) the number of subjects and \( X \in \mathbb{R}^{n \times p} \) denoted the covariates matrix for all subjects.

3.2 Modeling recurrent events

3.2.1 Standard statistical models

Andersen-Gill (AG), Prentice, William et Peterson (PWP), Wei-Lin-Weissfeld (WLW) and the frailty models were developed as extensions of the Cox model [Andersen and Gill, 1982; Prentice et al., 1981; Wei et al., 1989; Vaupel et al., 1979; Cox, 1972]. These methodologies commonly used models to handle recurrent event data. Their characteristics are summarized in Table 2. Further details on time scales and how models accounted for subject at risk can be found in Appendix.

| Model | Components and specificities |
|-------|-----------------------------|
| AG    | Conditional model, accounts for the counting process as a time scale and unrestricted set for subjects at risk | Recurrent events within individuals are independent and share a common baseline hazard function |
|       | Intensity of the model: \( \lambda_i(t) = Y_i(t) \star \lambda_0(t) \star \exp(\beta^t X_i) \) |
| PWP   | Conditional model, counting process as time scale and restricted set for subjects at risk | Stratified AG, stratum \( k \) collects all the \( k \)th events of the individuals |
|       | Hazard function: \( \lambda_{ik}(t) = Y_i(t) \star \lambda_{0k}(t) \star \exp(\beta^t X_i) \) |
| WLW   | Marginal model, also stratified, calendar time scale and semi-restricted set for subjects at risk | Intra-subject dependence |
|       | Hazard function: \( \lambda_{ik}(t) = Y_i(t) \star \lambda_{0k}(t) \star \exp(\beta^t X_i) \) |
| Frailty | Extension of AG model | Random term \( z_i \) for each individual to account for unobservable or unmeasured characteristics |
|       | Intensity of the model: \( \lambda_i(t) = Y_i(t) \star \lambda_0(t) \star z_i \star \exp(\beta^t X_i) \) |

AG = Andersen-Gill; PWP = Prentice, William et Peterson; WLW = Wei-Lin-Weissfeld.

3.2.2 Learning algorithms for variable selection

A common approach to address high-dimension challenge is variable selection. Penalizing models help to reduce the space of parameter coefficients, which is called shrinkage. Widely used for regression and classification problems, Lasso penalization accepts null coefficients to select variables and Ridge helps to deal with multicollinearity in the data. Both penalization approaches have been extended to Cox models in standard survival analysis framework [Tibshirani, 1997; Simon et al., 2011]. The purpose is to solve a constrained optimization problem of the partial log-likelihood of the Cox model, which is written

\[
\mathcal{L}(\beta) = \sum_{i=1}^{n} \delta_i \beta^t X_i - \sum_{i=1}^{n} \delta_i \star \log \sum_{j \in R(\tau_i)} \exp(\beta^t X_i) \tag{1}
\]
With \( \mathcal{R}(t) \) the set of individuals who are “at risk” for the event at time \( t \). For CoxLasso, regularization is performed using an \( L_1 \) norm penalty and \( \hat{\beta} = \arg \max_{\beta} L(\beta), \|\beta\|_1 \leq s \) and for CoxRidge an \( L_2 \) norm penalty and \( \hat{\beta} = \arg \max_{\beta} L(\beta), \|\beta\|_2 \leq s \), with \( s \geq 0 \). The lower the value of \( s \), the stronger the penalization. Hyperparameters, named penalty coefficients, are used to determine its value and enable to control the impact of the penalty.

Zhao et al. [2018] proposed an extension of these methods to recurrent events by developing the broken adaptive ridge (BAR) regression. The first iteration consists of a penalized \( L_2 \) model

\[
\hat{\beta}^{(0)} = \arg \min_{\beta} \left(-2 * L_{mod}(\beta) + \xi_n \sum_{j=1}^{p} \beta_j^2\right), \xi_n \geq 0
\]

If penalization hyperparameter \( \xi_n \geq 0 \), this is a Ridge penalty, and if \( \xi_n = 0 \) then \( \beta^{(0)} \) is not penalized. We update for each iteration \( \omega \):

\[
\hat{\beta}^{(\omega)} = \arg \min_{\beta} \left(-2 * L_{mod}(\beta) + \theta_n \sum_{j=1}^{p} \frac{\beta_j^2}{\beta^{(\omega-1)}_j}\right), \omega \geq 1
\]

BAR estimates are defined by \( \hat{\beta} = \lim_{k \to \infty} \hat{\beta}^{(\omega)} \). The estimator benefits from the oracle properties of both penalties for model covariate selection and estimation. Cross-validation is recommended to optimize values of hyperparameters \( \xi_n \) and \( \theta_n \). According to Kawaguchi et al. [2020], estimates are not sensitive to variations of \( \xi_n \) and optimization can be performed only on \( \theta_n \). In the absence of a consensual single measure on cross-validation under recurrent events, two values for \( \theta_n \) were studied in this paper, thereby considering two separate models.

### 3.2.3 Deep neural network

RankDeepSurv is a deep neural network proposed by [Jing et al. 2019] with fully connected layers (all neurons in one layer are connected to all neurons in another layer) (Figure 3).

![Figure 3: RankDeepSurv Neural Network Diagram (sourced from Jing 2019)](image)

The specificity of the RankDeepSurv neural network lies in the loss function adapted to survival, which results from the sum of two terms: one to constrain the survival model using an extension of the mean square error and the other to evaluate the rank error between observed and predicted values for two individuals. The loss function is written as

\[
L_{loss}(\theta) = \alpha_1 * L_1(\theta) + \alpha_2 * L_2(\theta) + \mu * \|\theta\|^2
\]

with
• $\alpha_1, \alpha_2 > 0$ constant values, $\theta$ the weights of the network, $\mu$ regularization parameter for $L_2$;

• $L_1 = \frac{1}{n} \sum_{i=1}^{n} I(i) (y_{i,pred} - y_{i,obs})^2, I(i) = 1$ if $i$ is censored or if the predicted time to event is before observed time, else 0;

• $L_2 = \frac{1}{n} \sum_{i,j=1}^{n} I(i,j) ((y_{i,obs} - y_{i,pred}) - (y_{j,obs} - y_{j,pred}))^2, I(i,j) = 1$ if $y_{j,obs} - y_{j,pred} > y_{i,obs} - y_{i,pred}$, else 0.

Gradient descent is utilized for solving the minimization of $L_{loss}$.

3.3 Evaluation criteria to measure performance

3.3.1 Harrell’s Concordance index

Harrell’s C-index is a common evaluation criterion in survival analysis [Harrell et al., 1996]. This measure is the proportion of pairs of individuals for which the order of survival times is concordant with the order of the predicted risk. In the presence of censoring, the denominator is the number of pairs of individuals with an event. The C-index is estimated as follows

$$\hat{C} = \frac{\sum_{i \neq j} I(\eta_i < \eta_j) * I(T_i > T_j) * \delta_j}{\sum_{i \neq j} I(T_i > T_j) * \delta_j}$$

(5)

With $\eta_i$ the risk of occurrence of the event. Of note, when two individuals are censored, then we cannot know which of the two has the event first. This pair is not included in the calculation. In the same way, if one of the individuals is censored and its censoring time is lower than the event time of another individual, we cannot know which of the two has the event first. This pair is also not included in the C-index calculation. If the C-index is equal to 1, it means a perfect prediction, and if the C-index $\leq 0.5$, it implies that the model behaves similarly or worse than random. Models with a higher C-index close to 1 are preferred. Harrell’s C-index was computed at each event.

3.3.2 Kim’s C-index

Kim et al. [2018] proposed a measure of concordance between observed and predicted event counts over a time interval of shared observations. It is the proportion of pairs of individuals for whom the risk prediction and the number of observed events are concordant:

$$\hat{C}_{rec} = \frac{\sum_{i=1}^{n} \sum_{j=1}^{n} I(N^*_i (T_i \wedge T_j) > N^*_j (T_i \wedge T_j)) * I(\beta^i X_i > \beta^j X_j)}{\sum_{i=1}^{n} \sum_{j=1}^{n} I(N^*_i (T_i \wedge T_j) > N^*_j (T_i \wedge T_j))}$$

(6)

This extension of the C-index implies:

• Two individuals are comparable up to the minimum time of follow-up;

• A pair contributes to the denominator if the two event counts are not equal.

As per Harrell’s C-index in Equation (5), a score close to 1 indicates a better performance of the model. As opposed to Harrell’s C-index, Kim’s C-index was computed once across all the events.

3.3.3 Error rate for active variables

When simulating the datasets, the active status of each variable is known. Methods report the significant variables with a p-value $< 0.05$ (except deep neural networks). Significant variables are considered as positive tests for their active status. Some active variables likely have a false negative test ($FN$), and some passive variables have a false positive test ($FP$). The error rate ($err$) is the proportion of misclassified variables after prediction:

$$err = \frac{FP + FN}{p}$$

(7)
3.4 Simulation scheme

The following assumptions were made:

- Active variables were continuous, and all have the same (non-zero) effect;
- The variables do not vary over time;
- Individuals were at risk continuously until end of follow-up;
- Censoring is not informative.

The generation of the covariates matrix, $X \sim N_m(\mu, \sigma(\rho))$. $\mu = (\mu_1 \ldots \mu_p) = (a \ldots a)$ and $\sigma(\rho)$ was the covariance matrix with an autoregressive correlation structure and $\rho \in (0, 1)$. The coefficients $\beta = (\beta_1 \ldots \beta_p) = (b, \ldots, b, 0, \ldots, 0)$ were associated with the $p$ covariates. $m$ coefficients were equal to a constant $b \in \mathbb{R}$ (the value of the active coefficients) and $p - m$ coefficients were equal to zero. The sparse rate was described by $\frac{m}{p}$. The baseline hazard function followed a Weibull distribution with scale $\alpha > 0$ and shape $\gamma > 0$, and $\lambda_0(t) = \alpha \gamma t^{\gamma - 1}$. The cumulated baseline hazard function could be expressed as $\Lambda_0(t) = \int_0^t \lambda_0(s) ds = \alpha t^\gamma$. Hence the cumulative hazard function could be expressed as $\Lambda(t) = \Lambda_0(t) \exp(\beta^t X_i)$. Conditional baseline hazard function was then defined as $\tilde{\Lambda}_t(u) := \tilde{\Lambda}_i(u \mid T_i - 1) = \Lambda(u + t) - \Lambda(t)$. A frailty term $z_i \text{i.i.d.}$ was incorporated to account for heterogeneity.

To maintain censoring rates, censored individuals were randomly drawn (censoring is not informative), as per Jahn-Eimermacher et al. [2015]. The algorithm of Jahn-Eimermacher [2008] was applied to simulate event times $k$ for each subject $i$:

$$t_{i,1} = \Lambda^{-1}(t)(-\log(\epsilon_1)), t_{i,k+1} = t_{i,1} + \tilde{\Lambda}^{-1}_{i,k}(-\log(\epsilon_{k+1}))$$  \(8\)

with $\epsilon_k \sim U[0, 1]$.

Train-test split was employed with a 70-30% distribution. Datasets were generated with:

- $N = 100$ subjects
- Censoring rate of 20%
- $\rho = 0.7$
- $b = 0.15$, $\alpha = 1$, and $\gamma = 2$
- $z \sim \text{Gamma}(0.25)$

Scenarios include variations of the number of covariates $p = 25, 50, 100, 150,$ and $200$ and the sparse rate = 0%, 25%, and 50%. For each of the 15 scenarios, 100 datasets were generated to account for variability.

4 Results

4.1 Data simulation overview

Datasets had identical characteristics in terms of number of individuals, structure of covariates, but differed across scenarios in terms of number of covariates and sparse rate. In the variance-covariance matrix, the covariates were highly correlated when they were close, then decreasingly close when they were further apart. Figure 4 captured this relationship across covariates with five datasets, regardless of the number of covariates. Figure 5 provided a visual representation of the history of nine individuals and their events over the follow-up period (and made it easier to understand Figure 1).
4.2 Evolution of average C-index

The evolution of average C-index was investigated across all 15 scenarios (Figure 6). As expected, the standard models failed as soon as $p > n$. Whereas the C-indices were also expected to be around 0.5 when the sparse rate was zero, they increased as the sparse rate increased. The best performance was obtained using the frailty model. Other models showed similar trends, except for the WLW and RankDeepSurv models. The C-indices of these two models remained around the value of 0.5 (and even below) regardless of the scenario. The Kim’s C-index was more stable across the different number of covariates and sparse rates, although it tended to decrease as the number of covariates increased with sparse rate = 50%. Small difference across penalty values was noticed as 0.05 penalized models and 0.1 penalized models followed similar trends.

4.3 Focus on the variability of C-indices for two extreme scenarios

Two extreme scenarios were thoroughly studied: one with no active variable and only 25 variables (A), and another on which models overall reported great performance with a sparse rate 25% and over 150 variables (B). Similar trends in variability were observed across the two scenarios and for each C-index (Appendix Figure 8). Kim’s C-index was less volatile across models and their penalties, with values ranging between 0.39 and 0.63 and 0.28 and 0.76 for (A) and (B), respectively. Harrell’s C-index was increasingly variable in the first event (A: min = 0.26 and max = 0.74; B: min =
0.24 and max = 0.81), second event (A: min = 0.30 and max = 0.75; B: min = 0.17 and max = 0.85), and third event (A: min = 1 and max = 0).

4.4 Error rate for active variables

The results on the average error rates were displayed in Appendix Figure 9. In the scenarios where the sparse rate was equal to 0%, all models reported average error rates below 0.5, except penalized WLW with error rates around 0.75. Average error rates appeared similar when no penalty was applied. AG model had the lowest average error rate for
each $p$, with a minimum value of 0.018 for the penalized model at $0.1 \times \log(p)$ and $p = 200$. The average error rate decreased when the penalty increased when $p > n$. For the scenarios with a sparse rate equal to 25%, the unpenalized frailty model had the best performance, while the other models provided higher values. Similarly, penalties decreased the average error rate. Penalized AG models reported average error rates lower than 0.3. Finally, when the sparse rate was equal to 50%, almost constant average error rates around 0.5 were observed for each model regardless of $p$.

5 Discussion

The literature review provided in this paper enabled the identification of emerging approaches. A total of seven publications were found, testifying the shortage of available resources in this area. At the same time, these approaches had not been compared with one another. This may lead to erratic behavior and confusion when researchers wish to conduct robust and reliable analyses in such a context. This study thus proposed to evaluate some of the innovative learning algorithms which were developed to solve the high-dimensional framework when considering recurrent events. The investigation of the above 15 scenarios on simulated data arose specificities of both methodology and measures used for their evaluation of performance.

Firstly, unpenalized standard approaches failed as soon as $p > n$ as expected, while penalized helped to improve their performance when $p < n$. This was typically expected as standard statistical models were not designed for $p > n$ cases. AG and PWP models reported equivalent performance, while the frailty model consistently had the best performance. This was due to the construction of the frailty term from the simulation scheme. The WLW model performed mediocrely, regardless of if it was penalized or not; this was consistent with previous findings in the literature, exposing WLW models to be more appropriate with events of different types rather than recurrent events [Ozga et al., 2018] [Ullah et al., 2014]. Nevertheless, these models, each with their own specificities, can respond to differing needs, especially related to the research questions, but only methodological issues were meant to be illustrated in this study [Rogers et al., 2014] [Amorim and Cai, 2015] [Charles-Nelson et al., 2019].

Secondly, variable selection with penalties did not significantly increase performance, and few variables were even selected when the sparse rate was zero. Since only two values for the hyperparameter were explored, it seemed quite unlikely these would maximize the model performance. The deep neural network reported poorer performance; one reason could be that the format of the data was not suitable for the code.

Then, average error rates increased with the sparse rate. When the number of active variables was higher, the models tended to select the wrong variables. It seemed as if the models had a hard time learning and selecting the true active variables with a high sparse rate, while they managed to report better C-indices. This was linked to the variance-covariance structure chosen for data simulation.

With regards to evaluation metrics, Kim’s C-index has shown higher stability and robustness compared to other metrics and stood for a criterion evaluating the entire set of events. Harrell’s C, on the other hand, was measured at each event, making it difficult to interpret in terms of global performance.

Nevertheless, some limitations should be noted. The literature review presented several drawbacks. Publications whose objective was variable selection without explicit dimension reduction, such as [Tong et al., 2009] and [Chen and Wang, 2013] could not be captured because of the elaborated research strategy. Also, it was not always easy to assess how the outcome was really considered, especially for neural networks which make little mention of the expected structure to process the data. Furthermore, as mentioned above, the lack of hyperparameter optimization for variable selection made BAR approach inconclusive. Also, a cross-validation would have highlighted the robustness of the results [Heinze et al., 2018]. Furthermore, other evaluation measures have been used in the literature, e.g., the mean square error, the mean absolute error, the log-likelihood [Wu, 2013] [Zhao et al., 2018] [Ullah et al., 2014]. An additional way to investigate active variables would be to assess the importance of the variables by permutation [Fisher et al.].

By choosing a performance measure beforehand, this consists in permuting k times the order of the covariates and calculating k times the performance of the model. Finally, the simulations scheme itself presented several drawbacks. Covariates were not time-dependent and shared the same effect on the outcome, which may seem implausible in real life and made the interpretation of the results hard to generalize. Also, although the simulation of the data maintained censoring rates, it was not based on a distribution of censoring time, while one should be able to genuinely control them [Wan, 2017] [Penichoux et al., 2015].
6 Conclusion

To the author’s knowledge, this study was the first to compare standard methods, variable selection algorithms, and a deep neural network in modeling recurrent events in a high-dimensional framework.

Progress in medical care is leading to the use of embedded artificial intelligence (AI) technologies. One illustration of this is the booming market for AI medical devices. Such systems are typically designed to prevent the occurrence of events either at the hospital, elderly care home or outpatient setting, etc. Should these events be likely to occur repeatedly, and should all available data/knowledge be captured, then thorough, robust and appropriate analysis of recurrent events is crucial [Berisha et al., 2021].

Overall, this work raises many concerns for recurrent event data analysis in high-dimensional settings and highlights the current need for developing further approaches and to assess their performance in a relevant manner.

7 Appendices

7.1 Data components for modeling recurrent events when using standard statistical approaches

7.1.1 Set of individuals at risk

Standard statistical models described do not encounter for individuals at risk in the same way. This induces prior data management for appropriate application.

- The set of individuals at risk for the \( k \)th event comprised individuals who were at risk for the event. Different definition existed for the set of individuals at risk, mainly based on baseline hazard function;
- The unrestricted set, in which each subject could be at risk for any event regardless of the number of events presented, at all-time intervals;
- The restricted set contained only the time intervals for the \( k \)th event of subjects who had already presented \( k - 1 \) events;
- The semi-restricted set contained for the \( k \)th event the subjects who had \( k - 1 \) or fewer events.

7.1.2 Timescales

Timescales also embody key components to address at the data management stage. Three common timescales are:

- Calendar time, in which the times denotes the time since randomization/beginning of the study until an event occurs;
- Gap time, or waiting scale, resets the time to zero when an event occurs, i.e., it corresponds to the time elapsed since the last event previously observed;
- Counting process is constructed as per calendar time, although it enables late inclusions and/or censoring.

Illustrations for timescales were provided in Figure[7]
Figure 7: Timescales in Recurrent Events Analysis
7.2 Further graphics from results

Figure 8: Variability of C-indices for Two Extreme Scenarios: Sparse Rate = 0%, \( p = 25 \) (A) and Sparse Rate = 25%, \( p = 150 \) (B)
Figure 9: Evolution of Average Error Rates with Sparse Rate Equal to 0% (A), 25% (B) et 50% (C)
References

Guide to the methods of technology appraisal 2013. page 94, 2013.

Leila D. A. F. Amorim and Jianwen Cai. Modelling recurrent events: a tutorial for analysis in epidemiology. *International Journal of Epidemiology*, 44(1):324–333, February 2015. ISSN 1464-3685. doi:10.1093/ije/dyu222.

P. K. Andersen and R. D. Gill. Cox’s Regression Model for Counting Processes: A Large Sample Study. *The Annals of Statistics*, 10(4):1100–1120, 1982. ISSN 0090-5364. URL https://www.jstor.org/stable/2240714.

Gregory S. Cooper. Modern methods for multiple recurrent events data: a review of existing methods. *Diagnosis and Prognosis Research*, 4:9, 2020. ISSN 2397-7523. doi:10.1002/sim.8168.

Lucy M. Bull, Mark Lunt, Glen P. Martin, Kimme Hyrich, and Jamie C. Sergeant. Harnessing repeated measurements of predictor variables for clinical risk prediction: a review of existing methods. *Diagnostic and Prognostic Research*, 4:9, 2020. ISSN 2397-7523. doi:10.1002/sim.8168.

Visar Berisha, Chelsea Krantsevich, P. Richard Hahn, Shira Hahn, Gautam Dasarathy, Pavan Turaga, and Julie Liss. Digital medicine and the curse of dimensionality. *NPJ digital medicine*, 4(1):153, October 2021. ISSN 2398-6352. doi:10.1038/s41746-021-00521-5.

Lucy M. Bull, Mark Lunt, Glen P. Martin, Kimme Hyrich, and Jamie C. Sergeant. Harnessing repeated measurements of predictor variables for clinical risk prediction: a review of existing methods. *Diagnostic and Prognostic Research*, 4:9, 2020. ISSN 2397-7523. doi:10.1002/sim.8168.

Anaïs Charles-Nelson, Sandrine Katsahian, and Catherine Schramm. How to analyze and interpret recurrent events data in the presence of a terminal event: An application on readmission after colorectal cancer surgery. *Statistics in Medicine*, page sim.8168, April 2019. ISSN 0277-6715, 1097-0258. doi:10.1002/sim.8168. URL https://onlinelibrary.wiley.com/doi/10.1002/sim.8168.

Xiaolin Chen and Qihua Wang. Variable selection in the additive rate model for recurrent event data. *Computational Statistics & Data Analysis*, 57(1):491–503, 2013. URL https://ideas.repec.org/a/eee/csda/v57y2013i1p491-503.html.

D. R. Cox. Regression Models and Life-Tables. *Journal of the Royal Statistical Society: Series B (Methodological)*, 34(2):187–202, January 1972. ISSN 00359246. doi:10.1111/j.2517-6161.1972.tb00899.x. URL https://onlinelibrary.wiley.com/doi/10.1111/j.2517-6161.1972.tb00899.x.

Frank E. Harrell, Kerry L. Lee, and Daniel B. Mark. MULTIVARIABLE PROGNOSTIC MODELS: ISSUES IN DEVELOPING MODELS, EVALUATING ASSUMPTIONS AND ADEQUACY, AND MEASURING AND REDUCING ERRORS. *Statistics in Medicine*, 15(4):361–387, February 1996. ISSN 0277-6715, 1097-0258. doi:10.1002/(SICI)1097-0258(19960229)15:4<361::AID-SIM168>3.0.CO;2-4. URL https://onlinelibrary.wiley.com/doi/10.1002/(SICI)1097-0258(19960229)15:4<361::AID-SIM168>3.0.CO;2-4.

Georg Heinze, Christine Wallisch, and Daniela Dunkler. Variable selection - A review and recommendations for the practicing statistician. *Biometrical Journal*, 60(3):431–449, May 2018. ISSN 03233847. doi:10.1002/bimj.201700067. URL https://onlinelibrary.wiley.com/doi/10.1002/bimj.201700067.

Julian P. T. Higgins, James Thomas, Jacqueline Chandler, Miranda Cumpston, Tianjing Li, Matthew J. Page, and Vivian A. Welch. *Cochrane Handbook for Systematic Reviews of Interventions*. John Wiley & Sons, September 2019. ISBN 978-1-119-53661-1. Google-Books-ID: cTqyDwAAQBAJ.

Antje Jahn-Eimermacher. Comparison of the Andersen-Gill model with poisson and negative binomial regression on recurrent event data. *Computational Statistics & Data Analysis*, 52(11):4989–4997, 2008. ISSN 0167-9473. URL https://econpapers.repec.org/article/eeecsdana/v_3a52_3ay_3a2008_3ai_3a11_3ap_3a4989-4997.htm.

Antje Jahn-Eimermacher, Katharina Ingel, Ann-Kathrin Ozga, Stella Preussler, and Harald Binder. Simulating recurrent event data with hazard functions defined on a total time scale. *BMC Medical Research Methodology*, 15(1):16, March 2015. ISSN 1471-2288. doi:10.1186/s12874-015-0005-2. URL https://doi.org/10.1186/s12874-015-0005-2.

Bingzhong Jing, Tao Zhang, Zixian Wang, Ying Jin, Kuiyuan Liu, Wenze Qiu, Liangru Ke, Ying Sun, Caisheng He, Dan Hou, Linquan Tang, Xing Lv, and Chaofeng Li. A deep survival analysis method based on ranking. *Artificial Intelligence in Medicine*, 98:1–9, July 2019. ISSN 1873-2860. doi:10.1016/j.artmed.2019.06.001.

Eric S. Kawaguchi, Marc A. Suchard, Zhengui Liu, and Gang Li. A surrogate l0 sparse Cox’s regression with applications to sparse high-dimensional massive sample size-time-to-event data. *Statistics in Medicine*, 39(6):675–686, 2020. ISSN 1097-0258. doi:10.1002/sim.8438. URL https://onlinelibrary.wiley.com/doi/abs/10.1002/sim.8438.
Ji-Yeon Kim, Yong Seok Lee, Jonghan Yu, Youngmin Park, Se Kyung Lee, Minyoung Lee, Jeong Eon Lee, Seok Won Kim, Seok Jin Nam, Yeon Hee Park, Jin Seok Ahn, Mira Kang, and Young-Hyuck Im. Deep Learning-Based Prediction Model for Breast Cancer Recurrence Using Adjuvant Breast Cancer Cohort in Tertiary Cancer Center Registry. *Frontiers in Oncology*, 11, May 2021. ISSN 2234-943X. doi:10.3389/fonc.2021.596364 URL https://www.frontiersin.org/articles/10.3389/fonc.2021.596364/full

Sehee Kim, Douglas E. Schaubel, and Keith P. McCullough. A C-index for recurrent event data: Application to hospitalizations among dialysis patients. *Biometrics*, 74(2):734–743, June 2018. ISSN 1541-0420. doi:10.1111/biom.12761

Ann-Kathrin Ozga, Meinhard Kieser, and Geraldine Rauch. A systematic comparison of recurrent event models for application to composite endpoints. *BMC medical research methodology*, 18(1):2, January 2018. ISSN 1471-2288. doi:10.1186/s12874-017-0462-x

R. L. Prentice, B. J. Williams, and A. V. Peterson. On the regression analysis of multivariate failure time data. *Biometrika*, 68(2):373–379, 1981. ISSN 0006-3444, 1464-3510. doi:10.1093/biomet/68.2.373 URL https://academic.oup.com/biomet/article-lookup/doi/10.1093/biomet/68.2.373

J. W. Vaupel, K. G. Manton, and E. Stallard. The impact of heterogeneity in individual frailty on the dynamics of mortality. *Demography*, 16(3):439–454, August 1979. ISSN 0070-3370.

Fei Wan. Simulating survival data with predefined censoring rates for proportional hazards models: Simulating censored survival data. *Statistics in Medicine*, 36(5):838–854, February 2017. ISSN 02776715. doi:10.1002/sim.7178 URL https://onlinelibrary.wiley.com/doi/10.1002/sim.7178

Ping Wang, Yan Li, and Chandan K. Reddy. Machine Learning for Survival Analysis: A Survey. *ACM Computing Surveys*, 51(6):110:1–110:36, 2019. ISSN 0360-3000. doi:10.1145/3214306 URL https://doi.org/10.1145/3214306

L. J. Wei, D. Y. Lin, and L. Weissfeld. Regression Analysis of Multivariate Incomplete Failure Time Data by Modeling Marginal Distributions. *Journal of the American Statistical Association*, 84(408):1065–1073, 1989. ISSN 0162-1459. doi:10.2307/2290084 URL https://www.jstor.org/stable/2290084

Tong Tong Wu. Lasso penalized semiparametric regression on high-dimensional recurrent event data via coordinate descent. *Journal of Statistical Computation and Simulation*, 83(6):1145–1155, 2013. ISSN 0094-9655. doi:10.1080/00949655.2011.652114 URL https://doi.org/10.1080/00949655.2011.652114

Hui Zhao, Dayu Sun, Gang Li, and Jianguo Sun. Variable selection for recurrent event data with broken adaptive ridge regression. *Canadian Journal of Statistics*, 46(3):416–428, 2018. ISSN 1708-945X. doi:10.1002/cjs.11459 URL https://onlinelibrary.wiley.com/doi/abs/10.1002/cjs.11459

18