Generalized Concordance for Competing Risks

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Summary

Existing metrics in competing risks survival analysis such as concordance and accuracy do not evaluate a model’s ability to jointly predict the event type and the event time. To address these limitations, we propose a new metric, which we call the generalized concordance. The different components of the generalized concordance correspond to the probabilities that a model makes an error in the event-type prediction only, or the discrimination only or both. We develop a consistent estimator for the new metric that accounts for the censoring bias. Using the real and synthetic data experiments, we show that models selected using the existing metrics are worse than those selected using generalized concordance at jointly predicting the event type and event time. We use the new metric to develop a variable importance ranking approach, which we call the stepwise competing risks regression. The purpose of this approach is to identify the factors that are important for predicting both the event type and the event time. We use real and synthetic datasets to show that the existing approaches for variable importance ranking often fail to recognize the importance of the event-specific risk factors, whereas, our approach does not.

Key words: Competing risks, Concordance, Survival, Multi-morbidity, Model comparison

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1. Introduction

The concordance index (Wolbers et al., 2014) is one of the most widely used metrics in survival analysis with competing risks (SA-CR) (Lee and others, 2018) for measuring a model’s discriminative ability, i.e., a model’s ability to correctly order the subjects based on their risk. As was pointed out in Wolbers et al. (2014), the concordance index is used to assess the prognostic ability of a model for one event type of interest in the presence of competing risks, but it is not adequate to assess the prognostic ability of a model when there is more than one event type of interest. We describe some important clinical scenarios with more than one event types below.

1. Treatment planning for multimorbid populations. Multi-morbidity – the accumulation of chronic diseases – has emerged as a major contemporary challenge of the ageing population (Wolbers et al., 2009) (Cardinale et al., 2004). More than two-thirds of people aged over 65 are multimorbid, i.e., have two or more chronic diseases (Agborsangaya and others, 2012) (Pefoyo and others, 2015). Adverse treatment reactions are one of the leading causes of death in the United States (Jacobs and Fisher, 2013). The current healthcare provision is not designed to consider diseases in combination leading to complications arising from unnecessary treatments. Therefore, it is important to develop treatment plans in multimorbid populations after assessing the overall risk profile, i.e. the risks of death from different conditions.

2. Treatment planning for critical care. SA-CR models have been used to develop early warning systems for predicting the event time and the event type (e.g., ventilation or discharged alive, different types of organ failures) Beyersmann and Schumacher (2008). In these applications, the joint prediction of the event type (e.g., ventilation) and the event time is helpful for planning the allocation of resources (e.g., ventilator).
1.1 Contributions

In this work, we propose a new metric that we call the generalized concordance. The generalized concordance is a vector, where each component of the vector is a probability defined as follows. For each event type under consideration, there are three components within the vector. The first component is the probability that a given model incorrectly predicts the event type only. The second component is the probability that a given model incorrectly ranks (according to the risk) a subject among other subjects within a specific event-type. The third component is the probability that a given model both incorrectly predicts the event type for a subject and also incorrectly ranks that subject among other subjects within a specific event-type. We prove (in Section 3) that the existing metrics such as concordance and accuracy can be expressed as a weighted sum of the components of the generalized concordance.

To assess the merits of generalized concordance and reasons it is useful, we focus on a natural special case: the sum (unweighted) of all components of the generalized concordance; we call this the joint concordance. The joint concordance index is the probability that a given model accurately predicts the event type for a subject while also ranking that subject’s risk correctly among the other subjects. We show that the joint concordance index can be interpreted by decomposing it into a metric that is similar to accuracy and concordance conditional on the correct predictions. We prove that the concordance and accuracy are not sufficient to determine the joint concordance thus establishing that joint concordance contains new information not contained in concordance and accuracy.

In most survival analysis settings, the most common form of censoring is right censoring; right censoring occurs when either the subject is lost in the follow-up, or the study ends. In these scenarios, the estimation of the joint concordance index can become more difficult as censoring can introduce bias in the population that is observed at different times in the follow-up. We use standard approaches Wolbers et.al. (2014) to adjust for the bias to construct our estimator. We
prove that the proposed estimator is consistent and we show that the difference between the estimator and the joint concordance converges to a normal distribution. We show that the results that are presented for the joint concordance extend to the generalized concordance.

We propose a variable importance ranking procedure based on the joint concordance that relies on backward elimination and stepwise regression (Thompson, 1995). We call this procedure *stepwise competing risk regression*. In this approach, we train a competing risks regression model and use backward elimination, i.e. drop the variable that leads to the least change in the joint concordance. This approach is useful as it identifies risk factors that are important for predicting both the event type and the event time unlike the existing approaches (further explanations in Section 4, 5 and Figure 3).

First, we carry out experiments similar to Wolbers et al. (2014) on synthetic datasets to evaluate the performance of the estimator in terms of the root mean squared errors, the standard errors, and the bias. Then we carry out real data based experiments. We show that a model selected based on the joint concordance has a higher chance to correctly predict the event type and the event time for a subject in comparison to a model based on the existing metrics.

We use our stepwise competing risks regression approach to find out the important risk factors that predict the overall risk of death due to cardiac events such as Coronary Heart Disease (CHD), Stroke (STR), etc. and also predict the cardiac event (CHD/STR), and compare with existing approaches (Thompson, 1995). It is well known that cholesterol is an important factor to predict the overall risk profile (Puddu and others, 2016) (Atkins et al., 1993). Existing approaches rank cholesterol to be very low thus underestimating its importance, while our approach ranks cholesterol to be the highest. These approaches treat the different event types as a single event, which leads to the estimation of inaccurate and biologically less meaningful models.

In Section 2, we give the definition and limitations of the existing concordance index. In Section 3, we define the generalized concordance and analyze it. In Section 4, we analyze in detail
Generalized Concordance for Competing Risks

a special case of the generalized concordance, which we call the joint concordance index and show that the results presented for joint concordance extend to the generalized concordance. In Section 5, we present the experiments. In Section 6, we give the conclusions. In the main manuscript, we discuss the works that are most relevant to our work, we discuss the other related works in the Supplementary Materials.

2. Existing Concordance Index for Competing Risks and its Limitations

2.1 Definition

We formally describe the most commonly used metric in SA-CR (Wolbers et. al., 2014) for evaluating prognostic models, which is a natural extension of Harrell’s concordance index (Harrell Jr and others, 1982). We begin by considering an uncensored dataset. We consider a dataset \( D \) comprising of the survival (event time) data for \( n \) subjects who have been followed up for a finite amount of time. Let \( D = \{X_i, T_i, D_i, \; i = 1, \ldots, n\} \), where \( X_i \in X \) is a \( d \)-dimensional vector of covariates associated with the subject \( i \) (for instance, the information collected at baseline such as gender, age, etc.), \( T_i \in \mathbb{R}^+ \) is the time until an event occurred, and \( D_i \in K \) is the type of event that occurred. The set \( K = \{E_1, E_2\} \) is a finite set of competing events that could occur to a subject \( i \), where \( E_1 \) is the event of the first type and \( E_2 \) is the event of the second type.

2.1.1 Time-dependent event-specific concordance index

The concordance index measures a model’s ability to discriminate the subjects. The concordance index is defined for each event type separately. Suppose a model \( M \) predicts the risk of event \( d \) until time \( t \) to be \( M(X, t, d) \). Consider an independent test set of i.i.d. realizations of \((X_i, T_i, D_i)\) from the joint distribution of the covariates and the competing risks outcome. For a random pair of subjects \((X_i, T_i, D_i)\) and \((X_j, T_j, D_j)\), we define two events as follows

\[
\text{Rord}(i, j, t, k) = M(X_i, t, E_k) > M(X_j, t, E_k)
\]  

(2.1)
where \( R_{ord} \) checks the risk ordering of the subjects, i.e., it checks if subject \( i \) is assigned a higher risk by the model than the subject \( j \) for event \( E_k \) until time \( t \). \( T_{ord} \) checks the time ordering of the subjects, i.e., if subject \( i \) has a lower time to death due to cause \( E_k \) than the subject \( j \), or if the two subjects experienced different event types. We use these events to define time-dependent concordance for the event type \( E_k \) given as

\[
C(t, E_k) = Pr\left( R_{ord}(i, j, t, k) \mid (D_i = E_k) \cap (T_i \leq t) \cap T_{ord}(i, j) \right) \tag{2.3}
\]

The concordance vector is defined as a vector consisting of the time-dependent concordance for every event type and it is given as \( \hat{C}(t) = [C(t, E_1), C(t, E_2)] \). (Note that the definition trivially extends to more than two event types.)

### 2.2 Limitations of the existing concordance index

Each element of the concordance vector \( \hat{C}(t) \) defined above consists of information regarding a model’s discrimination ability for each event type. However, it does not consist of information on whether the model is good at predicting the event type as well. In many applications, the evaluation of a model’s ability to jointly predict the event type and the event time is critical. For instance, treatment planning in multimorbid populations (Daskivich et.al., 2011), treatment and resource planning in critical care (Beyersmann and Schumacher, 2008) (See Table 1).

### 3. Generalized Concordance Index

#### 3.1 Naive solution

We first describe an intuitive solution to overcome the limitations of concordance index discussed in Section 2.2. Define a model \( M' \)’s prediction for the event type up to time \( t \) for subject \( X_i \) as
\( M_c(X_i, t) \). Define an event that checks for correct prediction of event type below

\[
C_{\text{pred}}(i, t) = \{ M_c(X_i, t) = D_i \}
\]

(3.4)

We define the accuracy of a model as

\[
A(t) = \Pr(C_{\text{pred}}(i, t) \mid T_i \leq t)
\]

(3.5)

In the definition, we condition on \( T_i \leq t \) because we can evaluate a model’s prediction only for the subjects who experienced the event before the stated time horizon, i.e., \( t \). We construct a vector of the concordance index for all the event types, and the accuracy given as

\[
\mathcal{V}(t) = [C(t, E_1), C(t, E_2), A(t)]
\]

(3.6)

Intuitively, it might seem that this vector is sufficient to capture a model’s ability to make the joint prediction of the event type and event time because the accuracy contains information about the ability of a model to predict the event type and the concordance captures the ability of the model to discriminate the event time for every event type separately. This solution is appealing because it is simple, but it has limitations that we discuss next. Suppose that a model makes a correct prediction of the event type for a subject \( X_i \). Therefore, the condition inside the probability in (3.5) is true for this subject. However, it is possible that for the same subject the discrimination condition inside (2.3) is not satisfied, which implies that the model is good at predicting the event type but not the event time for the predicted event type for this subject. Therefore, concordance and accuracy (that comprise the vector \( \mathcal{V}(t) \)) evaluate the marginal probabilities and not the joint probabilities. The joint evaluation is not trivial as the accuracy, and the concordance events are neither independent nor completely correlated (See the Appendix D in the Supplementary Materials for justification).
3.2 Definition of Generalized Concordance

The generalized concordance is defined in terms of the following events: correct prediction of the event type (3.4) and correct discrimination of the subject from other subjects (2.1). The generalized concordance is a vector of probabilities. We define each component of the vector next. The probability that a model makes an error in prediction for event type $k$ only is

$$ GC(t, E_k, 1) = Pr\left( Rord(i,j,t,k) \cap Cpred(i,t) \cap D_i = E_k \mid T_i \leq t \cap Tord(i,j) \right) $$ (3.7)

The probability that a model makes error in discrimination for event type $k$ only is given as

$$ GC(t, E_k, 2) = Pr\left( Rord(i,j,t,k)^c \cap Cpred(i,t) \cap D_i = E_k; \mid T_i \leq t \cap Tord(i,j) \right) $$ (3.8)

The probability that a model makes an error in both predicting the event type $k$ and also an error in discriminating for event type $k$ is given as

$$ GC(t, E_k, 3) = Pr\left( Rord(i,j,t,k)^c \cap Cpred(i,t)^c \cap D_i = E_k \mid T_i \leq t \cap Tord(i,j) \right) $$ (3.9)

The generalized concordance vector is given as $GC(t) = [GC(t, E_k, s), \forall k \in \{1, ..., 3\}, \forall s \in \{1, 2\}]$. Define a weighted sum of the generalized concordance vector as

$$ GC_w(t) = -w^t GC(t) + u $$ (3.10)

where $u$ is the intercept and $w$ is the weight vector, and $w^t GC(t)$ is the dot product of the weight and the generalized concordance vector. In the next proposition, we analyze some important properties of the generalized concordance. Define the generalized concordance vector for two models A and B as $GC_A(t)$ and $GC_B(t)$ respectively.

Proposition 1 Properties of the generalized concordance
The existing metrics (concordance index and accuracy) can be expressed as a weighted sum of the different components of the generalized concordance vector.

If Model A Pareto dominates Model B, i.e., $\bar{GC}_A(t) > \bar{GC}_B(t)$, then the Model B is strictly better than the Model A in terms of the existing metrics (concordance index and accuracy).

The proof of Proposition 1 is given in Appendix A in the Supplementary Materials. If all the weights are zero but $w_3 = w_5 = 1$, then we obtain the standard concordance for event 1. If all weights are zero but $w_1 = w_2 = w_5 = w_6 = 1$, then we obtain the accuracy* (defined in (4.12)).

The second part of the proposition states that if the Model A Pareto dominates another Model B in terms of the generalized concordance vector, then the Model B is strictly preferable to the Model A in terms of all the existing metrics - concordance, accuracy. It is ideal to have a model that outperforms other models in terms of the generalized concordance. However, this may not always be possible. In such scenarios, the correct weights should be specified. In Table 1, we give some natural examples of the applications and the appropriate weights corresponding to them. For instance, in settings where one of the event types is more important to be predicted (for instance, ventilation as opposed to discharge, cancer as opposed to cardiac disease), a higher weight is assigned to the correct predictions of the events that the clinician deems to be of higher importance. For other applications, the clinicians can set the weights based on a cost-benefit analysis of the treatment and its impact on different multimorbidities; see Guthrie et.al. (2012).

4. Special Case: Joint Concordance Index

In this section, our goal is to analyze the generalized concordance and also develop the estimator for it. For ease of exposition, we focus on a special case of the generalized concordance, which is defined as follows. We set the value of the intercept and all the weights equal to 1 in (3.10) and the resulting metric is called the joint concordance. The expression for the joint concordance can
be simplified and written as

\[ JC(t) = Pr\left( Rord(i, j, t, k) \cap Cpred(i, t) \mid (T_i \leq t) \cap Tord(i, j) \right) \]  

(4.11)

In the equation (4.11), the model’s ability to predict the event type for the subject \( i \) and discriminate that subject from the other subjects is jointly evaluated. The event inside the probability in (4.11) checks the discrimination and accuracy criterion for the same subject simultaneously as opposed to the events in (3.5), (2.3).

4.1 Relationship with the existing metrics and interpretation

In Proposition 1, we showed that the existing metrics such as concordance and accuracy could be expressed in terms of the generalized concordance. In this section, we study the relationship between the joint concordance and the existing metrics. We decompose the joint concordance into two terms that are easier to interpret given as

\[ JC(t) = Pr\left( Rord(i, j, t, k) \cap Cpred(i, t) \mid (T_i \leq t) \cap Tord(i, j) \right) \frac{Pr(Cpred(i, t) \mid T_i \leq t \cap Tord(i, j))}{\text{Accuracy}^*} \]  

(4.12)

In equation (4.12), the first term is concordance conditional on the event that the model correctly predicts the event type. The conditional concordance (4.12) is evaluated for the subjects for which the events are predicted correctly unlike the concordance index in (2.3) that is evaluated even for the subjects for which the wrong event type was predicted.

The second term in the decomposition (4.12) is similar to the accuracy in (3.5). The difference between the accuracy term in (4.12) and (3.5) is that the event in the conditional probabilities is different. In the proposition below, we show that the joint concordance cannot be expressed as a function of the vector of the existing metrics defined in (3.6).
Proposition 2 Joint concordance vs. Existing metrics. There exists no function $f : \mathbb{R}^3 \to \mathbb{R}$ such that $JC(t) = f(V(t))$

For the proof of the above proposition see Appendix B in Supplementary Materials. From the above proposition, it follows that the joint concordance cannot be expressed as a function of $V(t)$. We also give a pictorial depiction of this proposition in Figure 1. In Figure 1, we contrast the two models A and B in terms of the existing metrics and the joint concordance. The joint concordance is represented as the intersection of the concordance and the accuracy (this is based on the definition of joint concordance in (4.11)). The two models have the same performance in terms of the existing metrics, i.e., the concordance and the accuracies, but these models have different joint concordance as the extent of intersection is different for the two models. This illustrates that the joint concordance cannot be expressed as a function of the existing metrics. Any of the two models can be selected based on the existing metrics. However, if we also look at joint concordance, then Model A is strictly preferable.

4.2 Range of values achieved by joint concordance

In this section, we describe the range of values achieved by the joint concordance. Consider a model $M_{\text{rand}}$ that assigns the risk values uniformly at random to each subject across all the event types. The risk values for all the subjects and for all the event types are independent and identically distributed (i.i.d.). Consider that there are $K$ event types.

Proposition 3 Range of joint concordance. The joint concordance for the random model is $JC_{M_{\text{rand}}}(t) = \frac{1}{K+1}$. Hence, the range of joint concordance is $\left[\frac{1}{K+1}, 1\right]$.

For the proof of Proposition 3 refer to the Appendix C in the Supplementary Materials. If there are $K$ event types, then random guessing can only be correct $\frac{1}{K}$ fraction of the times, which implies
that the joint concordance decays as $\approx \frac{1}{K}$. When there are two event types $JC_{M_{rand}}(t) = \frac{1}{3}$. Hence, the joint concordance can take values in the range $[\frac{1}{3}, 1]$. Suppose the joint concordance of a model is 0.5. If we use the decomposition in (4.12), then this value of 0.5 would mean that the conditional concordance and accuracy are both close to 0.7 (if both conditional concordance and accuracy are assumed to be equal). (Conditional Concordance and accuracy are positively correlated, and it is unlikely that the two of them take values 0.5 and 1 respectively.)

We can compute each component of the generalized concordance as well for the model $M_{rand}$ and thus arrive at the range of values achieved by each component of the generalized concordance.

**Remark:** The range of concordance index in (2.3) is $[1/2, 1]$ (when there are two event types). From Proposition 3, we know that the range of joint concordance is $[1/3, 1]$, where the value $1/3$ is achieved by random guessing based model and value $1$ is achieved by a perfect prediction model. Hence, the range of joint concordance is larger than the concordance.

### 4.3 Estimators of the joint concordance

In this section, we develop the estimator for the joint concordance (4.11) and then we use the same principles to also develop the estimator for the generalized concordance. In the description of the dataset in Section 2, we assumed that there was no censoring. In real survival datasets, right censoring is the most common form of censoring. We propose an estimator that adjusts for the bias that occurs due to censoring.

**Weighted estimator to account for censoring.** We now introduce censoring variables. $C_i$ is defined as the censoring time for subject $i$. For subject $i$ we observe $X_i, \tilde{T}_i, \tilde{D}_i, \Delta_i$, where $\tilde{T}_i = \min\{T_i, C_i\}$ is the event time, $\Delta_i = I(T_i \leq C_i)$, type of event $\tilde{D}_i = \Delta_i D_i$. We make the standard assumption that the censoring is independent of other variables conditional on the covariates. The probability that the subject $i$ is uncensored up to time $t$ is given as $G(t) = Pr(C_i > t|X_i)$. We use the inverse probability of censoring weighted (IPCW) (See Wolbers et.al. (2014)) to adjust for
the bias that is introduced by censoring. We can use different models to estimate the censoring bias; we denote the estimated model of censoring as $\hat{G}$. We use the censoring as the event and the occurrence of the other event types as censoring. The two most natural choices for estimating the censoring models are:

1. Kaplan-Meier Kaplan and Meier (1958) estimator of the censoring distribution

2. Cox model estimator of the censoring distribution: The estimator computed from the Cox model Cox et.al. (1984) for the censoring distribution is given as $\hat{G}(t|X_i) = \exp(- \int_0^t \exp(\gamma^* X_i) \hat{\Gamma}_o(s) ds)$, where $\hat{\Gamma}_o$ is the Breslow estimator for the baseline hazard and $\gamma$ are the maximum likelihood regression coefficients.

We define some notation as follows.

\[ \tilde{A}_{ij} = I(\tilde{T}_i < \tilde{T}_j), \quad \tilde{B}_{ij}(d) = I(\tilde{T}_i > \tilde{T}_j, \tilde{D}_j \neq d), \quad \tilde{N}_i(t,d) = I(\tilde{T}_i \leq t, \tilde{D}_i = d), \]

\[ \tilde{C}_{ij}(d) = I(\tilde{T}_i < \tilde{T}_j \text{ or } \tilde{D}_j \neq d), \quad Q_{ij}(t,d) = I(\text{Rord}(i,j,t,E_k) \& \text{Cpred}(i,t)) \]

where $\hat{W}_{ij}^1 = \frac{1}{\hat{G}(T_i|X_i) \hat{G}(T_j|X_j)}$, $\hat{W}_{ij}^2 = \frac{1}{\hat{G}(T_i|X_i) \hat{G}(T_j|X_j)}$ are the weights used for adjusting for the censoring bias. The weighted estimator is given as

\[ \hat{J}\text{C}_{wtd}(t) = \frac{\sum_{d \in K} \sum_{i,j} (\tilde{A}_{ij} \hat{W}_{ij}^1 + \tilde{B}_{ij}(d) \hat{W}_{ij}^2) N_i(t,d) Q_{ij}(t,d)}{\sum_{d \in K} \sum_{i,j} (\tilde{A}_{ij} \hat{W}_{ij}^1 + \tilde{B}_{ij}(d) \hat{W}_{ij}^2) N_i(t,d)} \quad (4.13) \]

Suppose we do not adjust for censoring. In that case we set the weights $\hat{W}_{ij}^1$ and $\hat{W}_{ij}^2$ as one. We refer to the estimator obtained in this case as the 
naive estimator. In the next proposition, we show that the weighted estimator (4.13) is consistent. Consistency implies that the difference between (4.13) and the joint concordance converges to a distribution with a zero mean. We also show that the difference between the weighted estimator and the joint concordance in (4.11) converges to a normal distribution. For the next proposition, we require that the model for censoring is correctly specified and it has an i.i.d representation in terms of the influence functions (the same assumptions were also made in Wolbers et.al. (2014).)
Proposition 4 Properties of the estimator

- \( \hat{J}_C_{\text{wtd}}(t) \) is a consistent estimator of the joint concordance \( J_C(t) \).
- \( \sqrt{n}(\hat{J}_C_{\text{wtd}} - J_C(t)) \) converges to a normal distribution with mean zero and variance \( \sigma^2_{J_C} \) (expression for the variance and its estimator is in the Appendix).

The proof of the above Proposition is based on (Wolbers et. al., 2014) and is provided in Appendix E in Supplementary Materials.

We use the same principles described above to construct the estimators for the generalized concordance as follows. Consider the first component of the generalized concordance defined in (3.7). Define an indicator function that checks if the condition inside (3.7) is met as follows:

\[
Q_{ij}(t,d) = I(Rord(i,j,t,E_k) & C_{\text{pred}}(i,t) & D_i = 1)
\]

If we replace the term \( Q_{ij}(t,d) \) from the estimator in (4.13) with \( Q_{ij}^{1}(t,d) \), we obtain the estimator for the first component of the generalized concordance, i.e., \( GC(t,E_1,1) \). In Proposition 4, we showed that (4.13) is consistent and the difference between the estimator and the joint concordance follows a normal distribution in the limit. We can extend the same results to the estimator of the first component of the generalized concordance discussed above. We can carry out the same exercise for all the other components of the generalized concordance in the same manner (Further details in Appendix F in the Supplementary Materials).

4.4 Variable importance ranking

In this section, our goal is to highlight the limitations of the existing approaches for ranking the variables for the overall risk profile and propose an alternative approach based on joint concordance that overcomes these limitations.

4.4.1 Existing approaches The two most common approaches that are used for variable importance ranking are - standardized regression coefficients based approaches (Murray and Con-
ner, 2009) and the stepwise regression based approaches (Thompson, 1995). The existing works (Puddu and others, 2016) (D’Agostino et al., 2008) rank the covariates for the overall risk profile by lumping the different event types into one common group, training a single risk survival model and then using the standardized regression coefficients or the stepwise regression methods to rank the covariates with respect to the risk of the lumped event (See Figure 3). In the comparisons to follow, for the stepwise regression methods, we use the concordance index defined in (2.3) as the measure that is compared in each step. We also contrast our results with the standardized regression coefficient based approach.

4.4.2 Stepwise competing risks (CR) regression approach We propose an approach, which we call stepwise competing risks regression approach. First, we first train a competing risks model on all the variables. We use backward elimination with stepwise regression with joint concordance as the metric. In each step of the backward elimination, we compute the joint concordance for the trained model. We drop the variable that leads to the least amount of change in the joint concordance when dropped (See Figure 3). The same procedure is repeated after dropping the variable. Note that the least important variable is dropped first and the most important variable is dropped last.

5. Experiments

In this section, we first discuss the synthetic data experiments and then discuss the real data experiments. These experiments are carried out with three goals in mind:

1. Existing metrics are not sufficient for joint evaluation: To show that the existing metrics are not sufficient for comparing models developed for jointly predicting the event type and the event time, and

2. Existing variable importance ranking methods are less useful than the proposed:
To compare the existing approaches for variable importance with the proposed stepwise competing risks regression approach.

3. **Compute the efficiency of the weighted estimator and the naive estimator:**

   To compare the naive and weighted estimators in terms of the root mean squared errors (RMSE), the standard errors (SE), and the bias.

All the experiments were conducted in the R programming language. In all the comparisons, apart from the metrics that were already discussed in the previous sections, we also compute the concordance when all the event types are lumped together into one category, which we denote as $C^*(t)$. If the different event types are lumped, then it is equivalent to learning a single event survival model, where the event time is the time any of the lumped events were experienced by the subject.

5.1 **Synthetic Data Experiments**

**Synthetic experiment setting.** We use an experiment setting that is very similar to Wolbers et al. (2014). The covariate of a subject is $X \in \mathbb{R}$. It is drawn from a standard normal distribution. Suppose that there are three event types - event of type 1, event of type 2, and censoring. We use an accelerated failure time model Crowder (2001) to model the event time. The latent time for event type $k$ is $T_k$ and it is drawn from an exponential distribution with arrival rate $\lambda_k(t|X) = \lambda_k(t)\exp(\beta_k X)$ for $k \in \{0, 1\}$ where the event type $k = 0$ is censoring and event type $k = 1$ is the event of type 1. The latent time for the event of second type is $T_2$ and it is also drawn from an exponential distribution with parameters $\lambda_2(t|X) = \lambda_2(t)\exp(\beta_2 \cos(X))$ The observed event time is $T = \min_{k \in \{0,1,2\}}\{T_k\}$ and the observed type of event is $d = \arg\min_{k \in \{0,1,2\}}\{T_k\}$.

The parameters above are chosen as follows $\lambda_0(t) = 5$, $\lambda_1(t) = 1$, $\lambda_2(t) = 2$, $\beta_1 = 1$, $\beta_2 = 1$. For $\beta_0$, we set two different values, $\beta_0 = 0$ for the covariate independent censoring and $\beta_0 = 1$ for the
We compare the different models in terms of the existing metrics and the joint concordance at the 75% quantile of the times. We use three models for comparisons here: i) Cause-specific Cox model (CSC) (Lunn and McNeil, 1995) (We used the riskRegression package in R for the CSC model.), ii) Fine-Gray model (FG) (Fine and Gray, 1999) (We used the cmprsk package in R for the FG model.) and iii) the exponential model (EXP) \( M(X, t, 1) = \exp(X), M(X, t, 2) = 2\exp(-\text{abs}(X)) \), where \text{abs}(X) is the absolute value of \( X \).

**Model comparisons.** Our goal is to show that the existing metrics can lead to the selection of models that are bad for joint prediction of the event type and event time. First, we compute the exact values for all the metrics (concordance, accuracy, and joint concordance) using a large data set of 100,000 subjects for the synthetic experiment setup described above but in the absence of censoring. We compare the models in terms of standard metrics (concordance index for each event type (Wolbers et al., 2014) and the accuracy) \( \mathcal{V}(t) \). We focus on the comparison between the CSC model and the EXP model. Based on the standard metrics (in Figure 3 and Table 4), the CSC model seems to be better than the EXP model. However, when we compare the joint concordance, we find that the EXP model is better even though the CSC model Pareto dominates the EXP model in terms of existing metrics. EXP model has a 4% higher chance of correctly predicting both the event type and event time for a subject. We use the decomposition in (4.12) to get further insights into this comparison. The concordance conditional on accuracy for the EXP model is 0.74, and the accuracy is 0.70. The concordance conditional on accuracy for CSC model is 0.61, and the accuracy is 0.78. Although the CSC model can predict the event type in more cases, it is very poor in discriminating the subject for which it predicts the event correctly from other subjects. Poor discrimination implies that the event time predictions are also poor. Therefore, the CSC model is worse in comparison to the EXP model for the joint prediction of the event type and event time. Hence, the existing metrics can lead to poor model selection.
Variable importance ranking comparison. We consider an example below where the two competing events have two risk factors and one of the risk factors has opposite effects on the two event types. This example is motivated from Puddu and others (2016), where cholesterol was shown to be associated with an increase in the risk of death due to CHD but at the same time, cholesterol was shown to be associated with a decrease in the risk of death from the other causes.

Consider a simple event time model given as follows. The event time is given as \( \log(T) = X_1 + 2X_2 I(D = 1) - 2X_2 I(D = 2) + Z \), where \( X_1 \) is the first covariate, \( X_2 \) is the second covariate, \( D \) is the type of event that occurs, and \( Z \) is the additive noise (the standard normal distribution). Also, \( Pr(D = 1) = 1 - Pr(D = 2) = \frac{1}{2} \). Suppose that we consider the risk of the subject only with respect to event type 1. In this case, a higher value of \( X_2 \) reduces the risk of event type 1. However, the opposite is true for event type 2. Therefore, \( X_2 \) is important to predict the event-specific times. The existing approaches based on the stepwise regression and the standardized regression coefficients only find covariate 1 to be relevant. The existing approaches cannot find that the second covariate as relevant because the lumping of the events causes the effect of the second covariate to cancel out (derivation in the Appendix I in the Supplementary Materials). On the other hand, in our approach, we find that the second covariate is ranked higher than the first. This example illustrates how the existing approaches can fail to discover some important risk factors.

Comparing the efficiency of the naive and weighted estimators: In this Section, we compare the efficiencies of the naive estimators and the weighted estimators. We use the synthetic experiment setting described above that was also used to compare the models. For the weighted estimator, we use the Kaplan Meier estimator for estimating the censoring distribution. We use the simulated datasets of size 1000 and 5000. We compute the RMSE, SE, and the bias by averaging over 100 such datasets. All the comparisons that are carried out are in-sample (as in (Wolbers et.al., 2014)). In Table 2, we show the RMSE, SE, and the bias of the naive and
the weighted estimators for many different settings. In Table 2, we see that in general when the censoring is independent of the covariates, the weighted estimator may or may not be strictly better than the naive estimator in terms of the Bias and RMSE. However, in Table 3, we see that when the censoring is dependent of the covariates, the weighted estimator is almost consistently better than the naive estimator in terms of Bias and RMSE. (This is explained based on the fact that the mismatch between the censoring model assumed by the naive estimator and the true censoring model is more when the censoring is covariate dependent in comparison to the case when the censoring is independent of covariates.)

5.2 Real Data Experiments

In this section, we use a real dataset to illustrate a real use case of the joint concordance index.

**Cardiology Dataset.** The dataset comprises of 1712 men (aged 40-59 years in 1960) from Italian Rural Areas of the Seven Countries Study Puddu and others (2016). During the 50-year follow-up, there were 12 different causes of death: 318 due to Coronary Heart Disease (CHD), 162 to Heart Disease of Uncertain Etiology (HDUE), 225 to Stroke (STR) and another 964 due to miscellaneous causes. Covariates measured at baseline were: Age, Arm Circumference, Cigarettes, Body Mass Index, Diabetes, Corneal Arcus, Serum Cholesterol, Blood Pressure, Heart Rate and Vital Capacity.

**Oncology Dataset.** We extracted 2 cohorts from the Surveillance, Epidemiology, and End Results (SEER) cancer registries, which cover approximately 28% of the US population Yoo and Coughlin (2019). In the first cohort, the outcome is the time to breast cancer (BCAN) deaths versus the time to digestive cancer (DCAN) deaths. In the second cohort, the outcome is time to breast cancer deaths versus the time to respiratory cancer (RCAN) deaths. There are 81 covariates and here we specify some important of them: Age, Age at Diagnosis, Histology, Tumor size, Family history, Tumor grade, Race, etc.
Model Comparisons. In this section, our goal is to compare the ranking of models obtained using existing metrics as opposed to the ranking based on the joint concordance. We estimate two models the CSC model and the FG model. We compare the predictions of the models at the time horizon of 15 years. We use in sample comparisons here. (In Appendix H, we show out of sample comparisons too.) We carry out two types of comparisons.

1. Comparison based on cardiology dataset. In the first comparison, the two competing events are the death due to CHD and death due to STR. The comparisons in Table 5 reveal that the FG model and the CSC model are similar in terms of the standard concordance metrics and FG model is better in terms of accuracy. In this comparison, the FG model Pareto dominates the CSC model in terms of the existing metrics. We find that the FG model is also better in terms of the joint concordance.

For the second comparison given in Table 6, the two competing events are the death due to HDUE and death due to STR. The comparisons in Table 6 reveal that the CSC model Pareto dominates the FG model. However, there is no difference (statistically significant) between the joint concordance of both the models.

2. Comparison based on oncology dataset. For the first comparison given in Table 7, the CSC model Pareto dominates FG model in terms of the existing metrics. However, the FG model is better in terms of the joint concordance. For the second comparison given in Table 8, the CSC model pareto dominates FG model in terms of the existing metrics and also the joint concordance. The takeaway from the comparisons in Tables 5-8 is that a comparison in terms of the existing metrics is not sufficient to deduce the performance in terms of the joint concordance.

Remark. From Tables 5 - 8, the range of values taken by joint concordance varies from 0.46 to 0.82 and the range of values taken by concordance varies from 0.73 to 0.87. Hence, the range of joint concordance is larger.

Variable importance ranking comparison: In this section, our goal is to compare the
standard approaches for variable importance ranking with the proposed approach (already de-
scribed in Section 5.1). We used the same real dataset that we described in Section 5.2. We carry
out two comparisons: CHD deaths vs. STR deaths and HDUE deaths vs. STR deaths. We use
the FG model to rank the risk factors.

In the first comparison given in Table 9, we compare the risk factor rankings when the two
events are the CHD deaths and the STR deaths. We show that the ranking arrived at using the
joint concordance index can be very different than the ranking arrived at using the standard
approach based on the stepwise regression. We see that the proposed approach ranks cholesterol
to be the highest, unlike the standard approach (cholesterol is ranked at seventh). Cholesterol is
a strong event-specific risk-factor; it matters much more for the CHD deaths in comparison to
the STR deaths (this is well known in the clinical literature Puddu and others (2016)Atkins et.al.
(1993)). This reinstates the point that we made through the synthetic example. The standard
approach can miss the important risk factors. We also ranked the variables using the standardized
regression based approach and we obtained the same conclusions.

In the second comparison in Table 10, we compare the risk factor rankings when the two
events are the HDUE deaths and the STR deaths. We show that the ranking arrived at using
the joint concordance index is not very different in comparison to the ranking arrived at using
the standard approach. This suggests that in this case for both the outcomes (HDUE deaths and
STR deaths) the dataset does not contain risk factors that are only specific to one of the events.

Therefore, from Tables 9, 10, we can see that in the cases when the dataset consists of risk
factors that are exclusively specific to some events, the existing approaches can often fail to
recognize their importance. On the other hand, the proposed approach is good at identifying the
importance of these factors.
6. Conclusion

In SA-CR, existing metrics such as concordance and accuracy do not evaluate a model based on its joint prediction of the event type and event time. We have proposed a new metric that we call the generalized concordance that overcomes the limitations of the existing metrics. We have shown that many of the existing metrics such as concordance and accuracy can be expressed as a weighted sum of the components of the generalized concordance vector. In general, the clinicians can specify the weights for the components of the generalized concordance depending upon the importance of predicting the different event types. We studied the natural setting when all the weights are the same and we call the resulting metric the joint concordance. We have proposed an estimator for the joint concordance (and for the generalized concordance) that adjusts for the bias that occurs due to censoring and we prove that it is consistent. We have shown that the existing methods for variable importance ranking can often fail to recognize the importance of the event-specific risk factors, which are crucial for predicting the event type. We have introduced a new ranking method based on joint concordance that overcomes these limitations.

Supplementary Materials

In Supplementary Materials, we provide the proofs to all the Propositions. We also provide a discussion of the extensions of this work and also discuss some other related works as well.

Software

The code for the generalized concordance index is available at (Ahuja and Schaar). We developed an application, which is available at https://mlinterpreter.shinyapps.io/concordance/, with following functionalities: a) Upload a standard competing risks dataset and select the model: Fine-Gray or Cause-Specific Cox model. b) The output shows the performance of the model: concordance for each cause, accuracy and the joint concordance. The above application can help the
users directly select the model that seems more appropriate.

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Figure 1. Pictorial depiction of the Proposition 1.

Figure 2. Comparing different models in terms of existing metrics for the synthetic setting.
Figure 3. Variable importance ranking for overall risk profile: standard vs proposed; CHD: Coronary Heart Disease, HDUE: Heart Disease of Uncertain Etiology

Table 1. Different cases of generalized concordance

| Clinical application                                      | Factors affecting the metric choice                                                                 | Weights                  | Resulting Metric |
|----------------------------------------------------------|------------------------------------------------------------------------------------------------------|--------------------------|------------------|
| Treatment planning for a target disease                  | Negative effects of a treatment Wolbers et.al. (2014) on the target disease                         | $w_3 = w_5 = 1,$         | $C(t, 1)$        |
|                                                          |                                                                                                     | $w_1 = w_2 = w_4 = 0,$   |                  |
|                                                          |                                                                                                     | $w_6 = 0$                |                  |
| Treatment planning for multimorbidities                  | Negative effects of polypharmacy on all the multimorbidities Daskivich et.al. (2011) Radner et.al. (2014) Diseases with equal importance (CHD vs STR) | $w_1 = w_2, \ldots, w_6 = 1$ | $JC(t)$          |
| Treatment planning for multimorbidities                  | Diseases with different importance (Cancer vs CHD)                                                 | $w_1 > w_2, w_3 > w_4, w_5 > w_6$ | $GC_w(t)$       |
| Treatment planning and resource allocation for critical care | Prioritize treatments and resources based on type and event time Beyersmann and Schumacher (2008)     | $w_1 > w_2, w_3 > w_4, w_5 > w_6$ | $GC_w(t)$       |
| Model | \( JC(t) \) | Number of samples | Estimator type | RMSE  | SE   | Bias  |
|-------|--------------|-------------------|----------------|-------|------|-------|
| CSC   | 0.48         | 1000              | Naive          | 0.0255| 0.0251| 0.0048|
| FG    | 0.46         | 1000              | Naive          | 0.0330| 0.0272| -0.0189|
| EXP   | 0.52         | 1000              | Naive          | 0.0188| 0.0163| 0.0095|
| CSC   | 0.48         | 1000              | Weighted       | 0.0249| 0.0247| 0.0039|
| FG    | 0.46         | 1000              | Weighted       | 0.0338| 0.0265| -0.0211|
| EXP   | 0.52         | 1000              | Weighted       | 0.0179| 0.0160| 0.0081|
| CSC   | 0.48         | 5000              | Naive          | 0.0180| 0.0135| 0.0120|
| FG    | 0.46         | 5000              | Naive          | 0.0236| 0.0108| -0.0210|
| EXP   | 0.52         | 5000              | Naive          | 0.0111| 0.0063| 0.0009|
| CSC   | 0.48         | 5000              | Weighted       | 0.0177| 0.0137| 0.0113|
| FG    | 0.46         | 5000              | Weighted       | 0.0259| 0.0106| -0.0236|
| EXP   | 0.52         | 5000              | Weighted       | 0.0103| 0.0067| 0.0082|

| Model | \( JC(t) \) | Number of samples | Estimator type | RMSE  | SE   | Bias  |
|-------|--------------|-------------------|----------------|-------|------|-------|
| CSC   | 0.48         | 1000              | Naive          | 0.047 | 0.017| -0.045|
| FG    | 0.46         | 1000              | Naive          | 0.032 | 0.017| -0.027|
| EXP   | 0.52         | 1000              | Naive          | 0.032 | 0.019| -0.027|
| CSC   | 0.48         | 1000              | Weighted       | 0.038 | 0.016| -0.035|
| FG    | 0.46         | 1000              | Weighted       | 0.024 | 0.016| -0.017|
| EXP   | 0.52         | 1000              | Weighted       | 0.034 | 0.018| -0.028|
| CSC   | 0.48         | 5000              | Naive          | 0.049 | 0.0061| -0.048|
| FG    | 0.46         | 5000              | Naive          | 0.036 | 0.0064| -0.036|
| EXP   | 0.52         | 5000              | Naive          | 0.029 | 0.0078| -0.028|
| CSC   | 0.48         | 5000              | Weighted       | 0.038 | 0.0060| -0.038|
| FG    | 0.46         | 5000              | Weighted       | 0.026 | 0.0063| -0.026|
| EXP   | 0.52         | 5000              | Weighted       | 0.033 | 0.0074| -0.032|

| Model | \( C(t, 1) \) | \( C(t, 2) \) | \( A(t) \) | \( C^*(t) \) | \( JC(t) \) |
|-------|----------------|--------------|-------------|---------------|-------------|
| FG    | 0.75            | 0.52         | 0.79        | 0.59          | 0.46        |
| CSC   | 0.75            | 0.60         | 0.78        | 0.59          | 0.48        |
| EXP   | 0.75            | 0.60         | 0.70        | 0.59          | 0.52        |
Table 5. Model comparisons in terms of existing metrics and proposed mal data: CHD deaths vs HDUE deaths

| Model | $C(t, CHD)$ | $C(t, STR)$ | $A(t)$ | $C^*(t)$ | $JC(t)$ |
|-------|-------------|-------------|--------|----------|--------|
| FG    | 0.76        | 0.79        | 0.56   | 0.77     | 0.45   |
| CSC   | 0.76        | 0.79        | 0.55   | 0.77     | 0.43   |

Table 6. Model comparisons in terms of existing metrics and proposed metric for real data: HDUE deaths vs STR deaths

| Model | $C(t, HDUE)$ | $C(t, STR)$ | $A(t)$ | $C^*(t)$ | $JC(t)$ |
|-------|--------------|-------------|--------|----------|--------|
| FG    | 0.73         | 0.79        | 0.68   | 0.79     | 0.55   |
| CSC   | 0.76         | 0.79        | 0.68   | 0.79     | 0.55   |

Table 7. Model comparisons in terms of existing metrics vs joint concordance: Breast Cancer vs Digestive Cancer deaths

| Model | $C(t, BCAN)$ | $C(t, DCAN)$ | $A(t)$ | $C^*(t)$ | $JC(t)$ |
|-------|--------------|--------------|--------|----------|--------|
| FG    | 0.82         | 0.87         | 0.72   | 0.75     | 0.82   |
| CSC   | 0.83         | 0.87         | 0.93   | 0.74     | 0.78   |

Table 8. Model comparisons in terms of existing metrics vs joint concordance: Breast Cancer vs Respiratory Cancer deaths

| Model | $C(t, BCAN)$ | $C(t, RCAN)$ | $A(t)$ | $C^*(t)$ | $JC(t)$ |
|-------|--------------|--------------|--------|----------|--------|
| FG    | 0.84         | 0.86         | 0.83   | 0.80     | 0.68   |
| CSC   | 0.84         | 0.85         | 0.90   | 0.80     | 0.75   |

Table 9. Variable importance for real dataset: CHD deaths vs. STR deaths

| Ranking | Standard approach     | Ranking based on the joint concordance |
|---------|-----------------------|----------------------------------------|
| 1       | Blood Pressure         | Cholesterol                            |
| 2       | Age                   | Blood pressure                         |
| 3       | Vital capacity         | BMI                                    |
| 4       | Arm circumference      | Age                                    |
| 5       | Corneal arcus          | Diabetes                               |
| Ranking | Standard approach | Ranking based on the joint concordance |
|---------|-------------------|----------------------------------------|
| 1       | Age               | Blood Pressure                         |
| 2       | Vital capacity    | Age                                    |
| 3       | Blood Pressure    | Vital capacity                         |
| 4       | Arm circumference | Arm Circumference                      |
| 5       | Heart Rate        | Heart Rate                             |