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ALTERNATIVES TO THE COX MODEL IN MULTI-STATE MODELS

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ABSTRACT

The introduction of time-dependent covariates in the survival process can make the patients survival change from one time point to the next as the values of the covariate change. A popular choice for the analysis of this data is the time-dependent Cox regression model. In the present work we present multi-state models as an alternative for the analysis of such data.

Keywords: Survival analysis; Cox model; Markov processes; time-dependent covariates; multi-state models.

1. MULTI-STATE MODELS

The experience of a patient in a survival study may be thought of as a process that involves two states, with one possible transition from a 'live' state to a 'dead' state. In some studies, however, the state representing those patients 'alive' may be partitioned into two or more intermediate (transient) states, each of which corresponding to a particular stage in the normal progress of the illness.

In a general multi-state model (MSM), an individual moves from one state to another through time. The next state to which the individual moves, and the time of change, are specified through transition intensities that provide the instantaneous hazard for movement out of one state into another. These models are based on stochastic processes in continuous time allowing individuals to move between a finite number of states. The MSM provides a comprehensive view of the disease process, giving a more efficient use of the incomplete information, when portions of the history of an individual's illness are known. In this framework, the so-called transition intensities can also be used to determine the mean sojourn time in a given state of illness, the number of individuals in different states at a certain moment, and survival proportions in each state. Covariates in transition intensities can also explain differences in the course of the illness among the population.

This multi-state process is fully characterized through transition intensities or through transition probabilities between states *h* and *j*, that we will express respectively by $\alpha_{hj}\left(t\middle|\mathfrak{F}_{t-}\right)$ and $p_{hj}(s,t)=\mathbb{P}\left(X(t)=j\middle|X(s)=h,\mathfrak{F}_{s-}\right)$, being $\mathfrak{F}_{l-}$ the observed history of the process up to time *l*. Thus, while the transition probabilities provide important measures to make long-term predictions, each transition intensity, $\alpha_{hj}\left(t\middle|\mathfrak{F}_{t-}\right)$, represents the instantaneous hazard of progression to state *j* conditionally on occupying state *h*:

$$\alpha_{hj}\left(t\left|\mathcal{F}_{t-}\right.\right)=\lim_{dt\to 0}\frac{p_{hj}\left(t,t+dt\right)}{dt}=\lim_{dt\to 0}\frac{\mathbb{P}\left(X\left(t+dt\right)=j\left|X\left(t\right)=h,\mathcal{F}_{t-}\right.\right)}{dt}.$$

This expression means that, given its prior history, the conditional probability of making a transition from state h into state j in the small time interval $\left[t,t+dt\right)$ is approximately $\alpha_{hj}\left(t\left|\mathcal{F}_{t-}\right.\right)dt$ for small dt. In practical situations, however, it might be interesting to relate the individual characteristics with the intensity rates through a set of covariates, Z. For a general regression model we can write $\alpha_{hji}\left(\cdot\right)=\varphi\left(\alpha_{hj0}\left(\cdot\right),\beta_{hj}^{\mathrm{T}}Z_{hji}\right)$, where $\alpha_{hj0}\left(\cdot\right)$ is the baseline intensity function between states *h* and *j*, β_{hj} is the vector of regression parameters, and Z_{hji} is the vector of covariates for subject *i*. A popular choice that simplifies the model for inference is the proportional hazards assumption, which is obtained by choosing $\varphi\left(u\left(\cdot\right),v\right)=u\left(\cdot\right)e^{v}$, that is, $\alpha_{hji}\left(t\right)=\alpha_{hj0}\left(t\right)\exp\left(\beta_{hj}^{\mathrm{T}}Z_{hji}\right)$.

Transition intensities can depend on the states previously visited, the time since the last event, covariates, etc. Furthermore, they may be constant over time or not. The most common models are characterized through one of the following assumptions:

1. *Time-Homogeneity*: the intensities are constant over time, that is, transition intensities are independent of *t*. Therefore we have $\alpha_{hj}\left(t\left|Z\right.\right)=\alpha_{hj}\left(Z\right)$.

2. *The Markov assumption*: future evolution only depends on the current state and not on the previous history of the individual. That is, transition intensities are independent of the history of the process, $\mathcal{F}_{t-}$. Therefore we have $\alpha_{hj}\left(t\left|Z,\mathcal{F}_{t-}\right.\right)=\alpha_{hj}\left(t\left|Z\right.\right)$.

3. *The semi-Markov assumption*: future evolution not only depends on the time *t* since origin, but also on the time spent in the current state *h*, that is, $t-t_{hj}$, where t_{hj} is the transition time from *h* to *j*. If we assume in addition that the transitions do not depend directly on *t*, we will have intensity functions of the general form $\alpha_{hj}\left(t-t_{hj}\left|Z\right.\right)$.

There is extensive literature on the analysis of such models; many results and references are given by Andersen et al. (1993).

In this presentation we pretend to show that MSMs present some advantages over the time-dependent Cox regression model (TDCM) (Cox, 1972). Differences between these approaches are discussed and illustrated using the data of Stanford heart transplantation study (Crowley and Hu, 1977). This study began in October 1967 and the available data in Crowley and Hu's article covers the period until April 1, 1974. In this period some patients died before an appropriate heart is found. Of the 103 patients, 69 received a heart transplant. The number of deaths was 75; the remaining 28 patients contributed with censored survival times. For each individual, an indicator of its final vital status (censored or not), the survival times from the entry of the patient in the study (in days), and a vector of covariates including age at acceptance, year of acceptance, previous surgery (coded as $1=\text{yes}$; $0=\text{no}$), and transplant (coded as $1=\text{yes}$; $0=\text{no}$) were recorded. The covariate transplant is the only time-dependent covariate, while the other covariates included are fixed. In the context of multi-state modeling, we may consider the covariate 'transplant' as an associated state of risk, and then use the illness-death model of Figure 1.

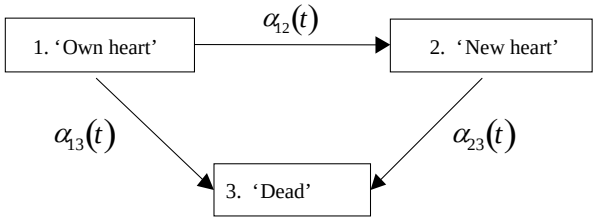

Figure 1. Illness-death model for Transplant Heart Data.

With this multi-state formulation of the Stanford data, main goals of this study include: (a) to assess whether or not a beneficial effect of heart transplant on survival exists. This will be carried out by comparing the transition intensities $\alpha_{13}(t)$ and $\alpha_{23}(t)$; and also (b) to explore the potential fixed covariate effects in each of the transitions.

2. TIME-DEPENDENT COX REGRESSION MODEL.

We construct various TDCMs all of them including the effect of transplant, among other covariates. In all the fitted models, the influence of age at acceptance on hazard is positive, while effects of year and surgery are both negative (see Table 1). When analyzing models showing smaller AIC (Akaike's Information Criterion) we see that the effect of the transplant leads to a small reduction in risk, but without reaching statistical significance.

Table 1. Cox regression models. Stanford Heart Transplantation data.

Model	Estimate	Transplante	Age	Year	Surgery	AIC
I	$\hat{\beta}$ (SE)	0.127 (0.301)				598.1
	P – value	0.67				
II	$\hat{\beta}$ (SE)	-0.004 (0.312)	0.031 (0.015)			595.1
	P – value	0.99	0.03			
III	$\hat{\beta}$ (SE)	0.123 (0.303)		-0.191 (0.070)		592.6
	P – value	0.68		0.01		
IV	$\hat{\beta}$ (SE)	0.158 (0.297)			-0.749 (0.360)	594.9
	P – value	0.59			0.04	
V	$\hat{\beta}$ (SE)	-0.031 (0.318)	0.027 (0.014)	-0.179 (0.070)		590.6
	P – value	0.92	0.06	0.01		
VI	$\hat{\beta}$ (SE)	0.016 (0.309)	0.031 (0.014)		-0.773 (0.360)	591.5
	P – value	0.96	0.03		0.03	
VII	$\hat{\beta}$ (SE)	-0.010 (0.314)	0.027 (0.014)	-0.146 (0.070)	-0.637 (0.367)	589.1
	P – value	0.97	0.05	0.04	0.08	

3. HOMOGENEOUS MARKOV MODEL

Multi-state processes are fully characterized through transition intensities or through transition probabilities between states *h* and *j*. Under homogeneous Markov model (HMM) we will express respectively by α_{hj} and $p_{hj}(s,t) = p_{hj}(0,t-s)$. In practical situations, the relation of individual

characteristics to their transition rates is often of interest, being the Cox proportional hazards model $\alpha_{hj}(Z) = \alpha_{hj} \exp\left(\beta_{hj}^{T} Z\right)$, a popular choice for modeling such relationship. Maximum likelihood estimates can be computed from the transition probability matrix. More details about this method can be found in Kay (1986).

The Markov assumption may be checked, among others, by including covariates in the modelling process. We have the null hypothesis that the data come from a Markov process:

H_0 : The Process is Markov ,

against the general alternative,

H_1 : The Process is not Markov .

For the illness-death model, we must show that the time spent in state 1 (past) is not important on the transition from state 2 into state 3. For doing that, we consider $Z =$ time spent in state 1 , and t the current time. Consider the model $\alpha_{23}(t) = \alpha_{230}(t) \exp(\beta Z)$. Now what we need is to test $\beta = 0$, i.e., we have the null hypothesis,

H_0 : β=0 ,

against the general alternative,

H_1 : $\beta \neq 0$.

This would asses the assumption that the transition rate from the state 2 into state 3 is unaffected by the time spent in the previous state. The results obtained for the Stanford transplantation study show that the effect of time spent in state 1 is not significant (P-value > 0.05). This allows us to conclude that Markov's model is satisfactory for the Stanford data.

The HMM offers a detailed description of the survival process, making use of all the available information to estimate the transition probabilities and intensity rates. By applying this modeling approach, we refit the Stanford data including the potential effects of age, year and surgery in all transitions. Results obtained from the fitted model are presented on Table 2. Results indicate that age is the only covariate showing a significant linear effect in all transitions. We also observe that the acceptance time in the study is a significant predictor, though only for the mortality intensity in patients without transplant.

Further, we use Wald's test to verify whether or not a relation between transplant and survival exists. Formally, the hypothesis of no relation is given by $H_0 : \alpha_{13} = \alpha_{23}$, and then Wald's test reduces to $W = \left(\hat{\alpha}_{13} - \hat{\alpha}_{23}\right)^2 / v_{11}$, being $v_{11} = \text{var}\left(\hat{\alpha}_{13} - \hat{\alpha}_{23}\right)$. With our data, under the null hypothesis the W statistic (which follows a χ_1^2) yields a value of 18.5, suggesting that the transplant is significantly associated to a diminishing in mortality risk. Note however that likelihood ratio tests (fitting unrestricted and restricted models) can also be used for constructing a test of H_0 against the general alternative (under the null hypothesis the test statistic has an approximately χ_1^2 distribution).

The goodness-of-fit of a MSM can be assessed by comparing the observed and predicted number of patients undergoing each transition. Through this comparison, we observe that, for lower survival times, the mortality is underestimated from the fitted homogeneous Markov model (results not shown). In many cases these discrepancies can be explained by the failure of the time homogeneity assumption.To assess this assumption, Kay (1986) suggests the use of a piecewise model. Likelihood ratio tests can be used to compare the piecewise model with the homogeneous model. For the Stanford heart transplantation data the test statistic (which follows a χ_4^2) suggests the use of a non-homogeneous model. Such model will now be constructed.

Table 2. Multi-state homogeneous Markov model. Estimated transition rates and hazard rates. Stanford heart transplantation data.

	TR (SE)		
$\hat{\alpha}_{12}$	$0.0137\ (0.0017)$		
$\hat{\alpha}_{13}$	$0.0054\ (0.0011)$		
$\hat{\alpha}_{23}$	$0.0018\ (0.0003)$		
	HR (95%CI)		
Transition	**Age**	**Year**	**Surgery**
$1 \to 2$	$1.068\ (1.039-1.098)$	$0.975\ (0.852-1.116)$	$1.368\ (0.737-2.539)$
$1 \to 3$	$1.056\ (1.020-1.093)$	$0.739\ (0.595-0.919)$	$0.959\ (0.277-3.315)$
$2 \to 3$	$1.076\ (1.030-1.125)$	$1.109\ (0.928-1.325)$	$0.306\ (0.128-0.730)$

TR=Transition rate; SE=Standard error; HR=Hazard ratio; CI=Confidence Interval.

4. PIECEWISE HOMOGENEOUS MODEL

In this section we build a piecewise constant intensities model (Kay, 1986; Pérez-Ocón et al., 2001) with one cut-off point, specified from the Stanford data covariates that showed a significant effect when fitting the homogeneous model. After examining the likelihood for several cut-off points θ, a value of $\theta = 90$ days was selected, and two intervals ($\text{time} \leq 90$ days, $\text{time} > 90$ days) were then considered. It is seen that in both intervals the resulting estimates for the mortality intensity were lower in transplanted patients, though only in the second interval ($\text{time} > 90$ days) a significant difference was found ($\widehat{\alpha_{12}} = 0.0028$ and $\widehat{\alpha_{23}} = 0.0006$). When examining the fixed covariate effects, we see that, for $\text{time} \leq 90$ days, age at acceptance is a significant predictor in all transitions (HR:1.032;95%CI:1.011-1.053), while the effect of year is only significant on the mortality intensity in patients without transplant (HR:0.716;95%CI:0.571-0.899), and the effect of surgery only on the mortality intensity in transplanted patients (HR:0.131;95%CI:0.018-0.968). For the second interval ($\text{time} > 90$ days), however, the only significant covariate was age at acceptance (HR:1.061;95%CI:1.008-1.116).

5. DISCUSSION

The MSMs present some advantages over the TDCM. Among others, these models (a) allow estimates for the number of patients in various states; (b) can reveal the effect of each covariate on different transitions; and (c) express the time-dependent covariates in a simpler way. Although MSMs may be preferable to the Cox regression model, there are some limitations with the use of such models: (a) multi-state methodology requires some assumptions concerning a Markov or semi-Markov structure of the data; (b) most of the existent software assume the process is Markov and time-homogeneous which can be very restrictive; (c) some of the MSMs may require large sample sizes so that accurate estimates may be achieved; (d) when using covariates, the number of parameters increases proportionally to the number of covariates. To overcome some of these difficulties, model assessment techniques can be used.

When analyzing Stanford Heart data through the multi-state methodology, the Markov's assumption was satisfactory. When applying an Homogeneous Markov model, we verified that

this model underestimates the ‘short-term’ mortality. The reason why this model turned out to fit the data poorly is due to the fact that the survival process is not homogeneous in time.

While TDCM suggested a negligible effect of the transplant, the multi-state HMM indicated that the transplant is significantly associated to a diminishing in mortality risk. The application of the piecewise model only confirmed such association when the ‘long-term’ survival is analyzed. We showed that, the acceptance time covariate (year), considered the most important predictor in the Cox regression model, only shows a statistically significant effect in the mortality transition for patients without transplant. The MSM used here showed a significant negative influence of previous surgery on hazard in mortality transition for transplanted patients, that is, having a previous surgery enlarges the survival of transplanted patients. Age at acceptance, on the other hand, was revealed to be a significant predictor of survival in any of the studied models, and its positive effect on the hazard indicates that younger patients have a better survival.

In conclusion, the multi-state modeling offers a flexible tool for the study of covariate effects on the various transition rates. These models may bring out important biological insights which may be ignored when using Cox regression models alone. In practice, MSMs can be used to confirm and thoroughly examine conclusions obtained by applying simpler survival models. Therefore, we should not see the multi-state models as merely an alternative to the TDCM but rather as supplements that offer additional information.

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