Testing the Markov assumption in general multi-state models

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Abstract. Tests of the Markov property for general multi-state models are constructed using a similar principle to the construction of the landmark Aalen-Johansen estimator (LMAJ). For a given starting state r and time t, the sets of patients who were, and who were not, in that state at that time can be identified and treated as two distinct groups. Under a Markov assumption, the transition intensities in these two groups at times greater than t will be equal. Thus, a series of log-rank test statistics for each of the relevant transition intensities can be combined to construct a local test of Markovianity. Moreover, the set of statistics across different times, t, and starting states, r, form a stochastic process allowing the construction of a global test. While the asymptotic null distribution of the statistic can be determined, a wild bootstrap procedure is proposed to better approximate the null distribution in finite samples.

Keywords. multi-state model, log-rank test, wild bootstrap, non-Markov process

1 Introduction

The transition probabilities are a key quantity of interest in multi-state models. The Aalen-Johansen (AJ) estimator (Aalen & Johansen, 1978) offers a non-parametric estimator which is consistent under a Markov assumption and is known to also provide a consistent estimator of the state-occupancy probabilities for non-Markov processes (Datta & Satten, 2001).

Recently there has been substantial interest in the construction of estimators of the transition probabilities for multi-state models from right-censored data, which remain robust for non-Markov processes. Initially the estimators were restricted to the progressive illness-death model (Meira-Machado *et al*, 2006; Allignol *et al*, 2014;). Titman (2015) proposed the first general estimator. Putter & Spitoni (2016) proposed a simpler and slightly more efficient estimator, the landmark Aalen-Johansen (LMAJ) estimator, which involves estimating $P_{rs}(t_0, t) = P(X(t)|X(t_0) = r)$, for process $\{X(t), t \geq 0\}$, by applying the standard Aalen-Johansen to the subset of patients who are under observation and in state r at time t_0. While this estimator remains consistent when the multi-state process of interest is non-Markov, the use of only a subset of the total patients leads to a reduction in efficiency compared to the standard AJ estimator. It is therefore of practical interest to determine whether the Markov property holds within a particular dataset in order to determine whether the AJ or LMAJ is more appropriate.

For the illness-death model without recovery, Rodríguez-Girondo and Uña-Álvarez (2012) proposed a non-parametric test of Markovianity based upon the Kendall's τ between the time of exit from the healthy state and time of death. The purpose of the current work is to propose a non-parametric test for general multi-state models with an arbitrary number of states and the potential inclusion of backward transitions.

2 Construction of the test

Consider an individual starting time, t_0 and a state of interest r. Let $X_i(t)$ denote the multi-state process for subject i at time t, and let $Y_i(t)$ be the corresponding at risk indicator. Two groups of subjects can be defined by $\mathcal{S} = \{i : X_i(t_0) = r, Y_i(t_0) = 1\}$ and $\mathcal{S}^c = \{i : X_i(t_0) \neq r, Y_i(t_0) = 1\}$. Under the LMAJ estimator, only the subjects in $\mathcal{S}$ would contribute to the estimate, whereas the AJ estimator would use both sets of subjects. Moreover, under a Markov process, the transition intensities of the process for $t > t_0$ will be the same in both groups. A local test of Markovianity can be constructed by considering the log-rank statistics for each of the transition intensities $\alpha_{lm}(t)$ for $l \in \mathcal{R}_r$ where $\mathcal{R}_r$ represents the set of states which are reachable from state r and can be reached if r has already been exited. Under the null hypothesis of a Markov process, each log-rank statistic, $Z_{lm}^{(r)}(t_0)$, will have an asymptotic $N(0,1)$ distribution. A weighted sum of the squared statistics, $W^{(r)}(t_0) = \sum_{l,m} w_{lm}(t_0) Z_{lm}^{(r)}(t_0)^2$, for weights, $w_{lm}(t_0)$, such as the number of subjects who enter state l after time t_0, can serve as an overall statistic. A 'local' test can thus be constructed by rejecting the null hypothesis if $W^{(r)}(t_0)$ is large compared to its null distribution.

Test statistics, $W^{(r)}(t_0)$ can be constructed for all times t_0 in a suitably chosen interval, $[\tau_0, \tau)$, and for all non-absorbing states r. A global test statistic can then be constructed using

$$W_g = \max_r \sup_t \bar{W}^{(r)}(t),$$

where $\bar{W}^{(r)}(t)$ is an appropriately standardized version of a statistic to give it a comparable null mean and variance.

3 Null distribution of the statistic

Through standard counting process methods, under the null hypothesis the log-rank statistics corresponding to a particular transition $(l \to m)$, $\mathbf{Z}_{lm}(t) = (Z_{lm}^{(1)}(t), \ldots, Z_{lm}^{(R-1)}(t)), t \in [\tau_0, \tau)$ can be shown to converge to a zero mean Gaussian process with a relatively straightforward covariance function. Moreover, under the null hypothesis, the log-rank processes from distinction transition intensities (i.e. where either $l' \neq l$ or $m' \neq m$) are asymptotically independent. As a consequence, the null distribution could be approximated by simulating a large number of supremum statistics from the appropriate Gaussian processes.

However, a better small sample approximation can be obtained by using a wild bootstrap (Lin, 1994) in which the increments of the counting processes are replaced by independent normal random variables.

4 Example: Illness-death model without recovery

To illustrate the test, consider the illness-death model without recovery, where subjects begin in state 1 (healthy) at time 0 and may proceed to state 2 (illness) or state 3 (death). In this case, when $r = 1$ the only transition intensity estimable from both $\mathcal{S}$ and $\mathcal{S}^c$ is α_{23}. Moreover, since subjects under observation are either in state 1 or state 2, $W^{(1)}(t) = W^{(2)}(t) = Z_{23}^{(1)}(t)^2$. As a consequence, the global statistic reduces to $W_g = \sup_t W^{(1)}(t)$. Such a test is particularly well suited to detecting pathological non-Markov processes where the transition intensity at future times depends specifically on which state was occupied at a fixed time in the past. For instance, consider the model used in Titman (2015), where $\alpha_{12} = 0.12, \alpha_{13} = 0.03$ and

$$\alpha_{23}(t) = \begin{cases} 0.05 & \text{if } X(4) = 1 \\ 0.1 & \text{if } X(4) \neq 0. \end{cases}$$

For each simulated dataset, 500 patients are simulated with independent right-censoring times $C \sim \text{Exp}(0.04)$. The statistic was computed for 10000 simulated datasets, where each time the supremum in the period $t \in [3, 15)$ was computed. The global test of Rodríguez-Girondo and Uña-Álvarez (2012) was also calculated over the same interval. In this, albeit favourable, situation the proposed test has a power of 96.6% compared to 31.3% for the Kendall's τ based test.

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