Robust estimates of state occupancy and transition probabilities for Non-Markov multi-state models

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26 March 2014
Overview

- Continuously observed data
  - Three-state illness-death
  - General robust estimator
- Interval censored data
  - Estimation of state occupancy probabilities
  - Estimation of transition probabilities
Continuous observation
Illness-death model

\[ \begin{array}{c}
\text{0} \\
\text{1} \\
\text{2}
\end{array} \]

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Aalen-Johansen estimator

Under a Markov assumption, the matrix of transition probabilities of an $R$ state multi-state model can be estimated non-parametrically using the Aalen-Johansen estimator. 

$$\hat{P}(t_0, t_1) = \prod_{k: t_0 \leq t_k \leq t_1} (I + \hat{\alpha}_k)$$

where $\hat{\alpha}_k$ is an $R \times R$ matrix with $(i, j)$ entry

$$\hat{\alpha}_{ijk} = \frac{d_{ijk}}{r_{ik}}$$

$d_{ijk}$: number of $i \rightarrow j$ transitions at $t_k$, $r_{ik}$: number of subjects under observation in state $i$ at $t_k$.

Robust to non-Markov processes for purposes of state occupation probabilities but not transition probabilities.
If we wish to estimate $P_{01}(t_0, t_1) = \mathbb{P}(X(t_1) = 1 | X(t_0) = 0)$ then define

$$\kappa_u = \begin{cases} 
0 & \text{if } X(u) \in \{0, 1\} \\
1 & \text{if } X(u) = 2 \cap I(t_0 < T_0 \leq t_1, t_1 < T) = 1 \\
2 & \text{if } X(u) = 2 \cap I(t_0 < T_0 \leq t_1, t_1 < T) = 0,
\end{cases}$$

for $u \geq t_0$, considering only the subjects under observation at $t_0$ with $X(t_0) = 0$, $T$: time of entry into state 2, $T_0$: time of exit from state 0.
Allignol et al estimator

- Can equate $P_{01}(t_0, t_1)$ to

\[ \lim_{u \to \infty} \mathbb{P}(\kappa_u = 1) \]

- $\kappa_u$, being a competing risks process, is trivially Markov and therefore the transition probabilities (or cumulative incidence functions) can be consistently estimated by the Aalen-Johansen estimator.

- Allows for left-truncation
  - i.e. subjects who enter the study at $t^*$, $0 < t^* \leq t_0$ would contribute to $\kappa_u$ if $X(t_0) = 0$.

- But requires that support of censoring distribution contains the support of the times-to-absorption $T$. 

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Efficiency of Allignol et al estimator

Subjects only contribute to the estimate of $P_{01}(t_0, t_1)$ if
- $X(t_0) = 0$
- Subject reaches state 2 before being censored

The efficiency of the estimator for $P_{01}(t_0, t_1)$ depends on
- Magnitude of transition intensities to state 2 after $t_1$
- Censoring rate
Efficiency of Allignol et al estimator

If original process has transition intensities $\alpha_{02}(t; F_t)$ and $\alpha_{12}(t; F_t)$. Can construct a process with transition intensities

$$\alpha^*_{j2}(t; F_t) = \begin{cases} 
\alpha_{j2}(t; F_t) & \text{if } t \leq t_1 \\
\alpha_{j2}(t; F_t) + K & \text{if } t > t_1,
\end{cases}$$

$j = 0, 1$, for some $K > 0$.

- Process has the same value of $P_{01}(t_0, t_1)$.
- Yet, under the same censoring regime the estimates of $P_{01}(t_0, t_1)$ will have higher precision.
Altered estimator

Taking this to its limiting cases is equivalent to constructing a process

\[ \kappa_u^* = \begin{cases} 
0 & \text{if } X(u) \in \{0, 1\} \\
1 & \text{if } X(u) = 2, 
\end{cases} \]

and equating

\[ P_{01}(t_0, t_1) = \mathbb{P}(\kappa_{t_1}^* = 0) \mathbb{P}(X(t_1) = 1 | \kappa_{t_1}^* = 0), \]

where the latter term can be consistently estimated without making a Markov assumption by simply considering

\[ \frac{\#\{X(t_1) = 1\}}{\#\{X(t_1) \in \{0, 1\}\}} \]
Suppose want to estimate $P_{ij}(t_0, t_1)$ for some general multistate process

$$A_j = \begin{cases} \{j\} & \text{if } j \text{ is an absorbing state} \\ \emptyset & \text{otherwise} \end{cases}$$

and let $R_j$ be the set of states from which $j$ cannot be reached.

Construct a competing risks process

$$Z(t) = \begin{cases} 0 & \text{if } X(t) \notin \{A_j \cup R_j\} \\ 1 & \text{if } X(t) \in A_j \\ 2 & \text{if } X(t) \in R_j \end{cases}$$
Relevance of $Z(t)$

Once again $Z(t)$, as a competing risks process, is Markov and hence can be estimated via Aalen-Johansen.

- If $j$ is an absorbing state then
  \[
P_{ij}(t_0, t_1) = \mathbb{P}(Z(t_1) = 1 | X(t_0) = i)
  \]

- If $j$ is not absorbing then
  \[
P_{ij}(t_0, t_1) = \mathbb{P}(Z(t_1) = 0 | X(t_0) = i) \mathbb{P}(X(t_1) = j | Z(t_1) = 0)
  \]

We can therefore obtain estimates of the transition probabilities by estimating the probabilities associated with $Z(t)$ and, if $j$ is not absorbing, also estimate $\mathbb{P}(X(t_1) = j | Z(t_1) = 0)$ based on the proportion of subjects at risk who are in state $j$ at $t_1$. 
Example: Illness-death with recovery

To estimate $P_{00}(t_0, t_1)$
take the subset of patients under observation in state 0 at time $t_0$.
Construct a survival process
$Z(t) = I\{X(t) = 2\}$

$$\hat{P}_{00}(t_0, t_1) = \hat{P}(Z(t_1) = 0)\hat{P}(X(t_1) = 0|Z(t_1) = 0).$$
Example: Illness-death with recovery

To estimate $P_{10}(t_0, t_1)$ take the subset of patients under observation in state 1 at time $t_0$. Construct a survival process $Z(t) = I\{X(t) = 2\}$.

$$\hat{P}_{10}(t_0, t_1) = \hat{P}(Z(t_1) = 0)\hat{P}(X(t_1) = 0|Z(t_1) = 0).$$
To estimate $P_{02}(t_0, t_1)$ take the subset of patients under observation in state 0 at time $t_0$. Construct a survival process

$Z(t) = I\{X(t) = 2\}$

$\hat{P}_{02}(t_0, t_1) = \hat{P}(Z(t_1) = 1)$. 
Example: All states are recurrent

In the most extreme case where it is possible to reach any state from any other state then

- No information can be established from censored observations, i.e. the sets $A_j$ and $R_j$ are both empty.
- Estimator of $P_{ij}(t_0, t_1)$ just reduces to

$$\hat{P}_{ij}(t_0, t_1) = \frac{\#\{X(t_1) = j, X(t_0) = i\}}{\#\{X(t_0) = i\}}$$

where count is amongst those under observation at $t_0$ and $t_1$. 
Data Example: Liver cirrhosis RCT

488 patients from a randomized clinical trial
- Consider abnormal prothrombin levels as a reversible illness state in an illness-death model with recovery.
- Up to 12 years of patient follow-up available.
- Observation assumed continuous
- Interested in quantifying the effect that treatment (placebo versus prednisone) has on dynamics of prothrombin levels.
Liver cirrhosis

Aalen–Johansen estimate

Time since randomisation (days)

Placebo
Prednisone

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Liver cirrhosis

Non-Markov estimate

Time since randomisation (days)

P_{10}(1000, t)

Placebo
Prednisone

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Liver cirrhosis

- Non-Markov features of dataset likely to be due to unobservable heterogeneity within the dataset
  - Some subjects switch many times between ‘normal’ and ‘elevated’ prothrombin levels
  - Others make a single switch and then do not return to elevated levels.
Interval censoring: State occupation probabilities
Interval censored multi-state data

- Assume we have a \textit{progressive} multi-state process \( \{X(t), t > 0\} \) taking values on \( \{0, \ldots, R\} \).
- Intermittent monitoring of the process, e.g. at discrete, patient specific clinic visits. \( t_{lk}, l = 1, \ldots, N, k = 1, \ldots, n_l \)
- Time of entry into absorbing state, \( R \), may be known up to right censoring (but the state occupied immediately before absorption may be unknown), or could also be subject to interval-censoring.
Aim of the estimator

- Want an estimator of the state occupancy probabilities

\[ \mathbb{P}(X(t) = j | X(0) = 0) \]

- Want an estimator that remains robust to time inhomogeneity, non-Markov processes etc.

- Want something relatively quick to implement
  - So that bootstrapping can be used to obtain some indication of uncertainty
  - Ideally less, or no more, complicated to fit than the parametric model.

- Want an estimator that can be applied to a reasonable range of different models.
Previous work

There has been relatively little work on non-parametric estimation of multi-state models under interval censoring and even less on robust estimates.

  - Interval-censored Pepe-type estimator
  - Based on the difference of two interval censored survival estimates (time to leave state 0, time to enter state 2)
Marginal estimation

Issue of obtaining state occupancy probabilities can be related to issue of estimating a mean from longitudinal data.

- Suppose firstly that the examination times $T_1, \ldots, T_n$ are completely independent of the observed states $X(T_k)$.
- In particular, assume observations continue regardless of whether a subject has reached the absorbing state.
- Can attempt to estimate the marginal mean, $\mathbb{E}\{I(X(t) = i)\}$, by making some smoothness assumption and applying a working independence assumption.
Special case

Suppose we have a progressive process $X(t)$. Can identify indicators $I(X(t) \in R_j)$ which can be assumed to be monotonically increasing in $t$.

- e.g. unidirectional processes have that $P(X(t) \geq r)$ for $r = 1, \ldots, R$ are each monotonically increasing and would fully characterise the state occupation probabilities.

Therefore isotonic regression methods appropriate for current status survival data can be applied.

- Generalisations to other progressive tree models are also possible.
- Pool-adjacent-violators algorithm (PAVA) gives $\hat{P}(X(t) \geq r)$ and hence $\hat{P}(X(t) = r)$ very quickly.
  - Algorithmic complexity is $O(N)$. 

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Conditional approach

- Assuming that observations will continue after reaching the absorbing state is too restrictive for most practical applications
  - If the absorbing state is death and there is not a predetermined set of observation times
- More reasonable to assume independence conditional on not having reached the absorbing state
- Therefore, model the conditional process
  \[ X^*(t) = \{ X(t) | X(t) < R \} \]
- Relate back to the overall process via
  \[ P(X(t) = r) = P(X^*(t) = r)P(X(t) < R) \]
  for \( r < R \)
- \( P(X(t) < R) \) can be estimated by Kaplan-Meier
Further assumptions

Note that we cannot trivially assume that $\mathbb{P}(X^*(t) \geq r)$ is an increasing function in $t$ even if $X(t)$ is a progressive process.

- e.g. with a sufficiently heterogenous population, for instance a mover-stayer model.

However, may be reasonable in a wide range of cases, and can be checked.
Cardiac allgraft vasculopathy progression in post-heart-transplantation patients. 4 state illness-death structure.

State 0: Disease Free
State 1: Mild/Moderate CAV
State 2: Severe CAV
State 3: Death

Transition rates:
- $\lambda_{01}(t, \mathcal{F}_t)$
- $\lambda_{12}(t, \mathcal{F}_t)$
- $\lambda_{13}(t, \mathcal{F}_t)$
- $\lambda_{03}(t, \mathcal{F}_t)$
- $\lambda_{23}(t, \mathcal{F}_t)$
Example: CAV data

To obtain the state occupancy probabilities we estimate:

- \( P(X(t) > 0 | X(t) \neq 3) \)
- \( P(X(t) > 1 | X(t) \neq 3) \)
- \( P(X(t) = 3) \)

and then combine to get \( P(X(t) = r) \), for \( r = 0, 1, 2, 3 \). Approximate pointwise 95% confidence intervals via bootstrap resampling.
Example: CAV data

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Example: CAV data

Robust estimates of state occupancy and transition probabilities for Non-Markov multi-state models
Example: CAV data
Limitations

The cost of computational simplicity and lack of Markov assumptions is some loss of efficiency compared to the full NPMLE (in the Markov case)

- Information about state occupancy between the last time a patient is observed alive and the time of death is not used

- Requires stronger assumptions about the observation process than is required for maximum likelihood estimation
Non-informative observation

- Standard likelihood based estimation only requires that the observation process is non-informative (Gruger et al, 1991).
- In particular, this allows ‘doctor’s care’ type observation where the next examination time is scheduled at the previous observation and may depend on the state observed at that time.
  - e.g. if observed to be in the illness state at time $t_i$ then the next scheduled time tends to be sooner than if in the healthy state
- Proposed estimates of $\hat{P}(X(t) = r)$ will be biased under such observation.
Inverse visit-intensity weighting


- Model the intensity of the visit/observation process as depending on the history of the observation times and pre-and the history of the observed states at those times.
- Fit two models:
  - a null model in which the visit intensity depends only on the history of observation times
  - a general model in which the visit intensity depends on both the history of observation times and the history of observed states
- Weight observations by null intensity divided by history dependent intensity
Interval censoring: Transition probabilities
A more challenging problem is the estimation of robust transition probabilities for interval censored data. E.g. suppose want to estimate $P_{ij}(t_0, t_1)$.

- Unless all subjects observed at $t_0$ will not be able to ascertain the set of subjects who meet the initial condition $X(t_0) = i$. 
From-To Plane

State occupancy involves using data only up the $x = 0$ line.
Estimation could proceed with some smoothness assumption e.g. assume

\[ P_{ij}(t_0, t_1) \approx P_{ij}(t_0 + \epsilon, t_1 + \epsilon) \]

within some window \( \epsilon \in (-E, E) \).
Will be biased to some extent dependent on \( E \).
CAV data

Estimates for $\hat{P}_{0j}(2.25, t_1)$

- State 0
- State 1
- State 2
- State 3

Time (years since transplant)
Further work

Continuously observed data

- Can more efficient estimators be found?
- Regression e.g. via pseudo-observations
- Robustness to state-dependent censoring via IPCW (Datta & Satten, 2002)

Interval censored data

- Any possibility of jointly estimating intermediate state occupancy and overall survival?
- Weighted methods for estimating transition probabilities from ‘neighbouring’ trajectories
References


