Continuous-Time Markov Chains

1.1 Overview

Suppose $X(t)$ is a continuous-time non-homogeneous Markov chain with a finite state space $\mathscr{S} = \{0, 1, \cdots, J\}$. Consider first the two-state chain $\mathscr{S} = \{0, 1\}$ underlying standard survival analysis:

$$\boxed{X = 0} \xrightarrow{\alpha_{01}(t)} \boxed{X = 1}$$

The *intensity* or *hazard matrix* is:

$$\boldsymbol{\alpha}(t) = \left(\begin{array}{cc} -\alpha_{01}(t) & \alpha_{01}(t) \\ 0 & 0 \end{array}\right).$$

Entry $(1, 2)$ is $\alpha_{01}(t)$, the hazard of transitioning from state 0 to state 1. Entry $(1, 1)$ is the negation of entry $(1, 2)$, indicating that if $X(t)$ enters state 1, then $X(t)$ has left state 0. The second row of $\boldsymbol{\alpha}(t)$ is zero, indicating that transitions from state 1 back to state 0 are not allowed. The event time T is defined as $T = \inf\{t > 0 : X_t \neq 0\}$. The *transition matrix* is:

$$\boldsymbol{P}(t) = \left(\begin{array}{cc} S(t) & 1 - S(t) \\ 0 & 1 \end{array}\right) = \left(\begin{array}{cc} e^{-A_{01}(t)} & 1 - e^{-A_{01}(t)} \\ 0 & 1 \end{array}\right)$$

where $A_{01}(t) = \int_0^t \alpha(s)ds$ is the cumulative hazard of transitioning $0 \to 1$ within $(0, t]$. More generally, for an inhomogeneous Markov chain, $\boldsymbol{P}(s, t)$ is the transition matrix with elements:

$$P_{ij}(s, t) = \mathbb{P}\big\{X(t) = j | X(s) = i\big\}.$$

The transition matrix is linked to the hazard matrix by:

$$\frac{\partial}{\partial t}\boldsymbol{P}(s, t) = \boldsymbol{P}(s, t)\boldsymbol{\alpha}(t), \tag{1.1.1}$$

where the hazard matrix is formally defined by:

$$\boldsymbol{\alpha}(t) = \lim_{\delta \downarrow 0} \frac{1}{\delta}\big\{\mathbb{P}(t, t + \delta) - \boldsymbol{I}\big\}.$$

(1.1.1) is the *forward Kolmogorov equation*. The complementary integral equation is:

$$\boldsymbol{P}(s, t) = \boldsymbol{I} + \int_s^t \boldsymbol{P}(s, u-)d\boldsymbol{A}(u).$$

This expression, using $d\boldsymbol{A}(u)$ in place of $\boldsymbol{\alpha}(u)du$, remains valid even when the elements of the transition matrix are not differentiable. The solution to (1.1.1) takes the form of a matrix-valued *product integral*:

$$\boldsymbol{P}(s,t) = \prod_{s<u\leq t} \big\{\boldsymbol{I} + d\boldsymbol{A}(u)\big\}. \tag{1.1.2}$$

In the absolutely continuous case, $d\boldsymbol{A}(u) = \boldsymbol{\alpha}(u)du$, where $\boldsymbol{\alpha}(u)$ is the matrix of element-wise derivatives of the cumulative hazard matrix $\boldsymbol{A}(u)$. For the simple two-state model:

$$\boldsymbol{A}(t) = \begin{pmatrix} -\int_0^t \alpha_{01}(u)du & \int_0^t \alpha_{01}(u)du \\ 0 & 0 \end{pmatrix},$$

and:

$$\boldsymbol{P}(0,t) = \prod_{0<u\leq t} \begin{pmatrix} 1-\alpha_{01}(t) & \alpha_{01}(t) \\ 0 & 1 \end{pmatrix} = \begin{pmatrix} e^{-A_{01}(t)} & 1-e^{-A_{01}(t)} \\ 0 & 1 \end{pmatrix}.$$

Closed forms for the product integral equation (1.1.2) are typically only available for simple models, such as the competing risk or illness-death models.

1.2 Aalen-Johansen Estimator

Let $\tau_1 < \cdots < \tau_K$ denote the distinct observation times. The transition matrix $\boldsymbol{P}(s,t)$ is consistently estimated via the **Aalen-Johansen** estimator:

$$\hat{\boldsymbol{P}}(s,t) = \prod_{s<\tau_j\leq t} \big\{\boldsymbol{I} + d\hat{\boldsymbol{A}}(\tau_j)\big\}. \tag{1.2.3}$$

1.2.1 Two-State Model

Example 1.2.1. Consider the two-state model. If τ_j is an event time:

$$\boldsymbol{I} + d\hat{\boldsymbol{A}}(\tau_j) = \begin{pmatrix} 1-\frac{dN(\tau_j)}{Y(\tau_j)} & \frac{dN(\tau_j)}{Y(\tau_j)} \\ 0 & 1 \end{pmatrix}.$$

Let $h_j = dN_j/Y_j$. The product of the first two Aalen-Johansen matrices is:

$$\begin{pmatrix} 1-h_1 & h_1 \\ 0 & 0 \end{pmatrix}\begin{pmatrix} 1-h_2 & h_2 \\ 0 & 0 \end{pmatrix} = \begin{pmatrix} (1-h_1)(1-h_2) & (1-h_1)h_2 + h_1 \\ 0 & 1 \end{pmatrix}$$

The product of the first three matrices will be:

$$\begin{pmatrix} (1-h_1)(1-h_2)(1-h_3) & (1-h_1)(1-h_2)h_3 + (1-h_1)h_2 + h_1 \\ 0 & 1 \end{pmatrix}$$

And in general, the product over the first k event times is:

$$\hat{\boldsymbol{P}}_k = \prod_{i=1}^{k} \{\boldsymbol{I} + d\hat{\boldsymbol{A}}_i\} = \begin{pmatrix} \hat{S}_k & \hat{F}_k \\ 0 & 1 \end{pmatrix},$$

where $\hat{S}_k$ is the standard Kaplan-Meier estimator:

$$\hat{S}_k = \prod_{i=1}^{k}(1 - h_i),$$

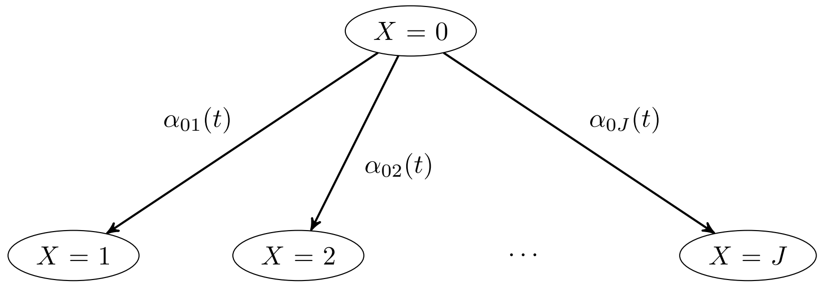
and $\hat{F}_k$ is a corresponding estimator of the cumulative incidence:

$$\hat{F}_k = \sum_{i=1}^{k} h_i \prod_{j<i}(1 - h_j).$$

♠

1.2.2 Competing Risks Model

Example 1.2.2. Consider the J-state competing risk model:



Define $N_{0\bullet}(t) = \sum_{j=1}^{J} N_{0j}(t)$ as the total number of transitions out of state 0 by time t. If τ_j is an event time:

$$\boldsymbol{I} + d\hat{\boldsymbol{A}}(\tau_j) = \begin{pmatrix} 1 - \frac{dN_{0\bullet}(\tau_j)}{Y_0(\tau_j)} & \frac{dN_{01}(\tau_j)}{Y_0(\tau_j)} & \frac{dN_{02}(\tau_j)}{Y_0(\tau_j)} & \cdots & \frac{dN_{01}(\tau_J)}{Y_0(\tau_j)} \\ 0 & 1 & 0 & \cdots & 0 \\ 0 & 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \cdots \\ 0 & 0 & 0 & \cdots & 1 \end{pmatrix}$$

Matrix multiplications, as in the two-state model, show that:

$$\hat{P}_{00}(s,t) = \prod_{s<u\leq t}\left(1 - \frac{dN_{0\bullet}(u)}{Y_0(u)}\right),$$

which is the Kaplan-Meier estimator based on the total number of events.

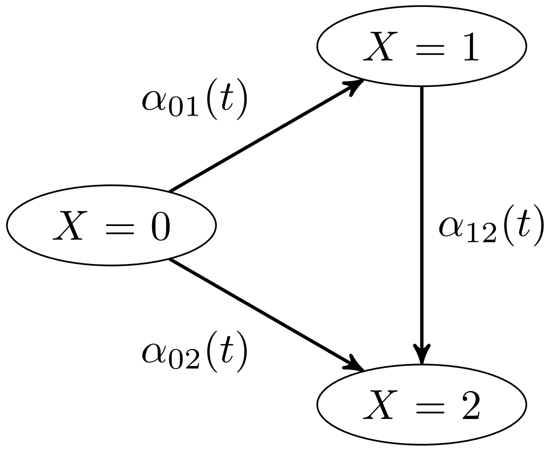
For $j \in \{1, \cdots, J\}$, the estimator of the cumulative incidence function is:

$$\hat{P}_{0j}(s,t) = \int_s^t \hat{P}_{00}(s,u-) \cdot \frac{dN_{0j}(u)}{Y_0(u)}.$$

Here $P_{0j}(s,t) = \mathbb{P}(s < T \leq t, X_T = j)$. ♠

1.2.3 Illness-Death Model

Example 1.2.3. Consider the illness-death model without recovery:



Let $Y_0(t)$ and $Y_1(t)$ denote the number of individuals in states 0 and 1 just prior to time t. Let $N_{01}(t)$, $N_{02}(t)$, and $N_{12}(t)$ count the numbers of transitions between the corresponding states by time t.
If τ_j is a transition time:

$$\boldsymbol{I} + d\hat{\boldsymbol{A}}(\tau_j) = \begin{pmatrix} 1 - \frac{dN_{0\bullet}(\tau_j)}{Y_0(\tau_j)} & \frac{dN_{01}(\tau_j)}{Y_0(\tau_j)} & \frac{dN_{02}(\tau_j)}{Y_0(\tau_j)} \\ 0 & 1 - \frac{dN_{12}(\tau_j)}{Y_1(\tau_j)} & \frac{dN_{12}(\tau_j)}{Y_1(\tau_j)} \\ 0 & 0 & 1 \end{pmatrix}$$

Matrix multiplications show that the survival function for state 0 is:

$$\hat{P}_{00}(s,t) = \prod_{s<u\le t}\left(1 - \frac{dN_{0\bullet}(u)}{Y_0(u)}\right),$$

which is analogous to the competing risk model.

The survival function for state 1 is:

$$\hat{P}_{11}(s,t) = \prod_{s<u\le t}\left(1 - \frac{dN_{12}(u)}{Y_1(u)}\right),$$

which is analogous to the two-state model.

The probability of starting in state 0 at time s and occupying state 1 at time $t > s$ is:

$$\hat{P}_{01}(s,t) = \int_s^t \hat{P}_{00}(s,u-) \cdot \frac{dN_{01}(u)}{Y_0(u)} \cdot \hat{P}_{11}(u,t).$$

The limiting expressions for the transition probabilities are:

$$P_{00}(s,t) = \exp\left\{-\int_s^t \alpha_{0\bullet}(u)du\right\}$$

where $\alpha_{0\bullet}(u) = \alpha_{01}(u) + \alpha_{02}(u)$;

$$P_{11}(s,t) = \exp\left\{-\int_s^t \alpha_{12}(u)du\right\};$$

and:

$$P_{01}(s,t) = \int_s^t P_{00}(s,u-)\alpha_{01}(u)P_{11}(u,t)du.$$

Finally, note that $P_{02}(s,t) = 1 - P_{00}(s,t) - P_{01}(s,t)$. ♠

1.3 Inference

Suppose again that $X(t)$ is a continuous-time Markov chain with finite state space $\mathscr{S} = \{0,1,\cdots,J\}$. The asymptotic distribution of the Aalen-Johansen estimator (1.2.3) may be derived by vectorizing $\hat{\boldsymbol{P}}(s,t)$, then expressing the covariance of $\text{vec}(\hat{\boldsymbol{P}})$ as a matrix-valued mean zero martingale. The resulting estimator of the covariance between $\hat{P}_{ab}(s,t)$ and $\hat{P}_{cd}(s,t)$ is: $\hat{\mathbb{C}}\{\hat{P}_{ab}(s,t),\hat{P}_{cd}(s,t)\} =$

$$\sum_{i=0}^{J}\sum_{k\neq i}\int_s^t \hat{P}_{ak}(s,u)\hat{P}_{ck}(s,u)\{\hat{P}_{ib}(u,t)-\hat{P}_{kb}(u,t)\}\{\hat{P}_{id}(u,t)-\hat{P}_{kd}(u,t)\}\cdot\frac{dN_{ki}(u)}{Y_k^2(u)} \tag{1.3.4}$$

When $a = c$ and $b = d$, such that the variance is of interest:

$$\hat{\mathbb{V}}\{\hat{P}_{ab}(s,t)\} = \sum_{i=0}^{J}\sum_{k\neq i}\int_s^t \hat{P}_{ak}^2(s,u)\{\hat{P}_{ib}(u,t)-\hat{P}_{kb}(u,t)\}^2\cdot\frac{dN_{ki}(u)}{Y_k^2(u)}$$

See [1] (IV.4.1.3) for details.

1.3.1 Two-State Model

Example 1.3.4. Consider the two-state chain $\mathscr{S} = \{0,1\}$. The Aalen-Johansen covariance estimator for $\hat{P}_{00}(0,t)$, which is the standard survival function. For this model, $\hat{P}_{10}(s,t) = 0$ and $dN_{10}(u) = 0$, such that only the $(i,k) = (1,0)$ term contributes:

$$\begin{aligned}\hat{\mathbb{V}}\{\hat{P}_{00}(0,t)\} &= \int_0^t \hat{P}_{00}^2(0,u)\{0-\hat{P}_{00}(u,t)\}^2\cdot\frac{dN_{01}(u)}{Y_0^2(u)} \\ &= \int_0^t \hat{P}_{00}^2(0,u)\hat{P}_{00}^2(u,t)\cdot\frac{dN_{01}(u)}{Y_0^2(u)}.\end{aligned}$$

The squared term simplifies as:

$$\hat{P}_{00}^2(0,u)\hat{P}_{00}^2(u,t) = \left\{\hat{P}_{00}(0,u)\hat{P}_{00}(u,t)\right\}^2 = \left\{\hat{P}_{00}(0,t)\right\}^2 = \hat{P}_{00}^2(0,t).$$

Thus, the variance estimator for $\hat{P}_{00}(0,t)$ is:

$$\hat{\mathbb{V}}\{\hat{P}_{00}(0,t)\} = \hat{P}_{00}^2(0,t)\int_0^t\frac{dN_{01}(u)}{Y_0^2(u)},$$

in agreement with the standard estimator. ♠

1.3.2 Competing Risks Model

Example 1.3.5. For the J-state competing risks model, the variance of the survival function $\hat{P}_{00}(0,t)$ is:

$$\hat{\mathbb{V}}\big\{\hat{P}_{00}(0,t)\big\} = \hat{P}_{00}(0,t)\int_0^t \frac{dN_{0\bullet}(u)}{Y_0^2(u)}.$$

To find the variance of $\hat{P}_{0j}$, note that $dN_{ki}(u) = 0$ for $k \neq 0$:

$$\hat{\mathbb{V}}\big\{\hat{P}_{0j}(0,t)\big\} = \sum_{i=1}^{J}\int_0^t \hat{P}_{00}^2(0,u)\big\{\hat{P}_{ij}(u,t) - \hat{P}_{0j}(u,t)\big\}^2 \cdot \frac{dN_{0i}(u)}{Y_0^2(u)}.$$

$\hat{P}_{ij} = 0$ for $i \neq j$ and $\hat{P}_{jj} = 1$:

$$\begin{aligned}\hat{\mathbb{V}}\big\{\hat{P}_{0j}(0,t)\big\} = &\sum_{i\neq j}\int_0^t \hat{P}_{00}^2(0,u)\big\{\hat{P}_{0j}(u,t)\big\}^2 \cdot \frac{dN_{0i}(u)}{Y_0^2(u)} \\ &+ \int_0^t \hat{P}_{00}^2(0,u)\big\{1 - \hat{P}_{0j}(u,t)\big\}^2 \cdot \frac{dN_{0j}(u)}{Y_0^2(u)}.\end{aligned}$$

Adding and subtracting $\int_0^t \hat{P}_{00}^2(0,u)\hat{P}_{0j}^2(u,t)\frac{dN_{0j}(u)}{Y_0^2(u)}$:

$$\begin{aligned}\hat{\mathbb{V}}\big\{\hat{P}_{0j}(0,t)\big\} = &\int_0^t \hat{P}_{00}^2(0,u)\hat{P}_{0j}^2(u,t) \cdot \frac{dN_{0\bullet}(u)}{Y_0^2(u)} \\ &+ \int_0^t \hat{P}_{00}^2(0,u)\big\{1 - \hat{P}_{0j}(u,t)\big\}^2 \cdot \frac{dN_{0j}(u)}{Y_0^2(u)} \\ &- \int_0^t \hat{P}_{00}^2(0,u)\hat{P}_{0j}^2(u,t) \cdot \frac{dN_{0j}(u)}{Y_0^2(u)}.\end{aligned}$$

Expanding the binomial gives:

$$\begin{aligned}\hat{\mathbb{V}}\big\{\hat{P}_{0j}(0,t)\big\} = &\int_0^t \hat{P}_{00}^2(0,u)\hat{P}_{0j}^2(u,t) \cdot \frac{dN_{0\bullet}(u)}{Y_0^2(u)} \\ &+ \int_0^t \hat{P}_{00}^2(0,u)\big\{1 - 2\hat{P}_{0j}(u,t)\big\} \cdot \frac{dN_{0j}(u)}{Y_0^2(u)}.\end{aligned}$$

♠

1.3.3 Illness-Death Model

Example 1.3.6. For the illness-death model without recovery, $\hat{P}_{00}(0,t)$ and $\hat{P}_{11}(0,t)$ are the standard Kaplan-Meier estimators, and their variance estimators are given by:

$$\hat{\mathbb{V}}\big\{\hat{P}_{00}(0,t)\big\} = \hat{P}_{00}(0,t)\int_0^t \frac{dN_{0\bullet}(u)}{Y_0^2(u)}, \qquad \hat{\mathbb{V}}\big\{\hat{P}_{11}(0,t)\big\} = \hat{P}_{11}(0,t)\int_0^t \frac{dN_{12}(u)}{Y_1^2(u)}.$$

For the variance of $\hat{P}_{01}(0,t)$, the non-zero terms are $(i,k) \in \{(1,0),(2,0),(2,1)\}$:

$$\begin{aligned}\hat{\mathbb{V}}\big\{\hat{P}_{01}(0,t)\big\} = &\int_0^t \hat{P}_{00}^2(0,u)\big\{\hat{P}_{11}(u,t) - \hat{P}_{01}(u,t)\big\}^2 \cdot \frac{dN_{01}(u)}{Y_0^2(u)} \\ &+ \int_0^t \hat{P}_{00}^2(0,u)\big\{0 - \hat{P}_{01}(u,t)\big\}^2 \cdot \frac{dN_{02}(u)}{Y_0^2(u)} \\ &+ \int_0^t \hat{P}_{01}^2(0,u)\big\{0 - \hat{P}_{11}(u,t)\big\}^2 \cdot \frac{dN_{12}(u)}{Y_1^2(u)}\end{aligned}$$

♠

1.4 Computation

- The **Nelson-Aalen** estimator $\hat{\boldsymbol{A}}(t)$ of the cumulative hazard matrix $\boldsymbol{A}(t)$ for multi-state models is implemented by the `mvna` function in the `mvna` package.
- The **Aalen-Johansen** estimator $\hat{\boldsymbol{P}}(s,t)$ of the transition matrix $\boldsymbol{P}(s,t)$ for multi-state models is implemented by the `etm` function in the `etm` package.
- See [2] for examples using the `mvna` and `etm`.

References

[1] PK Andersen et al. *Statistical Models Based on Counting Processes*. 2nd. Springer-Verlag, 1997.

[2] J Beyersmann, A Allignol, and M Schumacher. *Competing Risks and Multistate Models with R*. Springer Science+Business Media, 2012.