Survival Models

Lecture VI. Multistate models (MSM). Continuous time Markov chains

Study materials for multistate models

The following lectures are based on different textbooks and course notes.

The main book:

- Meira-Machado, Una-Alvarez, Cardarso-Suarez, Andersen (2007). *Multi-state models for the analysis of time to event data.*

Supplementary reading:

- Aalen, Borgan, Gjessing (2008). *Survival and event history analysis. A process point of view.*
- Beyersmann, Schumacher & Allignol (2012). *Competing risks and multistate models with R.*
- Dickson, Hardy, Waters (2013). *Actuarial mathematics for life contingent risks.*
- Hougaard (2001). *Analysis of multivariate survival data.*

Survival model in framework of random processes

Let us first notice that since a survival model models time to an event, this model can be written in terms of a random process.

Simple mortality model:

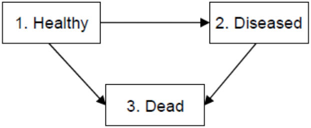
$$\boxed{\text{State 1 (alive)}} \longrightarrow \boxed{\text{State 2 (dead)}}$$

Obviously, a model with just two states (and one of them is absorbing) is more convenient to handle by a time-to-event random variable.

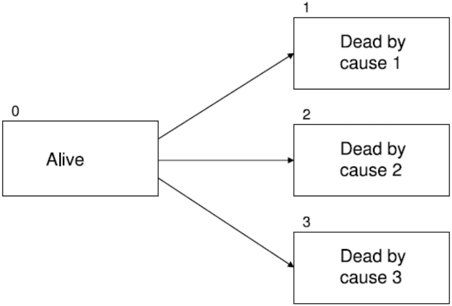
But using the random processes' framework, it is fairly simple to generalize the model by including more states.

Examples of multistate models (1)

Illness-death model (with terminal illness)

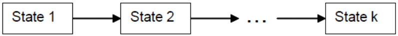


Competing risks model

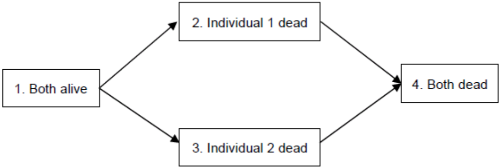


Examples of multistate models (2)

k-progressive model



Bivariate model



HIV disease progression

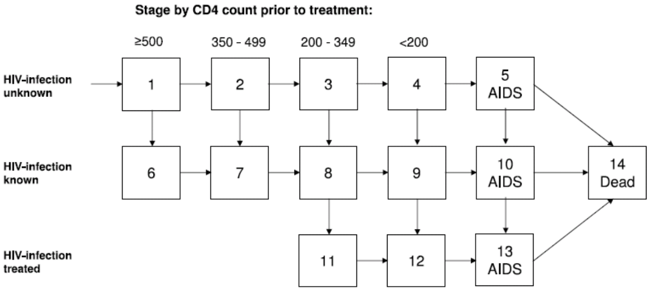


Fig. 1.12 *Model for progression of HIV disease, according to level of CD4 count and whether the infection was known (by positive HIV test) or not.*

Multistate models. Notation

Let us denote:

- $\{X(t), t \geq 0\}$ – a (continuous time) stochastic process (describing the health status of an individual). For each fixed t, $X(t)$ is a random variable
- $\mathcal{S}$ – (countable) state space corresponding to the process (i.e. the set of possible values for $X(t)$). For example
  - in simple mortality model $\mathcal{S} = \{1, 2\}$:
    - 1 – alive
    - 2 – dead
  - in competing risks model with two competing risks $\mathcal{S} = \{1, 2, 3\}$:
    - 1 – alive
    - 2 – dead (cause 1)
    - 3 – dead (cause 2)
  - in illness-death model $\mathcal{S} = \{1, 2, 3\}$:
    - 1 – alive (healthy)
    - 2 – ill
    - 3 – dead

Transition probabilities. Markov property

To describe a multistate model, the key question is to find or estimate the following transition probabilities

$$\mathbb{P}\{X(t+s) = j | X(t) = i, X(u) = x(u), 0 \leq u < t\},$$

where $s,\ t \geq 0$, and $i,\ j,\ x(u),\ 0 \leq u < t$ are possible states for given model.

Modelling such process is in general a fairly complex task. Usually, certain simplifactions are assumed, most popular of them is the Markov property:

$$\mathbb{P}\{X(t+s) = j | X(t) = i, X(u) = x(u), 0 \leq u < t\} = \mathbb{P}\{X(t+s) = j | X(t) = i\}$$

In other words, the process has no memory, the (probabilistic) future behaviour is given by the last known state. This property also allows us to use notation $P_{ij}(t, t+s)$.

A stochastic process with Markov property is called a Markov chain

Transition intensities

Alternative option is to describe the model via transition intensities:

$$\lim_{\Delta t \to 0} \frac{\mathbb{P}(X(t+\Delta t) = j \mid X(u) = x(u),\ 0 \leqslant u < t,\ X(t) = i)}{\Delta t},$$

which, in case of a Markov model, simplify to

$$h_{ij}(t) = \lim_{\Delta t \to 0} \frac{P_{ij}(t, t+\Delta t)}{\Delta t}$$

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NB!

The similarity of this notation to the notation of hazard function is intentional. The transition intensities in case of a survival model can be interpreted as "state changing" hazards.

Important preliminaries about Markov chains (1)

Chapman-Kolmogorov equation

$$P_{ij}(z, t + \Delta t) = \sum_{k \in \mathcal{S}} P_{ik}(z, t) P_{kj}(t, t + \Delta t)$$

Kolmogorov forward equation (KFE)

$$\frac{dP_{ij}(z,t)}{dt} = \sum_{k \in \mathcal{S} \setminus \{j\}} P_{ik}(z,t) h_{kj}(t) - h_j(t) P_{ij}(z,t),$$

where $h_j(t) = \sum_{i : i \neq j} h_{ji}(t)$

Kolmogorov backward equation (KBE)

$$\frac{dP_{ij}(z,t)}{dz} = h_i(z) P_{ij}(z,t) - \sum_{k \in \mathcal{S} \setminus \{i\}} h_{ik}(z) P_{kj}(z,t),$$

where $h_i(z) = \sum_{j : j \neq i} h_{ij}(z)$

Important preliminaries about Markov chains (2)

Idea of proof.

- For KFE: apply the Chapman-Kolmogorov equation to

$$P_{ij}(z, t + \Delta t)$$

  and consider the limit

$$\lim_{\Delta t \to 0} \frac{P_{ij}(z, t + \Delta t) - P_{ij}(z, t)}{\Delta t}$$

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Important preliminaries about Markov chains (3)

A Markov chain is called homogeneous if it satisfies

$$P_{ij}(t, t+s) = P_{ij}(0, s) = P_{ij}(z, z+s),$$

for any $t, z, s > 0$ and $i, j \in \mathcal{S}$

Such assumption obviously simplifies the formulas (and thus the estimation of all the required quantities) significantly

Question(s)

What restrictions does the homogeneity assumption imply? Is a homogeneous Markov chain suitable model for general practice?

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What restrictions does the homogeneity assumption imply? Is a homogeneous Markov chain suitable model for general practice?

In case of survival models, a homogeneous Markov chain is obviously an oversimplified model, because it implies that all the transition intensities (=hazards!) are constant. A more general option is to use piecewise constant transition intensities, which retains most of the simplicity, but allows to model the changes in hazard.

Multistate models. Additional notation

Cumulative hazards:

$$H_{ij}(s,t) = \int_s^t h_{ij}(u)du$$

and

$$H_i(s,t) = \int_s^t h_i(u)du$$

Probability of not changing the state in a time interval:

$$P_{\underline{ii}}(0,t) = e^{-H_i(0,t)} = e^{-\int_0^t h_i(u)du},$$

and, more generally

$$P_{\underline{ii}}(z,t) = e^{-H_i(z,t)} = e^{-\int_z^t h_i(u)du}$$

Competing risks model (1)

Consider an competing risks model with two competing risks. Let us denote the states of the model as follows:

- 1 – alive (healthy)
- 2 – dead (cause of risk 1)
- 3 – dead (cause of risk 2)

Then the only possible transitions are $1 \to 2$ and $1 \to 3$.

Competing risks model (2)

Let us now apply KFE to $P_{11}(z,t)$:

$$\frac{dP_{11}(z,t)}{dt} = \sum_{k\in\{2,3\}} P_{1k}(z,t)h_{k1}(t) - P_{11}(z,t)h_1(t) = -P_{11}(z,t)h_1(t)$$

This differential equation is easy to solve, because

$$\frac{d\ln P_{11}(z,t)}{dt} = \frac{\frac{dP_{11}(z,t)}{dt}}{P_{11}(z,t)} = -h_1(t),$$

thus the solution is on the form

$$\ln P_{11}(z,t) = -\int_z^t h_1(u)du + C$$

or, equivalently

$$P_{11}(z,t) = e^{-\int_z^t h_1(u)du}e^C = e^{-H_1(z,t)}$$

Competing risks model (3)

Applying KFE to $P_{12}(z,t)$ results in

$$\frac{dP_{12}(z,t)}{dt} = P_{11}(z,t)h_{12}(t),$$

which implies (since $P_{12}(z,z) = 0$):

$$P_{12}(z,t) = \int_z^t P_{11}(z,u)h_{12}(u)du$$

Finally, $P_{13}(z,t)$ can be found from

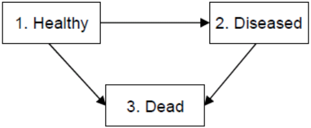
$$P_{13}(z,t) = 1 - P_{11}(z,t) - P_{12}(z,t)$$

Illness-death model (1)

Consider an illness-death model with terminal illness. Let us denote the states of the model ad follows:

- 1 – alive (healthy)
- 2 – (terminally) ill
- 3 – dead

Then the only possible transitions are $1 \to 2$, $1 \to 3$ and $2 \to 3$.



Illness-death model (2)

Applying KFE (similarly to previous) implies:

$$P_{11}(z,t) = e^{-H_1(z,t)}$$

and

$$P_{22}(z,t) = e^{-H_2(z,t)}$$

Furthermore, it can be shown that

$$P_{12}(z,t) = \int_z^t P_{11}(z,u)h_{12}(u)P_{22}(u,t)du$$