Multi-state models: Rates, Risks, and Pseudo-Values
Overview of course

I **Introduction to multi-state models**

II Non-parametric estimation and regression models for intensities (Cox)

III Estimation of marginal parameters using plug-in

IV Direct regression models for marginal parameters (Cox, Fine-Gray, Ghosh-Lin)

V Pseudo-values

Based on the book 'Models for Multi-State Survival Data: Rates, Risks, and Pseudo-Values' by Per Kragh Andersen and Henrik Ravn.
Companion: https://multi-state-book.github.io/companion
Course: https://multi-state-book.github.io/Salerno25

I: Introduction to multi-state models

- Multi-state models: parameters
  - Marginal parameters (state occupation probabilities, expected length of stay in a state, 'ELOS')
  - Conditional parameters (transition probabilities and intensities)
- Multi-state models: examples
  - Two-state model for survival data
  - Competing risks
  - Recurrent events
  - Illness-death model
- Observations: counting processes and at risk processes; censoring

Multi-state models

- Models consist of *states* and possible *transitions* between states
- Models are useful for studying events that happen when subjects are observed (continuously) over time
- An *event* is an observed transition between two states
- We denote the multi-state process for subject i by $V_i(t)$ indicating the state occupied by i at time t
- The *state space* is the finite set $\mathcal{S} = \{0, 1, \ldots, k\}$, and a state $h \in \mathcal{S}$ is *absorbing* if no transitions out of h are possible
- The two-state model for *survival data* is a simple and important special case

Parameters in multi-state models

- $V(t) \in \mathcal{S}$: *state* occupied at time t

  Marginal parameters:

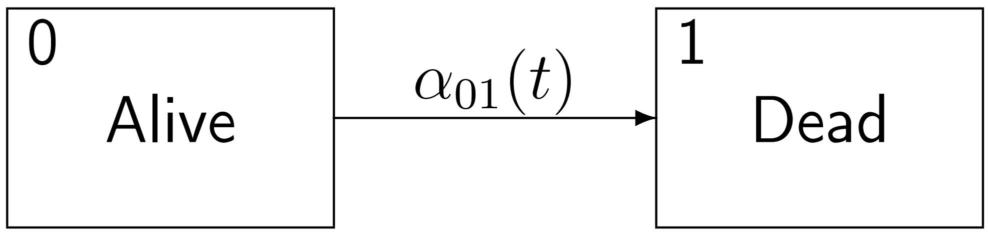
- $Q_h(t) = P(V(t) = h) = E(I(V(t) = h)), h \in \mathcal{S}$ *state occupation probabilities*
- $\varepsilon_h(\tau) = E(\int_0^\tau I(V(t) = h)dt) = \int_0^\tau Q_h(t)dt$ *expected length of stay* (ELOS) in state $h \in \mathcal{S}$ in $[0, \tau]$

  Conditional parameters:

- $P_{hj}(s,t) = P(V(t) = j \mid V(s) = h, \text{past information in } [0, s))$ *transition probabilities*
- $\alpha_{hj}(t) = \lim_{dt \to 0} P_{hj}(t, t + dt)/dt$ *transition intensities*

The transition intensities (hazards, rates) are the basic building blocks for multi-state models, but marginal parameters often have more direct interpretations.

Two-state model for survival data



Transition intensity: *hazard function*

$\alpha(t) = \alpha_{01}(t) \approx P(\text{state } 1 \text{ time } t + dt \mid \text{state } 0 \text{ time } t)/dt$.

State occupation probabilities: *survival function*,

$Q_0(t) = S(t) = P(\text{state 0 time } t) = P(T > t)$, ($T$: *survival time*)

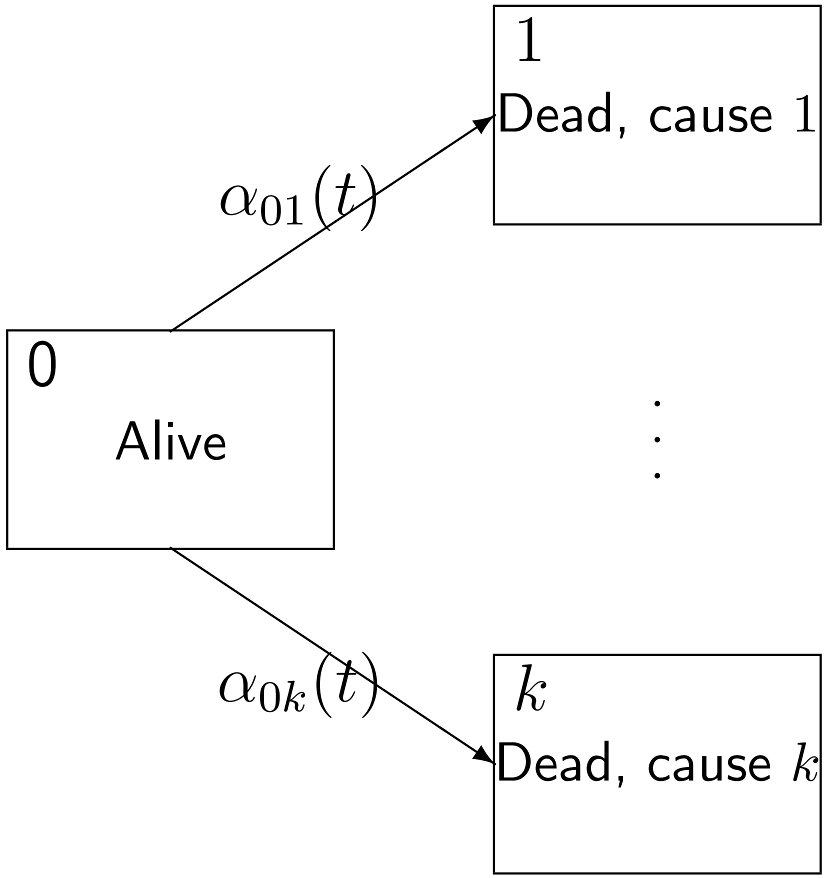
and *cumulative probability of death before time* t, Eq. (1.2):

$Q_1(t) = 1 - Q_0(t) = F(t) = P(\text{state 1 time } t) =$
$1 - \exp(-\int_0^t \alpha_{01}(u)du) = \exp(-A_{01}(t))$, ($A_{01}(\cdot)$: *integrated* hazard).

The PBC-3 trial in liver cirrhosis

- Lombard et al. (1993, *Gastroenterol.*)
- Multi-centre randomized trial in patients with primary biliary cirrhosis.
- Patients ($n = 349$) recruited 1 Jan, 1983 - 1 Jan, 1987 from six European hospitals and randomized to CyA (176) or placebo (173).
- Followed until death or liver transplantation (no longer than 31 Dec, 1989); CyA: 30 died, 14 were transplanted; placebo: 31 died, 15 were transplanted; 4 patients were lost to follow-up before 1989.
- Primary outcome variable: time to death, incompletely observed, due to: liver transplantation, loss to follow-up, alive 31 Dec, 1989.
- In some analyses, the outcome is defined as 'time to failure of medical treatment', i.e., time to the composite end-point of either death or liver transplantation, whatever came first - this fits with the two-state model.

Competing risks model



Competing risks model

Transition intensities: *cause-specific hazards* $h = 1, \ldots, k$:

$$\alpha_h(t) = \alpha_{0h}(t) \approx P(\text{state } h \text{ time } t + dt \mid \text{state } 0 \text{ time } t)/dt.$$

State occupation probabilities: *overall survival function*:

$$Q_0(t) = S(t) = P(\text{alive time } t) = P(T > t)$$
$$= \exp(-\textstyle\int_0^t (\alpha_{01}(u) + \cdots + \alpha_{0k}(u))du),$$

and *cumulative incidences* $h = 1, \ldots, k$, Eq. (1.3):

$$Q_h(t) = F_h(t) = P(\text{dead from cause } h \text{ before time } t) = \int_0^t S(u)\alpha_{0h}(u)du.$$

An example is the PBC-3 trial with the end-points transplantation and death without transplantation.

Expected length of stay

In both models, the t_0-restricted mean survival time (RMST), $\varepsilon_0(t_0) = E(\min(T, t_0))$, Eq. (1.10), is:

$$\varepsilon_0(t_0) = \int_0^{t_0} S(t)dt.$$

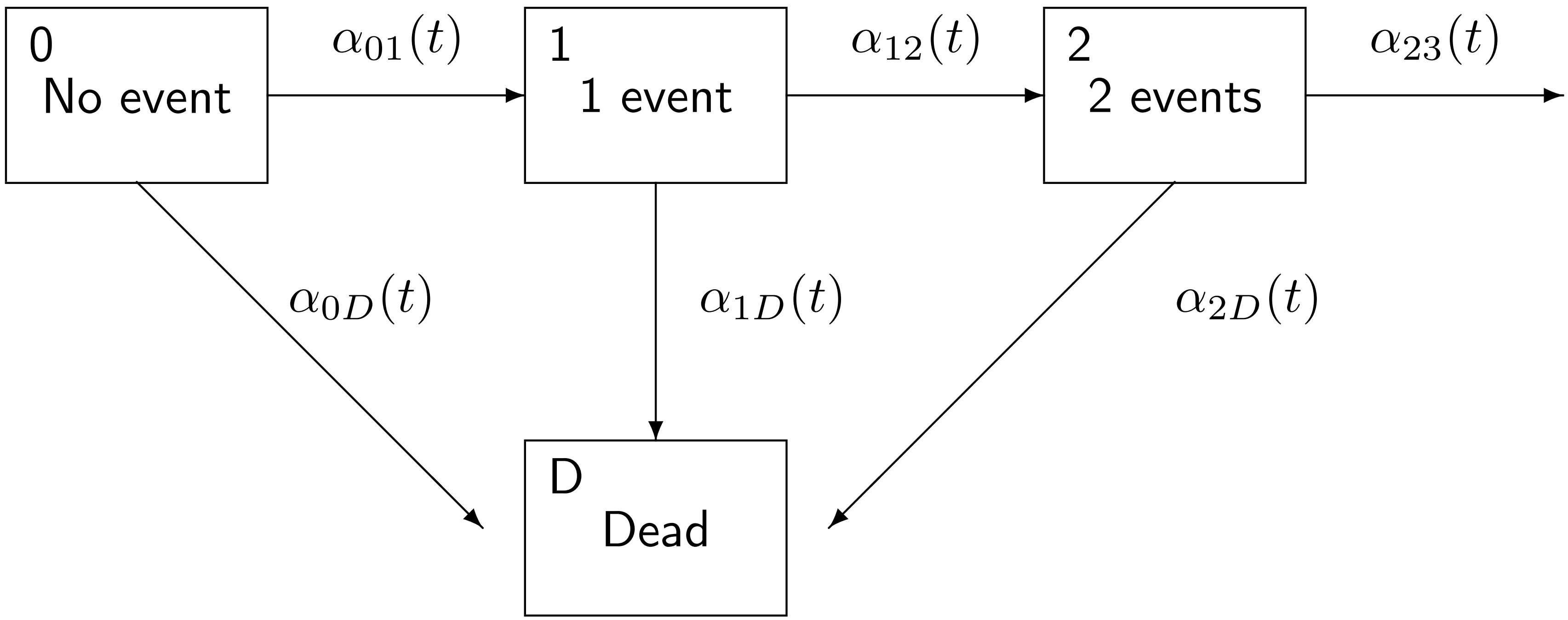
In the two-state survival model: $\varepsilon_1(t_0) = \int_0^{t_0} Q_1(t)dt$ is the expected time lost before time t_0, i.e., $t_0 - E(\min(T, t_0))$.

In the competing risks model,

$$\varepsilon_h(t_0) = \int_0^{t_0} Q_h(t)dt$$

is the expected time lost 'due to cause h' before time t_0.

Recurrent events (with competing risks)



Transition intensities $\alpha_{hj}(t)$ may depend on the past of the process at time t, e.g., number of previous events.

Recurrent events: marginal parameters

The most important marginal parameter is

$$\mu(t) = E(N(t)) = \int_0^t S(u)\alpha^*(u)du,$$

with $N(t) =$ number of events in $[0, t]$, and $\alpha^*(\cdot)$ the *marginal rate function given survival*

$$\alpha^*(t) \approx E(dN(t) \mid T > t)/dt.$$

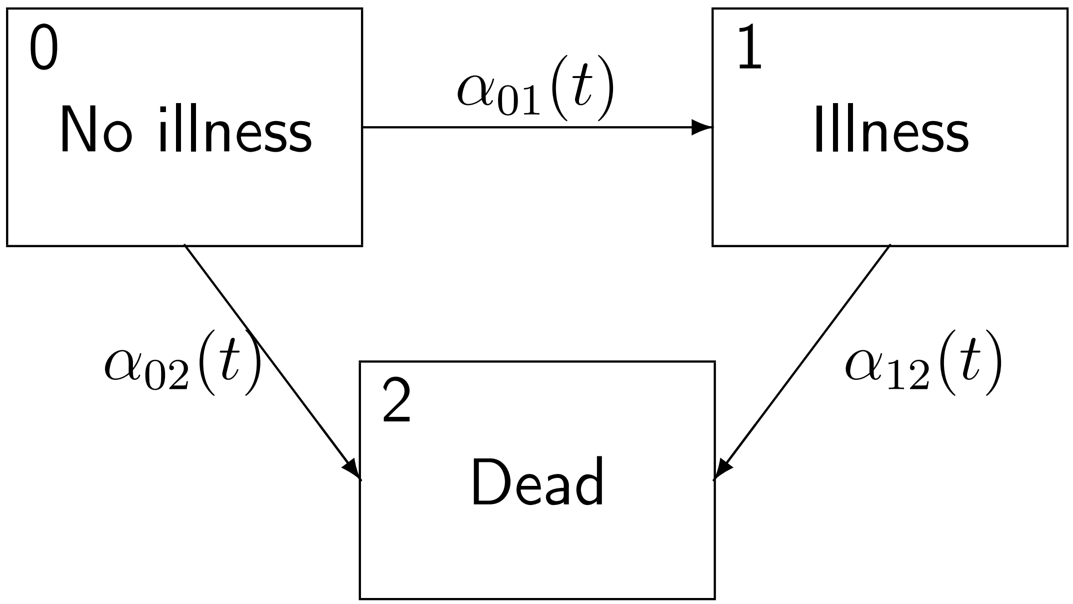
In the model without the final death state, $\mu(t) = \int_0^t \alpha^*(u)du$ with $\alpha^*(\cdot)$ now being the marginal rate function $\alpha^*(t) \approx E(dN(t))/dt$.

However, in principle, there will always be competing risks.

Example: Recurrent episodes in affective disorder

- Kessing, Hansen, Andersen, Angst (2004, *Acta Psych. Scand.*)
- 119 patients with 'unipolar' (depressive, 98) or 'bipolar' (manic-depressive, 21) disorder had their first episode recorded 1959-63 at hospital in Zürich, Switzerland
- Followed up until 1985 with respect to new episodes (on average 5.6) and death (78)
- Purpose: study how repeated episodes is related to on initial diagnosis (unipolar vs. bipolar)

The irreversible illness-death model



PBC-3 trial: no event, liver transplantation, death with or without liver transplantation (‘in principle’ – information after liver transplantation is not available)

Observations

Observation of

$$(V_i(t), t \in [0, \tau_i], i = 1, \ldots, n),$$

(where τ_i is either the time when $V_i(\cdot)$ reaches an *absorbing state*, or a time C_i of *right-censoring*) can be represented by *counting processes*:

$$N_{hji}(t) = \text{ number of direct } h \to j \text{ transitions } (h \neq j)$$

$$\text{observed in } [0, t] \text{ for subject } i = 1, \ldots, n,$$

and *at risk processes*

$$Y_{hi}(t) = \text{ indictor for } i \text{ being observed in state } h \text{ at time } t- .$$

Independent censoring

We will assume throughout that censoring is *independent*, i.e.,

$$\frac{P(V(t+dt)=j \mid V(t)=h, \text{ past for } s<t \textbf{ and } \boldsymbol{C>t})}{dt} \approx \alpha_{hj}(t)$$

(Eq. (1.6)).

In other words, the additional knowledge that, at time t, a subject is not only at risk for a $h \to j$ transition, but also uncensored should not alter the intensities

Censoring by liver transplantation in the PBC-3 trial?