

# Competing Risks and Multistate Models



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Outline, \_\_\_\_\_

## Competing Risks

- » Context & definitions
- » Different **likelihood** functions
- » **Multiple** Decrement Functions and **Identifiability**
- » **Counting Process** & **Asymptotic Results**

## Life-History Processes

- » **Multistate Models**
- » Markov and Modulated **(Semi-)Markov Processes**



- » an underlying **failure time**  $T$  that may be subject to (independent) censoring
- » a vector of possibly **time-dependent** covariates,  $X(t) = \{x(u) : 0 \leq u < t\}$
- » when failure occurs, it may be of any one of  **$m$  distinct types or causes** denoted by  $J \in \{1, 2, \dots, m\}$

As before, the **overall** rate or hazard function at time  $t$  is

$$\lambda[t; X(t)] = \lim_{h \rightarrow 0} h^{-1} \mathbb{P}[t \leq T < t + h \mid T \geq t, X(t)].$$

To model **competing risks**, we consider a **type-specific** or **cause-specific** hazard function or process

$$\lambda_j[t; X(t)] = \lim_{h \rightarrow 0} h^{-1} \mathbb{P}[t \leq T < t + h, J = j \mid T \geq t, X(t)],$$

for  $j = 1, \dots, m$  and  $t > 0$ .



In words,

type-specific hazard function,  $\lambda_j[t; X(t)]$  represents the **instantaneous** rate for failures of type  $j$  at time  $t$  given  $X(t)$  and in the presence of all other failure types.

Without **ties** of the failure types,

$$\lambda[t; X(t)] = \sum_{j=1}^m \lambda_j[t; X(t)].$$

The overall survivor function is

$$F(t; X) = \mathbb{P}[T > t \mid X] = \exp \left\{ - \int_0^t \lambda(u; X) du \right\},$$

and the **(sub)**density function for the **time to a type  $j$  failure** is

$$\begin{aligned} f_j(t : X) &= \lim_{h \rightarrow 0} h^{-1} \mathbb{P}[t \leq T < t + h, J = j \mid X] \\ &= \lambda_j(t; X) F(t; X), \quad j = 1, \dots, m. \end{aligned}$$



When the covariates are of the **fixed** or **external** type,

the likelihood on a sample subject to **independent right censorship** is written as a product of the **survivor functions** for the censored data and the **subdensities** for the observed failure times, i.e., the likelihood function can be written entirely in terms of the **type-specific hazard functions**.

The **cumulative incidence function** for type  $j$  failures corresponding to the **external** covariate is

$$\begin{aligned}\bar{F}_j(t; X) &= \mathbb{P}[T \leq t, J = j; X] \\ &= \int_0^t f_j(u; X) du, \quad t > 0,\end{aligned}$$

for  $j = 1, \dots, m$ . Note that

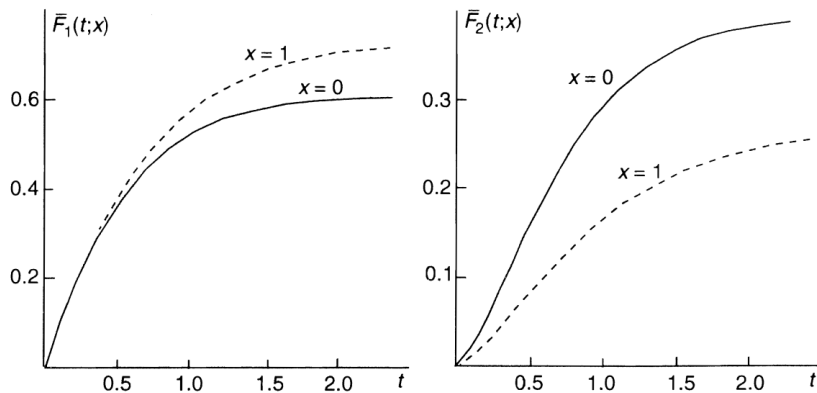
$$p_j = \mathbb{P}[J = j] = \lim_{t \rightarrow \infty} \bar{F}_j(t; X), \quad j = 1, \dots, m$$

and  $\sum_{j=1}^m p_j = 1$ .



$F_j(t; X)$  has **no** simple probability interpretation within the **competing risks** model, at least not without introducing strong additional assumptions.

**Example 8.1.** Suppose that  $m = 2$  and that the covariate is a treatment indicator  $x = 0, 1$ .



**Figure 8.1** Cumulative incidence functions for Example 8.1.



# Likelihoods

Consider  $\{t_i, \delta_i, j_i, X_i(t_i)\}_{i=1}^n$ .

If the **censoring is independent**, the likelihood (or partial likelihood) is proportional to

$$\begin{aligned} L &= \prod_{i=1}^n \left( \{\lambda_{j_i}[t_i; X_i(t_i)]\}^{\delta_i} \prod_{j=1}^m \exp \left\{ - \int_0^{t_i} \lambda_j[u; X_i(u)] du \right\} \right) \\ &= \prod_{j=1}^m \left( \{\lambda_j[t_i; X_i(t_i)]\}^{\delta_{ji}} \exp \left\{ - \int_0^\infty \sum_{i=1}^n Y_i(t) \lambda_j[t; X_i(t)] dt \right\} \right). \end{aligned}$$

Any of the methods of preceding chapters can be used for inference about the  $\lambda_j[t; X(t)]$ 's.



We can also generalize simple explanatory methods such as [Kaplan-Meier](#) and [Nelson-Aalen](#) estimators to [competing risks data](#).

Let  $t_1 < t_2 < \dots < t_k$  denote the  $k$  distinct failure times for all failure types combined. Then, the likelihood function can be written

$$L = \prod_{i=1}^k \left( \prod_{j=1}^m \{[F_j(t_i^-) - F_j(t_i)]F(t_i^-)\}^{d_{ji}} \prod_{l=1}^{C_i} [F(t_{il})]^{c_{il}} \right).$$

Its nonparametric MLE places mass only at the observed failure times  $1, \dots, k$ , so the partially maximized likelihood can be rewritten using expressions for discrete models, to obtain

Multinomial likelihood : 
$$\hat{L} = \prod_{i=1}^k \left[ \prod_{j=1}^m \lambda_{ji}^{d_{ji}} (1 - \lambda_i)^{n_i - d_i} \right].$$





Maximization of the multinomial likelihood gives the MLE  $\hat{\lambda}_{ji} = d_{ji}/n_i$ .

The **cumulative hazard function** is then estimated by

$$\hat{\Lambda}_j(t) = \sum_{i=1}^k \mathbf{1}(t_i \leq t) d_{ji}/n_i, \quad t \geq 0.$$

- » This yields the **Nelson-Aalen** estimate of the total cumulative hazard and the **Kaplan-Meier** estimate of the overall survivor function  $F(t)$ .

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The estimated **cumulative incidence function** is also discrete, and is given by

$$\hat{\bar{F}}_j(t) = \sum_{\{i | t_i \leq t\}} d_{ji} n_i^{-1} \hat{F}(t_i^-), \quad j = 1, \dots, m.$$



# Likelihoods

Consider now a relative risk or Cox model for the **cause-specific hazard functions**

$$\lambda_j[t; X(t)] = \lambda_{0j}(t) \exp\{Z(t)^\top \beta_j\}, \quad j = 1, \dots, m.$$

The corresponding partial likelihood is

$$L(\beta) = \prod_{j=1}^m \prod_{i=1}^{k_j} \frac{\exp\{Z_{ji}(t_{ji})^\top \beta_j\}}{\sum_{l \in R(t_{ji})} \exp\{Z_l(t_{ji})^\top \beta_j\}}.$$

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If applicable, a **proportional** risks model

$$\lambda_j[t; X(t)] = \lambda_0(t) \exp\{\gamma_j + Z(t)^\top \beta_j\}, \quad j = 1, \dots, m,$$

would yield more efficient  $\beta_j$  estimators, in which the **cause-specific hazards** are assumed to be **proportional** to each other (for uniqueness set  $\gamma_1 = 0$ ).



# Likelihoods

The partial likelihood of the **proportional** risk model can then be written

$$\prod_{i=1}^k \frac{\exp\{\gamma_{\mathbf{j}_i} + \mathbf{Z}_i(t_i)^\top \boldsymbol{\beta}_{\mathbf{j}_i}\}}{\sum_{\mathbf{j}=1}^m \sum_{l=1}^n Y_l(t_i) \exp\{\gamma_{\mathbf{j}} + \mathbf{Z}_l(t_i)^\top \boldsymbol{\beta}_{\mathbf{j}}\}}.$$

As is the general relative risk model,  
an adjustment is needed to handle **tied** failure times.

Although it would often be more restrictive than is desirable, the **proportional risk model** has some attractive properties. For instance, the **probability** that an individual with fixed covariate  $\mathbf{Z}$  has failure type  $\mathbf{j}$  is

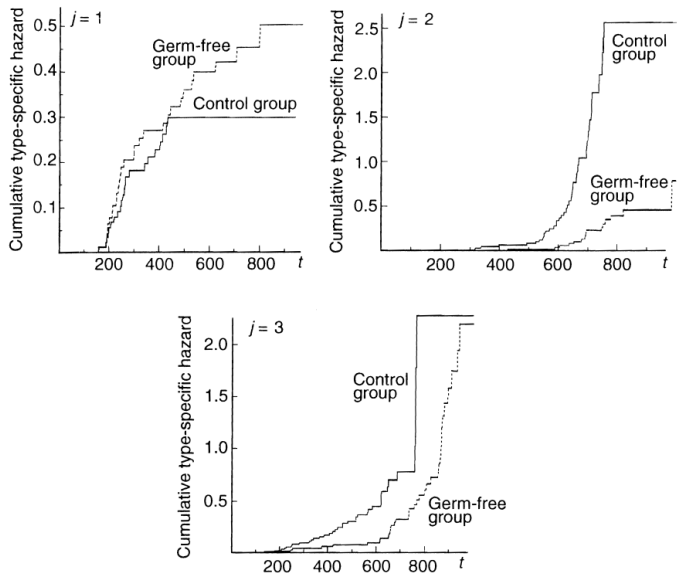
$$\mathbb{P}[\mathbf{J} = \mathbf{j}; \mathbf{Z}] = \frac{\exp\{\gamma_{\mathbf{j}} + \mathbf{Z}^\top \boldsymbol{\beta}_{\mathbf{j}}\}}{\sum_{\mathbf{h}=1}^m \exp\{\gamma_{\mathbf{h}} + \mathbf{Z}^\top \boldsymbol{\beta}_{\mathbf{h}}\}}, \quad \mathbf{j} = 1, \dots, m,$$

regardless of  $\lambda_0(\cdot)$ .

The corresponding MLEs of the proportionality factors  $\exp\{\gamma_{\mathbf{j}}\}$ , subject to  $\gamma_1 = 0$ , are  $\exp\{\hat{\gamma}_{\mathbf{j}}\} = k_{\mathbf{j}}/k_1$ ,  $\mathbf{j} = 2, \dots, m$ .



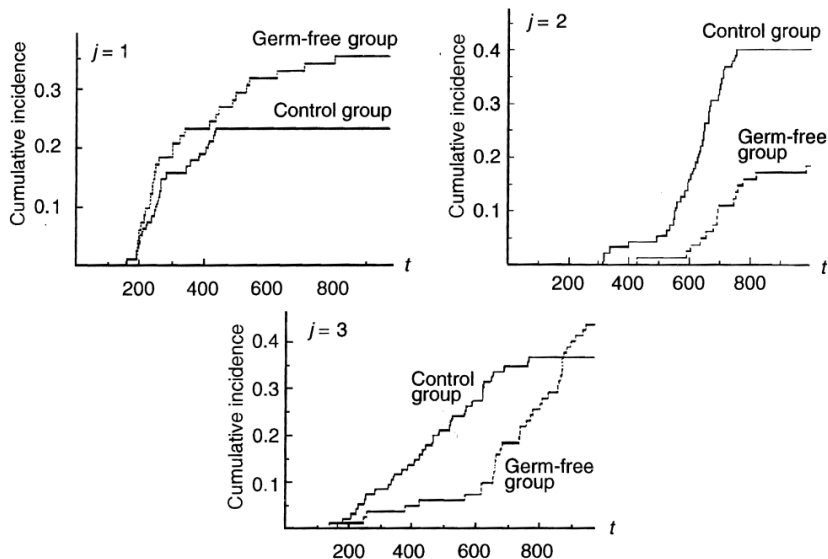
## Example 8.2, $m = 3$ .



**Figure 8.2** Estimates of the cumulative type-specific hazard functions for the data of Example 8.2.



## Example 8.2, $m = 3$ .



**Figure 8.3** Estimates of the cumulative incidence functions (8.11) for the data of Example 8.2.



# Multiple Decrement Function

**Idea:** A joint distribution for the latent failure times,  $\bar{T}_1, \dots, \bar{T}_m$ .

The **multiple decrement function** or **joint survivor function**,

$$Q(t_1, \dots, t_m; x) = \mathbb{P}[\bar{T}_1 > t_1, \dots, \bar{T}_m > t_m; x].$$

- » This model gives a complete specification of the probability laws for the  $m$  variate failure time model.
- » Thus, quantities introduced earlier can be expressed in terms of  $Q$ , such as the **overall survivor function**

$$F(t; x) = \mathbb{P}[T > t; x] = Q(t, t, \dots, t; x),$$

and the **type-specific hazard functions**

$$\begin{aligned} \lambda_j(t; x) &= \lim_{\Delta t \rightarrow 0} \frac{\mathbb{P}[t \leq T_j < t + \Delta t \mid T \geq t; x]}{\Delta t} \\ &= \frac{-\partial \log Q(t_1, \dots, t_m; x)}{\partial t_j} \bigg|_{t_1 = \dots = t_m = t}, \end{aligned}$$

$$j = 1, \dots, m.$$



# Nonidentifiability

Quantities that cannot be expressed as functions of the **type-specific hazard functions**, are **nonidentifiable**, and so, cannot be estimated without introducing additional model assumptions.

e.g.,

» the **marginal survivor functions** are generally **nonidentifiable**.

» **why?**

We don't know the **dependence structure** of the latent failure times.



## how 2 solve

### Nonidentifiability of the marginal survivor functions

- » With a **internal time-dependent covariate**  $\tilde{x}_j(t)$ , that given other variables in the model, are highly predictive of the rate of type  $j$  failures
  - » A test for **no** association between  $\tilde{x}_j(t)$  and the failure rate for type  $j'$  failures

### Dependent censoring

- » Insertion of a **time-dependent covariate**
  - » If the censoring mechanism were well explained by the **time-dependent covariate**, the censoring scheme would become **independent**.

Possible problem? Confounding.





# Counting Processes & Asymptotic Results

Under independent censoring and the other conditions that we **already** know,

$$\mathbb{P}[dN_{jl}(t) = 1 \mid \mathcal{F}_{t-}] = Y_l(t)\lambda_j[t; X_l(t)]dt$$

for  $0 < t$  and all  $l, j$ . It follows that

$$M_{jl}(t) = N_{jl}(t) - \int_0^t Y_l(u)\lambda_j[u; X_l(u)]du, \quad j = 1, \dots, m, \quad l = 1, \dots, n$$

are orthogonal **martingales** wrt the filtration  $\mathcal{F}_t$ .

The score vector is expressed as a stochastic integral of a predictable process wrt a martingale, where

$$\begin{aligned} U_j(t) &= \int_0^t \sum_{l=1}^n [Z_l(u) - \mathcal{E}(\beta_j, u)] dN_{jl}(u) \\ &= \int_0^t \sum_{l=1}^n [Z_l(u) - \mathcal{E}(\beta_j, u)] dM_{jl}(u), \quad j = 1, \dots, m, \end{aligned}$$

$t > 0$  and  $\mathcal{E}(\beta_j, u)$  is the weighted average of  $Z_l(u)$  over the risk set as before.



The score process  $U(t)$  is a martingale whose predictable variation process can be seen to be a block diagonal matrix.

The asymptotic arguments and results of Chapter 5 apply directly here.

To finish the competing risks part,

- » The Nelson-Aalen estimator for the  $j$ th failure type can be written as

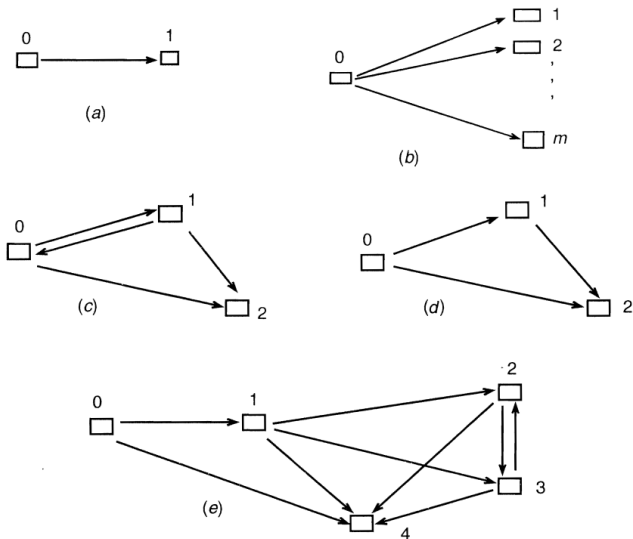
$$\hat{\Lambda}_{0j}(t) = \int_0^t \frac{dN_{j\cdot}(u)}{\sum_{l=1}^n Y_l(u) \exp\{Z_l(u)^\top \hat{\beta}_j\}}.$$

- » In the case of external (or fixed) covariates, estimators of the baseline cumulative incidence functions can be obtained as

$$\hat{\tilde{F}}_{0j}(t) = \int_0^t \exp\left\{-\sum_{j'=1}^m \hat{\Lambda}_{0j'}(u)\right\} d\hat{\Lambda}_{0j}(u).$$



# Multistate Models



**Figure 8.4** Compartment illustrations of multistate models for (a) failure time process; (b) competing risks; (c) illness-death model; (d) progressive illness death model; and (e) HIV, AIDS, and opportunistic infections.

# Markov Processes

First, with no covariates

Let the Markov process  $A(t)$  be the state occupied at time  $t$ ,  $t > 0$ .

The **transition rate** or **intensity** from  $i$  at time  $t^-$  to  $j$  at time  $t$  is given by the **memoryless** process

$$\begin{aligned} d\Lambda_{ij}(t) &= \mathbb{P}[A(t^- + dt) = j \mid A(u), 0 \leq u < t, A(t^-) = i] \\ &= \mathbb{P}[A(t^- + dt) = j \mid A(t^-) = i]. \end{aligned}$$

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It is convenient to define

$$d\Lambda_{ii}(t) = - \sum_{j \neq i} d\Lambda_{ij}(t)$$

so that the row sums of the matrix

$$d\Lambda(t) = [d\Lambda_{ij}(t)]_{q \times q}$$

are all 0.



# $r$ -step transition probability matrix

## Discrete case

$$\begin{aligned} \mathbf{P}^{(r)} &= \prod_{k=1}^r \mathbf{P}_k = \mathbf{P}_1 \mathbf{P}_2 \dots \mathbf{P}_r, \quad r = 0, 1, \dots, \\ &= \prod_{k=1}^r [I + d\Lambda(a_k)] = \prod_{k=1}^r (\mathbb{P}[A(a_k) = \textcolor{red}{j} \mid A(a_k^-) = \textcolor{red}{i}])_{q \times q} \\ &= (p_{ij}^r)_{q \times q} = (\mathbb{P}[A(a_r) = \textcolor{red}{j} \mid A(0) = \textcolor{red}{i}])_{q \times q}. \end{aligned}$$

## Continuous case

$$\begin{aligned} \mathbf{P}(t) &= (\mathbb{P}_{ij}(t))_{q \times q} = (\mathbb{P}[A(t) = \textcolor{red}{j} \mid A(0) = \textcolor{red}{i}])_{q \times q} \\ &= \mathcal{P}_0^t[I + d\Lambda(u)] = \lim_{M \rightarrow \infty} \prod_{i=1}^M [I + \Lambda(u_i) - \Lambda(u_{i-1})], \end{aligned}$$

where the limit is taken as  $M \rightarrow \infty$  and  $\Delta u_i = u_i - u_{i-1} \rightarrow 0$ .



## Transition probabilities in different scenarios

**Failure time model:**  $\hat{\mathbb{P}}_{00}(t)$  is the Kaplan-Meier estimate of the survivor function.

**Competing risks model:**  $\hat{\mathbb{P}}_{0j}(t) = \hat{\bar{F}}_j(t)$ , the estimates of the  $j$ th cumulative incidence function.

Now, with time-dependent covariates, i.e.,  
Continuous-time modulated Markov models

Intensity function,

$$\lambda_{ijl}(t) = \lim_{h \rightarrow 0} h^{-1} \mathbb{P}[A_l(t^- + h) = j \mid A(t^-) = i, X_l(u), 0 < u < t].$$



# Continuous-time modulated Markov models

## Parametric model

With  $\mathbb{P}[dN_{ijl}(t) = 1 \mid \mathcal{F}_{t-}] = Y_{il}(t)\lambda_{ijl}(t)$ ,  
the full log-likelihood on data over the interval  $[0, \tau]$  is

$$\log L_M = \sum_{i \neq j} \left\{ \int_0^\tau \sum_{l=1}^n [\log \lambda_{ijl}(t; \theta) dN_{ijl}(t) - Y_{il}(t) \lambda_{ijl}(t; \theta) dt] \right\}.$$

## Semiparametric relative risk model

With a contribution term to the partial likelihood given by

$$\mathbb{P}[dN_{ijl}(t) = 1 \mid dN_{ij\cdot}(t) = 1, \mathcal{F}_{t-}] = \frac{Y_{il}(t) \exp\{Z_l(t)^\top \beta_{ij}\}}{\sum_{u=1}^n Y_{iu}(t) \exp\{Z_u(t)^\top \beta_{ij}\}}.$$



# Continuous-time modulated Markov models

The log partial likelihood is then

$$\sum_{\text{all } i,j} \left\{ \int_0^\tau \sum_{l=1}^n Z_l(t)^\top \beta_{ij} dN_{ijl}(t) - \log \left[ \sum_{l=1}^n Y_{il}(t) \exp\{Z_l(t)^\top \beta_{ij}\} dN_{ij.}(t) \right] \right\}.$$

The procedures that we [already know](#), can be used for estimation here. The [asymptotics](#) follows the general results outlined in Chapter [5](#).





The modulated Markov model uses **time since on study** as the basic time variable. In some instances, however, there may be a strong dependence on **time since entry to a state**. Such dependencies can be accommodated by considering

### modulated semi-Markov models

**key:** time since the individual entered the stated occupied at time  $t^-$ ,  
 $B(t) = \inf[s \mid A(t-s) \neq A(t^-)]$ .

With covariates and under a **parametric model**, the likelihood can be written as

$$\log L_{SM} = \sum_{i \neq j} \sum_{l=1}^n \left\{ \int_0^{\infty} \log \lambda_{ijl}[B_l(t); \theta] dN_{ijl}(t) - Y_{il}(t) \lambda_{ijl}[B_l(t); \theta] dt \right\}.$$



# Modulated Semi-Markov Models

Now, under a **relative risk model** and partial likelihood analysis with

- »  $\nu = B_l(t)$  representing the current sojourn time;
- » and with the idea of having the **s**th visit to state **i**.

The log partial likelihood can be written

$$\begin{aligned} \log L = & \sum_{l=1}^n \int_0^\infty Z_l(a_{ijl} + \nu)^\top \beta_{ijs} dN_{ijsl}^*(\nu) \\ & - \int_0^\infty \log \left\{ \sum_{u=1}^n Y_{isu}^* \exp\{Z_u(a_{isu} + \nu)^\top \beta_{ijs}\} \right\} dN_{ijs}^*(\nu), \end{aligned}$$

where  $a_{isl}$  is the time at which individual  $l$  enters the state **i** for the **s**th time.



