Principled Estimation and Prediction with Competing Risks: a Bayesian Nonparametric Approach

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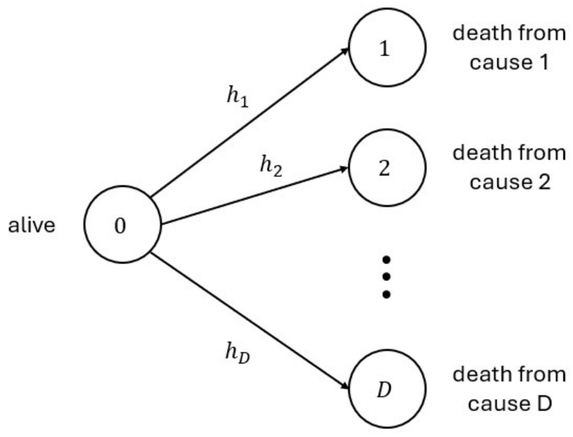
Competing risks in survival analysis

In **survival analysis**, researchers may be interested in different types of events (sources of risk), which are **competing events** if the occurrence of an event prevents the occurrence of other events [4].

Multi–state approach to competing risks

Competing risks data are modelled through multi–state models with a transient state (**alive**) and multiple absorbing states (**causes of death**):



- the **time-to-event** $T \in \mathbb{R}^+$ is the **time of transition** away from state 0;
- the **cause of death** $\Delta \in \{1, \dots, D\}$ is the target **absorbing state**;
- the cause–specific **hazard rates** $h_1(t)$, $\dots, h_D(t)$ are the **transition rates**.

Functionals of interest in competing risks

The main quantities of interest in a competing risks framework are:

- the **survival function**, i.e. the probability of surviving every competing event up to a certain time,

$$S(t) = \mathbb{P}(T \geq t) = \exp\left(- \sum_{\delta=1}^{D} \int_0^t h_\delta(u)\, du \right);$$

- the cause–specific **cumulative incidence functions**, i.e. probabilities of experiencing a certain type of event within a certain time;
- **(prediction viewpoint)** the probabilities of experiencing a certain type of event, given the survival time, termed prediction curves,

$$\pi_\delta(t) = \mathbb{P}(\Delta = \delta \mid T = t), \qquad \delta = 1, \dots, D.$$

Modeling mixture hazard rates

In a Bayesian setting, a prior is defined over **hazard rate functions** [3], i.e. the instantaneous risks of occurrence of each competing event, given survival up to that time:

$$\tilde{h}_\delta(t) = \int_{\mathbb{R}^+} k(t; x)\, \tilde{\mu}_\delta(dx), \qquad \delta = 1, \dots, D,$$

where $k(t, x)$ is a deterministic kernel and $\tilde{\mu}_1, \dots, \tilde{\mu}_D$ are random measures.

The model for an **exchangeable sequence** of time-to-event and event type pairs is

$$(T_1, \Delta_1), \dots, (T_n, \Delta_n) \mid \tilde{\boldsymbol{\mu}} \overset{\text{i.i.d.}}{\sim} \tilde{p}, \qquad \tilde{\boldsymbol{\mu}} = (\tilde{\mu}_1, \dots, \tilde{\mu}_D) \sim \mathcal{Q},$$

where the directing random probability measure $\tilde{p}$ depends on random measures through hazard rates:

$$\tilde{p}(dt, \delta) = \underbrace{\int_{\mathbb{X}} k(t; x)\, \tilde{\mu}_\delta(dx)}_{\text{hazard rate for cause } \delta} \exp\left(- \sum_{\ell=1}^{D} \int_0^t \underbrace{\int_{\mathbb{X}} k(s; x)\, \tilde{\mu}_\ell(dx)}_{\text{hazard rate for cause } \ell} ds \right) dt.$$

Hierarchical prior specification

The prior specification $\mathcal{Q}$ introduces dependence among hazard rates through a **hierarchical structure** of completely random measures [2]:

$$\tilde{\mu}_1, \dots, \tilde{\mu}_D \mid \tilde{\mu}_0 \overset{\text{i.i.d.}}{\sim} \text{CRM}(\tilde{\nu}), \qquad \tilde{\mu}_0 \sim \text{CRM}(\nu_0),$$

having homogeneous **Lévy intensities**

$$\tilde{\nu}(ds, dx) = \rho(ds)\, \tilde{\mu}_0(dx), \qquad \nu_0(ds, dx) = \rho_0(ds)\, P_0(dx).$$

A natural choice for hierarchical CRMs is the **hierarchical gamma** process.

Latent variables and partition structure

The marginal, predictive and posterior distributions are conveniently described via the introduction of two sequences of **latent variables**:

$$\boldsymbol{X} = (X_1, \dots, X_n), \qquad \boldsymbol{Z} = (Z_1, \dots, Z_n).$$

Because of the discreteness of CRMs, variables in each sequence admit **ties** with positive probability → **nested partition structure** (Chinese restaurant franchise metaphor [5]).

Posterior characterization

The posterior distribution of random measures, given observations and latent variables, is **structurally conjugate**, as the hierarchical form is preserved a posteriori:

$$\tilde{\mu}_\delta(dx) \mid (\boldsymbol{T}, \boldsymbol{\Delta}, \boldsymbol{X}, \boldsymbol{Z}),\ \tilde{\mu}_0 \ \sim\ \tilde{\mu}^*(dx) + \sum_{j=1}^{k} \sum_{h=1}^{r_{dj}} J_{djh}\, \delta_{X_j^*}(dx),$$

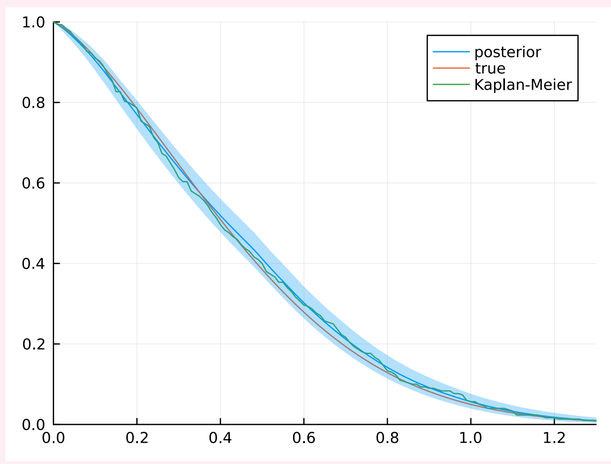
$$\tilde{\mu}_0(dx) \mid (\boldsymbol{T}, \boldsymbol{\Delta}, \boldsymbol{X}, \boldsymbol{Z}) \ \sim\ \tilde{\mu}_0^*(dx) + \sum_{j=1}^{k} I_j\, \delta_{X_j^*}(dx),$$

where $\tilde{\mu}^*$ and $\tilde{\mu}_0^*$ are CRMs with **non–homogeneous** Lévy intensities, while J_{djh}'s and I_j's are **independent** random variables.

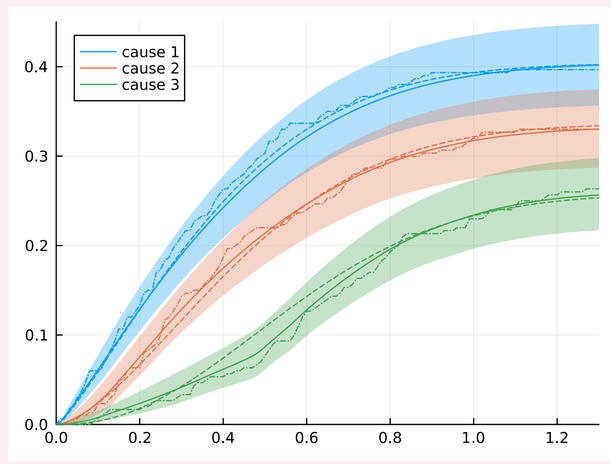
Numerical illustration on simulated data

Consider three **independent** competing risks and record the minimum time–to–event and the corresponding event type, for $n = 300$ observations.

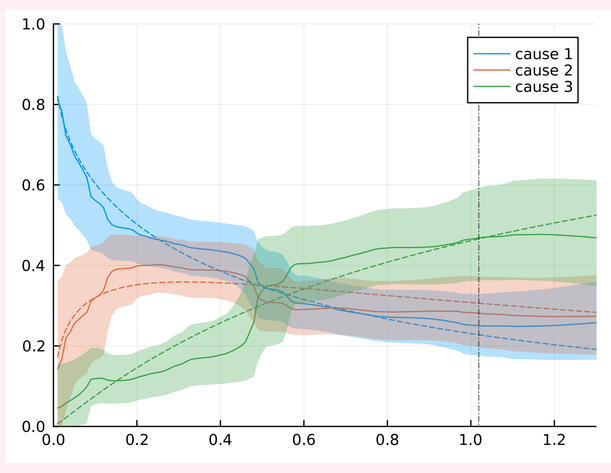
Survival function



Cumulative incidence functions



Prediction curves



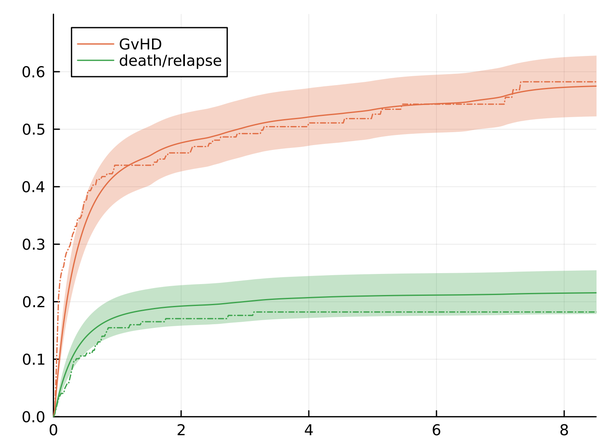
- **Full conditional distributions** of latent variables $(\boldsymbol{X}, \boldsymbol{Z})$ are derived from the marginal distribution, and exploited to devise a **Gibbs sampling scheme**.
- **Posterior estimates** of quantities of interest are obtained at each step, conditionally on latent variables.

Application to bone marrow transplant data

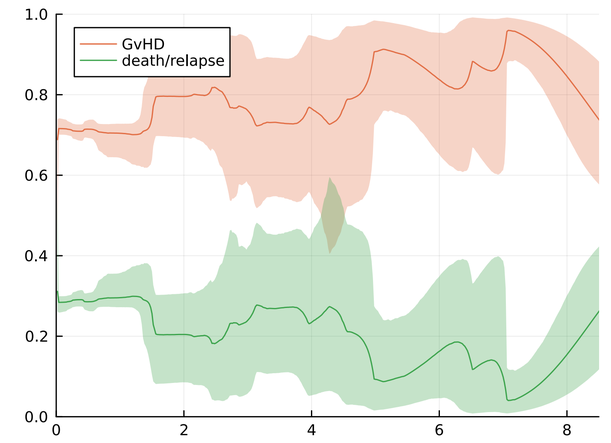
The dataset includes data for 400 patients diagnosed with acute **myeloid leukemia**, who underwent a bone marrow transplantation:

- the primary event of interest is occurrence of **Graft–versus–Host-Disease** (GvHD);
- **death or relapse** without GvHD are competing events.

Cumulative incidence functions



Prediction curves



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