A multistate additive relative survival semi-Markov model

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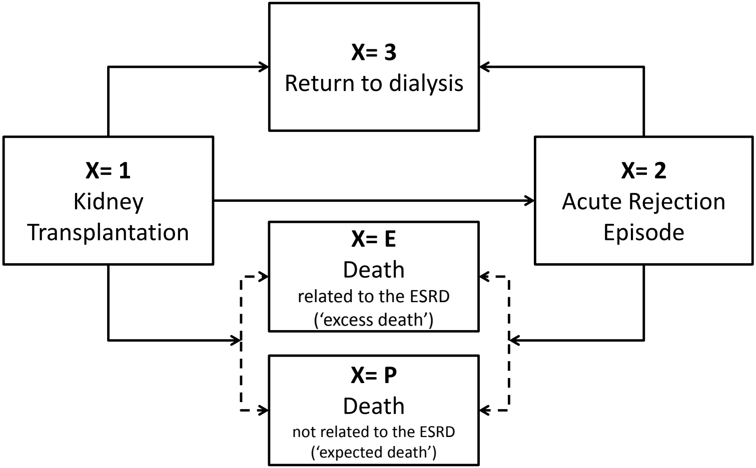
27 August 2014

Motivating example : kidney transplantation



ESRD=End Stage Renal Disease

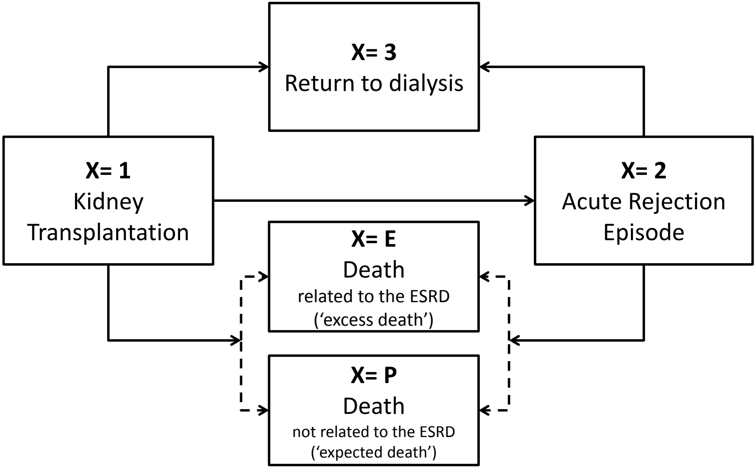
The idea

- multiple time-to-events data (disease progression, death)
  ⇒ multistate models
- association with excess death associated to the disease
  ⇒ relative survival analysis *
- litterature
  - Belot et al. [2011] : competing risks + relative survival (excess mortality related to colon cancer)
  - Huszti et al. [2012] : Markov NH + relative survival (excess mortality related to colon cancer in an illness-death model)

⇒ Gillaizeau et al. [2014] : **semi-Markov additive relative survival model (SMRS)**

* Hakulinen and Tenkanen [1987], Esteve et al. [1990], Perme et al. [2012]

Additive relative survival



ESRD=End Stage Renal Disease

Notations

- T : chronological time from baseline
- S : duration (or sojourn time) in a state
- $\mathscr{X}$: finite space of the possible clinical states
- ϵ : set of possible transitions ij with $(i,j) \in (\mathscr{X},\mathscr{X})$, with i transient state with $j \neq i$
- X_m : state of the patient after the m-th transition occurring at time T_m, with $T_0 < T_1 < \ldots < T_m$ ($T_0 = 0$ and $X_0 = 1$)
- Z : overall vector of patient characteristics
- Z_{ij} : subvector of characteristics specifically associated to the transition ij

Instantaneous hazard function

semi-Markovian property

transition intensities between two states depend on the duration in the current state

- instantaneous hazard function specific from state $X_m = i$ to the state $X_{m+1} = j$ after a duration s, given patient characteristics $Z_{ij} = z_{ij}$:

$$\lambda_{ij}(s|z_{ij}) = \lim_{\Delta s \to 0^+} \frac{P(s \le T_{m+1} - T_m < s + \Delta s, X_{m+1} = j | T_{m+1} - T_m > s, X_m = i, z_{ij})}{\Delta s}$$

with $\Lambda_{ij}(s|z_{ij}) = \int_0^s \lambda_{ij}(u|z_{ij})\mathrm{d}u$ the corresponding cumulative hazard function.

Expected mortality

- $X = E$: death related to the disease
- $X = P$: death related to other causes
- A : random variable for patient's age at death
- a_i : patient age observed at entry in state i
- y : patient's birthyear
- g : patient's gender

Instantaneous hazard function for the mortality not related to the disease after a duration s in the state i :

$$\lambda_P(s + a_i | y, g) = \lim_{\Delta s \to 0^+} \frac{P(s + a_i \leq A < s + a_i + \Delta s, X = P | A > s + a_i, y, g)}{\Delta s}$$

$\Rightarrow$ calculated from life tables
(available by calendar year × birthdate × gender)

Observed mortality

Instantaneous hazard function :

$$\lambda_{iO}(s|z_{iE}, a_i, y, g) = \lambda_{iE}(s|z_{iE}) + \lambda_P(s + a_i|y, g)$$

Cumulative hazard :

$$\Lambda_{iO}(s|z_{iE}, a_i, y, g) = \Lambda_{iE}(s|z_{iE}) + \Lambda_P(s + a_i|y, g) - \Lambda_P(a_i|y, g)$$

$\Rightarrow \Lambda_P(s + a_i|y, g) - \Lambda_P(a_i|y, g)$ represents the cumulative hazard of death between age a_i and $a_i + s$ in the general population.

Marginal survival function and subdensity

Probability for a patient to stay at least a duration s in state i :

$$S_{i.}(s|z,a_i,y,g) = exp\left[-\left(\sum_{\substack{j:ij\in\epsilon \\ j\neq \text{death}}} \Lambda_{ij}(s|z_{ij})\right) - \Lambda_{iE}(s|z_{iE}) - \Lambda_P(s+a_i|y,g) + \Lambda_P(a_i|y,g)\right]$$

$\Rightarrow$ density function specific to transition ij, after a duration s :

$$f_{ij}(s|z,a_i,y,g) = \left(\mathbb{1}_{\{j\neq \text{death}\}}\lambda_{ij}(s|z_{ij}) + \mathbb{1}_{\{j=\text{death}\}}\lambda_{iO}(s|z_{iE},a_i,y,g)\right)S_{i.}(s|z,a_i,y,g)$$

Contribution to the likelihood

- s_{ij} : duration time in state i before transition to state j
- $\delta_{ij} = 1$ if the transition ij is observed, $\delta_{ij} = 0$ otherwise

Patient in an absorbing state at his/her last time of follow-up

$$\prod_{ij \in \epsilon} \{f_{ij}(s_{ij}|z, a_i, y, g)\}^{\delta_{ij}}$$

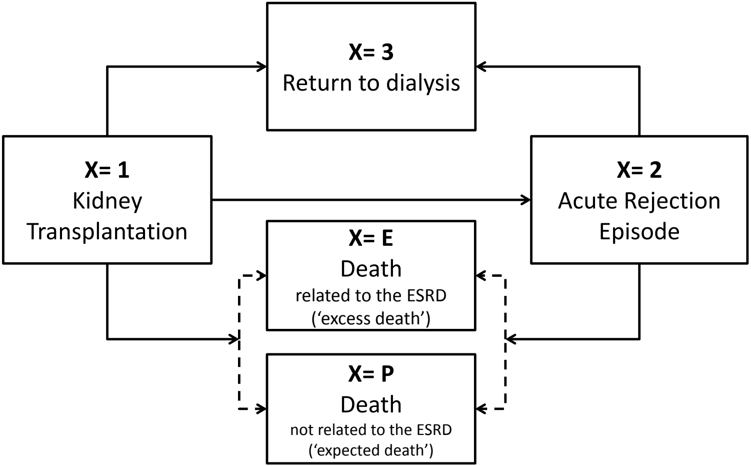
Patient censored in the transient state k (for a duration s_k) at his/her last time of follow-up

$$\prod_{ij \in \epsilon} \{f_{ij}(s_{ij}|z, a_i, y, g)\}^{\delta_{ij}} S_{k.}(s_k|z, a_k, y, g)$$

- $\lambda_{.}(.)$: parametric PH models with time-fixed covariates
- estimations : maximization of the likelihood function + Hessian matrix (Nelder and Mead algorithms)

Performances of 2 models

- SMRS model
- 5-state SM model (causes of death known)



Distributions

Simulations based on kidney transplant recipients data :

- year of entry into the study $\sim$ U([1998 ;2010])
- gender g : men $\sim \mathscr{B}(0.61)$
- explicative variable $z \sim \mathscr{B}(0.30)$
- age a at baseline $\sim$ truncated $\mathscr{N}$ (from 18 to 80 years old) with parameters varying according to g and z

The 5 sojourn time distributions $\sim \mathscr{W}$ depending on (a, g, z).

Scenarios :

- 3 sample sizes (N=500, N=1000, N=3000 subjects)
- 3 censoring rates (15%, 30%, 60%)

Bias and coverage rate

300 simulated samples, N=3000 patients, censoring rate=60%

Coefficient	Theoretical value	Mean estimate		Absolute bias		Coverage rate(%)	
		5 SM	SMRS	5 SM	SMRS	5 SM	SMRS
β_{12} Male	0.160	0.167	0.167	0.007	0.007	93.67	93.67
β_{12} Age	-0.012	-0.012	-0.012	0.000	0.000	96.00	96.00
β_{12} z	0.210	0.216	0.216	0.006	0.006	94.67	94.67
β_{13} Male	-0.160	-0.180	-0.179	-0.020	-0.019	93.67	93.67
β_{13} Age	0.014	0.014	0.015	0.000	0.001	94.33	94.33
β_{13} z	0.910	0.912	0.912	0.002	0.002	97.00	96.67
β_{1E} Male	0.180	0.191	0.193	0.011	0.013	96.67	95.67
β_{1E} Age	-0.050	-0.050	-0.050	0.000	0.000	96.67	96.33
β_{1E} z	0.600	0.590	0.600	-0.010	0.000	94.00	95.67
β_{23} Male	-0.420	-0.413	-0.412	0.007	0.008	96.33	96.33
β_{23} Age	-0.008	-0.008	-0.008	0.000	0.000	97.00	97.00
β_{23} z	0.400	0.408	0.408	0.008	0.008	96.00	96.00
β_{2E} Male	-0.150	-0.122	-0.122	0.028	0.028	96.00	96.67
β_{2E} Age	-0.035	-0.035	-0.035	0.000	0.000	92.33	93.33
β_{2E} z	0.740	0.748	0.762	0.008	0.022	94.67	95.00

Variability

300 simulated samples, N=3000 patients, censoring rate=60%

Coefficient	Theoretical value	RMSE 5 SM	RMSE SMRS	Empiric SE 5 SM	Empiric SE SMRS	Asymptotic SE 5 SM	Asymptotic SE SMRS
β_{12} Male	0.160	0.077	0.077	0.077	0.077	0.075	0.075
β_{12} Age	-0.012	0.003	0.003	0.003	0.003	0.003	0.003
β_{12} z	0.210	0.080	0.080	0.080	0.080	0.077	0.077
β_{13} Male	-0.160	0.158	0.158	0.157	0.158	0.151	0.151
β_{13} Age	0.014	0.007	0.006	0.006	0.006	0.006	0.006
β_{13} z	0.910	0.155	0.155	0.156	0.155	0.151	0.151
β_{1E} Male	0.180	0.170	0.235	0.170	0.235	0.176	0.229
β_{1E} Age	-0.050	0.007	0.010	0.007	0.010	0.007	0.010
β_{1E} z	0.600	0.181	0.235	0.181	0.235	0.180	0.233
β_{23} Male	-0.420	0.224	0.224	0.224	0.224	0.223	0.223
β_{23} Age	-0.008	0.009	0.009	0.009	0.009	0.009	0.009
β_{23} z	0.400	0.232	0.232	0.233	0.233	0.229	0.229
β_{2E} Male	-0.150	0.229	0.283	0.228	0.282	0.235	0.284
β_{2E} Age	-0.035	0.010	0.013	0.010	0.013	0.009	0.012
β_{2E} z	0.740	0.251	0.293	0.251	0.293	0.232	0.284

Conclusion

- Good performances of the SMRS model
  - as good as the SM model where the causes of death are known
  - similar results for other simulation scenarios
- Application to data from kidney transplant recipients (DIVAT cohort, N=5943)

Model	Transition	Coefficient	HR	[95%CI]
SMRS model	$1E$ *(transplantation to death related to the disease)*	Age<35 years	0.06	[0.01 ;0.31]
		Age 35 to 50 years	0.34	[0.19 ;0.61]
		Age 50 to 65 years	0.55	[0.32 ;0.93]
		Male recipient	0.78	[0.53 ;1.16]
		Delayed Graft Function	3.02	[1.96 ;4.64]
4-state SM model	$1O$ *(transplantation to observed death)*	Age<35 years	0.06	[0.03 ;0.13]
		Age 35 to 50 years	0.22	[0.15 ;0.31]
		Age 50 to 65 years	0.45	[0.33 ;0.60]
		Male recipient	1.14	[0.89 ;1.48]
		Delayed Graft Function	1.93	[1.52 ;2.44]

Use and perspectives

- Package R : eSemiMarkov (`www.divat.fr`)
- Model needs extensions :
  - time-dependent variables
  - non-proportional hazards
  - interval-censored data

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Thanks for your attention