A SEMI-MARKOV MODEL WITH INTERVAL CENSORING AND NON-PROPORTIONAL HAZARDS

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Outline

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- Multistate approaches are becoming increasingly used.
- Semi-Markov models explicitly define distributions of waiting times.
- Proportionality of hazards is the most frequently assumption used in order to take into account covariates.
- Objective : The development of a flexible semi-Markov model which does not assume any proportionality of hazards.

Outline

Embedded Markov chain

$$P_{ij} = P(X_{n+1} = j | X_n = i)$$

- If state i is not persistent then $P_{ij} \geq 0$ and $P_{ii} = 0$.
- If state i is persistent then $P_{ij} = 0$ and $P_{ii} = 1$.

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Distribution of waiting times

- $F_{ij}(x) = P(T_{n+1} - T_n \leq x | X_{n+1} = j, X_n = i)$.
- $F_{ij}(x) = F^{(ij)}(x, \varphi_{ij})$. $\Longrightarrow S_{ij}(x),\ f_{ij}(x)$ et $\lambda_{ij}(x)$
- $F_{i.}(x) = P(T_{n+1} - T_n \leq x | X_n = i) = \sum_{j \neq i} F_{ij}(x) P_{ij}$.

Contribution of an r*th* transition for subject h

- Let $d_{h,r} = T_{h,r+1} - T_{h,r}$, the waiting time.
- Right censoring $(d^0_{h,r} \leq d_{h,r})$: $\sum_{j \neq i} P_{ij} S_{ij}(d^0_{h,r})$.
- Interval censoring $(d^0_{h,r} < d_{h,r} \leq d^1_{h,r})$: $P_{ij}(S_{ij}(d^0_{h,r}) - S_{ij}(d^1_{h,r}))$.
- Left censoring $(d_{h,r} \leq d^1_{h,r})$: $P_{ij} F_{ij}(d^1_{h,r})$.
- Time exactly observed $P_{ij} f_{ij}(d_{h,r})$.

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Contribution of the initial observation for the subject h

- multinomial logistic regression :

$$P(X_{h,1} = j) = \frac{exp(\gamma_{0j} + \beta_{0j} z_{h,0j})}{\sum_{k=1}^{c} exp(\gamma_{0k} + \beta_{0k} z_{h,0k})} \quad \text{for } j = 1, .., c$$

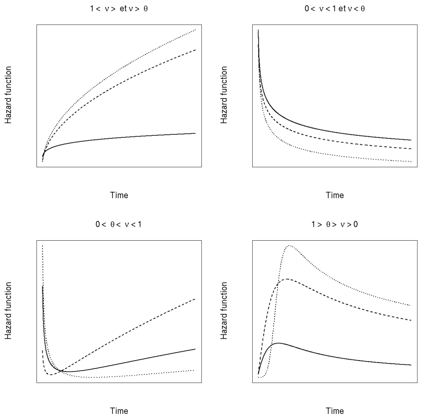
logLikelihood

$$
\begin{aligned}
ln\mathcal{L} &= \sum_{h} \Big\{ \gamma_{0x_{h,1}} + \beta_{0x_{h,1}} z_{h,0x_{h,1}} - ln(\sum_{i=1}^{c} exp(\gamma_{0i} + \beta_{0i} z_{h,0x_{h,1}})) \\
&+ \sum_{ij} \sum_{X_{h,r}=i, X_{h,r+1}=j} \Big\{ \delta^{E}_{h,r} \big[ln\, P_{ij} + ln\, S_{ij}(d_{h,r}) + ln\, \lambda_{ij}(d_{h,r}) \big] \\
&+ \delta^{I}_{h,r} \big[ln\, P_{ij} + ln(S_{ij}(d^{0}_{h,r}) - S_{ij}(d^{1}_{h,r})) \big] \Big\} \\
&+ \sum_{i} \sum_{X_{h,r}=i} \Big\{ \delta^{R}_{h,r} \big[ln(\sum_{j \neq i} P_{ij} S_{ij}(d^{0}_{h,r})) \big] \Big\} \Big\}
\end{aligned}
$$

where $\gamma_{0c} = \beta_{0c} = 0$.

Generalised Weibull distribution ($\nu_{ij}, \sigma_{ij}, \theta_{ij} > 0$)

- Hazard, $\lambda_{ij}(x) = \frac{1}{\theta_{ij}}\left(1 + (\frac{x}{\sigma_{ij}})^{\nu_{ij}}\right)^{\frac{1}{\theta_{ij}}-1} \frac{\nu_{ij}}{\sigma_{ij}}\left(\frac{x}{\sigma_{ij}}\right)^{\nu_{ij}-1}$
- Survival, $S_{ij}(x) = exp\left(1 - (1 + (\frac{x}{\sigma_{ij}})^{\nu_{ij}})^{\frac{1}{\theta_{ij}}}\right)$



Incorporation of covariates (PH)

- Proportional Hazard (PH) assumption.

$$S_{ij}(x, \eta_{h,ij}^{PH}) = S_{0,ij}(x)^{exp(\eta_{h,ij}^{PH})}$$

$$\lambda_{ij}(x, \eta_{h,ij}^{PH}) = \lambda_{0,ij}(x) exp(\eta_{h,ij}^{PH})$$

- Respect of the PH assumption.

  plotting $log(-log(S_{ij}(x)))$ against the survival time x.

Flexible incorporation of covariates

$$S_{ij}\left(x, \eta_{h,ij}^{AFT}(x), \eta_{h,ij}^{NPH}(x)\right) = S_{0,ij}\left(xexp(\eta_{h,ij}^{AFT}(x))\right)^{exp(\eta_{h,ij}^{NPH}(x))}$$

$$\begin{aligned}\lambda_{ij}\left(x, \eta_{h,ij}^{AFT}(x), \eta_{h,ij}^{NPH}(x)\right) &= exp\left(\eta_{h,ij}^{NPH}(x)\right)\left\{\lambda_{0,ij}\left(xexp(\eta_{h,ij}^{AFT}(x))\right)exp(\eta_{h,ij}^{AFT}(x))\right. \\ \times(1 + x\frac{\partial\eta_{h,ij}^{AFT}(x)}{\partial x}) &- \left.\frac{\partial\eta_{h,ij}^{NPH}(x)}{\partial x}\left(1 - \left(1 + \left(\frac{xexp(\eta_{h,ij}^{AFT}(x))}{\sigma_{ij}}\right)^{\nu_{ij}}\right)^{\frac{1}{\theta_{ij}}}\right)\right\}\end{aligned}$$

If $\eta_{h,ij}^{AFT}(x) = 0$ and $\eta_{h,ij}^{NPH}(x) = \eta_{h,ij}^{NPH}$ then $\lambda_{ij}(x, \eta_{h,ij}^{PH}) = \lambda_{0,ij}(x)exp(\eta_{h,ij}^{PH})$
If $\eta_{h,ij}^{AFT}(x) = \eta_{h,ij}^{AFT}$ and $\eta_{h,ij}^{NPH}(x) = 0$ then $\lambda_{ij}(x, \eta_{h,ij}^{PH}) = \lambda_{0,ij}(xexp(\eta_{h,ij}^{AFT}))exp(\eta_{h,ij}^{AFT})$

Time varying effects

- Polynomial function

$$\eta_{h,ij}^{NPH}(x) = \beta_{ij}^{(1)} z_{h,ij} + \beta_{ij}^{(2)} z_{h,ij} x + \beta_{ij}^{(3)} z_{h,ij} x^2$$

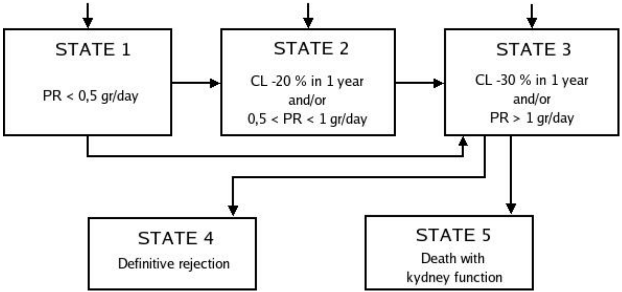
$$\eta_{h,ij}^{AFT}(x) = \gamma_{ij}^{(1)} y_{h,ij} + \gamma_{ij}^{(2)} y_{h,ij} x + \gamma_{ij}^{(3)} y_{h,ij} x^2$$

- $\partial \eta_{h,ij}^{NPH}(x)/\partial x$ and $\partial \eta_{h,ij}^{AFT}(x)/\partial x$ easily derivable.
- Use a reduced number of parameters.

Outline

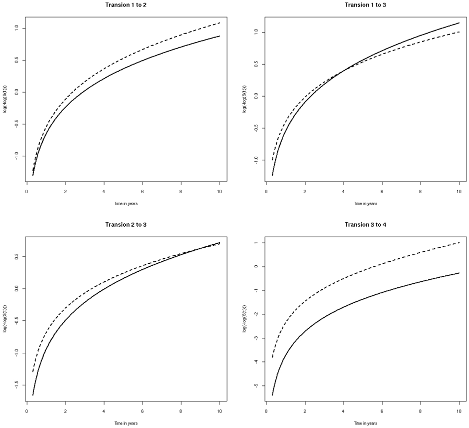
Multistate structure

- 3-gravity states with two markers :
  - Creatinine clearance (CL)
  - Proteinuria (PR)
- 2-terminal states : chronic rejection of the kidney and death of the patient.



Test of the PH assumption

- An example for recipient age.
- PH assumption seems to hold only for the transition $3 \rightarrow 4$.



PH multivariate semi-Markov model

Transition	Covariate	Estim.	SE	RR	p-value
$0 \longrightarrow 1$	Intercept	2.85	0.19	.	0.0001
$0 \longrightarrow 1$	Recipient Gender	-0.39	0.17	.	0.0226
$0 \longrightarrow 1$	Delayed graft function	-0.53	0.17	.	0.0014
$0 \longrightarrow 2$	Intercept	-0.67	0.44	.	0.1258
$0 \longrightarrow 2$	Cold ischemia time	1.13	0.44	.	0.0092
$1 \longrightarrow 2$	Year of transplantation	-0.80	0.12	0.45	0.0001
$1 \longrightarrow 3$	Recipient Gender	0.29	0.15	1.34	0.0484
$1 \longrightarrow 3$	Year of transplantation	-1.20	0.21	0.30	0.0001
$2 \longrightarrow 3$	Year of transplantation	-0.54	0.12	0.59	0.0001
$3 \longrightarrow 5$	Recipient age	1.48	0.39	4.41	0.0001

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$$ln\mathcal{L}_{ph} = -4864.62 \text{ with 26 parameters (10-regression parameters)}$$

Flexible multivariate semi-Markov model

$$ln\mathcal{L}_{flex} = -4846.70 \text{ with 31 parameters (18-regression parameters)}$$

$$LRS = -2(ln\mathcal{L}_{ph} - ln\mathcal{L}_{flex}) = 17.92 \ (p < 0.0001)$$

The flexible model is more informative than the PH model.

Flexible multivariate semi-Markov model

Transition	Incorporation	Covariates	Estim.	SE	p-value
$0 \longrightarrow 1$	.	Intercept	2.83	0.19	0.0001
$0 \longrightarrow 1$	.	Recipient gender	-0.38	0.17	0.0270
$0 \longrightarrow 1$	.	Delayed graft function	-0.52	0.17	0.0016
$0 \longrightarrow 2$	.	Intercept	-0.66	0.43	0.1275
$0 \longrightarrow 2$	.	Cold ischemia time	1.12	0.43	0.0096
$1 \longrightarrow 2$	AFT	Year of transplantation	-1.84	0.27	0.0001
$1 \longrightarrow 2$	AFT	Year of transplantation $\times$ x	0.14	0.03	0.0001
$1 \longrightarrow 3$	PH	Year of transplantation	-1.31	0.17	0.0001
$2 \longrightarrow 3$	NPH	Year of transplantation	-0.75	0.14	0.0001
$2 \longrightarrow 3$	NPH	Year of transplantation $\times$ x	0.06	0.02	0.0009
$2 \longrightarrow 3$	NPH	Recipient age	0.34	0.18	0.0551
$2 \longrightarrow 3$	NPH	Recipient age $\times$ x	-0.14	0.06	0.0199
$2 \longrightarrow 3$	NPH	Recipient age $\times$ x^2	0.01	0.01	0.0219
$3 \longrightarrow 4$	NPH	Cold ischemia time	1.57	0.60	0.0093
$3 \longrightarrow 4$	NPH	Cold ischemia time $\times$ x	-0.42	0.13	0.0014
$3 \longrightarrow 4$	NPH	Cold ischemia time $\times$ x^2	0.02	0.01	0.0037
$3 \longrightarrow 4$	PH	Year of transplantation	0.41	0.23	0.0792
$3 \longrightarrow 5$	AFT	Recipient age	0.86	0.29	0.0033

Outline

1. Introduction
2. Semi-Markov framework
3. Illustration for kidney transplant recipients
4. **Concluding remarks**

Summary of the results

- Relevance of the flexible incorporation of covariates.
- Multinomial logistic regression.
- Parcimony of the generalized Weibull distribution ($\bigcup -$ or $\bigcap -$ shape).

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Work in progress

- Estimate the cut-off of the markers in order to determine the best states of gravity.
- Construction of an hidden semi-Markov model in order to take into account the short-term fluctuation.