Modeling Prediction of the Nosocomial Pneumonia with a Multistate model

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VAP definition and Epidemiology

1. Ventilator-Associated nosocomial Pneumonia (VAP): lung infection occurring within 48 hours or more after hospital admission.
2. Incidence 8% to 28% Patients receiving mechanical ventilation (MV).

Consequences

1. Increases the length of the stay in ICU (5 days).
2. Mortality Increasing vs decreasing (controversial literature). Possible reasons:
   - Definition and diagnosis of VAP is problematic.
   - Heterogeneity (observable or unobservable).
3. Increasing the cost of expenditures.

Problematic of the VAP

1. Using anti-microbial problematic

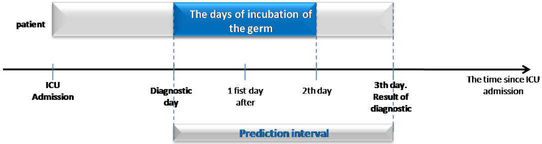


Figure: Monitoring of a patient in ICU

2. Prediction of the VAP

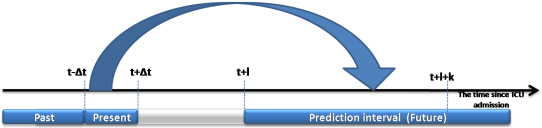


Figure: Prediction of VAP in ICU

3. Identification of patients with hight risk to contract VAP.

OUTCOMEREA database

1. November 1996 to April 2009 / 16 French ICUs.
2. Data collected daily by senior physicians.
3. patients Information at admission and during the stay (Iatrogenic events,Simplified Acute Physiology Score...)

Selection criteria of study population

- Being in ICU at least 48h.
- Receiving MV since the first 48h after admission.
- Stop observation at discharge (48 h after MV) or death.

Study population : 2871, 433(15.1%) VAP, 470(16.4%) Death without VAP and 1968(68.5%) Discharge.

Among 433 VAP, 119(27.5%) Death with VAP and 314(72.5%) Discharge with VAP.

Movement of ICU patient

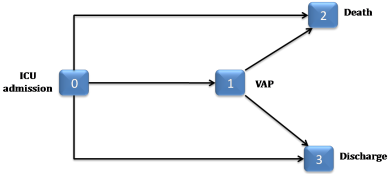


Figure: Multistate of ICU patient

Transition	n (%)	Min.time	Max.time	Median	Mean
$0 \rightarrow 1$	433(15.1)	3	56	7	9.28
$0 \rightarrow 2$	470(16.4)	3	73	6.5	9.98
$0 \rightarrow 3$	1968(68.5)	3	111	6	9.14
$1 \rightarrow 2$	119(27)	1	70	7	13.27
$1 \rightarrow 3$	315(73)	1	135	11	16.19

Definition and notation

1. **Basic definitions**
   - $\{X(t), t \in T = [0, \tau]\}$ a stochastic process on the finite state space $E = \{0, 1, 2, 3\}$.
   - $\mathcal{F}_t$ σ-algebra integrating all past of process until the time t.
   - $\mathcal{E} := \{0 \to 1, 0 \to 2, 0 \to 3, 1 \to 2, 1 \to 3\}$.
2. **Transition probability**

$$P_{hj}(s, t; \mathcal{F}_{s^-}) = \mathbf{Pr}(X(t) = j | X(s) = h; \mathcal{F}_{s^-}) \qquad (1)$$

3. **Transition intensity**

$$\alpha_{hj}(t; \mathcal{F}_{t^-}) = \lim_{\Delta t \to 0} \frac{P_{hj}(t, t + \Delta t; \mathcal{F}_{t^-})}{\Delta t} \qquad (2)$$

Different Model

Different model assumptions can be made about the dependence of the transition rate (2) on time. These include:

1. **Time homogeneous models:**
   The intensities are constant over time.

   Kay R. Markov model for analysing cancer markers and disease states in survival studies

   Biometrics 1986;42:855-65

2. **Markov Models:**
   The transition intensities only depend on the history of the process through the current state.
   $\alpha_{hj}(t; \mathcal{F}_{t^-}) = \alpha_{hj}(t)$

   Cox DR, Miller HD. the theory of stochastic processes. Chapman & Hall 1965

3. **Semi-Markov Model:**
   Future evolution not only depends on the occurent state h, but also on the entry time T_h in to h.
   $\alpha_{hj}(t; \mathcal{F}_{t^-}) = \alpha_{hj}(t, T_h) = \alpha_{hj}(t - T_h)$

   Andersen PK, Esbjerg S,Sorensen TIA. Multistate models for bleeding episodes and mortality in liver cirrhosis.

   Statistics in Medicine 2001;19:587-99

Use of covariates in multistates model

1. **General regression model**

$$\mathbf{Z}_{hj}(t) = \left(\bar{Z}^1_{hj}, \dots, \bar{Z}^{p_{hj}}_{hj}, \widetilde{Z}^1_{hj}(t), \dots, \widetilde{Z}^{q_{hj}}_{hj}(t)\right)^{\mathtt{T}}$$

set of covariates for the transition $h \to j$.

$$\alpha_{hj}(t; \mathbf{Z}_{hj}(t)) = \Phi\left(\alpha_{hj_0}(t; \boldsymbol{\mu}_{hj}); \boldsymbol{\beta}^{\mathtt{T}}_{hj}\mathbf{Z}_{hj}(t)\right) \quad (3)$$

2. **Cox Model**

   - $\Phi(u(.); v) = u(.)\exp(v)$
   - $\alpha_{hj}(t; \mathbf{Z}_{hj}(t)) = \alpha_{hj_0}(t; \boldsymbol{\mu}_{hj})\exp(\boldsymbol{\beta}^{\mathtt{T}}_{hj}\mathbf{Z}_{hj}(t))$
   - Assumption of Cox model
     The influence of a covariates is constant over time (Proportionality).
     Continuous covariates are log-linear
     All individuals have the same base line intensity.

$\boldsymbol{\beta}_{hj} = \left(\bar{\beta}^1_{hj}, \dots, \bar{\beta}^{p_{hj}}_{hj}, \widetilde{\beta}^1_{hj}, \dots, \widetilde{\beta}^{q_{hj}}_{hj}\right)^{\mathtt{T}}$; $\boldsymbol{\mu}_{hj}$ m_{hj}−vector of distribution parameters

Use of covariates in multistate model

$\mathbf{Z}_h(t) = \{\mathbf{Z}_{hj}(t); j \in E, h \to j \in \mathcal{E}\}$

1. **Integrated intensity**

$$A_{hj}(t; \mathbf{Z}_{hj}(t)) = \int_0^t \exp(\boldsymbol{\beta}_{hj}^{\mathsf{T}} \mathbf{Z}_{hj}(u)) \alpha_{hj_0}(u) du.$$

2. **Survival function** $h \to j$

$$S_{hj}(t; \mathbf{Z}_{hj}(t)) = \exp(-\int_0^t \exp(\boldsymbol{\beta}_{hj}^{\mathsf{T}} \mathbf{Z}_{hj}(u)) \alpha_{hj_0}(u) du).$$

3. **Survival function in state h**

$$S_h(t; \mathbf{Z}_h(t)) = \prod_{h \to j \in \mathcal{E}} S_{hj}(t; \mathbf{Z}_{hj}(t)).$$

Likelihood of multistate model

$\mathcal{I}_h$ set of patient in the state h. d_h duration , t_h entry time, τ_h release time. $d_h^i = \tau_h^i - t_h^i$. $\boldsymbol{\theta}$ parameters vector of model.

1. Likelihood of multistate model using the paths $L^{\bullet}(\boldsymbol{\theta})$
2. Likelihood of survival model $L_{hj}^{\bullet}(\boldsymbol{\theta}_{hj})$
3. Important result

$$L^{\bullet}(\boldsymbol{\theta}) = \prod_{(h \to j) \in \mathcal{E}} L_{hj}^{\bullet}(\boldsymbol{\theta}_{hj}), \quad \bullet = M, SM$$

where $\boldsymbol{\theta}_{hj} = \left(\boldsymbol{\beta}_{hj}^{\mathtt{T}}, \boldsymbol{\mu}_{hj}^{\mathtt{T}}\right)^{\mathtt{T}}$.

Parametric estimation $\widehat{A}_{hj}(.;\mathbf{Z}_{hj}(.))$ $h \to j \in \mathcal{E}$

1. **Likelihood of transition $h \to j$ with $j \in \{1,2,3\}$**

$$L^{\bullet}_{0j}(\boldsymbol{\theta}_{0j}) = \prod_{i \in \mathcal{I}_0} \left(\alpha_{0j}(d_0^i; \mathbf{Z}^i_{0j}(d_0^i))\right)^{\Delta N_{0j}(\tau_0^{i-})} S_{0j}(\tau_0^i; \mathbf{Z}^i_{0j}(\tau_0^i)).$$

Where $\Delta N_{0j}(\tau_0^{i-}) = N_{0j}(\tau_0^i) - N_{0j}(\tau_0^{i-})$
$\tau_0^i = d_0^i, \quad t_0^i = 0.$

$$S_{0j}(\tau_0^i; \mathbf{Z}^i_{0j}(\tau_0^i)) = \exp(-\int_0^{\tau_0^i} \exp(\boldsymbol{\beta}_{0j}^{\mathsf{T}} \mathbf{Z}^i_{0j}(u)) \alpha_{0j_0}(u; \boldsymbol{\mu}_{0j}) du).$$

1. **Likelihood**
   Markov

$$L_{1j}^{M}(\boldsymbol{\theta}_{hj}) = \prod_{i\in\mathcal{I}_h} \left(\alpha_{1j}(\tau_1^i;\mathbf{Z}_{1j}^i(\tau_1^i))\right)^{\Delta N_{1j}(\tau_1^{i-})} \frac{S_{1j}(\tau_1^i;\mathbf{Z}_{1j}^i(\tau_1^i))}{S_{1j}(t_1^i;\mathbf{Z}_{1j}^i(t_1^i))}$$

   Semi-Markov

$$L_{1j}^{SM}(\boldsymbol{\theta}_{hj}) = \prod_{i\in\mathcal{I}_h} \left(\alpha_{1j}(d_1^i;\mathbf{Z}_{1j}^i(d_1^i))\right)^{\Delta N_{1j}(d_1^{i-})} S_{1j}(d_1^i;\mathbf{Z}_{1j}^i(d_1^i))$$

2. **Practical Notes**
   $t_h^i \leq s_0 \leq, \dots, s_{k_i} \leq \tau_h^i$ the time when covariates value change for the ith patient. Integrals used in previous equation are equal to:

$$\int_{t_h^i}^{\tau_h^i} \exp(\boldsymbol{\beta}_{hj}^{\mathsf{T}}\mathbf{Z}_{hj}^i(u))dA_{hj}(u) = \sum_{l=0}^{k_i-1} \exp(\boldsymbol{\beta}_{hj}^{\mathsf{T}}\mathbf{Z}_{hj}^i(s_l))\Delta A_{hj}(s_l). \qquad (4)$$

Parametric estimation $\widehat{A}_{hj}(.;\mathbf{Z}_{hj}(.))\ h \rightarrow j \in \mathcal{E}$

1. Optimization of $L(\boldsymbol{\theta}_{hj}) \Rightarrow \widehat{\theta}_{hj}$ (Method Quasi-Newton)
2. Asymptotic results
   $\sqrt{n}(\widehat{\theta}_{hj} - \boldsymbol{\theta}_{hj})$ converges to a zero-mean normal distribution with a covariance matrix that is estimated by $\frac{1}{n}\mathbf{F}(\widehat{\theta}_{hj})^{-1}$.
   Variance of the parameters

$$\mathbf{var}(\widehat{\theta}_{hj}) = diag(\frac{1}{n}\mathbf{F}(\widehat{\theta}_{hj})^{-1}) \qquad (5)$$

Under the hypothesis $\widehat{\theta}_{hj} = \boldsymbol{\theta}_{hj}$ the Wald statistic defined by:

$$(\widehat{\theta}_{hj} - \boldsymbol{\theta}_{hj})^{\mathtt{T}}\mathbf{F}(\widehat{\theta}_{hj})(\widehat{\theta}_{hj} - \boldsymbol{\theta}_{hj})$$

is approximately distributed as the chi-square distribution with $p_{hj} + q_{hj} + m_{hj}$ degrees freedom.

Non-parametric estimation $\widehat{A}_{hj}(.;\mathbf{Z}_{hj}(.))$ $h \rightarrow j \in \mathcal{E}$

$N_{hj}(t) = \sum_{i \in \mathcal{I}_h} N^i_{hj}(t)$, $Y_h(t) = \sum_{i \in \mathcal{I}_h} Y^i_h(t)$ counting process.

1. **Markov**
   $1 \rightarrow j$ with $j \in \{2,3\}$ $N^i_{1j}(t) = \mathbf{1}_{\{t^i_1 \leq \tau^i_1 \leq t\}}$ $Y^i_1(t) = \mathbf{1}_{\{t^i_1 \leq t \leq \tau^i_1\}}$.

$$PL(\boldsymbol{\beta}_{hj}) = \prod_{i \in \mathcal{I}_h} \prod_{\tau^i_h \geq 0} \left\{ \frac{\exp(\boldsymbol{\beta}^{\mathsf{T}}_{hj}\mathbf{Z}^i_{hj}(\tau^i_h))}{\sum_{l \in \mathcal{I}_h} Y^l_h(\tau^i_h)\exp(\boldsymbol{\beta}^{\mathsf{T}}_{hj}\mathbf{Z}^l_{hj}(\tau^i_h))} \right\}^{\Delta N^i_{hj}(\tau^i_h)}, \tag{6}$$

2. **Semi-Markov**
   $1 \rightarrow j$ with $j \in \{2,3\}$ $N^i_{hj}(t) = \mathbf{1}_{\{d^i_h \leq t\}}$ $Y^i_h(t) = \mathbf{1}_{\{d^i_h \geq t\}}$.

$$PL(\boldsymbol{\beta}_{hj}) = \prod_{i \in \mathcal{I}_h} \prod_{d^i_h \geq 0} \left\{ \frac{\exp(\boldsymbol{\beta}^{\mathsf{T}}_{hj}\mathbf{Z}^i_{hj}(d^i_h))}{\sum_{l \in \mathcal{I}_h} Y^l_h(d^i_h)\exp(\boldsymbol{\beta}^{\mathsf{T}}_{hj}\mathbf{Z}^l_{hj}(d^i_h))} \right\}^{\Delta N^i_{hj}(d^i_h)}, \tag{7}$$

Non-parametric estimation $\widehat{A}_{hj}(.;\mathbf{Z}_{hj}(.))$ $h \rightarrow j \in \mathcal{E}$

1. Optimization of $PL(\boldsymbol{\beta}_{hj}) \Rightarrow \widehat{\boldsymbol{\beta}}_{hj}$.
2. **Breslow estimator**

$$\widehat{A}_{hj_0}(t) = \sum_{i \in \mathcal{I}_h} \int_0^t \frac{dN^i_{hj}(u)}{\sum_{l \in \mathcal{I}_h} Y^l_h(u) \exp(\widehat{\boldsymbol{\beta}}^{\mathtt{T}}_{hj} \mathbf{Z}^l_{hj}(u))}.$$

3. **Estimator of integrated intensity**

$$\widehat{A}_{hj}(t;\mathbf{Z}_{hj}(t)) = \sum_{s^i_{hj} \leq t} \exp(\widehat{\boldsymbol{\beta}}^{\mathtt{T}}_{hj} \mathbf{Z}_{hj}(s^i_{hj})) \Delta \widehat{A}_{hj_0}(s^i_{hj})$$

4. **Asymptotic results** $\sqrt{n}(\widehat{A}_{hj_0}(t) - A_{hj_0}(t))$ converges to a zero-mean Gaussian process and the covariance function can be estimated (see **Andersen et al. 1992**)

Non-parametric estimation $\widehat{\alpha}_{hj}(.;\mathbf{Z}_{hj}(.))$ $h \to j \in \mathcal{E}$

1. **Estimator of transition intensity**

$$\widehat{\alpha}_{hj}(t;\mathbf{Z}_{hj}(t)) = \frac{\Delta \widehat{A}_{hj}(t;\mathbf{Z}_{hj}(t))}{\Delta t}$$

2. **Smoothing estimator of transition intensity**

$$\widehat{\widehat{\alpha}}_{hj}(t;\mathbf{Z}_{hj}(t)) = \sum_{s^i_{hj} \leq t} \frac{1}{b} \exp(\widehat{\boldsymbol{\beta}}^{\mathtt{T}}_{hj} \mathbf{Z}_{hj}(s^i_{hj})) K\left(\frac{s^i_{hj} - t}{b}\right) \Delta \widehat{A}_{hj_0}(s^i_{hj}).$$

Gaussian $K(t) = \frac{1}{\sqrt{2\pi}} \exp(\frac{-1}{2} t^2)$. $\Delta U(t) = U(t) - U(t^-)$. $b : bandwidth$

1. **Selection Covariates**
   - **step 1**: Test the log-linearity of continuous covariates (Using Poisson regression)
   - **step 2**: Test the Proportionality of covariates (the time dependent coefficients and Schoenfeld residuals)
2. **Non-parametric Model (Cox)**
   - Use stepwise selection with Cox model where the entry threshold is equal to 0.25 and the stay threshold is equal to 0.05.
   - The model of each transition is validated by the C index defined by

     $$C^t = \int_0^t AUC(u)w^t(u)du$$

$AUC(t) = \int_0^t ROC_t^{I/D}(p)dp$, $ROC_t^{I/D}(p)$ is the true-positive rate, $w^t(u)$ are weigths

Application 1: OUTCOMEREA database

Result 1: estimation of the covariates effects

Transition	covariates	β	HR	SE	P-value
0->1	sirs	1.14	4.37	0.26	2.2e-8
	ablsp	0.24	1.28	0.09	0.012
	lod>6	0.14	1.16	0.10	0.155
	Mal gender	0.36	1.44	0.10	0.000
	pnc	0.33	1.39	0.11	0.003
	Ards	0.43	1.55	0.19	0.022
0->2	ablsp	-0.07	0.92	0.09	0.44
	lod>6	3.18	24.1	0.17	2.e-16
	dnr	2.00	7.4	0.09	2.e-16
	age>74	0.15	1.17	0.10	0.117
	Immun	0.15	1.16	0.12	0.235
0->3	ablsp	-0.47	0.62	0.04	2e-16
	lod3a4	-0.70	0.49	0.05	2e-16
	Lod5a6	-0.95	0.38	0.06	2e-16
	Lod>6	-2.15	0.11	0.10	2e-16
	Age>74	-0.10	0.89	0.05	0.04
	Typemed	-0.21	0.81	0.04	4.1e-6
	Chro.ill	-0.17	0.84	0.04	0.000
1->2 SM	t°C	-0.32	0.72	0.21	0.12
	Lod>6	2.84	17.2	0.27	2e-16
	Dnr	2.10	8.2	0.19	2e-16
	Chr.ill	0.26	1.2	0.18	0.16
1->2 M	T°C	-0.11	0.88	0.21	0.57
	Lod>6	2.88	17.91	0.28	2e-16
	Dnr	2.04	7.70	0.19	2e-16
	Chr.ill	0.24	1.27	0.19	0.20

1. C index

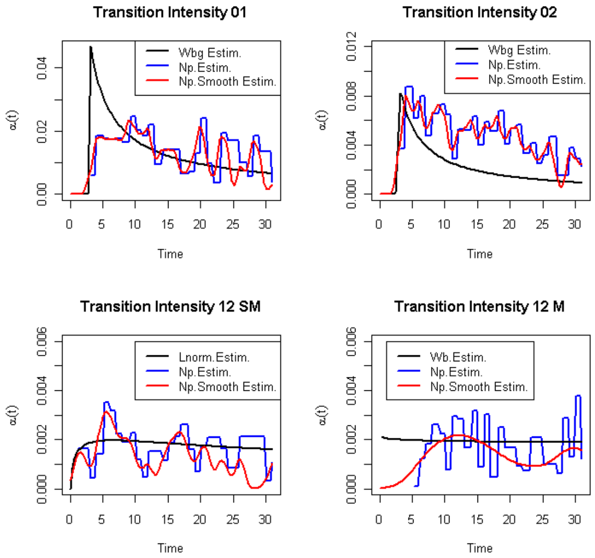
Transition	01	02	03	$12M$	$13M$	$12SM$	$13SM$
C index	0677	0.924	0741	0.888	0.713	0.891	0.702

2. **Selection of model distribution**

Transition	Wbg	Wb	Lnorm	Llog	BrS	InG	Gamma	Exp
0->1	4087.97	4295.92	4206.02	4255.18	4167.92	4169.7	4286.21	4357.35
0->2	3055.79	3330.45	3272.13	3326.89	3326.65	3551.28	3329.58	4165.59
0->3	13477.74	13083.17	12227.40	12024.66	14012.82	13627.03	12819.29	13231.61
1->2 (SM)	938.61	877.64	869.02	876.90	918.20	1058.65	879.45	876.60
1->3 (SM)	2749.50	2534.24	2526.74	2524.52	2557.56	2605.60	2530.33	2541.63
1->2 (M)	875.84	877.45	933.08	......	902.64	954.66	879.02	876.66
1->3 (M)	2670.71	2495.27	2543.03	......	....	2595.88	2542.54	2541.63

Values AIC for each distribution

Estimation $\alpha_{hj_0}(.)$ Markov/semi-Markov



Application 1: Description of profile

Subject 1 : VAP after 10 days (mal gender=1, pnc=1, ards=0)

sirs	1	1	1	1	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ablsp	1	1	1	1	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lod>6	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Days 1 2 3 4 5 6 7 8 9 10 ....30 31

Subject 2 : Died without VAP after 16 days (mal gender=1, pnc=0, ards=0)

sirs	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ablsp	0	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lod>6	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

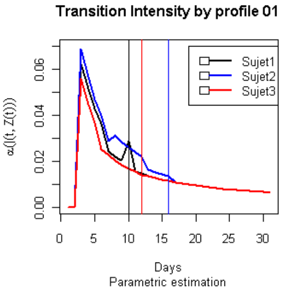
Days 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 ....30 31

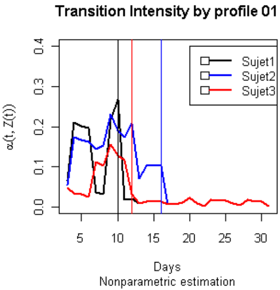
Subject 3: Discharge without VAP after 12 days (mal gender=1, pnc=0, ards=0)

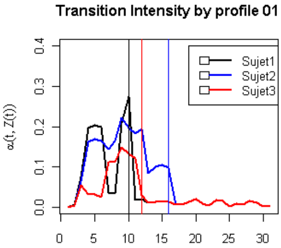
sirs	1	1	1	0	0	0	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ablsp	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lod>6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Days 1 2 3 4 5 6 7 8 9 10 11 12 ....30 31

Estimator $\widehat{\alpha}_{01}(., \mathbf{Z}_{hj}(.))$ by profile







Definition of individualized prediction

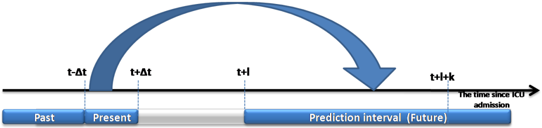


Figure: Prediction of VAP in ICU

$\mathcal{H}_{hj}(s,t) = \{\mathbf{Z}_{hj}(x); x \in [s,t]\}$ the covariates history over the interval $[s,t]$ associated to the transition $h \to j$. $\mathcal{H}_h(s,t) = \{\mathbf{Z}_h(x); x \in [s,t]\}$ the covariate history for all transitions from the state h and $\mathcal{H}_h^i(s,t) = \left\{\mathbf{Z}_h^i(x); x \in [s,t]\right\}$.

Definition of individualized prediction

The prediction of the VAP for the ith individual over time interval $[t+k, t+k+l]$ for all $l, k > 0$

$$\varphi^i(t,k,l;\boldsymbol{\mathcal{H}}_0^i(x(k),x(k+l))) = \int_{x(k)}^{x(k+l)} P_{00}(x(k),u;\boldsymbol{\mathcal{H}}_0^i(x(k),u))$$

$$\times dA_{01_0}(u)\exp(\boldsymbol{\beta}_{01}^{\mathsf{T}}\mathbf{Z}_{01}^i(u)).$$

$$\varphi^i(t,k,l;\boldsymbol{\mathcal{H}}_0^i(x(k),x(k+l))) = \frac{1}{S_0(x(k);\mathbf{Z}_0^i(x(k)))}$$

$$\times \int_{x(k)}^{x(k+l)} S_0(u;\mathbf{Z}_0^i(u))\exp(\boldsymbol{\beta}_{01}^{\mathsf{T}}\mathbf{Z}_{01}^i(u))dA_{01_0}(u$$

With $x(v) = t+v$

Estimation of the profile

1. **problematic: missing values in the prediction interval**

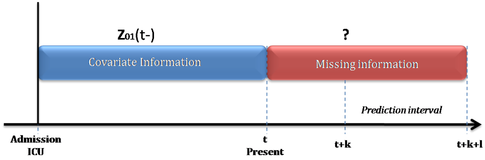


Figure: history of covariate of time-dependent

2. **hypothetical solution**
   The prediction of the VAP for ith individual over time interval $[t+k, t+k+l]$ for all $l, k > 0$ we pose $\mathbf{Z}_{hj}^{i}(t) = \mathbf{Z}_{hj,t}^{i}$ and we define the profile of ith patient by

$$\mathbf{Z}_{hj,t}^{i}(x) = \mathbf{Z}_{hj}^{i}(x)\mathbf{1}_{[0,t]} + \mathbf{Z}_{hj,t}^{i}\mathbf{1}_{]t,+\infty[},$$

Parametric estimator of prediction

$$\widehat{\varphi}^i(t,k,l;\mathbf{Z}^i_{h,t}(x)) = \frac{\exp(\widehat{\boldsymbol{\beta}}_{01}^{\mathrm{T}}\mathbf{Z}^i_{01,t})}{\widehat{S}_0(t+k;\mathbf{Z}^i_{0,t}(t+k))}\int_{t+k}^{t+k+l}\widehat{S}_{0j}(u;\mathbf{Z}^i_{0,t})\widehat{\alpha}_{01_0}(u)du.$$

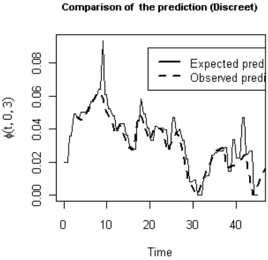
Non-parametric estimator of prediction

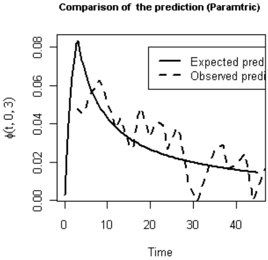
$$\widehat{\varphi}^i(t,k,l;\mathbf{Z}^i_{h,t}(x)) = \frac{\exp(\widehat{\boldsymbol{\beta}}_{01}^{\mathrm{T}}\mathbf{Z}^i_{01,t})}{\widehat{S}_0(t+k;\mathbf{Z}^i_{0,t}(t+k))}\sum_{\substack{t+k\leq s_i\\ t+k+l\geq s_i}}\widehat{S}_0(s_i;\mathbf{Z}^i_{0,t})\Delta\widehat{A}_{01_0}(s_i).$$

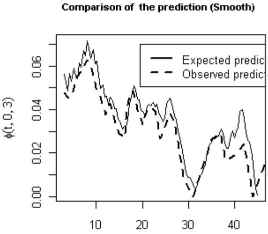
Smoothed estimator of prediction

$$\widehat{\varphi}^i(t,k,l;\mathbf{Z}^i_{h,t}(x)) = \frac{1}{\widehat{S}_0(t+k;\mathbf{Z}^i_{0,t}(t+k))}\sum_{\substack{t+k\leq s_i\\ t+k+l\geq s_i}}\widehat{\widetilde{S}}_0(u;\mathbf{Z}^i_{0,t})\widehat{\widetilde{\alpha}}_{hj}(s_i;\mathbf{Z}^i_{0j,t})\Delta s_i.$$

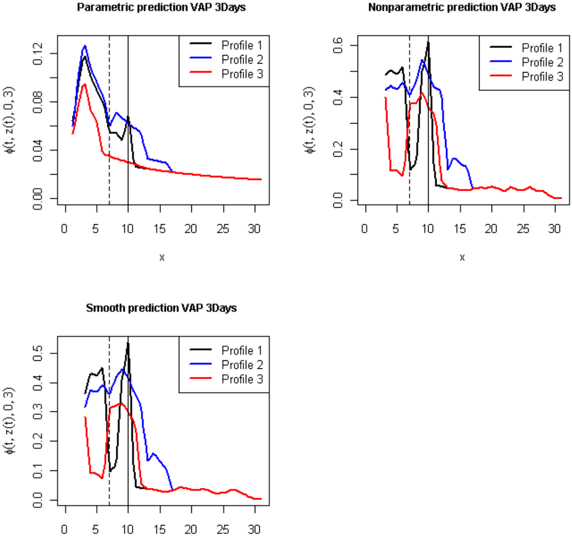
Base prediction







Individualyzed prediction



Comments

1. Assumptions of the Cox model
2. Heterogeneity
3. Model validation

Thank you your attention !!!!!