Modeling Prediction of the Nosocomial Pneumonia with a Multistate model

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Ventilator-Associated nosocomial Pneumonia (VAP): lung infection occurring within 48 hours or more after hospital admission.

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

2. Prediction of the VAP

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

Figure: Monitoring of a patient in ICU

Figure: Prediction of VAP in ICU
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

<table>
<thead>
<tr>
<th>Transition</th>
<th>n (%)</th>
<th>Min.time</th>
<th>Max.time</th>
<th>Median</th>
<th>Mean</th>
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<td>0 → 1</td>
<td>433 (15.1)</td>
<td>3</td>
<td>56</td>
<td>7</td>
<td>9.28</td>
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<td>0 → 2</td>
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<td>3</td>
<td>73</td>
<td>6.5</td>
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<tr>
<td>0 → 3</td>
<td>1968 (68.5)</td>
<td>3</td>
<td>111</td>
<td>6</td>
<td>9.14</td>
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<tr>
<td>1 → 2</td>
<td>119 (27)</td>
<td>1</td>
<td>70</td>
<td>7</td>
<td>13.27</td>
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<tr>
<td>1 → 3</td>
<td>315 (73)</td>
<td>1</td>
<td>135</td>
<td>11</td>
<td>16.19</td>
</tr>
</tbody>
</table>
1. **Basic definitions**
   - \( \{X(t), t \in T = [0, \tau]\} \) a stochastic process on the finite state space \( E = \{0, 1, 2, 3\} \).
   - \( \mathcal{F}_t \) \( \sigma \)-algebra integrating all past of process until the time \( t \).
   - \( \mathcal{E} := \{0 \rightarrow 1, 0 \rightarrow 2, 0 \rightarrow 3, 1 \rightarrow 2, 1 \rightarrow 3\} \).

2. **Transition probability**
   \[
   P_{h,j}(s, t; \mathcal{F}_{s-}) = \Pr(X(t) = j|X(s) = h; \mathcal{F}_{s-}) \tag{1}
   \]

3. **Transition intensity**
   \[
   \alpha_{h,j}(t; \mathcal{F}_{t-}) = \lim_{\Delta t \to 0} \frac{P_{h,j}(t, t + \Delta t; \mathcal{F}_{t-})}{\Delta t} \tag{2}
   \]
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.
   
   \[ \alpha_{hj}(t; F_{t^-}) = \alpha_{hj}(t) \]

   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 \(h\).
   
   \[ \alpha_{hj}(t; F_{t^-}) = \alpha_{hj}(t, T_h) = \alpha_{hj}(t - T_h) \]

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

Use of covariates in multistates model

1. General regression model

\[ Z_{hj}(t) = \left( \bar{Z}_{hj}^1, \ldots, \bar{Z}_{hj}^{p_{hj}}, \tilde{Z}_{hj}^1(t), \ldots, \tilde{Z}_{hj}^{q_{hj}}(t) \right)^T \]

set of covariates for the transition \( h \rightarrow j \).

\[ \alpha_{hj}(t; Z_{hj}(t)) = \Phi \left( \alpha_{hj0}(t; \mu_{hj}); \beta^T_{hj} Z_{hj}(t) \right) \] (3)

2. Cox Model

- \( \Phi(u(.); v) = u(.) \exp(v) \)
- \( \alpha_{hj}(t; Z_{hj}(t)) = \alpha_{hj0}(t; \mu_{hj}) \exp(\beta^T_{hj} Z_{hj}(t)) \)
- 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.

\[ \beta_{hj} = \left( \bar{\beta}_{hj}^1, \ldots, \bar{\beta}_{hj}^{p_{hj}}, \tilde{\beta}_{hj}^1, \ldots, \tilde{\beta}_{hj}^{q_{hj}} \right)^T; \quad \mu_{hj} m_{hj} - \text{vector of distribution parameters} \]
Use of covariates in multistate model

\[ \mathbf{Z}_h(t) = \{ \mathbf{Z}_{hj}(t); j \in E, h \rightarrow j \in \mathcal{E} \} \]

1 Integrated intensity

\[
A_{hj}(t; \mathbf{Z}_{hj}(t)) = \int_0^t \exp(\beta_{hj}^T \mathbf{Z}_{hj}(u)) \alpha_{hj0}(u) du.
\]

2 Survival function \( h \rightarrow j \)

\[
S_{hj}(t; \mathbf{Z}_{hj}(t)) = \exp(- \int_0^t \exp(\beta_{hj}^T \mathbf{Z}_{hj}(u)) \alpha_{hj0}(u) du).
\]

3 Survival function in state \( h \)

\[
S_h(t; \mathbf{Z}_h(t)) = \prod_{h \rightarrow j \in \mathcal{E}} S_{hj}(t; \mathbf{Z}_{hj}(t)).
\]
Likelihood of multistate model

\[ \mathcal{I}_h \] set of patient in the state \( h \). \( d_h \) duration, \( t_h \) entry time, \( \tau_h \) release time.

\[ d_h^i = \tau_h^i - t_h^i. \]

\( \theta \) parameters vector of model.

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

\[
L^\bullet(\theta) = \prod_{(h \rightarrow j) \in \mathcal{E}} L_{hj}(\theta_{hj}), \quad \bullet = M, SM
\]

where \( \theta_{hj} = \left( \beta_{hj}^T, \mu_{hj}^T \right)^T \).
Likelihood of transition $h \rightarrow j$ with $j \in \{1, 2, 3\}$

$$L_{0j}^{\bullet}(\theta_{0j}) = \prod_{i \in \mathcal{I}_0} \left( \alpha_{0j}(d_0^i; Z_{0j}^i(d_0^i)) \right)^{\Delta N_{0j}^{i-}(\tau_0^i)} S_{0j}(\tau_0^i; Z_{0j}^i(\tau_0^i)).$$

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

$$\tau_0^i = d_0^i, \quad t_0^i = 0.$$
Parametric estimation $\widehat{A}_{hj}(.; \mathbf{Z}_{hj}(.))$ $h \rightarrow j \in \mathcal{E}$

1. **Likelihood**

Markov

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

Semi-Markov

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

2. **Practical Notes**

$t_h^i \leq s_0 \leq \ldots \leq s_{k_i} \leq \tau_h^i$ the time when covariates value change for the $i$th patient. Integrals used in previous equation are equal to:

$$\int_{t_h^i}^{\tau_h^i} \exp(\beta_{hj}^T \mathbf{Z}_{hj}(u))dA_{hj}(u) = \sum_{l=0}^{k_i-1} \exp(\beta_{hj}^T \mathbf{Z}_{hj}(s_l)) \Delta A_{hj}(s_l). \quad (4)$$
Parametric estimation $\hat{A}_{hj}(.; Z_{hj}(.)) \; h \rightarrow j \in \mathcal{E}$

1. Optimization of $L(\theta_{hj}) \Rightarrow \hat{\theta}_{hj}$ (Method Quasi-Newton)

2. Asymptotic results
   \[ \sqrt{n}(\hat{\theta}_{hj} - \theta_{hj}) \] converges to a zero-mean normal distribution with a covariance matrix that is estimated by $\frac{1}{n} F(\hat{\theta}_{hj})^{-1}$.

Variance of the parameters

\[ \text{var}(\hat{\theta}_{hj}) = \text{diag}\left(\frac{1}{n} F(\hat{\theta}_{hj})^{-1}\right) \quad (5) \]

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

\[ (\hat{\theta}_{hj} - \theta_{hj})^T F(\hat{\theta}_{hj}) (\hat{\theta}_{hj} - \theta_{hj}) \]

is approximately distributed as the chi-square distribution with $p_{hj} + q_{hj} + m_{hj}$ degrees freedom.
Non-parametric estimation $\hat{A}_{hj}(.;Z_{hj}(.))$ $h \rightarrow j \in \mathcal{E}$

$$N_{hj}(t) = \sum_{i \in I_h} N_{hj}^i(t), \quad Y_h(t) = \sum_{i \in I_h} Y_h^i(t) \text{ counting process.}$$

1. **Markov**
   1 $\rightarrow$ $j$ with $j \in \{2, 3\}$
   $$N_{hj}^i(t) = 1\{t_i \leq \tau_i \leq t\} \quad Y_h^i(t) = 1\{t_i \leq t \leq \tau_i\}.\quad \Delta N_{hj}^i(\tau_h^i)$$

   $$PL(\beta_{hj}) = \prod_{i \in I_h} \prod_{\tau_h^i \geq 0} \left\{ \frac{\exp(\beta_{hj}^T Z_{hj}^i(\tau_h^i))}{\sum_{l \in I_h} Y_h^l(\tau_h^i) \exp(\beta_{hj}^T Z_{hj}^l(\tau_h^i))} \right\}^{\Delta N_{hj}^i(\tau_h^i)}, \quad (6)$$

2. **Semi-Markov**
   1 $\rightarrow$ $j$ with $j \in \{2, 3\}$
   $$N_{hj}^i(t) = 1\{d_i \leq t\} \quad Y_h^i(t) = 1\{d_i \geq t\}.\quad \Delta N_{hj}^i(d_h^i)$$

   $$PL(\beta_{hj}) = \prod_{i \in I_h} \prod_{d_h^i \geq 0} \left\{ \frac{\exp(\beta_{hj}^T Z_{hj}^i(d_h^i))}{\sum_{l \in I_h} Y_h^l(d_h^i) \exp(\beta_{hj}^T Z_{hj}^l(d_h^i))} \right\}^{\Delta N_{hj}^i(d_h^i)}, \quad (7)$$
Non-parametric estimation $\hat{A}_{hj}(.; Z_{hj}(.))$ $h \rightarrow j \in \mathcal{E}$

1. Optimization of $PL(\beta_{hj}) \Rightarrow \hat{\beta}_{hj}$.

2. Breslow estimator

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

3. Estimator of integrated intensity

$$\hat{A}_{hj}(t; Z_{hj}(t)) = \sum_{s_{hj}^i \leq t} \exp(\hat{\beta}^T_{hj} Z_{hj}(s_{hj}^i)) \Delta \hat{A}_{hj_0}(s_{hj}^i)$$ 

4. Asymptotic results $\sqrt{n}(\hat{A}_{hj_0}(t) - A_{hj_0}(t))$ converges to a zero-mean Gaussian process and the covariance function can be estimated (see Andersen et al. 1992)
Non-parametric estimation $\hat{\alpha}_{hj}(.; Z_{hj}(.))$ $h \to j \in \mathcal{E}$

1. Estimator of transition intensity

$$\hat{\alpha}_{hj}(t; Z_{hj}(t)) = \frac{\Delta \hat{A}_{hj}(t; Z_{hj}(t))}{\Delta t}$$

2. Smoothing estimator of transition intensity

$$\hat{\tilde{\alpha}}_{hj}(t; Z_{hj}(t)) = \sum_{s^i_{hj} \leq t} \frac{1}{b} \exp(\beta^T_{hj} Z_{hj}(s^i_{hj})) K\left(\frac{s^i_{hj} - t}{b}\right) \Delta \hat{A}_{hj0}(s^i_{hj}).$$

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

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 $C^t$ 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

<table>
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<tr>
<th>Transition</th>
<th>covariates</th>
<th>$\beta$</th>
<th>HR</th>
<th>SE</th>
<th>P-value</th>
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<tr>
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</tr>
<tr>
<td></td>
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<td>1.16</td>
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<tr>
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<td>0.24</td>
<td>1.27</td>
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### Application 1: OUTCOMEREA database

#### C index

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<th>03</th>
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#### Selection of model distribution

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<td>......</td>
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</tr>
</tbody>
</table>

*Values AIC for each distribution*
Estimation $\alpha_{hj0}(.)$ Markov/semi-Markov

Transition Intensity 01

Transition Intensity 02

Transition Intensity 12 SM

Transition Intensity 12 M
## Application 1: Description of profile

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

<table>
<thead>
<tr>
<th></th>
<th>sirs</th>
<th>ablsp</th>
<th>Lod&gt;6</th>
</tr>
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### Subject 2: Died without VAP after 16 days (mal gender=1, pnc=0, ards=0)

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

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</tr>
</tbody>
</table>

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M.Nguile Makao (Team 11 Inserm U) Multistate/prediction VAP September 23, 2009 21 / 29
Estimator $\hat{\alpha}_{01}(., Z_{hj}(.))$ by profile

Transition Intensity by profile 01

Days
Parametric estimation

Days
Nonparametric estimation

Transition Intensity by profile 01
Definition of individualized prediction

\[ H_{h,j}(s,t) = \{Z_{h,j}(x); x \in [s,t]\} \] the covariates history over the interval \([s,t]\) associated to the transition \(h \rightarrow j\).

\[ H_h(s,t) = \{Z_h(x); x \in [s,t]\} \] the covariate history for all transitions from the state \(h\) and

\[ H^i_h(s,t) = \{Z^i_h(x); x \in [s,t]\} \].

Figure: Prediction of VAP in ICU
Definition of individualized prediction

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

\[
\varphi^i(t, k, l; \mathcal{H}_0^i(x(k), x(k + l))) = \int_{x(k)}^{x(k+l)} P_{00}(x(k), u; \mathcal{H}_0^i(x(k), u)) \times dA_{010}(u) \exp(\beta_{01}^T Z_{01}^i(u)).
\]

\[
\varphi^i(t, k, l; \mathcal{H}_0^i(x(k), x(k + l))) = \frac{1}{S_0(x(k); Z_0^i(x(k)))} \times \int_{x(k)}^{x(k+l)} S_0(u; Z_0^i(u)) \exp(\beta_{01}^T Z_{01}^i(u)) dA_{010}(u)
\]

With \(x(v) = t + v\)
Estimation of the profile

1. **Problematic: Missing values in the prediction interval**

   ![Figure: history of covariate of time-dependent](image)

   **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 \(Z_{h_j}^i(t) = Z_{h_j,t}^i\) and we define the profile of ith patient by

   \[
   Z_{h_j,t}^i(x) = Z_{h_j}^i(x)1_{[0,t]} + Z_{h_j,t}^i1_{t,+\infty[}
   \]
Estimation of prediction

**Parametric estimator of prediction**

\[
\hat{\phi}^i(t, k, l; Z_{h,t}^i(x)) = \frac{\exp(\hat{\beta}^T_0 Z_{01,t}^i)}{\hat{S}_0(t + k; Z_{00,t}^i(t + k))} \int_{t+k}^{t+k+l} \hat{S}_{0j}(u; Z_{00,t}^i)\hat{\alpha}_{010}(u)du.
\]

**Non-parametric estimator of prediction**

\[
\hat{\phi}^i(t, k, l; Z_{h,t}^i(x)) = \frac{\exp(\hat{\beta}^T_0 Z_{01,t}^i)}{\hat{S}_0(t + k; Z_{00,t}^i(t + k))} \sum_{t+k \leq s_i, t+k+l \geq s_i} \hat{S}_0(s_i; Z_{00,t}^i)\Delta \hat{A}_{010}(s_i).
\]

**Smoothed estimator of prediction**

\[
\hat{\phi}^i(t, k, l; Z_{h,t}^i(x)) = \frac{1}{\hat{S}_0(t + k; Z_{00,t}^i(t + k))} \sum_{t+k \leq s_i, t+k+l \geq s_i} \hat{S}_0(u; Z_{00,t}^i)\hat{\alpha}_{nj}(s_i; Z_{00,j,t})\Delta s_i.
\]

M.Nguile Makao (Team 11 Inserm U823-Joseph Fourier University Team Biostatistic Inserm U897-Victor Segalen Bordeaux 2 University Team SAGAG-Pierre Mendes-France University)
Base prediction
Individually predicted prediction

Parametric prediction VAP 3Days

Nonparametric prediction VAP 3Days

Smooth prediction VAP 3Days
Assumptions of the Cox model

Heterogeneity

Model validation

Thank you your attention !!!!!