Semi-Markov model with Generalized Weibull distribution for multistate data in kidney transplant recipients

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8-9 novembre 2012
• Angiotensin II Type 1 Receptor (AT\textsubscript{1}R) = Non-HLA antigen

• Antibodies against AT\textsubscript{1}R (AT\textsubscript{1}R-Abs) found during acute rejection episode (ARE) in kidney transplants

⇒ Association between AT\textsubscript{1}R-Abs and time to first ARE?
Higher frequency of ARE during the first months of the transplantation
High pre-graft level of AT1R ⇒ increased risk of return to dialysis after 3 years post-transplantation
Raised Issue:

Delayed effect of AT1R for the risk of return to dialysis?

OR

Increased risk due to ARE?

⇒ Multistate model
The different possible states for the patient

STATE 1
Functional graft without acute rejection episode

STATE 2
Functional graft with at least one acute rejection episode (ARE)

STATE 3
Return to dialysis

STATE 4
Death with a functional graft

- Not persistent state
- Persistent state
- Transition
1. Introduction
   Context
   Problematic

2. Methods
   Semi-Markov process
   Modelling

3. Results
   Descriptive statistics
   Parameter estimations
   Interpretation

4. Conclusion
Next state to be visited + time of occurrence will depend on:

- the present state
- the time since entry of that state

⇒ Adapted for time-to-event in Kidney Transplants
Notations

Transition

\[ X_0 = 1 \]
Functional graft without acute rejection episode

\[ T_0 = 0 \]

\[ X_1 = 2 \]
Functional graft with at least one acute rejection episode

\[ T_1 \]

Transplantation

\[ X_0 = 1 \]
Functional graft without acute rejection episode

\[ T_0 = 0 \]

\[ X_1 = 2 \]
Functional graft with at least one acute rejection episode

Return to dialysis

\[ X_2 = 3 \]
Dialysis

\[ T_2 \]
The Semi-Markovian process

Two characteristics of interest:

- **Transition probability** $p_{ij}$
  Probability that a patient in state $i$ enters in state $j$ on its next transition
  ⇒ Probability to do a Trajectory

- **Instantaneous hazard rate** $\lambda_{ij}(d)$ of the sojourn time from state $i$ to state $j$
  ⇒ Speed of transition
Modelling of transition probabilities $p_{ij}$

Probability that a patient in state $i$ enters in state $j$ on its next transition:

$$p_{ij} = P(X_{m+1} = j|X_m = i) \text{ and } \sum_j p_{ij} = 1, \text{ for } ij \in \epsilon \quad (1)$$

- Multinomial distributions + covariates

$$p_{ij}(W) = \frac{\exp(\gamma_{ij0} + \gamma_{ij} W)}{\sum_r \exp(\gamma_{ir0} + \gamma_{ir} W)}$$

- $r$: possible states following the transient states $i$
- $W$: covariate matrix
- $\gamma_{ij} = \{\gamma_{ij1}, \gamma_{ij2}, \ldots, \gamma_{ijR}\}'$: vector of associated regression coefficients.

- Constraint $\sum_{i \neq j} p_{ij}(W) = 1 \Rightarrow$ reference transition $ij_{ref}$. 
Transition probability $p_{ij}$ & Interpretation

If $AT_1 R = \begin{cases} 1 & \text{si } AT_1 R \geq 10 \\ 0 & \text{si } AT_1 R < 10 \end{cases}$

$$O_{R_{ij}} = \frac{AT_1 R = 1}{AT_1 R = 0} = \exp(\gamma_{ij})$$

⇒ Risk to experience the event $j$ as next event (after event $i$) relative to the
Risk to experience the referent event $j_{ref}$ as next event for high values of $AT_1 R$
Modelling of the sojourn time distributions $\lambda_{ij}(d)$

**Instantaneous hazard rate** $\lambda_{ij}(d)$ of the sojourn time from state $i$ to state $j$:

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

(2)

- **Hazard function** from state $i$ to state $j$ at time $d$:

$$
\lambda_{ij}(d|Z) = \lambda_{0,ij}(d) \exp(\beta_{ij}'Z)
$$

where

- $Z = \{Z_1, Z_2, ..., Z_L\}'$: vector of $L$ covariates
- $\beta_{ij} = \{\beta_{ij1}, \beta_{ij2}, ..., \beta_{ijL}\}'$: vector of associated regression coefficients
- $\lambda_{0,ij}(d)$: baseline hazard function
Instantaneous hazard rate $\lambda_{ij}$ & Interpretation

If $AT_1^R = \begin{cases} 1 & \text{si } AT_1^R \geq 10 \\ 0 & \text{si } AT_1^R < 10 \end{cases}$

\[
HR_{ij}^{AT_1^R=1/AT_1^R=0}(d) = \exp(\beta_{ij})
\]

$\Rightarrow$ Risk to do the trajectory $ij$ quickly for high values of $AT_1^R$
(1)+(2)

- Instantaneous joint probability of jumping towards the state $j$ from state $i$, after a certain sojourn time $d$ in this state $i$

\[
\alpha_{ij}(d) = \lim_{\Delta d \to 0^+} \frac{P(d \leq T_{m+1} - T_m < d + \Delta d, X_{m+1} = j | T_{m+1} - T_m > d, X_m = i)}{\Delta d}
\]

- and:

\[
\alpha_{ij}(d) = \frac{p_{ij} \lambda_{ij}(d) S_{ij}(d)}{\sum_{j:j \in \epsilon} p_{ij} S_{ij}(d)}
\]

with $S_{ij}(d)$ the survival function from state $i$ to state $j$
The likelihood function

- **Likelihood for a sample** $H$ **of subjects**:

$$L = \prod_{h \in H} \prod_{ij \in \epsilon_h \cup \epsilon'_h} \left[ p_{ij}(W_{ij}^h)f_{ij}(d_{ij}|Z_{ij}^h) \right]^{\delta_{\epsilon_h}} \left[ \sum_{jr \in \epsilon'_h} p_{jr}(W_{jr}^h)S_{jr}(d_{jr}|Z_{jr}^h) \right]^{1-\delta_{\epsilon_h}}$$

- **subject** $h$ **who jumps from state** $i$ **to state** $j$ **after a sojourn time** $d_{ij}$ **in this state** $i$ **given its covariates** $W_{ij}^h$ **and** $Z_{ij}^h$

- **subject** $h$ **right censored** **in the state** $i$ **after a sojourn time** $d_i$ **in this state** $i$ **given covariates** $W_{i}^h$ **and** $Z_i^h$

- $\lambda_{0,ij}(d)$: Parametric distribution
  $\Rightarrow$ Simple expression $\Rightarrow$ Easy computation to maximise likelihood
Model strategy

1. Parametric sojourn time distributions (Generalized Weibull, Weibull or Exponential)

2. $AT_1R$ forced in the SMM on the transition probabilities and the transition intensities (with possible time-varying effect)

3. Stepwise selection for covariate adjustment (with possible time-varying effect)

Generalized Weibull distribution

$$\lambda_{0,ij}(d) = \nu_{ij} \left( \frac{1}{\sigma_{ij}} \right)^{\nu_{ij}} d^{\nu_{ij}-1}, \text{with } \sigma_{ij} > 0 \text{ and } \nu_{ij} > 0$$
599 kidney transplant recipients
63 acute rejections/105 returns to dialysis/50 deaths
<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Estimate</th>
<th>SE</th>
<th>Wald</th>
<th>exp(Est)</th>
<th>95%CI</th>
<th>p.value</th>
</tr>
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<tbody>
<tr>
<td><strong>Intercept</strong></td>
<td></td>
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<tr>
<td>$\gamma_{13}$</td>
<td>1.91</td>
<td>0.27</td>
<td>7.04</td>
<td>6.74</td>
<td>[3.97-11.44]</td>
<td>0.0000</td>
</tr>
<tr>
<td>$\gamma_{14}$</td>
<td>0.90</td>
<td>0.40</td>
<td>2.27</td>
<td>2.46</td>
<td>[1.13-5.4]</td>
<td>0.0230</td>
</tr>
<tr>
<td>$\gamma_{24}$</td>
<td>-0.05</td>
<td>0.56</td>
<td>-0.08</td>
<td>0.95</td>
<td>[0.32-2.86]</td>
<td>0.9337</td>
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</table>

<table>
<thead>
<tr>
<th>Transition probabilities</th>
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<tbody>
<tr>
<td>$\gamma_{13}$ AT1R</td>
<td>-1.41</td>
<td>0.54</td>
<td>-2.62</td>
<td>0.24</td>
<td>[0.08-0.7]</td>
<td>0.0088</td>
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<tr>
<td>$\gamma_{14}$ AT1R</td>
<td>-1.74</td>
<td>0.50</td>
<td>-3.45</td>
<td>0.18</td>
<td>[0.07-0.47]</td>
<td>0.0006</td>
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<tr>
<td>$\gamma_{13}$ AgeR&gt;55</td>
<td>-0.52</td>
<td>0.43</td>
<td>-1.22</td>
<td>0.59</td>
<td>[0.25-1.38]</td>
<td>0.2233</td>
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<tr>
<td>$\gamma_{14}$ AgeR&gt;55</td>
<td>1.67</td>
<td>0.43</td>
<td>3.90</td>
<td>5.30</td>
<td>[2.28-12.3]</td>
<td>0.0001</td>
</tr>
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<tbody>
<tr>
<td>log($\sigma_{12}$)</td>
<td>-4.12</td>
<td>0.19</td>
<td>-22.08</td>
<td>0.02</td>
<td>[0.01-0.02]</td>
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<tr>
<td>log($\nu_{12}$)</td>
<td>1.66</td>
<td>0.45</td>
<td>3.68</td>
<td>5.28</td>
<td>[2.18-12.75]</td>
<td>0.0002</td>
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<tr>
<td>log($\theta_{12}$)</td>
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<td>0.50</td>
<td>5.95</td>
<td>19.95</td>
<td>[7.49-53.15]</td>
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<tr>
<td>$\beta_{12}$ AT1R, t&lt;4 months</td>
<td>-1.16</td>
<td>0.44</td>
<td>-2.65</td>
<td>0.31</td>
<td>[0.13-0.74]</td>
<td>0.0081</td>
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<tr>
<td>$\beta_{12}$ AT1R, t≥4 months</td>
<td>-2.70</td>
<td>0.65</td>
<td>-4.16</td>
<td>0.07</td>
<td>[0.02-0.24]</td>
<td>0.0000</td>
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<td>$\beta_{12}$ IncompABDR&gt;5</td>
<td>1.16</td>
<td>0.48</td>
<td>2.41</td>
<td>3.19</td>
<td>[1.24-8.17]</td>
<td>0.0161</td>
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<tr>
<td>$\beta_{13}$ AT1R t&lt;3 years</td>
<td>1.90</td>
<td>0.48</td>
<td>3.99</td>
<td>6.72</td>
<td>[2.62-17.21]</td>
<td>0.0001</td>
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<tr>
<td>$\beta_{13}$ AT1R t≥3 years</td>
<td>0.49</td>
<td>0.38</td>
<td>1.30</td>
<td>1.64</td>
<td>[0.78-3.45]</td>
<td>0.1928</td>
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<tr>
<td>log($\sigma_{13}$)</td>
<td>3.58</td>
<td>0.33</td>
<td>10.74</td>
<td>35.73</td>
<td>[18.71-68.22]</td>
<td>0.0000</td>
</tr>
<tr>
<td>log($\nu_{13}$)</td>
<td>0.26</td>
<td>0.14</td>
<td>1.83</td>
<td>1.29</td>
<td>[0.98-1.7]</td>
<td>0.0673</td>
</tr>
<tr>
<td>$\beta_{13}$ AgeR&gt;55</td>
<td>0.10</td>
<td>0.49</td>
<td>0.21</td>
<td>1.11</td>
<td>[0.43-2.9]</td>
<td>0.8298</td>
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<tr>
<td>$\beta_{13}$ PRA.T&gt;25</td>
<td>0.86</td>
<td>0.43</td>
<td>2.02</td>
<td>2.37</td>
<td>[1.02-5.5]</td>
<td>0.0430</td>
</tr>
<tr>
<td>log($\sigma_{14}$)</td>
<td>3.68</td>
<td>0.23</td>
<td>15.80</td>
<td>39.49</td>
<td>[25.16-61.98]</td>
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<tr>
<td>$\beta_{14}$ PRA.B&gt;25</td>
<td>0.94</td>
<td>0.44</td>
<td>2.12</td>
<td>2.56</td>
<td>[1.08-6.08]</td>
<td>0.0341</td>
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<tr>
<td>log($\sigma_{23}$)</td>
<td>3.43</td>
<td>0.85</td>
<td>4.04</td>
<td>30.85</td>
<td>[5.83-163.23]</td>
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<td>$\beta_{23}$ AT1R</td>
<td>1.38</td>
<td>0.75</td>
<td>1.83</td>
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<td>0.65</td>
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<td>5.54</td>
<td>[1.55-19.8]</td>
<td>0.0087</td>
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<tr>
<td>log($\sigma_{24}$)</td>
<td>4.03</td>
<td>0.56</td>
<td>7.23</td>
<td>56.03</td>
<td>[18.7-167.93]</td>
<td>0.0000</td>
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N=575 (24 patients were excluded because of missing data)

$\text{t} : \text{time since graft transplantation (years)}$

$\text{AT1R} : \text{pre-graft level of angiotensin II type 1 receptor greater or equal to 10}$

$\sigma_{ij}, \nu_{ij}, \theta_{ij} : \text{parameters of the Weibull distribution}$
Transition probabilities (first event)

- Significant association between pre-graft level of AT1R and first trajectory
- High pre-graft level of AT1R was associated to a increased risk to do an ARE after transplantation.
Patients who had an ARE had a decreased risk to do it quickly (increase of time to ARE) with high values of AT1R.

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<tr>
<td>$\beta_{12}$ AT1R, t\geq4 months</td>
<td>-2.70</td>
<td>0.65</td>
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<td>0.07</td>
<td>[0.02-0.24]</td>
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...
• The pre-graft level of AT1R seemed to not influence the time-to-return directly to dialysis in the 3 years following the transplantation.

• Patients who returned to dialysis directly after transplantation had a faster time-to-return to dialysis after three years post-transplantation with an high pre-graft level of AT1R.
• Association between the pre-graft level of AT1R and time to death was not significant
  ⇒ Not included in the model.
Transition probabilities (second event)

- No covariate candidate for the transition probabilities $p_{23}, p_{24}$ (few events).
Transition 2 → 3

- After an ARE, patients who returned to dialysis tended to have a faster time-to-return to dialysis with high level of AT1R.

**Transition intensities**

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<td>3.98</td>
<td>[0.91-17.29]</td>
<td>0.0672</td>
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</table>
Transition 2 → 4

- No covariate candidate for the transition intensity $\lambda_{24}(d)$ (few events).
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4. Conclusion
• Overcome the limits of traditional survival models

• Parametric distributions $\Rightarrow$ Likelihood simple & easy computable

• Interpretation
  • Probability of trajectory $(OR_{ij}^\gamma)$
  • Speed/Waiting time in a state $(HR_{ij}^\beta)$

$\Rightarrow$ Combination : Hazard ratio from the transition intensity of the Semi-Markov Model $\alpha_{ij} \ (HR_{ij}^\beta, \gamma(d))$
Future

- Hazard ratio from the transition intensity of the Semi-Markov Model with the time since graft transplantation \( (HR_{ij}^{\beta,\gamma}(t)) \)?

- Study other biomarkers in the complete cohort DIVAT
Merci de votre attention!
Affiliations

- Institut de transplantation urologie-néphrologie (Itun), **INSERM UMR 1064, CHU de Nantes**

- Equipe d’Accueil 4275 Biostatistique, recherche clinique et mesures subjectives en santé, **Université de Nantes**

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- Ministère de la Santé (PHRC National 2011)
- Agence Nationale de la Recherche (JCJC 2011)