ESTIMATION OF MIXED HIDDEN MARKOV MODELS WITH SAEM APPLICATION TO DAILY SEIZURES DATA

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Lewis Sheiner Student Session - PAGE 2010 Berlin
1 The data

2 Model development
   - Screening model
   - Placebo/drug model
   - Methodology
   - Results

3 Conclusion and perspectives
1 The data

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3 Conclusion and perspectives
Clinical design:

- double-blind, placebo-controlled, parallel-group and multicenter study
- 788 epileptic patients
- 12 weeks screening phase
  → standard antiepileptic therapy
- 12 weeks active treatment phase
  → standard antiepileptic therapy + placebo/pregabalin (0.6, 0.9, 1.2, 1.8g TID)

The data:

- the 788 individual sequences of daily seizure counts
  → 134,196 daily seizures counts
The data

We want to develop a placebo/drug model for this data.
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3 Conclusion and perspectives
Screening model
The existence of two (hidden) disease stages could be assumed.
The number of seizures at day $j$ ($y_{ij}$) is a random variable.

The distribution of $y_{ij}$ depends on the hidden state $z_{ij}$

- Poisson distribution with parameter $\lambda^{(i)}_{1}$ in state 1
- Poisson distribution with parameter $\lambda^{(i)}_{2}$ in state 2

$\lambda^{(i)}_{2} > \lambda^{(i)}_{1}$
The data show that epileptic patients are more likely to stay in the same state than to switch to the other state.

→ The sequences of hidden states have a Markovian dynamics.
Consider individual $i$

- $y_{ij}$: number of seizures at day $j$
- $z_{ij}$: hidden state at day $j$

$(z_{ij})$ is a hidden Markov chain with transition matrix

$$P_i = \begin{pmatrix} p_{11}^{(i)} & p_{12}^{(i)} \\ p_{21}^{(i)} & p_{22}^{(i)} \end{pmatrix}$$

- $y_{ij}|z_{ij} = 1 \sim \mathcal{P}(\lambda_1^{(i)})$ and $y_{ij}|z_{ij} = 2 \sim \mathcal{P}(\lambda_2^{(i)})$
Screening model

1. **n individual hidden Markov models**

   The transition matrix of $Z_i$ is defined by $p_{11}^{(i)}$ and $p_{21}^{(i)}$. Poisson distributions are chosen for the observations in each state $(\lambda_1^{(i)}, \lambda_2^{(i)})$.

2. **population approach**

   
   \[
   \begin{align*}
   \text{logit}(p_{11}^{(i)}) &= \beta_1 + \eta_{1i} \\
   \text{logit}(p_{21}^{(i)}) &= \beta_2 + \eta_{2i} \\
   \log(\lambda_1^{(i)}) &= \log(\lambda_1) + \eta_{3i} \\
   \log(\alpha^{(i)}) &= \log(\alpha) + \eta_{4i} \\
   \lambda_2^{(i)} &= \lambda_1^{(i)} + \alpha^{(i)}
   \end{align*}
   \]

   \[
   \eta_i = (\eta_{1i}, \eta_{2i}, \eta_{3i}, \eta_{4i}) \sim i.i.d. \mathcal{N}(0, \Omega)
   \]

3. **Here, the population parameters $\theta$ are $\beta_1$, $\beta_2$, $\lambda_1$, $\alpha$ and the elements of $\Omega$.**
We want to develop two mixed hidden Markov models simultaneously (screening phase vs treatment phase).

In the treatment model, the treatment dose could influence both the mean number of seizures in each state and the transition structure of the hidden Markov chain.
Placebo/drug model (1)

**Screening phase**

\[
\begin{align*}
\text{logit}(p_{11i}^S) & = \beta_1^S + \eta_1i \\
\text{log}(\lambda_{1i}^S) & = \lambda_1^S + \eta_3i \\
\log(\alpha_i^S) & = \alpha_i^S + \eta_4i \\
\lambda_{2i}^S & = \lambda_{1i}^S + \alpha_i^S
\end{align*}
\]

**Treatment phase**

\[
\begin{align*}
\text{logit}(p_{11i}^T) & = \beta_1^S + \delta_1i + \gamma_1 D_i \\
\text{log}(\lambda_{1i}^T) & = \log(\lambda_{1i}^S) + \delta_3i + \gamma_3 D_i \\
\log(\alpha_i^T) & = \log(\alpha_i^S) + \delta_4i + \gamma_4 D_i \\
\lambda_{2i}^T & = \lambda_{1i}^T + \alpha_i^T
\end{align*}
\]

\[
\begin{align*}
\delta_{1i} & = \delta_1 + \eta_5i \\
\delta_{2i} & = \delta_2 + \eta_6i \\
\delta_{3i} & = \delta_3 + \eta_7i \\
\delta_{4i} & = \delta_4 + \eta_8i
\end{align*}
\]
Placebo/drug model (2)

**Screening phase**

\[
\begin{align*}
\text{logit}(p_{11i}) &= \beta_1^S + \eta_1i \\
\text{logit}(p_{21i}) &= \beta_2^S + \eta_2i \\
\log(\lambda_{1i}^S) &= \lambda_1^S + \eta_3i \\
\log(\alpha_i^S) &= \alpha_i^S + \eta_4i \\
\lambda_{2i}^S &= \lambda_{1i}^S + \alpha_i^S
\end{align*}
\]

**Treatment phase**

\[
\begin{align*}
\text{logit}(p_{11i}^T) &= \beta_1^S + \delta_{1i} + \gamma_1 D_i \\
\text{logit}(p_{21i}^T) &= \beta_2^S + \delta_{2i} + \gamma_2 D_i \\
\log(\lambda_{1i}^T) &= \log(\lambda_{1i}^S) + (\delta_{3i} + \gamma_3 D_i)(1 - e^{-K_3 t}) \\
\log(\alpha_i^T) &= \log(\alpha_i^S) + (\delta_{4i} + \gamma_4 D_i)(1 - e^{-K_4 t}) \\
\lambda_{2i}^T &= \lambda_{1i}^T + \alpha_i^T \\
\delta_{1i} &= \delta_1 + \eta_{5i} \\
\delta_{2i} &= \delta_2 + \eta_{6i} \\
\delta_{3i} &= \delta_3 + \eta_{7i} \\
\delta_{4i} &= \delta_4 + \eta_{8i}
\end{align*}
\]
1) **Estimation of the population parameters (M.L.E.)**

\[
\hat{\theta} = \arg\max_{\theta} p(Y; \theta)
\]

→ **SAEM algorithm**

→ The **Baum Welch algorithm** is used to compute

\[
p(Y_i, \Psi_i; \theta) = \sum_{Z_i} p(Y_i, Z_i, \Psi_i; \theta)
\]

at each iteration of SAEM.
2) Estimation of the individual parameters (M.A.P.)

\[ \hat{\psi}_i = \arg\max p(\psi_i | y_i; \hat{\theta}) \]

3) Estimation of the sequences of hidden states (MAP)

\[ \hat{z}_i = \arg\max p(z_i | y_i, \hat{\psi}_i; \hat{\theta}) \]

→ Viterbi algorithm

Our methodology has been implemented in MONOLIX 3.1.
Convergence of SAEM

SAEM converges in few iterations (25’ for the complete data).
### Population parameters estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>s.e.</th>
<th>r.s.e. (%)</th>
<th>p-value</th>
<th>Estimate</th>
<th>s.e.</th>
<th>r.s.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_1^S$</td>
<td>2.31</td>
<td>0.057</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>$\beta_2^S$</td>
<td>-0.435</td>
<td>0.074</td>
<td>17</td>
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<tr>
<td>$\log(\lambda_1^S)$</td>
<td>-1.87</td>
<td>0.056</td>
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<tr>
<td>$\log(\alpha^S)$</td>
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<td>0.055</td>
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<td></td>
</tr>
<tr>
<td>$\delta_1$</td>
<td>5.19</td>
<td>0.67</td>
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<td></td>
</tr>
<tr>
<td>$\gamma_1$</td>
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<td>0.00065</td>
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</tr>
<tr>
<td>$\delta_2$</td>
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<td>0.21</td>
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<td></td>
</tr>
<tr>
<td>$\gamma_2$</td>
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<td>0.00046</td>
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<td></td>
</tr>
<tr>
<td>$\delta_3$</td>
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<td>0.17</td>
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<td></td>
</tr>
<tr>
<td>$\gamma_3$</td>
<td>0.000769</td>
<td>0.00016</td>
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<td>$4.10^{-5}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\delta_4$</td>
<td>-0.307</td>
<td>0.13</td>
<td>42</td>
<td>$10^{-6}$</td>
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</tr>
<tr>
<td>$\gamma_4$</td>
<td>-0.00971</td>
<td>0.00024</td>
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<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Variance Term ($\omega^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>$\delta_1$</td>
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<tr>
<td>$\delta_2$</td>
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<tr>
<td>$\delta_3$</td>
</tr>
<tr>
<td>$\delta_4$</td>
</tr>
<tr>
<td>$\gamma_1$</td>
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<tr>
<td>$\gamma_7$</td>
</tr>
<tr>
<td>$\gamma_8$</td>
</tr>
</tbody>
</table>
The individual parameters and the sequences of hidden states have then been estimated.
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3 Conclusion and perspectives
(A) Application of MHMM to seizure count data

- Mixed hidden Markov models are easy to interpret and provide a possible description of the seizure dynamics.
- Our models can also handle a dose effect.
(B) **Our new methodology**

→ Monte Carlo studies showed that our methodology has **good practical properties**:  
  - The population parameters are accurately estimated with SAEM (small bias and RMSE).
  - The estimated s.e. give a good evaluation of the estimates’ uncertainty.
  - SAEM is fast.

→ Our algorithms are implemented in the **Monolix** software.

→ Our methodology for discrete state space models can be extended for continuous state space models (ex: SDE, see poster PAGE 2010).
Dose and time-dependent drug effect.

Extension to Generalized Poisson distributions.

Selection of the number of hidden states.

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