Joint Modelling of Event Counts and Survival Times: Example Using Data from the MESS Trial

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Outline

Motivation and Introduction
  Epilepsy
  MRC Multicentre Trial for Early Epilepsy and Single Seizures

Modelling
  Survival Analysis
  Joint Modelling of Event Counts and Survival Times

Application to MESS
  Exploratory Analysis
  Some Results

Further Work
  Modifications and Extensions
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To Treat or not to Treat

- Antiepileptic drugs (AEDs) come with side effects.
- In the case of early epilepsy are AEDs absolutely necessary?
- Does seizure type have an effect on risk of future seizure, particularly risk of future tonic-clonic seizure (regarded as a major seizure)?
Early Epilepsy and Single Seizures

- On average 50% of people do not experience a recurrence after a single seizure
- Around 20 – 30% of people will never achieve long-term remission
- Risk of future seizures increases with the number of previous seizures

(Marson et al. 2005)
The MESS Trial

- MESS randomised 1443 patients to either immediate or deferred treatment
- Eligibility criteria:
- Outcomes of interest - time to first seizure, time to first tonic-clonic seizure
The MESS Trial

- MESS randomised 1443 patients to either immediate or deferred treatment
- Eligibility criteria:
  1. Aged at least one month
- Outcomes of interest - time to first seizure, time to first tonic-clonic seizure
The MESS Trial

- MESS randomised 1443 patients to either immediate or deferred treatment
- Eligibility criteria:
  2. Had experienced at least one epileptic seizure
- Outcomes of interest - time to first seizure, time to first tonic-clonic seizure
MRC Multicentre Trial for Early Epilepsy and Single Seizures

The MESS Trial

- MESS randomised 1443 patients to either immediate or deferred treatment
- Eligibility criteria:
  3. Both clinician and patient uncertain whether to proceed with treatment
- Outcomes of interest - time to first seizure, time to first tonic-clonic seizure
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Modelling Survival Data

- Time to event
- Two functions are of central interest:
  - Survivor function - $S(t) = \Pr(T \geq t)$
  - Hazard function - $h(t) = \lim_{\delta t \to 0} \left\{ \frac{\Pr(t \leq T \leq t + \delta t | T \geq t)}{\delta t} \right\}$
- Censoring: actual survival time not observed for an individual
  - Right Censoring: observed, censored survival time is less than actual, but unknown survival time
Joint Modelling of Event Counts and Survival Times

The Data

Data arrives in two parts:

- **Pre-randomisation event count** - the number of seizures an individual has experienced in a given period of time prior to entry to the trial, and

- **Post-randomisation survival times** - following randomisation to an antiepileptic treatment, time to first seizure is measured for each individual.

(Cowling et al. 2006)
The Model I

- Standard survival analysis may treat the event count information as a covariate
- We jointly model the pre-randomisation seizure counts and post-randomisation survival times
The Model I

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Joint Modelling of Event Counts and Survival Times

The Model I

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- We allow the pre-randomisation seizure count to depend on the influential baseline covariates
- Random effects encapsulate additional heterogeneity within the population
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- We jointly model the pre-randomisation seizure counts and post-randomisation survival times
- We assume a Poisson process for seizures
- We allow the pre-randomisation seizure count to depend on the influential baseline covariates
- Random effects encapsulate additional heterogeneity within the population
- For post-randomisation survival times the rate is updated to allow for treatment
The Model II

Therefore the joint model is specified by the following equations:

\[
\begin{align*}
    f_{X|\nu}(x_i | \nu_i; \lambda_i, u_i) &= \frac{(\lambda_i u_i \nu_i)^{x_i} \exp(-\lambda_i u_i \nu_i)}{x_i!}, \\
    f_{Y|\nu}(y_i | \nu_i; \lambda_i, \psi_i) &= \lambda_i \psi_i \nu_i \exp(-\lambda_i \psi_i \nu_i y_i), \\
    g_{\nu}(\nu_i; \alpha) &= \frac{\alpha^\alpha \nu_i^{\alpha-1} \exp(-\alpha \nu_i)}{\Gamma(\alpha)},
\end{align*}
\]

with \( \lambda_i = \exp(\beta'_1 z_{1i}) \) and \( \psi_i = \exp(\beta'_2 z_{2i}) \).
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Seizures of Any Type

- Partial seizures perform worst
- Treatment doesn’t appear to have an effect for partial
- For all others groups, immediate treatment favoured
- Deferred in all groups asymptote at about $S(t) = 0.4$
Tonic-Clonic Seizures

- Partial seizures perform best
- Treatment doesn’t appear to have an effect for partial
- For all others groups immediate treatment favoured
- Deferred groups asymptote at different levels
### Parameter Estimates

<table>
<thead>
<tr>
<th>Term</th>
<th>Regression Coefficient</th>
<th>Estimates (standard errors) for the following models:</th>
<th>Negative Binomial</th>
<th>Lomax</th>
<th>Joint Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha )</td>
<td></td>
<td></td>
<td>0.666 (0.026)</td>
<td>0.203 (0.007)</td>
<td>0.800 (0.033)</td>
</tr>
<tr>
<td>( \lambda_i )</td>
<td>( \beta_{1,0} )</td>
<td></td>
<td>-2.544 (0.146)</td>
<td></td>
<td>-2.793 (0.151)</td>
</tr>
<tr>
<td></td>
<td>( \beta_{1,age} )</td>
<td></td>
<td>-0.004 (0.002)</td>
<td></td>
<td>-0.006 (0.002)</td>
</tr>
<tr>
<td></td>
<td>( \beta_{1,2^\circ \text{gen}} )</td>
<td></td>
<td>-0.473 (0.150)</td>
<td></td>
<td>-0.541 (0.161)</td>
</tr>
<tr>
<td></td>
<td>( \beta_{1,\text{gen}} )</td>
<td></td>
<td>-0.327 (0.143)</td>
<td></td>
<td>-0.351 (0.151)</td>
</tr>
<tr>
<td></td>
<td>( \beta_{1,\text{other}} )</td>
<td></td>
<td>-1.195 (0.313)</td>
<td></td>
<td>-1.036 (0.348)</td>
</tr>
<tr>
<td>( \psi_i )</td>
<td>( \beta_{2,0} )</td>
<td></td>
<td>-4.145 (0.418)</td>
<td>-2.992 (0.281)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( \beta_{2,\text{trt}} )</td>
<td></td>
<td>0.905 (0.181)</td>
<td>-1.716 (0.351)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( \beta_{2,\text{age}} )</td>
<td></td>
<td>-0.007 (0.005)</td>
<td>-0.003 (0.004)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( \beta_{2,\text{trt} \times \text{age}} )</td>
<td></td>
<td>-0.0871 (0.371)</td>
<td>-0.710 (0.292)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( \beta_{2,2^\circ \text{gen}} )</td>
<td></td>
<td>-1.168 (0.356)</td>
<td>-0.977 (0.280)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( \beta_{2,\text{gen}} )</td>
<td></td>
<td>-2.264 (0.665)</td>
<td>-1.456 (0.709)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( \beta_{2,\text{other}} )</td>
<td></td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>( \beta_{2,\text{trt} \times 2^\circ \text{gen}} )</td>
<td></td>
<td>2.152 (0.383)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>( \beta_{2,\text{trt} \times \text{gen}} )</td>
<td></td>
<td>2.067 (0.366)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>( \beta_{2,\text{trt} \times \text{other}} )</td>
<td></td>
<td>3.954 (0.873)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>( \beta_{2,\text{ln(rate)}} )</td>
<td></td>
<td>0.148 (0.052)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Log-likelihood (d.f.)</td>
<td></td>
<td></td>
<td>3701 (1414)</td>
<td>5484 (1412)</td>
<td>9739 (1404)</td>
</tr>
</tbody>
</table>

- Considerable heterogeneity overall
- Covariate effects for seizure count slightly increased in joint model
- Joint model picks up interactions Lomax could not
Motivation and Introduction

Modelling

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Interpretation of $\hat{\psi}$

What percentage of seizures experienced by an individual pre-randomisation will be experienced post-randomisation?

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>Percentage (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immediate</td>
</tr>
<tr>
<td>Partial</td>
<td>5.9 (2.9,8.8)</td>
</tr>
<tr>
<td>$2^\circ$ Gen</td>
<td>2.5 (1.7,3.5)</td>
</tr>
<tr>
<td>Generalised</td>
<td>1.9 (1.4,2.6)</td>
</tr>
<tr>
<td>Other</td>
<td>1.2 (0.3,4.5)</td>
</tr>
</tbody>
</table>

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Extensions to the Model
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- Inclusion of further survival times - Model developed for first and second seizures
Extensions to the Model

- Inclusion of further survival times
- Cure rate models - Large proportion of individuals never experience another seizure
Extensions to the Model

- Inclusion of further survival times
- Cure rate models
- Modifications to $\psi$ - Evidence to suggest that $\psi$ may change through time
Extensions to the Model

- Inclusion of further survival times
- Cure rate models
- Modifications to $\psi$
- Residuals - Examine residuals to assess performance of our model
For Further Reading
