Joint modelling of longitudinal outcomes and clinical endpoints

JoineR & JoineR-M

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Introduction
- In clinical trials or cohort studies, measurements are repeatedly measured over time (e.g. blood pressure), which we call **longitudinal data**
- In addition, the time to one or more clinical endpoints (e.g. death) is recorded, which we call **time-to-event data**
- Historically, these data have been **analysed separately**

Longitudinal outcomes

<table>
<thead>
<tr>
<th>Correlated?</th>
<th>Example</th>
<th>Time-to-event outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interest = longitudinal data</strong></td>
<td><img src="image1" alt="Left: two biomarkers measured from blood tests repeatedly over time for 312 patients with primary biliary cirrhosis randomised to a new drug" /></td>
<td><img src="image2" alt="Right: cumulative incidence curves for 2 competing events" /></td>
</tr>
<tr>
<td><strong>Standard model:</strong> (generalised) linear mixed effects regression model</td>
<td>Why does it matter?</td>
<td><strong>Interest = time-to-event data</strong></td>
</tr>
<tr>
<td><strong>Potential problems:</strong></td>
<td>Ignoring the correlation between information from the same patient can result in <strong>incorrect conclusions</strong> about the new treatments and predictions of clinical endpoints</td>
<td><strong>Standard model:</strong> Cox proportional hazards regression model</td>
</tr>
<tr>
<td>• Sickest patients more likely to drop out of study</td>
<td></td>
<td><strong>Potential problems:</strong></td>
</tr>
<tr>
<td>• We call this <strong>informative missingness</strong></td>
<td></td>
<td>• Biomarkers measured with error</td>
</tr>
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<td></td>
<td></td>
<td>• Time-varying covariates modelled as constant between measurement times</td>
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</tbody>
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Why does it matter?

- **Correlated?**
- **Standard model:** Cox proportional hazards regression model
- **Potential problems:**
  - Biomarkers measured with error
  - Time-varying covariates modelled as constant between measurement times

Why does it matter?

- Ignoring the correlation between information from the same patient can result in **incorrect conclusions** about the new treatments and predictions of clinical endpoints

Proposed solution

**Combined analysis** of the outcomes (joint modelling) using some unknown variables to capture the association between the two types of outcome

Benefits of joint modelling

- **More efficient** estimates of treatment effects = **reduced number of patients required for studies and increased power**
- **Less biased** estimates of the treatment effects = **closer to ‘truth’**
- **More accurate** predictions of events = **better medical decision-making**

Extension to multivariate data (JoineR-M)

- Joint modelling methodology has been predominantly focused on univariate (single longitudinal and event outcome) data
- In practice, multiple longitudinal outcomes and event times will be recorded (multivariate data)
- Multivariate data greatly increases the complexity of model estimation:
  - **Computational time** grows with increasing number of outcomes
  - **Longitudinal outcomes** take different types (e.g. continuous, binary, ordinal)

Software development

- **joineR** is a freely available user-friendly software package, currently fit joint models for univariate data
- **JoineR** will be **expanded** over the next 2-years to:
  - Include multivariate longitudinal outcomes
  - Model competing risks outcomes
  - Provide model diagnostics to allow inspection of model fit
  - **Training workshops** for biomedical researchers to inform the joint modelling methods and software

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