Challenges and opportunities for sequential knowledge integration within a Bayesian PK/PD modeling framework

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Outline

• Case Study & Proposed K-PD model for synergy

• Sequential Integration: Modeling Aspects
  1. Prior specification
  2. Choice of random effects
  3. Types of sequential integration

• Simulation study

• Discussion
Case Study & Proposed K-PD model for synergy
Case study

**Aim:** To assess the safety (decrease of body temperature) resulting from the co-administration of a novel molecule with a marketed compound using in-vivo data.

11 studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marketed compound dose (mpk)</td>
<td>10</td>
<td>2.5</td>
<td>10</td>
<td>0.63</td>
<td>10</td>
<td>0.16</td>
<td>2.5</td>
<td>0.63</td>
<td>0.16</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>Novel compound dose (mpk)</td>
<td>40</td>
<td>40</td>
<td>10</td>
<td>40</td>
<td>2.5</td>
<td>40</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>40</td>
</tr>
</tbody>
</table>
Case study – Example from study 1

No change

Effect in line with historical data

More pronounced change, later maximal effect
Proposed Bayesian K-PD model for synergy

PK Part: One compartment model with oral absorption

\[
\begin{align*}
\frac{dA_{e, it}}{dt} &= -k_a A_{e, it} \\
\frac{dC_{it}}{dt} &= k_a A_{e, it} - k_e C_{it}
\end{align*}
\]

PD part: Indirect response (turnover) model

\[
R_{it} \sim N(\bar{R}_{it}, \sigma_R^2)
\]

\[
\frac{d\bar{R}_{it}}{dt} = k_{in} \left(1 - \frac{I_{max}C_{it}}{IC_{50} + C_{it}}\right) - k_{out} \bar{R}_{it} \quad R_{i0} = \frac{k_{in}}{k_{out}}
\]

\[
IC_{50} = e^{\alpha D_{n,i} + \beta D_{e,i} D_{n,i}}
\]

Response: body temperature
Plasma concentration of the marketed compound (virtual)
Marketed compound dose
Novel compound dose
Main effect of the novel compound
Interaction coefficient
Proposed Bayesian K-PD model for synergy

Initial analysis:

- Historical data $\rightarrow$ Frequentist approach (NONMEM)
- Study 1-11 $\rightarrow$ Bayesian approach (Stan)

Different ways of pooling data:

- **Simple pooling**: Pooling study 1-11 together
- **Sequential integration**: The posteriors from a study are used to determine the hyperparameters of the priors of the following study
Sequential Integration: Modeling Aspects
1. Prior Specification
Prior Specification – Methods

The prior distributions were initially chosen by setting:

- Expected values $\rightarrow$ point estimates
- Standard deviations $\rightarrow$ double s.e.

From the analysis of historical data of the marketed compound

Prior specification study

Different priors chosen for $I_{max}$:
- Original prior (SD=0.02)
- Prior with doubled SD (SD=0.04)
- Uniform distribution (SD=0.29)

Analysis run on studies 1, 2, 3 pooled
Prior Specification – Results

Prior for $I_{max}$: SD=0.02
Prior Specification – Results

Prior for $I_{max}$: SD=0.04
Prior Specification – Results

Prior for $I_{max}$: SD=0.29
## Prior Specification – Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$I_{\text{max}}$ SD=0.02</th>
<th>$I_{\text{max}}$ SD=0.04</th>
<th>$I_{\text{max}}$ SD=0.29</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\bar{R}_0$</td>
<td>37.12 (36.99; 37.26)</td>
<td>37.15 (37.03; 37.27)</td>
<td>37.16 (37.04; 37.28)</td>
</tr>
<tr>
<td>$k_e$</td>
<td>0.53 (0.39; 0.71)</td>
<td>0.55 (0.41; 0.71)</td>
<td>0.61 (0.44; 0.82)</td>
</tr>
<tr>
<td>$k_{\text{out}}$</td>
<td>1.15 (0.88; 1.52)</td>
<td>0.91 (0.63; 1.29)</td>
<td>0.78 (0.48; 1.12)</td>
</tr>
<tr>
<td>$I_{\text{max}}$</td>
<td>0.15 (0.12; 0.19)</td>
<td>0.20 (0.14; 0.27)</td>
<td><strong>0.24</strong> (0.17; 0.34)</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>-1.42 (-2.09; -0.51)</td>
<td>-1.58 (-2.08; -1.00)</td>
<td>-1.55 (-2.04; -1.09)</td>
</tr>
<tr>
<td>$\beta$</td>
<td>-2.85 (-7.34; -0.15)</td>
<td>-0.51 (-3.29; 0.48)</td>
<td>-0.13 (-1.17; 0.67)</td>
</tr>
<tr>
<td>$\sigma_{R_0}^2$</td>
<td>0.31 (0.19; 0.51)</td>
<td>0.26 (0.15; 0.44)</td>
<td>0.25 (0.15; 0.41)</td>
</tr>
<tr>
<td>$\sigma_R^2$</td>
<td>0.41 (0.36; 0.48)</td>
<td>0.41 (0.36; 0.48)</td>
<td>0.41 (0.36; 0.48)</td>
</tr>
</tbody>
</table>

The less informative the prior is specified, the larger the bias is observed; The correlated parameters compensate each other.
Sequential Integration: Modeling Aspects
2. Choice of Random Effect
Choice of Random Effect – Methods

Different random effect choices considered:

- Random baseline: $R_{i0} \sim N(\bar{R}_0, \sigma^2_{R_0})$
- Random $k_{out}$: $\log(k_{out,i}) \sim N(\log(\bar{k}_{out}), \sigma^2_{\log(k_{out})})$
- Random $k_{in}$: $\log(k_{in,i}) \sim N(\log(\bar{k}_{in}), \sigma^2_{\log(k_{in})}) \rightarrow$ convergence issues

Model run on data pooled altogether
Choice of Random Effect – Results

Posterior predictions and predictive intervals, study 1

Random baseline model

Random $k_{out}$ model
Choice of Random Effect – Results

Distributions of the posterior means of subject-specific random effects

Random baseline model

Random $k_{out}$ model

$k_{out}$ for combination group
Choice of Random Effect – Results

Distributions of the posterior means of subject-specific random effects

Random baseline model

Random \( k_{out} \) model

Overcompensation between \( k_{out} \) and \( \beta \)

\( k_{out} \) for combination group
Sequential Integration: Modeling Aspects
3. Types of Sequential Integration
**Types of sequential integration – Methods**

Different types of sequential pooling compared with simple pooling:

1. Pooling of 1 study at a time*, keeping the original study order
2. Pooling of 1 study at a time*, order permutation

**Permuted order:**

<table>
<thead>
<tr>
<th>Study</th>
<th>5</th>
<th>3</th>
<th>8</th>
<th>11</th>
<th>6</th>
<th>1</th>
<th>2</th>
<th>9</th>
<th>7</th>
<th>4</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ex. treatment dose (mpk)</td>
<td>10</td>
<td>10</td>
<td>0.63</td>
<td>0.04</td>
<td>0.16</td>
<td>10</td>
<td>2.5</td>
<td>0.16</td>
<td>2.5</td>
<td>0.63</td>
<td>0.04</td>
</tr>
<tr>
<td>Nov. treatment dose (mpk)</td>
<td>2.5</td>
<td>10</td>
<td>10</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>10</td>
<td>10</td>
<td>40</td>
<td>10</td>
</tr>
</tbody>
</table>

*The first three studies were pooled together to guarantee the identifiability of $\beta$. 
Types of sequential integration – Methods

Different types of sequential pooling compared with simple pooling:

3. Pooling of 3 studies at a time, keeping the original study order

4. Sequentially pooling 5 “optimal” studies, which were sampled from the existing data so that each of them contains all possible dose combinations
Types of sequential integration – Methods

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Types of sequential integration – Results

Posterior predictions and predictive intervals, study 1

1. Sequential integration, 1 study at a time

2. Sequential integration, permuted order
Types of sequential integration – Results

Posterior predictions and predictive intervals, study 1

3. Sequential integration, 3 studies at a time

4. Sequential integration, optimal studies
Types of sequential integration – Results

Posterior predictions and predictive intervals, study 1

Bayesian integration type

1. One study at a time
2. Permuted order
3. Three studies at a time
4. Five optimal studies
Simple pooling
Simulation study
Simulation study

Aim: Assess to what extent of model complexity the sequential integration deviates from the simple pooling

<table>
<thead>
<tr>
<th>Model</th>
<th>Informative</th>
<th>Non-hierarchical</th>
<th>Hierarchical (2 uncorrelated R.E.)</th>
<th>Hierarchical (2 correlated R.E.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear model</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Informative</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Uninformative</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>1-comp PK model*</td>
<td>Informative</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Uninformative</td>
<td>✓</td>
<td>!</td>
<td>!</td>
</tr>
<tr>
<td>Sigmoidal Emax model</td>
<td>Informative</td>
<td>✓</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Uninformative</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

* Linear kinetics, non-linear over time, sequential integration over doses
Discussion
Discussion

• The Bayesian sequential integration is an appealing approach, as it allows to analyze each study immediately instead of waiting for the end of data collection.

• If a **linear** model is performed, this technique produces **unbiased** estimates.

• Mitigating the risk of bias when a **nonlinear** model is performed can be achieved via:
  • Carefully designed integration of studies, to avoid the risk of parameter identifiability issues
  • The specification of informative prior distributions
  • The allocation of random effects on parameters that are not highly correlated with other parameters.
References


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