Bayesian sequential integration within a preclinical PK-PD modeling framework
Lessons learned

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Drouville, Dragonfish
Drouville is a patient, graphic designer and artist from Argentina who has survived Multiple Myeloma and a relapse.
Outline

• Case Study & Proposed (P)K-PD model for synergy

• Bayesian Sequential Integration: Modeling Aspects
  1. Prior specification
  2. Choice of random effect
  3. Design of experiments

• Simulation study

• Discussion
Case Study & Proposed (P)K-PD model for synergy
**Case study**

**Aim:** To assess the safety (decrease of body temperature) resulting from the co-administration of marketed and novel compounds using 11 in-vivo trials.

One specific dose combination for each trial, collected over different time points.

<table>
<thead>
<tr>
<th>Trial</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 trial 1

More pronounced decrease, later maximal effect

Body temperature decrease

No change

No change
Proposed (P)K-PD model for synergy

**Turnover model** assuming that a **virtual** concentration of the marketed compound inhibits the production of body heat

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

The novel compound **increases the potency** of the marketed compound

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

\(D_{e,i}\)=Marketed compound dose  
\(D_{n,i}\)=Novel compound dose
Initial analysis: Bayesian pooling

Frequentist analysis (NONMEM)

Historical trial

Trial 1

Trial 2

Trial 3

Trial 1-11: Bayesian analysis (Stan)

Informative priors chosen by setting:

- Expected values $\rightarrow$ point estimates
- Standard deviations $\rightarrow$ double of s.e. from the analysis of historical data
Bayesian sequential integration

The posteriors from one trial are used to determine the hyperparameters of the priors of the next trial.

Benefits:
• Analyze the data from every **single** trial **immediately**, instead of waiting for the end of data collection
• The parameter estimates resulting from each integration step may be used for the **design** of the next trials

Challenge:
Performing a complex nonlinear hierarchical model on small data during the first integration steps may cause **practical identifiability issues**
Bayesian Sequential Integration: Modeling Aspects
1. Prior Specification
Different priors chosen for $I_{max}$:

- Prior used for the initial analysis (SD=0.02)
- Prior with doubled SD (SD=0.04)
- Uniform distribution (SD=0.29)

Analysis run on trials 1, 2, 3 pooled together (to allow for identifiability of parameter $\beta$)
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>$I_{max}$ SD=0.02</th>
<th>$I_{max}$ SD=0.04</th>
<th>$I_{max}$ SD=0.29</th>
</tr>
</thead>
<tbody>
<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>$k_{out}$</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>$I_{max}$</td>
<td>0.15 (0.12; 0.19)</td>
<td>0.20 (0.14; 0.27)</td>
<td>0.24 (0.17; 0.34)</td>
</tr>
<tr>
<td>$\overline{R}_0$</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>$\alpha$</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>$\sigma^2_{\overline{R}_0}$</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>$\sigma^2_R$</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.

**Take home message n.1** It is better to use informative priors, whenever possible.
Bayesian Sequential Integration: Modeling Aspects

2. Choice of random effect
Choice of random effect – Methods

Different random effect choices considered:

- Random baseline
- Random $k_{out}$
- Random $k_{in} \rightarrow$ convergence issues

Model run on all trials pooled together
Choice of random effect – Results

Posterior predictions and predictive intervals, trial 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
Choice of random effect – Results

Distributions of the posterior means of subject-specific random effects

Random baseline model

Random $k_{out}$ model

Take home message n.2  Better to allocate the random effect on a parameter that is easier to estimate, to avoid overcompensations
Bayesian Sequential Integration: Modeling Aspects
3. Design of experiments
Design of experiments – Methods

Different types of sequential integrations compared with simple pooling:

1. Pooling of 1 trial at a time*, keeping the original trial order
2. Pooling of 1 trial at a time*, order permutation
3. Pooling of 3 trials at a time, keeping the original trial order
4. Sequentially pooling 5 “optimal” trials: sampled from the existing data so that each of them contains all possible dose combinations

*The first three trials were pooled together to guarantee the identifiability of $\beta$. 
Design of experiments – Results

Posterior predictions and predictive intervals, trial 1

1. Sequential integration, 1 trial at a time

2. Sequential integration, permuted order
Design of experiments – Results

Posterior predictions and predictive intervals, trial 1

1. Sequential integration, 1 trial at a time

3. Sequential integration, 3 trials at a time
Design of experiments – Results

Posterior predictions and predictive intervals, trial 1

1. Sequential integration, 1 trial at a time

4. Sequential integration, optimal trials
Design of experiments – Results

Posterior predictions, trial 1

Practical identifiability issues at first integration steps when trials are poorly designed.

Take home message n.3
Trial design plays a crucial role in the performance of Bayesian sequential integration.
Simulation study
Aim

To compare Bayesian pooling with sequential integration using linear and nonlinear models (1000 simulation runs):

1. Linear model
2. One-compartment PK model
3. Sigmoidal Emax model

• For each model, both absence and presence of inter-individual variability (IIV) is assessed → different scenarios

• For each scenario, informative and uninformative prior distributions are considered → different sub-scenarios

All scenarios reflect the setting of pre-clinical trials (small sample size, one or few doses per trial).
## Results

<table>
<thead>
<tr>
<th>Model</th>
<th>Non-hierarchical</th>
<th>Hierarchical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear model</td>
<td>Informative</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Uninformative</td>
<td>✓</td>
</tr>
<tr>
<td>1-comp PK model*</td>
<td>Informative</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Uninformative</td>
<td>✓</td>
</tr>
<tr>
<td>Sigmoidal Emax model</td>
<td>Informative</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Uninformative</td>
<td>✓</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 every single trial immediately without reanalyzing the data up to the current study.

• If a linear model is performed and the parameters are not correlated, this technique produces unbiased and precise 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 practical identifiability issues
  • The specification of informative prior distributions
  • The allocation of random effects on parameters that are easier to estimate
Thank you!

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