A Bayesian PK/PD model for synergy

A case study

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Improving drug development

Outline

- Case study
- Methods
- Results
- Conclusions and future perspectives

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Case study

Aim: To assess the safety resulting from the co-administration of a novel molecule with an existing treatment using in-vivo data

Case study

Data sets:

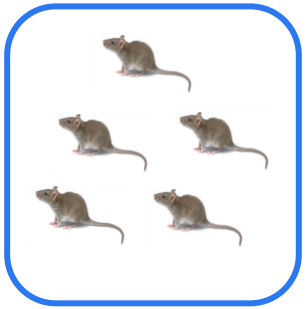
- **Historical study**: Dose-response longitudinal data where only the existing treatment is administered (55 rats in total).
- **11 Synergy studies**: Both existing and novel treatments are assessed.

Case study

Synergy studies design. In each study: 20 rats, 5 for each treatment group

Vehicle

Existing treatment only



Novel treatment only

Treatments combination

Study	1	2	3	4	5	6	7	8	9	10	11
Existing treatment dose (mpk)	10	2.5	10	0.63	10	0.16	2.5	0.63	0.16	0.04	0.04
Novel treatment dose (mpk)	40	40	10	40	2.5	40	10	10	10	10	40

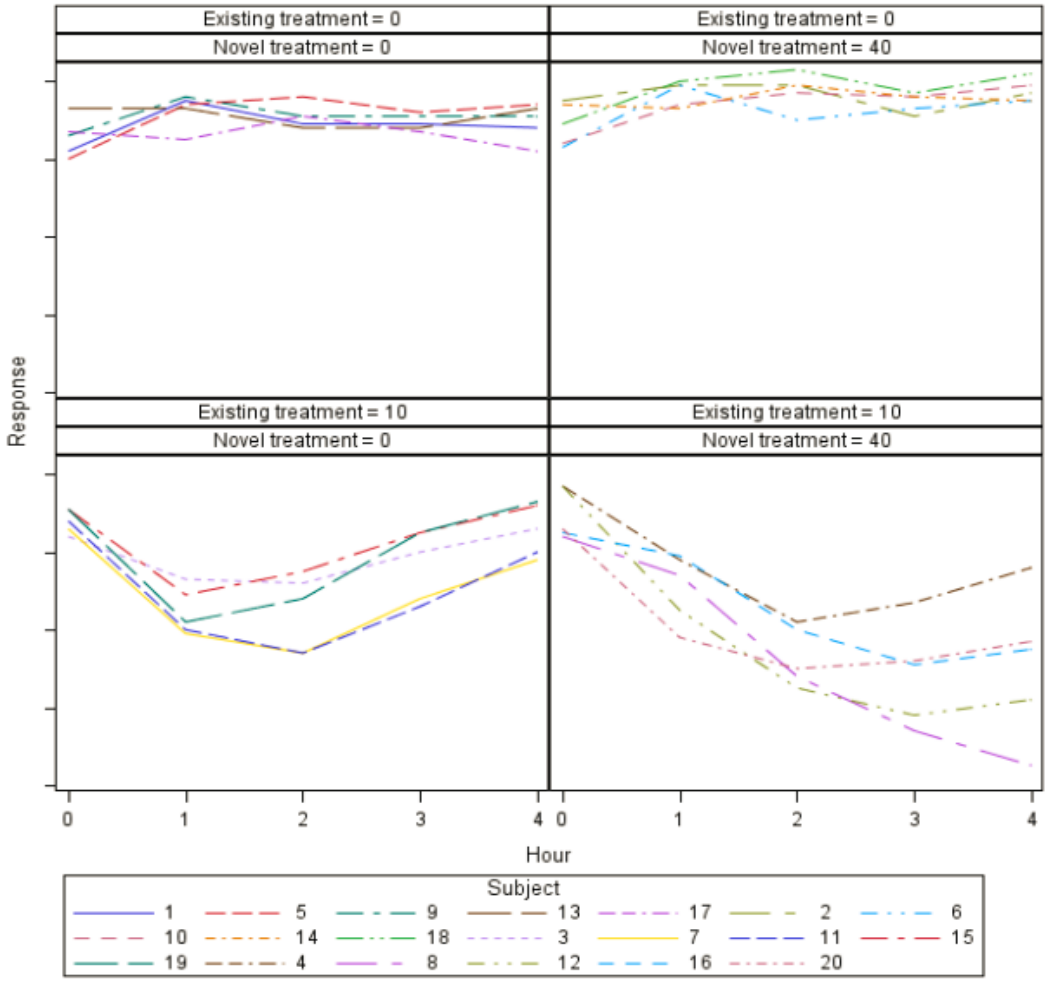
Case study

Synergy studies variables:

- Existing treatment dose
- Novel treatment dose
- Continuous safety biomarker, measured at the moment of oral administration, and after 1, 2, 3, 4 hours

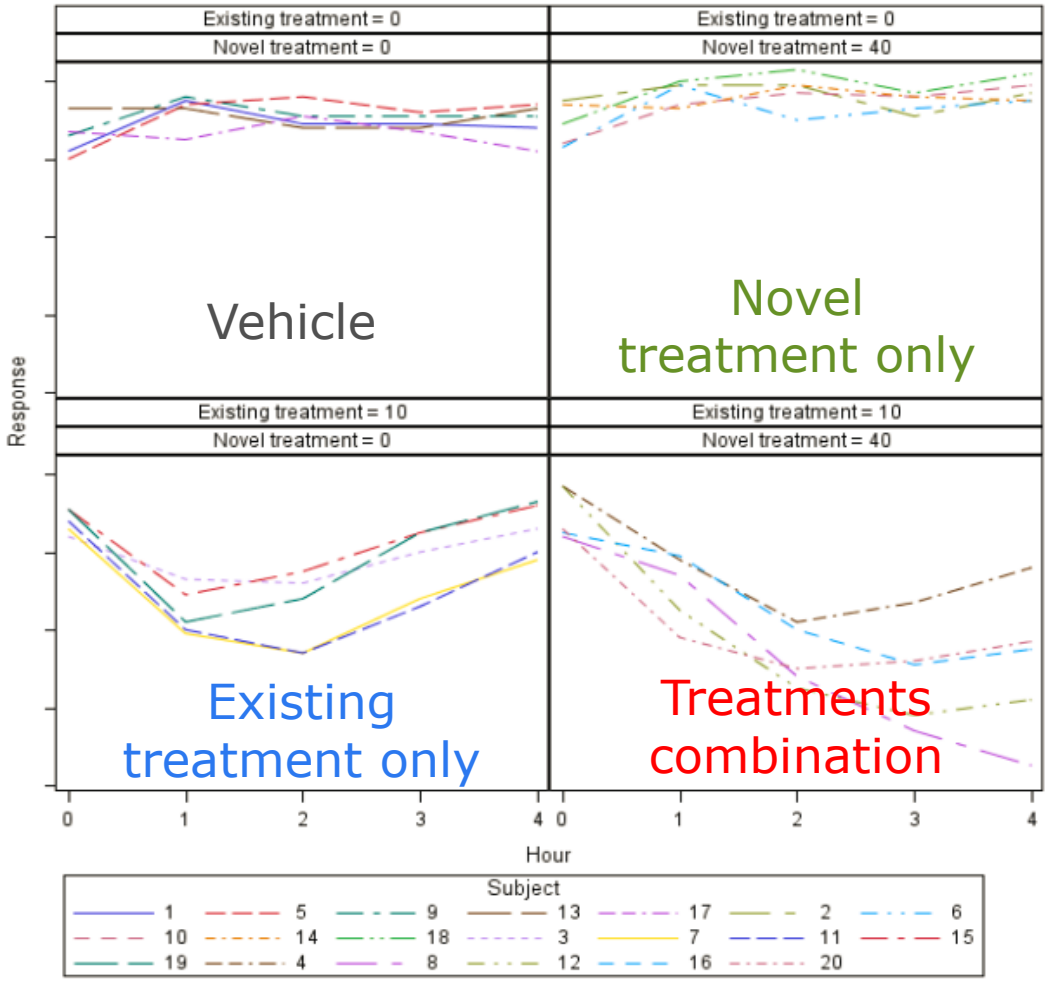
Case study – How does the data look like?

Example from study 1



Case study – How does the data look like?

Example from study 1



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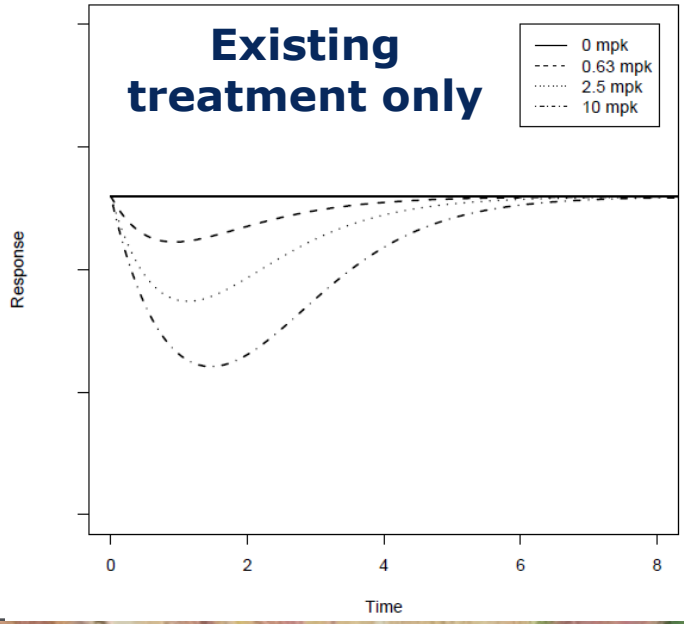
Methods – Turnover model with latent PK profile

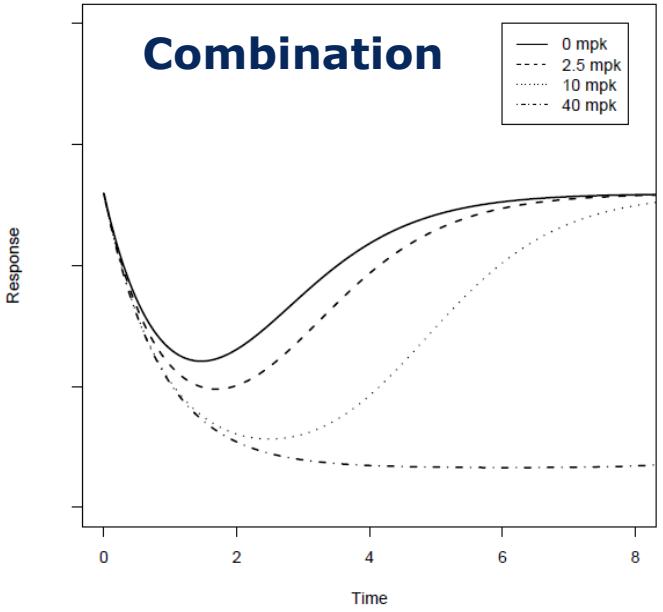
$$\frac{d\bar{R}_{it}}{dt} = k_{in}\left(1 - \frac{I_{max}C_{it}}{IC_{50} + C_{it}}\right) - k_{out}\bar{R}_{it}$$

$$With:\ \bar{R}_{it=0} = k_{in}/k_{out}$$

$$IC_{50} = e^{\beta D_{ei} D_{ni}}$$

R_{it}=Response: $R_{it} \sim N(\bar{R}_{it}, 1/\tau_R)$
C_{it}=Plasma concentration of the existing treatment (latent)
D_{ei}=Existing treatment dose
D_{ni}=Novel treatment dose
β=PD interaction coefficient





Methods – Synergy

- Loewe additivity (in-vitro)

If treatment 2 is inactive*: $\frac{d_1}{D_{y,1}} \begin{cases} =1 \text{ Additivity} \\ <1 \text{ Synergy} \\ >1 \text{ Antagonism} \end{cases}$

- Our "synergy" model (in-vivo)

$$IC_{50} = e^{\beta D_1 D_2} \begin{cases} =1 \text{ Additivity} \rightarrow \beta = 0 \\ <1 \text{ Synergy} \rightarrow \beta < 0 \\ >1 \text{ Antagonism} \rightarrow \beta > 0 \end{cases}$$

*Harbron C. A flexible unified approach to the analysis of pre-clinical combination studies. Stat Med 2010;29(16):1746-56.

Methods – How to pool data from different studies?

- Historical data → Frequentist approach (NONMEM)
- Study 1-11 → **Bayesian approach** (WinBUGS)

The posteriors from the previous study are used in order to build the priors for the current study.

Two models performed:

- Model without random effects
- Model with random k_{out}

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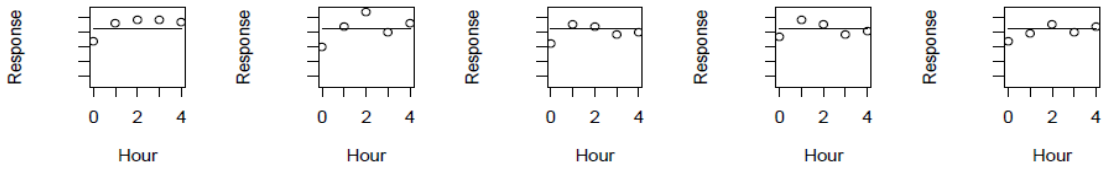
Results – Fixed vs Random effects model

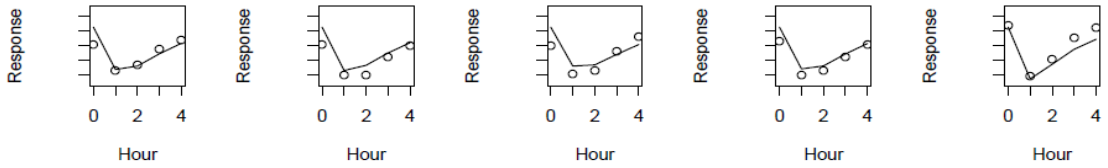
	No random effects			Random kout		
	Posterior mean	2.5% CI	97.5% CI	Posterior mean	2.5% CI	97.5% CI
$\log(k_e)$	-0.411	-0.535	-0.309	-0.326	-0.378	-0.263
$\log(k_{out})$	0.264	0.078	0.460	-0.166	-0.283	-0.040
I_{max}	0.261	0.240	0.281	0.292	0.271	0.312
$\log(\bar{R}_0)$	3.615	3.614	3.617	3.616	3.615	3.617
τ_R	2.742	2.525	2.977	2.860	2.663	3.065
β	-2.655	-3.374	-1.919	-2.952	-3.578	-2.486
τ_{kout}	-	-	-	1.959	1.476	2.540
DIC	148.230			144.653		

Results – Fitting, random kout (e.g. study 5)

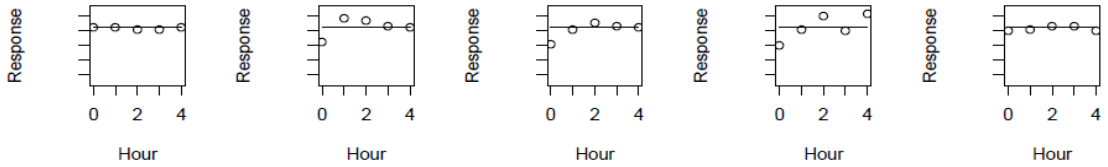
Vehicle



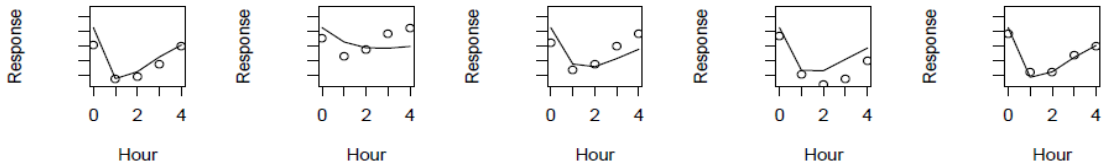
Existing treatment



Novel treatment



Combination



Results – Fixed vs Random effects model

	No random effects			Random kout		
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$\log(k_{out})$	0.264	0.078	0.460	-0.166	-0.283	-0.040
I_{max}	0.261	0.240	0.281	0.292	0.271	0.312
$\log(\bar{R}_0)$	3.615	3.614	3.6	16	3.615	3.617
τ_R	2.742	2.525			2.663	3.065
β	-2.655	-3.374			-3.578	-2.486
τ_{kout}	-	-			1.476	2.540
DIC		148.230			144.653	

Are the estimates reliable?

Results – What is the impact of a permutation?

Study	1	2	3	4	5	6	7	8	9	10	11
Existing treatment dose (mpk)	10	2.5	10	0.63	10	0.16	2.5	0.63	0.16	0.04	0.04
Novel treatment dose (mpk)	40	40	10	40	2.5	40	10	10	10	10	40

Study	5	3	8	11	6	1	2	9	7	4	10
Existing treatment dose (mpk)	10	10	0.63	0.04	0.16	10	2.5	0.16	2.5	0.63	0.04
Novel treatment dose (mpk)	2.5	10	10	40	40	40	40	10	10	40	10

Results – What is the impact of a permutation?

	Original sequence			Permutation		
	Posterior mean	2.5% CI	97.5% CI	Posterior mean	2.5% CI	97.5% CI
$\log(k_e)$	-0.326	-0.378	-0.263	-0.315	-0.378	-0.245
$\log(k_{out})$	-0.166	-0.283	-0.040	0.005	-0.094	0.107
I_{max}	0.292	0.271	0.312	0.294	0.277	0.315
$\log(\bar{R}_0)$	3.616	3.615	3.617	3.615	3.614	3.615
τ_R	2.860	2.663	3.065	2.957	2.735	3.232
β	-2.952	-3.578	-2.486	-2.628	-3.061	-2.247
τ_{kout}	1.959	1.476	2.540	2.81	1.809	4.089
DIC	144.653			148.485		

Results – WinBUGS vs Stan, sequential vs pooled*

	WinBUGS Sequential	Stan Sequential	Stan Pooled
	Posterior mean (2.5% CI, 97.5% CI)	Posterior mean (2.5% CI, 97.5% CI)	Posterior mean (2.5% CI, 97.5% CI)
$\log(k_e)$	-0.41 (-0.54, -0.31)	-0.37 (-0.46, -0.30)	-0.42 (-0.55, -0.30)
$\log(k_{out})$	0.26 (0.08, 0.46)	0.09 (-0.01, 0.18)	-0.15 (-0.36, 0.03)
I_{max}	0.26 (0.24, 0.28)	0.26 (0.24, 0.28)	0.27 (0.23, 0.30)
$\log(\bar{R}_0)$	3.62 (3.61, 3.62)	3.62 (3.61, 3.62)	3.62 (3.61, 3.62)
τ_R	2.74 (2.53, 2.98)	2.49 (2.33, 2.65)	2.44 (2.26, 2.64)
β	-2.66 (-3.37, -1.92)	-3.06 (-3.72, -2.41)	-1.10 (-1.33, -0.87)

*Fixed effects models performed.

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Conclusions and future perspectives

- The order of this 'sequential pooling' affects the results
- Even the best sorting may lead to unreliable estimates

Single dose combination for each study might be responsible for this

Future research:

- Consider design of experiments
- Priors choice

Thank you for your attention!

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