LUNDS UNIVERSITET

Pharmacological models - How to improve them?

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Contents

Background

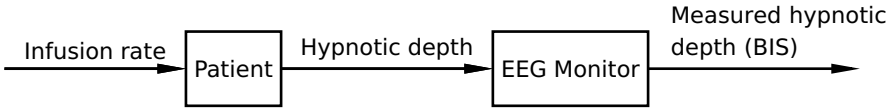

Figure: A schematic overview of open-loop anesthesia where the depth of consciousness is measured with EEG.

Motivation

Variability between individuals in the response to anesthetic drugs.

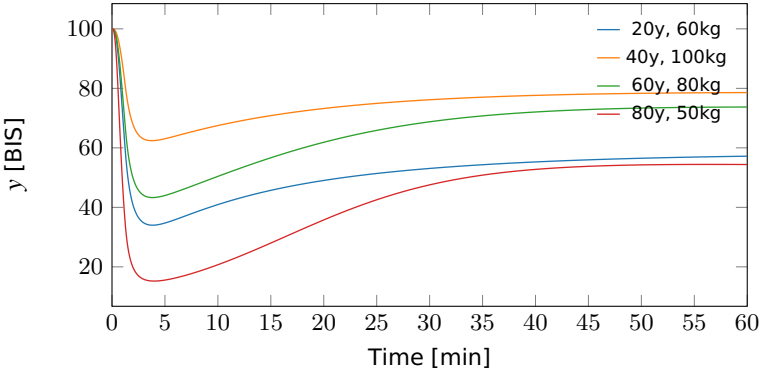

Figure: Simulated effect y for four patients with the same input.

PKPD model

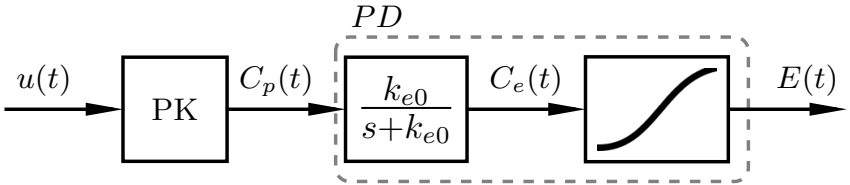

Figure: PKPD model structure describing the relationship between drug infusion rate and clinical effect.

Simulated example

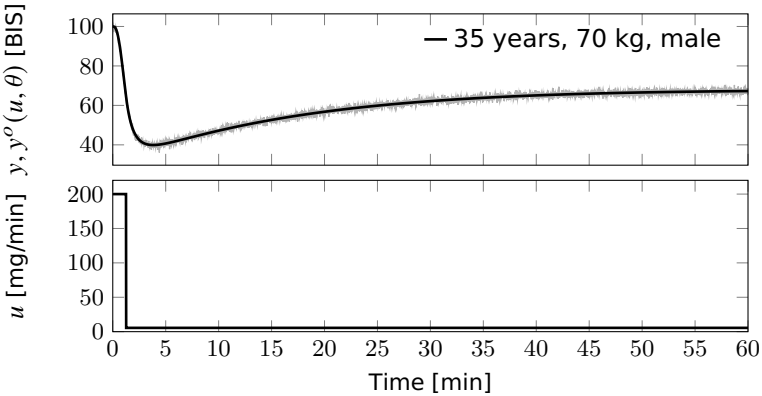

Figure: *Top:* Simulated true effect y^0 (black) and noise-corrupted observation y (gray). *Bottom:* Propofol infusion profile u.

Simulated example

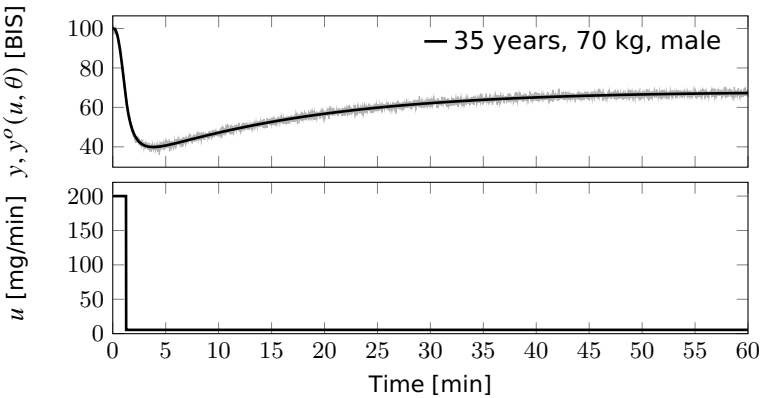

Figure: *Top:* Simulated true effect y^0 (black) and noise-corrupted observation y (gray). *Bottom:* Propofol infusion profile u.

Problem: Poor input excitation!

Identifiability

Local identifiability:

Study the Fischer Information Matrix to find which parameter is least sensitive. Here, k_{12} the rate constant between the first and second compartment was the least sensitive.

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Study the Fischer Information Matrix to find which parameter is least sensitive. Here, k_{12} the rate constant between the first and second compartment was the least sensitive.

Global identifiability:
By fixing each parameter – one at a time –, to a value that was off by a factor 100 it was possible to investigate how well the remaining parameters could compensate for this. Most parameters could be compensated for by the others.

Identifiability

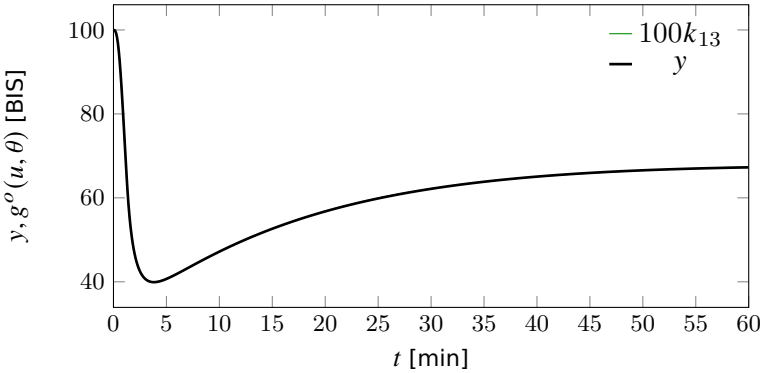

Figure: Simulated true effect y (black). The green curve (not visible) show model output $g^o(u, \theta)$ where all parameters have been optimized with k_{13} fixed with to a factor 100 times its true value.

Identifiability

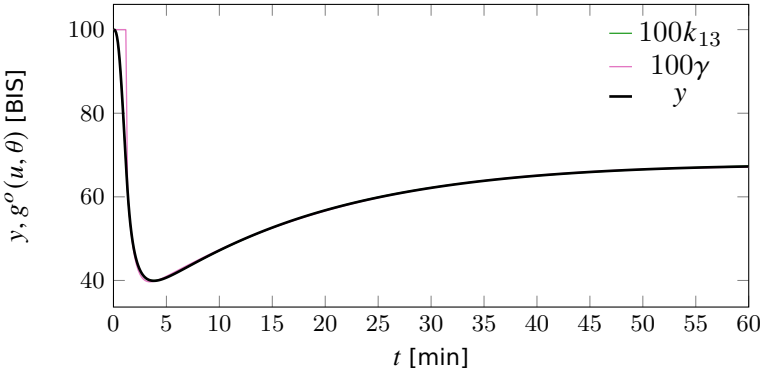

Figure: Simulated true effect y (black). The green and pink curve show model output $g^o(u, \theta)$ where all parameters have been optimized with k_{13} and γ, respectively, fixed with to a factor 100 times its true value.

Pole-zero cancellation

The transfer function from input u to $z = C_e/EC_{50}$ (linear part of PKPD model)

$$Gz, u(s) = K\frac{(s+z_1)(s+z_2)}{(s+p_1)(s+p_2)(s+p_3)(s+k_{e0})}.$$

Identifiability

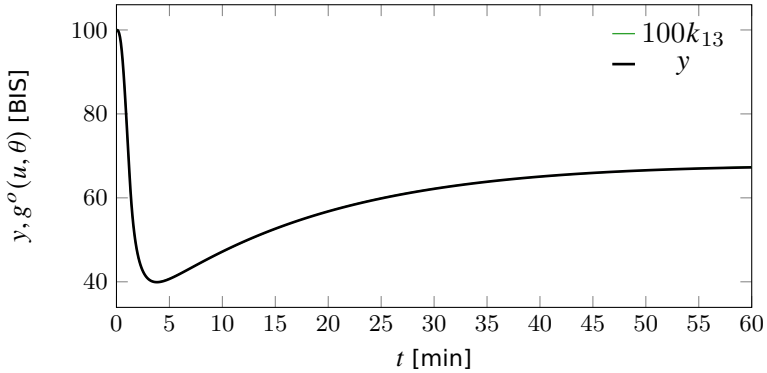

Figure: Simulated true effect y (black) and the green curve (not visible) show model output $g^o(u, \theta)$ where all parameters have been optimized with k_{13} fixed with to a factor 100 times its true value.

Ongoing work: Population model

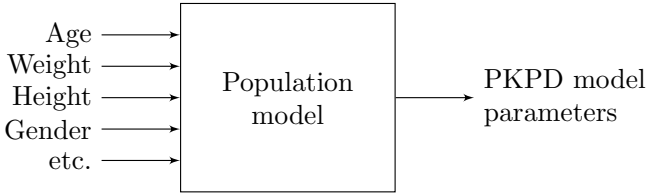

Figure: Population model with coviariates as input and PKPD model as output.

Ongoing work: Population model

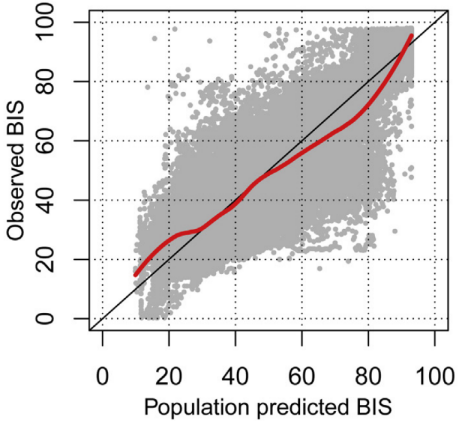

Figure: Population predictions vs observed BIS.[1]

[1] Eleveld, D., Colin, P., Absalom, A., and Struys, M. (2018). Pharmacokinetic– pharmacodynamic model for propofol for broad application in anaesthesia and sedation.

Ongoing work: Population model

Expression for one parameter of a population model used today:

$$Q_2\,(\text{litre/min}) = \theta_5 \left(\frac{V2}{V2_{\text{ref}}}\right)^{0.75} \left(1 + \theta_{16}\left(1 - \frac{\text{AGE + 40weeks}}{(\text{AGE + 40weeks}) + \theta_{14}}\right)\right)$$

where

$$V2(l) = \theta_2 \frac{\text{WGT}}{\text{WGT}_{\text{ref}}} \exp\left(\theta_{10}\left(\text{AGE} - \text{AGE}_{\text{ref}}\right)\right)$$

Code

Code for replicating results in the paper “Identifiability of pharmacological models for onlien individualization” can be found at
`https://gitlab.control.lth.se/ylva/pkpdidentifiability`

Bode plots

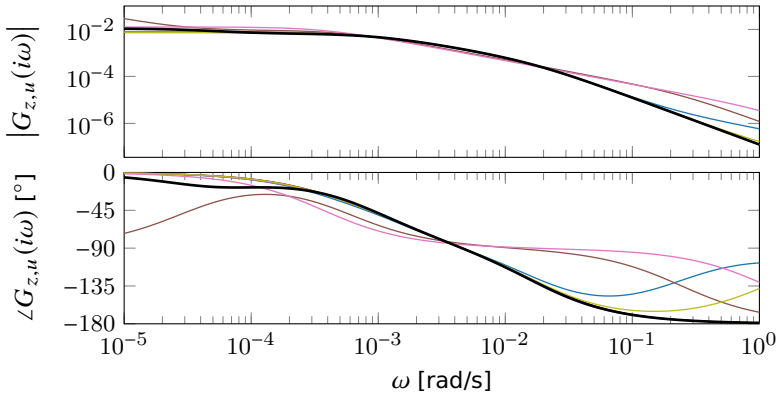

Figure: Bode plots of the models in Fig. 5. See Fig. 5 for further specification of the individual models.