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Background

- Models of increased complexity are commonly used, i.e., in **quantitative systems pharmacology**
- Model structure motifs of **increasing complexity** and/or **nonlinearity** may limit ability to estimate drug effect **correctly**.
- Does including **non-linear motifs**, such as a precursor compartment or feedback loops lead to: **challenges** with identifying a drug effect or **bias** in the parameter estimates?

Aim

Determine for common turn-over models with increasing complexity:

- Identifiability of drug effects on the correct system parameters.
- Bias in drug- and system specific parameter estimates.

Method

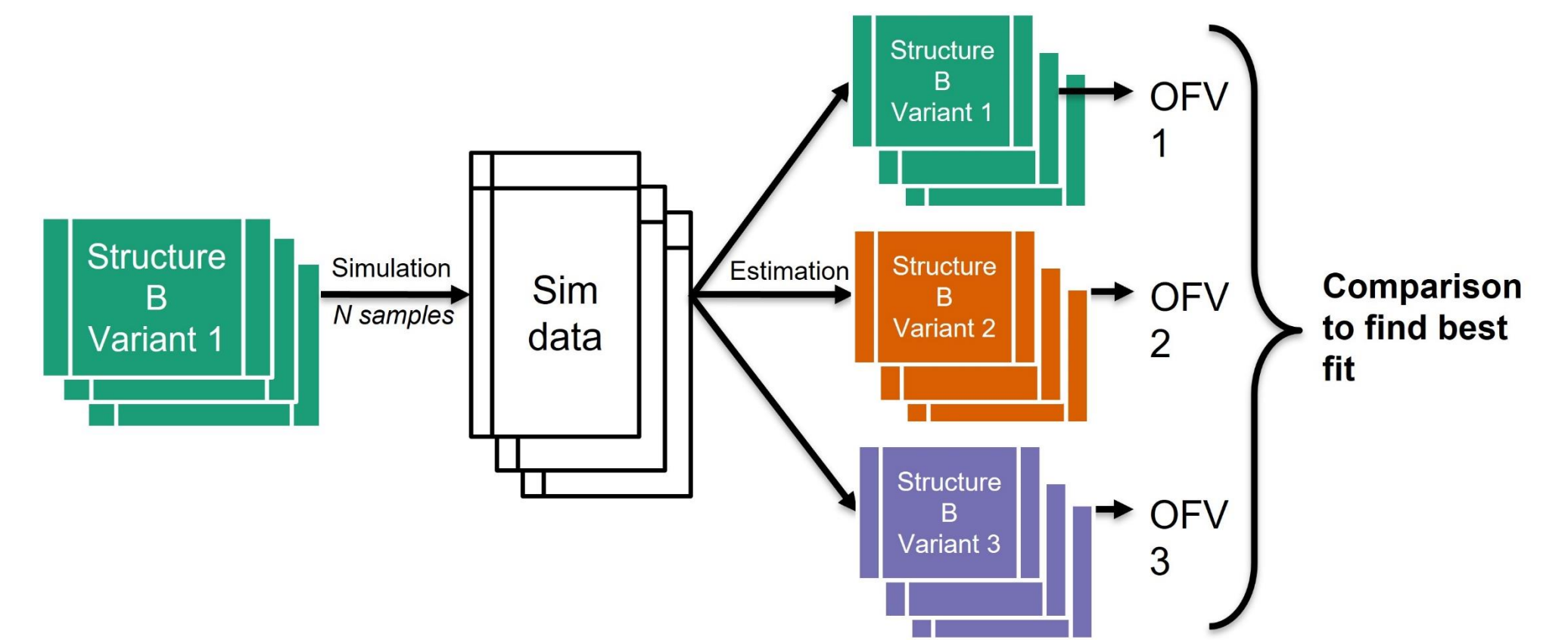


Figure 1: Schematic overview of the SSE process. For each sample, using the simulation model to simulate a simulated dataset, which is used for re-estimation with all variants of the model structure. The OFVs are compared and identify the statistically superior model fit.

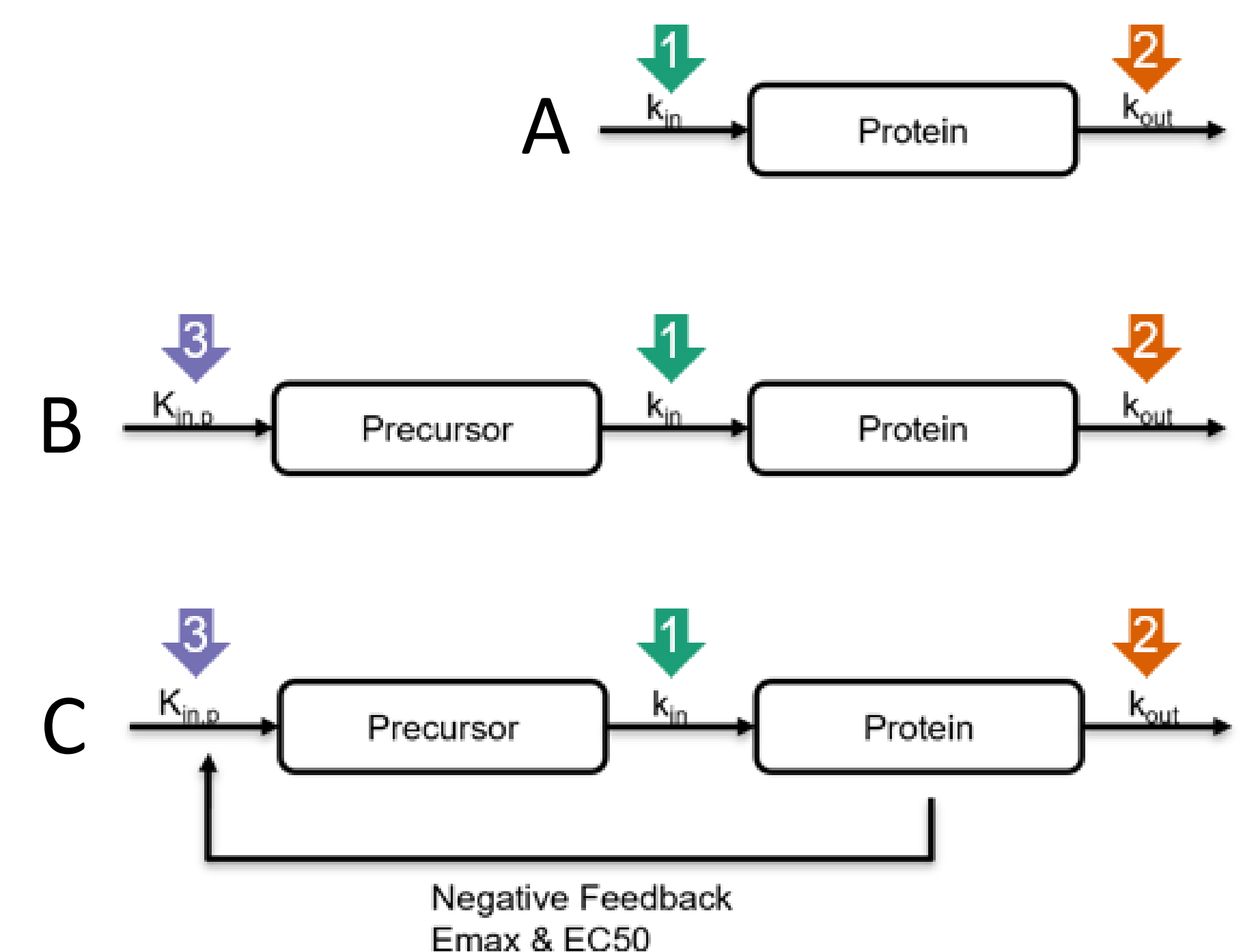


Figure 2: Schematic overview of the studied model structures (A,B,C) and variants indicating drug effects that lead to increase in protein concentration (1-3). A. Turn-over model, B. Turn-over model with precursor. C. Turn-over model with precursor and negative feedback loop.

Results

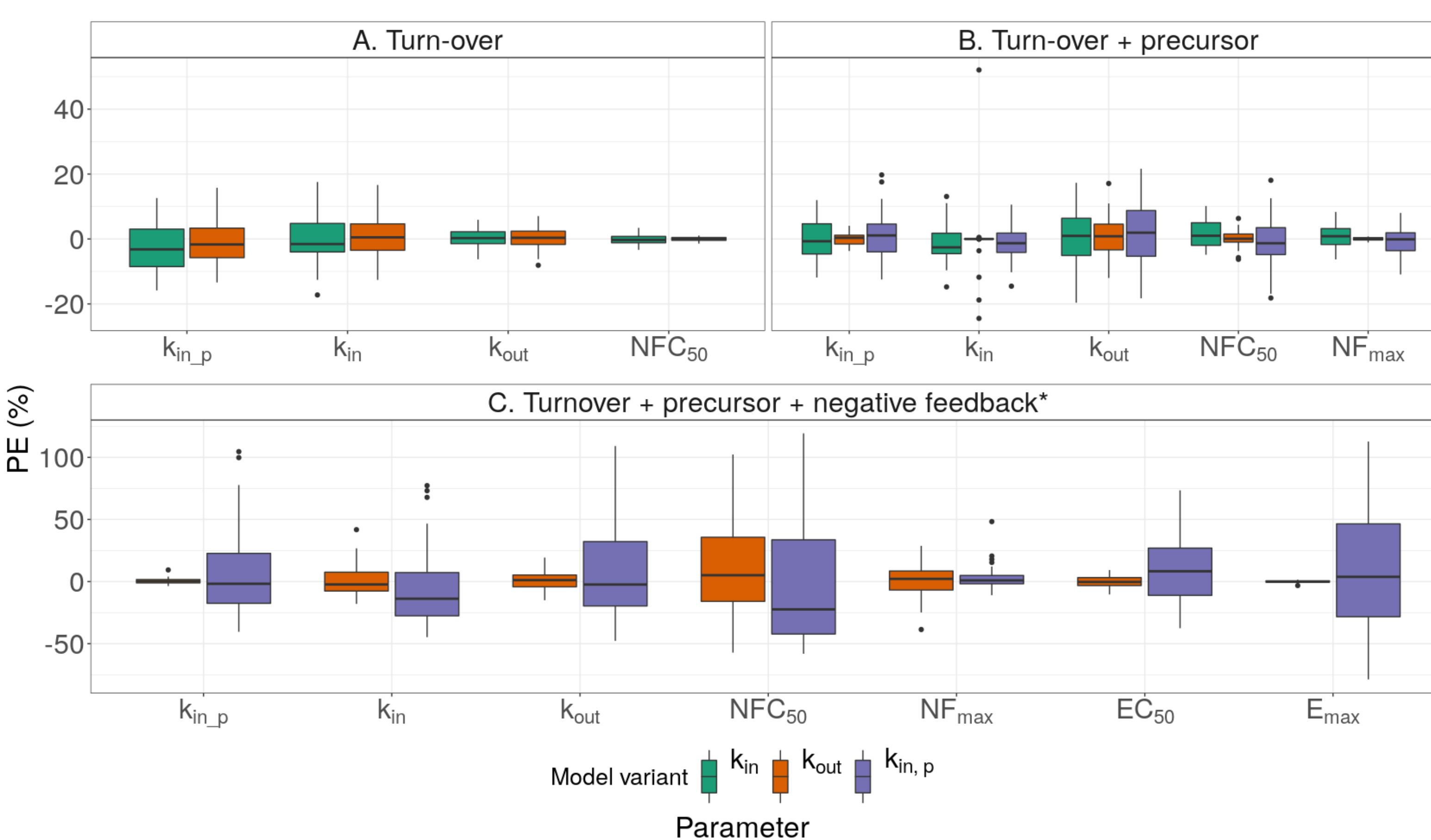


Figure 3: Distribution of Percentage Error (PE) of the different parameters in all variants of the different model structures. Boxes indicate the interquartile range (IQR), with the median shown as line in the middle. Whiskers are drawn to 1.5 times IQR, with values above or below that shown as outliers with black dots. 19 extreme outliers were removed from plot C. Please note the different ranges on the y-axes. *Model C – k_{in} is not included in the graph.

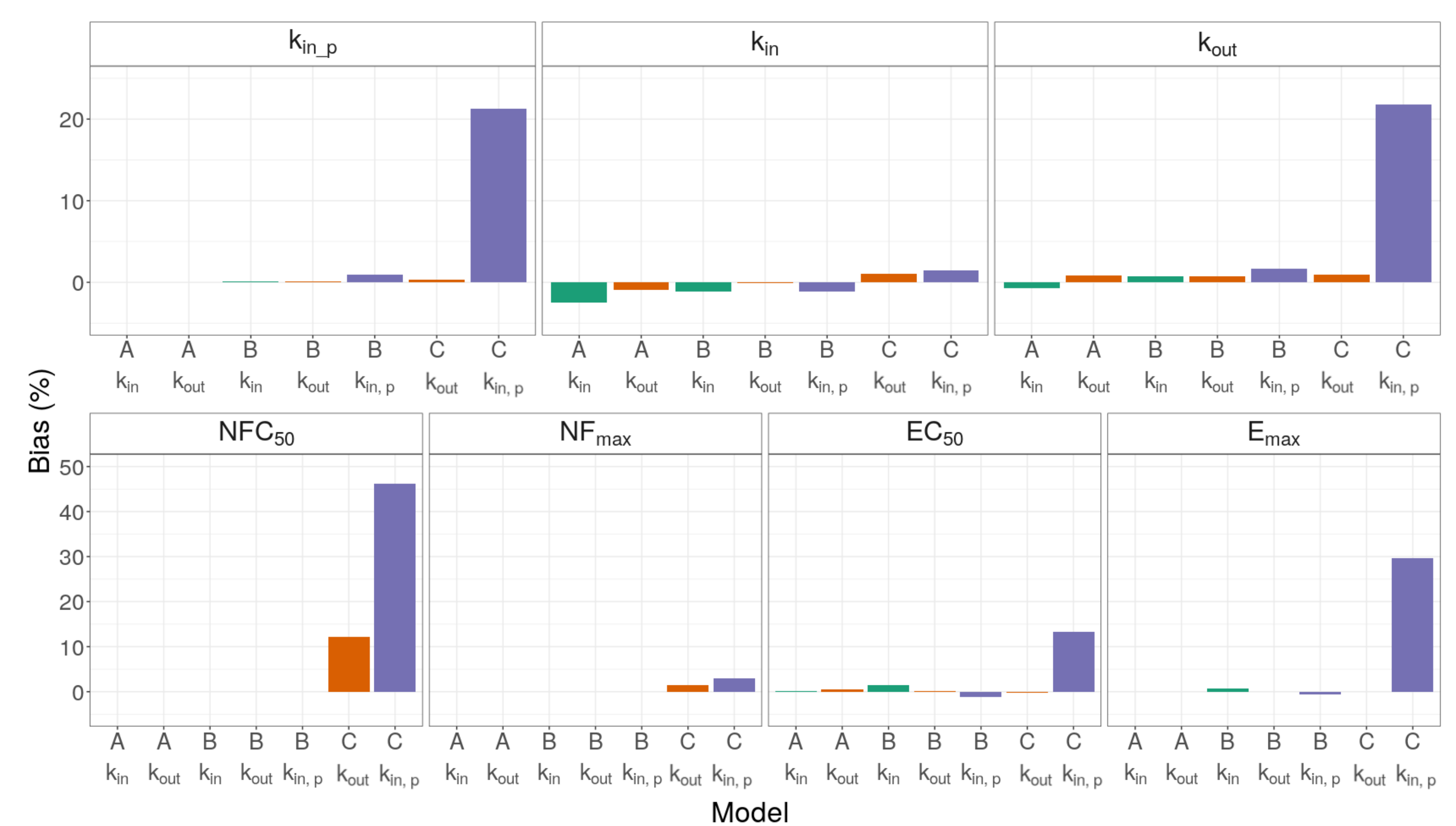


Figure 4: Bias of the different parameters for all variants of the different model structures. Bars indicate the mean bias across 50 samples from SSE for all relevant parameters. Model structure A does not have $k_{in,p}$ in the model, model structures A and B do not have a feedback loop and are therefore not visible for NFC_{50} and Nf_{max} . Model C – k_{in} is not included in the graph.

Conclusions

- ✓ Size of the drug effect influences the structural identifiability for all model structures (data not shown)
- ✓ Structural identifiability is not influenced by the model structure in the studied structures
- ✓ Bias and variance in percentage error is larger in the model structure with negative feedback compared to the model structures without feedback loops

