



Introduction

- The **cardiovascular system (CVS)** is complex and highly regulated. Early prediction and quantification of cardiovascular drug effects is crucially important to support decision making during drug development.
- Previously a **hemodynamic CVS model** was developed using rat data by Snelder et al ("Snelder model") (Figure 1) ^[1,2].
- System-specific parameters were distinguished from drug-specific parameters by challenging the system with eight compounds with different mechanism of action (MoA).
- Initial simulations showed that the **CVS model** can be used to elucidate the MoA of novel compounds using MAP and HR measurements only.

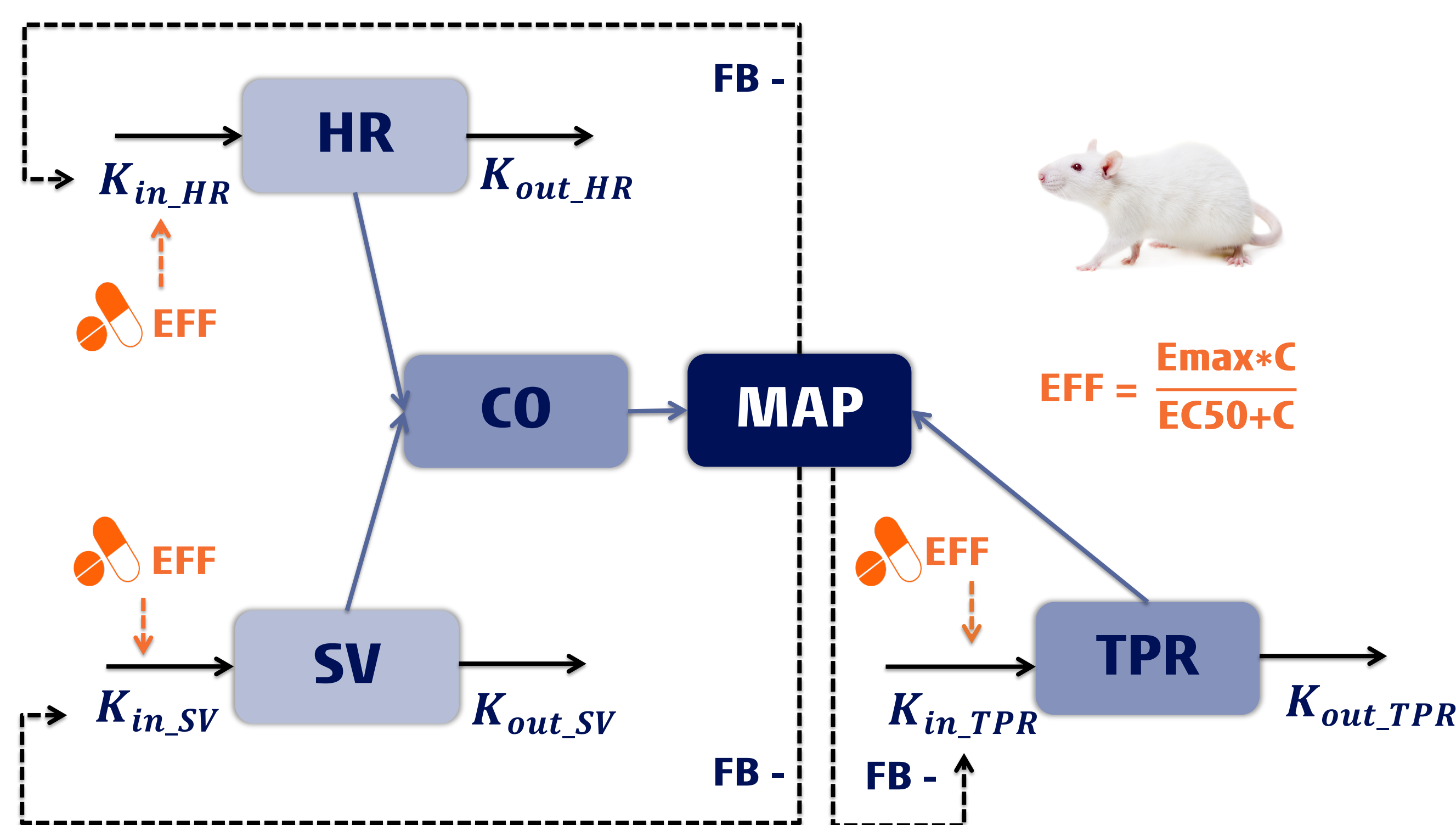


Figure 1. Model structure of Snelder model. (HR: heart rate; SV: stroke volume; TPR: total peripheral resistance; CO: cardiac output; MAP: mean arterial pressure) ^[1,2]

Try our shiny web application: <http://hemodynamic-simulator.eu>



Objectives

- To further evaluate if the mode of action of new drugs can be identified while keeping the system-specific parameters fixed
- To identify the minimal required data to translate the model to other species by evaluating if the system-specific parameters can be identified using data from only one compound with known MoA

Methods

- A **structural identifiability analysis** was performed using the Matlab toolbox GenSSI 2.0 ^[3]
- Practical identifiability** was evaluated using stochastic **simulation and estimation (SSE)** in Perl-speaks-NONMEM to determine if the model can be used to identify and quantify drug mode of action (Figure 2).

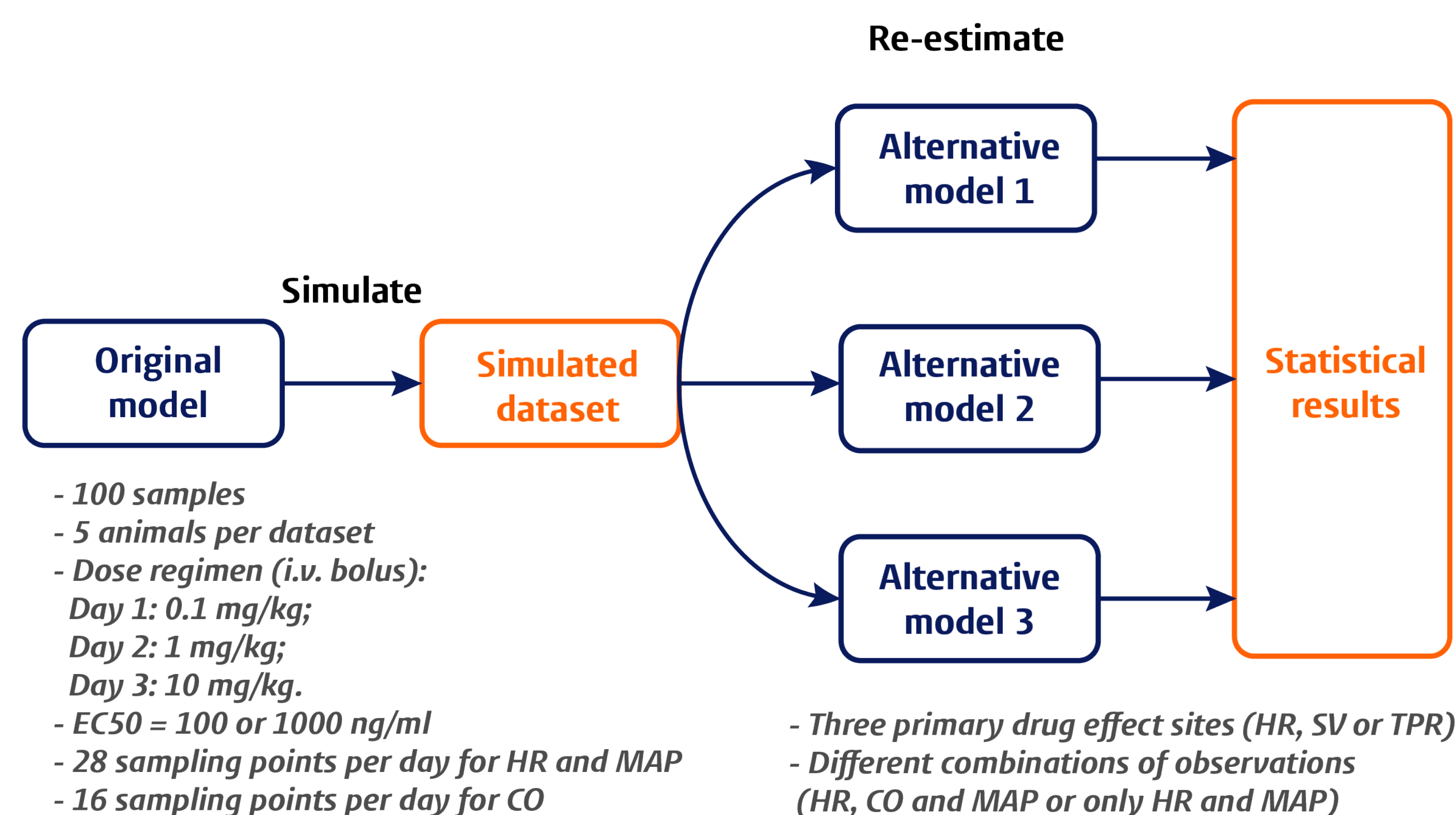


Figure 2. Flow diagram of stochastic simulation and estimation (SSE).

Results: Structural identifiability

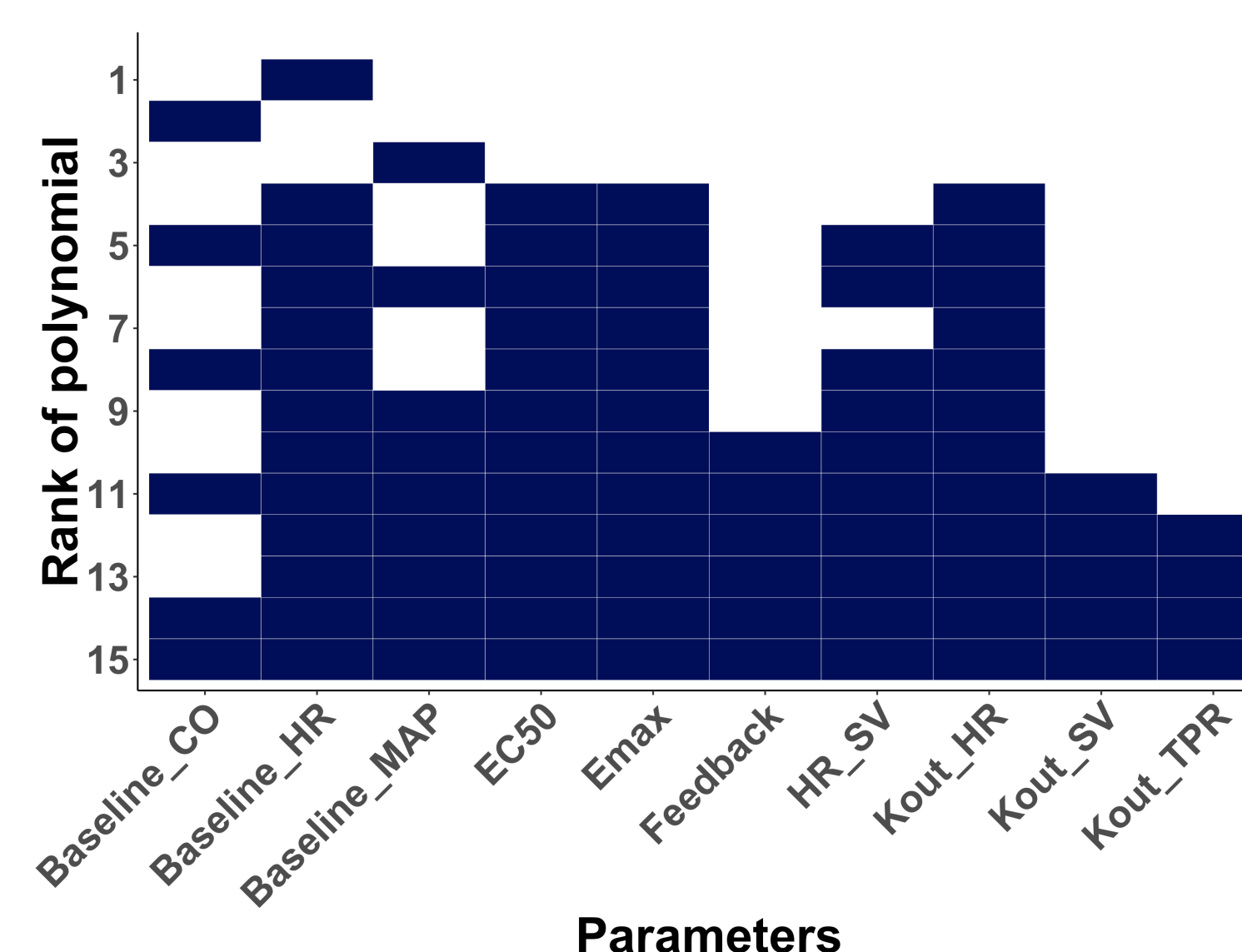


Figure 3. Structure identifiability tableau generated by GenSSI 2.0.

- The structurally *globally identifiable* parameters are: [Baseline_HR, Baseline_MAP, Baseline_CO].
- Other parameters are structurally *locally identifiable*.
- The Snelder model is **structurally locally identifiable** based on observations of HR, CO and MAP.

Results: Practical identifiability

Mode-of-action identification

- SSE analyses indicated that mode-of-action of drug effect could be identified for different EC₅₀ and Emax values (p<0.05, power = 100%, Figure 4).

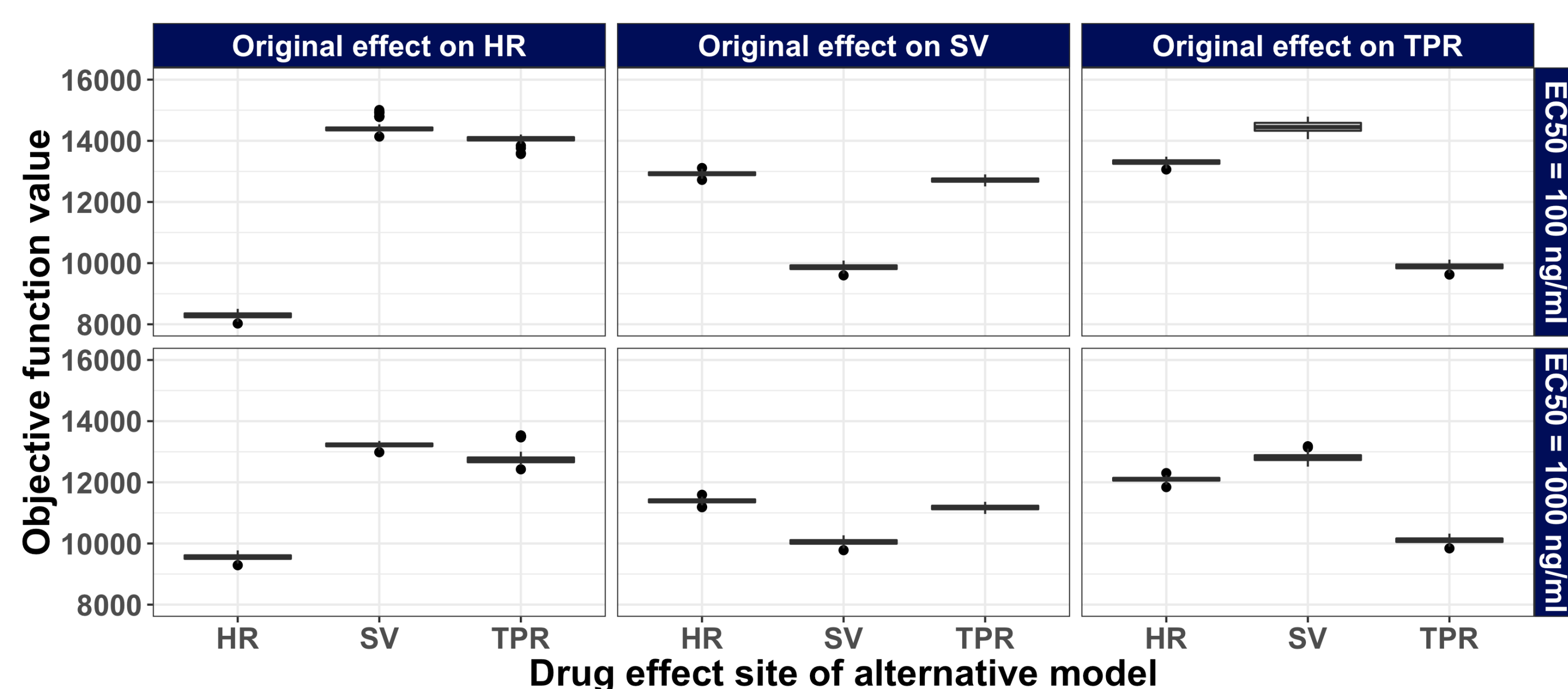


Figure 4. Objective function values of re-estimated models.

Quantification of system- and drug-specific parameters

- Both system-specific parameters and drug-specific parameters can be estimated precisely with a minimal bias (Figure 5).
- Models including observations for CO showed an increased percentages of successful minimization compared to models without CO.

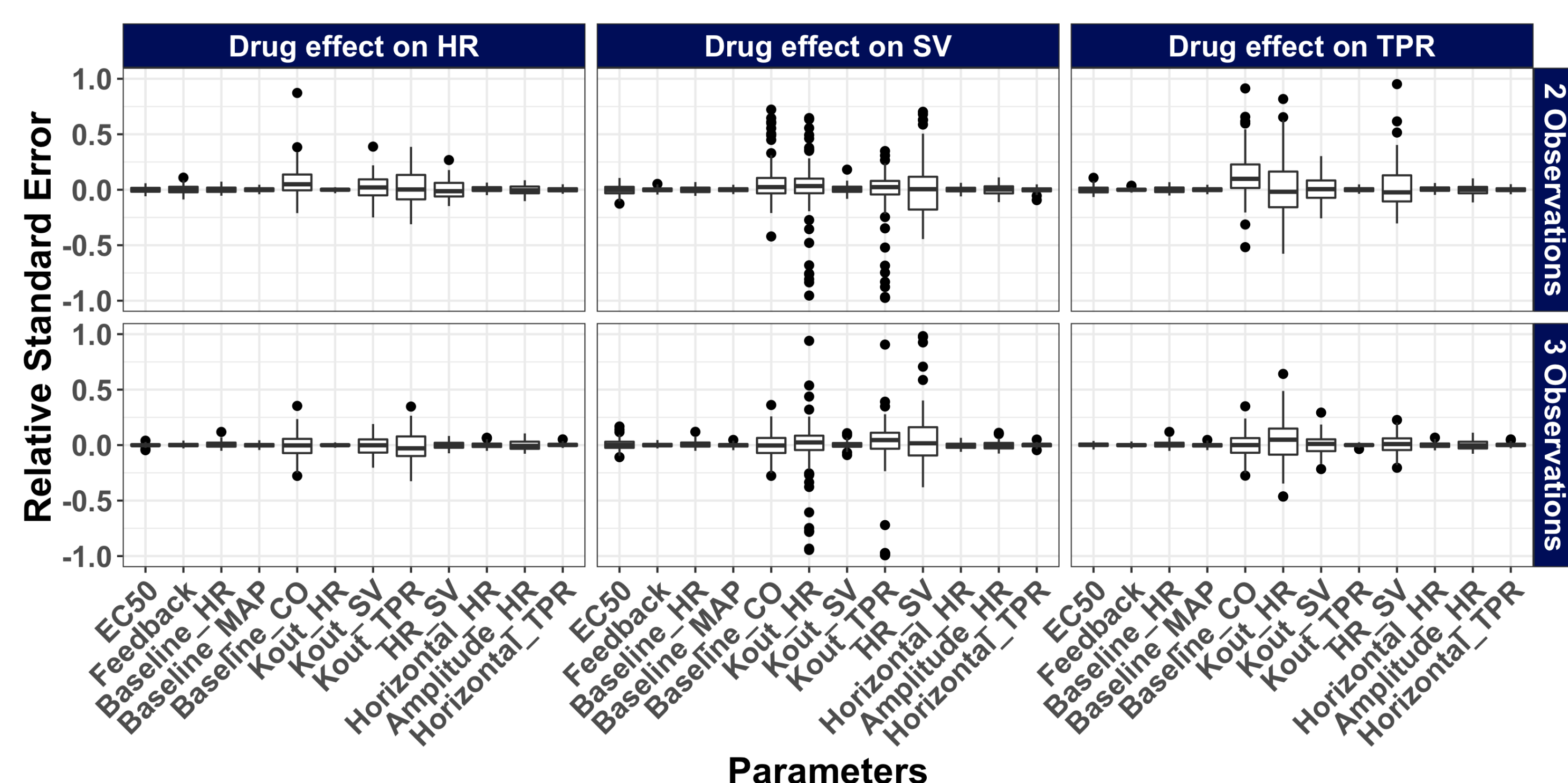


Figure 5. Simulation-Estimation results of system-specific and drug-specific parameters.

Conclusions

- Our analysis supports the use of the Snelder model to identify and quantify drug mode of action in preclinical cardiovascular experiments.
- MAP, HR and CO measurements following administration of one compound with known MoA provide a good starting point for translating this model to other species and guide study design.

