

INTRODUCTION AND OBJECTIVES

Reserpine (RSP) administration has been used to generate fibromyalgia (FM) disease in rodents by reproducing both the main and comorbid symptoms [1]. This may be due to its action on monoamines (MA), which are involved in the regulation of these affected systems [2]. However, a quantitative framework able to characterize and explore disease dynamics for FM is still lacking. Therefore, the aims of this study are:

- Developing a **population PK/PD model** able to characterize the time course of **RSP and MA** in prefrontal cortex (PFC), amygdala (Amy) and spinal cord (SC) in rats.
- Optimizing** the **RSP-induced FM disease status** using alternative dosing regimens.

MATERIALS AND METHODS

RSP administration, as well as PK and PD sampling were performed as shown in **figure 2**. Data analysis was performed by using the non-linear mixed effects (NLME) analysis, in Monolix software (v2024R1). Deterministic and stochastic simulations were conducted in Simulx software (v2024R1) to evaluate disease-related PD outcomes with experimental and additional (2 and 4 mg/kg) dose levels. A summary of the modelling workflow is presented in **figure 1**.

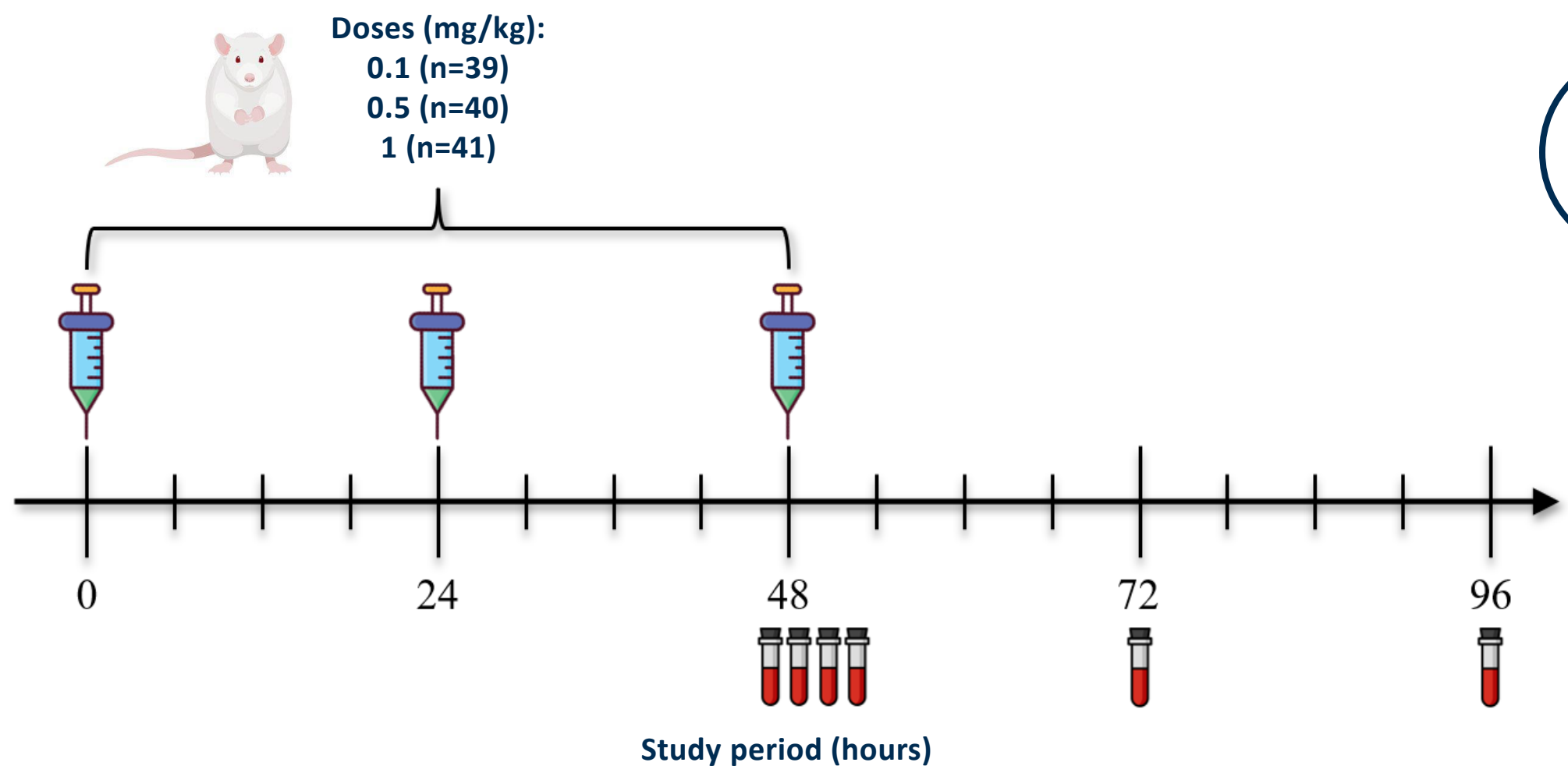


Figure 1. Reserpine administration and sampling schedule scheme.

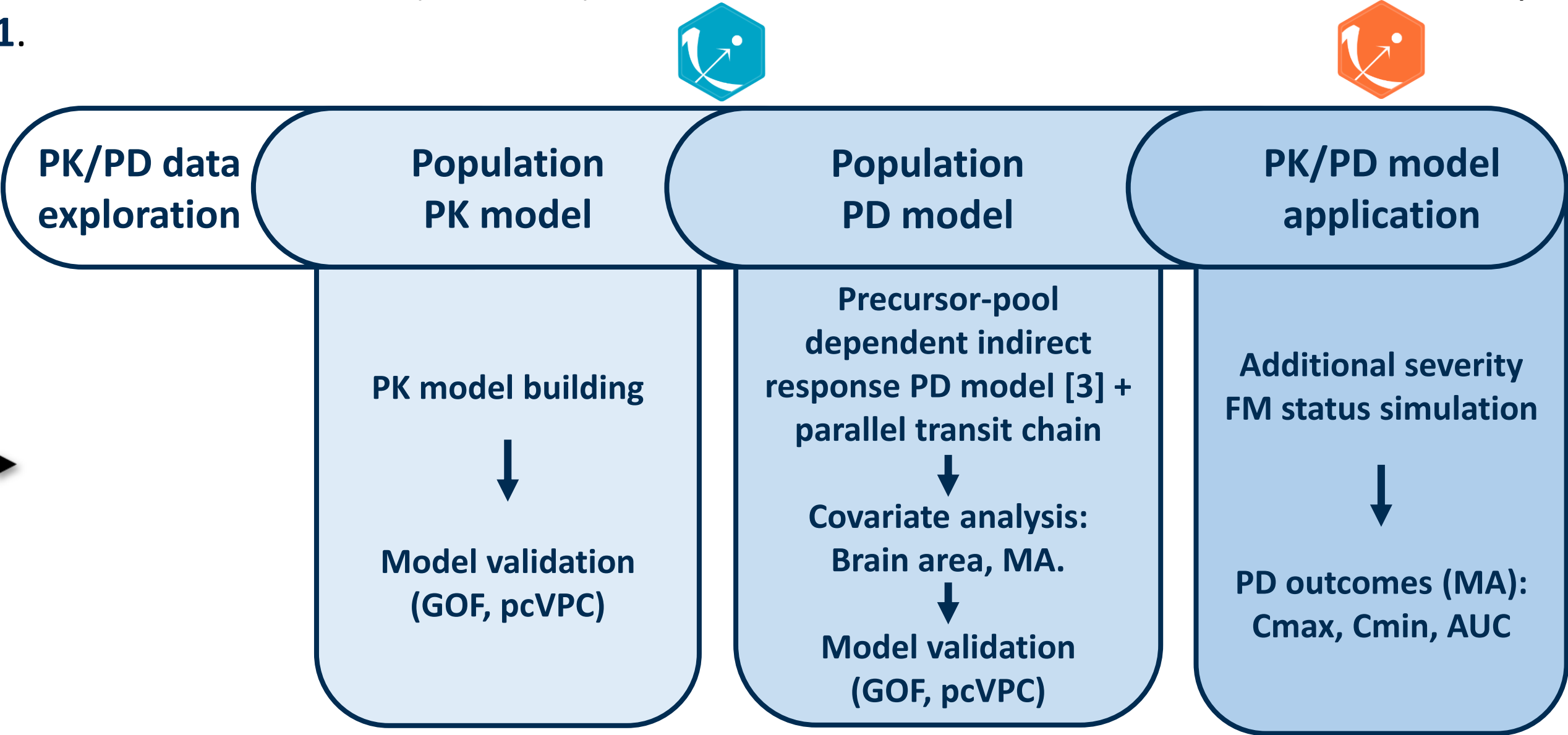


Figure 2. Modelling workflow.

Dose (mg/kg)	Number of PK samples	
	5-HT	NE
0.1	39	31
0.5	40	31
1.0	41	31
Total	120	93

Dose (mg/kg)	Number of PD samples								
	5-HT			DA			NE		
0.1	31	31	31	30	28	31	29	31	31
0.5	30	31	31	31	31	31	28	31	31
1.0	31	31	31	31	32	31	31	31	31
Total	278	276	274	276	276	274	274	274	274

Table 1. Samples obtained per dose group (PK model) and per NT and nervous tissue (PD model).

RESULTS

Model building

Parameters	Pop. PK/PD model estimates		Inter-animal variability	
	Value	RSE (%)	Value	RSE (%)
ka_1 (h ⁻¹)	19.14	-	209	32
ka_2 (mg/h)	44.69	12	32	-
F_1	0.96	3	170	24
V (mL)	1.3	24	65	32
CL (mL/h)	4.5×10^{-1}	11	35	29
k_{in} (mg/h) AMY	6.97	18	97	9
k_{in} (mg/h) PFC	2.10	18		
k_{in} (mg/h) SC	1.78	19		
k_p (h ⁻¹)	8.6×10^{-4}	14	29	37
k_{out} (h ⁻¹)	2.7×10^{-2}	11	22	24
SLP_1 (h)	1.1×10^{-1}	47	358	11
k_0 (h ⁻¹)	1.9×10^{-1}	6	9	67
SLP_2 (h)	1.25	20	74	18
Residual unexplained variability				
PK (%)	56	10		
PD (%)	71	9		

Table 2. Final population PK/PD parameters of RSP and MA in rats.

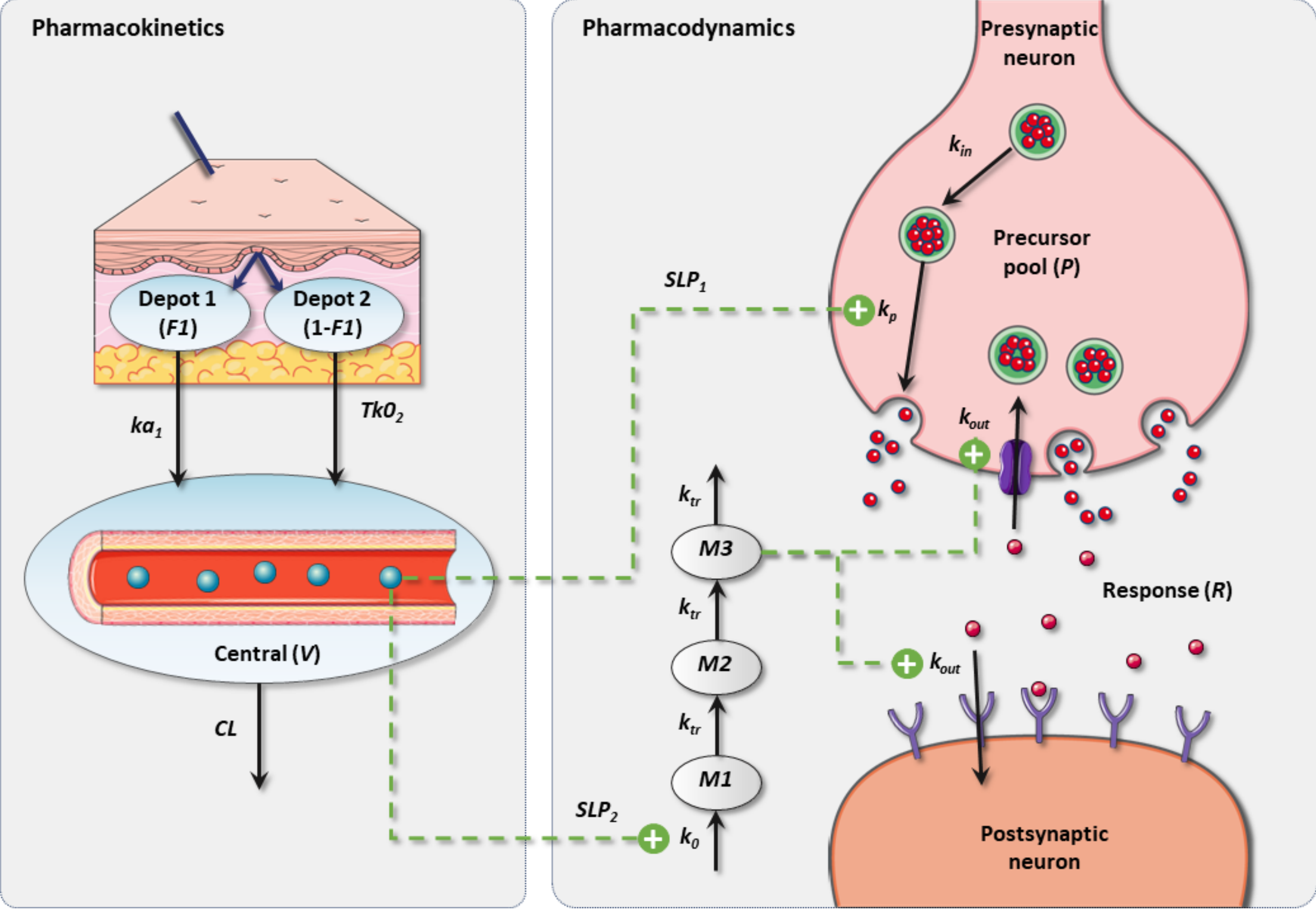


Figure 3. Schematic representation of the final PK/PD model in rats.

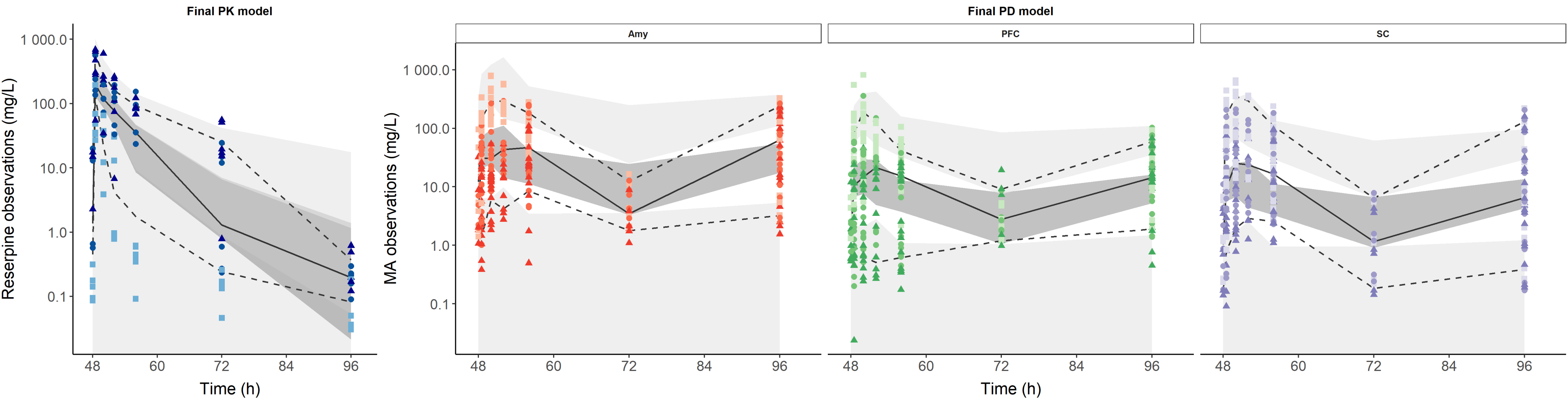


Figure 4. Prediction-corrected visual predictive check of the final population PK/PD model. Dashed and solid lines represent the experimental 2.5th, 50th, and 97.5th percentiles. Grey shaded areas represent the 95% prediction interval of these percentiles. Colored dots represent the RSP and monoamine observations. Circles, triangles, and squares represent the 0.1, 0.5 and 1 mg/kg dose.

CONCLUSIONS

- This study developed and validated a **PK/PD model** to characterize the **rapid depletion of a precursor-pool** with a **delayed effect on the degradation** of the MA in different brain regions.
- The evaluation of PD outcomes revealed that the **concentration of MA** in the different brain regions **changed proportionally across the dose levels** evaluated, with a **greater MA synthesis from the AMY precursor pool**.
- The developed PK/PD model can be a powerful tool for **correlating MA levels with behavioral and biochemical results** obtained with the RSP-induced model. This may be useful in **searching for biomarkers in FM** and **translating the results of preclinical studies to human research**.

REFERENCES

- Brum, E. S., Becker, G., Fialho, M. F. P., & Oliveira, S. M. (2022). Pharmacology & therapeutics, 230;107959.
- Govindarajulu M, Shankar T, Patel S, Fabbrini M, Manohar A, Ramesh S, et al. (2021). Medicinal Herbs and Fungi, 293-313.
- Sharma, A., Ebling, W. F., & Jusko, W. J. (1998). Journal of pharmaceutical sciences, 87(12);1577–1584.

Model application

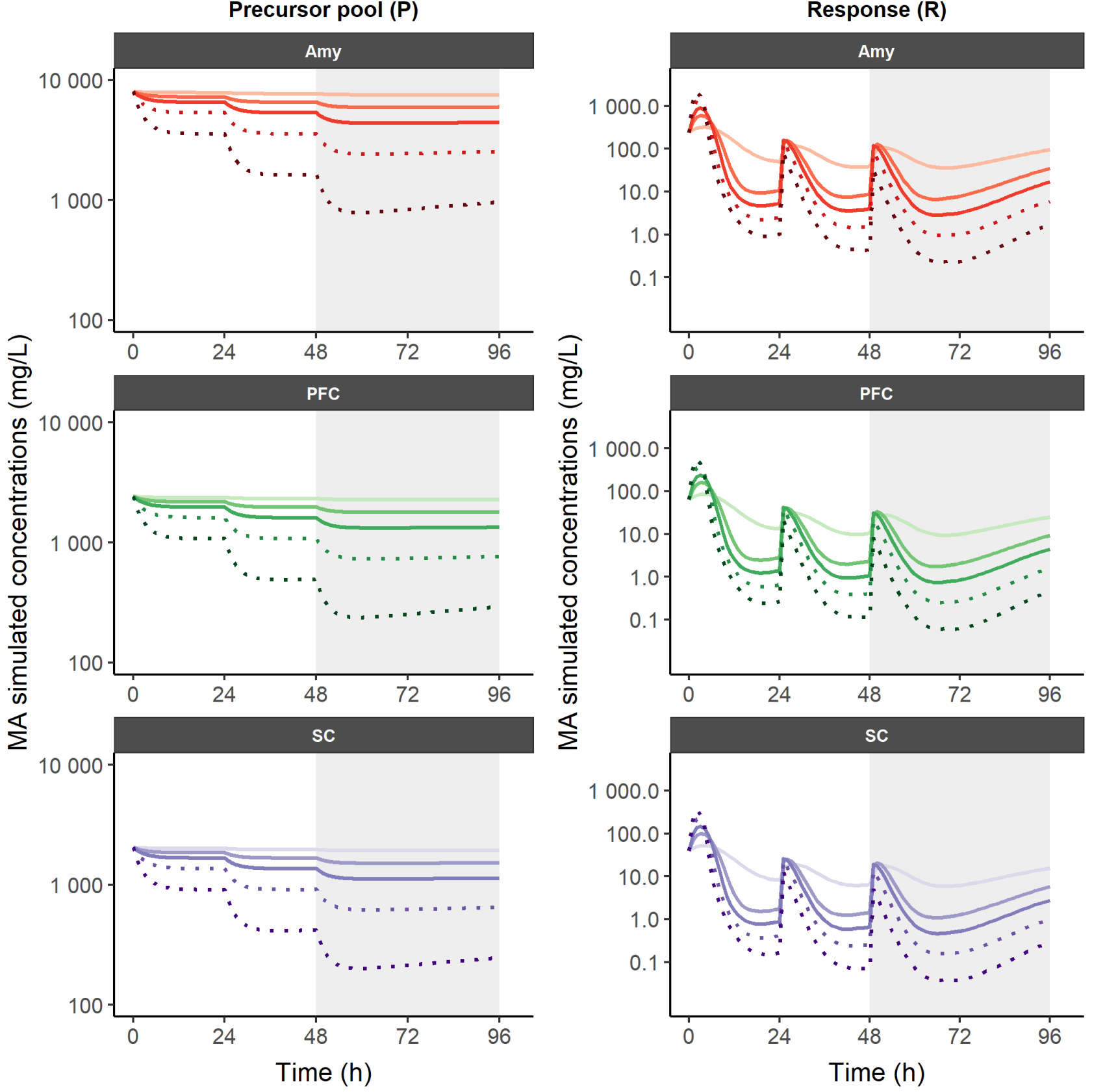
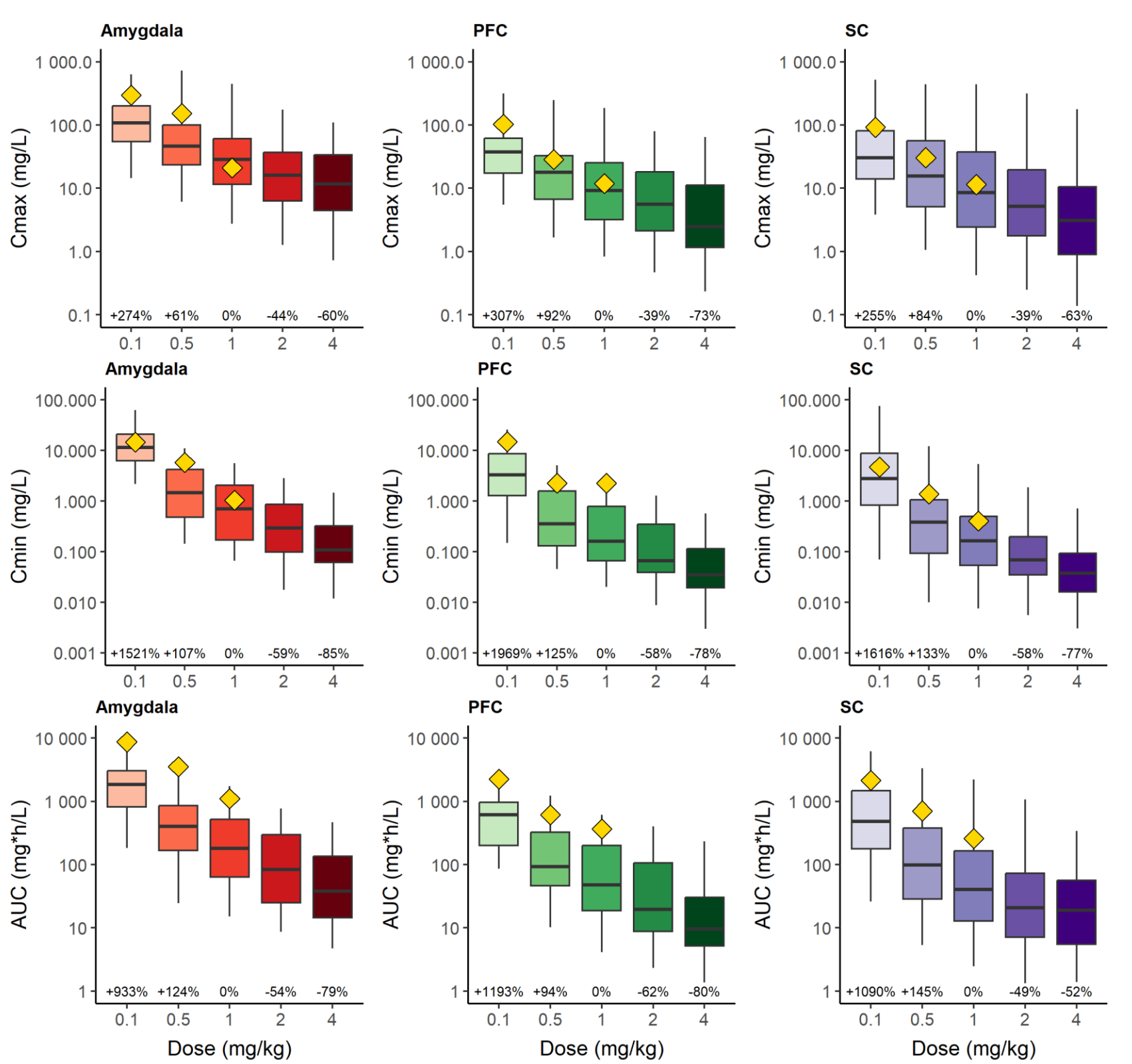


Figure 5. Simulation of time-course profiles on different nervous tissues obtained by using PK/PD model for MA after different RSP dosage regimens. Experimental doses are represented as solid lines, additional simulated doses are represented as dotted lines. A gradual increase in color intensity represents the level of dose considered (0.5 to 4 mg/kg). Shaded areas represent the study period in the experimental protocol.

Figure 6. Numerical predictive check. Simulated C_{max} (top), C_{min} (middle) and pharmacodynamic AUC (bottom) of MA at different simulated dosage regimens of RSP. Evaluation was performed for the study period after the third RSP administration (48h) and until the end of the study period (96h). Yellow diamonds represent the experimental median values for each parameter. Percentage values represent the percentage change in the median with respect to 1 mg/kg dose.



ACKNOWLEDGEMENTS

