

Introduction

- Due to their superior drug loading capacity, stability, and stimuli-responsive release profile, silica nanoparticles (SiNPs) have entered multiple clinical trials.[1]
- SiNP clinical approval as drug delivery agents in humans is impeded due to off-target effects and poor predictability of their pharmacokinetics (PK).
- To predict their PK accurately in vivo, we are using a physiologically-based pharmacokinetic (PBPK) modeling approach adapted from a rat model of SiNPs.[2]
- The model is calibrated with extracted data from literature involving a biodistribution study of three SiNPs (mesoporous SiNPs with distinct geometrical features (aspect ratio 8 nanorods, AR8), and amine-modified analogs (MA and 8A) in CD-1 mice.[3]
- Utilizing empirical and mechanistic parameters, it predicts whole-body biodistribution and clearance of SiNPs.

Methods

- The PBPK model was formulated as a system of ordinary differential equations to characterize the biodistribution processes using MATLAB R2023A.
- The model included the following compartments: plasma, kidney, lung, mononuclear phagocyte system (MPS) (liver and spleen), excretion (urine and feces), and “others” (brain, heart, small intestine, large intestine, stomach, tail, carcass).
- Physiological parameters for the mice were known a priori and the unknown model parameters were fit through nonlinear least squares regression.
- Global sensitivity analysis (GSA) was performed to understand the relative significance of various model parameters on model outputs of interest.
- Non-compartmental analysis (NCA) was performed with PKanalix® Lixoft.

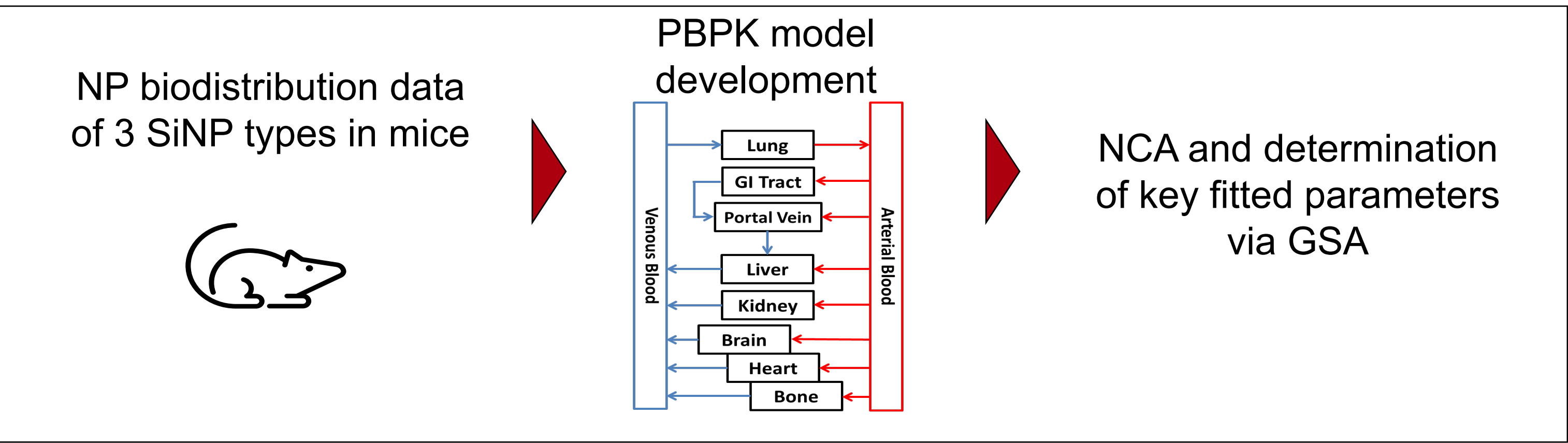


Figure 1 – PBPK modeling workflow.

Results

- The model exhibits strong concordance with the observed data, as evidenced by the robust Pearson correlation coefficient, with a value of >0.97 the goodness of fit (Figure 2), affirming the reliability and accuracy of the predictive model.
- Fitted parameters were within physiological parameters reported for mice.
- The observed data is within the 90% prediction interval of the model.
- GSA (Figure 3) identified the fraction unbound in the kidney compartment and the rate of excretion in the kidney compartment as the most influential in the plasma compartment fit.
- AR8 has the highest AUC_{0-∞} in the plasma compartment as shown in Table 1.

Table 1 – NCA results for MA, AR8, and 8A SiNPs.

NP Type	Plasma	Lungs	MPS	Kidneys
MA				
C _{max} (µg/mL)	29.4	16	480	8.4
T _{max} (hr)	0.083	0.083	0.5	0.083
AUC _{0-∞} (hr*µg*mL ⁻¹)	60.7	150	29720	90
CL (mL/hr)	6.59	2.61	0.013	4.45
AR8				
C _{max} (µg/mL)	21	770	330	12
T _{max} (hr)	0.083	0.083	0.5	0.083
AUC _{0-∞} (hr*µg*mL ⁻¹)	121	2680	60050	490
CL (mL/hr)	3.3	0.15	0.0067	0.82
8A				
C _{max} (µg/mL)	32.6	320	240	12
T _{max} (hr)	0.083	0.083	2	0.083
AUC _{0-∞} (hr*µg*mL ⁻¹)	76.4	720	18230	91
CL (mL/hr)	5.24	0.56	0.022	4.41

NCA was performed with mean data for n=5 mice.

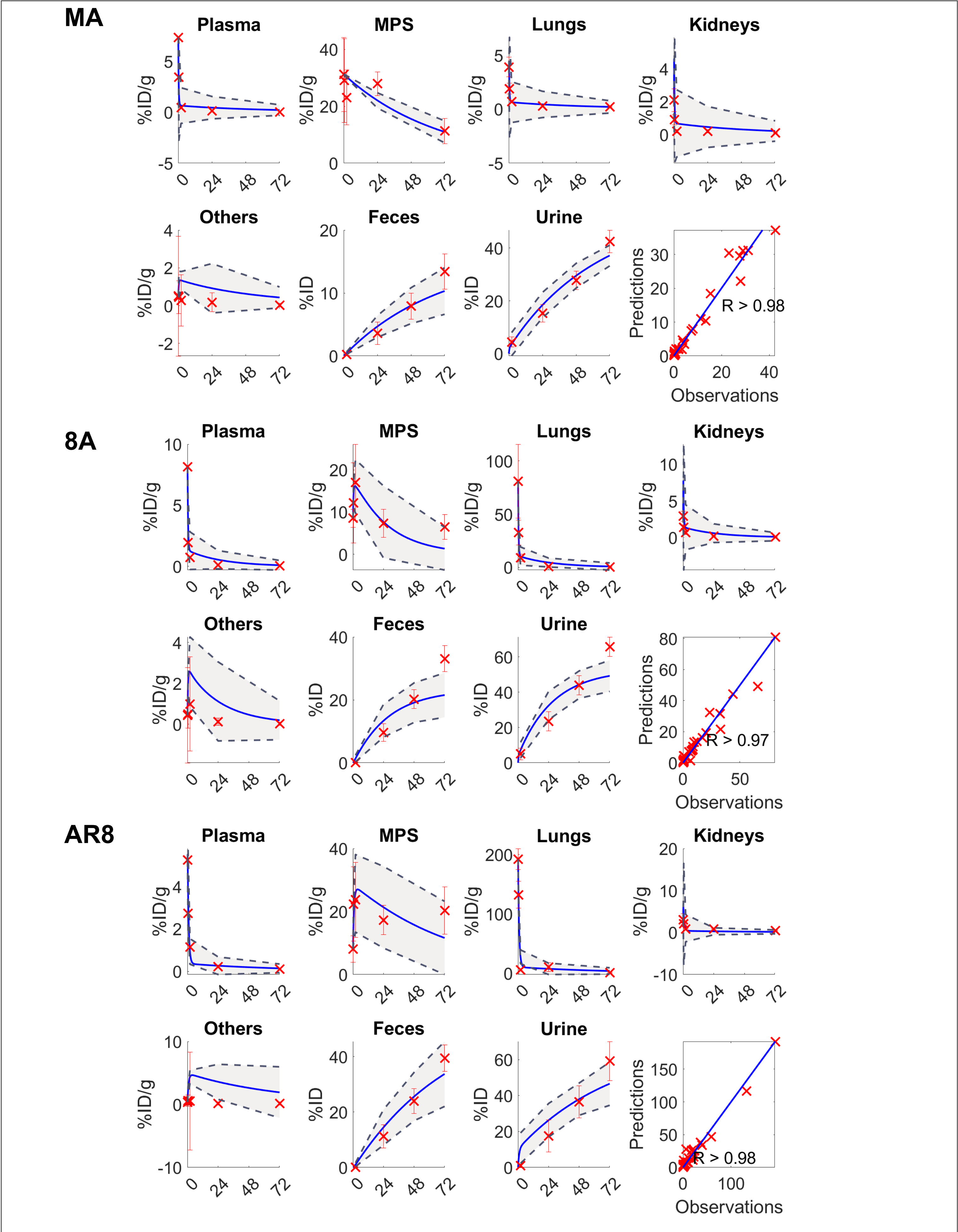


Figure 2 – Mouse model results for all 3 NP types including the 5-95% prediction confidence interval and Pearson correlation coefficient.

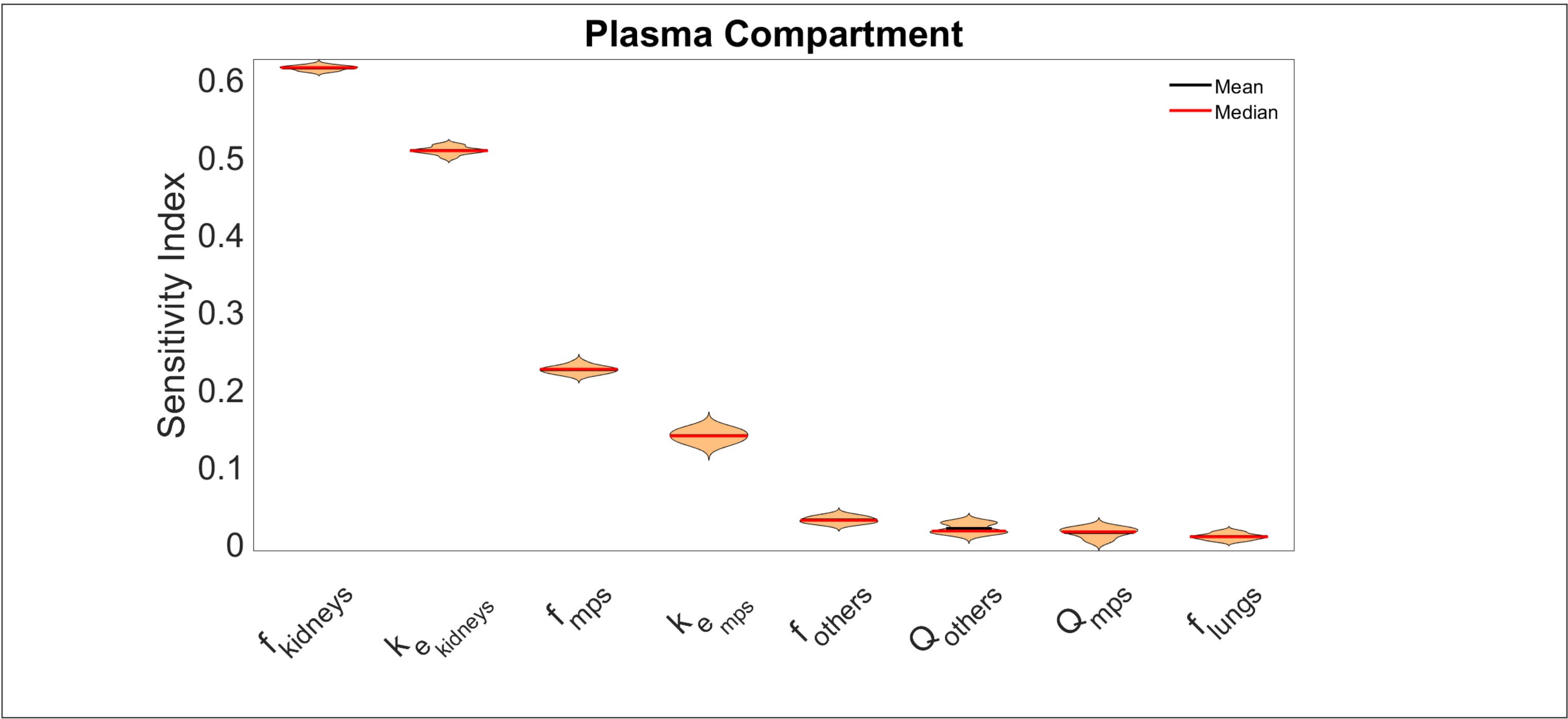


Figure 3 – GSA of the plasma compartment for the mouse model of all 3 SiNP types. Where f is the fraction unbound, k_e is the excretion rate constant, and Q is the blood flow rate.

Conclusions

- The development of a minimal PBPK model for SiNPs in mice provides a tool for understanding the intricate interactions between SiNPs of differing sizes/geometries and biological systems.
- This research has the potential to impact the translational t, safety assessments, and regulatory evaluations of nanoparticle-based therapeutics, ultimately contributing to the safe and effective use of these innovative therapies.

Acknowledgments

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References

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