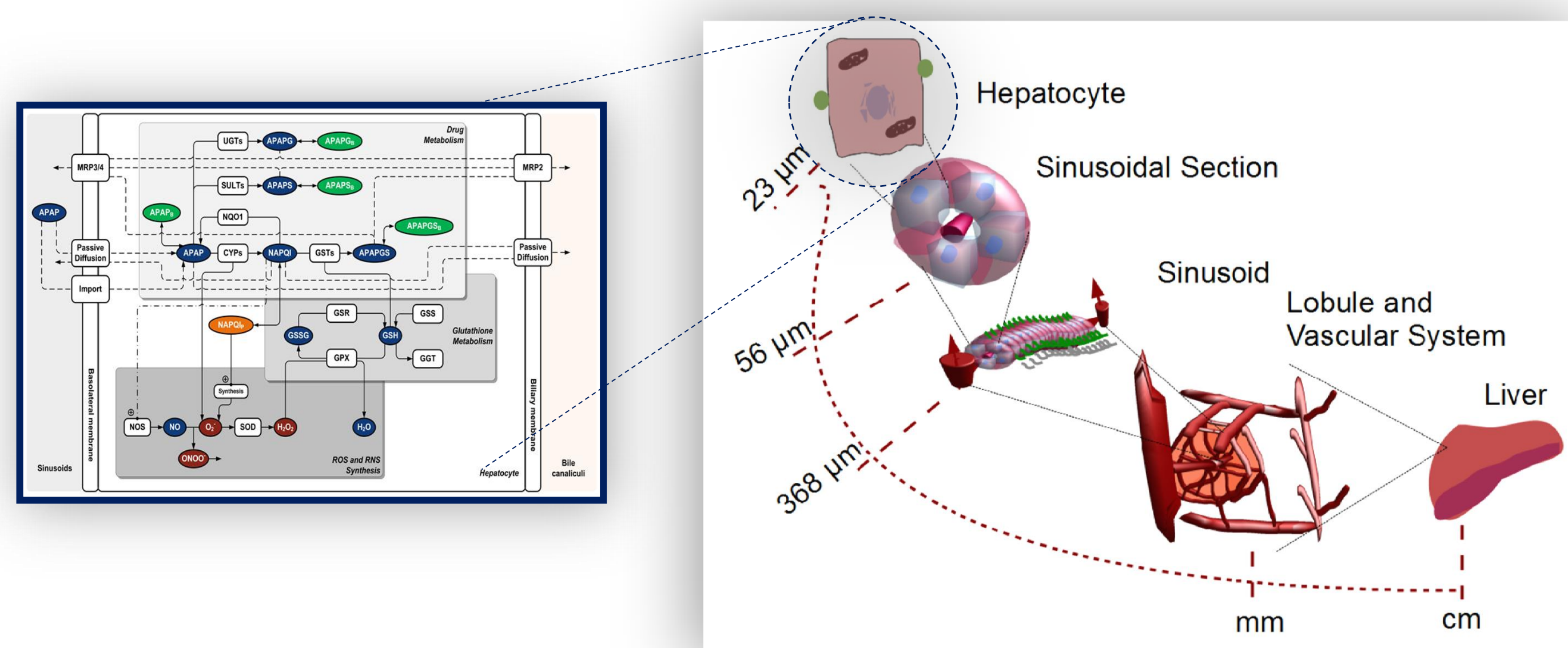


## Introduction and Aims

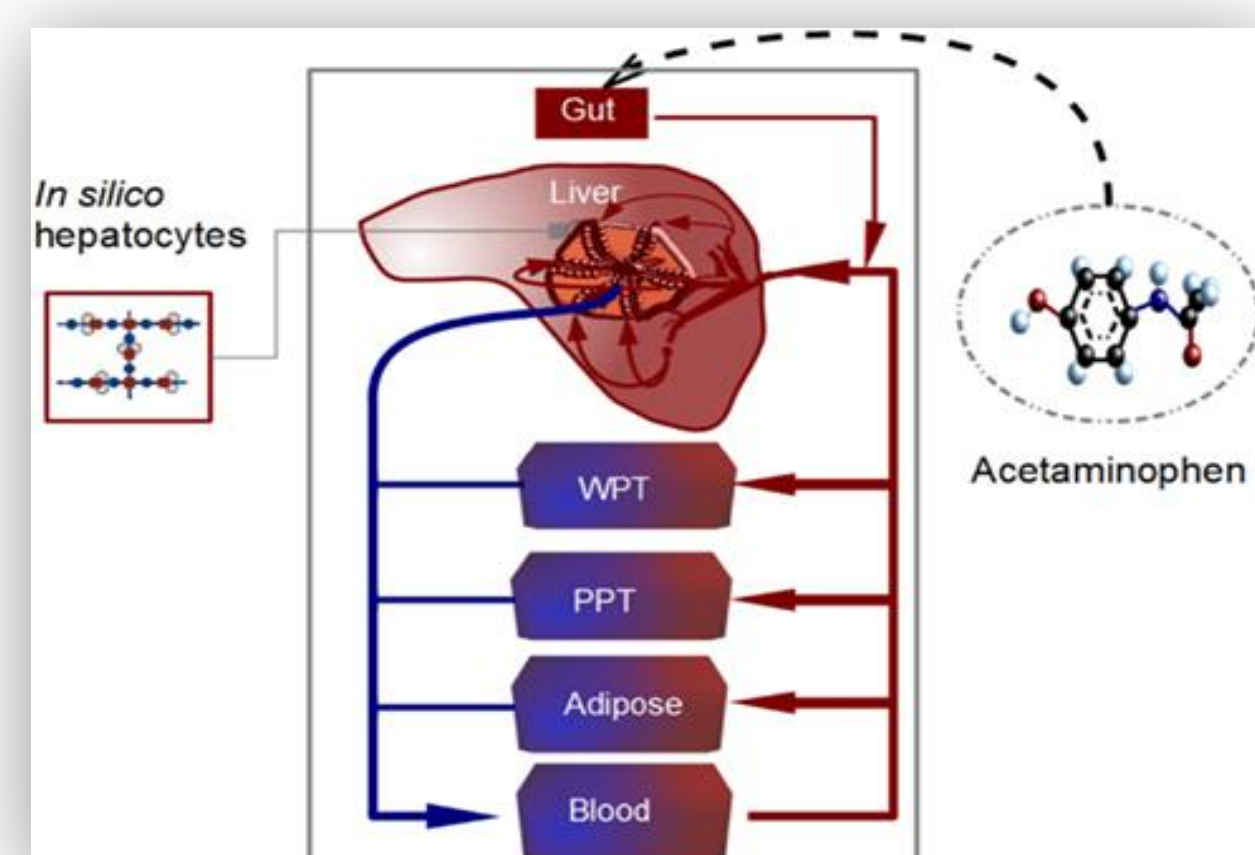
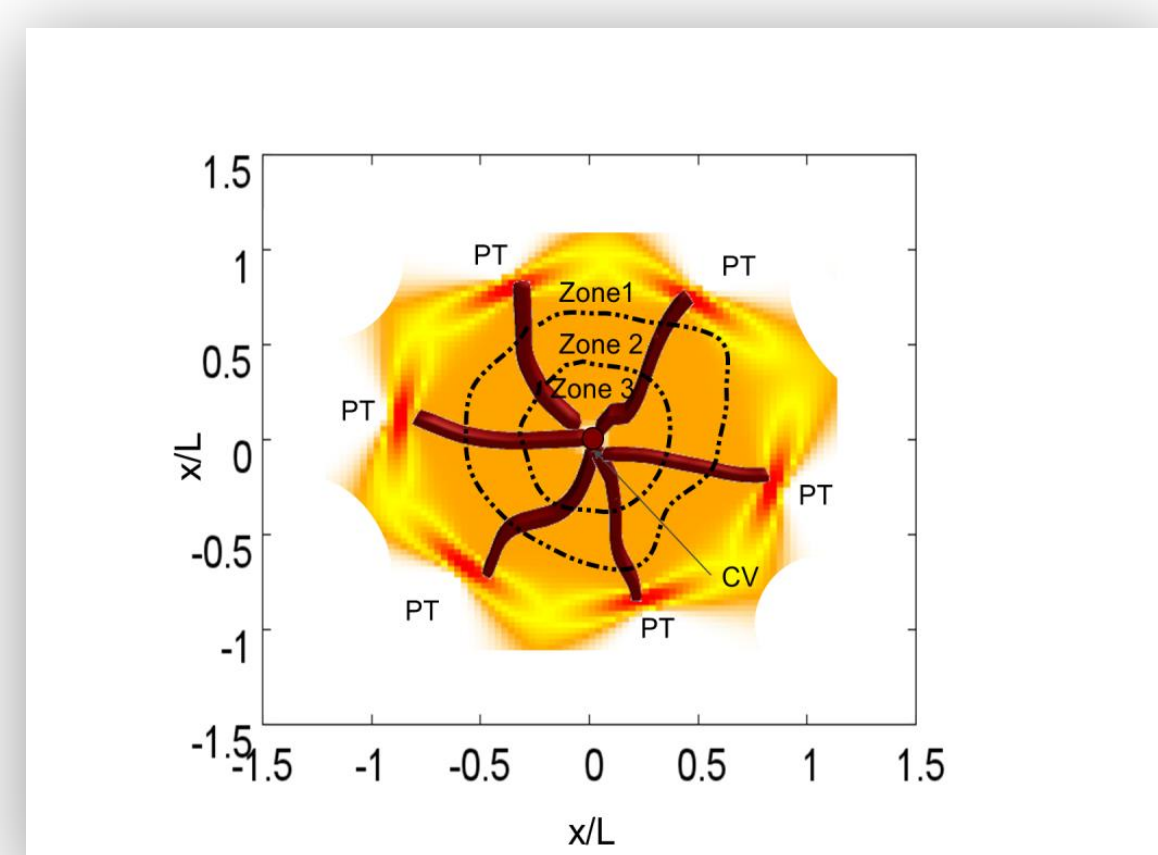
We present a multidimensional model for the liver which is coupled to *in silico* cells performing a metabolic function. The primary goals of this study were (i) to set-up and verify a whole body model coupled with an *in silico* liver, (ii), to predict the distribution of substances *in silico* for acetaminophen, and (iii) to extrapolate critical doses from *in vitro* data. In this model we reconstructed a network for acetaminophen metabolism, integrated this into an *in silico* liver model, simulated uptake and distribution, and performed simulations upon administration of different single doses.

## Model

The metabolic network model for the hepatocytes, based on ordinary differential equations for metabolism and toxicity of acetaminophen (APAP), was set-up based on literature data.



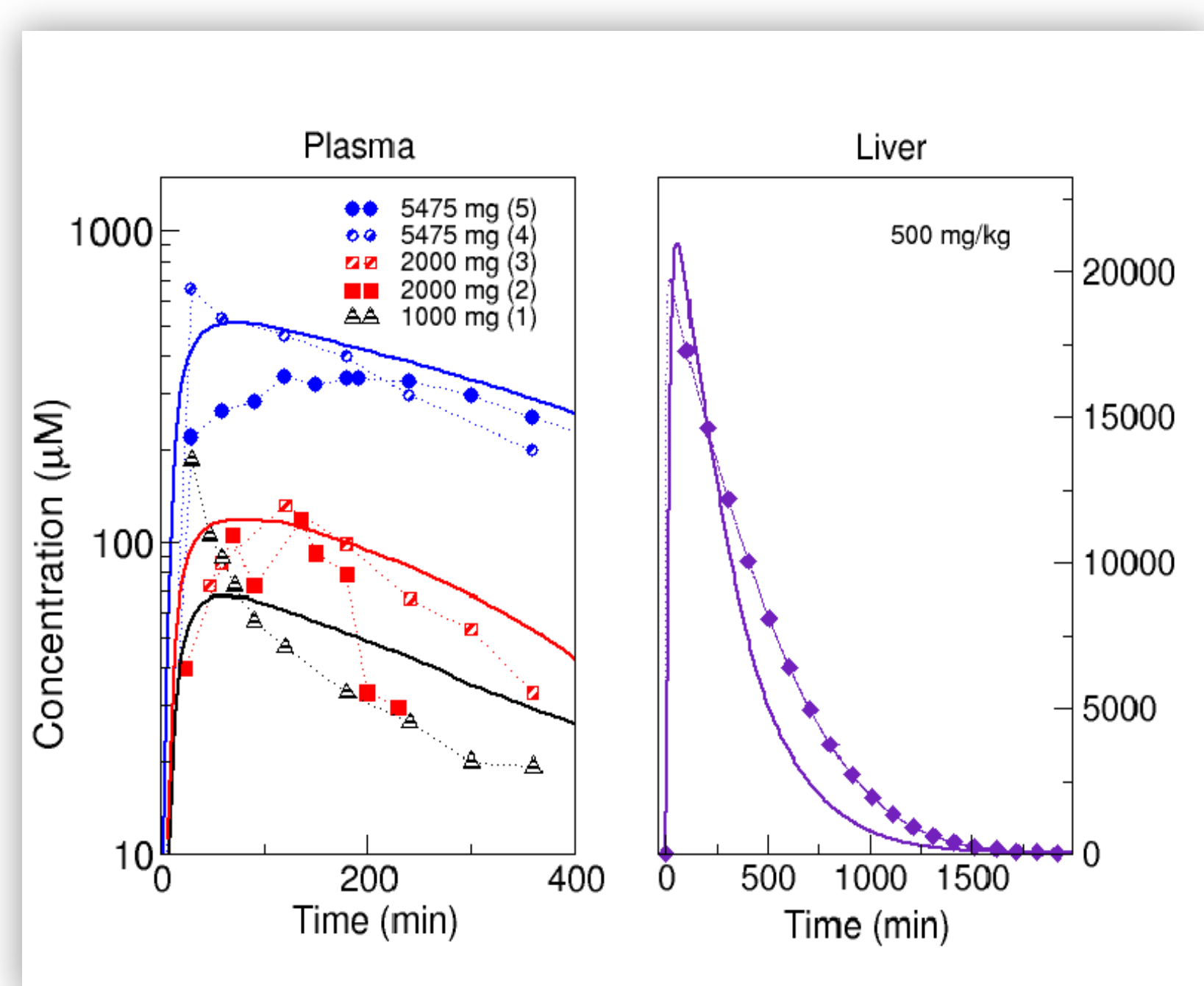
Individual cells are integrated to a multiscale model of the organ consisting on a set of cells ordered along a sinusoid, which is then integrated to a model of the lobule. We assume that the substance disperses along the sinusoid. Cells are necrotic when a critical concentration of a toxic metabolite ( $H_2O_2$ ) is reached.



Blood is transported through sinusoids from the portal to the central vein. The hepatocyte population has different CYP factors in the lobule (zonation).

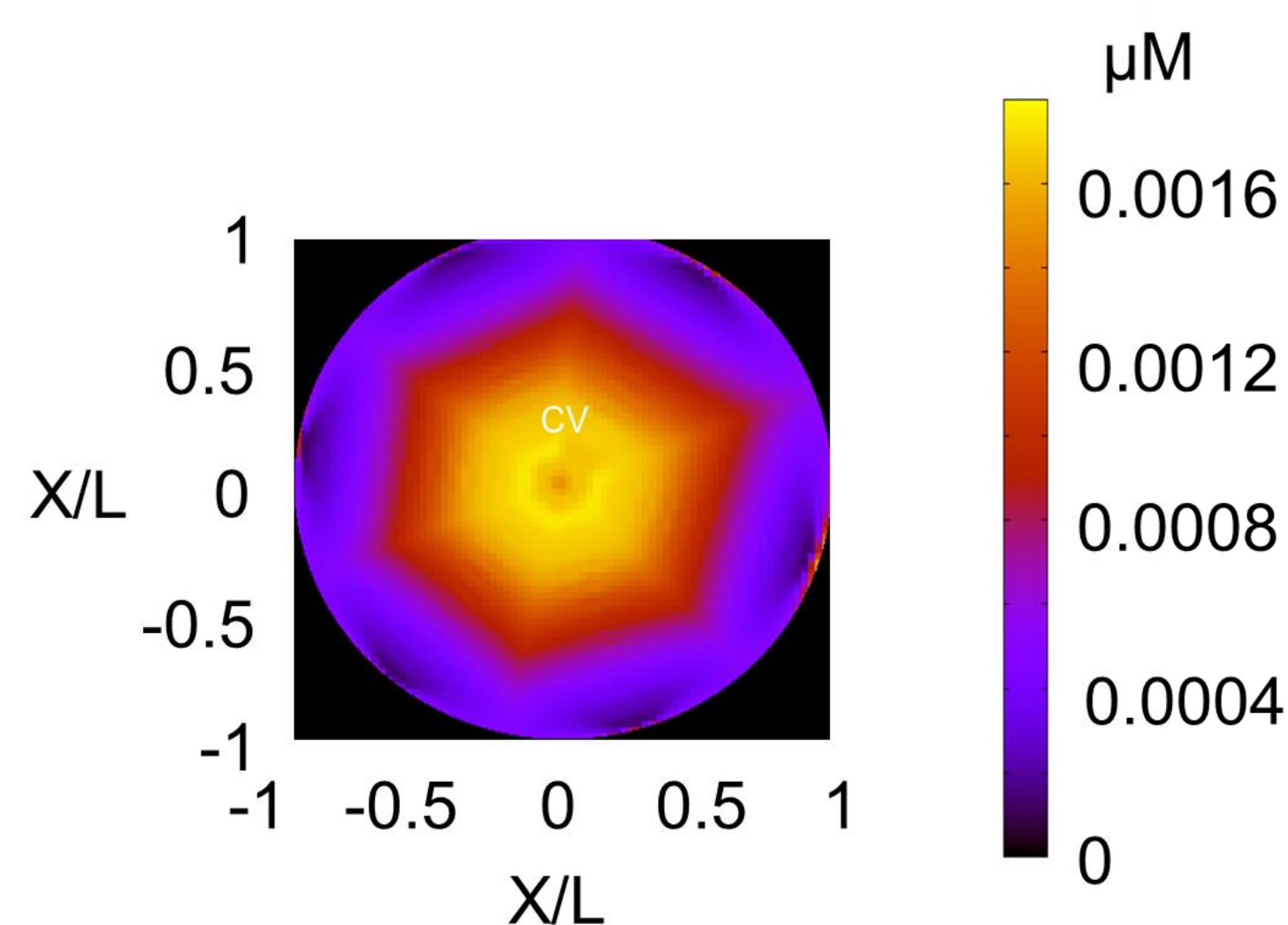
The model for the liver is then integrated into a whole body model where the other organs are represented as compartments.

## Results

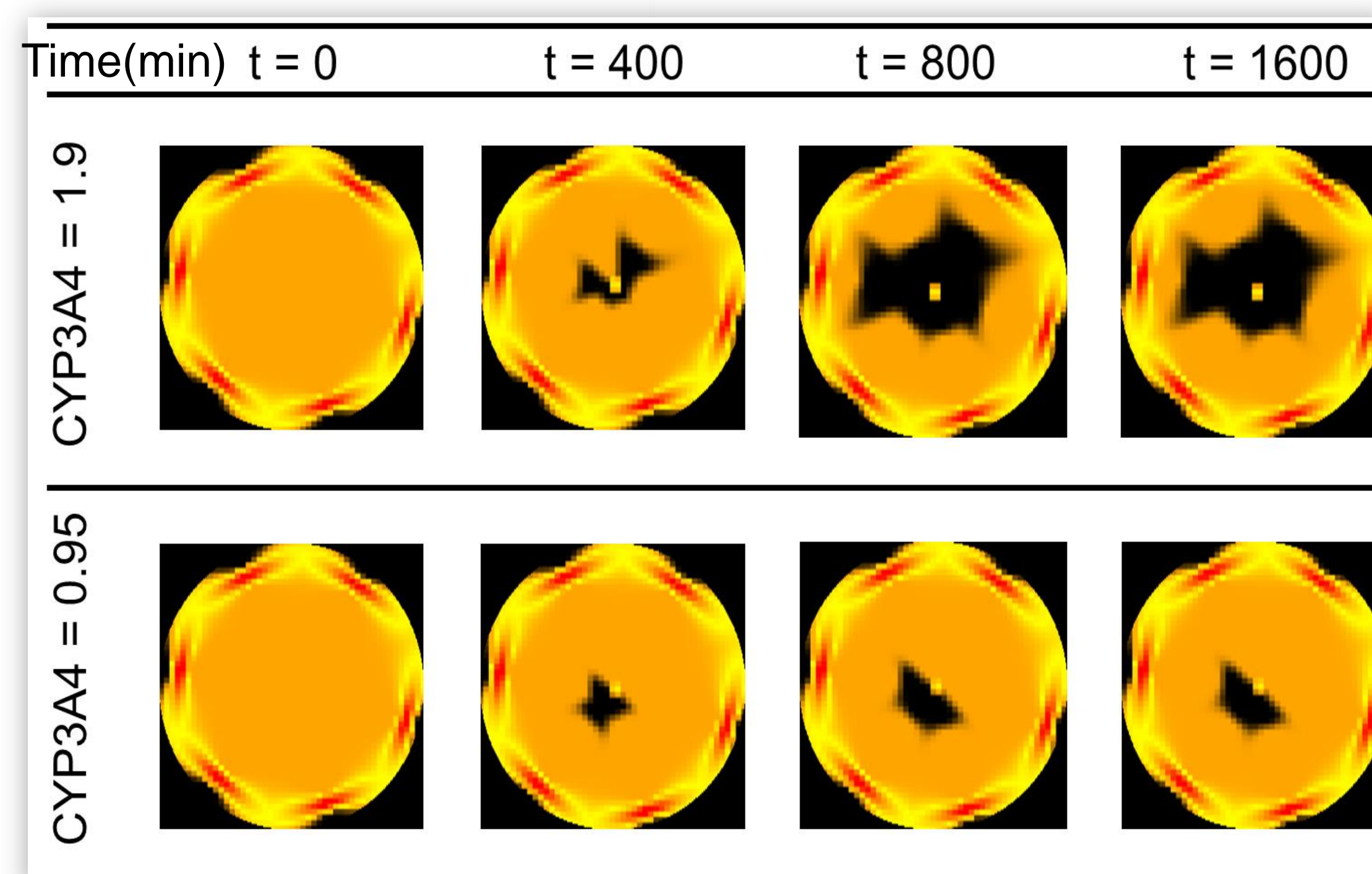


A good agreement between model simulations (lines) and experiments as well as other PBPK models (points) was observed.

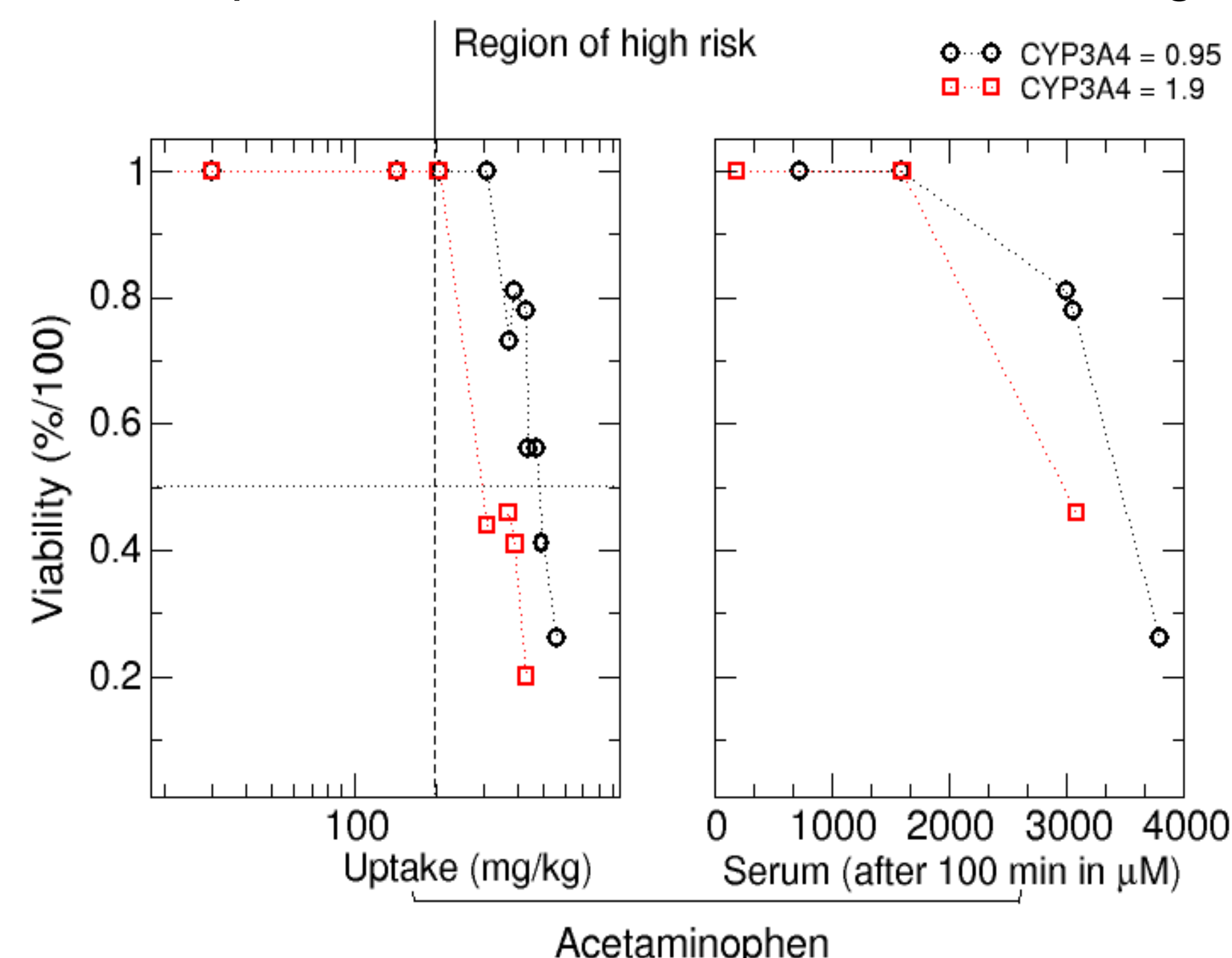
## Results



Prediction of distribution of substances in the liver lobule. Concentration of toxicity marker NAPQI is much larger in the centrilobular region which is more sensitive to acetaminophen toxicity (zonation).



High acetaminophen load results in high concentration of hydrogen peroxide and subsequent liver failure. Prediction of the viability of the hepatocytes *in vivo* and prediction of  $LD_{50}$  value depending on CYP3A4 expression. CYP expression factor is defined as an average value.



Prediction of the viability of the hepatocytes *in vivo* and prediction of  $LD_{50}$  value depending on CYP3A4 expression.

## Conclusions

We present a multi-scale modeling approach integrating cellular and organ models in a whole body environment suitable for predicting spatiotemporal variations in drug response and toxicity.

The presented work is a basis for efficiently analysing inter-individual differences upon exposure to chemicals or drug treatment *in silico* and hence a significant step forward on the road to improved risk assessment or individualised prediction of drug effects.

## References

- J.G. Diaz Ochoa, J. Bucher, A.R.R. Péry, J.M. Zaldivar Comenges, J. Niklas, *Front. Pharmacol.*, **3**, 204 (2012)  
J. Niklas, J. G. Diaz Ochoa, J. Bucher, K. Mauch, *Molecular Informatics*, **32**, 14 (2013)