

Mechanistic Model to Predict DDIs in the Liver.

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Introduction

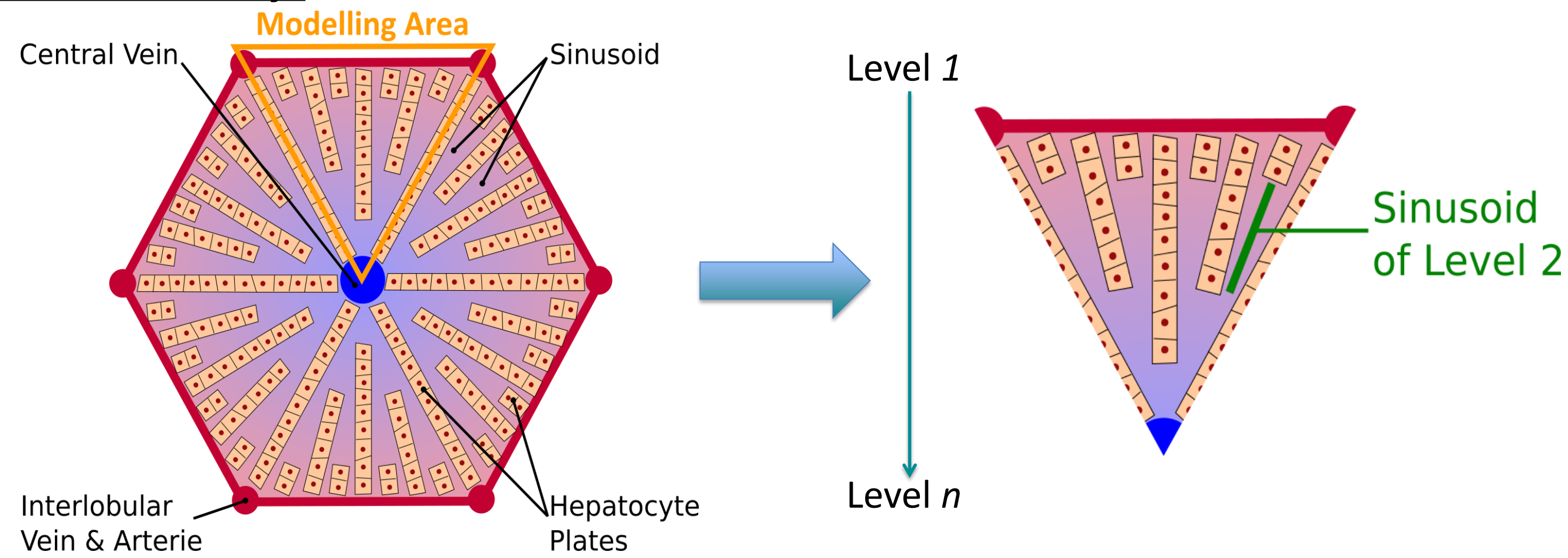
Background and Aim:

New drugs are developed every year and with poly-pharmacy becoming more common there is a higher potential risk of Drug-Drug Interactions (DDIs). Once a New Chemical Entity (NCE) has been discovered and tested in the laboratory, it is necessary to launch a risk assessment study of its potential DDIs before the drug is administered to humans for clinical study. Mathematical models have the ability to predict the DDI, but many of the current models focus on one particular interaction at a time such as reversible inhibition of an enzyme [1], mechanistic based inhibition (MBI) or induction due to the enzyme up-regulation.

The aim here is to generate a mechanistic dynamic model for the prediction of DDIs, which results from time-processes within hepatocytes, taking into account the spatial distribution of the drugs in a lobule, the uptake at the sinusoidal membrane, the enzyme inhibition/induction [2,3].

Materials and Methods

Lobule Geometry:



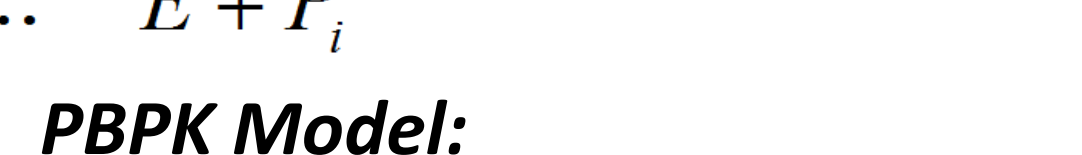
Liver Blood Equations:

At level k , there are 2^{n-k} sinusoids of length L_k and blood flow $Q_k = Q_1 * 2^{k-1}$. The conservation equation of the free level of the perpetrator A and the victim I gives:

$$\begin{cases} S_k^{BI}(x) \frac{\partial C_{A,k}^{BI}}{\partial t} + Q_k \frac{\partial C_{A,k}^{BI}}{\partial x} = -f_{u,A}^{BI} \ell_k(x) [P_A(C_{A,k}^{BI} - C_{A,k}^H) + \rho_{in,A} C_{A,k}^{BI} - \rho_{out,A} C_{A,k}^H] \\ C_{A,k}^{BI}(x=0) = C_{A,k-1}^{BI}(x=L_{k-1}) \\ S_k^{BI}(x) \frac{\partial C_{I,k}^{BI}}{\partial t} + Q_k \frac{\partial C_{I,k}^{BI}}{\partial x} = -f_{u,I}^{BI} \ell_k(x) [P_I(C_{I,k}^{BI} - C_{I,k}^H) + \rho_{in,I} C_{I,k}^{BI} - \rho_{out,I} C_{I,k}^H] \\ C_{I,k}^{BI}(x=0) = C_{I,k-1}^{BI}(x=L_{k-1}) \end{cases}$$

Hepatocytes Equations:

Induction by: A or I



Parameters:

The physiological parameters; liver geometry, flow, hepatic and renal clearance and blood fraction unbound were obtained from the literature and an average body weight of 70kg was assumed.

In vitro input parameters; inhibition, MBI, induction (mRNA), enzyme degradation and uptake were measured by Vertex Pharmaceuticals.

Clinical Data:

32 perpetrator and 5 victim drugs from 70 clinical studies were used to validate the model. These 70 clinical studies were simulated using the PBPK model to compare the predicted AUC ratio with the observed.

Model Comparison:

In order to evaluate the model performance, it was compared to a combined static model [2] where the geometric mean fold error (GMFE) was used as a score index:

$$GMFE = 10^{\frac{1}{n} \sum_{i=1}^n \left| \log \left(\frac{\text{Predicted } AUC_{Ratio}}{\text{Observed } AUC_{Ratio}} \right) \right|}$$



Results

Pharmacokinetics:

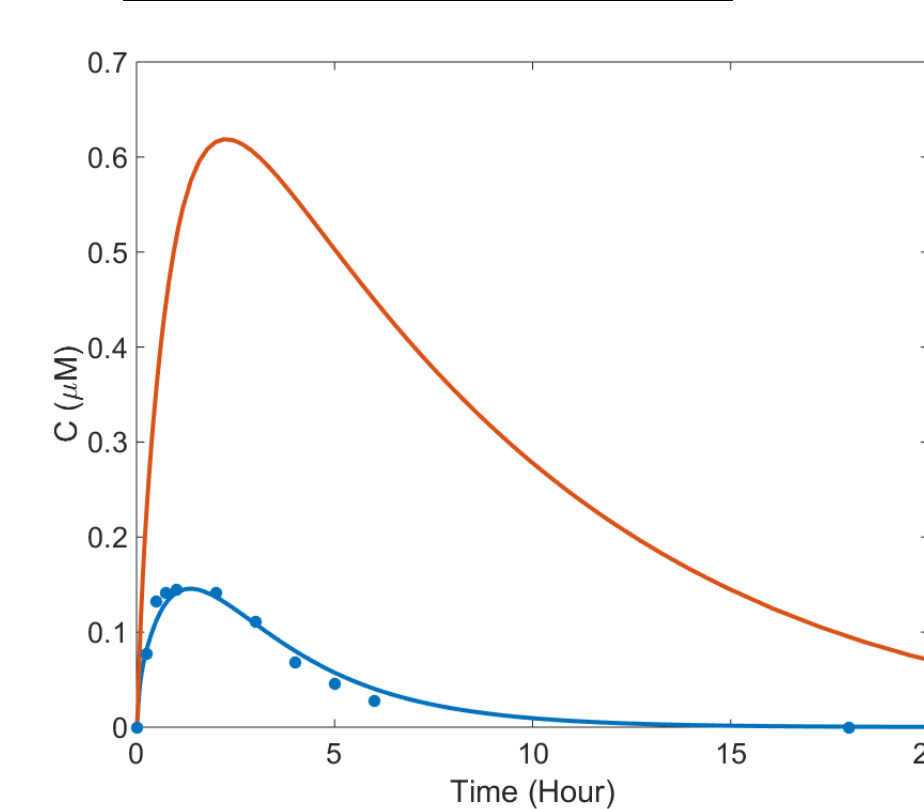


Fig 1: Blood Concentration of Midazolam (15mg) after an oral dose with and without Clarithromycin (Data from [4]).

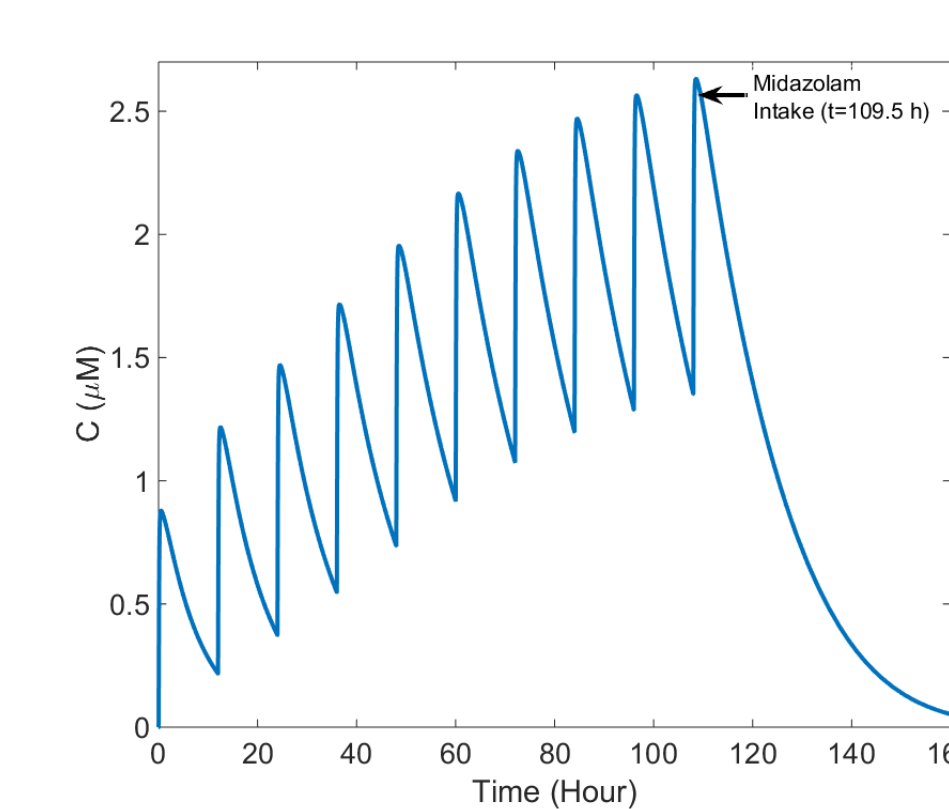


Fig 2: Blood Concentration of Clarithromycin (250mg - b.i.d).

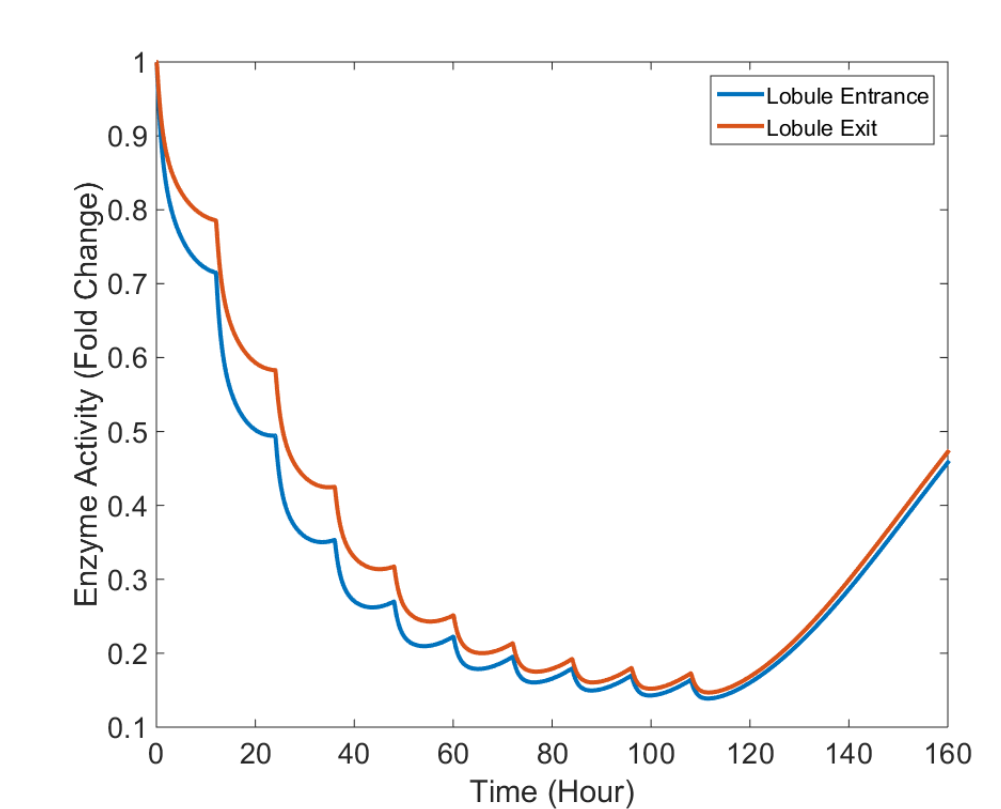


Fig 3: Enzyme Activity (Fold Change) at the entrance and exit of the lobule

Predicted DDI due to CYP3A4:

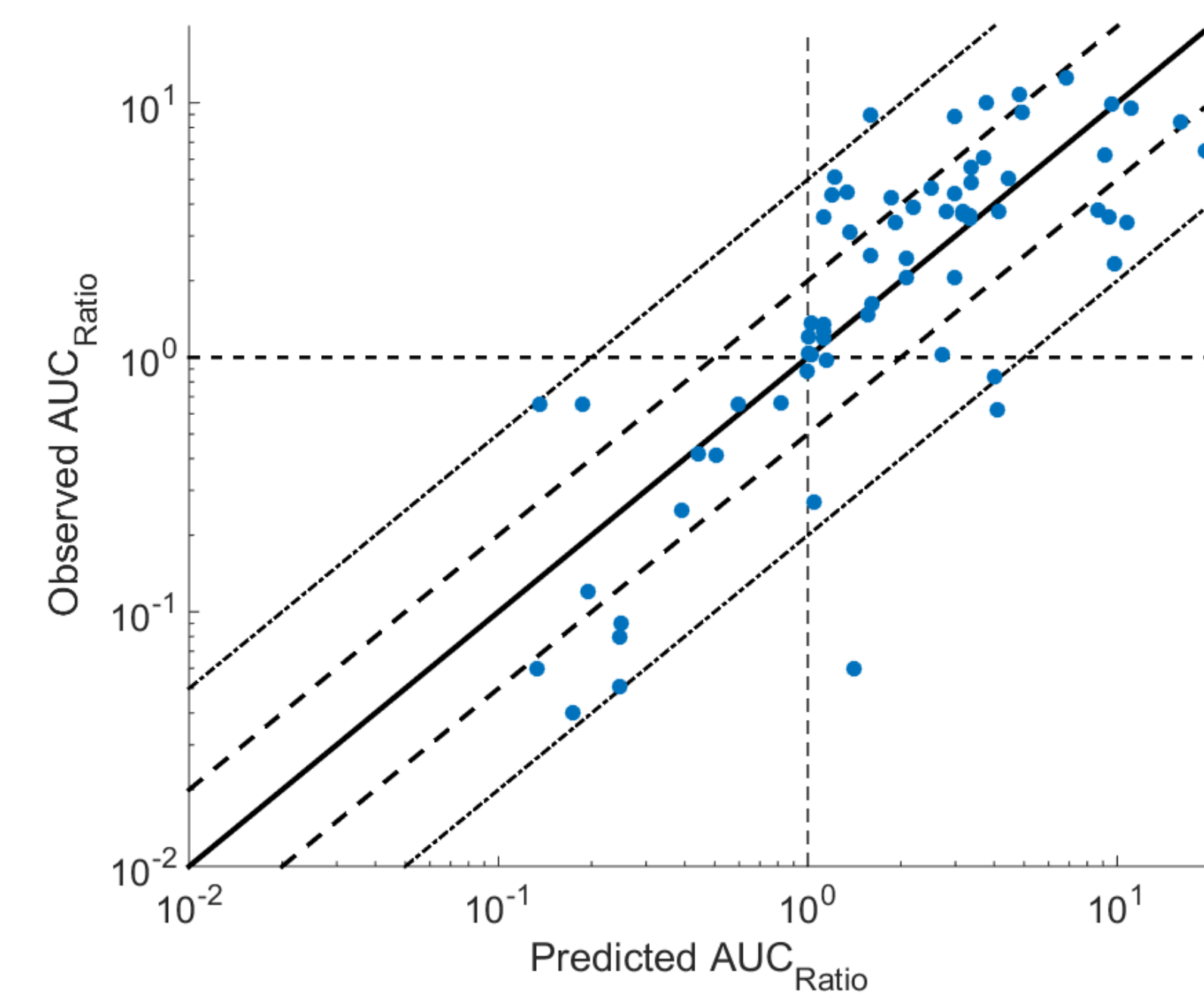


Fig 4: Observed vs Predicted AUC ratio. The dashed lines represent 2 and 5 fold error.

Category	New Model	Combined Model 1	Combined Model 2
Inhibition	1.76	1.45	1.60
MBI	1.61	1.69	1.88
Induction	2.18	2.72	2.91
Inhibition & Induction	4.83	2.72	2.53
MBI & Induction	2.44	2.00	1.89
All	1.99	1.84	1.95

Table 1: GMFE score of different models. Model 1 interaction in Liver only (X=Y=Z=1) whereas Model 2 includes Gut as well.

Model 1:

$$AUC_{Ratio} = \frac{1}{A \cdot B \cdot C \cdot f_m + (1 - f_m) \cdot X \cdot Y \cdot Z \cdot (1 - F_G) + F_G}$$

$$A = \frac{1}{1 + \frac{C_I^H}{K_i}}, B = \frac{k_{deg}}{k_{deg} + \frac{k_{inact}^I C_I^H}{K_i}}, \text{ and } C = 1 + \frac{(E_{max} - 1)}{EC_{50} + C_I^H}$$

$$X = \frac{1}{1 + \frac{C_I^H}{K_i}}, Y = \frac{k_{deg}}{k_{deg} + \frac{k_{inact}^I C_I^H}{K_i}}, \text{ and } Z = 1 + \frac{(E_{max} - 1)}{EC_{50} + C_I^H}$$

$$C_I^H = f_{u,I}^H \frac{F_u F_s Dose}{CLT_p} \text{ and } C_I^G = \frac{F_u Dose}{CLT_p}$$

Discussion and Conclusion

- The proposed model gives similar results than the combined model.
- Because the uptake is taking into account, the model is sensitive to the *in vitro* parameters (inhibition/MBI/induction).
- In addition to the DDI, the model is able to describe the drug kinetics and the changes in the enzyme activity; temporally and spatially.
- The model is also able to give a population description (not shown) by varying the geometry of the liver/lobule, the blood flow and/or the normal enzyme activity.
- In conclusion, the model can be used for compounds where a rich description of the liver interaction is needed.

References:

- Z. Zhang and Y. Wong, "Enzyme Kinetics for Clinically Relevant CYP inhibition." *Current Drug Metabolism*, 6(3), pp. 241-257, 2005.
- O. A. Fahim, T. S. Maurer, M. Kish, E. Cardenas, S. Boldt and D. Nettleton, "A Combined Model for Predicting CYP3A4 Clinical Net Drug-Drug Interaction Based on CYP3A4 Inhibition, Inactivation and Induction Determined *In Vitro*." *Drug Metabolism and Disposition*, 36(8), pp. 1698-1708, 2008.
- B. J. Kirby, A. C. Collier, E. D. Kharasch, D. Whittington, K. E. Thummel and J. D. Unadkat, "Complex Drug Interactions of HIV Protease Inhibitors 1: Inactivation, Induction and Inhibition of Cytochrome P450 3A by Ritonavir or Nelfinavir." *Drug Metabolism and Disposition*, 29, pp. 1-21, 2003.
- K. T. Oikola, K. Aranko, H. Luurila, A. Hiller, L. Saarnivaara, J. J. Himberg and P. J. Neuvonen, "A Potentially Hazardous Interaction between Erythromycin and Midazolam." *Clinical Pharmacology and Therapeutics*, 53, pp. 298305, 1993.
- D. Ridgway, J. A. Tuszynski and Y. K. Tam, "Reassessing Models of Hepatic Extraction." *Journal of Biological Physics*, 29, pp. 1-21, 2003.
- K. Ito, H. S. Brown and J. B. Houston, "Mathematical Database Analyses for the Prediction of *in vivo* Drug-Drug Interactions from *in vitro* Data." *British Journal of Clinical Pharmacology*, 57(4), pp. 473-486, 2004.11