# A Multi-Compartment Liver Model for the Prediction of Toxicokinetics

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## INTRODUCTION

Drug metabolizing enzymes and transporters are differentially expressed across the liver resulting in regional differences in drug kinetics. This can impact the manifestation of drug induced liver injury, resulting in regionally specific lesions. For example, acetaminophen overdose results in centrilobular lesions due to the high regional expression of CYP2E1 that mediates the generation of the reactive metabolite, N-acetyl-p-benzoquinone imine.

Well-stirred, single compartment liver models are widely used in predicting the pharmacokinetics of compounds in PBPK models. However, they don't account for the zonal nature of gene/protein expression.

Here we propose a multi-compartment liver model framework incorporating differential gene-expression across the acinus to investigate the impact of regional differences in drug metabolizing enzyme expression on the metabolism of acetaminophen.

## METHODS

A human PBPK model for acetaminophen has previously been published (Jiang *et al*, 2013); this model was reconstructed as a minimal-PBPK in R (v3.2.0) using a single, well-stirred compartment to represent the liver (*figure 1A*). Subsequently, a second model using the same framework, but incorporating a multi-compartment liver model based on (Anissimov and Roberts, 2002), was constructed; it's structure and is shown in the schematic (*figure 1B*). In this model the liver is represented as eight individual compartments, two of which have a variable perfusion rate which can be used to account for the complex architecture of the hepatic vasculature adjacent to the portal triad. The different sections of the model can be parameterised to represent the differential expression gradient of drug metabolising enzymes from the periportal to the centrilobular region (Johansson *et al*, 1990; Godoy *et al*, 2013). This is done using a zonality scalar, z, to attribute different fractions of hepatic intrinsic clearance to different regions of the liver; the equations for this model are given opposite and parameters for both models are given in (*table 1)*. Here, the multi-compartment model is parameterised with both uniform and zonated metabolism.

| Parameter | Units | Value | Reference |
|---|---|---|---|
| **Physicochemical Properties** | | | |
| MW | g/mol | 151.16 | drugbank |
| Log $P_{o:w}$ | | 0.46 | *drugbank* |
| Compound type | neutral | | |
| pKa | | 9.38 | *drugbank* |
| Polar surface area | $Å^2$ | 49.33 | *drugbank* |
| Hydrogen bond donor | | 2 | *drugbank* |
| **Protein Binding** | | | |
| fu | | 0.82 | *Strougo et al, 2012* |
| BP | | 1.58 | *Jiang et al, 2013* |
| **Absorption** | | | |
| fa | | 1 | *Jiang et al, 2013* |
| ka | | 15 | *Jiang et al, 2013* |
| **Elimination** | | | |
| $CL_{uint\ Hep}$ | $Lhr^{-1}$ | 26.52 | *Jiang et al, 2013* |
| $CL_R$ | $Lhr^{-1}$ | 0.62 | *Clements et al, 1984* |

***Table1. Physicochemical properties and parameters for acetaminophen***

## RESULTS

The PBPK models generated were used to simulate paracetamol concentrations in human plasma following a 1000mg oral dose and compared against observed data *(figure 2, top row)*. The observed data show significant inter-individual variability in plasma concentrations however, the models show reasonable recovery of the plasma concentration profile of acetaminophen. The multi-compartment liver model allows the prediction of both uniform and zonated distributed metabolism (figure 2) resulting from differential metabolic clearance. Here we do not account for the subsequent clearance of primary metabolites in order to better demonstrate model behaviour, although this could be incorporated in future iterations of the model. The multi-compartment model with uniformly distributed metabolism, shows comparable performance to the single compartment liver model. However, redistributing clearance (85% centrilobular) shifts hepatic exposure to parent compounds and metabolite.

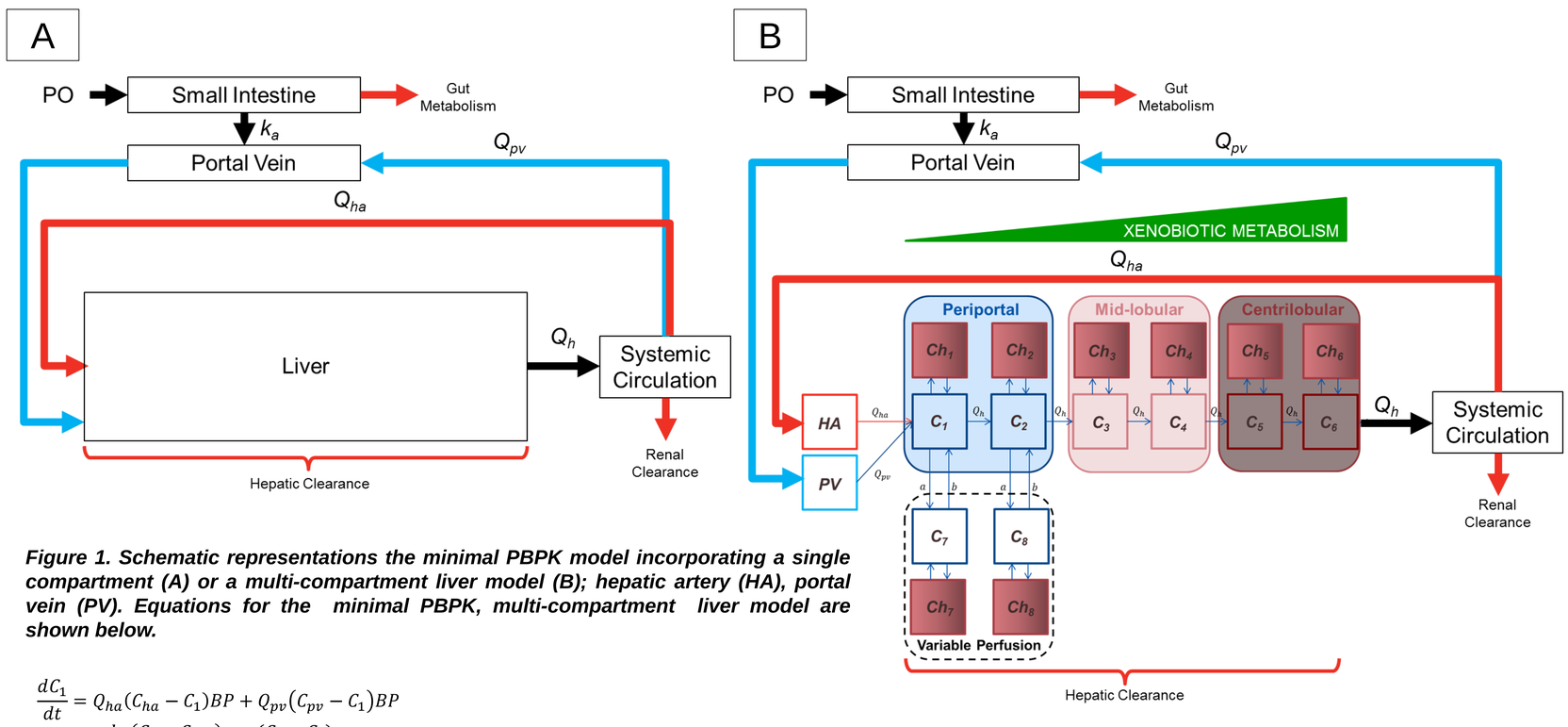


***Figure 1. Schematic representations the minimal PBPK model incorporating a single compartment (A) or a multi-compartment liver model (B); hepatic artery (HA), portal vein (PV). Equations for the minimal PBPK, multi-compartment liver model are shown below.***

$$\frac{dC_1}{dt} = Q_{ha}(C_{ha} - C_1)BP + Q_{pv}(C_{pv} - C_1)BP - k_p(C_1 - C_{ch1}) - a(C_1 - C_7)$$

$$\frac{dC_2}{dt} = Q_h(C_1 - C_2)BP - k_p(C_2 - C_{ch2})BP \quad - a(C_2 - C_8)BP$$

$$\frac{dC_x}{dt} = Q_h(C_{x-1} - C_x)BP - k_p(C_x - C_{chi})BP$$

$$x = 3, \dots, 6$$

$$\frac{dC_7}{dt} = b(C_1 - C_7)BP - k_p(C_7 - C_{ch7})BP$$

$$\frac{dC_8}{dt} = b(C_2 - C_8)BP - k_p(C_8 - C_{ch8})BP$$

$$C_{pv} = \frac{Q_{pv}C_pBP + f_a k_a F_g \cdot dose \cdot exp^{(-k_a \cdot t)}}{Q_{pv}BP}$$

$$\frac{dC_{ha}}{dt} = Q_{ha}(C_p - C_{ha})BP$$

$$\frac{dC_p}{dt} = Q_h(C_6 - C_p)BP - CL_R C_p$$

$$\frac{dC_{hi}}{dt} = k_p(C_i - C_{h_i})BP - z \cdot CL_{u,int}C_{uh_i}$$

$$C_{uh_i} = f_u\left(\frac{C_{h_i}}{k_p}\right)$$

$$i = 1, \dots, 8$$

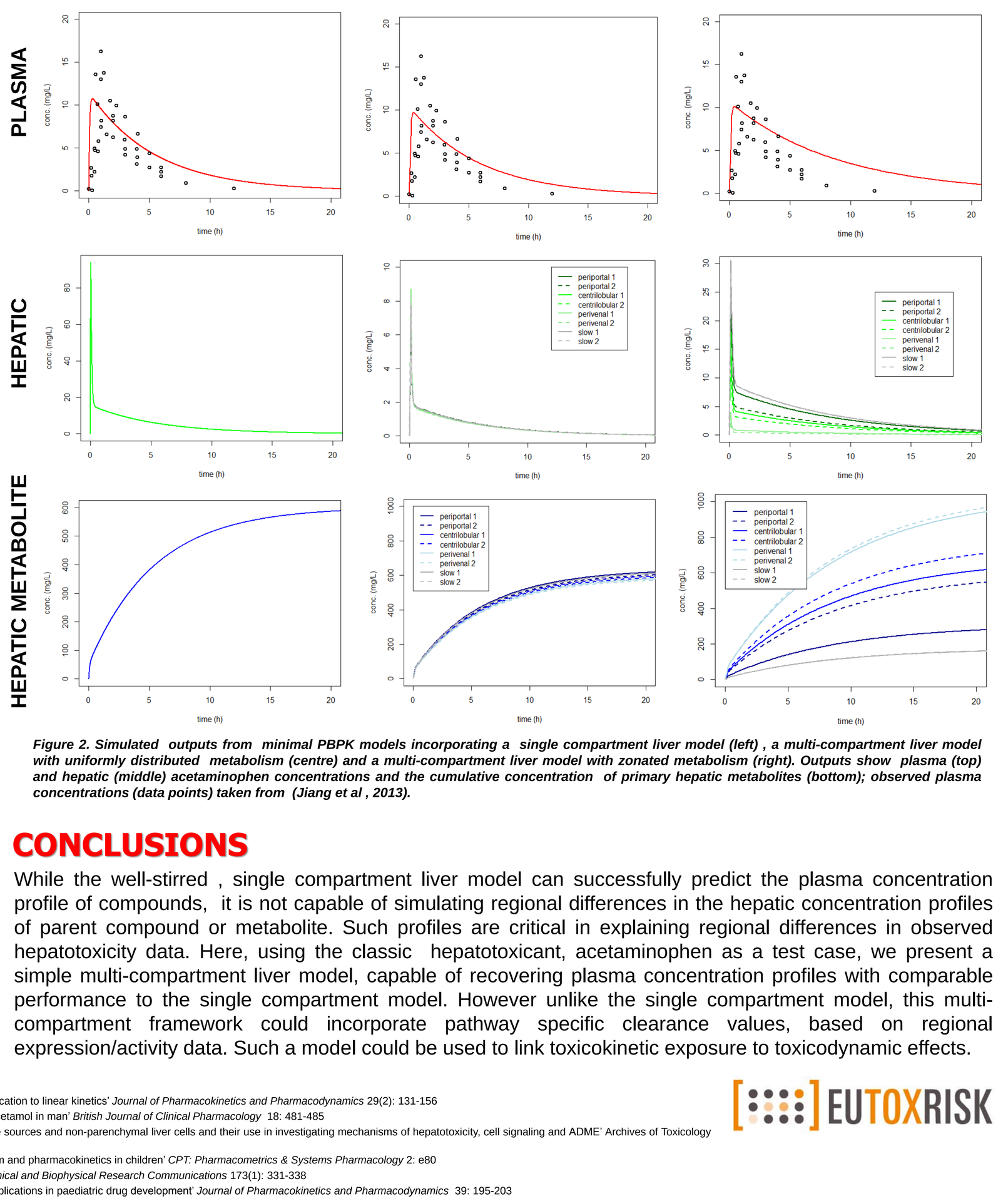


***Figure 2. Simulated outputs from minimal PBPK models incorporating a single compartment liver model (left) , a multi-compartment liver model with uniformly distributed metabolism (centre) and a multi-compartment liver model with zonated metabolism (right). Outputs show plasma (top) and hepatic (middle) acetaminophen concentrations and the cumulative concentration of primary hepatic metabolites (bottom); observed plasma concentrations (data points) taken from (Jiang et al , 2013).***

## CONCLUSIONS

While the well-stirred , single compartment liver model can successfully predict the plasma concentration profile of compounds, it is not capable of simulating regional differences in the hepatic concentration profiles of parent compound or metabolite. Such profiles are critical in explaining regional differences in observed hepatotoxicity data. Here, using the classic hepatotoxicant, acetaminophen as a test case, we present a simple multi-compartment liver model, capable of recovering plasma concentration profiles with comparable performance to the single compartment model. However unlike the single compartment model, this multi-compartment framework could incorporate pathway specific clearance values, based on regional expression/activity data. Such a model could be used to link toxicokinetic exposure to toxicodynamic effects.

### *References*

Anissimov and Roberts (2002) 'A compartmental model of hepatic disposition kinetics: 1. Model development and application to linear kinetics' *Journal of Pharmacokinetics and Pharmacodynamics* 29(2): 131-156

Clements et al (1984) 'The role of sulphate conjugation in the metabolism and disposition of oral and intravenous paracetamol in man' *British Journal of Clinical Pharmacology* 18: 481-485

Godoy et al (2013) 'Recent advances in 2D and 3D in vitro systems using primary hepatocytes, alternative hepatocyte sources and non-parenchymal liver cells and their use in investigating mechanisms of hepatotoxicity, cell signaling and ADME' Archives of Toxicology 87(8): 1315-1530

Jiang *et al* (2013) 'Application of physiologically based pharmacokinetic modelling to predict acetaminophen metabolism and pharmacokinetics in children' *CPT: Pharmacometrics & Systems Pharmacology* 2: e80

Johansson et al (1990) 'Transcriptional control of CYP2E1 in the perivenous liver region and during starvation' *Biochemical and Biophysical Research Communications* 173(1): 331-338

Strougo et al (2012) 'First dose in children: physiological insights into pharmacokinetic scaling approaches and their implications in paediatric drug development' *Journal of Pharmacokinetics and Pharmacodynamics* 39: 195-203