A Spatial-Temporal Model for Zonal Hepatotoxicity of Acetaminophen

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Introduction

APAP is widely used for the relief of pain and minor fever. Acetaminophen overdose can cause acute liver failure. We investigate sinusoidal heterogeneity in all three pathways of the APAP metabolism. We introduce sinusoidal gradients of glucuronidation, sulphation, and glutathione (GSH) into a Finite Element Method based reaction-diffusion solver for handling the spatial distribution of enzyme activities/concentrations in live lobules (Fig. 1). Through multiscale modelling (from lobule to hepatocytes and to APAP molecules) we aim to shed light into the rich metabolism dynamics of zonal hepatoxicity induced by APAP.

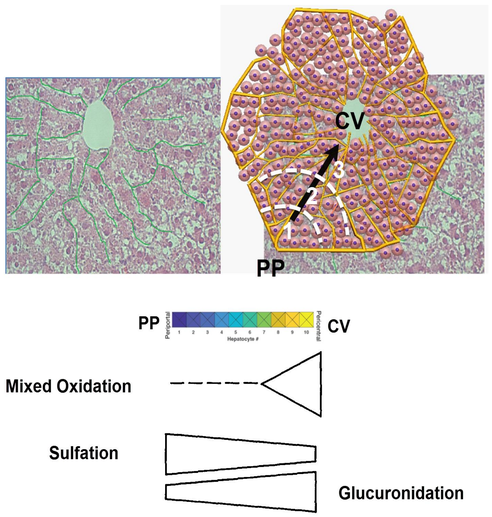


Fig. 1: Spatial distribution of CYP450, sulphation and glucuronidation activities

Methods

We adopt the intracellular APAP metabolism model of [1], which uses an ODE system of five equations to capture the time course of APAP and its metabolites under normal and overdose conditions. We exploited a currently available finite element method (FEM) based reaction-diffusion solver [2] for handling the spatial distribution of compounds in hepatocytes.

We calculate the dosage of APAP given total intake of subject converted into exposure to an individual hepatocyte. Spatial heterogeneity is pre-scribed per Fig. 2(c).

$$\frac{dP}{dt} = -k_S SP - k_G P - k_{450} P + k_N N \quad (1)$$

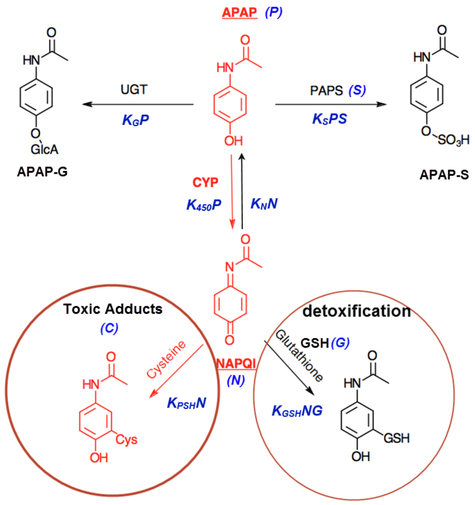
$$\frac{dS}{dt} = -k_S SP + b_S - d_S S \quad (2)$$

$$\frac{dN}{dt} = k_{450} P - k_N N - k_{GSH} NG - k_{PSH} N \quad (3)$$

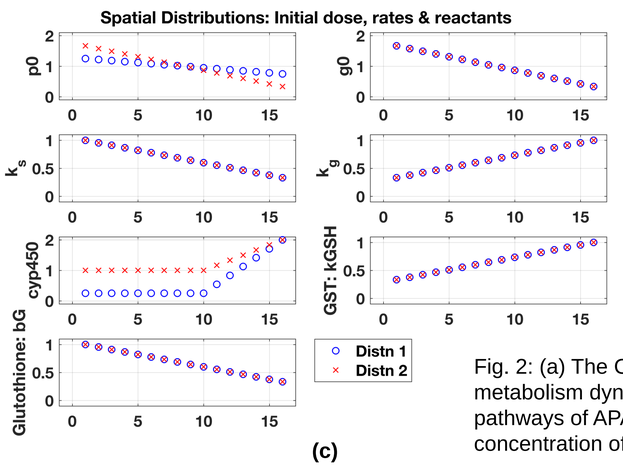
$$\frac{dG}{dt} = -k_{GSH} NG + b_G - d_G G \quad (4)$$

$$\frac{dC}{dt} = k_{PSH} N \quad (5)$$

(a)



(b)



(c)

Fig. 2: (a) The ODE system for the intracellular APAP metabolism dynamic; (b) The three metabolism pathways of APAP; (c) The spatial distribution of concentration of CYP 450 along the sinusoidal axis.

Results [3]

One temporal-spatial simulation result is shown in Fig. 3. By variation of the two distributions of Fig. 2(c), we see a shift in the localised peak of toxic compounds, 'C'. With a higher level of APAP at the pericentral end combined with a concentrated peak of cyp450 activity, the amount of toxic C formation is focused on the pericentral region (Panel B) and moreover is considerably higher than in the alternative distribution. By sharpening the gradient for initial APAP – raising the periportal levels and reducing the pericentral – in tandem with an overall increase in cyp450 activity, peak C levels are now shifted to the periportal.

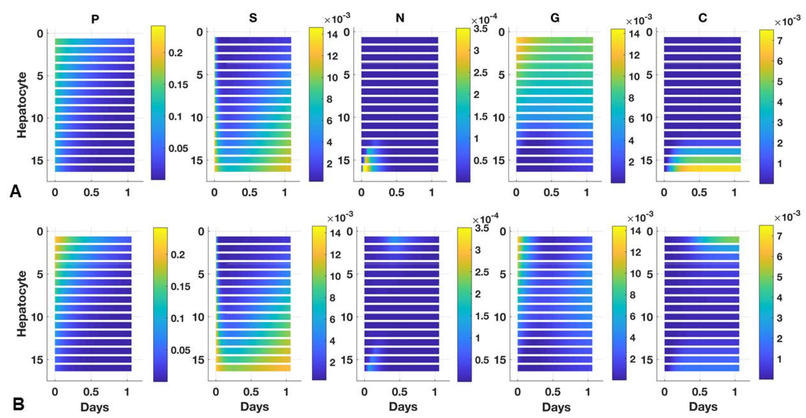


Fig. 3: Comparison for heterogeneous distributions with therapeutic 4g dose APAP as ribbon plots over all hepatocytes from day 0 (dosing) to day 1. Ribbon plot in Panel A corresponds to 'Distribution 1' and Panel B to 'Distribution 2.'

Metabolism of acetaminophen (APAP)

A majority (~90%) of APAP are transformed into non-toxic glucuronide (APAP-G) and sulphate (APAP-S) through conjugation with UGT and PAPS. A small portion (about 5-8%) of acetaminophen are transformed into a toxic compound NAPQI. (Fig. 2b)

The parameters follow the qualitative spatial depictions

1. sulphation via reaction parameter k_S;
2. glucuronidation via parameter k_G;
3. oxidation by cytochome P450 via parameter k_{450};
4. GSH binding of NAPQI via parameter k_{GSH}; and
5. glutothione production via parameter b_G.

References

[1] Reddyhoff D, *et al*. J Theor Biol 2015;386:132–46.
[2] Means S. PhD Thesis. The University of Auckland, 2010.
[3] Means S. and Ho H. Drug Metab Pharmacokinet; 2018 (In Press)

Acknowledgements

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