Explanatory, Concrete Insight Into Location-Dependent, Multiscale Aspects of APAP-Induced Liver Injury

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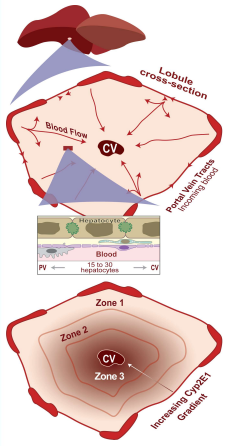
Key Multiscale Biological Features



Objective

Longer Term: Discover multi-level explanatory, causal analog cascades, which when measured achieve multiple, multiscale validation targets for key APAP-induced injury phenomena (in mice) following an infusion of a toxic APAP dose.

Hypothesis: there is a critical level in the accumulation of macromolecular damage product: a tipping point. When reached, necrosis is triggered irreversibly.

This Work: following a toxic APAP dose, and constrained by requirements to achieve multiple, multiscale validation targets, seek literature-consistent, coarse-grained analog mechanisms such that the PV-to-CV damage differential enables a tipping point to be reached in Zone 3, but not in Zones 1 and 2.

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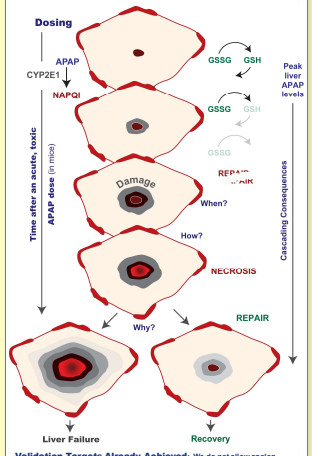
Key, Toxic Effects Caused by APAP's Reactive Metabolite, NAPQI



Validation Targets Already Achieved: We do not allow analog mechanism additions or changes that cause significant deviation from these quantitative and qualitative attributes. APAP hepatic clearance; single pass hepatic disposition profiles; measures of two inactive and one reactive (NAPQI) metabolite; responsible enzymes exhibit different PV-to-CV patterns; NAPQI production increases PV-to-CV.

Constraining Facts: Normal GSH levels decline PV-to-CV; NAPQI is known to deplete GSH; thereafter NAPQI creates disruptive damage products. Hepatocyte damage (and later necrosis) always occurs first near CV. There is considerable heterogeneity at all levels, from within and between lobules to individual mice.

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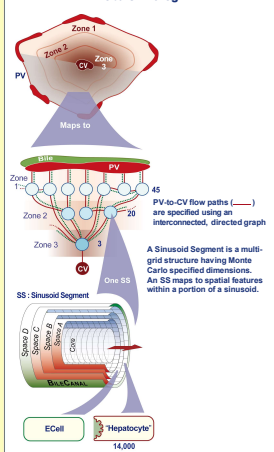
Key Features of Concrete, Lobule Analog



A Sinusoid Segment is a multi-grid structure having Monte Carlo specified dimensions. An SS maps to spatial features within a portion of a sinusoid.

PV-to-CV flow paths (——) are specified using an interconnected, directed graph

> 95% of B grid is occupied by ECell objects. They map to endothelial cells. "Hepatocytes" occupy ~ 90% of C grid. They map to hepatocytes.

"Binders" within ECells "bind" APAP reversibly. "Hepatocyte" "Enzymes" transform one object (e.g. APAP) into another (e.g. NAPQI). "Hepatocytes" manage object entry and exit to another space.

"Hepatocytes" per Zone: Z1: 69%; Z2: 29%; Z3: 5%

Approach: The simplest tipping point scenario requires accumulation of considerably more Damage Product (D) in Zone 3 "Hepatocytes." We started with *Lobule 0* and explored consequences of adding two mechanism features (but no more complicated than needed):
GSH depletion and repair of NAPQI-caused damage. We sought parameterizations that would enable achieving the preceding scenario.

All experiments: 1 "APAP" = 8.33 x 10^{-4}% dose; infusion dose: 120,000 "APAP" objects; one experiment: 24 MC lobules; "Enzymes"/"Hepatocyte" increases 4x PV-to-CV; APAP hepatic extraction = 0.5; p(metabolizing unbound APAP/sec) = 0.5; A & B (but not N) are cell permeable (they exit the lobule in blood & bile (50/50)).

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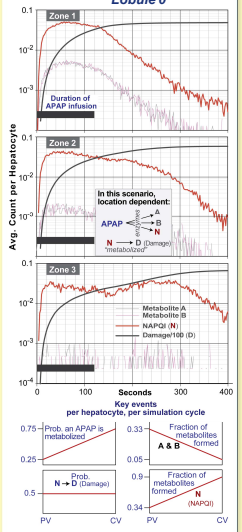
Lobule 0



Key Observation: D in Z3 > Z2 > Z1, but not by much. A much greater difference is needed to achieve the target of the simple tipping point scenario.

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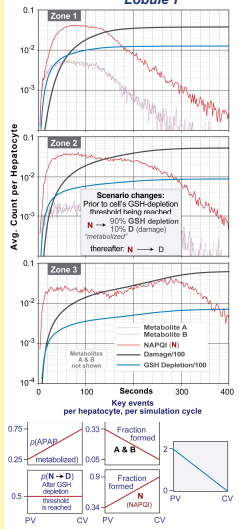
Lobule 1



Key Observations: GSH depletion per cell achieves semiquantitative validation target. D in Z3 (0.06) > Z2 (0.043) > Z1 (0.038), but insufficient for the simple tipping point scenario.

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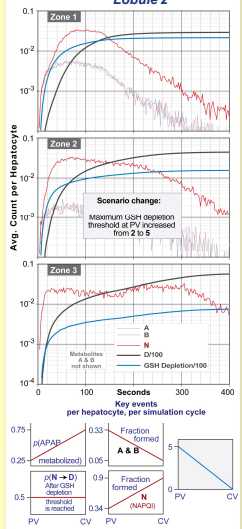
Lobule 2



Key Observations: GSH depletion per cell achieves semiquantitative validation target. D in Z3 (0.057) > Z2 (0.045) > Z1 (0.03), but still insufficient for the simple tipping point scenario.

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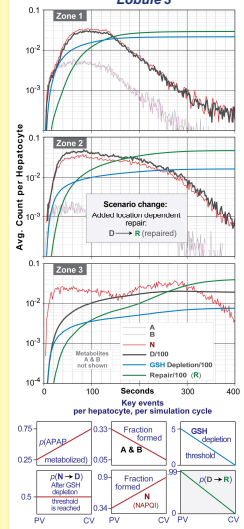
Lobule 3



Key Observations: Zonation in repair achieves qualitative validation target. However, mechanism falsified because maxD in Z2 (0.045) > Z1 (0.03) > Z3 (0.02).

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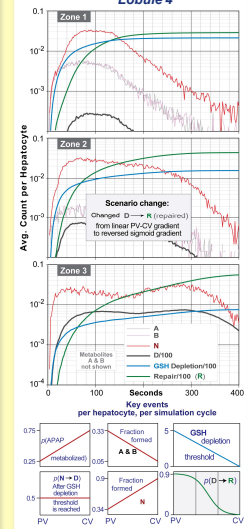
Lobule 4



Key Observations: Simple tipping point scenario achieved: maxD in Z3 (0.0075) > Z2 (0.00075) > Z3 (0.0028). However, there is no current experimental evidence suggestive of such extreme zonation changes.

Observations:

1) Linear gradients for the specified analog mechanisms are insufficient to enable the tipping point scenario.

2) Although a reverse sigmoid repair gradient enabled achieving the tipping point scenario, it seems counterintuitive. Because damage and necrosis most often occur first near the CV, one might expect macromolecular damage repair mechanisms to be enhanced near the CV.

3) We will explore alternatives to the sigmoid repair gradient. One will be an analog mechanism that amplifies damage. There is evidence that reactive oxygen species accumulate more quickly in Zone 3 hepatocytes.

4) We expect to discover multiple, fundamentally different, equally explanatory yet comparably-grained analog mechanisms capable of achieving the tipping point scenario and the same quantitative validation targets.