Agent-based models of immune-mediated P450 down-regulation using modularity and integration techniques

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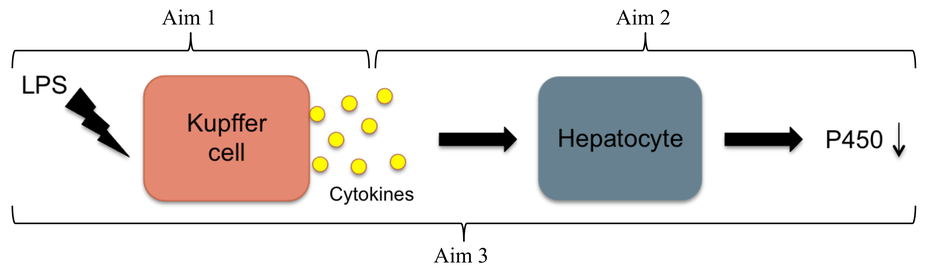
Abstract

We use synthetic, agent-based modeling and simulation methods to instantiate and challenge concrete, mechanistic hypotheses. The objective is to explore plausible mechanisms of the roles of immune system components in drug metabolism. We achieve validation targets for several in silico mechanisms using a variety of wet-lab data.

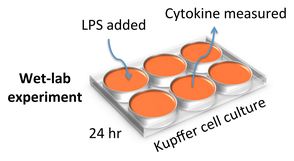
Validation targets

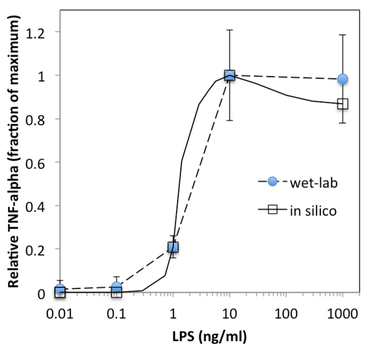
In response to an inflammatory stimulus like lipopolysaccharide (LPS), Kupffer cells down-regulate hepatic P450 enzyme expression via cytokines. This can result in reduced intrinsic clearance of xenobiotic both in vitro and in vivo.

- Aim 1: Develop a Kupffer Cell analog that yields a dose-response between LPS and Cytokine.
- Aim 2: Add Hepatocyte mechanisms that down-regulate P450 levels in response to Cytokine.
- Aim 3: Integrate the Kupffer Cell and Hepatocyte analogs to simulate immune-mediated P450 down-regulation in response to LPS.

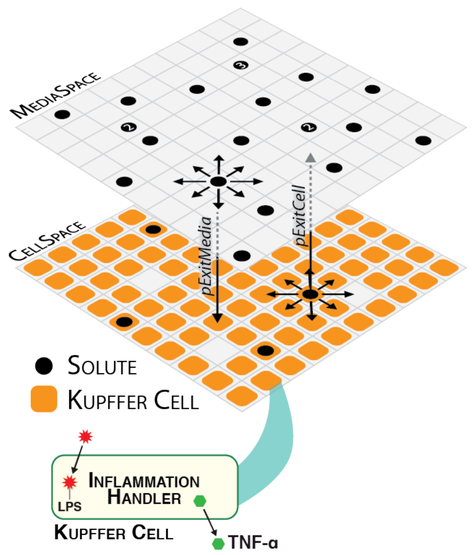


Aim 1

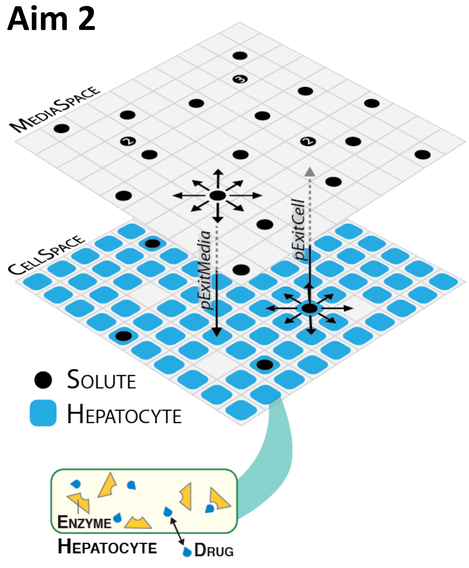


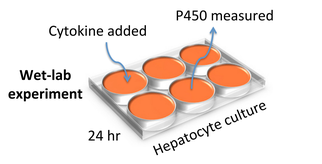


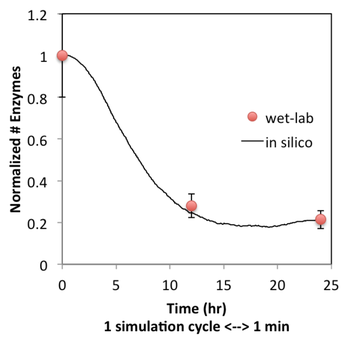
Dose-response curve between LPS stimulus and cytokine response. One LPS object maps to 350 ng/ml LPS.



Aim 2

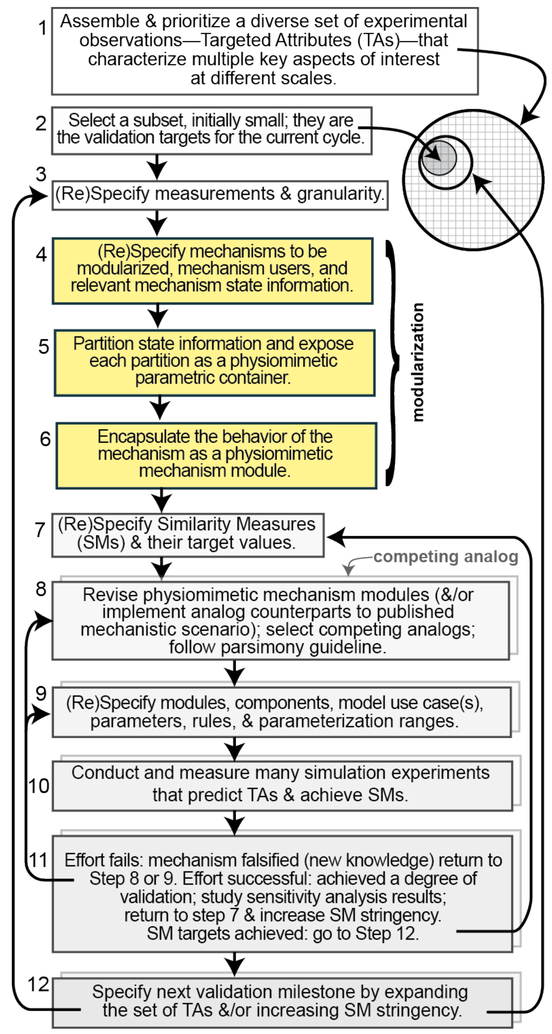




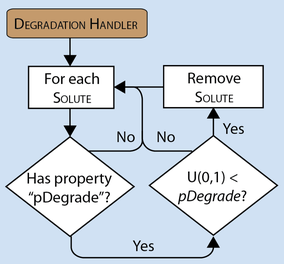


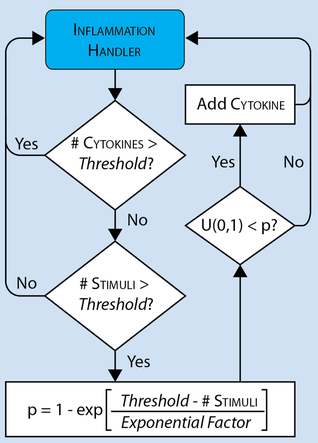
Time-course response between IL-1 treatment and P450 protein levels in hepatocyte cultures.

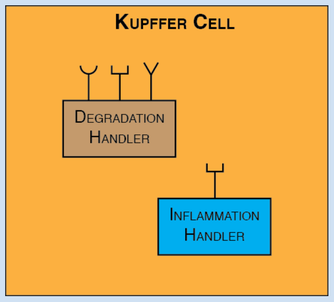
Methods: iterative refinement

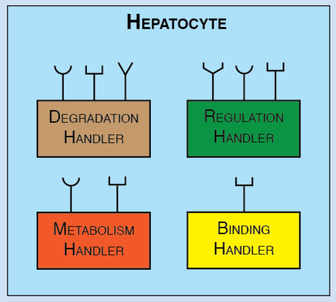


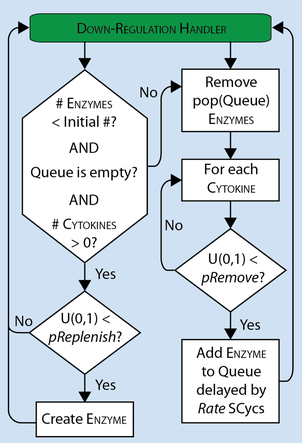
Software space







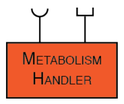




software integration

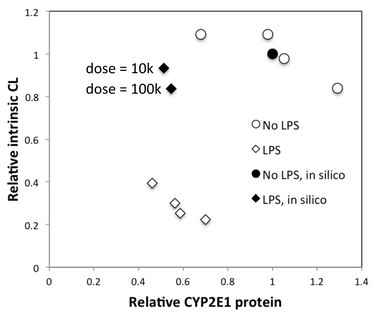
Modularity

Each mechanism is modularized into a software component called a *physiomimetic mechanism module* (PMM), illustrated below.

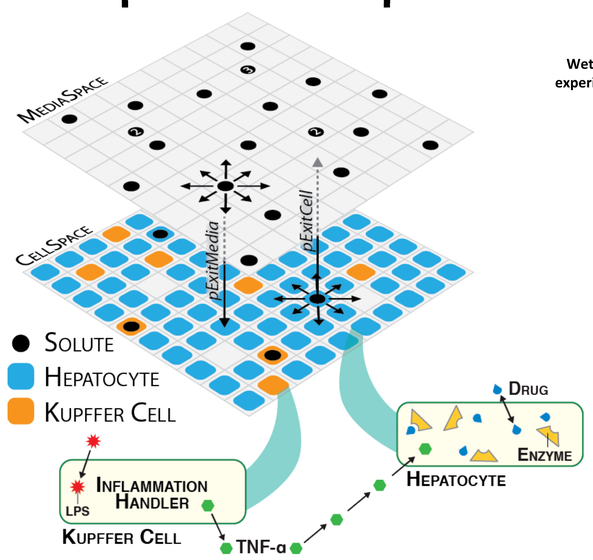


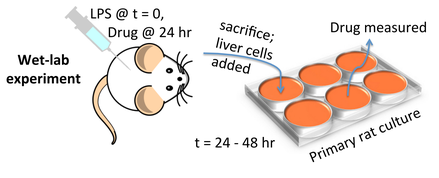
A mechanism user (i.e. Kupffer Cell, Hepatocyte) uses a PMM by first exposing the correct state information (illustrated using "sockets"), then instantiating it. PMMs facilitate model integration by allowing different models (i.e. liver and immune system) to interact without requiring a priori knowledge of each other.

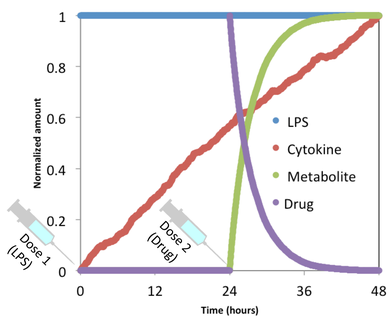
Aim 3



Correlation between P450 levels and intrinsic clearance with (orange) or without (gray) LPS stimulus.







Time-course levels of normalized LPS, Cytokine, Metabolite, and Drug.

Conclusions

- Mechanisms and components developed in Aims 1 and 2 achieve validation targets within acceptable levels of similarity. (Similarity criteria: in silico points fall within ±1 standard deviation of the corresponding wet-lab value.)
- The integrated analog was falsified against wet-lab intrinsic clearance data. Thus, the current mechanisms are too simple to sufficiently explain the wet-lab phenomena. Iterative model refinement will lead to a more complex analog. As additional analogs are falsified, the space of plausible, explanatory mechanisms shrinks, thereby improving mechanistic insight.

References

BK Petersen, GEP Ropella, and CA Hunt, Toward modular biological models: defining analog modules based on referent physiological mechanisms, BMC Systems Biology 8(95) 2014.