Maximizing data value in MPS ADME experiments using *in silico* modeling

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Introduction

Microphysiological systems (MPS) are increasingly used to generate human-relevant ADME data during drug discovery. However, experimental design in MPS platforms is constrained by limited working volumes, experimental cost, fixed dosing strategies, and for multi-organ systems, the need to capture interacting kinetic processes such as absorption and metabolism. These constraints often limit the number and timing of samples that can be collected which can lead to lower quality datasets and reduced confidence in parameter estimation.

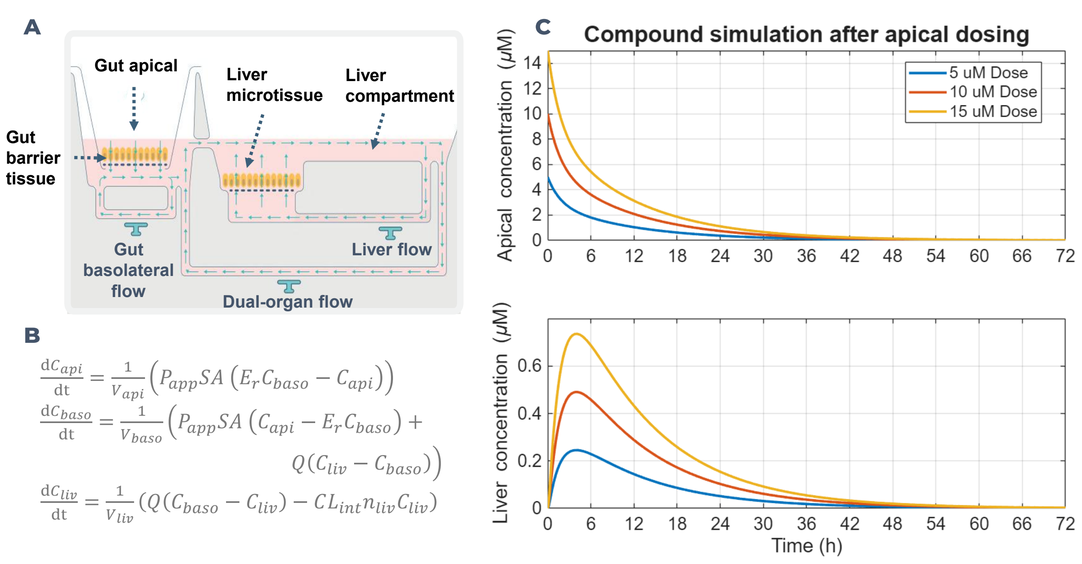
To maximize the value of MPS experiments, there is a need for model-based approaches as they provide an opportunity to use prior information and a mechanistic understanding of the system to design experiments that extract maximal information from limited datasets.

We have developed a workflow to support planning of PhysioMimix® ADME studies using mechanistic modeling and information-based experimental design. Compound transport and metabolism across MPS compartments are described using ordinary differential equations (ODEs), enabling simulation of concentration–time profiles. Furthermore, the sampling schedules are optimized using a Bayesian approach to best identify parameters such as permeability, efflux ratio and liver clearance – parameters that are important descriptors of a drug's pharmacokinetics and influence its bioavailability.

Methods

A mechanistic model of the CN Bio PhysioMimix® Dual-organ plate was constructed using ordinary differential equations incorporating parameters for apparent permeability (P_{app}), efflux ratio (E_r) and intrinsic clearance of the liver (CL_{int}). The model can simulate the concentration-time curves of candidate compounds within the Dual-organ plate. These simulations can be used to make decisions about dosing strategies, volumes and concentrations.

Figure 1. By describing the Gut/Liver MPS as a set of ordinary differential equations we can simulate the concentration-time curves of a compound within the plate.



(A) PhysioMimix Dual-organ Gut/Liver MPS schema. The interconnecting flow connects the gut and liver compartments to simulate first pass metabolism. [1] (B) Rate equations describing the changing concentrations within the Gut/Liver MPS. (C) Time-course simulation of a test compound in the Gut/Liver MPS. Three different concentrations are simulated allowing for informed decision on dosing concentrations.

Following initial simulations, we evaluated the impact of sampling schedules on how well parameters like P_{app}, E_r and CL_{int} could be estimated. The information gained about each parameter from a sampling schedule was quantified using the Fischer Information matrix (FIM) which can be constructed from the Jacobian matrix (J). So, for a given sampling schedule $S = \{t_1, t_2, \ldots t_n\}$, with equal time point weighting

$$F_S(\theta) = \sum_{t \epsilon S} F(t;\theta)$$

where

$$F(t;\theta) = J(t;\theta)^T J(t;\theta)$$

where θ is the parameter set of a specific compound (P_{app}, E_r, CL_{int}). To find the best sampling times for a given parameter set we aimed to maximize the identifiability of the worst identified parameter (E-optimality) [2]. Parameter identifiability can be estimated by the eigenvalues of the FIM. By maximizing the smallest eigenvalue of the FIM a set of optimal sampling times can be defined as

$$S^* = \underset{S}{\operatorname{argmax}}\, \lambda_{min}(F_S(\theta))$$

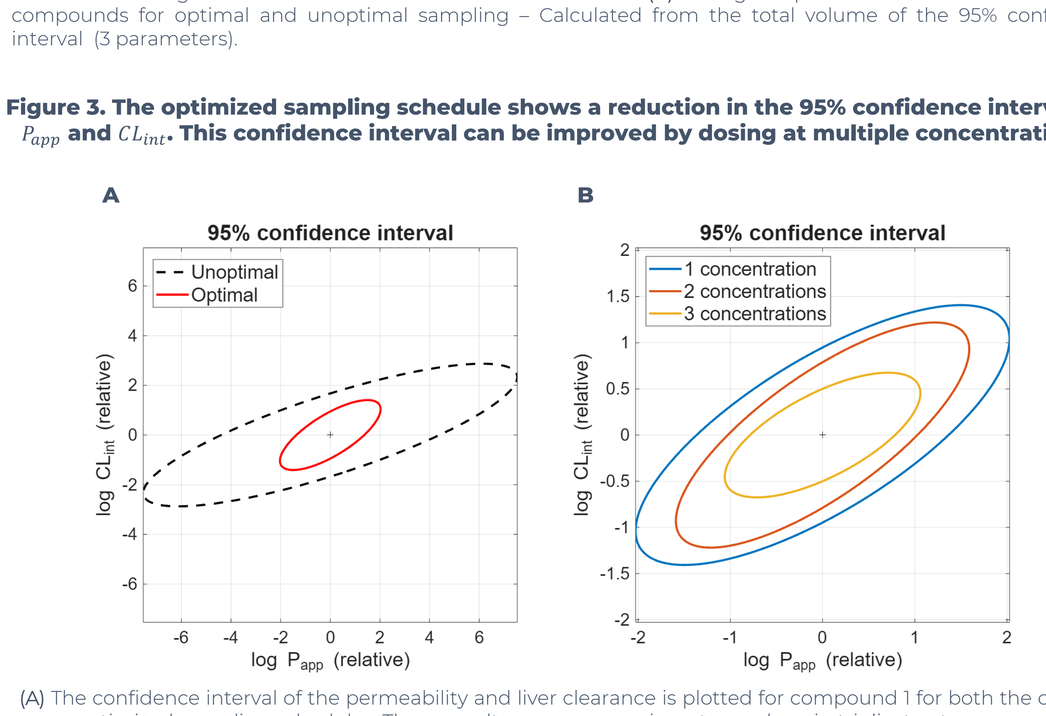
where λ_{min} yields the smallest eigenvalue. Often, there is uncertainty in parameter inputs and finding the best sampling schedule should take this uncertainty into account. To take parameter uncertainty into account, parameters were drawn from a uniform distribution between 0.5 and 2 times their nominal value. The sampling schedules were then optimized over the expected minimum eigenvalue across the distribution of the sampled parameter sets

$$S^* = \underset{S}{\operatorname{argmax}}\, \frac{1}{N_p}\sum_{p=1}^{N_p} \lambda_{min}\left(\sum_{t \epsilon S} F(t;\theta^p)\right)$$

We assessed this workflow using 20 theoretical compounds spanning a range of permeabilities, efflux ratios, and intrinsic liver clearance values. The optimized sampling schedules were compared against 4 unoptimized sampling strategies to assess the improvement in parameter estimations.

Results

Figure 2. Optimal sampling schedules for 20 theoretical drugs resulted in better parameter certainty and confidence when compared to 4 unoptimized sampling schedules.



(A) Optimal sampling schedule of drug 1 compared to the unoptimized sampling schedules. (B) Change in parameter certainty across the 20 compounds for optimal and unoptimal sampling schedules – Calculated from the minimum eigenvalue from the Fischer information matrix. (C) Change in parameter confidence across 20 compounds for optimal and unoptimal sampling – Calculated from the total volume of the 95% confidence interval (3 parameters).

Figure 3. The optimized sampling schedule shows a reduction in the 95% confidence interval of P_{app} and CL_{int}. This confidence interval can be improved by dosing at multiple concentrations.

(A) The confidence interval of the permeability and liver clearance is plotted for compound 1 for both the optimized an unoptimized sampling schedules. These results assume experiments are done in triplicate at one concentration. (B) The 95% confidence interval can be improved by dosing at multiple concentrations. Each additional dose increases confidence in P_{app} and CL_{int} estimates.

Conclusion

- Mechanistic modeling of the dual-organ MPS allows pre-experiment optimization by simulating compound concentration-time curves, providing valuable information about dosing concentrations to ensure compound quantification throughout the experiment.
- Optimizing sampling schedules by incorporating parameter uncertainty yields results that outperform unoptimized schedules in both parameter certainty (identifiability) and confidence (95% confidence interval).
- Furthermore, by increasing the number of conditions tested (multiple dosing concentrations), parameter certainty can be further improved upon.
- These methods allow MPS experiments to be optimized before entering the lab, increasing the success and quality of the data generated. This workflow has been captured in a standalone MATLAB application that allows for the simulation and optimization of candidate compounds.

References

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