

Integration of physics-informed neural networks (PINNs) with physiologically-based pharmacokinetic (PBPK) modelling: A novel physics-based framework for parameter discovery

Kenneth Hor Cheng KOH¹, Sheng Yuan CHIN¹, Zhao WEI², Jian Cheng WONG³, Chin Chun Ooi^{2,3}, James Chun Yip CHAN^{1,4}

¹Singapore Institute of Food and Biotechnology (SIFBI), Agency for Science, Technology and Research (A*STAR)

²Centre for Frontier AI Research (CFAR), A*STAR

³Institute of High Performance Computing (IHPC), A*STAR

⁴A*STAR Skin Research Labs (A*SRL), A*STAR



Background

Current challenges in PBPK modelling

- Appropriate and accurate parameter estimation [1]**
 - Data-intensive requirement for model building
 - Limited *in vitro* and clinical data in literature (especially newer drugs)
- Suboptimal empirical fitting of unknown parameters [2]**
 - Constraints are poorly defined leading to physiologically unrealistic values
 - Parameter optimization algorithm converges to local minimum instead of global minimum
 - Unsatisfactory fitting to observed clinical data

Physics-informed neural network (PINN)

- A robust type of neural network that invokes physical laws as constraints during the machine learning process (**Fig. 1**) [3]
- PINNs can provide accurate and realistic predictions for modeling complex systems (e.g. fluid flow, drug distribution, or heat transfer) by incorporating known scientific principles, especially when data is limited

PINNs may help to refine current approaches for parameter estimation in PBPK modelling

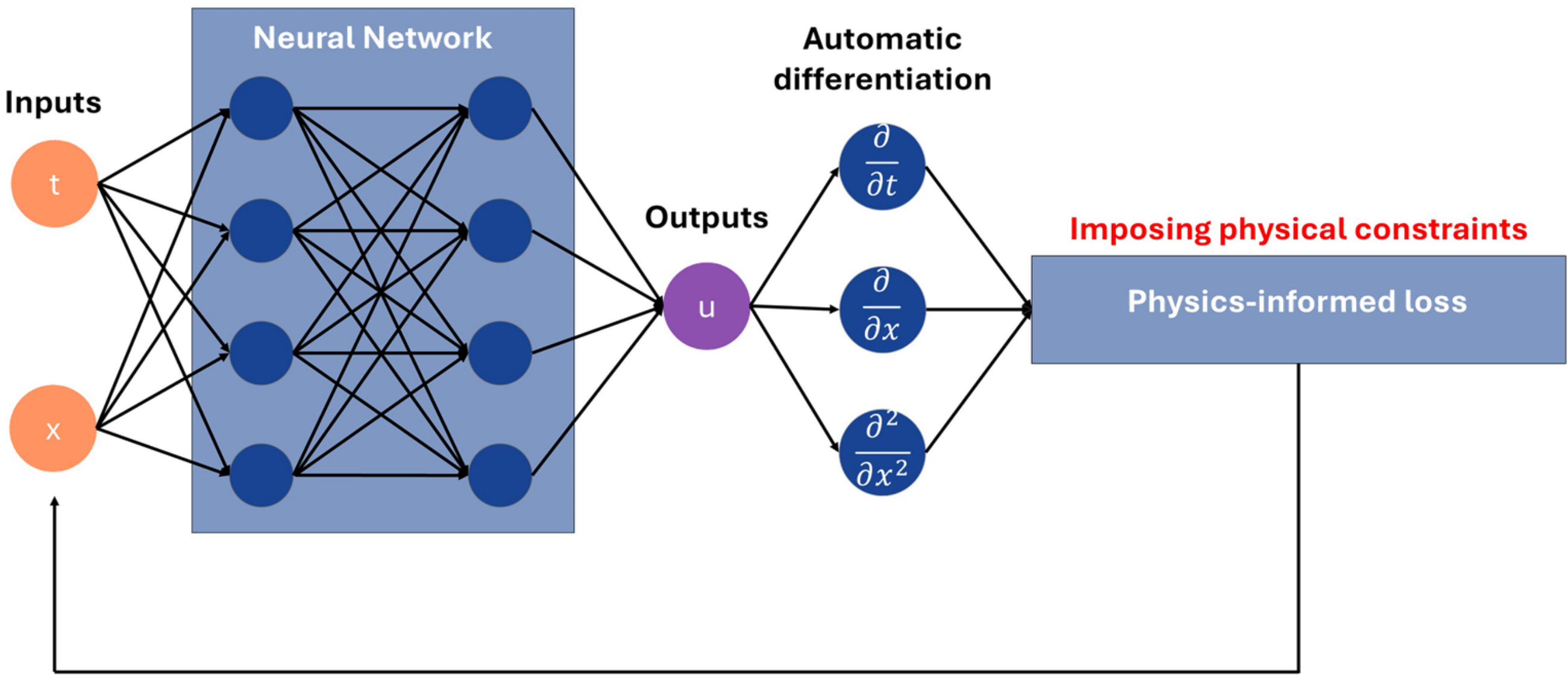


Figure 1. A simplified illustration of PINN.

Objective

To design a proof-of-concept framework incorporating **PBPK modelling with PINNs for parameter discovery** and to assess its accuracy and performance.

Method

PBPK-PINN model construction

- A whole-body PBPK model (**Fig. 2A**) was developed in MATLAB (R2024a) using the Simbiology module
- Stage 1 involves feature learning on the NN and pseudo-inverse learning on the final layer to match the PBPK model's ODEs and initial conditions while Stage 2 uses the learned parameters to optimize the PBPK-PINN with experimental data for unveiling masked or unknown parameters (**Fig. 2B**)

Case study: Paracetamol (APAP)

- Enzyme kinetics for APAP metabolism by multiple enzymes in the liver (**Fig. 3**) were incorporated into the PBPK-PINN model:
 - Oxidation.** CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4
 - Sulfation.** SULT1A1, SULT1A3, SULT1E1, SULT 2A1
 - Glucuronidation.** UGT1A1, UGT1A9, **UGT2B15**
- Both V_{max} and K_m for **UGT2B15** metabolic clearance were masked (**major clearance pathway**) for both the MATLAB in-built Suite of Nonlinear and Differential/Algebraic Equation Solvers (SUNDIALS) and PINNs to predict
- A 20 mg/kg intravenous (IV) infusion for 2 h was used as the dosing scenario

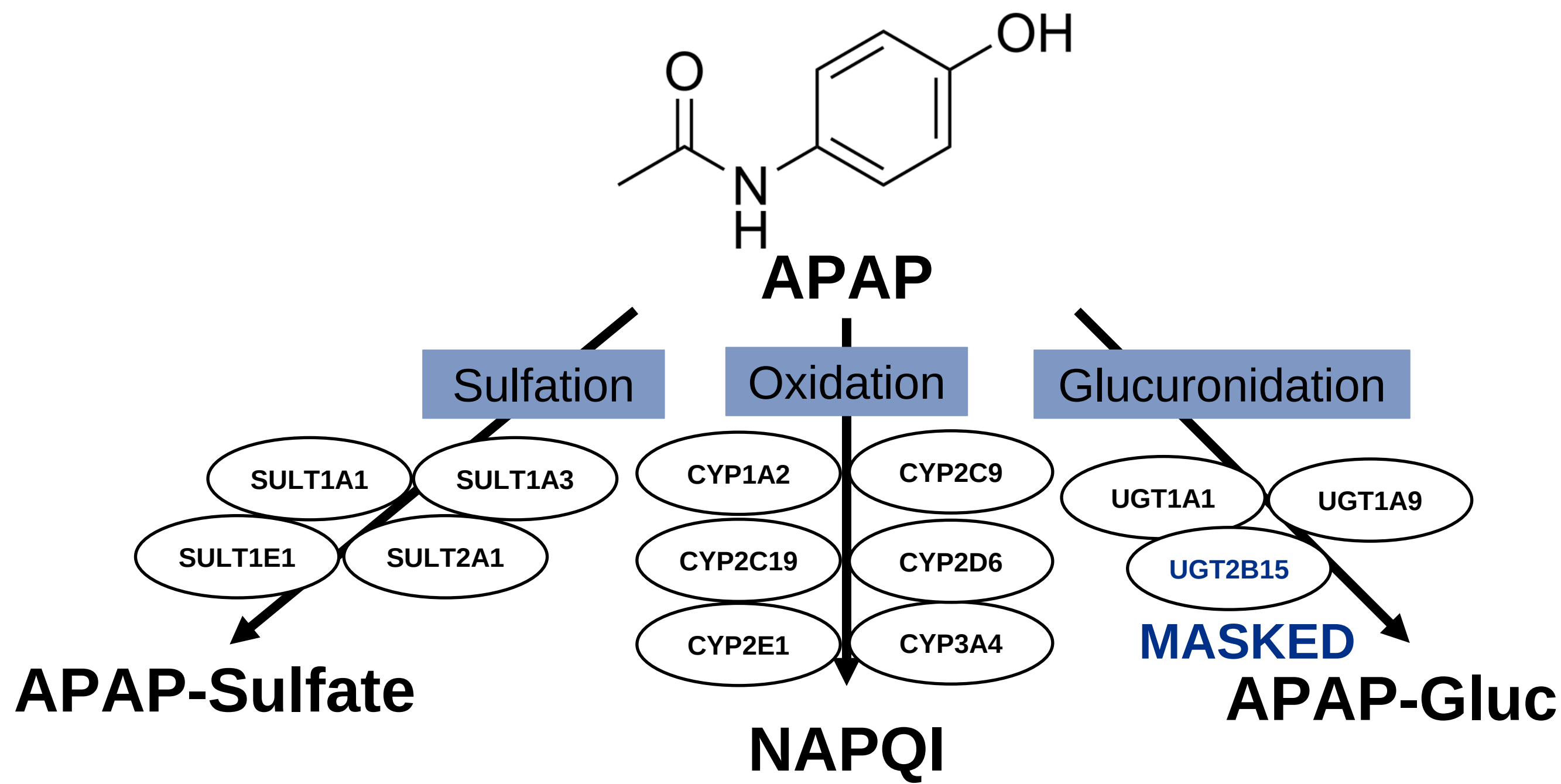


Figure 3. Metabolic pathways and enzymes involved in APAP hepatic clearance.

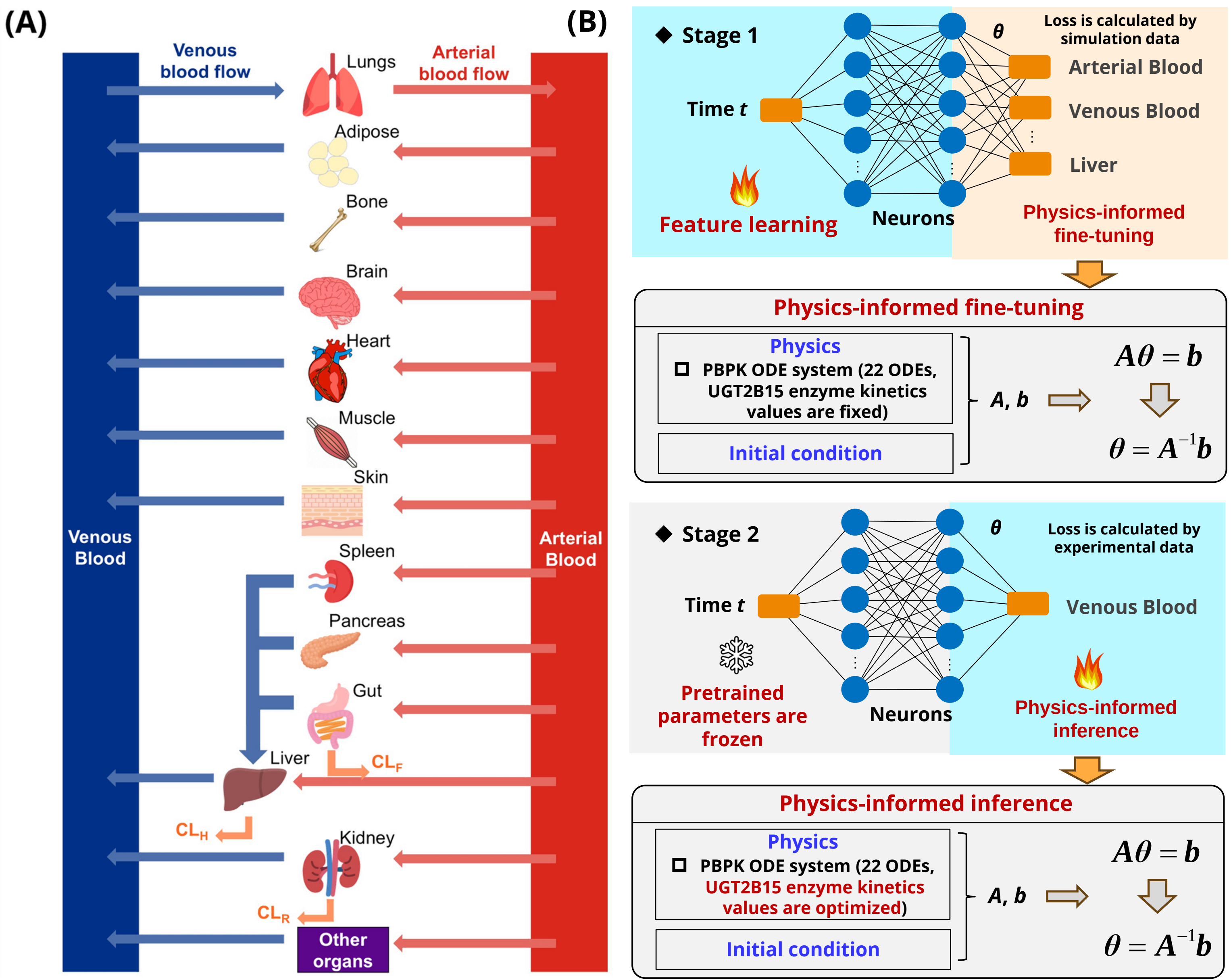


Figure 2. Schematic of the PBPK-PINN framework featuring a classical whole-body PBPK model (A) and the PINN architecture that was incorporated (B).

Results

- Excellent fit of simulated profiles to observed clinical data regardless of parameter estimation using SUNDIALS or PINNs (**Fig. 4**)
- However, UGT2B15 enzyme kinetics values were much closer to literature reported values when predicted by PINNs versus SUNDIALS (**Table 1**)

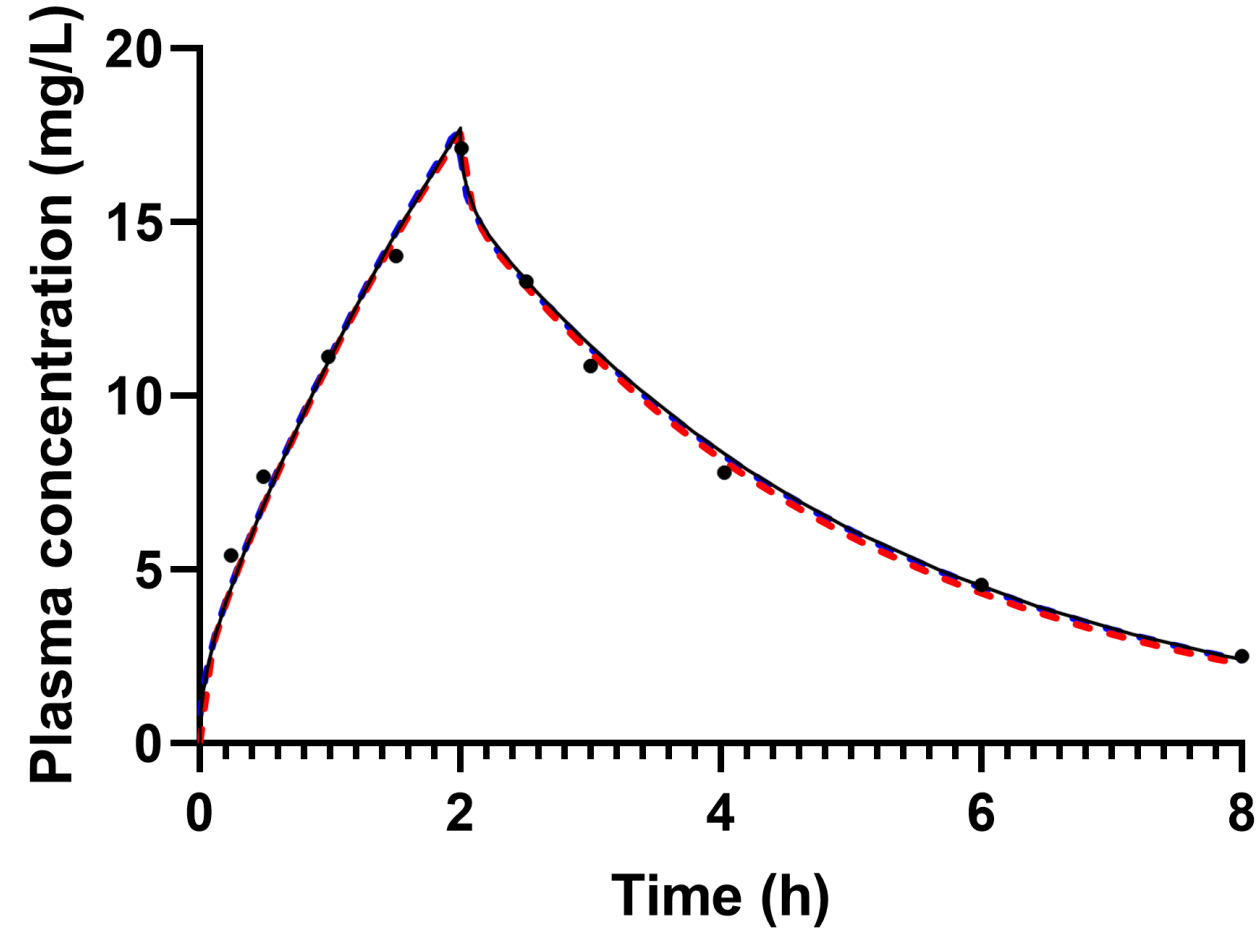


Figure 4. Simulated concentration-time profiles for paracetamol involving a 20 mg/kg 2 h IV infusion simulation for 8 h. Black circles (•) represent the observed clinical data. The **solid black line** (—) represents the simulated profile when using the literature reported UGT2B15 enzyme kinetics values, the **red dashed line** (---) represents the simulated profile when using UGT2B15 values predicted by the in-built SUNDIALS in MATLAB, and the **blue dashed line** (---) represents the simulated profile when using UGT2B15 values predicted by PINNs.

Table 1. UGT2B15 K_m and V_{max} predicted by the in-built SUNDIALS in MATLAB versus PINNs.

UGT2B15 parameters	Original UGT2B15 enzyme kinetics values	SUNDIALS		PINNs	
		Predicted	Fold-change	Predicted	Fold-change
K_m (mM)	23.00	100.00	4.35	19.10	0.83
V_{max} (pmol/min/mg)	30,016	147,632	4.92	24,197	0.81
CL_{int} (μL/min/mg)	1.31	1.48	1.13	1.27	0.97

Conclusion

- ✓ Demonstrated a working proof-of-concept for a **PBPK-PINNs framework in parameter estimation**
- ✓ PINN demonstrated excellent prediction capabilities for **estimating unknown parameters with close to actual reported values**
- ✓ We anticipate the use of our novel framework for **more complex parameter discovery scenarios**

Contact us:



Kenneth Koh



James Chan



Chin Sheng Yuan

Acknowledgement

This project and travel funding are supported by the **Agency for Science, Technology and Research (A*STAR) CSF (Project number C240314053)**. The authors declare no conflict of interest.

References

- Tsamandouras *et al.* *Br J Clin Pharmacol.* 2015, 79:48-55.
- Woodruff *et al.* *Toxicol Lett.* 1993, 69:181-196.
- Farea *et al.* *AI.* 2024, 5:1534-1557.