

# UDE Know It If UDE Saw It: Leveraging Deep Machine Learning for QSP Model Development and Evaluation

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# **Biography**

- PhD in Biomedical Sciences from the University of Connecticut in 2017.
- The same year, I joined Metrum Research Group as a Research Associate in the TSP (Translational and Systems Pharmacology) group.
- Currently, I am a Senior Scientist at Metrum with many interests like PBPK and QSP modeling and integrating those with Bayesian analysis and machine learning tools.

## In an ideal QSP world ...



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# However, in reality ...



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# Why not replace the QSP model with a neural network?

### Multilayer Feedforward Networks are Universal Approximators

#### Kurt Hornik

Technische Universität Wien

MAXWELL STINCHCOMBE AND HALBERT WHITE

University of California, San Diego

(Received 16 September 1988; revised and accepted 9 March 1989)

#### **Issues:**

- A relatively large amount of data is required
- Extrapolatability
- Interpretability
- Wasted domain-specific knowledge

# Universal Differential Equations (UDEs) bring the best of both worlds!

### Universal Differential Equations for Scientific Machine Learning

Christopher Rackauckas<sup>a,b</sup>, Yingbo Ma<sup>c</sup>, Julius Martensen<sup>d</sup>, Collin Warner<sup>a</sup>, Kirill Zubov<sup>e</sup>, Rohit Supekar<sup>a</sup>, Dominic Skinner<sup>a</sup>, Ali Ramadhan<sup>a</sup>, and Alan Edelman<sup>a</sup>

Predator-prey model

$$\dot{x} = \alpha x + U_1(\theta, x, y)$$
$$\dot{y} = -\theta_1 y + U_2(\theta, x, y)$$

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# QSP + UDE = Deep QSP (DQSP)



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# **Application – Cholesterol QSP model**



Gadkar et al (2014)

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# **Untrained UDE still carries valuable information**



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# **Trained UDE characterized the missing term**



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# **Trained UDE characterized the recovered term**





Symbolic regression recovered the missing term

$$\varphi = k * LDL_c$$

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# Bayesian analysis quantified the uncertainty on the recovered term

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Recovered term	Probability
$\varphi \sim k * LDL_c$	0.87
$\varphi \sim k_1 * LDL_c + k_2 * PCSK9$	0.13



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# Summary

- A workflow was introduced that integrates QSP modeling and machine learning in the form of UDEs.
- The workflow utilizes machine learning to learn missing parts in our knowledge of a QSP system while quantifying the uncertainty around the learned dynamics using Bayesian analysis.
- The workflow also applies symbolic regression to recover the missing dynamics from the trained neural networks.
- Uncertainty can be used to guide further experimentation or to judge through sensitivity analyses the expected level of impact that the uncertainty will have on our ability to inform certain MIDD-driven decisions.

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