Deep QSP Modeling: Leveraging Machine Learning for QSP Model Development and Evaluation

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Abstract

Objectives: QSP models characterize the interaction between biological systems and pharmacological therapies. As such, they require a robust mechanistic knowledge of the system of interest, which is often limited, uncertain, and incomplete. Universal differential equations (UDEs) provide a framework for integrating scientific modeling with data-driven machine learning approaches, such as deep learning. Within such a framework, the scientific model provides enough structural knowledge that alleviates the need for large amounts of data, typically required by deep learning models. This work introduces the concept of Deep QSP (DQSP) modeling that applies UDEs to QSP models using open-source Julia tools. This framework employs deep learning to fill in the gap in our knowledge of the biological system.

Methods: A simple QSP model of the effect of the antipsychotic drug, remoxipride, on the lactotroph-prolactin system, was used to demonstrate the proposed framework [1, 2]. The model assumed a positive feedback effect of plasma prolactin on lactotroph prolactin production. This positive feedback was considered unknown and replaced by an artificial neural network (ANN) in the DQSP framework. Symbolic regression, using sparse differential equations (SINDy), was used to retrieve the actual unknown positive feedback effect on the lactotroph-prolactin system dynamics from the trained ANN. An integrated Bayesian DQSP (BaDQSP) framework was also introduced to quantify the uncertainty around the missing dynamics and the retrieved symbolic term.

Results: Observed versus predicted profiles, convergence, and error estimates showed that the ANN was efficiently trained to replace the unknown dynamics using a limited training dataset. Symbolic regression was able to retrieve the actual underlying missing term, which was a saturable positive feedback effect on lactotroph prolactin production. BaDQSP was able to quantify the uncertainty around the recovered term and assigned it a probability of 0.712 of being the true missing term.

Conclusions: DQSP/BaDQSP framework was introduced in this work using open-source tools in Julia. A QSP model for the effect of remoxipride on the lactotroph-prolactin system was used as a case study to demonstrate the training of an ANN to replace unknown dynamics, retrieving the actual dynamics using symbolic regression, and integrating with Bayesian inference to quantify the uncertainty around the retrieved symbolic term. The coincidence of the proposed DQSP/BaDQSP framework makes it accessible to the audience interested in applying deep learning and Bayesian analysis to QSP models.

Methods

Figure 1. Generate DQSP workflow. The generic DQSP workflow depends on building the QSP UDE model based on domain-specific knowledge of the reaction network and UDEs to learn the unknown/missing fluxes. Symbolic regression can then follow to recover the unknown flux underlying dynamics. Bayesian analysis is then used to obtain posterior probabilities for the ANN and the recovered term.

Figure 2. Prolactin UDE Model Structure. The UDE model structure for prolactin (PRL) demonstrates the 2-compartment PK of remoxipride and its effect on stimulating PRL release from lactotrophs to plasma. A nonlinear positive feedback loop, where plasma PRL stimulates the production of lactotroph PRL, was included in the original model, and synthetic data were generated from this flux model. The feedback loop was then untrained, and an ANN was used to learn that missing flux. In the UDE model structure. The model was solved using the Julia open-source package DifferentialEquations.jl.

Figure 3. Data versus initial QSP model predictions without the plasma PRL feedback. Data and predictions are represented by orange dots and blue line, respectively.

Figure 4. Data versus trained UDE model predictions. Data and predictions are represented by orange dots and blue line, respectively.

Figure 5. The loss function value over optimization iterations. Loss function values decreased to the 0.48 iteration of optimization (1000 initial iteration with ADAM and 1000 subsequent iterations with LBFGS).

Figure 6. ANN prediction versus the ideal flux. The trained ANN time-course prediction overlaid with the ideal missing positive feedback flux.

Figure 7. Bayesian analysis loss function value over iterations. Loss function values for the SGLD Bayesian analysis over 2000 iterations (1000 warmup and 1000 sampling). The optimized parameters from the LBFGS run were used as initial values for the SGLD algorithm.

Figure 8. PPC for plasma PRL Bayesian analysis. Posterior plasma PRL samples (red) were overlaid on top of the data (dots). The black line represents the best fit prediction among the posterior samples.

Table 1. Posterior probability for the possible missing terms. R = baseline plasma PRL concentration; C = plasma concentration of remoxipride; Emax = maximum positive feedback effect; 0.158 = plasma PRL difference from baseline that was 50% of Emax.

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<th>Flux Term</th>
<th>Probability</th>
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<tr>
<td>R × C2 + Emax (R - R0) / EC50 + (R - R0)</td>
<td>0.288</td>
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<tr>
<td>R × C2 + Emax (R - R0) / EC50 + (R - R0)</td>
<td>0.712</td>
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References
