

Integrating Random Effects in Scientific Machine Learning for Pharmacokinetic Modelling



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Background

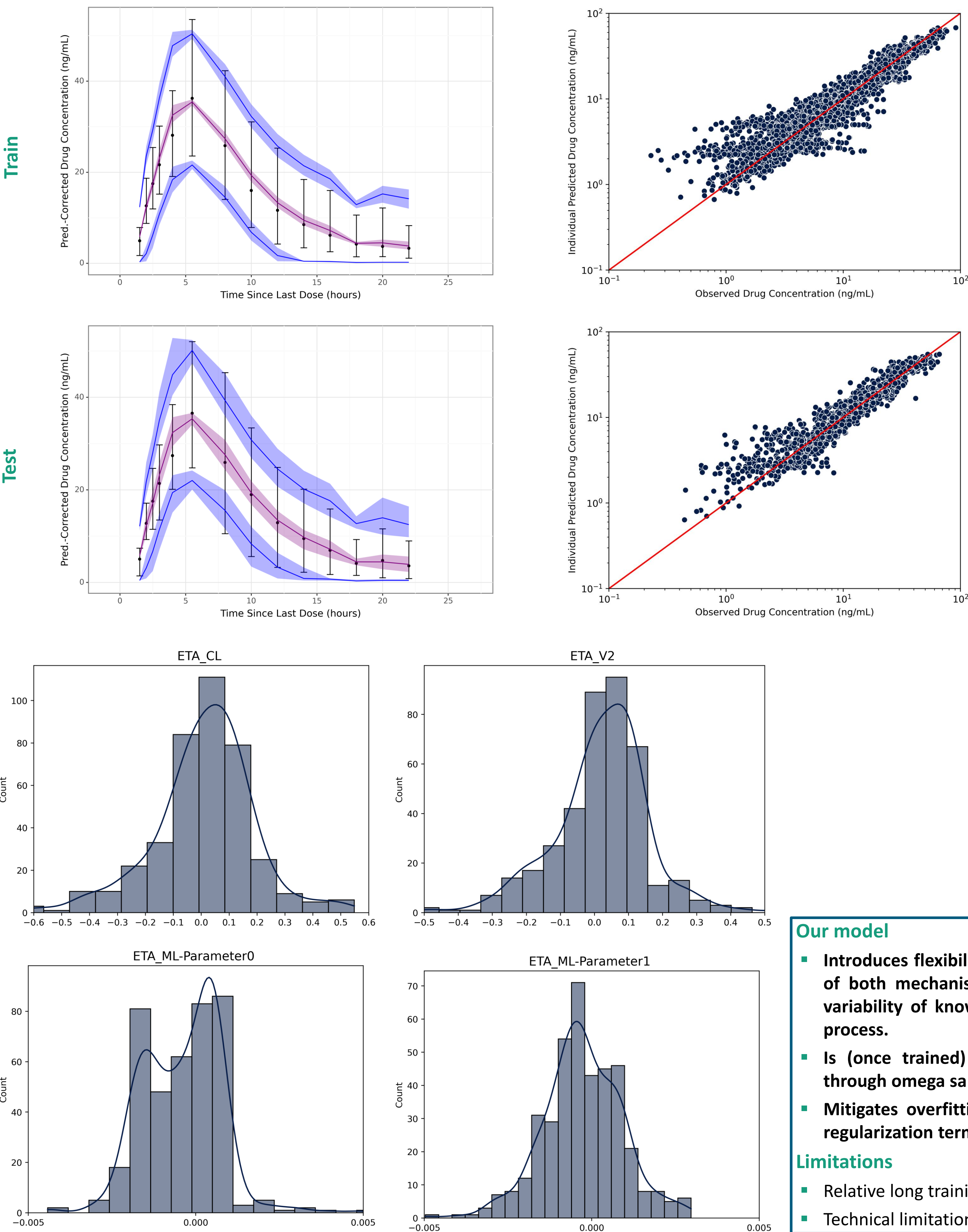
- Different machine learning (ML) methods and approaches have shown utility in clinical pharmacology from PK to PD modeling [1-5].
- PK-SciML [6] obtained accurate pharmacokinetic population level predictions for different dose groups while learning a complex absorption.
- RE-SciML is a SciML approach that is based on PK-SciML and overcomes some of its limitations for PK prediction.
 - Introduces a **time-series encoder** that learns inter-individual variability (**IIV**) of **mechanistic and ML terms** allowing patient specific concentration-time predictions and thus separates explainable and unexplainable variability.
 - Offers the user the **flexibility to define** the number of ML terms and whether their population ML parameters need to be learned.
 - Considers a **FOCE-based loss function**.
 - Can **handle realistic data** settings e.g. different sampling schemes and number of observations, without requiring individual patient-level data processing.

Test scenario

- PK data from 500 patients (80-20% train-test split) was simulated with different dose regimens and with both sparse (7 samples) and intense (32 samples) sampling.
- The PK model consisted of mixed zero-and-first-order absorption with linear clearance and interindividual variability on clearance, volume and absorption.

Model details

- A two-compartment model with a linear clearance and a neural network term to represent the absorption.
- The **unknown absorption term** is being learned for each time step using a multi-layer-perceptron and the following input data: last dose, central compartment information, time since last dose and the ML patient specific parameters.
- Mechanistic and Absorption-ML IIVs** are being learned using a time aware LSTM encoder which considers the concentration, the cumulative sum of doses since last concentration and the time since last dose.
- Considers Omega as a diagonal matrix.
- Assumes an additive error model.



Population Parameters

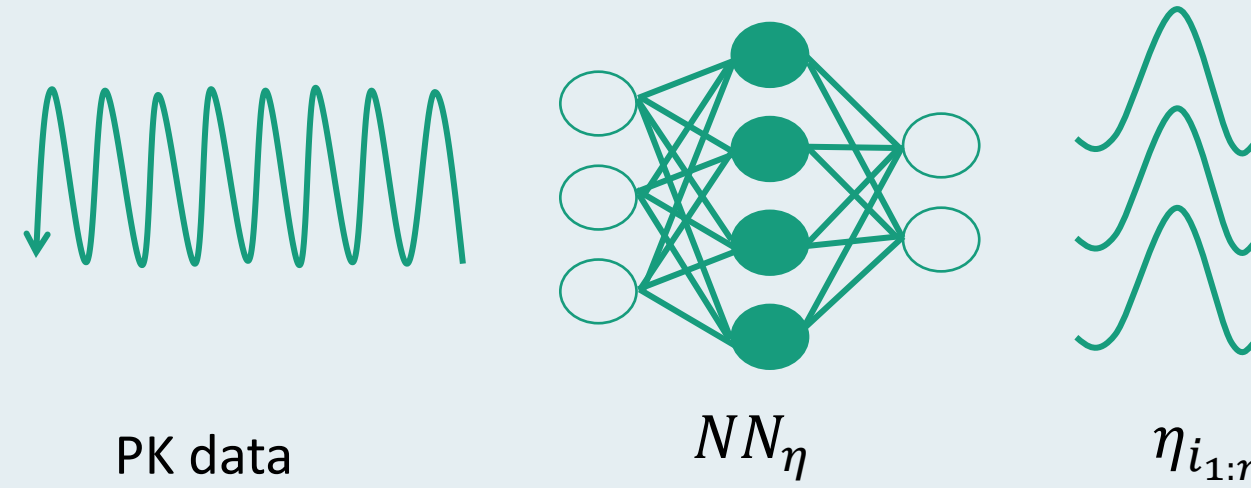
Parameter	KA [1/h]	KE [1/h]	K23 [1/h]	K32 [1/h]
Used for data creation	0.08	0.23	0.01	0.06
First-order absorption model	0.18	0.19	1.2×10^{-6}	0.002
Mixed-order absorption model	0.058	0.24	0.015	0.114
RE-SciML (ours)	-	0.29	0.106	0.123

Inter-Individual Variability

Parameter	IIV Abs / IIV PAbs1	IIV PAbs2	IIV CL	IIV V2	σ_1^2	σ_2^2
Used for data creation	0.02	-	0.1	0.03	0.04	0.022
First-order absorption model	3.54×10^{-5}	-	0.059	0.03	37.45	-
Mixed-order absorption model	0.45	-	0.096	0.03	7.177	-
RE-SciML (ours)	0.071	0.082	0.049	0.134	16.636	-

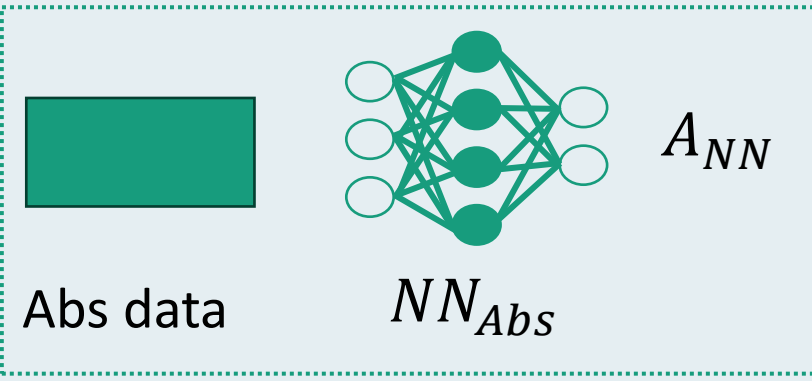
Overview

Step 1: Estimation of IIV of mechanistic and NN terms and population parameters



For all times

Step 2: Determination of absorption term

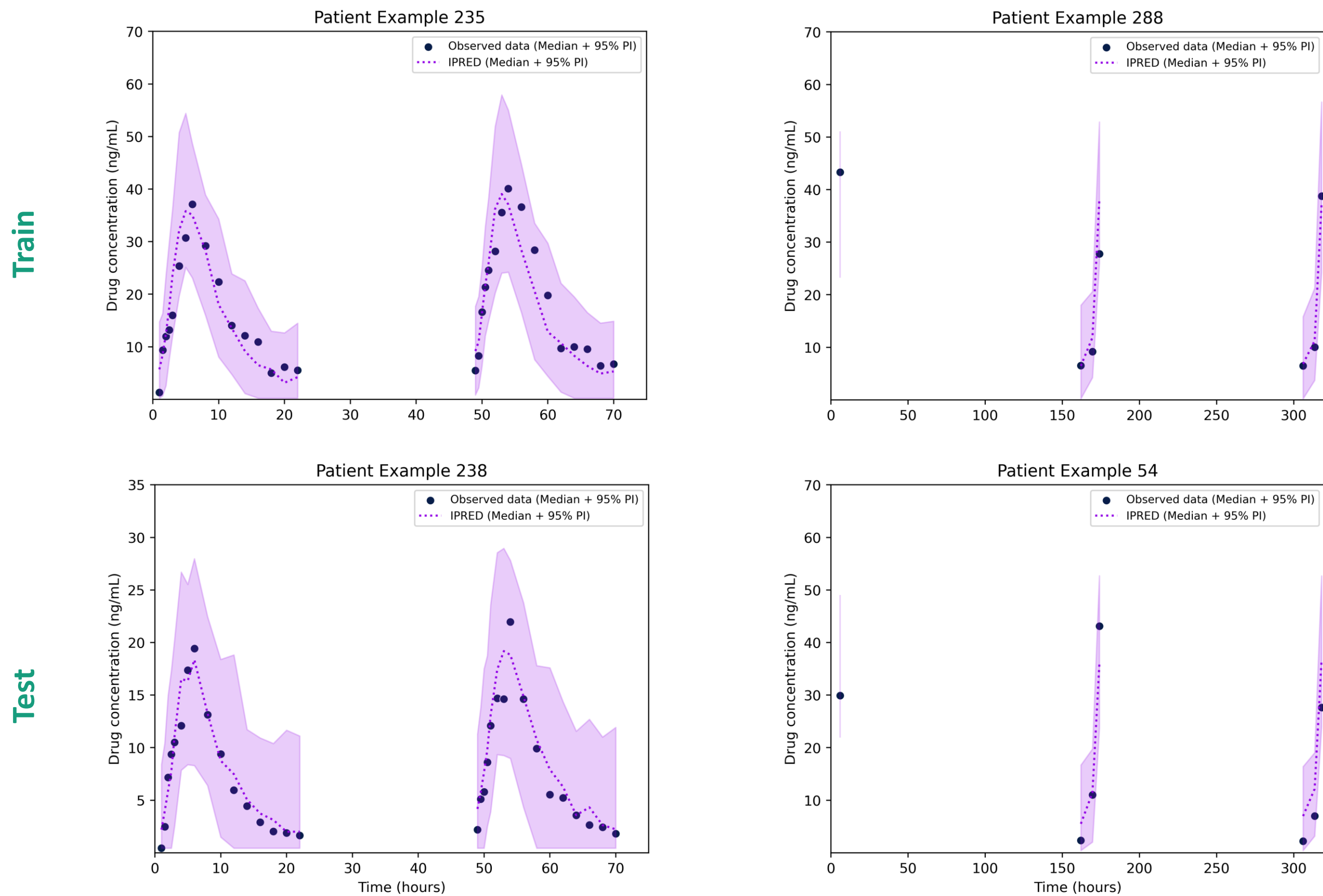


Step 3: Solving the ODE system for all individuals

$$\begin{aligned} \frac{dC1}{dt} &= -A_{NN} * C1 \\ \frac{dC2}{dt} &= A_{NN} * C1 - \frac{CL}{V2} * C2 - \frac{Q}{V2} * C2 + \frac{Q}{V3} * C3 \\ \frac{dC3}{dt} &= \frac{Q}{V2} * C2 - \frac{Q}{V3} * C3 \end{aligned}$$

Step 4: Calculation of the loss function

$$\mathcal{L}_{FOCE_i} = \log \left| \frac{\partial f(\eta_i, \theta)}{\partial \eta_i} \right|^T \Omega \frac{\partial f(\eta_i, \theta)}{\partial \eta_i} + \Sigma + \eta_i \Omega^{-1} \eta_i + \frac{(Y_i - f(\eta_i, \theta))^2}{\sigma_1^2}$$



Our model

- Introduces flexibility by incorporating an innovative encoder to learn the IIV of both mechanistic and ML terms, enabling differentiation between the variability of known mechanistic parameters and the unknown absorption process.
- Is (once trained) a fully generative model allowing patients generation through omega sampling.
- Mitigates overfitting by utilizing a FOCE based loss function that includes regularization terms on the magnitude of eta and omega.

Limitations

- Relative long training time
- Technical limitations in approximating the loss function for faster computation

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Disclosure of potential conflict of interest:

Ana Victoria Ponce-Bobadilla, Sven Mensing, and Sven Stodtmann are employees of AbbVie and may hold stock or options in the company. Holger Fröhlich sat on the Editorial Boards of the EPMA journal and Frontiers of Artificial Intelligence. Diego Valderrama has no conflict of interest to declare.

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