

Modelling Pharmacokinetic Variability with Physics-Informed Neural Networks



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BACKGROUND

In many studies, individual measurements of a state variable are not reported; instead, summary statistics such as the mean and variance are provided. This is common in pharmacokinetic studies, where concentration–time profiles are often summarized across subjects. To incorporate this aggregated information into parameter estimation, we propose a methodology that leverages **Physics-Informed Neural Networks (PINNs)** [1] to learn the parameters of a predefined distribution. Our approach compares the derivatives of the mean and variance obtained via automatic differentiation of the neural network (NN) with those derived analytically from the underlying ordinary differential equation (ODE) system through sampling, enabling the propagation of population-level variability into the parameter inference process.

OBJECTIVES

- ✓ Develop a methodology based on **PINNs** to estimate the parameters of a predefined distribution of model parameters, using observed time-series data of the state variable's mean and variance.
- ✓ Demonstrate the effectiveness of the proposed approach through a **proof-of-concept** study using **synthetic data**.
- ✓ Using a simple **one-compartment** pharmacokinetic model and assuming the true form of the underlying distribution, show that the framework can accurately **recover the parameters of that distribution**.

METHODS

A. Synthetic Data Generation

A 1-compartment pharmacokinetic model was employed, characterised by two parameters: the **volume of distribution**, V_d , with a mean population value of 15 L and a coefficient of variation (CV) equal to 10%, and the **elimination rate**, k_e , calculated from the corresponding half-life, with a mean population half-life value of 6 hours and CV = 40%. The parameters were drawn from a multivariate distribution, considering a negative correlation of -0.2 between V_d and k_e :

$$\theta = [V_d, k_e] \sim MVLN(\mu, \Omega)$$



The ODE system was used to simulate the pharmacokinetics of a **300 mg IV bolus** administration in **30 virtual patients** with varying drug biodistribution parameters. The amount (A) and concentration (C) in serum were given by:

$$\frac{dA}{dt} = k_e C, C(t) = \frac{A(t)}{V_d}, C(0) = \frac{D}{V_d},$$



For each virtual patient, samples were drawn at 0.5, 1, 2, 4, 6, 8, 12, 24 hours post injection. Proportional error was applied to simulate residual variability. The data were then **summarized** by calculating the **mean and variance at each time point** across all patients.

$$C_i = C_{i,ODE} \cdot (1 + \varepsilon), \varepsilon \sim N(0, 0.1)$$

B. PINNs

The proposed methodology is presented in Figure 1.

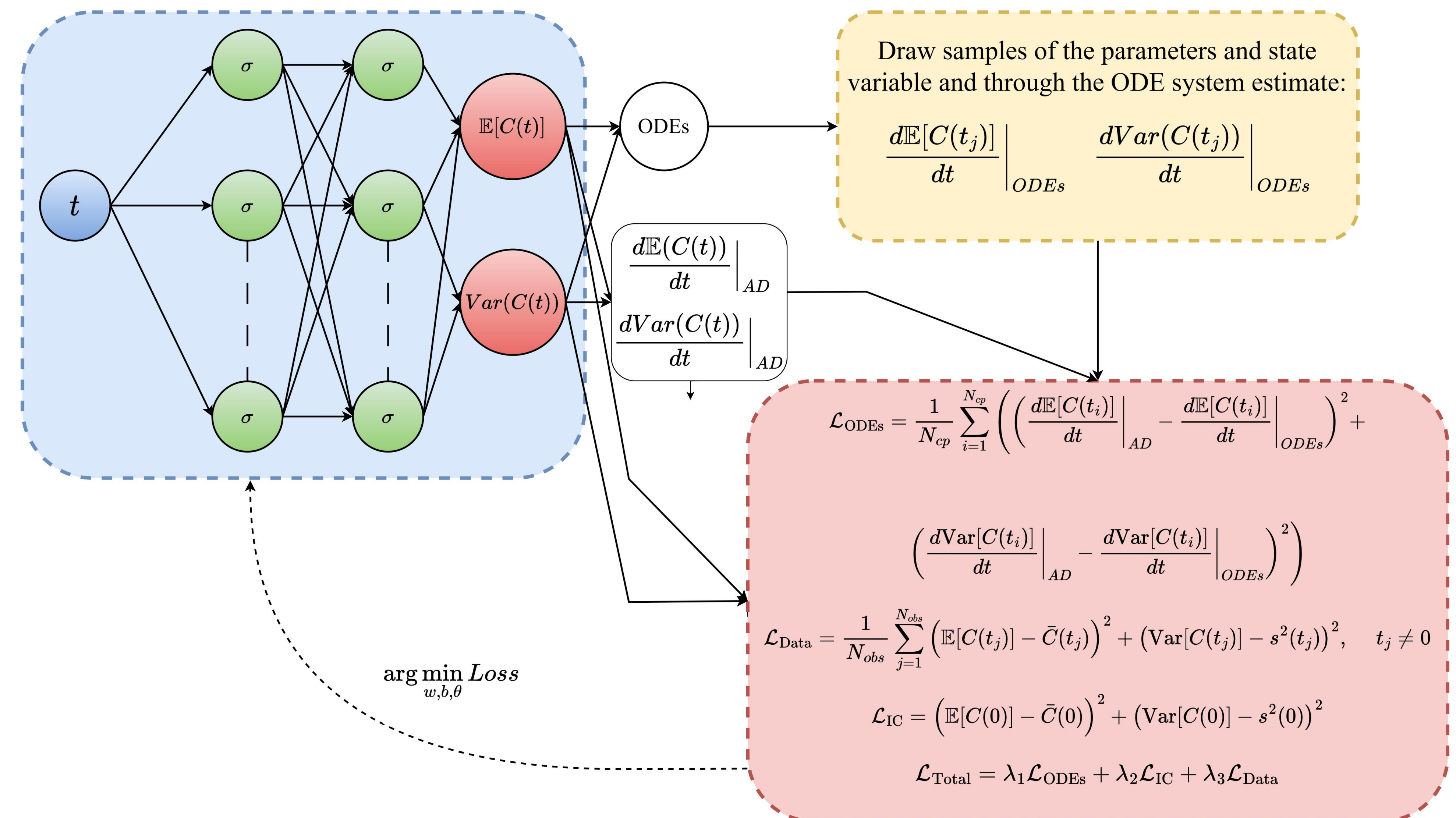


Figure 1: Schematic representation of the PINNs framework for inferring the distribution of ODE parameters using the observed mean and variance of the state variable. The optimizer estimates the hyperparameters, in this case the location and scale of the lognormal distribution. Based on these, parameter samples are drawn at each iteration from the resulting distributions and are used for estimating the derivative of the mean and variance of the state variable (yellow box).

RESULTS and CONCLUSIONS

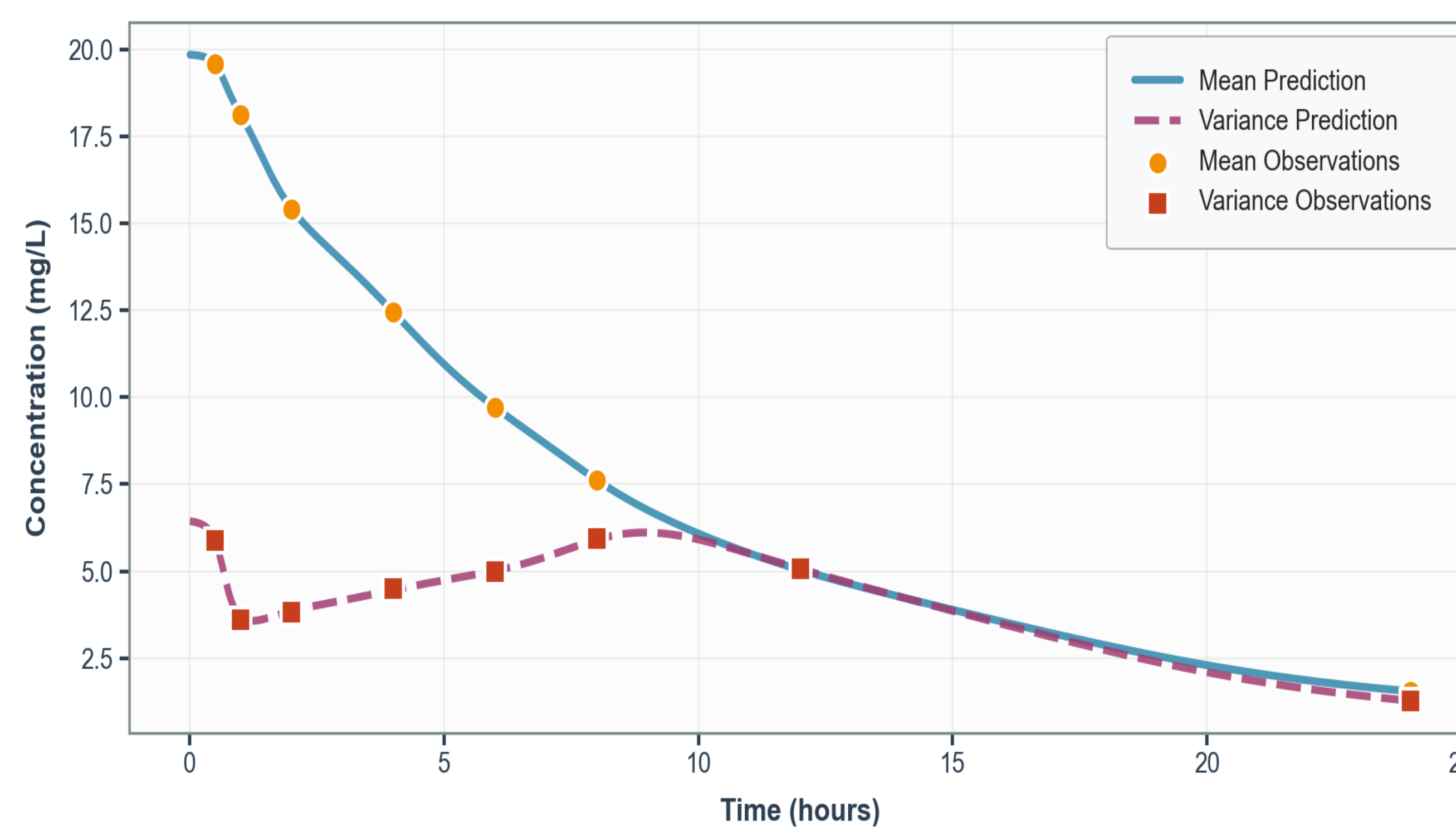


Figure 2: Model fit to observed mean and variance data.

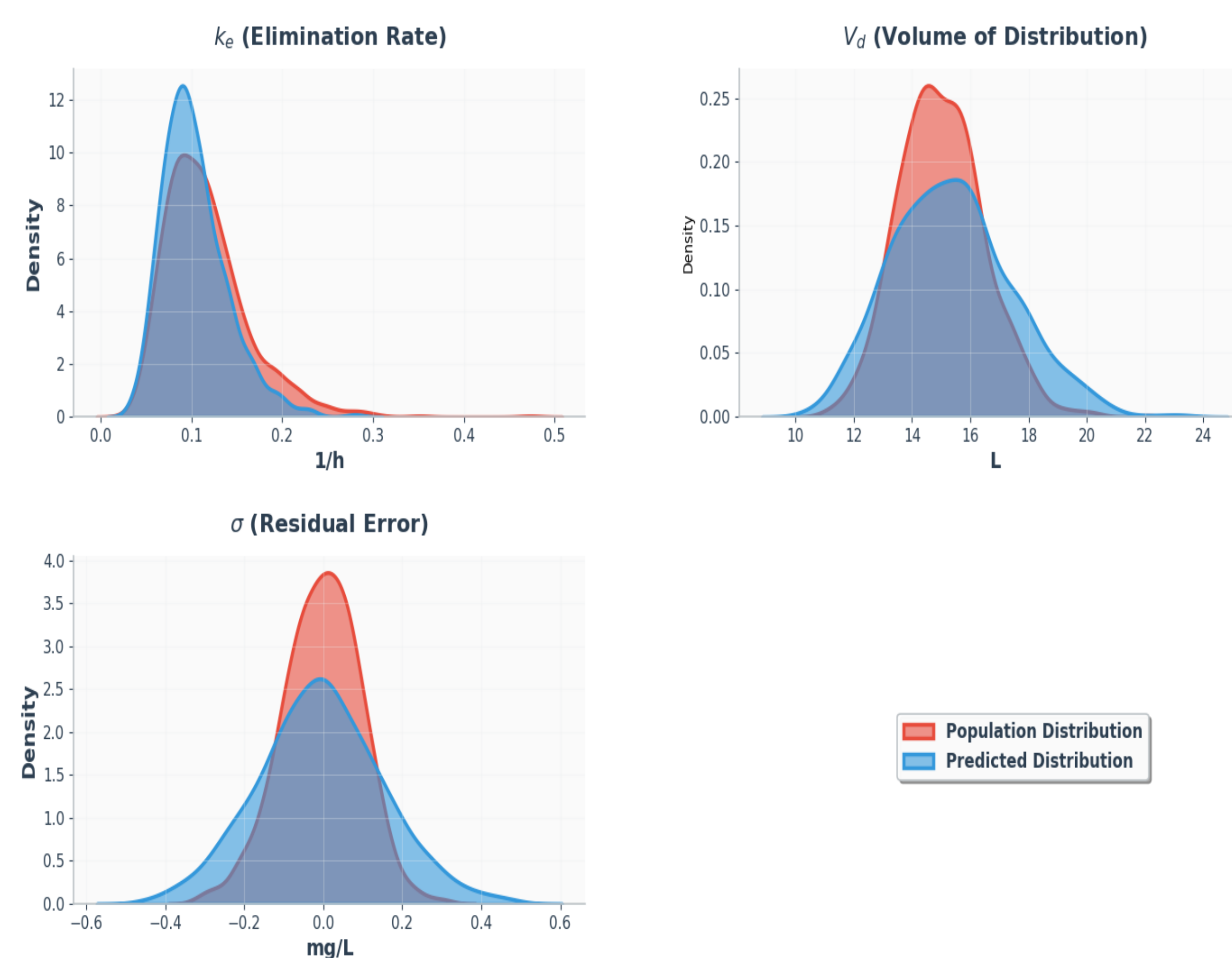


Figure 3: Predicted vs. population parameter distributions, generated from 1,000 samples.

- ✓ A simple feed forward NN architecture with time as the only input was employed to predict the mean and variance of the serum concentration. The structure of the network consisted of 2 hidden layers with 5 nodes each. This **simple structure was sufficient** to predict the observed concentration mean and variance across time with high precision (Figure 2).
- ✓ The model managed to **estimate with high accuracy the underlying population parameter distributions**, as well as the variance of the residual error (Figure 3).
- ✓ The results demonstrate the ability of the proposed PINNs methodology to **infer statistical information about population parameter distributions** by using only statistical information related to the state of the ODE system.
- ✓ This study highlights the potential of integrating **novel machine learning-driven methodologies** into pharmacokinetic parameter estimation.

ACKNOWLEDGEMENTS

The authors acknowledge financial support from the SCENARIOS project (Grant Agreement 101037509) which has been funded by the European Commission under the Horizon 2020 Programme.

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