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Low-Dimensional Neural ODE Representations of Multi-Dose Pharmacokinetics

Avni Vemuri

Abstract: ***Pharmacokinetic (PK) modeling plays a crucial role in developing and optimizing drug therapies, enabling the prediction of drug concentration in the plasma over time and thus informing dosage regimens for maximum efficacy with minimal toxicity. Traditional PK models, while useful, often rely on discrete and linear representations that may not fully capture the complex dynamics of drug interaction within the human body. This limitation is particularly evident in scenarios involving multiple doses where the interactions between successive doses can significantly influence overall drug behavior. Neural Ordinary Differential Equations (NODEs) provide a novel computational approach by modeling the continuous dynamics of biological systems through a deep learning framework. Unlike traditional discrete models, NODEs integrate the derivative of the state with respect to time, offering a flexible and powerful tool for continuously simulating biological processes. This study presents a NODE-based model specifically tailored for the pharmacokinetics of multi-dose drug administration. The proposed NODE model utilizes a single-layer neural network with 50 neurons in the hidden layer, focusing exclusively on drug concentration without direct time input. This design ensures that the model remains invariant to shifts in time, enhancing its applicability across varied clinical settings. Simulated pharmacokinetic profiles with double dosing were generated, incorporating Gaussian noise to mimic real-world measurement variations and biological variability. After 1000 epochs, the NODE demonstrated high accuracy in predicting pharmacokinetic profiles, indicating its potential as a robust tool in pharmacology. The success of this NODE model in accurately simulating double-dose scenarios showcases its capability to enhance the precision of drug dosing guidelines, ultimately improving patient outcomes by tailoring therapies to individual pharmacokinetic responses.***

Keywords: Neural Ordinary Differential Equations, pharmacokinetics, multi-dose modeling, computational pharmacology, personalized medicine

1. Introduction

Modern medicine is one of, if not the most, significant contributors to the rapid growth of the average lifespan of humans. Of medicine's most important inventions are drugs, synthetic or natural chemicals designed to interact with and control the human body's chemical composition. Pharmacology is the field studying the design, use, and effects (intended and unintended) of these drugs, and today is one of the most invested-in areas of study. Pharmacodynamics (PD) and pharmacokinetics (PK) are two subfields of pharmacology that examine the mechanisms of drug activity in the body. PK studies drugs' kinetics ("movement") through the body, particularly their absorption, distribution, metabolism, and excretion. Conversely, PD looks at the dynamics ("change over time") of drugs and their physiological effects. It is important to note that although some use PK and PD interchangeably, the terms are distinct.

Recently, many studies in pharmacology have been focused on implementing computational methods to improve the analysis of data and modeling of drug-body systems. Many of these computational methods include improvements to existing mathematical methods, which include differential equations, algebraic systems, and small-step approximations. These mathematical models create deterministic, exact predictions. Parameters used in these mathematical models are often estimated or fitted to real-world data. Other computational models used in pharmacology include molecular dynamics simulations, statistical models, and network models.

However, a new computational modeling field, machine learning (ML), has emerged. ML methods use models that are (canonically) trained to fit purely real-world data and make predictions about some systems. One of the most commonly used types of ML models is the neural network (NN), which has various derivative models that emerge in various use cases.

Neural networks are universal approximators and, according to the Universal Approximation Theorem, can approximate a real-valued, differentiable function across a closed domain. Neural networks are composed of neurons arranged in layers: an input layer that receives the data, one or more hidden layers that process the data, and an output layer that produces the final prediction. Each neuron in a layer is connected to several others in the previous and next layers, and these connections are weighted. During the training phase, the neural network uses a dataset to adjust these weights based on the prediction errors, typically using a method called backpropagation. The network learns to reduce error through iterative adjustments, refining its model of the underlying data patterns. This process allows neural networks to make predictions or classifications based on input data, making them incredibly useful for complex problems ranging from image recognition to drug discovery.

Expanding the capabilities of traditional computational models, Neural Ordinary Differential Equations (NODEs) offer a novel approach by integrating concepts from differential equations and deep learning. NODEs utilize a neural network to parameterize the derivative of a hidden state with respect to depth, effectively treating the depth of the network as the time variable in a dynamic system. This setup allows the model to learn continuous-time dynamics, providing a flexible and adaptive framework that is particularly well-suited for modeling time-dependent or sequential data. The continuous nature of NODEs makes them an excellent tool for simulating biological systems and other dynamic environments.

NODEs are particularly useful in pharmacokinetic (PK) modeling. Their continuous modeling approach enables

capturing intricate drug behaviors in various biological environments, leading to more precise predictions of drug concentration-time profiles in individual patients. NODE modeling can facilitate the tailoring of dosing regimens and enhance the predictive accuracy of pharmacokinetic studies, significantly improving personalized medicine strategies and optimizing therapeutic outcomes.

Distinct from existing research on the application of Neural Ordinary Differential Equations (NODEs) in pharmacokinetic (PK) modeling, this study aims to pioneer the development of a low-dimensional NODE framework tailored specifically for multi-dose scenarios (Fig. 1). In these scenarios, the drug of interest is administered multiple times, in contrast to a single dose situation. This repeated administration poses unique challenges, including the complexities of drug accumulation, interaction between doses, and the body's adaptive responses over time, which can significantly influence efficacy and safety. The proposed NODE framework aims to accurately capture and model these dynamics, providing a more nuanced understanding of drug behavior across multiple dosing events, which is crucial for optimizing therapeutic strategies and improving patient outcomes.

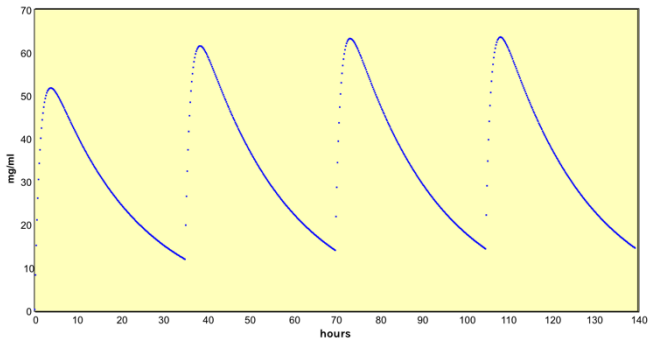

Figure 1: Pharmacokinetic Plot for a Multi-Dose System

Figure 1: Plot of the concentration of a drug with ideal behavior against time, in a case where the drug is administered 4 times, with an equal space between each injection. The periodic peaks, with growing height, are characteristic of multi-dose pharmacokinetics

To validate and refine this novel framework, this work will focus on creating and employing an NODE specifically designed for modeling the dynamics of a double-dose scenario to elucidate the extension of the NODE framework to multi-dose cases. This model will then be fit to synthetically generated double-dose data. Modeling these multi-dose scenarios with NODEs allows for increased pharmacokinetics study depth. It would be a valuable resource for those in the medical and professional fields.

a) Traditional Pharmacokinetic Models

Traditional pharmacometrics models, such as compartmental models, have been widely used to describe drugs' PK profiles. These models typically divide the body into compartments (e.g., central and peripheral), with differential equations describing the transfer of drugs between compartments. For instance, a two-compartment model might include equations for the central compartment (representing the bloodstream) and the peripheral compartment (representing tissues) [1].

Mechanistic models, another class of traditional pharmacometric models, incorporate detailed biological mechanisms into their equations. These models can include enzyme kinetics, receptor binding, and other physiological processes. Despite their complexity and ability to provide deep insights, mechanistic models can be limited by their reliance on well-defined biological mechanisms and parameters, which are not always available [2].

b) Neural Networks

Neural networks (Fig. 2) are computational models loosely inspired by the structure of biological brains. The most basic form of a neural network consists of multiple layers, which are each composed of nodes. The first layer of the network is the input layer, in which each node is some numerical input to the neural network. The last layer of the network is the output layer, which returns the network outputs. Layers between the input and output are called hidden layers. The nodes of each layer are connected to all other nodes in neighboring layers by edges. The number of nodes in each layer, as well as the number of hidden layers, is arbitrary and is often chosen based on the requirements of the network.

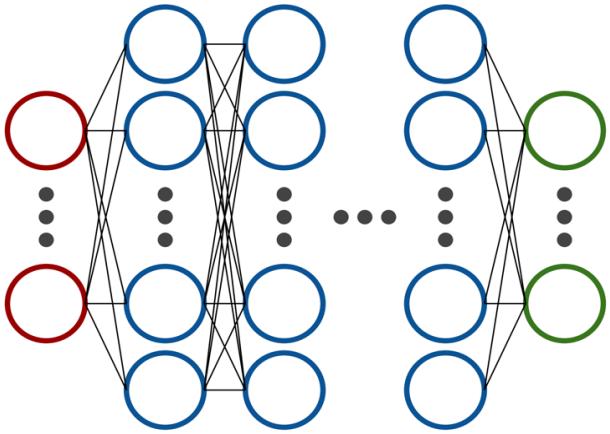

Figure 2: Graphical Representation of a Neural Network

Figure 2: Above is a neural network with arbitrary input (red), output (green), and hidden (blue) layer size and an arbitrary number of hidden layers. Each node is connected to every node in neighboring layers by edges.

Figure 3: Fundamentally, neural networks are nothing except large functions that take numerical inputs and return numerical outputs. Typically, the input values "move" and are transformed through the layers, starting in the input layer and finishing at the output layer. The movement of the input values through the network is quantified as activations of each node (a term defined more formally later), and results in a numerical output of the network.

Below are mathematical representations of each layer's activations in vector form, along with matrix-vector representations of the network's weight and biases.

$$\mathbf{W}^{(k-1\to k)} = \begin{bmatrix} w_{11}^{(k-1\to k)} & w_{12}^{(k-1\to k)} & \cdots & w_{1n_{k-1}}^{(k-1\to k)} \\ w_{21}^{(k-1\to k)} & w_{22}^{(k-1\to k)} & \cdots & w_{2n_{k-1}}^{(l-1\to l)} \\ \vdots & \vdots & \ddots & \vdots \\ w_{n_k1}^{(k-1\to k)} & w_{n_k2}^{(k-1\to k)} & \cdots & w_{n_kn_{k-1}}^{(k-1\to k)} \end{bmatrix}, \quad \mathbf{b}^{(k)} = \begin{bmatrix} b_1^{(k)} \\ b_2^{(k)} \\ \vdots \\ b_{n_k}^{(k)} \end{bmatrix} \tag{1}$$

$$\mathbf{x} = \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_{n_0} \end{bmatrix}, \quad \mathbf{h}^{(1)} = \begin{bmatrix} h_1^{(1)} \\ h_2^{(1)} \\ \vdots \\ h_{n_1}^{(1)} \end{bmatrix}, \quad \ldots, \quad \mathbf{h}^{(l)} = \begin{bmatrix} h_1^{(l)} \\ h_2^{(l)} \\ \vdots \\ h_{n_l}^{(l)} \end{bmatrix}, \quad \mathbf{y} = \begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_{n_{l+1}} \end{bmatrix} \tag{2}$$

The activations propagate through layers as follows:

$$\mathbf{h}^{(k)} = \varphi^{(k)}(\mathbf{W}^{(k-1\to k)}\mathbf{h}^{(k-1)} + \mathbf{b}^{(k)}) \tag{3}$$

The full network computation can be summarized as follows:

$$\mathbf{y} = \varphi^{(l+1)}(\mathbf{W}^{(l\to l+1)}(\varphi^{(l)}(\mathbf{W}^{(l-1\to l)}(\ldots) + \mathbf{b}^{(l)})) + \mathbf{b}^{(l+1)}) \tag{4}$$

c) Neural Ordinary Differential Equations (NODEs)

The development of neural ordinary differential equations (NODEs) represents a significant advancement in combining the strengths of traditional differential equation models and neural networks. NODEs integrate the structure of differential equations with the learning capabilities of neural networks, allowing for the data-driven modeling of dynamic systems. This approach offers a flexible yet interpretable framework for pharmacometrics modeling [3].

NODEs have shown promise in various applications, including pharmacokinetics. For instance, NODEs have been used to model complex PK profiles, such as multi-compartmental behavior and target-mediated drug disposition. These models can learn from data to identify the underlying dynamics, making them particularly useful for capturing non-linear relationships and complex dosing regimens [4].

Below is the mathematical representation of the action of a traditional neural network: applying a transformation repeatedly to inputs.

$$x_{l+1} = x_l + f(x_l, \theta_l) \quad \text{for } l = 0, 1, \ldots, L-1 \tag{5}$$

In contrast, a NODE is a neural network defined as computing the derivative of the input with respect to some variable. In most cases, this NODE is simply a one-layer network. This can be conceptualized as a neural network replacing one side of an ordinary differential equation (ODE).

$$\frac{d\mathbf{h}(t)}{dt} = f(\mathbf{h}(t), t, \theta) \tag{6}$$

Like ODEs, NODEs must be solved. When NODEs are solved (integrated), the resulting values are matched to the data. This is how the loss of a NODE is calculated and is behind it's training process.

$$\mathbf{h}(T) = \mathbf{h}(0) + \int_0^T f(\mathbf{h}(t), t, \theta)\, dt \tag{7}$$

In the context of pharmacokinetic modeling, the development of low-dimensional NODEs represents a strategic advancement aimed at enhancing the computational efficiency and accessibility of these tools. Low-dimensional NODEs simplify the complexity of the models by reducing the number of parameters and dimensions involved, without significantly compromising their ability to capture critical biological processes and dynamics. This reduction is crucial in scenarios where computational resources are limited or where real-time analysis is required, such as in clinical settings or remote monitoring situations. By focusing on essential dynamics and minimizing unnecessary complexity, low-dimensional NODEs facilitate quicker iterations and adaptations, making pharmacokinetic modeling more practical and applicable in everyday medical decision-making. This approach not only streamlines the modeling process but also improves the interpretability of the results, enabling clinicians and researchers to make informed decisions based on clear and concise data representations.

d) NODEs in Single-Dose Scenarios

Initial applications of NODEs in pharmacokinetics have primarily focused on single-dose scenarios. Studies have demonstrated that NODEs can accurately model drug concentration-time profiles and predict outcomes based on single-dose data. For example, Lu et al. (2021) applied NODEs to predict the pharmacokinetics of drugs with linear and non-linear kinetics, showing that these models could handle various PK scenarios effectively. [5]

However, single-dose models do not fully capture the complexities of repeated drug administration, which is common in clinical practice. Multi-dose scenarios introduce additional challenges, such as drug accumulation, varying dosing intervals, and changes in pharmacokinetic parameters over time. Addressing these challenges requires extending NODEs to multi-dose PK modeling.

e) NODEs in Multiple Dose Scenarios

Extending NODEs to multi-dose scenarios involves several key considerations. The differential equations must be adapted to account for repeated dosing and the resulting pharmacokinetic profiles. This includes incorporating terms representing multiple doses and their cumulative impact on drug concentration over time. Additionally, training NODEs on multi-dose data is essential to ensure that the models can learn the relevant dynamics from empirical data.

Recent studies have started to explore the application of NODEs in multi-dose scenarios. For example, Rackauckas et al. (2021) developed methods for integrating NODEs with mechanistic models to capture complex dosing regimens and

drug interactions. These hybrid models combine the interpretability of mechanistic models with the flexibility of NODEs, offering a robust approach for multi-dose pharmacometric modeling. [4]

2. Methodology

This work proposes a general outline for creating a NODE-based model for multi-dose cases, but only a double-dose case is simulated and proven to work.

The NODE proposed here is a single-layer network defined by 50 neurons in the hidden layer. Additionally, the only input to this network is the current drug concentration. This allows the system to rely only upon the current drug dosage and not the actual time. Thus, the model is protected from any effects in which time being shifted affects the ability of the model to make predictions. For example, if the model were initialized with data starting at 50 instead of time 0, the model would not be affected. This model's lack of time dependence makes it a continuous heuristic model.

The Neural ODE's design to exclude explicit time dependency in its input layer streamlines the model, focusing solely on the pharmacokinetics of drug concentration, regardless of the initial time point of administration. This approach underscores the model's utility in scenarios where the exact timing of dose administration may vary or be subject to data entry errors, ensuring its performance remains consistent across different starting times.

A robust simulation environment was implemented using Python to train and evaluate the NODE. Each pharmacokinetic profile was generated through numerical integration of a one-compartment model with first-order kinetics, describing how the drug concentration decreases over time due to metabolism and excretion. For the simulation of double dosing, initial conditions for the second dose were adjusted to include the residual drug concentration from the end of the first dose simulation. This setup mirrors real-life treatment courses where subsequent doses are administered before the previous dose has been entirely cleared from the body.

Upon simulation, Gaussian noise was added to the concentration values to simulate real-world measurement inaccuracies and biological variability. The noisy dataset thus generated was used as the training data for the NODE, where the true dynamics of the drug concentration were known and could be used to supervise the learning process.

Training the NODE involved optimizing its parameters (weights and biases) using the Adam optimizer, a popular choice for deep learning applications due to its efficient computation of first and second moments of gradients. The loss function used was the mean squared error between the predicted and true concentrations, which provides a clear metric for regression tasks, pushing the model toward precise predictions at each time point.

The learning process spanned 1000 epochs, with periodic evaluations every 100 to monitor the training progression and make adjustments if necessary. This iterative training process allows the model to gradually refine its predictions, reducing the loss over time as it becomes better at forecasting the pharmacokinetic profile after a double dose of medication.

Finally, predictions were plotted against actual data after the training period to assess the trained NODE model's performance visually. This visual comparison served as a qualitative assessment of the model's accuracy. It highlighted potential areas for further refinement, such as adjusting the network architecture or training duration to improve the fit between predicted and observed pharmacokinetic profiles.

a) Simulating Data

In this study, the simulation of pharmacokinetic data was achieved using a one-compartment model with first-order elimination, representing a simplified yet effective approach to understanding drug kinetics. The mathematical framework utilized to simulate drug concentration over time employs a straightforward ordinary differential equation (ODE), given by:

$$\frac{dC}{dt} = -k_{\text{el}} \cdot C \tag{7}$$

This first-order kinetic model assumes that the rate of drug elimination is proportional to the drug concentration, a common assumption in pharmacokinetics.

For the simulation, initial conditions were set for two sequential drug doses. The first dose was initialized by setting the initial concentration:

$$z_0^{\text{first dose}} = \left[\frac{\text{dose}}{V}\right] \tag{8}$$

The second dose was simulated by considering the concentration remaining at the end of the first dose. The initial condition for the second dose was thus given by:

$$z_0^{\text{second dose}} = \left[\text{concentration\_at\_24h} + \frac{\text{dose}}{V}\right] \tag{9}$$

This setup reflects a real-world scenario where a subsequent dose is added to the residual drug concentration in the system. The simulation for the second dose then proceeded from 24 to 120 hours. To introduce a realistic component of variability, normally distributed noise was added to the simulated concentration data from both doses. This method of adding noise mimics the measurement errors and biological variations typically encountered in pharmacokinetic studies.

The data from both simulation phases were concatenated to form a comprehensive profile representing the drug's concentration over time due to both dosing events.

3. Results

a) Simulated Pharmacokinetic Data: Single Dose

Single-dose data was first successfully simulated using the one-chamber differential equation model. Adding random samples from the Gaussian distribution further increased

variability among different curves on the plot. The code used to generate this figure was adapted from Bräm et al. (2024).

Graphical Representation of Twenty Simulated Single Dose Scenarios

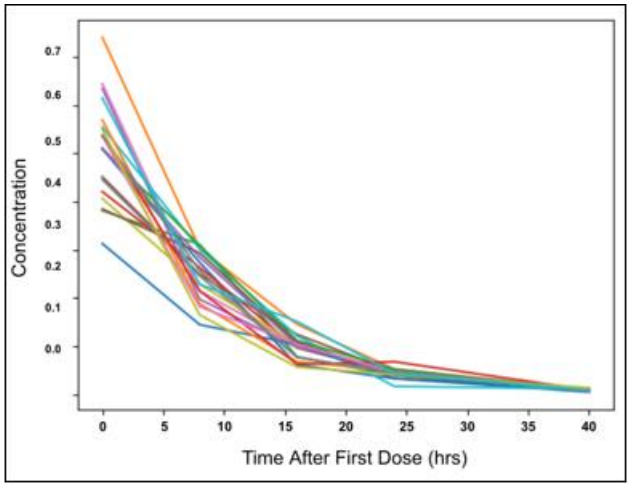

Figure 4: 20 simulated profiles from the single dose case.

20 simulated profiles from the single dose case. This simulation of single-dose data served as proof of the simulation of drug concentrations with the one-chamber differential equation.

b) Simulated Pharmacokinetic Data: Double-Dose

Double-dose data was successfully simulated using a custom-built model. Introducing an additional administration at a specific time interval allowed for the examination of drug accumulation effects and the interaction between successive doses. The author developed the code to generate this figure independently for this specific analysis. This approach provided unique insights into the dynamics of double-dose pharmacokinetics, showcasing the model's ability to predict complex drug behavior in the plasma over time.

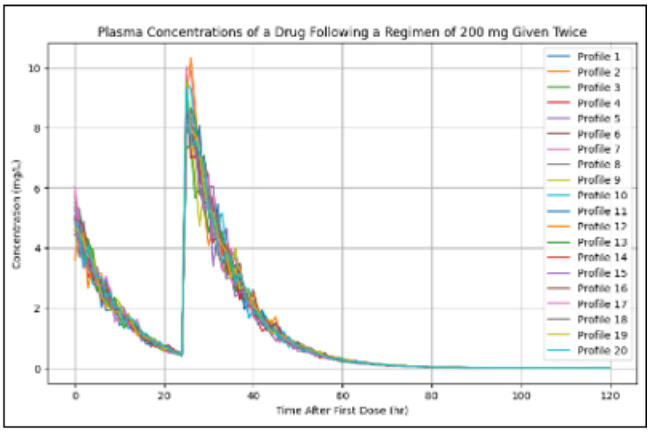

Figure 5: 20 simulated profiles from the double dose case.

20 simulated profiles from the double dose case. This simulation of double-dose data served as proof of the simulation of drug concentrations with the one-chamber differential equation.

c) NODE fit of Simulated Double-Dose Data

Double-dose pharmacokinetic data was successfully simulated using a Neural Ordinary Differential Equation (NODE) model specifically developed for this analysis. By leveraging the continuous dynamics capabilities of NODEs, the model adeptly handled the administration of two sequential doses at defined intervals, allowing for a detailed examination of drug accumulation effects and interactions between the doses. This model was built and the simulations were carried out using code independently developed by the author, tailored to capture the complex behaviors of pharmacokinetics in a double-dosing regimen. The NODE approach provided unique insights, demonstrating its robustness in predicting intricate drug behavior over time.

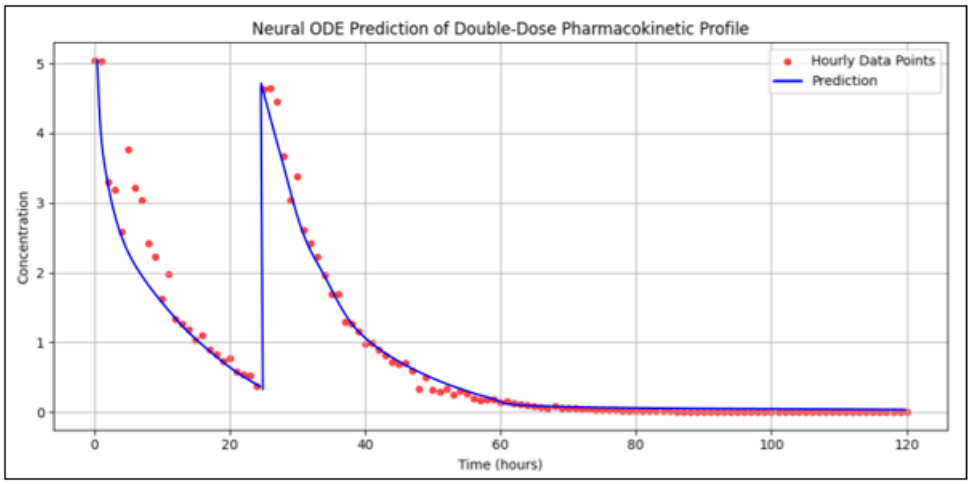

Figure 6: NODE fit of Simulated Double Dose PK Profile

Concentration-time profile predicted by the NODE model for a drug administered in two doses (Fig. 5). The blue line represents the NODE's prediction, closely matching the simulated data points shown in red. The initial peak reflects the concentration after the first dose, followed by a second peak due to the subsequent dose, effectively capturing the pharmacokinetic response to double dosing. This visualization validates the accuracy of the NODE model in simulating such scenarios and highlights its effectiveness in understanding the dynamics of drug distribution and elimination over time.

4. Discussion

This study underscores the utility of Neural Ordinary Differential Equations (NODEs) in capturing the dynamics of drug concentration profiles in double-dose pharmacokinetic simulations. The ability of NODEs to model continuous changes over time provides a strong basis for their application in more complex multi-dose pharmacokinetic scenarios, which are typical in chronic therapy regimens.

a) Double-Dose Pharmacokinetic Modeling

The NODE framework has shown promising results in simulating double-dose pharmacokinetic scenarios. The model effectively captured the primary peaks and troughs indicative of consecutive dosing, illustrating its potential in pharmacokinetic studies. However, while generally decent, the fit demonstrated more than slight discrepancies between the predicted and actual data points. These notable discrepancies highlight the need for further refinement of the model to enhance its ability to accurately capture the complex interactions between doses and more precisely, reflect the cumulative effects of repeated dosing. These results suggest that while the NODE model is a robust tool for simulating pharmacokinetic profiles, adjustments are necessary to improve its precision, especially in complex dose regimens. Enhancing the model's accuracy is crucial for its application in clinical settings where precise dose adjustments are essential for patient safety and efficacy of therapy.

b) Transition to Multi-Dose Studies

The insights from double-dose simulations are instrumental in evolving these models for multi-dose applications. Multi-dose pharmacokinetic modeling is critical for designing and optimizing dosing regimens in chronic disease management, where patients receive medication over extended periods. The current model's framework will be expanded to include simulations of multiple dosing intervals, allowing us to study the impact of various dosing strategies on drug accumulation, efficacy, and safety.

c) Future Work and Personalized Medicine

The ultimate goal of extending the NODE model to multi-dose scenarios is to refine a computational tool and forge pathways toward personalized medicine. Personalized medicine, which tailors medical treatment to the individual characteristics of each patient, relies heavily on the ability to predict how different patients respond to the same drug under various dosing regimens. With its capacity to simulate dynamic biological processes continuously, the neural ODE model presents a unique opportunity to integrate more detailed patient-specific variables such as genetic makeup, age, weight, renal and liver function, and even previous drug exposure histories.

Enhancements for Model Precision

To advance the NODE model towards this goal, several specific enhancements are envisioned:

1) **Integration of Patient Data:** Incorporating real-world patient data into the NODE model will allow for more accurate simulations that reflect individual variabilities. This data can include patient-specific pharmacokinetic and pharmacodynamic parameters, significantly influencing drug behavior and therapeutic outcomes.
2) **Complex Regimen Simulation:** Expanding the model to simulate more complex regimens that involve varying dosages, different administration routes, or intermittent dosing schedules will make the simulations more applicable to real-world therapeutic scenarios, especially in chronic disease management.
3) **Advanced Parameter Optimization:** Employing advanced machine learning techniques for parameter optimization, such as genetic algorithms or deep learning-based optimization strategies, can enhance the model's ability to learn from complex datasets and improve its predictive accuracy.
4) **Coupling Pharmacokinetics with Pharmacodynamics (PK/PD):** Future versions of the NODE model could benefit from coupling pharmacokinetic data with pharmacodynamic effects, thereby not only predicting drug concentration over time but also its therapeutic and adverse effects, further personalizing the dosing recommendations.

5. Conclusion

The NODE model presents a promising methodological advancement for pharmacokinetic studies, with its current application to double-dose scenarios laying the groundwork for future research into multi-dose regimens. This progression is essential for developing personalized medicine and optimizing therapeutic strategies across different patient populations. With further refinement, NODE models can become a cornerstone in the pharmacokinetic modeling of drug therapy, enhancing our ability to tailor treatments to individual patient needs effectively.

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