

Drug cycle simulation with machine learning

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I. INTRODUCTION

Drug cycle simulation, also referred to as PK-PD modeling and simulation and pharmacokinetic-pharmacodynamic (PK-PD) modeling, is a computational method used in pharmaceutical research and development to forecast and analyze how drugs are absorbed, distributed, metabolized, and excreted (pharmacokinetics) and how these processes relate to the drug's effects on the body (pharmacodynamics). This technique simulates a drug's complete lifecycle inside the body and runs computer simulations to determine its effectiveness and safety.

Drug candidates are assessed for physical-chemical characteristics, absorption, metabolism, distribution, and excretion (ADME), efficacy, and safety in a range of animal models and in vitro systems during drug discovery and pre-clinical development. As compounds proceed towards development, the decision-making process is guided by this enormous amount of data [1].

By design, biological mechanism-based models, which enable the separation of biological and compound-specific components, are able to incorporate data on a variety of pharmacokinetic, pharmacodynamic (including efficacy and toxicity), and formulation-related processes. They can be used to forecast the full drug concentration and effect time course in vivo in addition to estimating summary in vivo pharmacokinetic parameters. The adoption of such models can significantly influence all stages of the discovery and development of new drugs and may ultimately lead to significant cost savings for the pharmaceutical industry.

An important application of drug simulation is ocular drug development [2]. Conducting experiments in the tiny eye is challenging, and invasive research methods are constrained by cost factors and ethical criticisms. And it brings challenges to understanding the various processes of ocular drug delivery, especially the interaction of drugs with the ocular biological systems. The development of non-invasive computational modeling techniques also offers renewed opportunities for ocular drug delivery understanding and for the rational ocular drug design. To date, multiscale in silico modeling & simulation approaches from the nanoscale to macroscopic perspectives have been developed to benefit drug delivery, providing pharmaceutical scientists with diverse perspectives on drug delivery details, including but not limited to mathematical approaches such as mechanistic modeling, numerical simulation and pharmacokinetic/pharmacodynamic (PK/PD) modeling; deductively driven "Newtonian" physical modeling such as molecular simulations; and data-driven "Keplerian" modeling represented by machine learning. Over the past decade or so, the aforementioned multiscale modeling techniques and data-driven machine learning methods have

been introduced to pharmaceutical research, generating a new scientific field known as "Computational Pharmaceutics", which offers ideas and tools for understanding ocular drug delivery details and revolutionizing pharmaceutical formulation development paradigms.

This passage will review some researches of ocular drug simulations and a detailed method based on machine learning.

A. Pharmacokinetic (PK) and pharmacodynamic (PD) modeling

The foundation for analyzing drug exposure over time and space, namely ocular pharmacokinetics, lies in the understanding obtained from mathematical modeling of the mechanistic dissection of ocular events and the fate of drugs within the eye. Ocular pharmacokinetics is a subfield of pharmacokinetics that quantitatively examines the absorption, metabolism, distribution, and excretion processes of drugs in various eye tissues, utilizing temporal functions that are more precise than those used in overall pharmacokinetics. The principle of PK and PD modeling is to analyze the in vivo behavior of a drug or the response of an organism to a drug, breaking it down into independent factors and quantifying these factors using mathematical tools to predict drug disposition and action under different conditions. This is directly related to drug exposure in ocular target tissues (PK problem), as it impacts drug efficacy (PD problem) and safety, assuming a correlation between drug concentration in target tissues and biological response.

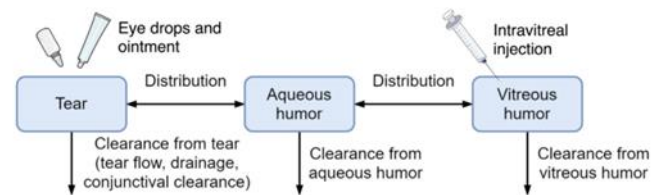


Fig. 1. The compartmental PK model.

1) Compartmental PK modeling:

The compartmental PK model divides the eye's overall structure into multiple fictitious compartments and assigns each compartment a separate set of kinetic properties. Different investigations use different model frameworks. However, Fig. 1 shows a typical compartmental model of the eyes. An ordinary deviation equation controls the change in drug concentration in each compartment at a given point:

$$V_{tar} \frac{dC_{tar}}{dt} = \sum_i k_{distotar_i} X_{oth_i} - \sum_i k_{distooth_i} X_{tar} - \sum_i k_{el_i} X_{tar} \quad (1)$$

Where V_{tar} , C_{tar} and X_{tar} are respectively the volume, drug concentration and drug amount of the target compartment. $k_{distotar_i}$ is the distribution rate constant from the i -th compartment to the target compartment and X_{oth_i} is the drug amount in the i -th compartment. $k_{distooth_i}$ is the distribution rate constant from the target compartment to the i -th compartment. k_{el_i} is the elimination rate constant via the i -th pathway. For example, the elimination of the drug from the tear is the sum of clearance due to normal tear flow, drainage due to lacrimation induced by eye drop instillation, and elimination to the conjunctiva [3]. The modeling of clearance via tear flow and lacrimation is in a special form compared to other clearance pathways:

$$k_{eltearflow} = \frac{Q}{V_{tear}} \quad (2)$$

$$k_{elteardrainage} = k_{dr} \frac{V_{tear} - V_{tear_0}}{V_{tear}} \quad (3)$$

Q is the normal tear flow, which represents the physiological tear turnover. V_{tear_0} is the initial tear volume, and k_{dr} is the drainage rate. Upon eye drop instillation, the tear volume will be enlarged, inducing lacrimation and accelerating drug clearance. The two equations describe the relationship between drug clearance rate and the tear volume at a certain time point.

2) Physiologically based pharmacokinetic (PBPK) modeling:

PBPK modeling methods enable the prediction of drug PK characteristics by integrating specific parameters of human physiological systems, specific physicochemical properties of drugs, and mechanistic PK data. The parameters and structures of PBPK models are physiologically relevant, which means such models are more interpretable.

Although such a physiologically relevant modeling strategy has been attempted in ophthalmic compartmental PK modeling, the PBPK model mentioned here is specifically referred to those with tissue layers that are specifically modeled, and Most drug transfer routes have been considered. Ranta and Urtti [4] showed the superior interpretability of a relatively simple PBPK model using the example of FITC-dextran 70 kDa through transscleral delivery in their review in 2006. They promoted PBPK uses for the delivery of ophthalmic drugs. PBPK modeling techniques have mostly been used up to this point to generate formulations that cover numerous delivery routes [5]. Regulatory organizations like the European Medicines Agency and the U.S. FDA support such development tactics.

A typical ophthalmic PBPK model is shown in Fig. 2, which illustrates the OCAT model integrated into the PBPK software GastroPlus.

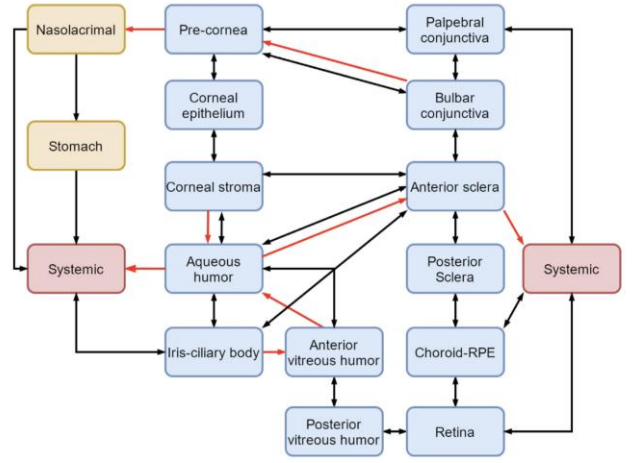


Fig. 2. The PBPK model.

By comprehensively considering the physiological process, PBPK models can provide more interpretable and accurate simulations and quantify the impact of extensive factors on drug delivery. Merdy et al. [6] have used the OCAT model to analyze the effect of formulation properties on their PK behavior with suspensions and ointments of dexamethasone and Fluorometholone as the model formulations.

The infusion of monoclonal antibodies (mAbs) intravitreally is the focus of a different ocular PBPK model that has been published [7]. The systemic model, which consists of the other 16 distinct organs involved in blood and lymph circulation, is connected to the eye compartment, which is further separated to resemble an actual eye globe (Fig. 3, the left panel).

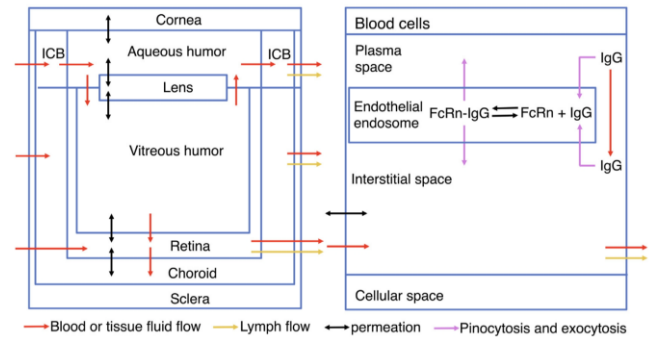


Fig. 3. The eye model structure of a PBPK model for intravitreal mAbs therapy.

3) PK-PD modeling:

The PK modeling replicates drug exposure at various tissue compartments, reflecting the organism's response to the medication. The PD modeling will also develop mathematical connections to characterize the kinetic mechanisms by which drug effects fluctuate with exposure, representing the impact of the drug on organisms, at the drug target site. For the purpose of drug development, a combined PK-PD model will link formulation traits to ADME and response dynamics processes.

One formulation that has been authorized for the treatment of dry eye syndrome is cyclosporine ophthalmic

emulsion. To evaluate the impact of the important quality parameters on its in vivo performance, Walenga et al. [8] modeled the bioavailability of such a cyclosporine product and the tear film breakup time (TBUT). The emulsion vehicle alone directly mediates the effect on TBUT at the start of therapy, and this effect could be predicted using a method based on fluid mechanics (dynamics of the tear film [9]). The TBUT is consequently linked to the viscosity, surface tension, and osmolality of formulations since it is reflected by the lowering height of the tear film over time under the complex effects of evaporation, osmolality, viscosity, and other pressures. This model created a plausible simulation despite being constructed on a number of assumptions. According to the PSA result, only viscosity has a major impact on TBUT and bioavailability. In the future, this approach appears to be useful for evaluating the bioequivalence of various cyclosporine ophthalmic emulsions.

B. Multiscale modeling with machine learning

In the realm of pharmacokinetic-pharmacodynamic (PK-PD) modeling and simulation, the integration of machine learning techniques has ushered in a new era of efficiency and accuracy. Machine learning algorithms play a pivotal role in data preprocessing by automatically cleansing and handling missing values, outliers, and noisy data, ensuring that the input data used for modeling is robust and reliable. Moreover, these algorithms excel at feature selection, simplifying complex datasets by identifying the most relevant variables, thus enhancing model interpretability. When it comes to model development, machine learning offers a diverse toolbox, ranging from regression models and decision trees to advanced neural networks capable of capturing intricate data patterns and relationships. Ensemble learning methods further refine predictions by combining multiple models, mitigating overfitting issues. Cross-validation techniques assess model generalization, while interpretability tools shed light on the rationale behind predictions. Machine learning not only optimizes model hyperparameters but also aids in data imputation, an essential step in many modeling endeavors. In essence, the synergy of machine learning with traditional modeling approaches elevates the quality of PK-PD simulations, empowering researchers to make informed decisions in drug development and personalized medicine.

1) Development of combined methods:

Over the past few decades, machine learning has made significant strides, opening up new possibilities for ocular drug delivery. It still encounters challenges including excessive data requirements, poor interpretability, and subpar generalization performance. Machine learning, which represents data-driven modeling, is intricately entwined with mathematical and physical modeling, paving the way for novel scientific concepts [10]. Machine learning offers strong discriminative or predictive capability by fitting high-dimensional nonlinear connections and identifying feature contributions to observed objects. By enhancing measurable data sets, mechanism-driven mathematical modeling, in contrast, can successfully make up for machine learning's lack of interpretability. The complementary nature of the two has greater practical relevance for mechanistic research and

clinical decision-making in specific contexts, such as medical practice [11]. A study by Guidoboni et al. [12] is a good illustration of this type of research, where observed intraocular pressure data were supplemented with unique hemodynamic output by a validated retinal circulation model. Then, a multivariate linear regression model based on physiology was created to examine the variables affecting primary open-angle glaucoma. It is encouraging to see that machine learning has made progress in increasing the speed and accuracy of molecular simulations [13, 14] and CFD [15], which is not surprising given that statistical mechanics-based physical modeling methods and machine learning both share some theoretical foundations [16].

2) Challenges:

In silico investigations on ocular drug delivery are still in their infancy, despite the fact that a sizable number of computational models with retrospective and predictive capabilities have been established, as presented above. There are still many obstacles to overcome and opportunity for improvement in the current in silico pharmaceutical investigations for the successful implementation of the suggested computer-driven formulation development methodology.

Computational modeling can't avoid the data challenge. Although reducing experimental labor is the ultimate goal of modeling, the modeling process significantly depends on trustworthy experimental data. Data is without a doubt a key component of machine learning that directly influences model performance. The availability of trustworthy data and crucial parameters on which model construction and validation depend is equally crucial for multiscale modeling. Unfortunately, the biomedical sciences face particularly difficult data issues [17]. For instance, unmeasured ocular factors may lead to parts of the model structures being neglected or simplified when creating mechanistic models for ocular behavior, which would harm model performance.

C. What ChatGPT thinks about this topic

1) The summary of this topic by ChatGPT:

Drug cycle simulation enriched by machine learning represents a paradigm shift in the realm of pharmaceutical research and development. This innovative approach harnesses the power of machine learning algorithms to enhance every facet of modeling, from the initial stages of data processing to the fine-tuning of predictive models. At its core, drug cycle simulation involves the intricate interplay of pharmacokinetics (PK) and pharmacodynamics (PD), focusing on how drugs are absorbed, distributed, metabolized, and eliminated in the body and how they exert their therapeutic effects on target receptors or biomolecules.

Machine learning's influence begins with data preprocessing, where it automates the arduous tasks of data integration, cleaning, and quality assurance. It's instrumental in identifying and addressing issues like missing data, outliers, and noise that can potentially skew the modeling process. This initial step ensures that the data used for modeling is of the highest quality, setting a solid foundation for subsequent analyses.

One of machine learning's notable contributions to drug cycle simulation lies in feature selection. In complex datasets

with numerous potential input variables, machine learning algorithms can autonomously determine the most relevant features, simplifying models and improving their interpretability. This is particularly vital in fields like pharmacology, where understanding the precise factors influencing drug behavior and efficacy is paramount.

The heart of drug cycle simulation is model development, and here, machine learning offers a diverse array of tools. From traditional regression models to decision trees and advanced neural networks, these algorithms excel at capturing intricate data patterns and relationships. Ensemble learning methods, such as random forests and gradient boosting, take it a step further by combining multiple models to enhance prediction accuracy and mitigate overfitting, particularly critical when dealing with noisy or uncertain data.

Cross-validation, a standard technique for assessing the generalization performance of a model, is made more efficient and reliable with machine learning. Interpretability tools provided by some machine learning algorithms shed light on the rationale behind model predictions, a crucial aspect of research in fields like healthcare and pharmaceuticals.

In the context of drug development, machine learning plays a pivotal role in optimizing model hyperparameters, ensuring that models perform at their best. It's also instrumental in data imputation, a common requirement when dealing with real-world data where missing values can be pervasive.

Furthermore, machine learning brings us closer to the realm of personalized medicine. By tailoring drug treatments to individual patient profiles based on their unique pharmacokinetic and pharmacodynamic characteristics, machine learning is revolutionizing the way we approach healthcare, increasing treatment efficacy, and reducing adverse effects.

In conclusion, the fusion of drug cycle simulation and machine learning ushers in a new era of efficiency and accuracy in pharmaceutical research and development. This synergy accelerates drug development timelines, reduces costs, and paves the way for safer, more effective medications. It represents a transformative force in the pharmaceutical landscape, promising innovative solutions and improved patient outcomes.

2) Analysis about the output of ChatGPT:

The output can be summarized as follows: Drug cycle simulation, can also be known as pharmacokinetic-pharmacodynamic (PK-PD) modeling and simulation. It can be enhanced by machine learning revolutionizing pharmaceutical research and development. Machine learning algorithms streamline the modeling process by automating data preprocessing, feature selection, and model development. This synergy optimizes drug dosing regimens, reduces side effects, and promotes personalized medicine. Machine learning's impact is felt throughout the drug development pipeline, from data quality assurance to model optimization. It accelerates drug development, lowers costs, and promises safer and more effective medications, fundamentally transforming the pharmaceutical landscape.

Basically, ChatGPT first defined what is so called drug cycle simulation as pharmacokinetic-pharmacodynamic (PK-

PD) modeling and simulation. Then it figured out how can machine learning enhance the mathematical model and what is its contributions towards this kind of researches. It also listed some basic features of machine learning as I mentioned it as a key word in my message, but what it included is actually of generality which means you can also say machine learning helps other technology to develop in the same way. Therefore, ChatGPT may doesn't know how can machine learning help this modeling in which exact aspect, but it has concept of drug cycle simulation and machine learning, plus knows the generous features of machine learning. One major issue is that in order to predict PK data for several dosing regimens, PK models must be built using data from one dosing regimen.

II. DETAILED REVIEW OF A CERTAIN MODELING BASED ON MACHINE LEARNING

What will be discussed is about a deep learning approach based on neural ordinary differential equations (neural-ODE) aiming to forecasting pharmacokinetics (PK) for individual patients [18]. They specifically used the PK data from two distinct trastuzumab and emtansine treatment regimens. When the training and test sets came from the same dosage schedule, the models performed similarly. However, the neural-ODE model performed noticeably better when it came to forecasting a new treatment plan. The most reliable PK model for predicting untested treatment regimens to yet is neural-ODE. This research shows This is the first application of neural-ODE to PK modeling, and the findings indicate that it is a broadly applicable method with the potential to have an impact on future research.

1) Guidelines and data processing:

In this work, they demonstrate how to build PK models automatically from clinical data for the first time using neural ODE. Additionally, they contrasted the suggested strategy with other ML/DL approaches and conventional NLME modeling. For clinical PK prediction, they used three ML/DL techniques: a unique neural-ODE variation, the LSTM neural network (Bianchi et al., 2017), and LightGBM (Ke et al., 2017). According to Hochreiter and Schmidhuber (1997), the base learner known as LSTM was created expressly for time course prediction problems. A well-liked tree-based algorithm is LightGBM. Like the majority of other classic base learners, it includes aspects whose relationships and ordering are thought to be immaterial; nonetheless, the number of features for each example must be of the same dimension.

In order to forecast future PK concentration values, the models they created for this work used first-cycle PK observation (of T-DM1 conjugate). In a traditional population-PK problem, patients are given a medication, and changes in the drug's concentration in the body are influenced by a number of variables, including age, gender, weight, and biomarkers. Predictions of PK response may be influenced by these variables in turn. The data from the first cycle can also be used to predict patient response in subsequent cycles because the medicine is supplied repeatedly.

39 patients on Q3W dosage schedules with only one cycle of dose evaluation were excluded from the analysis. The models have the following characteristics: AMT is the dosage amount in milligrams, TFDS is the amount of time in

hours between each dose, TIME is the amount of time in hours from the start of the therapy, and CYCL is the number of the current dosing cycle. Additionally, the models have access to the first cycle of the observation, PK_cycle1, as a predictive feature. They attempted to forecast the PK dynamics after the first cycle, or after 168 hours for the Q1W data and after 504 hours for the Q3W data, using the information above. In total, 16,472 records of T-DM1 dosage and PK measurements from 675 individuals were included in the study (observations below the minimum measurable concentration were excluded from the analysis) (Lu et al., 2014). The information contained two different dose regimens: weekly dosing (Q1W, 28 individuals, 2,086 records overall), and three-weekly dosing (Q3W, 647 individuals, 14,385 records overall). The two categories have different dosage regimens, and the Q1W data has more measurements. points per patient, more dosing cycles, lower doses, and measurements were gathered over a longer period of time. Due to these variations, we were able to assess how effectively the models extrapolate data when tested on one kind of schedule and trained on another.

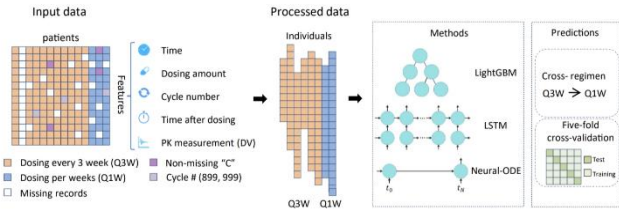


Fig. 4. Patients are treated every three weeks (Q3W) and once a week (Q1W) in T-DM1 studies. Time since the initial treatment beginning point, dosage, the number of treatment cycles, the interval since the last dose, and first cycle PK measurements are all input variables. The analysis did not include patient data that had been flagged with non-missing values in the "C" columns. The PK values in later cycles are the training objective.

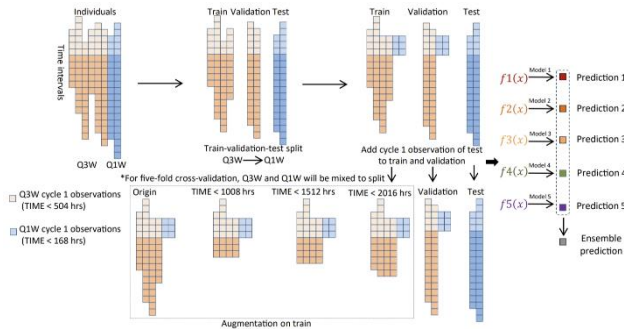


Fig. 5. Data from patients who had Q3W treatment are divided into training and validation sets, with the latter being utilized to retrieve the best epoch of the former in cross-regimen validation of LSTM and neural-ODE. Data from people who received Q1W treatment are utilized as the test set to gauge performance. Q1W and Q3W are blended to create the train, validation, and test sets in five-fold cross-validation. By truncating the observation time at various intervals, augmenting was applied to the training set. They trained five

models and split the train-validation set five times using various random seeds. The average of the five models serves as the final projection.

2) Model construction:

They created many machine learning models and the associated feature engineering techniques that could possibly forecast future PK dynamics and patient PK response. The following were chosen: LightGBM (Ke et al., 2017) (Figure 2A), LSTM (Figure 2B), and neural-ODE. The feature engineering and model development techniques they utilized to integrate PK challenges into the aforementioned base learners are discussed below.

At this time, TFDS, TIME, AMT, and CYCL are the fundamental properties used in the lightGBM models. In addition, they flattened the first dosing's timing and PK findings. Any observations of $TIME < 168$ are therefore included for Q1W, and any observations of $TIME < 504$ are included for Q3W. They iterated through the TIME and PK values from the first time point to the last time point during the first cycle, padding the vector with zeros to make it 20 elements long. Next, there is an additional set of TFDS, TIME, AMT, and CYCL values for the desired prediction of the present time point. Concatenating the 20-element-long vector and these four values resulted in 24 features as the input of lightGBM.

PK_cycle1, a feature copied from the PK observations, and TFDS, TIME, CYCL, AMT were incorporated as input features for the LSTM model. Values with $TIME \geq 504$ or 168 were replaced with 0 in the input features. Non-dosing times, or time periods without AMT, were filled with 0. A 2-layer LSTM architecture with 128 hidden units on each layer was then fed with the data. As stated in the lightGBM version, the outputs of the LSTM layers were concatenated with the 20-long flattened first dosage features made up of the PK observations and TIME. To produce the predictions, they were then fed into a fully connected layer with a linear activation. In the model training process, we masked off the time points without PK observation (i.e., dosing periods without PK records).

For both the neural ODE and LSTM models, the same data preprocessing was employed. The encoder (GRU unit), ODE solver, and decoder components of the neural-ODE model make up its general structure. The ODE solver solves the system throughout the time intervals between doses, and the decoder creates the predictions from the output of the ODE solver and the initial dosing data. The encoder encodes an initial state for the ODE solver. Following the neural-ODE official sample codes, a GRU layer with 128 hidden units scans the entire time series (5 channel input, TFDS, TIME, CYCL, AMT, and PK_cycle1, like in the LSTM model) backwards (that is, from the end to the beginning) during the encoding stage (Chen, 2018). The data is encoded in a length-12 array. The results are not affected by changing these numbers.

The 12-element array in the ODE solver output defines the mean and standard deviation of the latent state distributions in accordance with the variational autoencoder theory, where we sample the latent variables z_{t0} of the same size as the initial status for the ODE solver. The mean values are estimated using six of the 12-element arrays, while the variance is estimated using the remaining six elements. The Gaussian distribution resulting from this mean and standard deviation is used to generate z_{t0} (of dimension 6). The ODE solver functions combine the time interval and the dosage information starting at z_{t0} . To be more precise, if a dosage event occurs at time point t_{i-1} , we first add the dosing quantity to z_{t1} for each time point t_i that is being taken into account. Then, the ODE solver function—a four-layer, fully linked network with 16 hidden dimensions—is given both z_{t1} and the time gap between t_i and t_{i-1} , the preceding time point. The z_{ti} is returned to the subsequent time point as the ODE function's output. We produce a series of z_t from the aforementioned stages, which are then input into a decoder. The decoder has one fully connected layer and 32 hidden units, and it generates a series of predictions for each z_t .

The five channels TFDS, TIME, CYCL, AMT, and PK_cycle1 as well as the input of the first dosing PK observations and time in either the decoder section or the last layer of the LSTM network are shared by the models of LSTM and neural-ODE, as previously mentioned. An RNN layer serves as the encoder in Neural-ODE. The ODE solver in the neural-ODE model, which tackles uneven time sampling of the data, is the primary distinction between it and the LSTM model. In contrast to the other machine learning techniques discussed in this work, Neural-ODE directly adds dosage data into the model. These characteristics, which we will go over in more detail below, help neural-ODE perform well when evaluated with different treatment modalities.

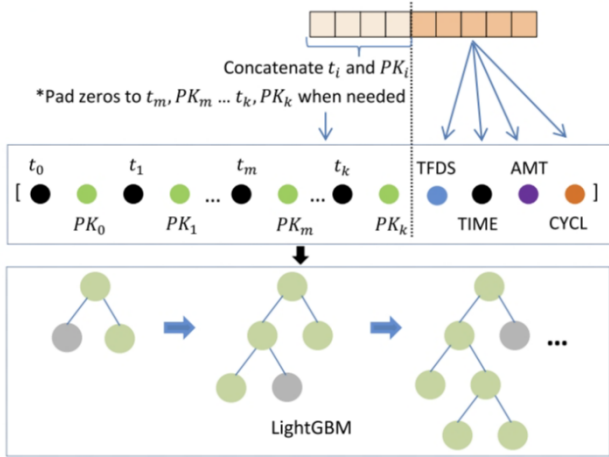


Fig. 6. First cycle time and PK information as well as the current data point TFDS, ATM, TIME, CYCL information as feature data.

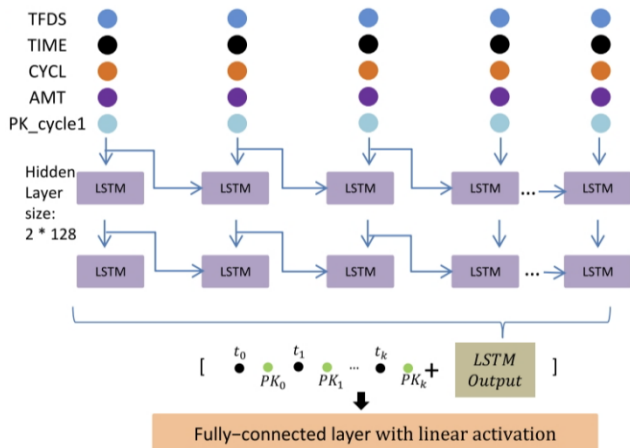


Fig. 7. In the LSTM model, TFDS, TIME, CYCL, AMT and PK cycle 1 observation padded with zero are input as five channels in the model.

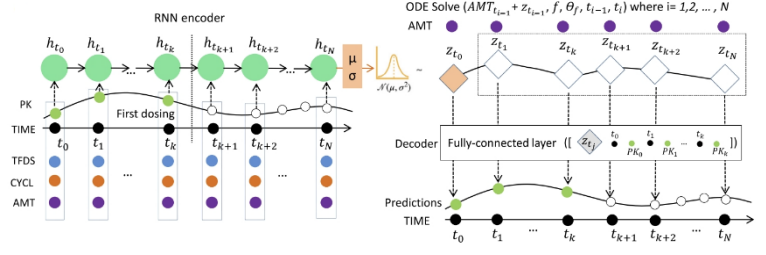


Fig. 8. Neural-ODE shares similarly with LSTM in the encoder part that TFDS, TIME, CYCL, AMT and PK cycle 1 observation are used as the input in the encoder part. Then ODE solvers are used to incorporate dosing information into the time sequence before the decoder generates the predictions..

III. PROSPECTIVE WORK

The target users or applications for drug cycle simulation enhanced by machine learning primarily include pharmaceutical researchers, drug developers, clinicians, and regulatory agencies involved in the development, evaluation, and approval of pharmaceutical products. Additionally, healthcare professionals aiming to provide personalized treatments based on a patient's unique pharmacokinetic and pharmacodynamic profiles are also part of the target audience. The needs, interests, and priorities of the target user or application determine the content and focus of the proposal. Different users may require varying levels of technical detail, emphasizing different aspects of the proposed solution. For example, a proposal aimed at a technical team might delve into the technical intricacies, while one for a non-technical audience would focus on high-level benefits and outcomes.

An example of application might come as follows. A more precise medicine can also be expected with the development of this technology. By combining cutting-edge technology and established medical research, precision medicine places an emphasis on the unique characteristics of each person and seeks to optimize the health benefits for both people and society. Additionally important facilitators for precision medicine are adaptable in-silico modeling and simulation techniques. For instance, PK modeling, a component of computational oncology, is now a trustworthy tool for developing individualized dosing regimens for cancer patients. A remarkable role in advancing precision medicine has also been played by machine learning-directed big data analytics in healthcare. The orientation toward desired delivery objectives is emphasized in the suggested computer-driven rational formulation design framework. The new framework represents a possible path towards more refined and even individualized pharmaceutical formulation creation when combined with cutting-edge drug manufacturing technologies like 3D printing of pharmaceuticals. It is acknowledged that the proposed framework must be implemented with more sophisticated computational modeling, which depends on the creation of specialized modeling platforms and specialized modeling tools.

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