

OBJECTIVES

- To evaluate a **hybrid PK modeling framework** that integrates neural networks with conventional compartmental models to learn **complex and unknown absorption dynamics** directly from data.
- To introduce and assess the **novel PK-NeuralDelay** model, which models absorption as a **neural-approximated delay kernel**, enabling flexible representation of multi-phase and delayed absorption.
- To compare the **predictive performance and flexibility** of PK-NeuralDelay and the standard PK-NeuralODE against a classical transit absorption model using simulated trimodal-release data.

INTRODUCTION

- Complex and delayed absorption remains a challenge for traditional PK models, especially in multi-phase formulations. [1]
- Classical models such as lag-time, transit, or parallel absorption paths, rely on predefined structures, limiting their ability to capture unknown or variable absorption kinetics.
- Neural-based models provide a flexible, data-driven alternative by learning the absorption process directly from observed PK data, while retaining interpretability.
- This is particularly useful for multi-phasic oral formulations, long-acting injectables, and RNA-based therapeutics, where absorption is often poorly characterized.

METHODS

Simulated Dataset

- PK profiles from 100 virtual subjects receiving a daily oral trimodal-release formulation (*Fig. 1*).
- Sampling on Day 1 and Day 4 at: 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24-hours post-dose.
- Profiles featured three distinct absorption peaks:
 - Immediate release (~35% of dose),
 - Sustained release (~3–4 h),
 - Delayed release (~7–8 h).

Model Framework

- All models were implemented in DeepPumas (v0.8.0). [2, 3]
- Distribution and elimination were described using a classical one-compartment model with linear clearance.

Model structure:

$$\frac{dCentral}{dt} = Absorption - \frac{CL}{V} \cdot Central$$

Evaluated absorption models were:

- Transit3**: model using 3 transit compartments with estimated mean absorption time (*Eq. 1*).

$$\text{Equation.1} \quad ktr = \frac{n}{\text{mean absorption time}} \text{ and } Absorption = ktr \cdot T_n$$

- PK-NeuralODE**: Absorption modeled as a neural network function (*Eq. 2*) trained directly on data.[4]

$$\text{Equation.2} \quad ka = \text{NN}(t - t_{\text{last dose}}, \eta) \text{ and } Absorption = ka$$

- PK-NeuralDelay**: Dissolution and absorption modeled as a convolution between drug administration and a neural-approximated delay kernel – similar to a distributed delay. (*Eq. 3*).

$$\text{Equation.3} \quad A_{i,k}(t; \eta) = \begin{cases} 0 & \text{if } t < t_{i,k} \\ \int_0^{t-t_{i,k}} u(\tau) \cdot k(t-t_{i,k}-\tau; \eta) d\tau & \text{if } t \geq t_{i,k} \end{cases}$$
$$Absorption = A(t; \eta) = \sum_k A_{i,k}(t; \eta)$$
$$\frac{dCentral}{dt} = A(t; \eta) - \frac{CL}{V} \cdot Central$$

where, $A_{i,k}(t)$ is the absorbed drug amount of the k -th dosing event, administered at time $t_{i,k}$, of patient i at time t . $u(\tau)$ is the dosing input, and $k(t; \eta)$ is a flexible transfer function $[NN(t, \eta)]$ that varies with time and individual-specific random effects η .

Note: PK-NeuralDelay is not currently an inbuilt function in DeepPumas, but it is planned for inclusion in an upcoming release of the toolkit.

Model Training and Validation

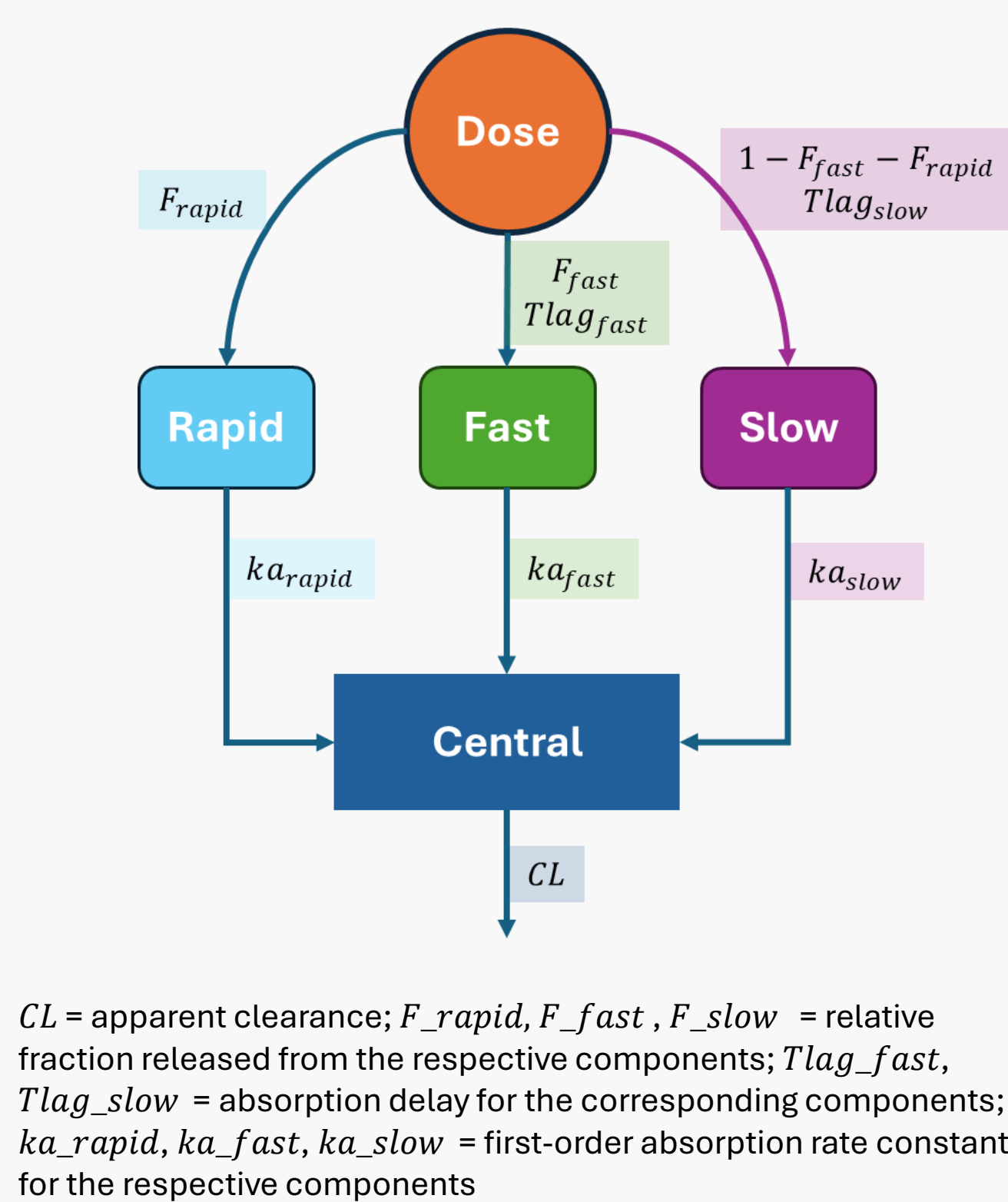
- 80 subjects used for model fitting; 20 subjects held out for validation.
- All models were assessed on:
 - Relative Error $[= \frac{(metric - truevalue)}{truevalue}]$: $AUC_{0-\text{last}}$, C_{max}
 - Marginal likelihood (model evidence).

RESULTS

Model Fit and Predictive Accuracy

- All three models—Transit3, PK-NeuralODE, and PK-NeuralDelay—were successfully fitted to the simulated trimodal absorption PK data using DeepPumas.
- Neural-based models outperformed the classical transit model in capturing the distinct immediate, sustained, and delayed absorption phases.
- PK-NeuralODE showed the best performance in estimating $AUC_{0-\text{last}}$, with the lowest bias and variance.
- PK-NeuralDelay was superior in predicting C_{max} , and achieved the highest marginal likelihood, indicating best overall model evidence.

Figure 1: A structural representation of the PK model used for simulations.



CONCLUSIONS

- Neural-based models** provide a flexible and interpretable **framework for capturing complex drug absorption patterns** without relying on predefined structures.
- This work introduces the novel **PK-NeuralDelay** model, which **outperformed** both a classical transit model and a prior neural approach in capturing trimodal-release kinetics.
- PK-NeuralDelay enables the model to **flexibly learn any combination of sequential, parallel, or delayed absorption processes**—in a single fit—offering a powerful step toward **automated absorption modeling**.
- This approach has the potential to reduce modeling time, increase predictive performance, and support more robust PK/PD analyses, especially for challenging formulations (e.g., LAIs, RNA-based, pulsatile oral forms).

RESULTS

Quantitative Evaluation

As shown in Table 1, the neural models delivered notable improvements over Transit3:

- $AUC_{0-\text{last}}$ bias reduced from +5.73% (Transit3) to -0.29% (NeuralODE),
- C_{max} bias improved from -12.4% (Transit3) to +2.21% (NeuralDelay),
- PK-NeuralDelay showed the highest marginal likelihood (-1575 vs. -1771 for Transit3).

Table 1. Summary of model performance across $AUC_{0-\text{last}}$, C_{max} , and marginal likelihood.

Model	$AUC_{0-\text{last}}$		C_{max}		Marginal Likelihood
	Relative Error (%)	Variance (CV %)	Relative Error (%)	Variance (CV %)	
Transit3	+5.73	25.4	-12.4	25.8	-1771
PK-NeuralODE	-0.29	26.5	+9.0	27.8	-1723
PK-NeuralDelay	0.88	21.9	+2.21	28.7	-1575

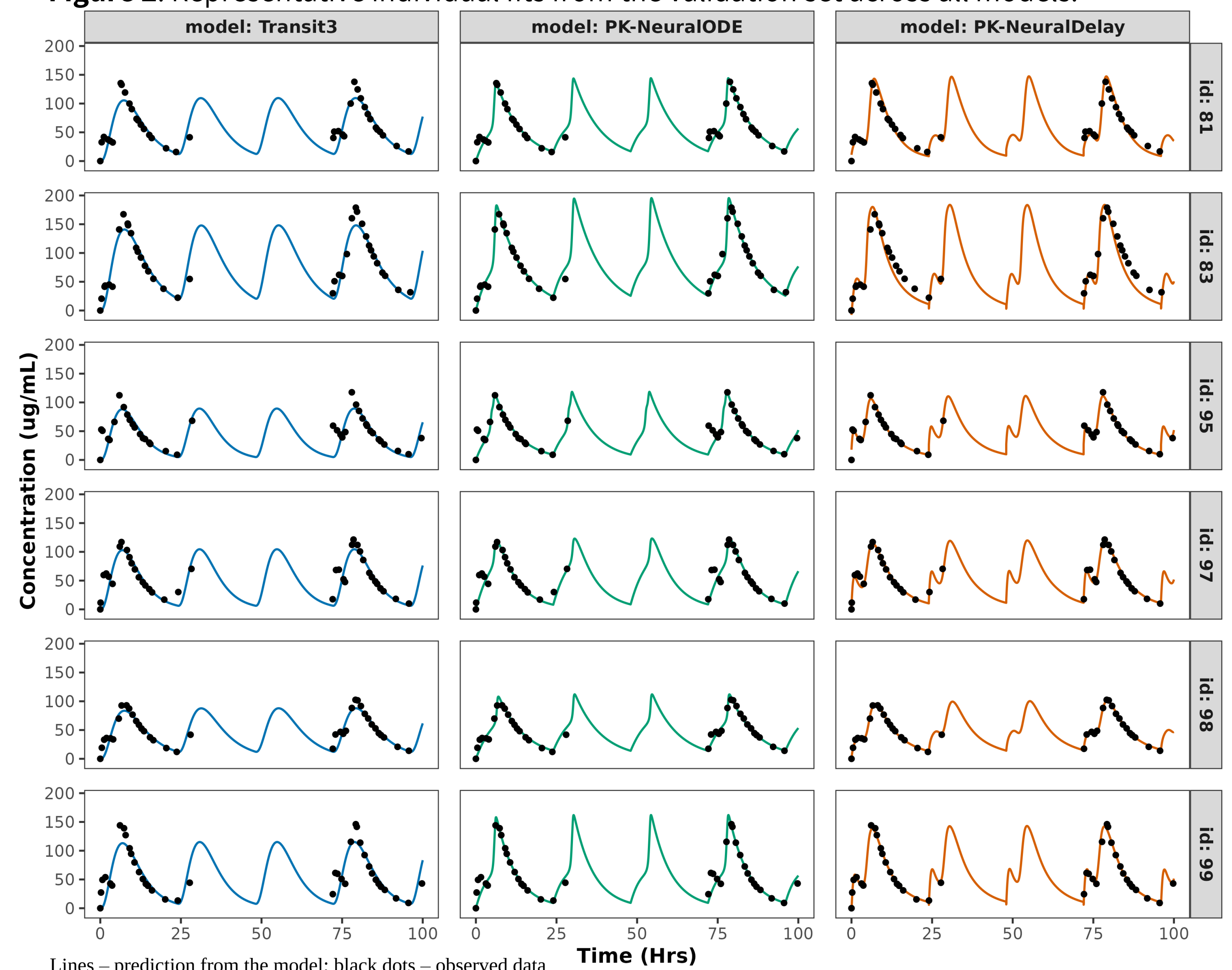
AUC – area under concentration curve; C_{max} – maximum concentration; CV – coefficient of variation.

Visual Model Fit Comparison

Figure 2 compare observed and predicted PK profiles across representative individuals:

- The Transit3 model struggled to capture multiple peaks reliably.
- PK-NeuralODE better aligned, particularly in elimination phases.
- PK-NeuralDelay demonstrated the most consistent fit across all timepoints and subjects.

Figure 2: Representative individual fits from the validation set across all models.



Lines – prediction from the model; black dots – observed data

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