

Application of a neural-ODE framework to support dose escalation decision during safety review meetings in first-in-human clinical trial

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Introduction

- First in human (FIH) clinical trials aim to study the human pharmacology, tolerability and safety of an investigational medicinal product (IMP). The highest priority of the FIH trial conduct is the safety and well-being of the recruited subjects [1]:
- ▶ The FIH trial design consists commonly of a single (SAD) - and multiple (MAD) ascending dose part.
 - ▶ Dose decisions are carefully taken to assess and evaluate the potential risk for the subjects to be treated.
 - ▶ Although the further dose escalation steps are pre-defined, clinical data from previous cohorts have to be taken into account for the dose decision of the following cohort [1]. In general these decisions are informed by predictions obtained from pharmacokinetic (PK) models constructed using all available PK information.
 - ▶ PK models based on deep learning approach using neural ordinary differential equations (ODE) have been successfully developed:
 - ▶ To predict untested treatment regimens [2].
 - ▶ To learn an unknown absorption process, while simultaneously estimating other PK parameters such as drug distribution and elimination [3].

Methods

- A population PK model was used to simulate a SAD dataset and to test the performance of two neural-ODE models.
- ▶ Simulated PK data-set.
 - ▶ PK model: zero and first order absorption, 2 compartment and first order elimination
 - ▶ 9 cohorts (10 subjects each) with different doses (5, 10, 20, 30, 45, 60, 75, 90 & 110 mg)
 - ▶ PK sampling scheme: 0.3, 0.5, 1.0, 1.5, 2.0, 4.0, 6.0, 8.0, 12.0, 14.0, 24.0 & 36.0 h.
 - ▶ Neural ODE model
 - ▶ Lu et. al. 2021 [2]
 - ▶ Hyperparameter settings: $lr=0.001$, epochs=75
 - ▶ Valderrama et. al. 2024 [3]
 - ▶ One compartment model structure
 - ▶ Absorption and clearance learned by neuronal network
 - ▶ Volume of distribution estimated
 - ▶ Hyperparameter settings: $lr=0.01$, epochs=350
 - ▶ Training data-set consisted of all lower dose levels (starting with lowest dose 5 mg)
 - ▶ Test data-set consisted of one or two higher dose levels as used for training data-set.
 - ▶ Prediction quality was evaluated by goodness-of-fit estimates such as graphical display and r^2 score.
 - ▶ Calculated PK parameter - $AUC_{t=0-24h}$ and C_{max}
 - ▶ Prediction error was estimated on calculated PK parameter

Literature

- 1 Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (europa.eu). https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-and-mitigate-risks-first-human-and-early-clinical-trials-investigational-medicinal-products-revision-1_en.pdf last accessed 16. Feb 2024
- 2 Lu J. et. al. iScience. 2021;24:102804.
- 3 Valderrama D. et.al. CPT Pharmacometrics Syst Pharmacol 2024

Conclusions

- The neural-ODE framework seems to be a promising tool:
- ▶ To support dose escalation decisions during safety review meetings of FIH trials.
 - ▶ To accurately estimate the exposure of higher dose levels.
 - ▶ Lu et. al.
 - ▶ It seems that at least data from 2 different cohorts are needed to make more robust predictions.
 - ▶ The first and second dose cohort seems to be sufficient for a training dataset to predict profile of the next unknown dose level.
 - ▶ Performed better as the training dataset is increasing.
 - ▶ For this studied used case, the Lu et. al. approach performed better than the Valderrama et. al. approach.
- However this approach has yet to be explored with more complex PK profiles and network optimization procedures.

Results - Model Prediction

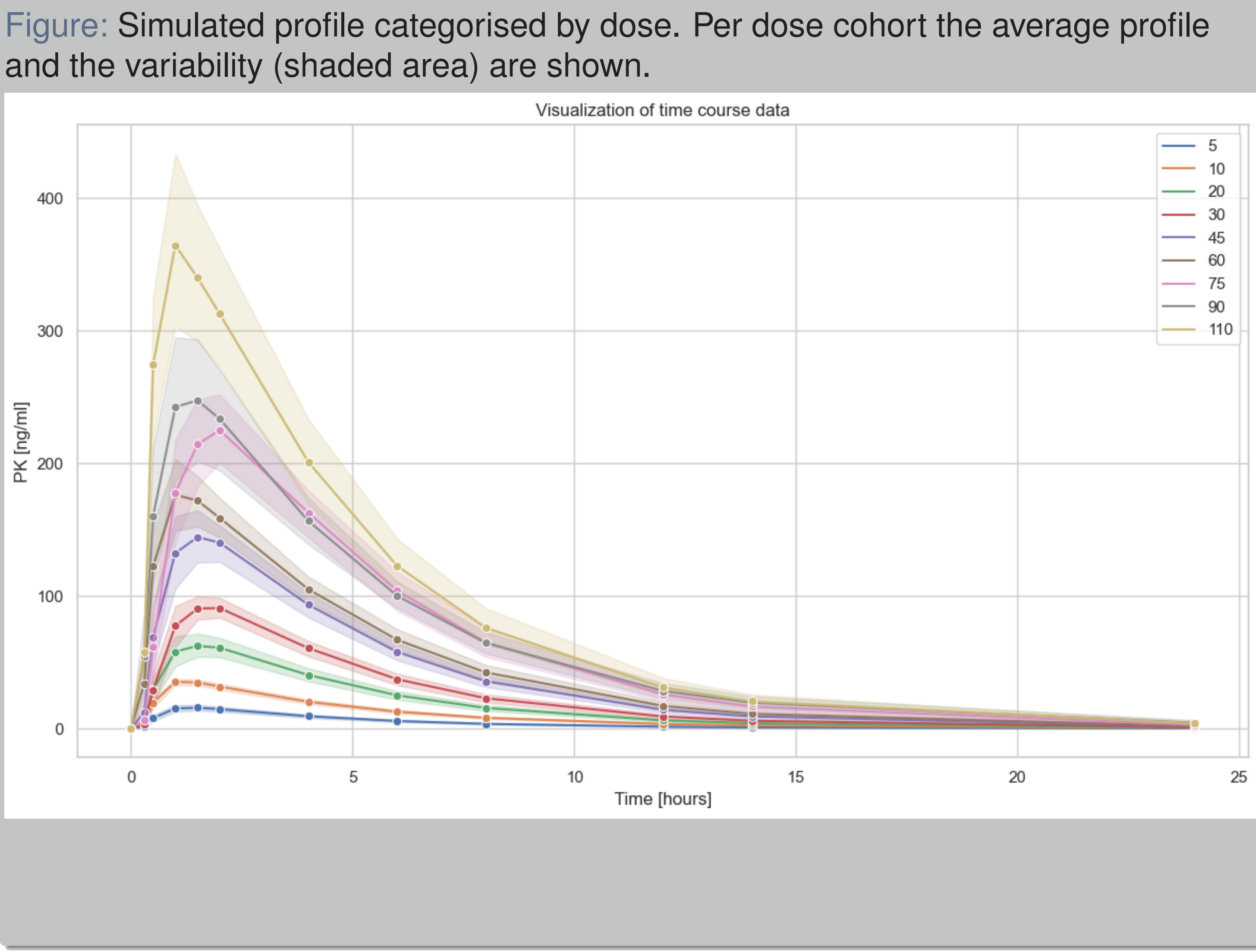
- ▶ Lu et. al.
 - ▶ The resulting r^2 score increased with increasing size of the training dataset
 - ▶ The prediction error of AUC and C_{max} decreased with increasing size of the training set.
 - ▶ The prediction error of AUC and C_{max} ranged between 4 and 57 %.
 - ▶ After the second cohort the prediction of the profile of the next higher dose was reasonably accurate.
- ▶ Valderrama et. al.
 - ▶ The resulting r^2 score seemed to be independent from the size of the training dataset.
 - ▶ The prediction error of AUC and C_{max} ranged between 18 and 56 %.

Validation dataset dose cohort [mg]	Training dataset dose [mg]	No. subjects		Lu et. al.			Valderrama et. al.		
		training	validation	r^2 -score	AUC	C_{max}	r^2 -score	AUC	C_{max}
110	≤ 90	80	10	0.95	5	4	0.63	54	24
90 & 110	≤ 75	70	20	0.84	10	6	0.63	34	56
75 & 90	≤ 60	60	20	0.86	19	11	0.63	34	22
60 & 75	≤ 45	50	20	0.92	14	8	0.68	48	26
45 & 60	≤ 30	40	20	0.84	6	11	0.71	30	23
30 & 45	≤ 20	30	20	0.64	17	14	0.71	32	20
20 & 30	≤ 10	20	20	0.82	22	10	0.67	38	26
10 & 20	≤ 5	10	20	0.45	57	23	0.69	18	22

Table: Quantitative assessment of the degree of goodness-of-fit of the validation dataset. The average prediction error ($100 \times \frac{|\text{observed} - \text{predicted}|}{\text{observed}}$) refers to the next higher unknown dose.

Data

- ▶ The data was split into a training and validation dataset
- ▶ Validation data-set comprised the data of up to two unknown (higher) dose levels.
- ▶ The training dataset consisted at least of the 5 mg dose cohort and increased step wise.



Objectives

Develop a neural-ODE framework to support dose escalation decision in FIH trials and to evaluate the minimal required PK information for model development to accurately predict PK profile of next doses.

Results - Goodness of Fit

Table: Goodness-of-fit plots based on training dataset dose ≤ 20 mg. Predicted dose: 30 and 45 mg

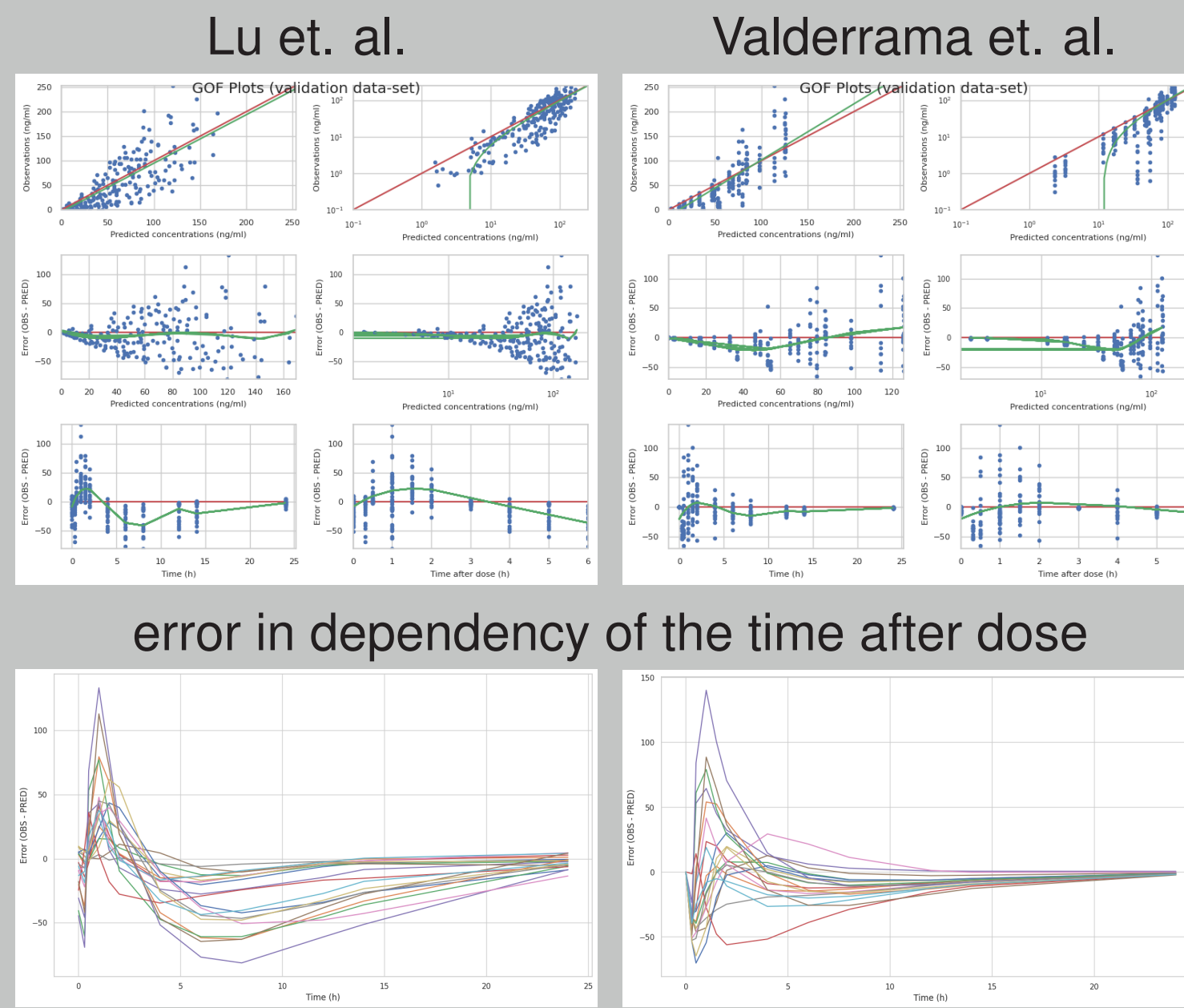
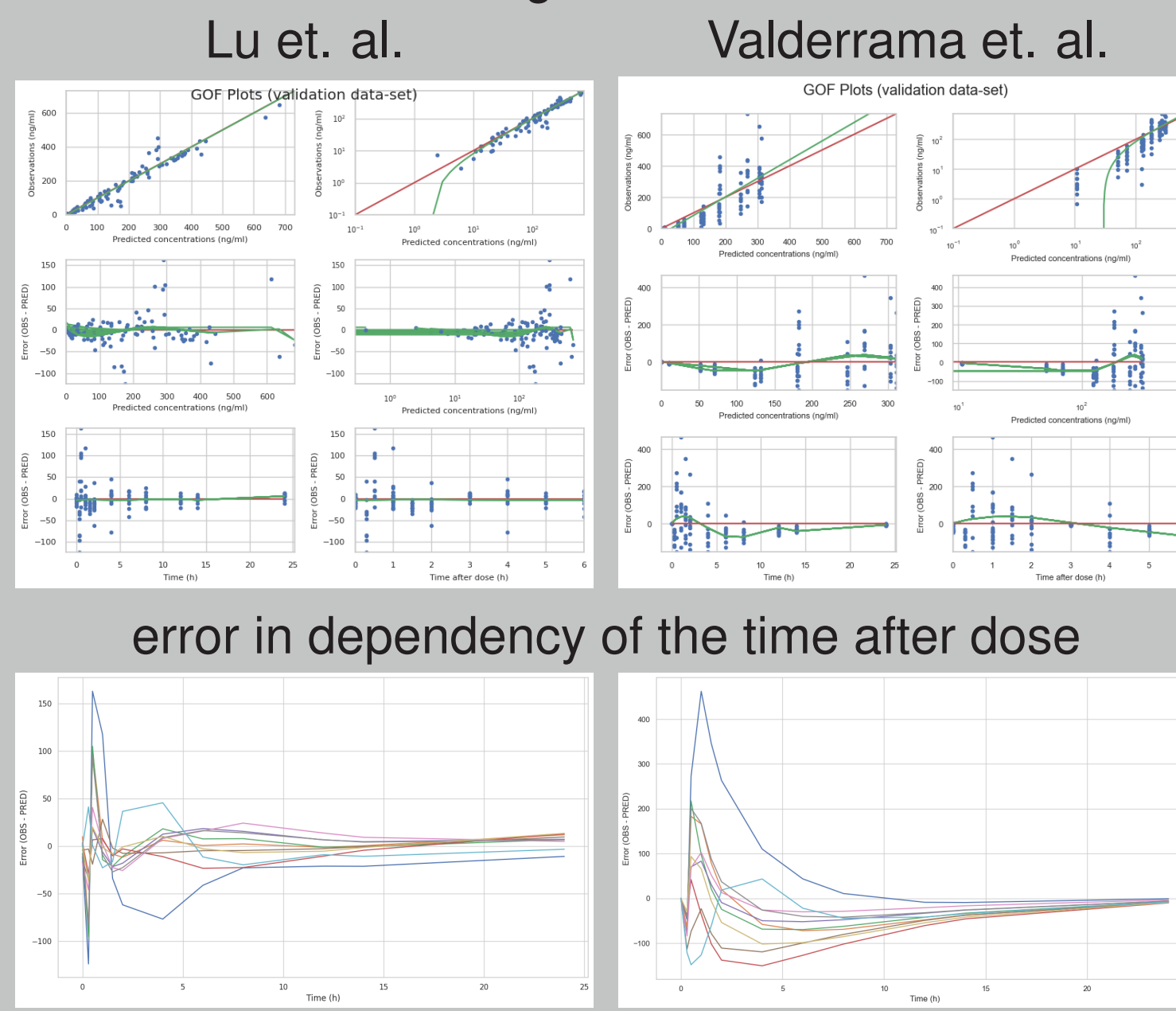


Table: Goodness-of-fit plots based on training dataset dose ≤ 90 mg. Predicted dose: 110 mg



Results - Predicted profile

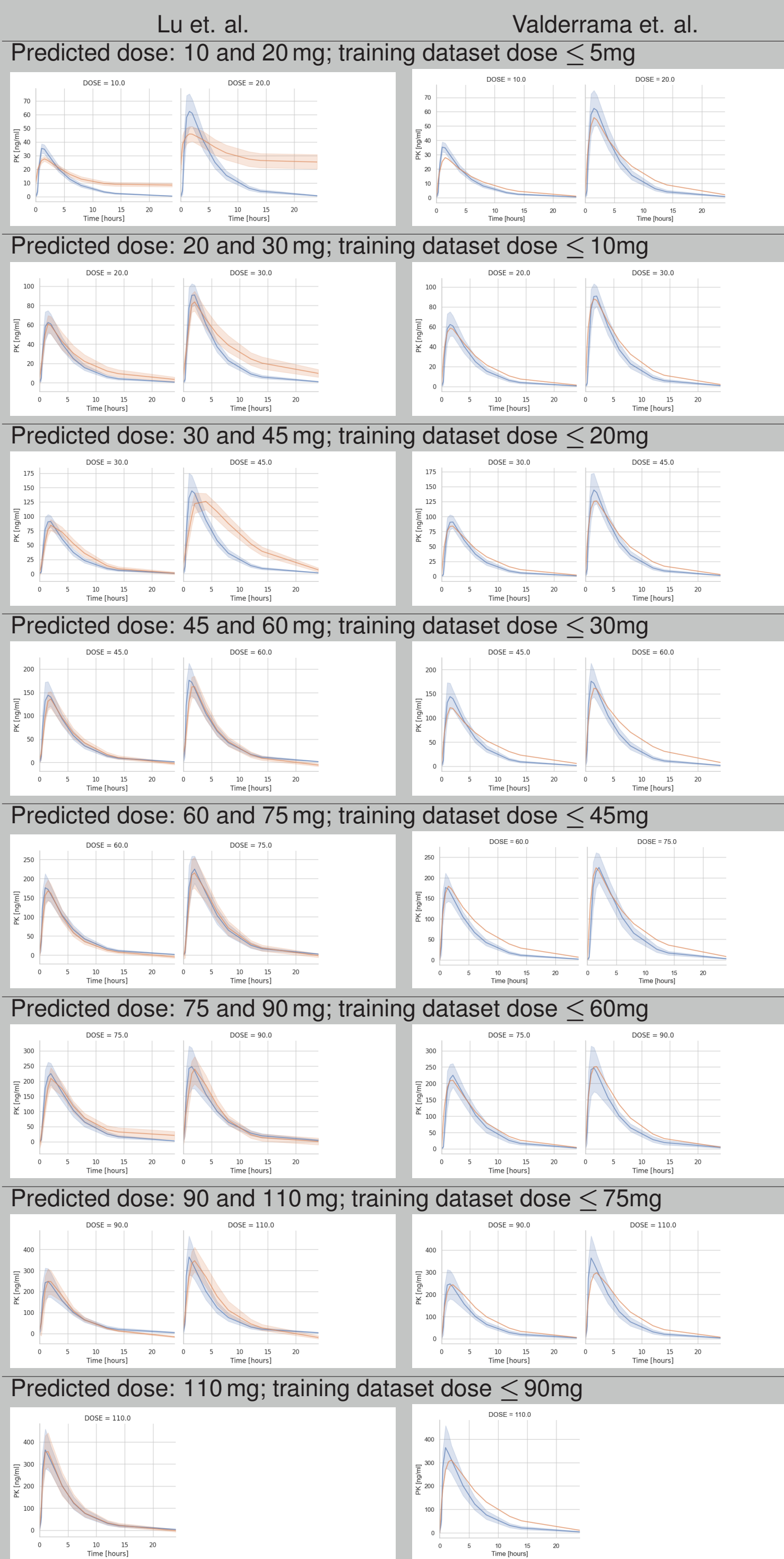


Table: Predicted profile (observed: blue, predicted: red).