



Explainable covariate screening method using Artificial Neural Network (ANN) for Non-linear Mixed Effect Modeling

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Objectives

As the fast growing of deep learning methodologies, there has been various attempt to incorporate deep learning method into pharmacometrics. Nevertheless, it is still difficult to use the deep learning library into the NLME model library at the same time in the Python circumstance, because of language differences. To overcome those limitation, we developed a non-linear mixed model library based on pytorch and efficient covariate screening method using an artificial neural network(ANN).

Methods

The NLME model could be implemented with ANN, since linear algebra operated in both of them. The Objective function valeues (OFV) was not only calculated by referring to the paper of Bae and Yim, 2016, but the prediction function was also conducted using the symbolic math library, 'sympy'. In addition, 'torchdiffeq' was used as a module for solving Ordinary differential equation (ODE) what it was based on Runge–Kutta methods and Dormand–Prince methods. and Limited-memory- Broyden–Fletcher–Goldfarb–Shanno algorithm was conducted as well for optimization algorithm. Theophylline dataset and PK base model, reported by Boeckmann, Sheiner, and Beal, n.d., was evaluated for verification of the developed library.

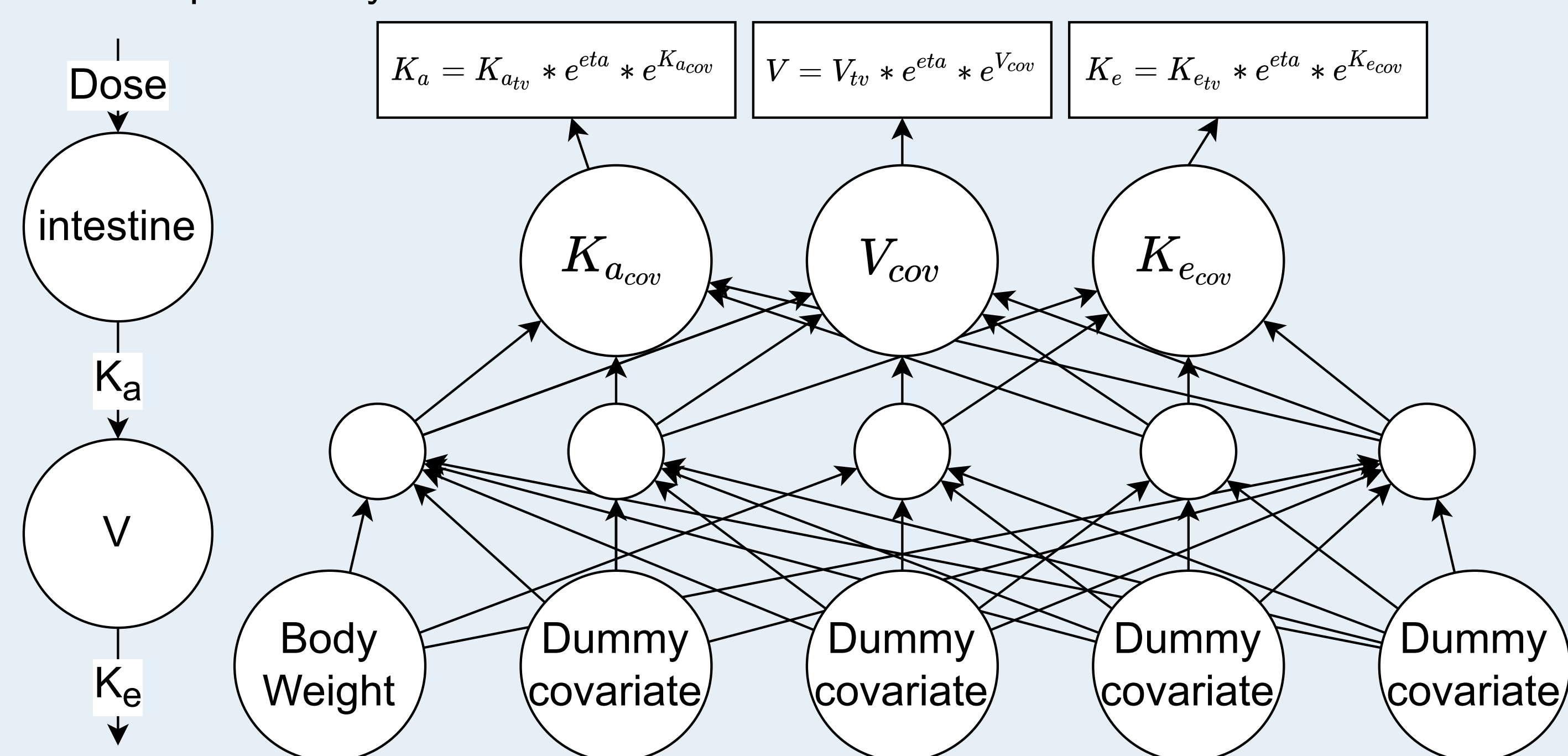


Figure 1. PK model and Artificial Neural Network of between covariates and pharmacokinetic parameters

Then, covariate screening method using ANN was attempted to estimate the relationship among covariates and PK parameters (Ka; absorption rate constant, Kel; elimination rate constant, and Vd: volume of distribution). The real covariate (Body weight, BWT) and dummy covariates having with or without relationship on BWT were tested as the covariates. Covariate screening was performed 100 times with randomly generated 100 datasets and counted the number of covariate selection.

ID	TIME	DV	...	BWT_Norm	fixed	rand-1+1	norm(0,1)	BWT_Cor.0.1	BWT_Cor.0.5
1	0	0	...	1.097082451	0	-0.415372719	-1.563662728	1.451803997	1.197082451
1	0	0.74	...	1.097082451	0	-0.415372719	-1.563662728	1.451803997	1.197082451
1	0.25	2.84	...	1.097082451	0	-0.415372719	-1.563662728	1.451803997	1.197082451

Table 1. Theophylline Data added columns

Results

It was confirmed that the NLME model implemented in the PyTorch environment showed similar performance compared to NONMEM. (Ex., difference of OFV and PK parameters < 3%) The results of the VPC using the PyTorch NLME model and NONMEM looks similar as well. For the covariate screening method using ANN, the BWT was not only selected, similar to the results of the original model using the existing NONMEM, but it also was confirmed that dummy covariates having a correlation with BWT were also selected depending on the correlation of BWT. And covariate searching was attempted as a backward elimination method using ANN. (Counts for selected covariates in 100 times covariate searching. 'covariate name': counts for selection / 'BWT_Norm': 82 / 'BWT_Cor.0.5(dummy covariates having correlation 0.5 with BWT)': 71 / 'BWT_Cor.0.1(dummy covariates having correlation 0.1 with BWT)': 63 / 'rand-1+1(random number between -1 and 1)': 62 / 'norm(0,1)(random variables of standard normal distribution': 55 / 'fixed(zero numbers)': 0) NLME model optimization was performed using torchpm. And for each ID, simulation was performed 300 times to draw a graph. The graph was plotted by displaying the 5 percentile, median, mean, and 95 percentile.

ANN Covarivates Searching Results

loss	removed covariates	loss difference	> 3.84	selection
69.53		0		
80.76	BWT_Norm	11.23	True	selected
69.53		-11.23		
69.49	fixed	-0.0357	False	removed
72.25	fixed,rand-1+1	2.76	False	removed
77.00	fixed,rand-1+1,norm(0,1)	4.75	True	selected
72.25	fixed,rand-1+1	-4.75		
75.54	fixed,rand-1+1,BWT_Cor.0.1	3.29	False	removed
79.52	fixed,rand-1+1,BWT_Cor.0.1,BWT_Cor.0.5	3.99	True	selected
75.54	fixed,rand-1+1,BWT_Cor.0.1	-3.99		

Table 2. Covariate searching history using ANN

Removed Covariates: 'fixed', 'rand-1+1', 'BWT_Cor.0.1'
Selected Covariates: 'BWT_Norm', 'norm(0,1)', 'BWT_Cor.0.5'
You can run it in Google Colab.(<https://bit.ly/3uHwSBZ>)



Counts for selected covariate in 100 times covariate searching
'BWT_Norm': 82 / 'BWT_Cor.0.5': 71 / 'BWT_Cor.0.1': 63 / 'rand-1+1': 62 / 'norm(0,1)': 55 / 'fixed': 0

torchpm Execution Results

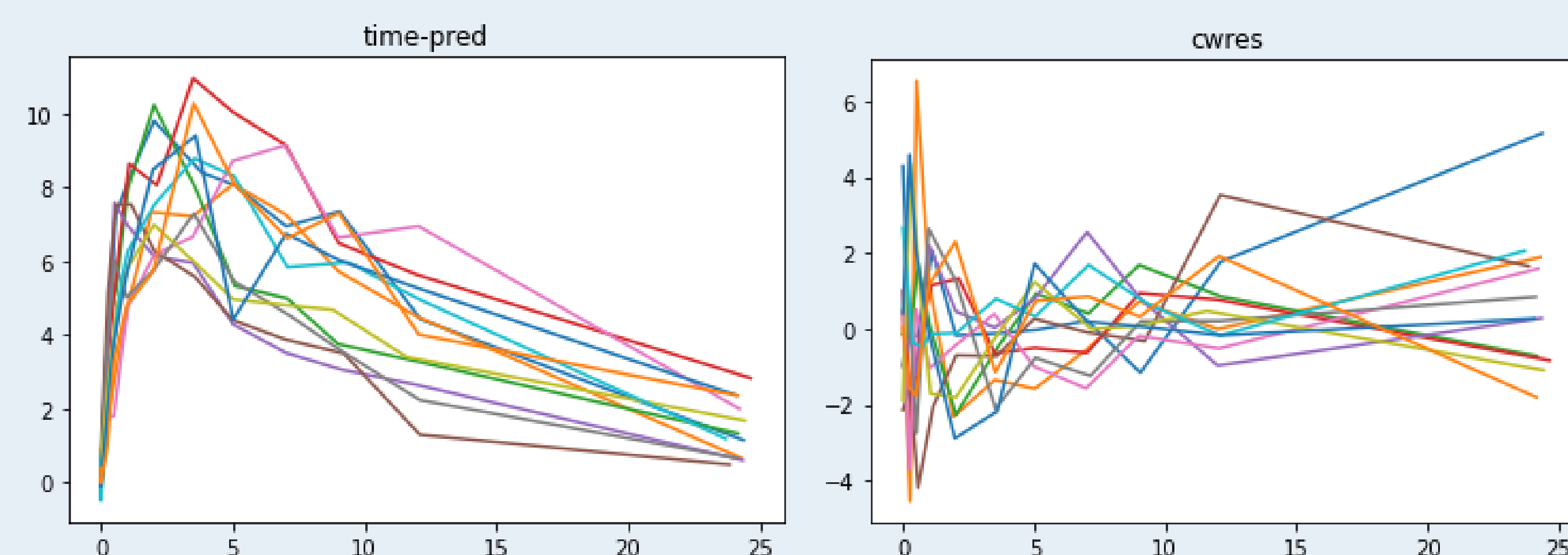


Figure 2. Theophylline Data Optimization Result, time-pred, time-cwres

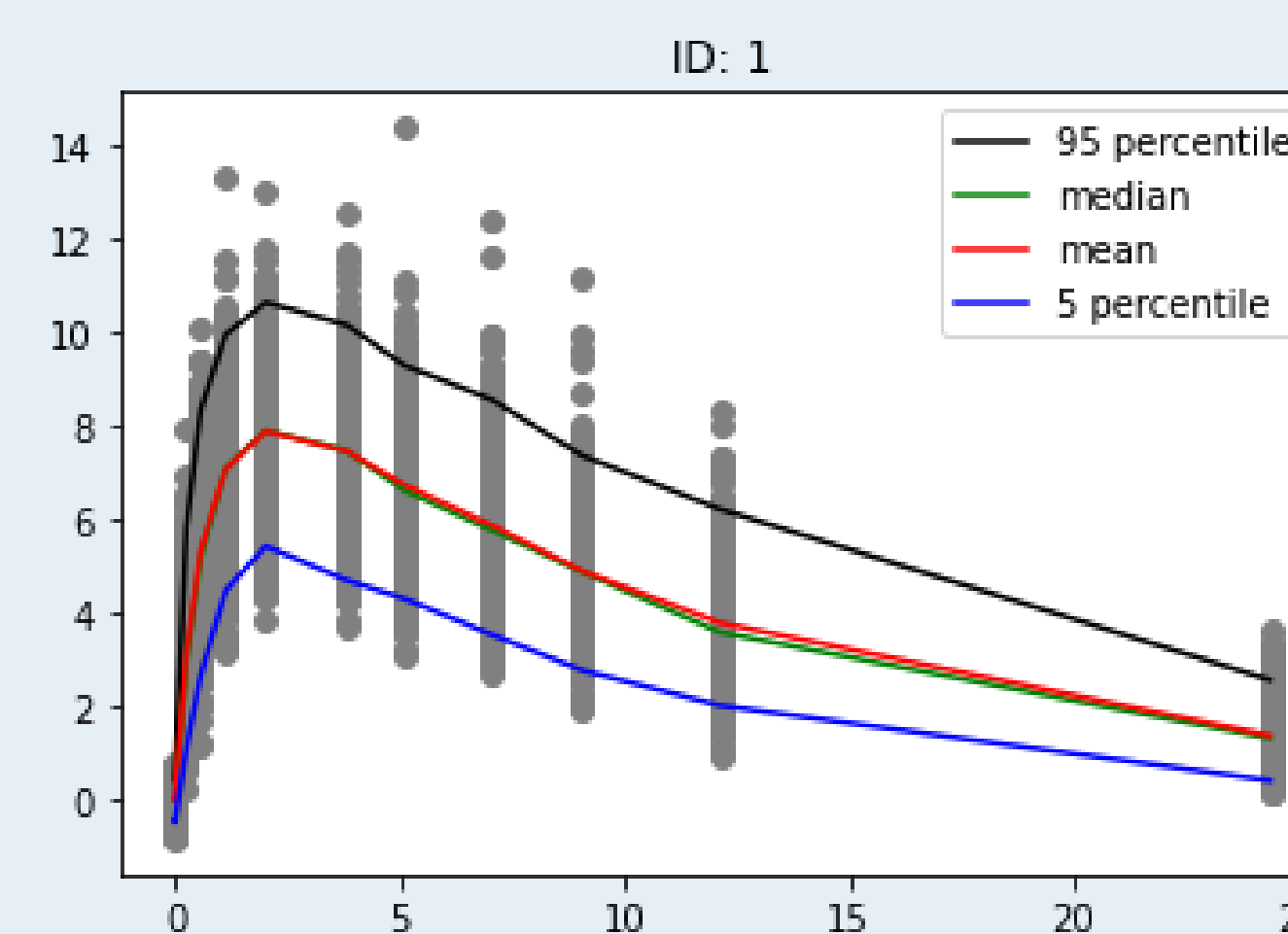


Figure 3. PK Simulation Results and Google Colab Code Example QR(<https://bit.ly/3NvS1YF>)

Parameter	Ka	V	Ke	Omega		Sigma	
value	1.405	32.176	0.087	0.440		0.018	
				0.058	0.020		0.076
				0.007	0.013	0.020	

Table 3. Theophylline Data Optimized Parameters

Conclusions

NLME model was successfully developed by implementation in the PyTorch environment and efficient covariate screening method using ANN in PyTorch was well conducted. Considering the cons of traditional covariate searching methods like stepwise covariate model(SCM), this methods could be used for alternative method for replace traditional covariate screening method for its strength on less time consuming and high performance even correlated covariates. In addition, it might contribute to the integration of deep learning into pharmacometrics. The entire code is shared on github. (<https://github.com/yeoun9/torchpm>) Those who are interested, please contribute to the code.

References

- Bae, Kyun-Seop and Dong-Seok Yim (2016). "R-based reproduction of the estimation process hidden behind NONMEM® Part 2: First-order conditional estimation". In: *Translational and Clinical Pharmacology* 24.4, pp. 161–168.
- Boeckmann, Alison J, Lewis B Sheiner, and Stuart L Beal (n.d.). *NONMEM users guide: Part V*.

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