Application of DeepNLME Framework to Characterize Distinct Platelet Dynamics in Patients Treated with Milademetan

Daiichi-Sankyo

Masato Fukae, PhD[1], Mohamed Tarek, PhD[2], Kazutaka Yoshihara, PhD[1]
[1]Daiichi Sankyo Co., Ltd., Tokyo, Japan, [2]PumasAI Inc., DE, USA

PumasAI

Objectives

Thrombocytopenia is one of the most common adverse events in oncology drug development, which is often a dose-limiting factor and determines dosing regimens. A longitudinal pharmacokinetic/pharmacodynamic (PK/PD) analysis using a nonlinear mixed-effects (NLME) model has played an integral role in modeling platelet count based on the mechanistic understanding of chemotherapy-induced myelosuppression. However, not every aspect of myelosuppression is fully understood, and uncommon platelet dynamics in which a typical longitudinal PK/PD model fails to capture the time course are frequently observed. In such a case, a novel hybrid methodology, scientific machine learning (SciML) using the DeepNLME technique, which combines mechanistic modeling, machine learning, and statistical modeling, is expected to adequately predict dynamics without compromising the mechanistic and individualizable nature of NLME models [1].

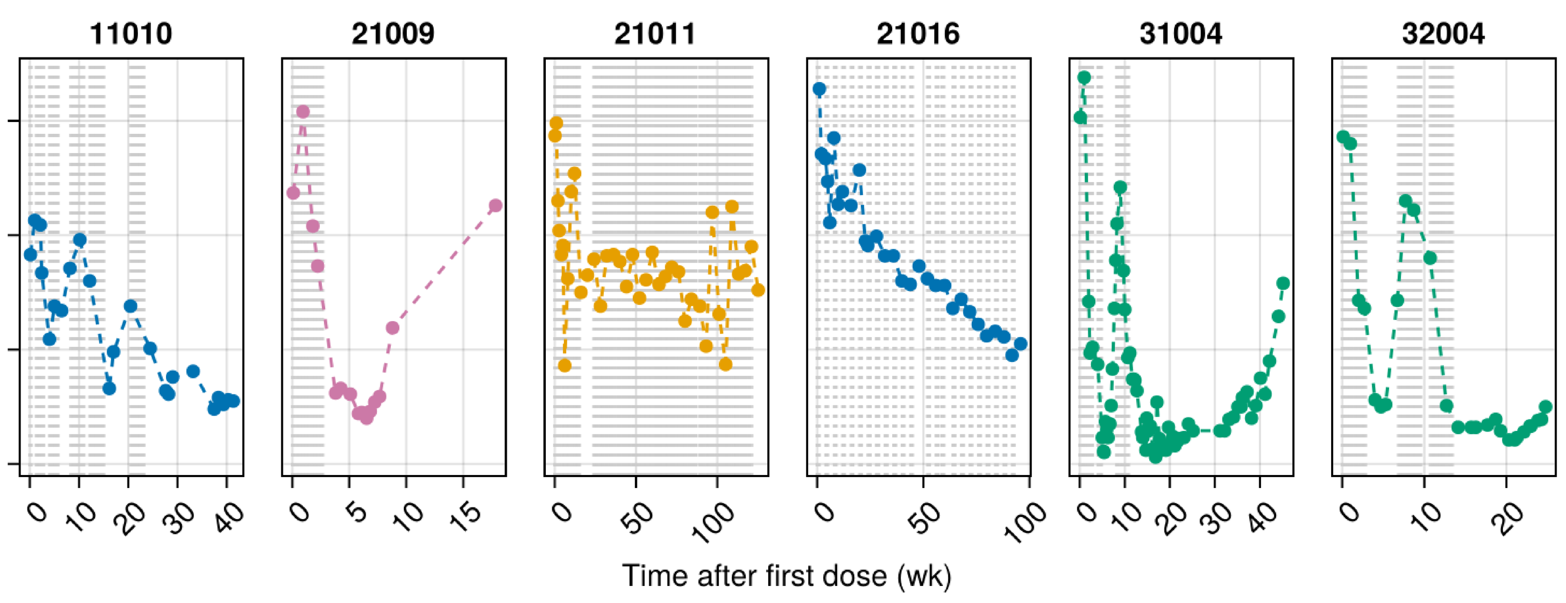
Milademetan is a selective small-molecule inhibitor of the murine double minute-2 and has been developed for advanced solid tumors or lymphoma. Milademetan induces thrombocytopenia with uncommon platelet profiles, which led to an intermittent dosing schedule of 3/14 in a phase 3 trial after various dosing regimens were tested in a phase 1 study [2]. In the present study, the DeepNLME-based SciML approach was applied to predict platelet dynamics under milademetan treatment.

Methods

Dataset

The dataset included two studies, a first-in-human (FIH) study mainly in the US and a subsequent phase 1 study in Japan, and was split into training (the FIH study, N=102) and validation (the Japan study, N=18) sets to assess generalizability. The data split was taken according the actual chronological order of these studies. The three-way split into training, validation, and test sets was not conducted because the dataset was relatively small. Some patients showed distinct platelet profile consisting of various types that could suggest milademetan altered the feedback with unknown mechanisms as shown in **Figure 1**: 1) typical platelet dynamics (ID: 21009), 2) gradually decreasing (IDs: 11010, 21016), 3) recovered once but not again (IDs: 31004, 32004), and 4) random fluctuation (ID: 21011).

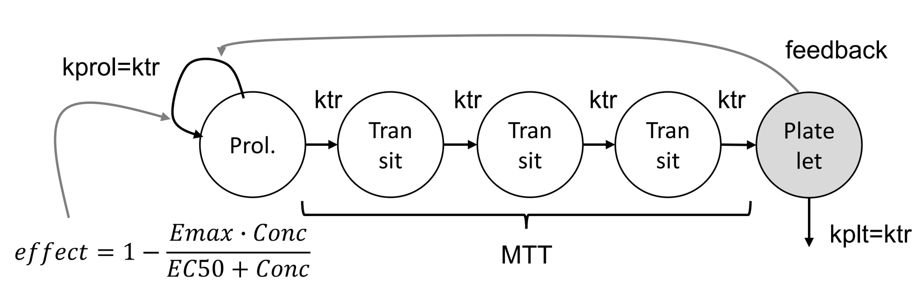
Figure 1 Platelet dynamics of six selected patients from the training set



Modeling

The training set was used to develop a model and estimate its parameters using both the standard NLME and the DeepNLME approach. The myelosuppression model was used as the NLME with a slight time-dependent modification added to the feedback parameter [3]. For the DeepNLME approach, the feedback parameter was replaced by a neural network (NN) that used the ratio of platelet count over time to baseline, treatment duration, and a random effect (i.e., between-subject variability) as input variables, while everything else remained the same as in the NLME (**Figure 2**). The NN comprised two hidden layers with 4 nodes each and with the hyperbolic tangent as activation functions, and an output layer with the softplus as an activation function. No regularization was applied, but early stopping was used to control overfitting.

Figure 2 Schematic representation of the NLME and DeepNLME models for platelet dynamics



NLME

$$feedback = \left(\frac{plt_0}{plt_t}\right)^{\gamma(1-fracfbss \cdot exp(-kfb \cdot t))}$$

DeepNLME

$$feedback = NN\left({}^{plt_t}/_{plt_0}, t, \eta_{nn}\right)$$

Performance metrics

Model performance was assessed primarily using the validation set, with numerical measures such as the -2x log-likelihood (LL) and visual diagnostics. Finally, the models were interpreted by investigating the time course of each variable and conducting a Shapley Additive exPlanations (SHAP) analysis.

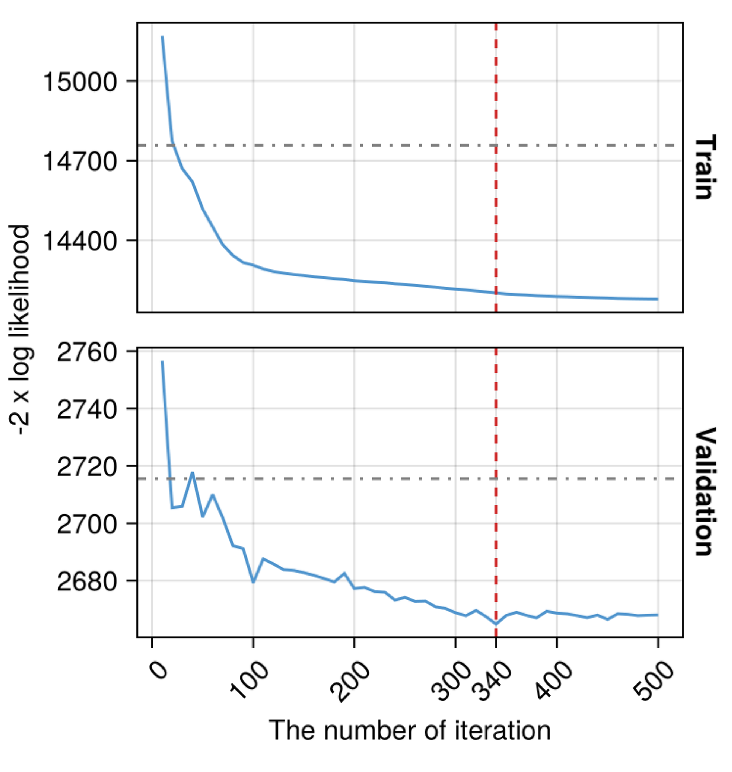
Estimation method and software

The first-order conditional estimation method was used for parameter estimation. Julia v1.10.8 and DeepPumas v0.8.1 were used throughout the analysis.

Results

The dose levels in the training set ranged more widely than in the validation set (15 to 340 mg vs. 60 to 120 mg), suggesting that prediction for the validation set is likely to be feasible. The performance of NLME and DeepNLME was compared on the validation set, and DeepNLME outperformed, with an improvement in the -2xLL by approximately 51 (**Figure 3**). Parameter estimation was stopped at 340th iteration as the -2xLL for the validation set showed the best value when monitoring every 10 iterations. The trace plot suggested marginal degree of overfitting as -2xLL of training and validation set changed over iteration of parameter estimation.

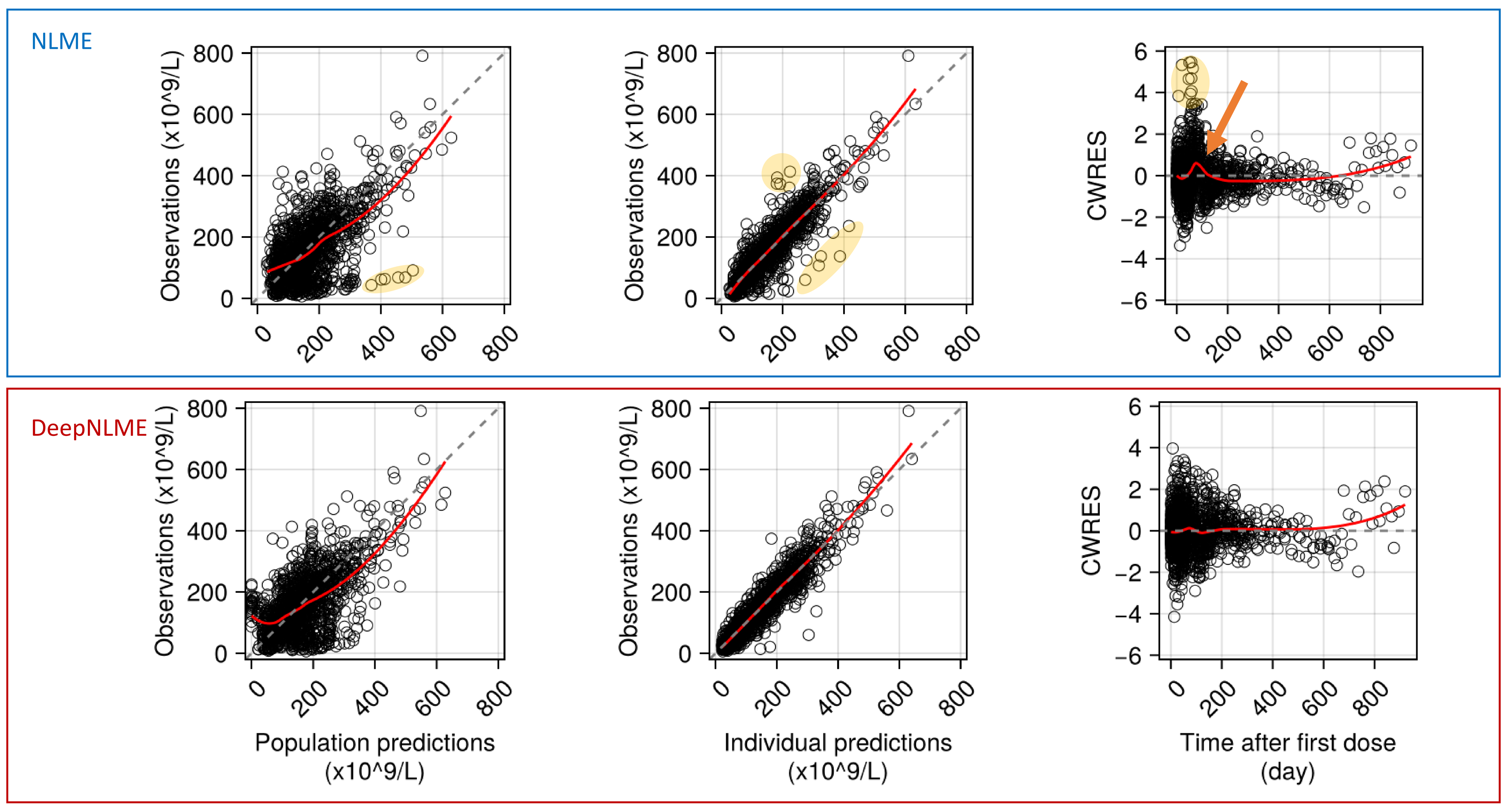
Figure 3 Trace plot for -2xLL of DeepNLME. Gray lines, -2xLL of NLME; Red lines, early stopping.



Results (cont.)

DeepNLME outperformed the standard NLME in adequate prediction per basic goodness-of-fit plots (**Figure 4**). Individual predictions from DeepNLME showed narrower concordance to observed platelets without noticeably higher shrinkage than NLME (data not shown in the poster). Systematic deviation of residuals over time observed with NLME disappeared with DeepNLME.

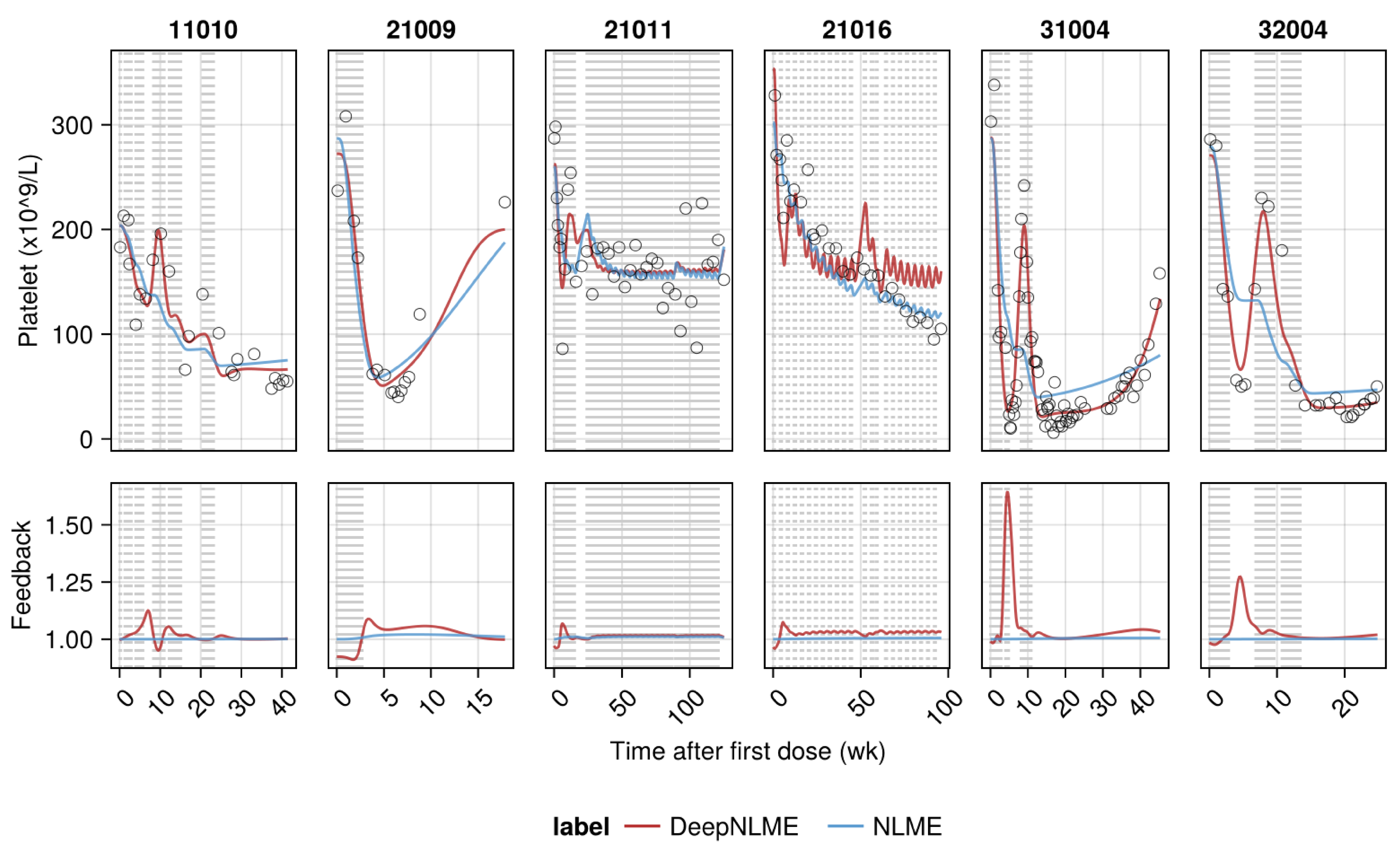
Figure 4 Basic goodness-of-fit plots of NLME (**top**) and DeepNLME (**bottom**) for training set



Individual predictions of DeepNLME captured distinct platelet dynamics, which NLME did not, in a quite flexible manner. (**Figure 5**). While a patient with typical platelet dynamics (ID: 21009) was comparably described by both approaches, patients who recovered only once (IDs: 31004, 32004) were adequately predicted only by DeepNLME. Neither NLME nor DeepNLME did not capture a patient with random fluctuation, suggesting DeepNLME does not overfit observations that should be considered random noise. One patient (ID: 21016) was captured better with NLME, but it was observed that DeepNLME also adequately described the patient if another number of iterations was applied (data not shown).

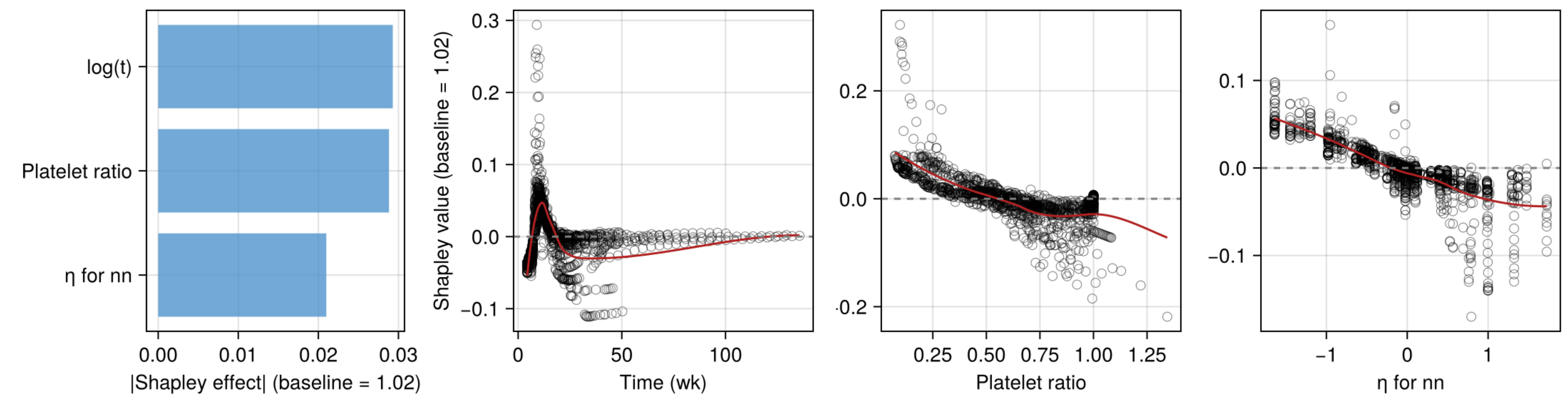
The time course of each variable suggested that the DeepNLME approach preserves the mechanistic nature of PK/PD modeling while acknowledging that a highly time-dependent feedback parameter can yield flexible predictions.

Figure 5 Individual plots of NLME (blue) and DeepNLME (red) for six selected patients



The SHAP analysis of the neural network that replaced the feedback parameter indicated that the platelet ratio contributed most to describing the dynamics (**Figure 6**). Contribution of time showed a non-monotonic shape, which was unlikely to be found by standard NLME.

Figure 6 Shapley values of NN in DeepNLME for each data point of training set. Absolute mean (**left**) and individual values (**rest**).



Conclusions

Overall, the DeepNLME-based SciML model demonstrated the ability to flexibly predict the platelet time course, providing an alternative to the standard NLME model for PK/PD modeling.

References

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[3] Friberg et al. (2002) Model of Chemotherapy-Induced Myelosuppression With Parameter Consistency Across Drugs J Clin Oncol 20, 4713-4721

Conflict of interest

Masato Fukae and Kazutaka Yoshihara are employees of Daiichi Sankyo Co., Ltd.