A Neural Networks-assisted NLME Framework: Case Study on Modeling Platelet Counts

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Objectives

Based on the example of thrombocytopenia induced by brigimadlin, a potent, oral murine double minute 2 homolog-tumor protein 53 antagonist, this work aimed to:

- Integrate neural networks (NN) into the nonlinear mixed-effects (NLME) method ("NN-assisted model")
- Compare model predictivity between the standard, refined and NN-assisted myelosuppression model

Introduction

- Thrombocytopenia, a frequent adverse event type in cancer therapy, requires clinical platelet management to avoid high-grade thrombocytopenia and to ensure treatment continuation.
- The semi-physiological model for myelosuppression [1] is frequently leveraged to characterize and predict myelosuppression ("standard myelosuppression model"), including platelet dynamics (platelet count over time).
- The standard myelosuppression model may require time-intense model refinement ("refined model") to reach adequate predictive performance, potentially hindering timely support of clinical drug development programs.
- Machine learning approaches, integrating standard NLME methods with NNs, promise to streamline model development in situations of incomplete mechanistic understanding or when further model refinement is required [2, 3].

Methods

- Model development was based on platelet counts in ≥2nd line patients with locally advanced and metastatic solid tumors (n=82, NCT03449381). Patients received oral brigimadlin administrations (5-80 mg on day 1 q3w, day 1 and 8 q4w, or day 1 and 3 q4w).
- The exposure-safety relationship was characterized by relating plasma exposure to platelet growth parameters of the myelosuppression model (see equations and figure below).
- Standard and refined myelosuppression models were implemented in NONMEM 7.4 and Pumas 2.5.0 and compared to the NN-assisted model.
- The conventional NLME-based approach using trial and error to refine the feedback function [decrease of the feedback parameter γ over time, Eq. 9] (i) lacked robustness and adaptability, particularly when additional patients were included in the dataset during the study and (ii) required significant time investment.
- NNs were used to identify an appropriate feedback function using DeepPumas (NN-assisted model).

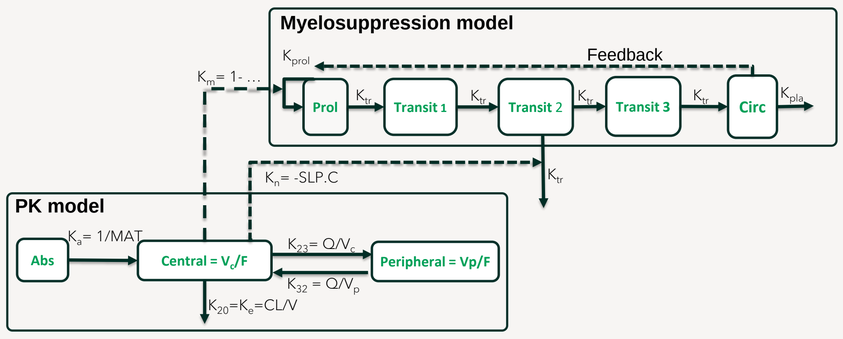


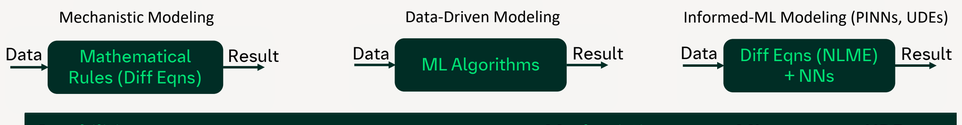
Figure 1. Illustration of the final platelet count model.

Differential equations:

1. $\frac{d(Abs)}{dt} = -K_a * Abs$
2. $\frac{d(Central)}{dt} = K_a * abs - K_{20} * Central - K_{23} * Central + K_{32} * Peripheral$
3. $\frac{d(Peripheral)}{dt} = K_{23} * Central - K_{32} * Peripheral$
4. $\frac{d(Circ)}{dt} = K_{tr} * Transit3 - K_{pla} * Circ$
5. $\frac{d(Prol)}{dt} = K_{prol} * Prol * (1 - EFF) * NN(BL, Circ, T) - K_{prol} * prol$
6. $\frac{d(Transit1)}{dt} = K_{tr} * Prol - K_{tr} * Transit1$
7. $\frac{d(Transit2)}{dt} = K_{tr} * Transit1 - K_{tr} * Transit2 - SLP * Central * Transit2$
8. $\frac{d(Transit3)}{dt} = K_{tr} * Transit2 - K_{tr} * Transit3$

9. $Feedback = (BL/A_4)^{\gamma}$

$$\gamma = \theta_1 + \left(1 - \frac{Time^{\theta_2}}{Time^{\theta_2} + \theta_3{}^{\theta_2}}\right) \times (Time \times \theta_4)$$



Capabilities	Mechanistic	ML	UDE
Interpretability	☑	☒	☑
Extrapolation	☑	☒	☑
Avoiding overfitting	☒	☒	☒
Modelling complex phenomena	☒	☑	☑
Able to handle small amount of data	☑	☒	☑
Pure data-driven insights	☒	☑	☒

Results

- The NN-assisted model reduced model development time by identifying a suitable feedback function and accomplishing parameter estimation in <2 h.
- Model execution times in Pumas 2.5.0 were approximately 15 min (refined model) and 60 min (NN-assisted model). A comprehensive comparison across models is illustrated in figure 2.

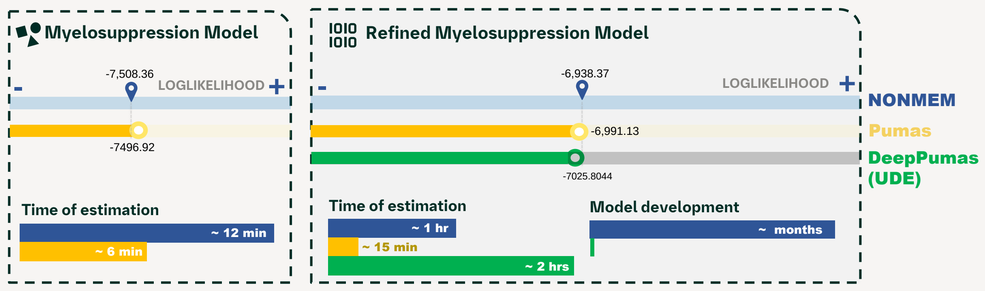


Figure 2. Performance comparison among the standard, refined and NN-assisted myelosuppression models in NONMEM, Pumas and DeepPumas.

- The predictive performance of the NN-assisted myelosuppression model slightly improved compared to the standard and refined myelosuppression models (see Figure 3) while significantly reducing model development time.
- The visual predictive check (VPC) of the standard myelosuppression model indicated that the observed platelet nadir (t = 4-5 weeks) fell outside the 95% CI of the predicted 10th and 50th percentiles.
- In the refined myelosuppression model, the predictions generally conformed to the observation patterns across all percentiles. However, the observed platelet nadir fell outside the 95% CI of the predicted 10th percentile, exhibiting -20% relative difference (i.e., overprediction) between the 10th observed percentile and the lower bound of the corresponding CI.
- VPCs indicated best predictivity at the platelet nadir for the NN-assisted model: No observations were outside the 95% CI of the 10th, 50th, 90th percentiles and the overall trend in platelets over time was adequately described.

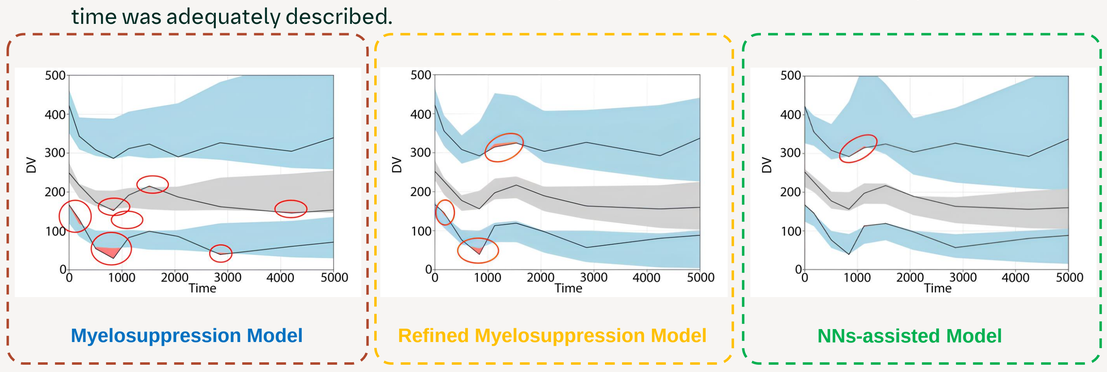


Figure 3. VPC plots of the standard model , refined model using NONMEM, and NNs-assisted NLME model using DeepPumas.

Table 1. Estimated parameter comparison for final model in NONMEM and NNs-assisted model in DeepPumas.

Estimated parameters	NNs-assisted model (DeepPumas)	Refined myelosuppression model (NONMEM)
BL	273	260
MMT	293.1	180.0
EC_{50}	4355	4140
σ_p	0.20	0.17
σ_{add}	11.5	27.2

Conclusions

Once the function which required more refinement was identified, the NN-assisted myelosuppression model reduced model development time substantially while improving predictivity, compared to the standard and refined myelosuppression model.

In contrast to the trial and error approach of refining the standard myelosuppression model, the application of NN enabled rapid and automated identification of the feedback function, enhancing its adaptability and generalizability when incorporating additional patient data.

This work advocates for NN integration in complex pharmacometrics scenarios with incomplete mechanistic understanding or when further model refinement is required.

Abbreviations

BL, platelet baseline [(10^9)/L]; Circ, circulating; EC_{50}, concentration at half maximum effect; MAT, mean absorption time; ML, machine learning; MMT, mean maturation time [h] = $4/K_{tr}$; Prol, proliferative cells; UDE, universal differential equations; V_p, peripheral volume of distribution; σ_p, proportional error; σ_{add} ,additive error;

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