# A full Bayesian-NLME framework predicts delayed MTX elimination in CNS lymphoma

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## Background

High doses of **methotrexate** (MTX) are first-line treatment for **central nervous system lymphoma**[1].

MTX is primarily **renally excreted** (80 – 90%) while inducing **nephrotoxicity,** potentially creating a **vicious cycle**[1].

**Delayed elimination** (> 3 days to decline below a threshold of $C_{MTX}$ < 0.2 µM) increases **toxicity** but is difficult to predict[2].

**PK NLME** appears suited to **support clinical decision making** by predicting **time to 0.2 µM ($t_{0.2µM}$)**, with several models published[3].

## Knowledge Gaps

**Predictive performance** and **utility** of MTX PK NLME models to support clinical decision-making are **rarely assessed**.

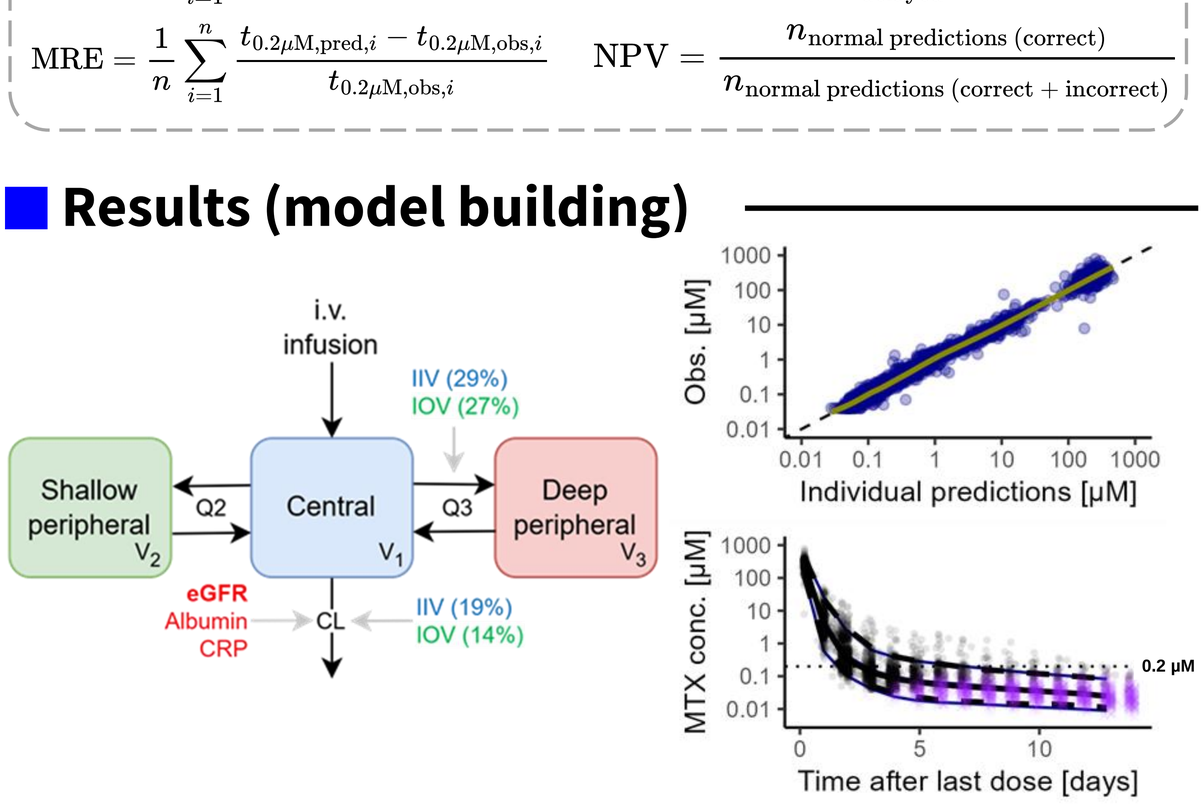
**Neglecting uncertainty** by simplifying to the **posterior mode (MAP)** remains a **limitation** of clinical decision-support tools.

## Objectives

How well does a newly developed NLME model **predict delayed eliminators** at clinically relevant decision time points?

Can translation into a **full-Bayesian**[4,5] framework preserve valid **uncertainty quantification** for $t_{0.2µM}$?

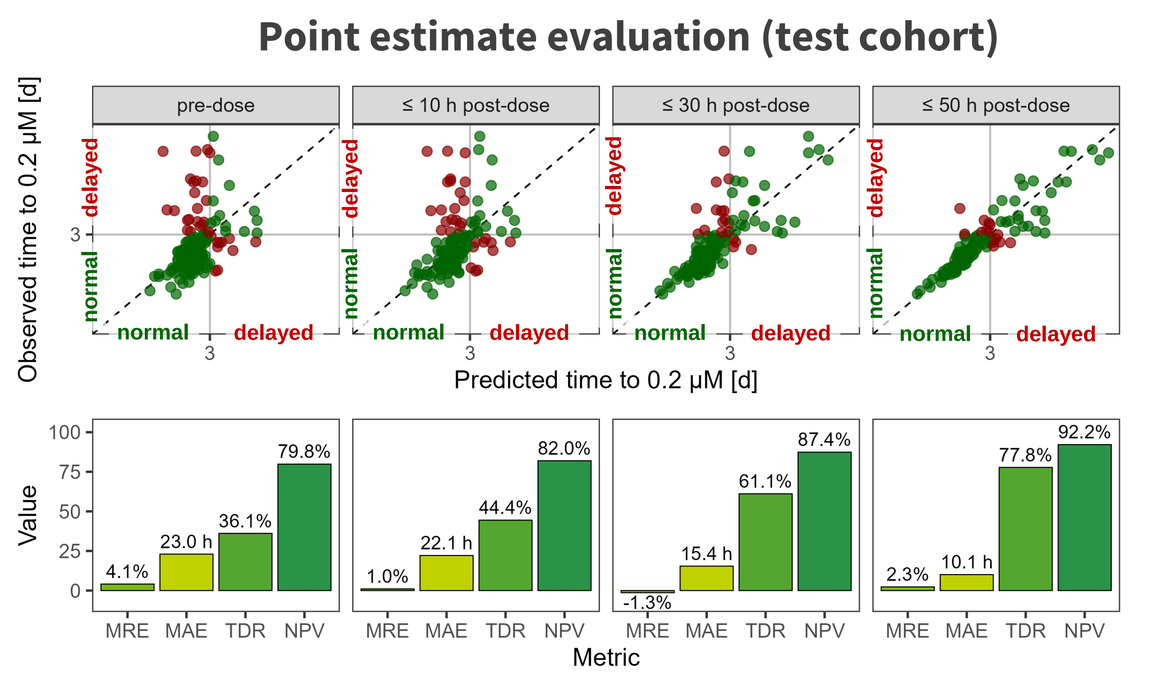
## Methods

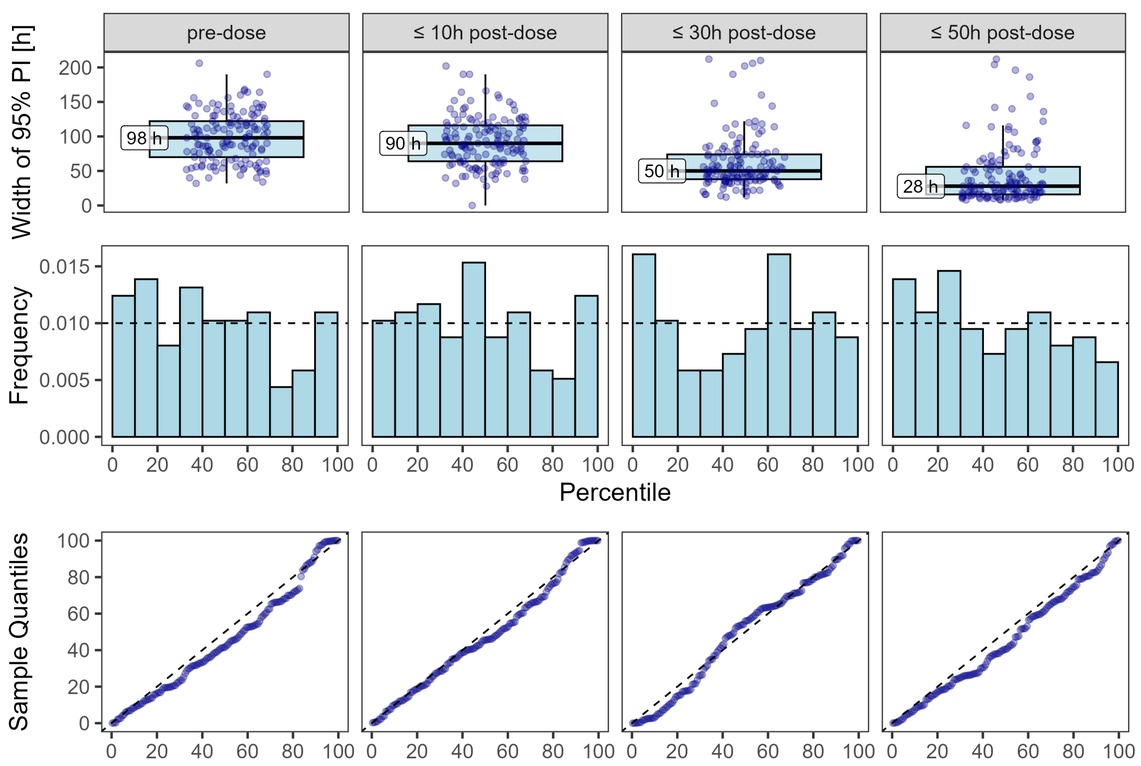



$$\mathrm{MAE} = \frac{1}{n}\sum_{i=1}^{n}\left|t_{0.2\mu\mathrm{M,pred},i} - t_{0.2\mu\mathrm{M,obs},i}\right| \qquad \mathrm{TDR} = \frac{n_{\text{delayed predictions (correct)}}}{n_{\text{delayed}}}$$

$$\mathrm{MRE} = \frac{1}{n}\sum_{i=1}^{n}\frac{t_{0.2\mu\mathrm{M,pred},i} - t_{0.2\mu\mathrm{M,obs},i}}{t_{0.2\mu\mathrm{M,obs},i}} \qquad \mathrm{NPV} = \frac{n_{\text{normal predictions (correct)}}}{n_{\text{normal predictions (correct + incorrect)}}}$$

## Results (model application)




## Results (model building)







## Discussion

- ✔ Selected MTX model showed good **descriptive** performance (training)
- ✔ **Uncertainty** in predicting $t_{0.2µM}$ was maintained via **full Bayesian**
- ✔ Good **predictive** performance ($t_{0.2µM}$) if data >30h was provided (test)
- ✘ **Insufficient** identification of delayed eliminators at **early** time points
- ? Are **competing approaches** (e.g., machine learning) more **predictive?**

## Conclusion

**The full Bayesian-NLME framework predicted delayed MTX elimination if informative TDM data was provided and preserved predictive uncertainty.**

[1]FDA Label, Methotrexate Injection, USP, 2011

[2]Stoller et al., N. Engl. J. Med., 1977

[3]Zhang et al., Eur J Drug Metab PK, 2022

[4]Margossian and Gillespie, J PK PD, 2016

[5]Stan Development Team, 2025

**Abbreviations** ALB: Albumin; CNS: Central Nervous System; CRP: C-reactive Protein; eGFR: Estimated Glomerular Filtration Rate; HD-MTX: High-Dose Methotrexate; MAE: Mean Absolute Error; MAP: Maximum A Posteriori; MRE: Mean Relative Error; NPV: Normal Predictive Value; PI: Prediction Interval; t0.2µM: Time to reach 0.2 µM; TDR: True Delayed Rate; Torsten: Pharmacometrics library for Stan.

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