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Introduction

- Reliable parameter estimation for in-host models is based on understanding the interplay between the data quality and model complexity, a balance primarily reflected in uncertainty metrics.
- The relative standard error (RSE) in non-linear mixed effects models is a measure that expresses the uncertainty of parameter estimates as a percentage of their estimated values, commonly used with a threshold of <50% considered '*precisely estimated*' [1-4].

AIM

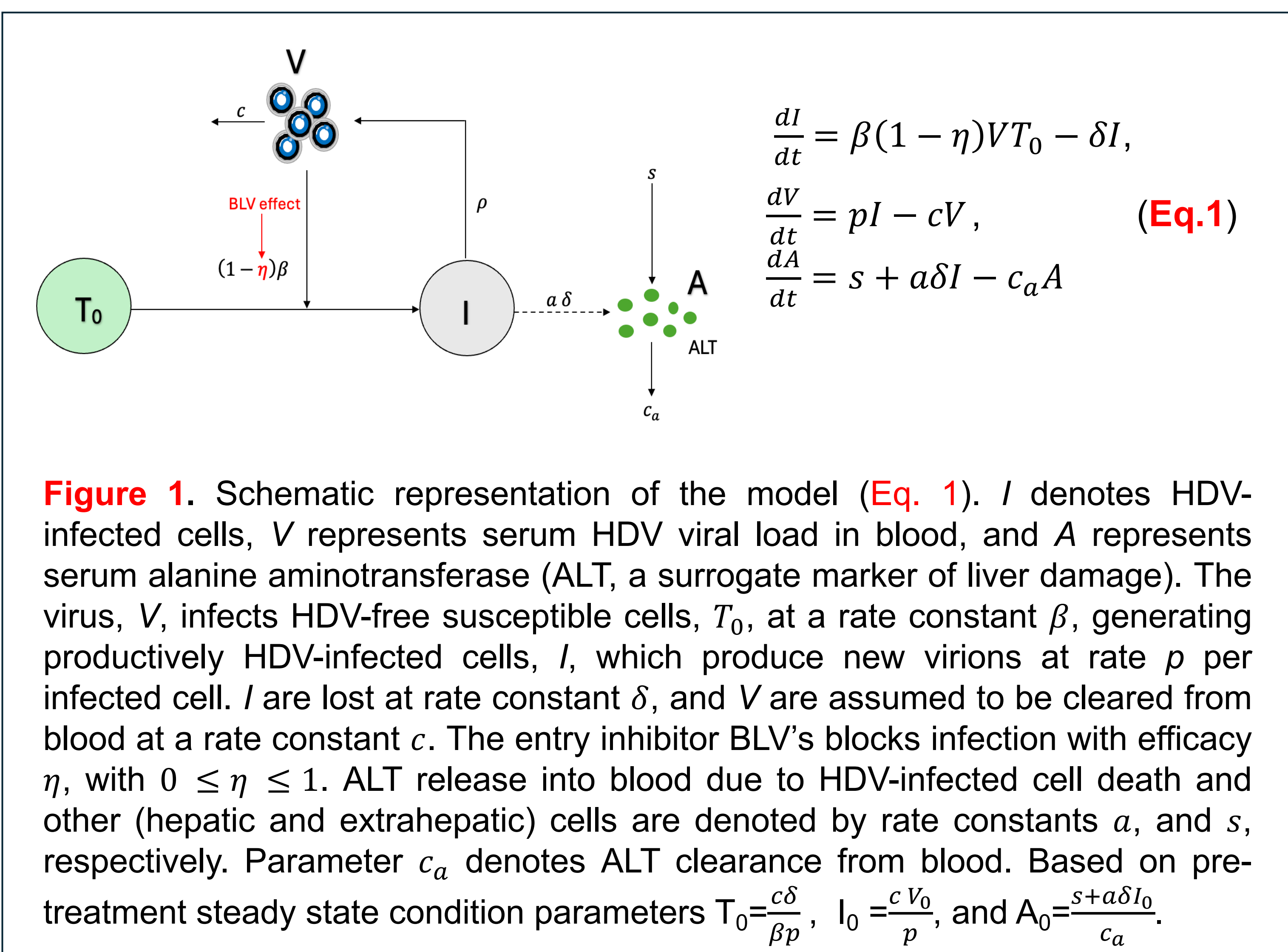
We aim to evaluate the limitations of relying on RSE for model accuracy by testing a recent model (Fig. 1) proposed by El Messaoudi et al. [5] against our patients' kinetic data [6].

Patients

- Thirty-eight patients with hepatitis D virus (HDV)-related compensated cirrhosis and clinically significant portal hypertension were treated with bulevirtide (BLV) 2 mg/day monotherapy for up to 96 weeks [6].
- All patients received either tenofovir disoproxil fumarate or entecavir to treat hepatitis B.
- Blood samples were collected at treatment initiation, weeks 4, 8, 16, 24, 32, 40, 48 and every 12 weeks thereafter.

Mathematical Model

- El Messaoudi et al. [5] model equations and schematic description is shown in (Fig. 1):



- Model parameters were estimated using the maximum-likelihood method implemented in Monolix version 2023R1. We assessed the precision of parameter estimates (pre-treatment HDV viral load, V_0 ; infected cells loss rate, δ ; blocking efficacy of BLV, η), using RSE values in Monolix.
- To further evaluate the goodness of fit for the model (Eq. 1), we utilized three methods: Root mean square (RMS), Coefficient of determination (R^2), and the Durbin-Watson (DW) test. All computations were performed using Python 3.11, with RMS and R^2 computed using NumPy (version 1.23.5), and the DW test using statsmodels (version 0.14.0).

References

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Results

Modeling results indicate:

- (i) a strong inverse correlation between the BLV efficacy and the loss rate of HDV-infected cells, indicating identifiability issues,
- (ii) the model failed to accurately capture HDV kinetics in 61% patients due to poor fits, and
- (iii) the model failed to accurately recover certain key parameters such as pretreatment serum HDV RNA levels, resulting in parameter estimates.
- Further examination of the covariance matrix confirmed a high negative correlation between BLV efficacy and the infected cell loss rate, reinforcing concerns about identifiability issues.
- Moreover, the goodness-of-fit metrics (RMS, R^2 , DW test), indicated poorer fits for patients with non-monophasic HDV decline (Fig. 2: patients 3 and 16), showing systematic bias in model performance.
- Confidence intervals analysis also revealed uncertainty in key parameters, particularly the estimated BLV efficacy.

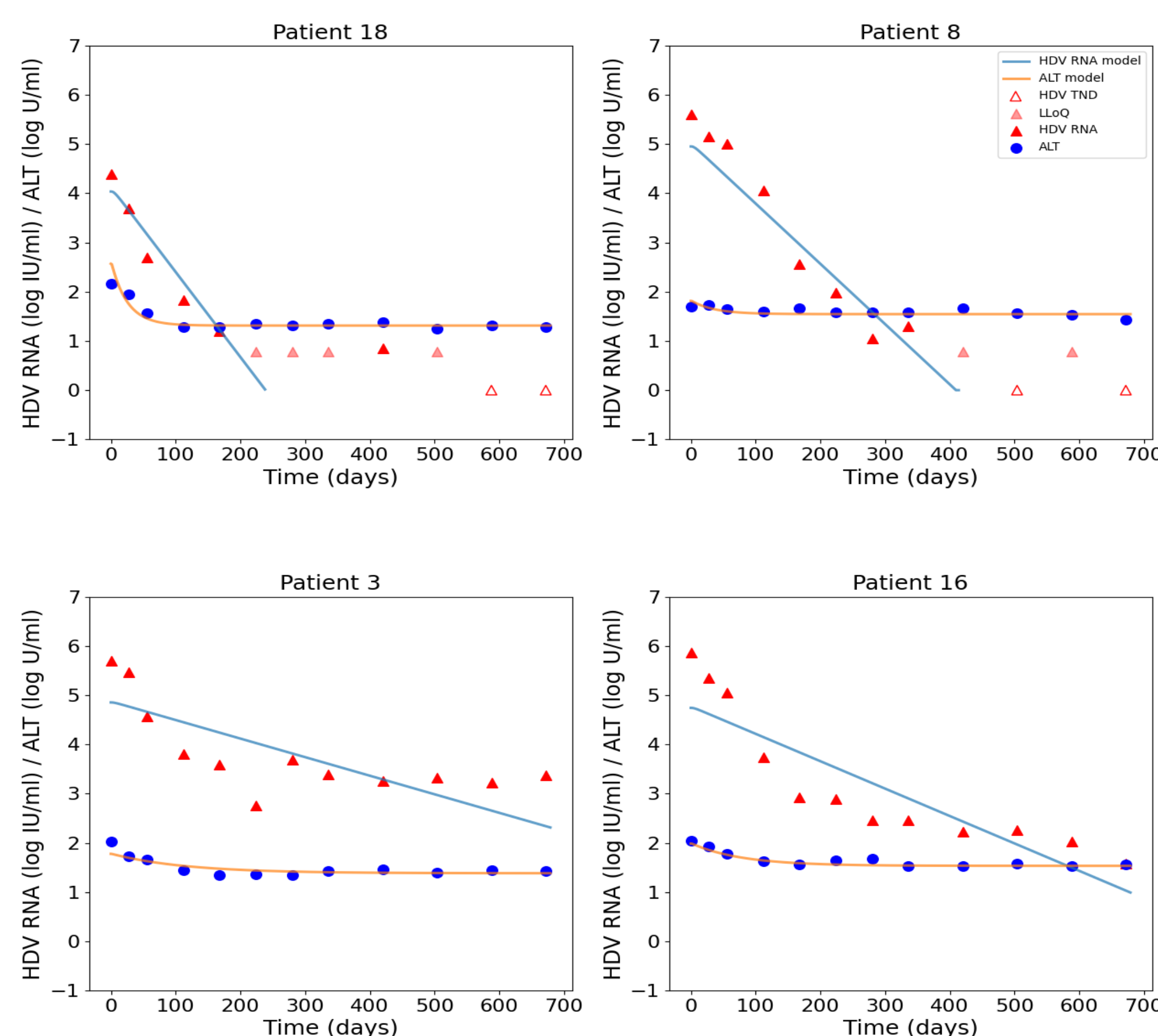


Figure 2. Model calibration (curves) with individual patients HDV RNA and ALT kinetic data (symbols) during 672 days of BLV monotherapy was performed in Monolix and visualized using Python version 3.11. Lower Limit of Quantification (LLOQ), Target not detected (TND) .

Conclusions

- Despite achieving RSE < 50% in Monolix for all parameter estimates, we observed significant discrepancies between the model (Eq. 1), outputs and actual patient data, indicating limitations in the model's ability to accurately explain HDV kinetics (see also [7]).
- Reliance on RSE may overlook critical issues such as parameter identifiability, inadequacy of model structures, goodness of fit, and overall model accuracy.
- The full analysis of the current study can be found at <https://doi.org/10.48550/arXiv.2505.12286>

Acknowledgments

This work was supported in part by a grant from "Ricerca Corrente RC2021/105-01", Italian Ministry of Health, and by NIH grants R01AI078881, R01AI144112 and R01AI146917. LS thanks the Binational Science Foundation grant 207745 for support.

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