A Physiologically Based Pharmacokinetic Framework for Predicting Drug Exposure in the Female Reproductive Tract

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Intro

Healthcare is advancing, and a deeper understanding of complex physiological systems is crucial for improving treatments. The female reproductive tract (FRT) - affected by conditions such as infections, endometriosis, and cancer - plays a key role in women's health. Nevertheless, the FRT is typically neglected in physiologically-based pharmacokinetic modeling (PBPK). To enhance exploration of drug exposure in the FRT following both local (*e.g.,* vaginal or uterine) and systemic administration routes, we developed a PBPK model extension for the FRT.

Explore drug exposure in the organs of the female reproductive tract with our Shiny app

Methods

A PBPK extension module (Figure 1) was developed in MoBi® V12. It integrates physiological data for the FRT organs [1] and allows for the simulation of different local drug administration routes. The extension module was validated for levonorgestrel and metronidazole by comparing predicted plasma, tissue, and fluid concentrations to clinical data, using goodness-of-fit plots and pharmacokinetic parameters. In total, we included 4 local (intrauterine device, vaginal gel/tablet/pessary) and two systemic (IV and oral) routes of administration. Release descriptions for the different formulations were parametrized using clinical data.

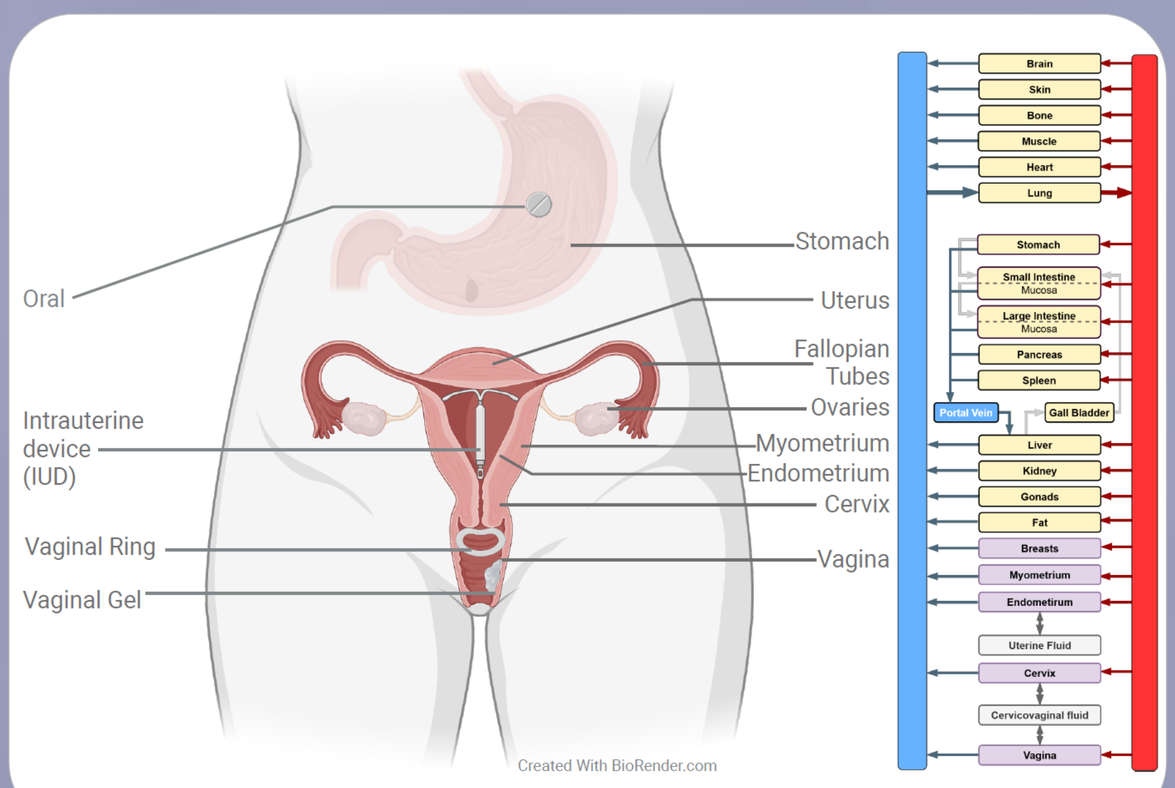
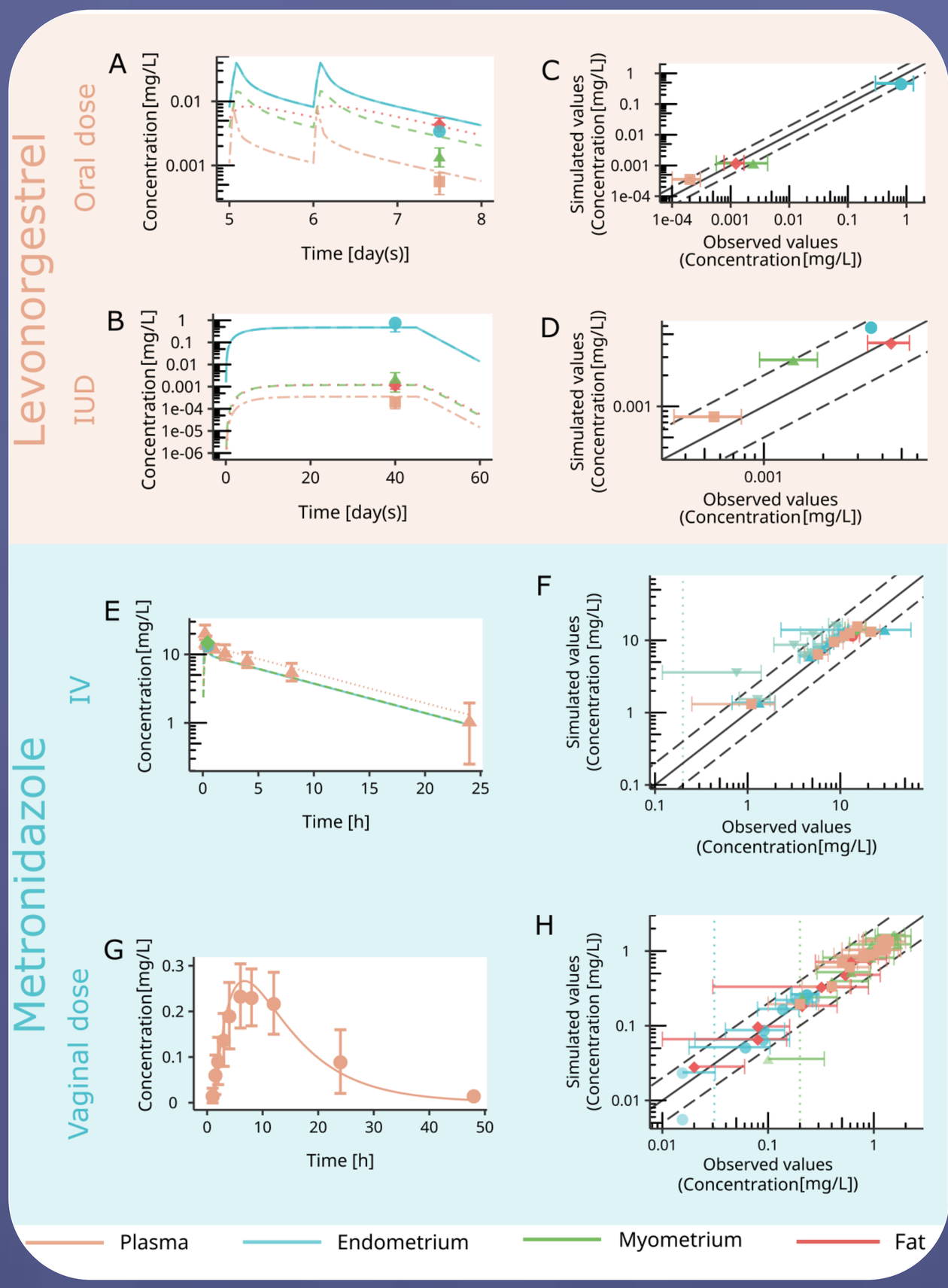


Figure 1: Female reproductive tract structure and representation of drug administrations. (A) Presentation of the anatomical structure of the female reproductive tract organs and the considered local routes for drug administration. (B) Schamatic representation of the PBPK human base model structure in PKSim extended by the organs (pink) and fluids (white) of the female reproductive tract.



Results

For both compounds, the PBPK models capture the plasma, tissue, and fluid exposure following different routes of drug administration well, as indicated in Figure 2. For metronidazole, time series data were available, allowing the calculation of AUC and C_{max} values. 81.25% of the derived ratios were in the range of 0.85 – 1.15. For levonorgestrel, mainly single-time point measurements were available; therefore, the model predictions were evaluated using the prediction error. 62.5% of prediction errors were in the range of ±50%, and all prediction errors were within the range ±100%.

Figure 2: The upper panel displays model predictions for levonorgestrel following oral and IUD administration. The lower panel shows predictions of metronidazole concentration after iv and vaginal dosing. The left column shows the simulation results in comparison to clinical data (one study was selected per administration route). The right column presents the predicted vs observed plots for all available clinical data for that drug administration route.

Conclusion

We developed a FRT extension module in MoBi V12 that is openly available on GitHub. The module has been validated for two compounds and six routes of administration. Overall, only minor parameter adjustments were needed to capture clinical data well. Due to the model modularization concept introduced in MoBi V12, the FRT module can easily extend any PBPK base model available in the Open System Pharmacology suite. Hence, this FRT module has significant potential for drug development and safety assessment in female-specific health areas, including infections, cancer, and reproductive toxicity.

Module on GitHub

References

[1] Fischer-Holzhausen S., et al. Enhancing PB(P)K Models for the Female Reproductive Tract: A Framework for Local and Systemic Drug Kinetics. PAGE, Greece, Thessaloniki, 2025

[2] Cicali, B., et al. "Quantitative assessment of levonorgestrel binding partner interplay and drug-drug interactions using physiologically based pharmacokinetic modeling." CPT: Pharmacometrics & Systems Pharmacology 10.1 (2021): 48-58.

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Modeling Scaling Coding

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