

A Physiologically Based Computational Model of Bilirubin Metabolism: Integrating Real-World Data for Enhanced Clinical Evidence

Ahenk Zeynep Sayin¹, Lars Kuepfer¹

¹Institute for Systems Medicine with Focus on Organ Interaction, University Hospital RWTH Aachen, Aachen, Germany

Background

- Bilirubin is a product resulting from heme degradation.
- Disorders like Gilbert, Crigler-Najjar, and Dubin-Johnson syndromes originate from genetic or metabolic issues that disrupt bilirubin metabolism.
- Here, we developed a physiologically-based model of bilirubin metabolism to evaluate the bilirubin levels in health and bilirubin-related disorders.
- To address the interindividual variability, population simulations were run.
- This study extends previous research by integrating clinical data from multiple U.S. health institutions, using the Explorys real-world database.

Methods

PBPK model development:

- Our model was developed with PK-Sim® and MoBi® from the OSP Suite.

Literature data:

- Published data were used (1-6), including labeled bilirubin studies (1, 6, 7).

Explorys data:

- Explorys is a commercial database of electronic health records from health institutions in the U.S. (~1M patients with liver-related health conditions).

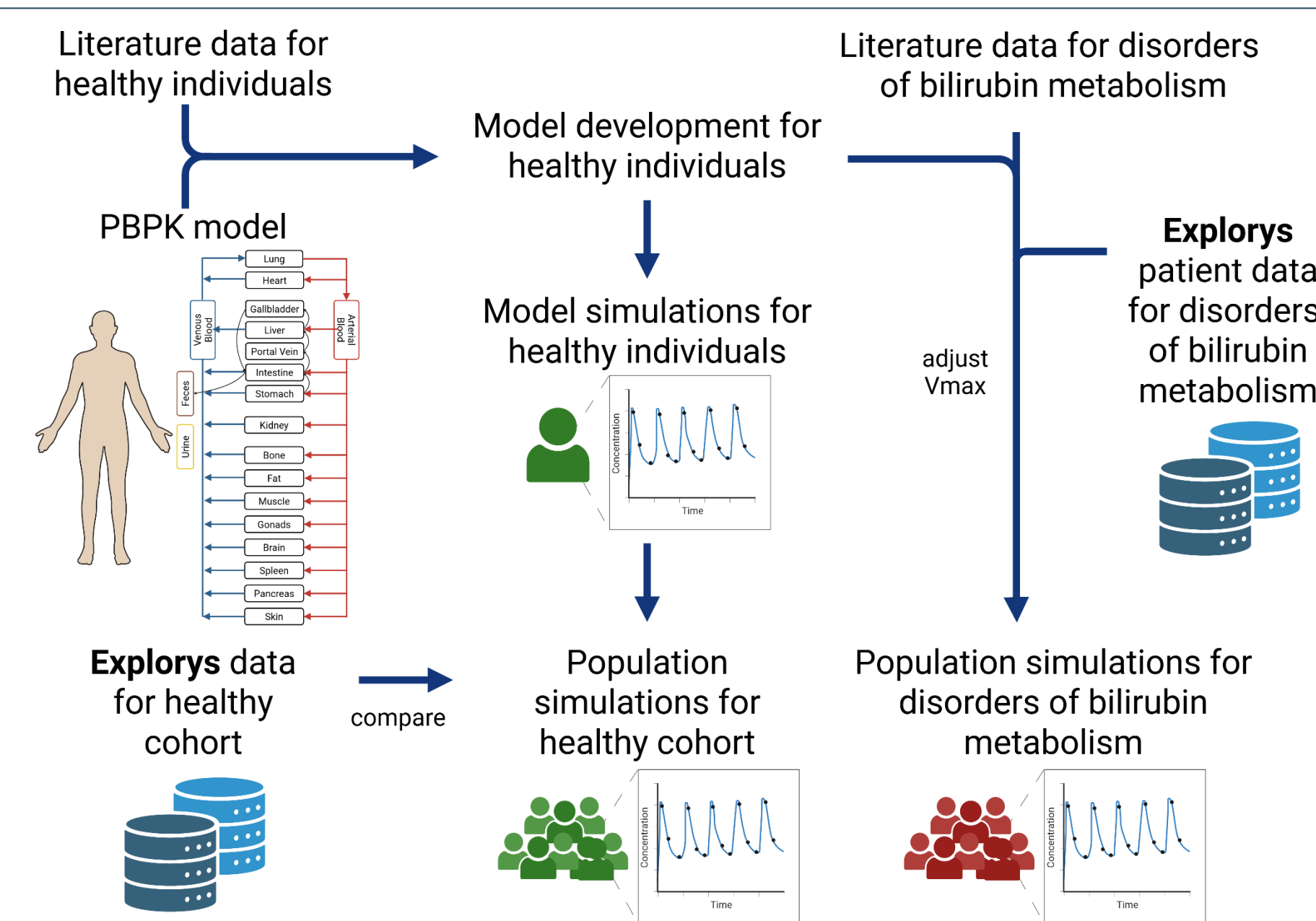


Fig 1. Overview of the workflow

Population simulations:

- A virtual population of 1,000 individuals was created.
- A normal distribution of Vmax values, with a standard deviation of 25% of the mean was applied (8).

Results

Model development for healthy individuals

- Our model includes bilirubin synthesis, hepatic uptake (OATP1B1), bilirubin conjugation (UGT1A1), biliary excretion (MRP2), and systemic efflux (MRP3), as shown in Figure 2.
- It also accounts for reduction of conjugated bilirubin to urobilinogen, as well as fecal and urinary excretion.
- The model was developed using data from literature (1-6), including time-dependent data from labeled bilirubin studies (1, 6, 7), which were used for parameter fitting.

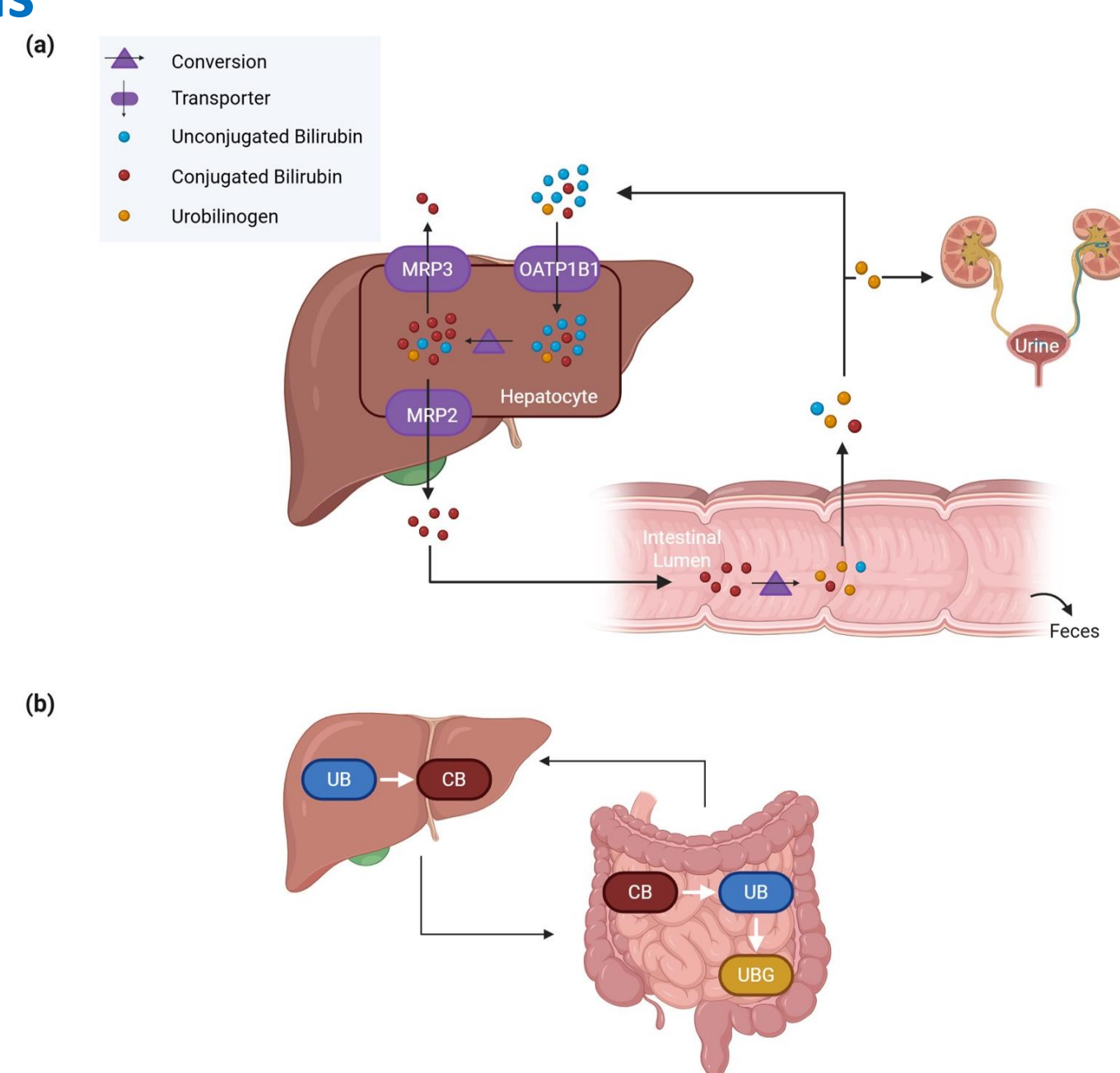


Fig 2. The systemic processes (a) and the reactions (b) in the PBPK model of bilirubin metabolism.

Model simulations for healthy individuals and populations

- For the time-dependent outputs of the model (Figure 3a-d), a model with intravenous administration of 0.5 mg bilirubin and no endogenous synthesis was used, based on labeled bilirubin studies. For steady state outputs (Figure 3e-i), the model with bilirubin synthesis was employed, with a long-term simulation.

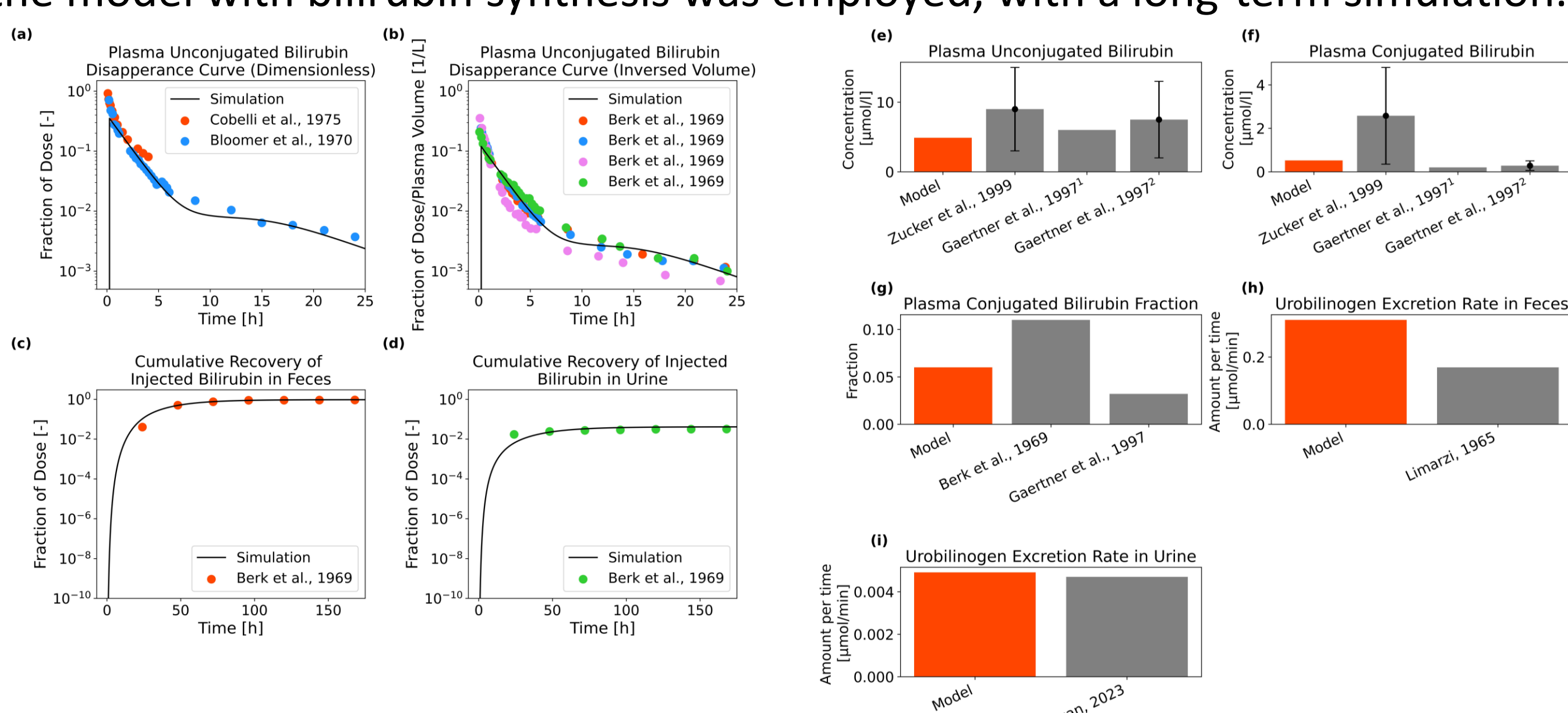


Fig. 3. Model outputs of the bilirubin metabolism model vs. measurements.

- In the healthy state, the model accurately describes plasma unconjugated and conjugated bilirubin levels, as well as cumulative bilirubin recovery in feces and urine. However, it overestimates fecal urobilinogen excretion, while urinary excretion matches literature values.
- To capture interindividual variability, virtual populations were simulated (Figure 4).

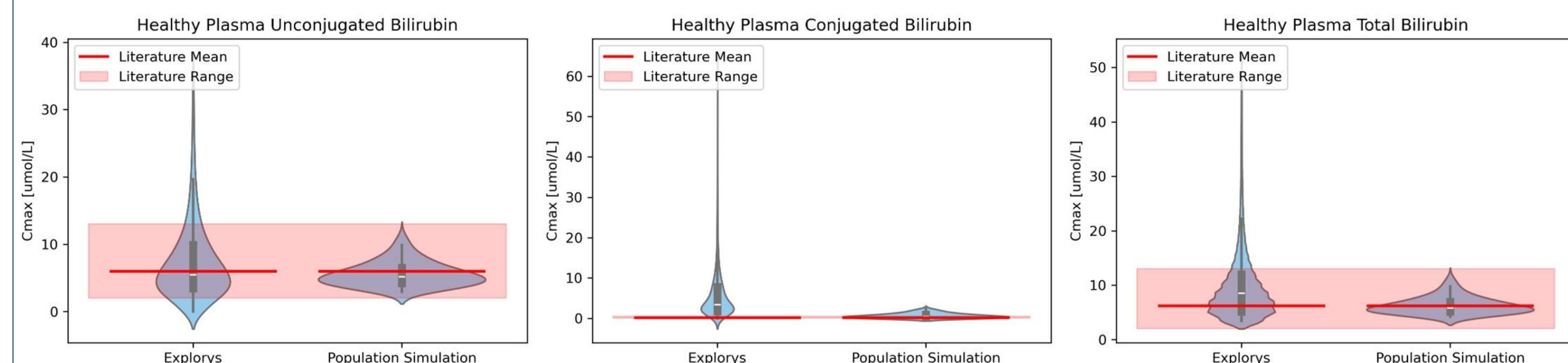


Fig 4. Plasma unconjugated, conjugated, and total bilirubin levels of population simulations in comparison to the literature and the Explorys data for the cohort of healthy bilirubin metabolism.

- With population simulations, our model accurately reproduced plasma unconjugated and total bilirubin levels from the literature. Most conjugated bilirubin values of virtual population were also within reported ranges. Explorys data showed some extreme values, with generally high conjugated bilirubin levels.

Model simulations for disorders of bilirubin metabolism

- We next tried to replicate the bilirubin levels in the literature and Explorys database by merely adjusting the Vmax of the enzyme/transporter affected in each disorder (Figure 5).

Table 1. Vmax adjustments for enzymes and transporters in bilirubin metabolism disorders

Syndrome	Affected Enzyme/Transporter	Percentage of Healthy-State Vmax	Literature Estimates
Gilbert	UGT1A1	4.5%	30-50% of normal activity (9)
Crigler-Najjar	UGT1A1	0.35%	Complete or near absence (10)
Dubin-Johnson	MRP2	2.8E-4%	Minimal or absent activity (10)

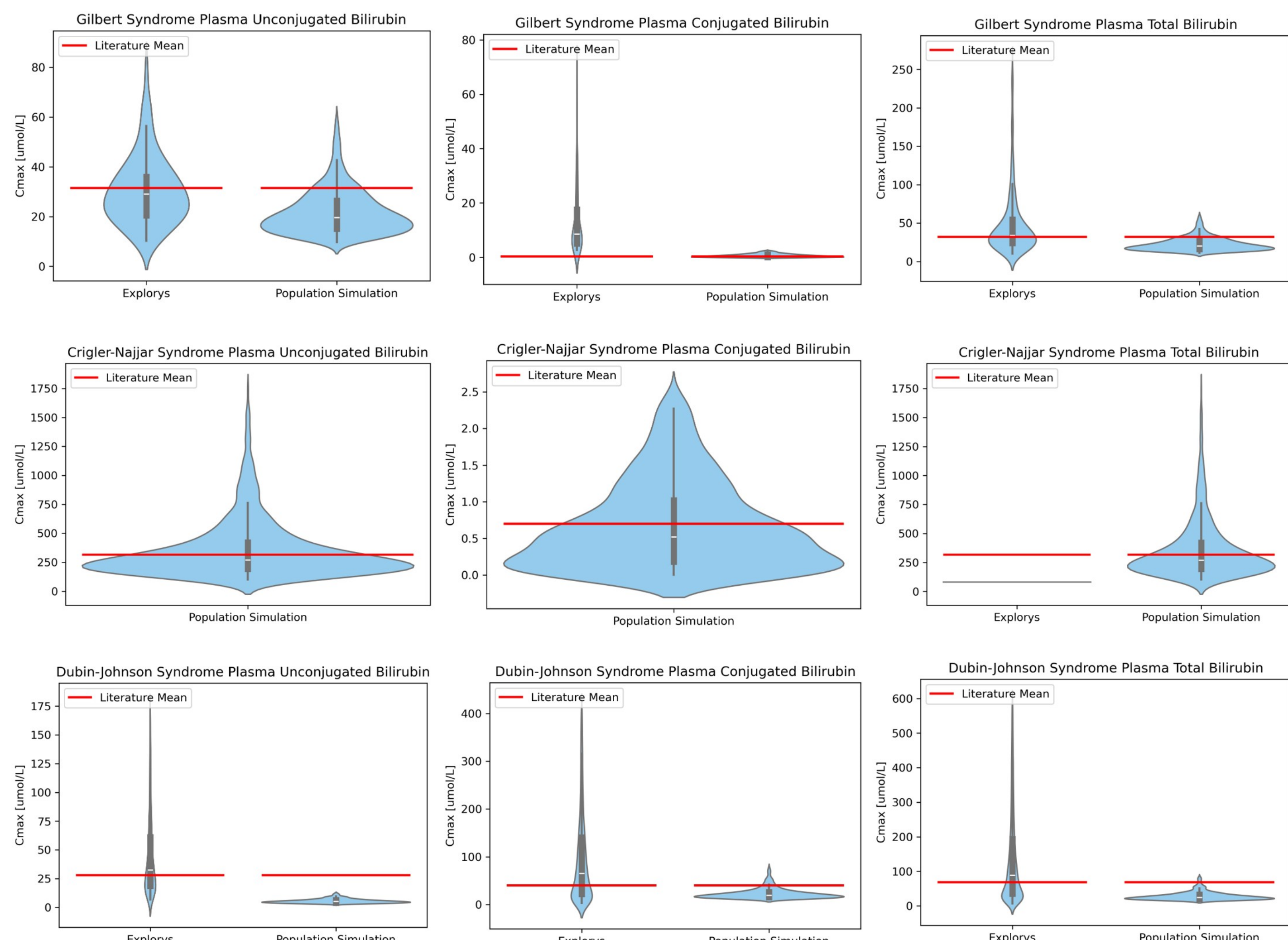


Fig. 5. Plasma unconjugated, conjugated, and total bilirubin levels of population simulations in comparison to the literature and the Explorys data for the disorders of bilirubin metabolism.

Conclusion

- This study presents a computational model of bilirubin metabolism in healthy and diseased states.
- By integrating real-world clinical data from the Explorys database and the literature, the model provides insights into the alterations of bilirubin metabolism in various disorders.
- The model can accurately represent disorders of bilirubin metabolism with adjusted parameters from the healthy reference model.
- The model provides a mechanistic framework for studying bilirubin metabolism, assessing liver function in different pathological states, and investigating interindividual variabilities that impacts disease severity and treatment outcomes.

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