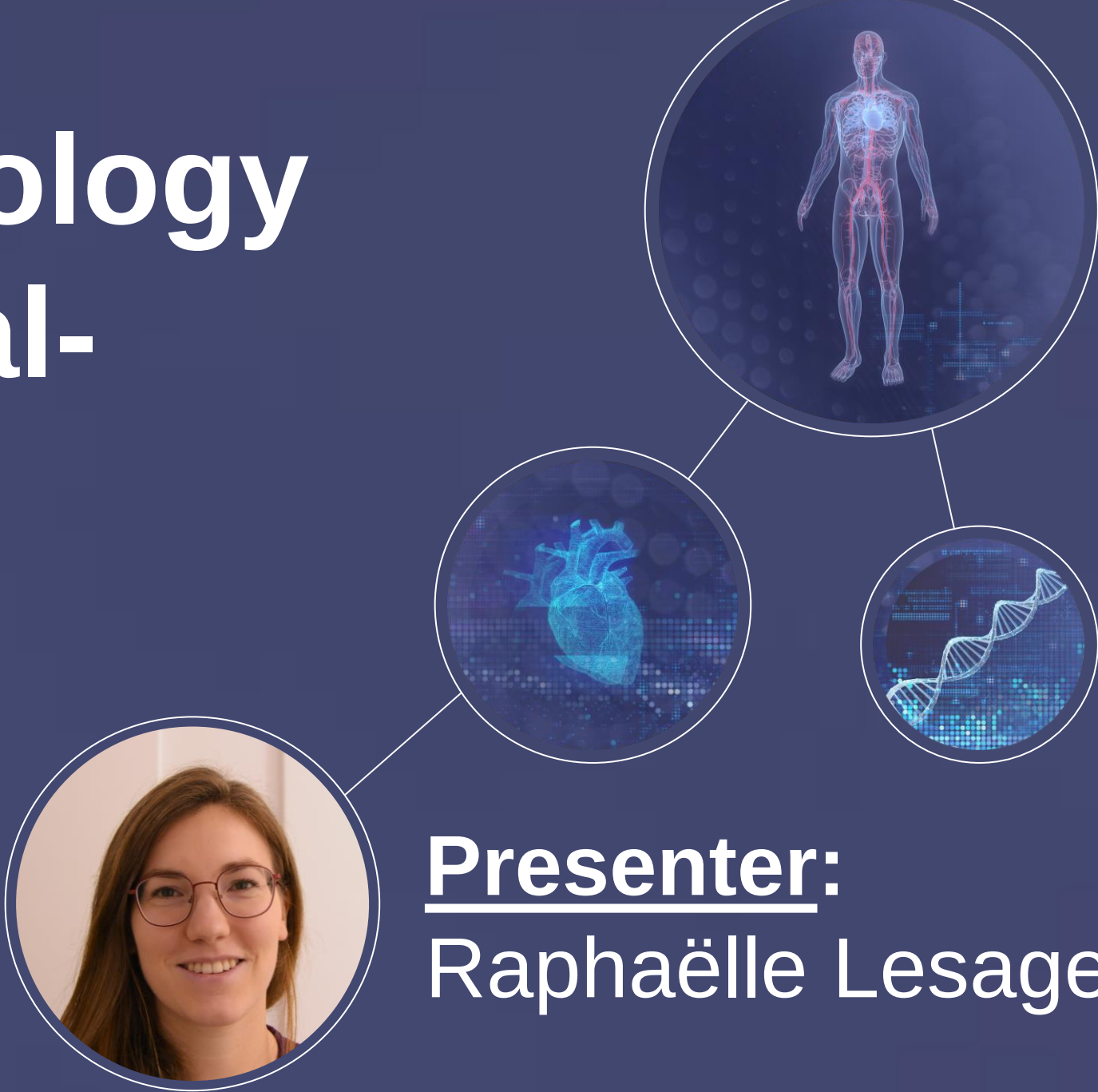


A Thyroid Quantitative System Toxicology model for the assessment of chemical-induced thyroid hormone disruption across species

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Intro

Disparities between human and preclinical species hamper the assessment of drug-induced thyroid hormones (TH) disruption and drug safety [1-2]. The purpose of this study is to develop and test a quantitative systems toxicology (QST) platform describing the regulation of TH regulation in rats and humans to assess species-specific effects of TH-disrupting chemicals (TDCs).

Methods

A physiologically based kinetic (PBK) TH model [3] was extended with new mechanisms to account for species-specific differences using MoBi® v11.2 (OSP Suite [4]). The original model included synthesis and regulation of the **thyroid stimulating hormone (TSH)** in the pituitary gland and **T3/T4** in the thyroid. The model was extended by the following mechanisms to account for the species differences:

- UGT and DIO-mediated metabolism of TH
 - Turnover and binding kinetics of TH binding proteins (plasma transporters), namely **Albumin**, **Transthyretin (TTR)**, and **Thyroid Binding Globulin (TBG)**.
- A common model structure is established and parametrized for adult humans and rats. Phenobarbital (**PB**) a known TH-disruptor is tested [5].

Parameters	Human	Rat
Half life of T4	5-9 days	0.5-1 day
Half life of T3	1 day	0.25 days
Preponderance of TH serum transport Proteins (affinity/abundance)	TBG TTR Albumin	TTR Albumin

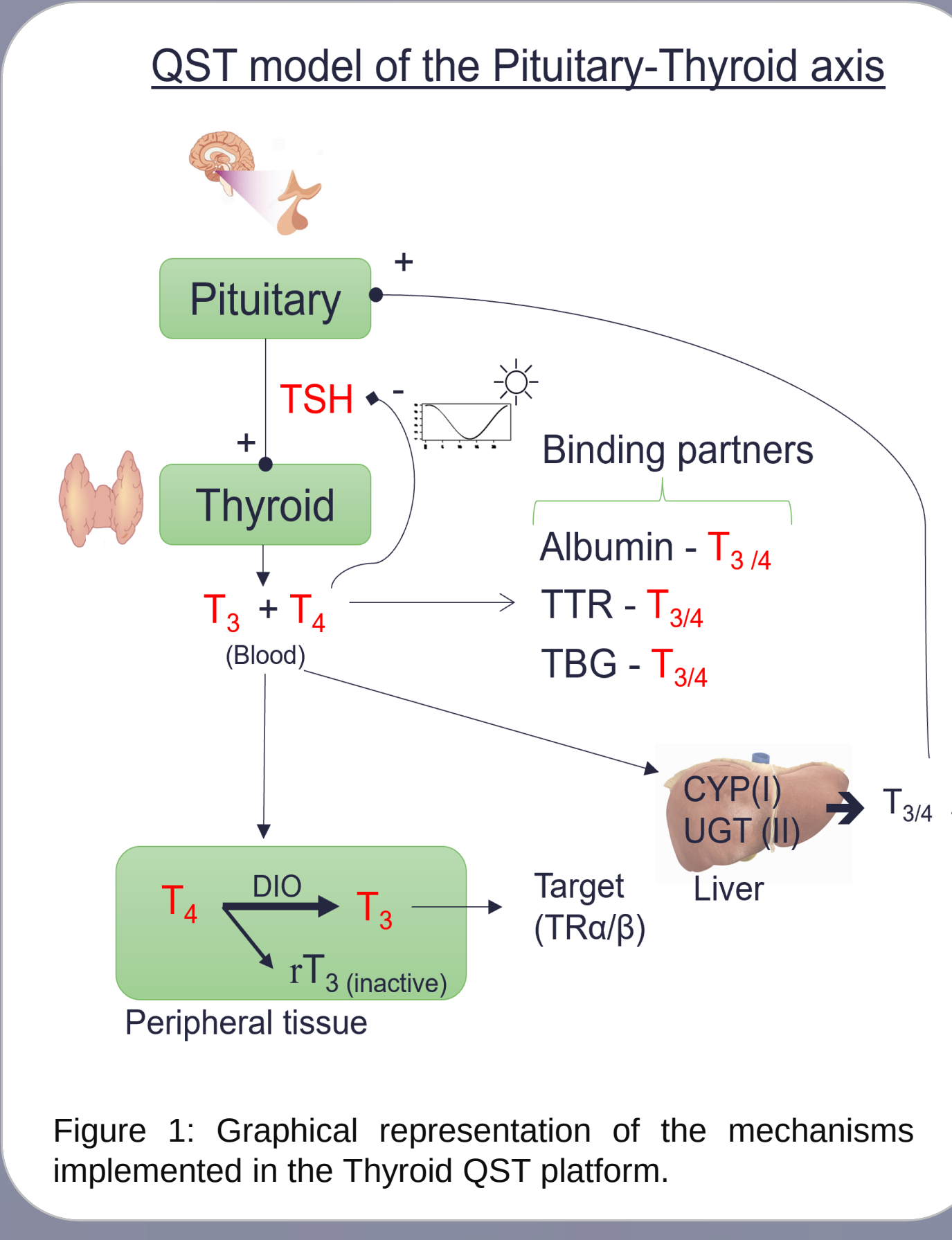
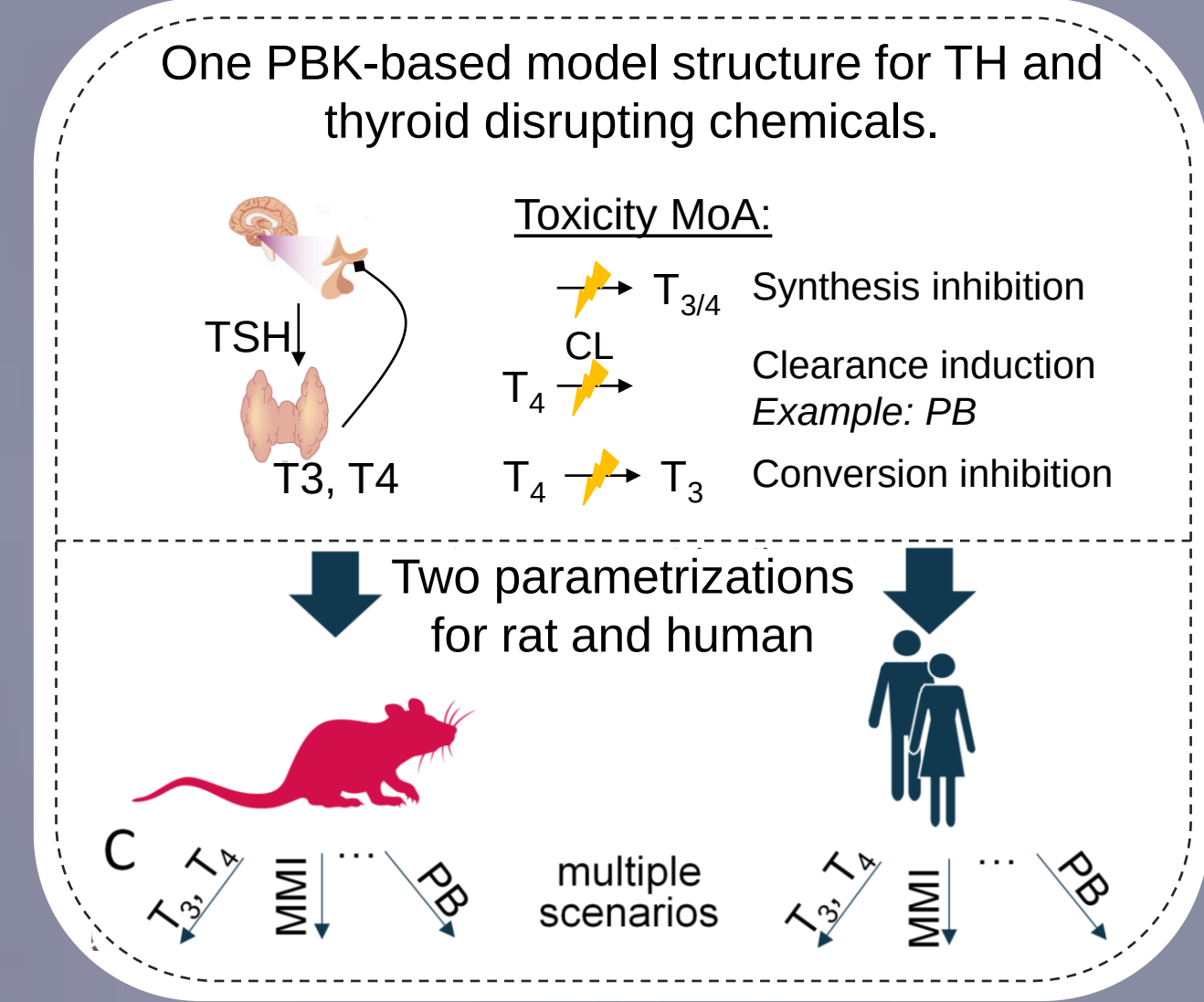


Figure 1: Graphical representation of the mechanisms implemented in the Thyroid QST platform.

Results

- Mechanisms pertaining to TH plasma transport allow to reproduce observed free T3/T4 and fraction bound in humans and rats (Fig 2).
 - In humans, TBG is the main TH carrier.
 - In adult rats, Albumin (resp. TTR) is the main T3 (resp. T4) carrier. (binding affinity in rats assumed same as human)
- TH turnover and regulation mechanisms replicate THs profiles (Fig3):
 - T4 and T3 natural decay are accurately predicted.
 - T3 inhibits TSH, which returns to normal after T3 decays (feedback)
- PBK & QST modelling of Phenobarbital (PB) (previous version) predicted higher clearance of T4 in rat compared to placebo (Fig4)
- Next step: effect of PB should be compared between rats and humans with new QST platform to conclude on species differences

Conclusion

The model captures dynamic binding of TH to plasma proteins and reproduces published data on the TH regulation system. It can be coupled with disruptor PBK models to predict adverse effects. By using species-specific parametrization, the model acts as a modular open QST platform predicting differential chemical-induced TH disruption across species for any xenobiotics. Future developments will focus on adapting the platform for special populations (e.g. pregnancy, lactation)

Predicted thyroid hormones fraction bound differ between humans and rats

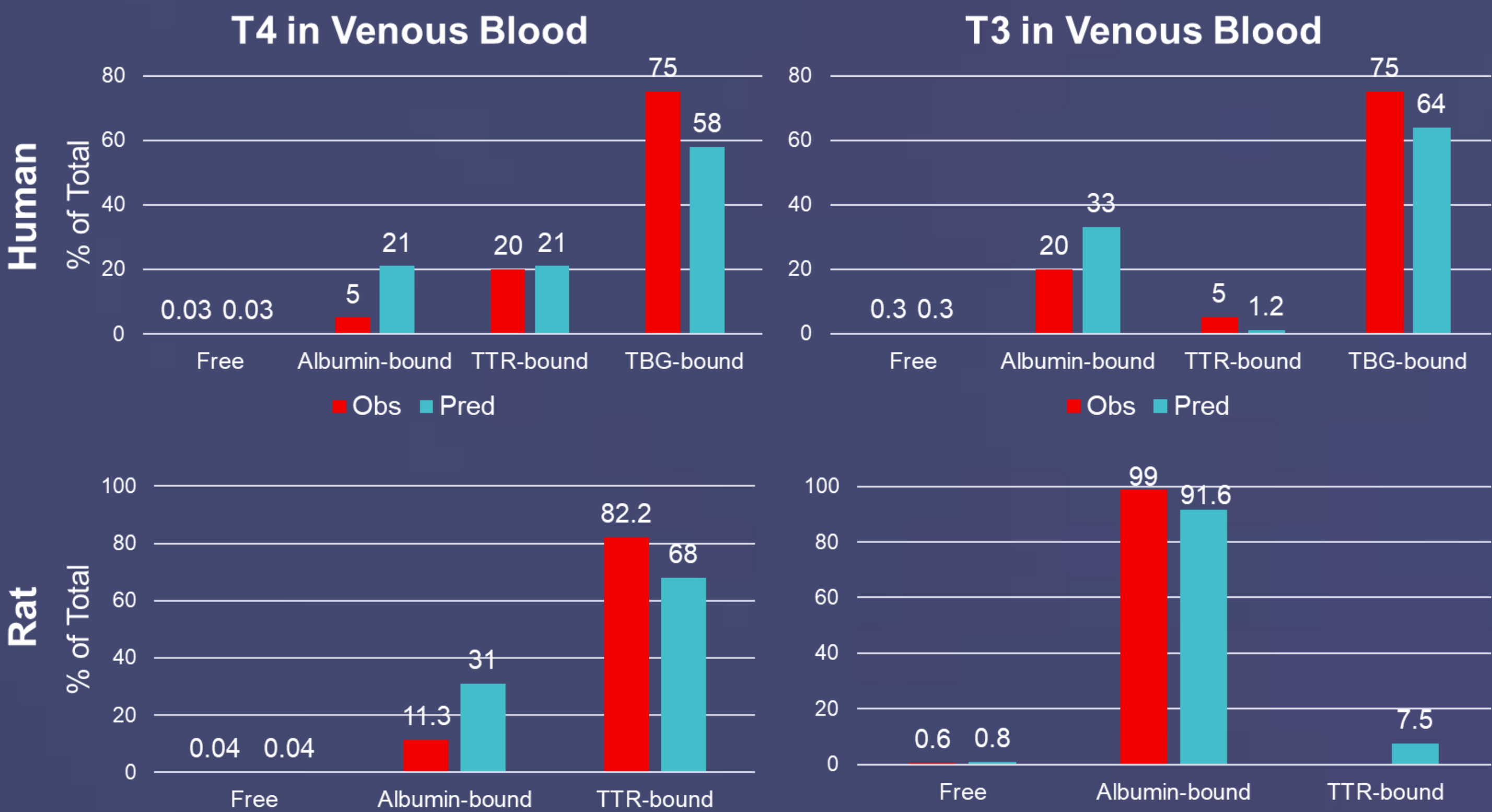


Figure 2: Predicted versus observed free TH hormone in plasma and fraction bound to the 3 carrier proteins. The upper graph depicts results for Human and the lower graphs for Rat. Data are presented as percentage of Total T4 (resp. T3) in venous blood plasma. Human data from Refetoff et al. (2000) and Schweizer et al. (2017), rat data from Davis (1970), Mendel et al. (1992) and Yang (2018)

Physiological behavior of TH regulation

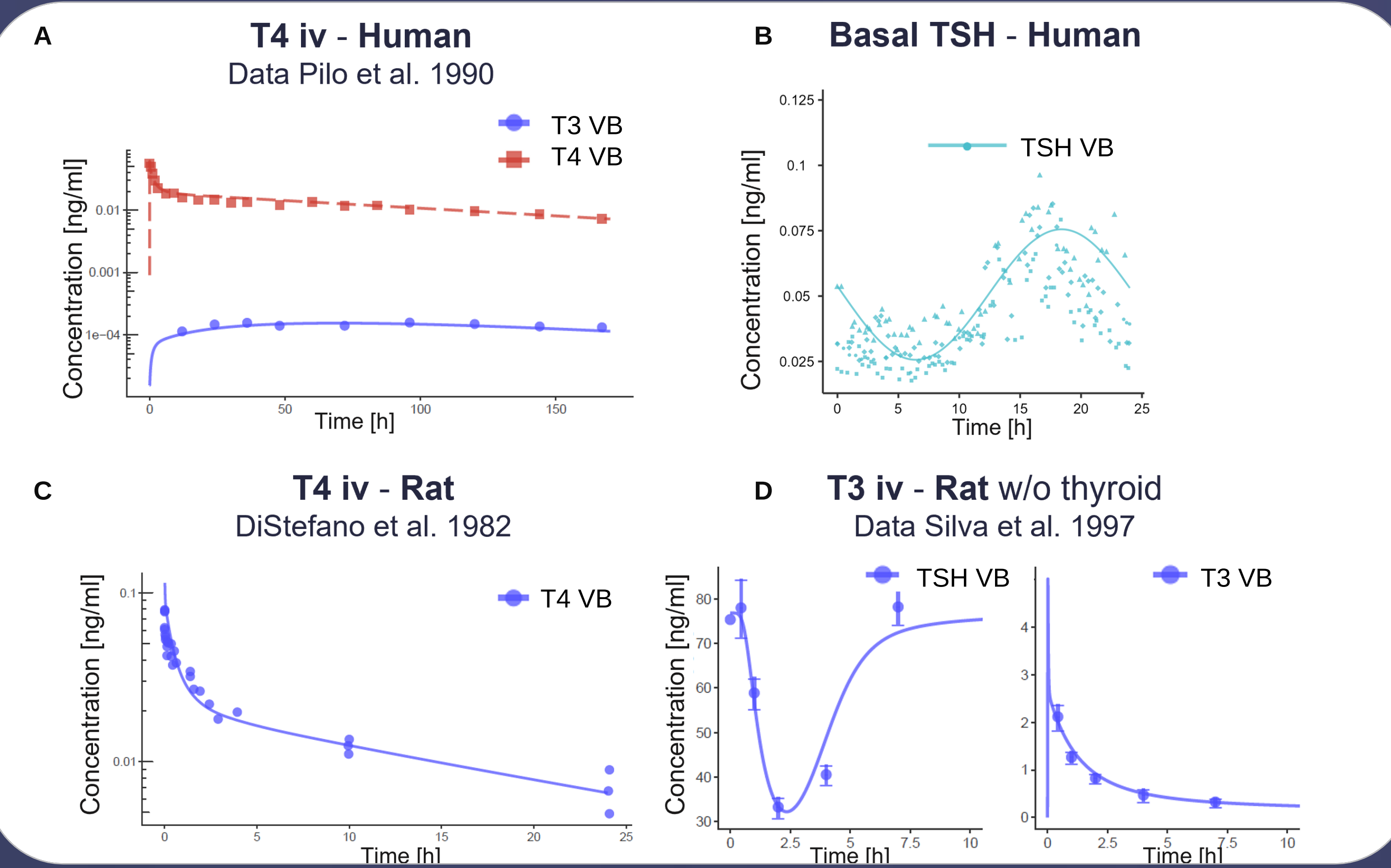


Figure 3: Comparison of simulated results and observed data of TH in Venous Blood (VB) after iv administration of (A) 0.17µg/kg T4 in humans, (C) 1.3E-5mg T4 in rats and (D) 0.7µg/kg T3 in thyroidectomized rats. (B) Basal TSH levels following a circadian cycle in humans. This basal level is altered upon injecting T3 as seen in rats (D) due to the feedback loop mechanism.

Perpetrator-induced disruption

Perpetrator (PB) iv in rats
Data Engasser et al. 1981.

Disrupted profile after T4 iv (+PB) in humans
Data Nelson et al 1982

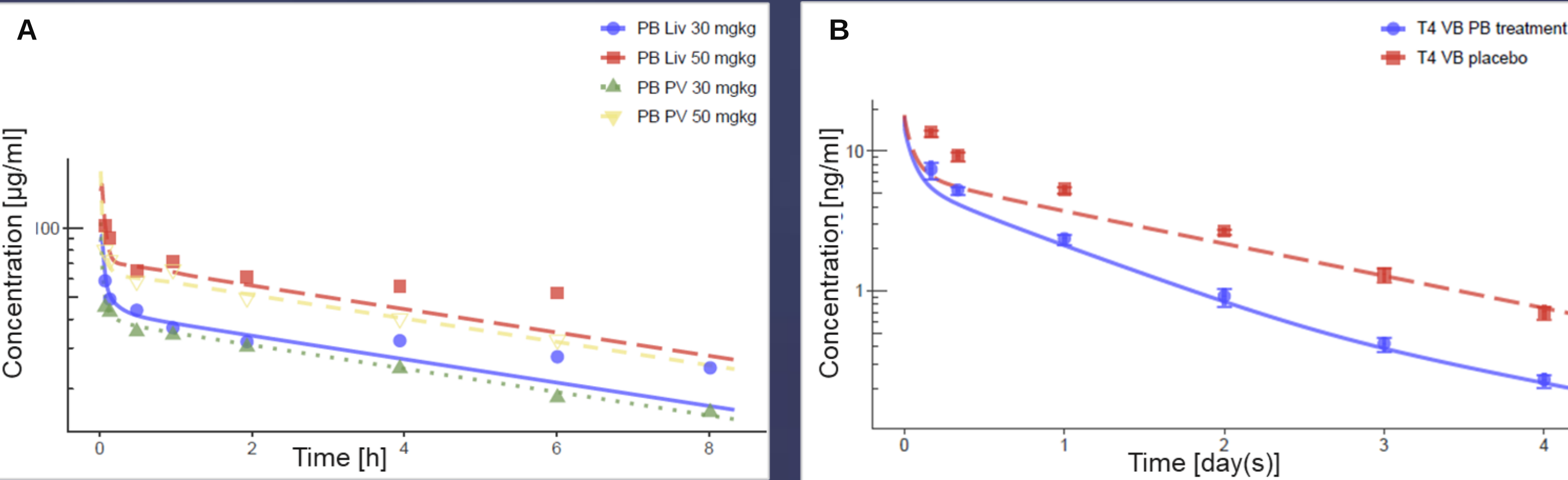


Figure 4: (A) Comparison of simulated results with observed data after iv administration of 30 and 50mg/kg bw PB. PB concentrations are reported for peripheral venous blood (PV) and liver tissue. PB is modeled as a small molecule with biliary and an unspecific liver plasma clearances. (B) tracer T4 after iv administration in untreated rats and animals treated with 100mg/kg bw/day PB for three weeks. The compound effect is modeled via induction of T4 hepatic clearance and increase of liver cell-to-plasma partition coefficient.

References

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Modeling



Scaling



Coding

