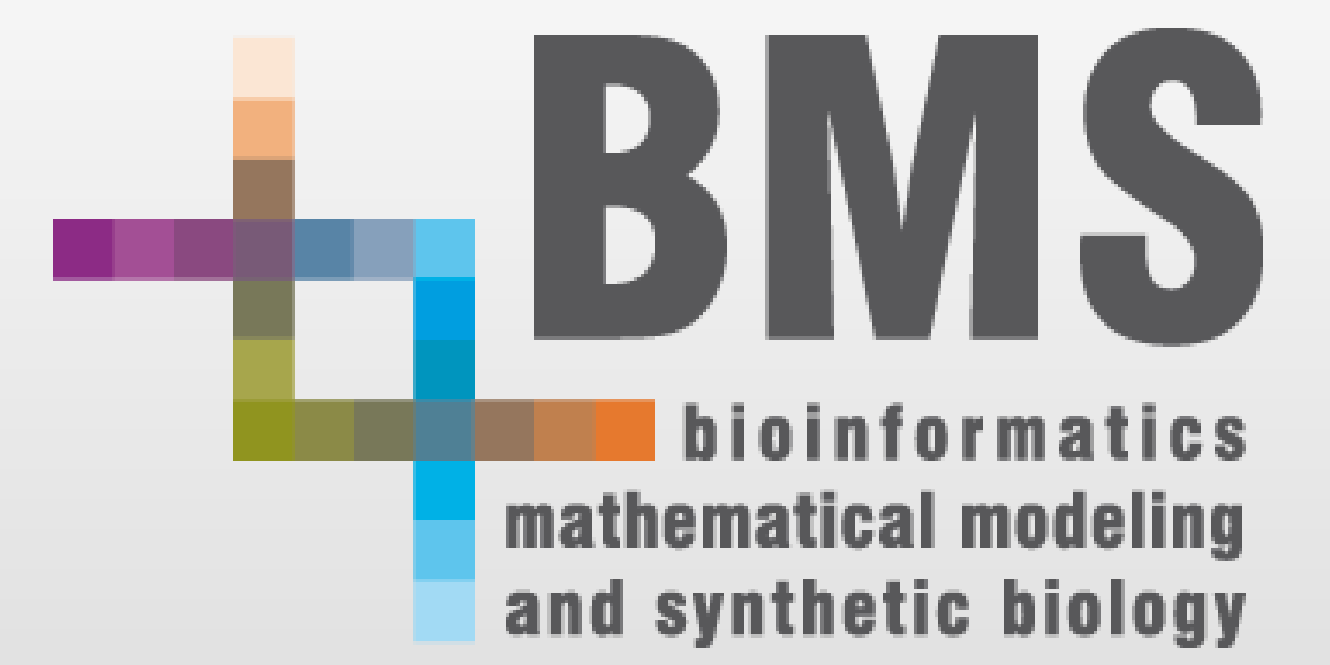


A PBPK model for the study of Azathioprine pharmacokinetics in rats and prediction in humans



Università degli studi di Pavia

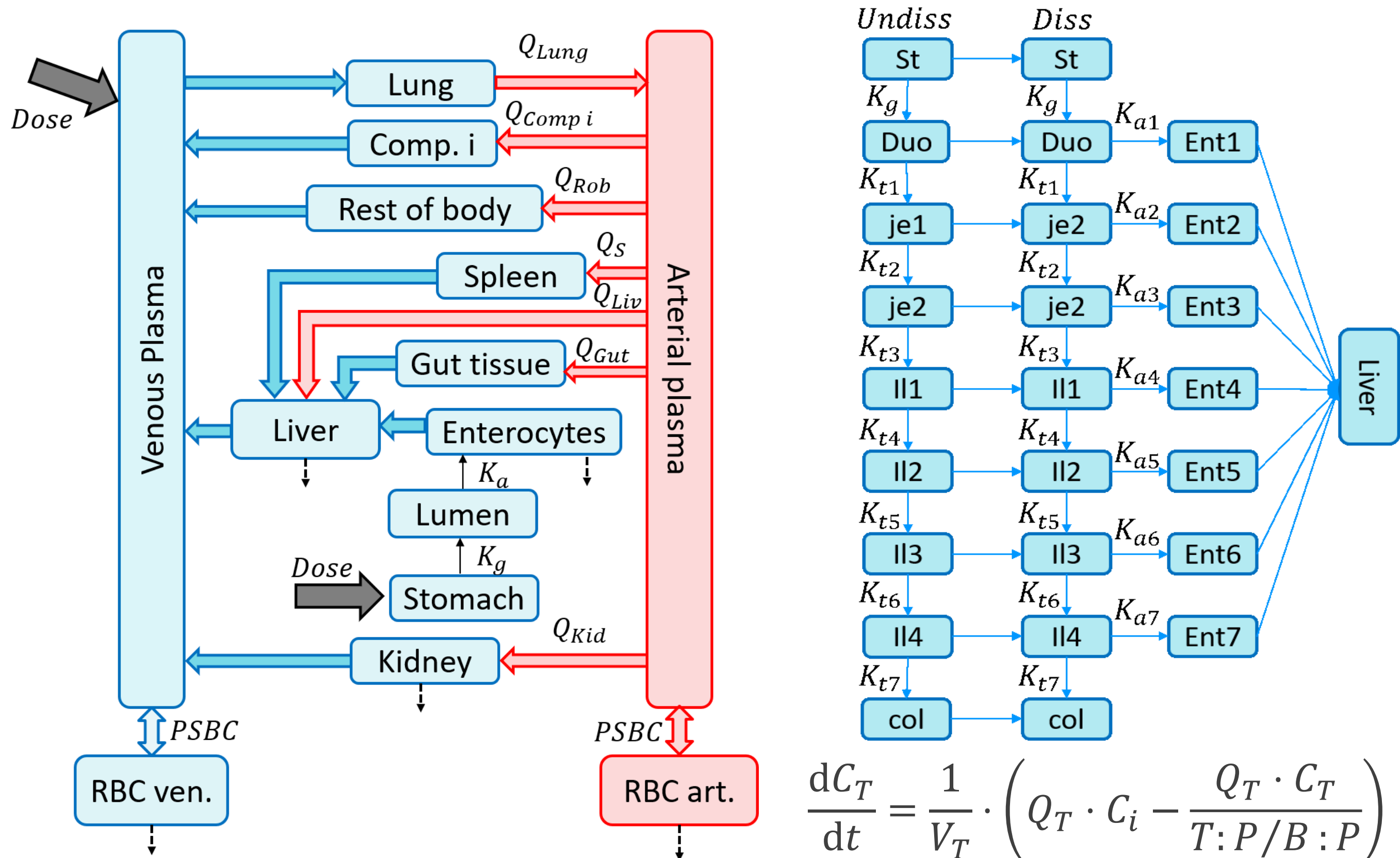
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BACKGROUND. Azathioprine (AZA) is an immunosuppressive, antimetabolite prodrug used in the treatment of autoimmune disorders [1]. A high interspecies and interindividual variability characterize the drug disposition and consequently the efficacy and toxicity. Therefore, a model that can effectively describes its metabolism is essential to investigate the causes of variability and to improve the predictions in the transition from preclinical to clinical phase. Despite AZA is a drug already on the market, it is still very studied for the Drug-Drug Interaction (DDI). A good description of AZA pharmacokinetics is therefore essential to better understand the DDI mechanism and to avoid possible toxic effects.

MATERIALS AND METHODS. Physiologically-Based Pharmacokinetics (PBPK) models were chosen to describe the plasma concentration vs time profiles of AZA and its first metabolite (both in rats and humans), as they allow to take into account physiological and anatomical differences [2].

PBPK structure. Two coupled PBPK model (for AZA and its metabolite) were developed in MATLAB with the following structure:



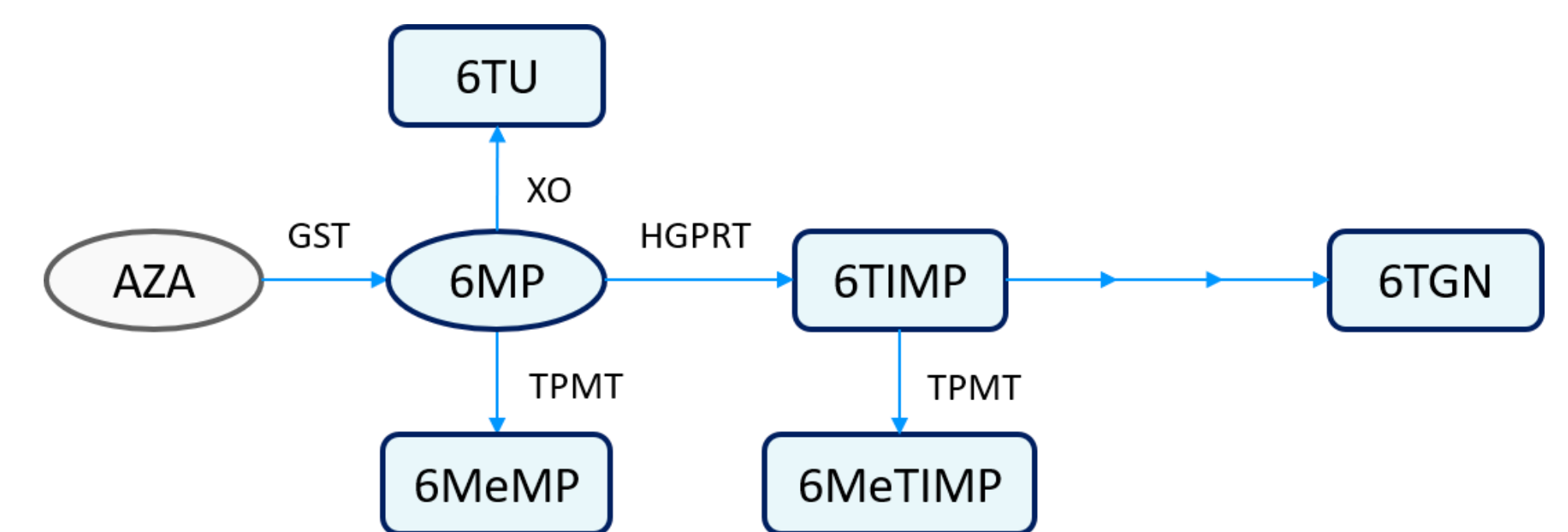
$$\frac{dC_T}{dt} = \frac{1}{V_T} \cdot \left(Q_T \cdot C_i - \frac{Q_T \cdot C_T}{T:P/B:P} \right)$$

- Physiological parameter values were obtained from literature.
- Poulin-Theil partition coefficients were adjusted with a factor K to consider active transports.
- Dissolution was modelled in humans with Noyes-Withney equation.
- PSBC is a permeability-area parameter for drug exchange with RBC.

Azathioprine metabolism. After absorption, AZA is rapidly converted in 6-Mercaptopurine (6MP) in enterocytes and hepatocytes.

6MP is metabolized by three competitive enzymes:

- Xanthine Oxidase (XO)
- Thiopurine S-methyl Transferase (TPMT)
- Hypoxanthine-Guanine Phosphoribosyl Transferase (HGPRT)



This pathway has been simplified to take into account only the conversion of AZA to 6MP and the elimination of 6MP, since the subsequent reactions are not important for the pharmacokinetic description of the two molecules.

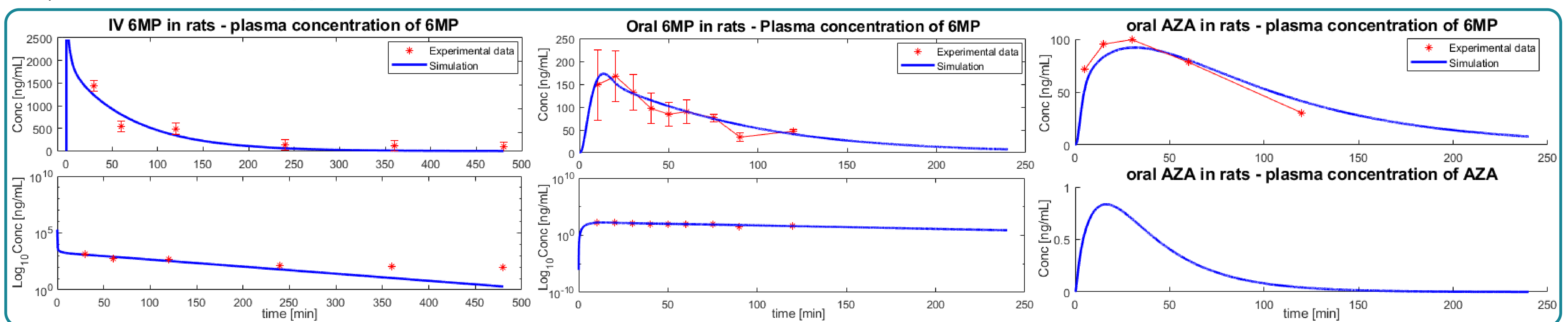
The conversion of AZA to 6MP was modelled as a first-order clearance in liver and gut mucosa, whereas 6MP metabolism was represented by Michaelis-Menten equations.

$$V = \frac{V_{max} \cdot C_T}{K_M + C_T}$$

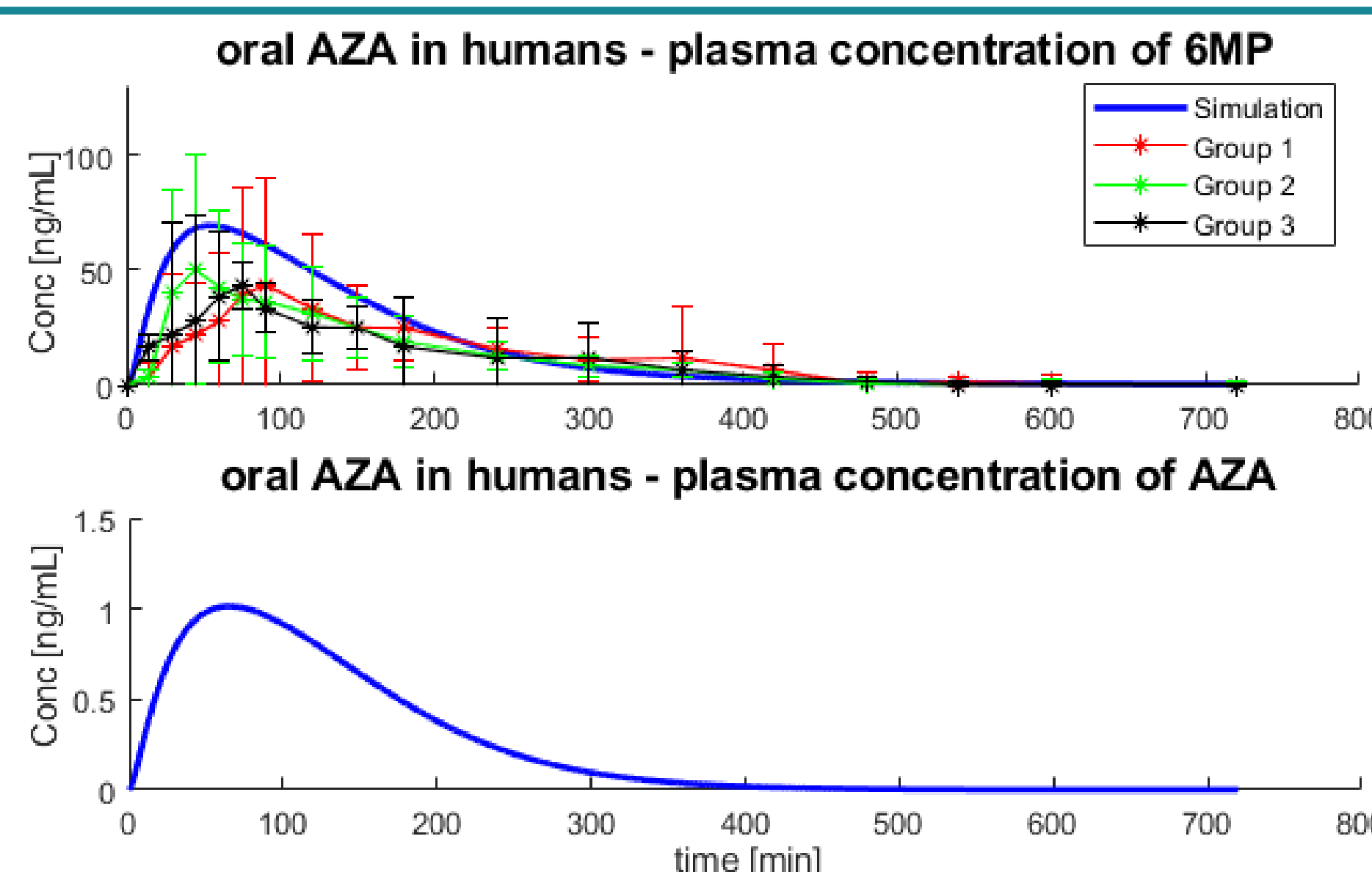
CT: concentration of the drug in the specific tissue T
Vmax, KM: Michaelis-Menten constants

The 3 reactions of 6MP were implemented in Enterocytes, Liver, kidney and Red Blood Cells (RBCs).

RESULTS. Three scenarios were simulated in rats using pre-clinical experimental data [3]-[4], in order to estimate 7 PK parameters that have not been found in literature. Physiological parameter were then scaled from rat to human under the assumption that all the physiological processes and the drug mechanism of action were the same. The model was hence used to simulate an oral administration of AZA in humans, and the predicted plasma concentration-time profile of 6MP was compared with literature data [5].



Estimated parameters		
PSBC	13.3	ml/s
K	4	---
Vmax _{XO,Liver}	50·1.5852	ng/ml·s
Peff _{6MP}	24·10 ⁻⁴	cm/s
Vmax _{TPMT,Ent}	415·16.1389	ng/ml·s
CL _{Liver}	1	1/s
CL _{Ent}	0.005	ml/s



	Cmax [ng/ml]	Tmax [s]	AUC [10 ⁵ ng·s/ml]
Predicted	69.33	54.23	6.93
Observed	43.58±45.86	90	4.93±5.61
	50.24±50.12	45	4.67±3.53
Mean	-	-	4.66
Fold Change	-	-	1.4

CONCLUSION. The transition from pre-clinical to clinical studies, a critical step in the drug development process, is generally addressed using empirical methods such as allometric scaling, which considers mainly the body weight [2]. In this work instead, a PBPK model was used to explicitly model the anatomical and physiological differences between species. The mechanistic description of AZA and 6MP metabolism in rats allowed to obtain a good prediction of the plasma concentration in humans. Therefore, the model should be useful for further DDI investigations.

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