

DEVELOPMENT AND EVALUATION OF DYNAMICAL WHOLE BODY PHYSIOLOGICALLY-BASED MODELS OF THE CIRCULATION AND THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM



Karina Claassen^{1,*}, Stefan Willmann², Thomas Eissing², Tobias Preusser^{1, 3}, Michael Block²

Bayer Technology Services

* karina.claassen@bayer.com

¹ Jacobs University Bremen, School of Engineering and Science, Campus Ring 1, 28759 Bremen, Germany

² Computational Systems Biology, Bayer Technology Services GmbH, Building 9115, 51368 Leverkusen, Germany

³ Fraunhofer MEVIS, Universitätsallee 29, 28359 Bremen, Germany



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Objectives

The Renin-Angiotensin-Aldosterone System (RAAS) plays an important role in the homeostasis of the water balance and blood pressure. It constitutes a key factor in cardiovascular disorders like hypertension, emphasizing it as a top target in drug design. This work is aimed to develop a whole body physiologically based pharmacokinetic (wb PBPK) model including a dynamic submodel of the RAAS including dynamically wb PKPB models for all main actors. In [figure 1] the enzymatic cascade for the main processes in the RAAS are depicted. Angiotensinogen (AGT) is secreted by the Liver which is then converted by the renally secreted enzyme renin to angiotensin 1 (Ang 1) and further to angiotensin 2 (Ang 2) by the membrane bound angiotensin1-converting-Enzyme (ACE). Ang 2 binds to the angiotensin 2 receptor type 1 (AT1), which then influences the aldosterone (Aldost) synthesis from the kidney. Additionally Ang 2 concentration acts in a negative feedback loop for the renin synthesis from prorenin. The applicability of this model is shown exemplary for the ACE inhibitor enalapril (Ena). Ena is a prodrug which is converted to enalaprilat (Enaat) intrahepatically. Two separate dynamical wb PBPK models were developed for Ena and Enaat. After coupling they were able to predict the Enaat conversion in the liver.

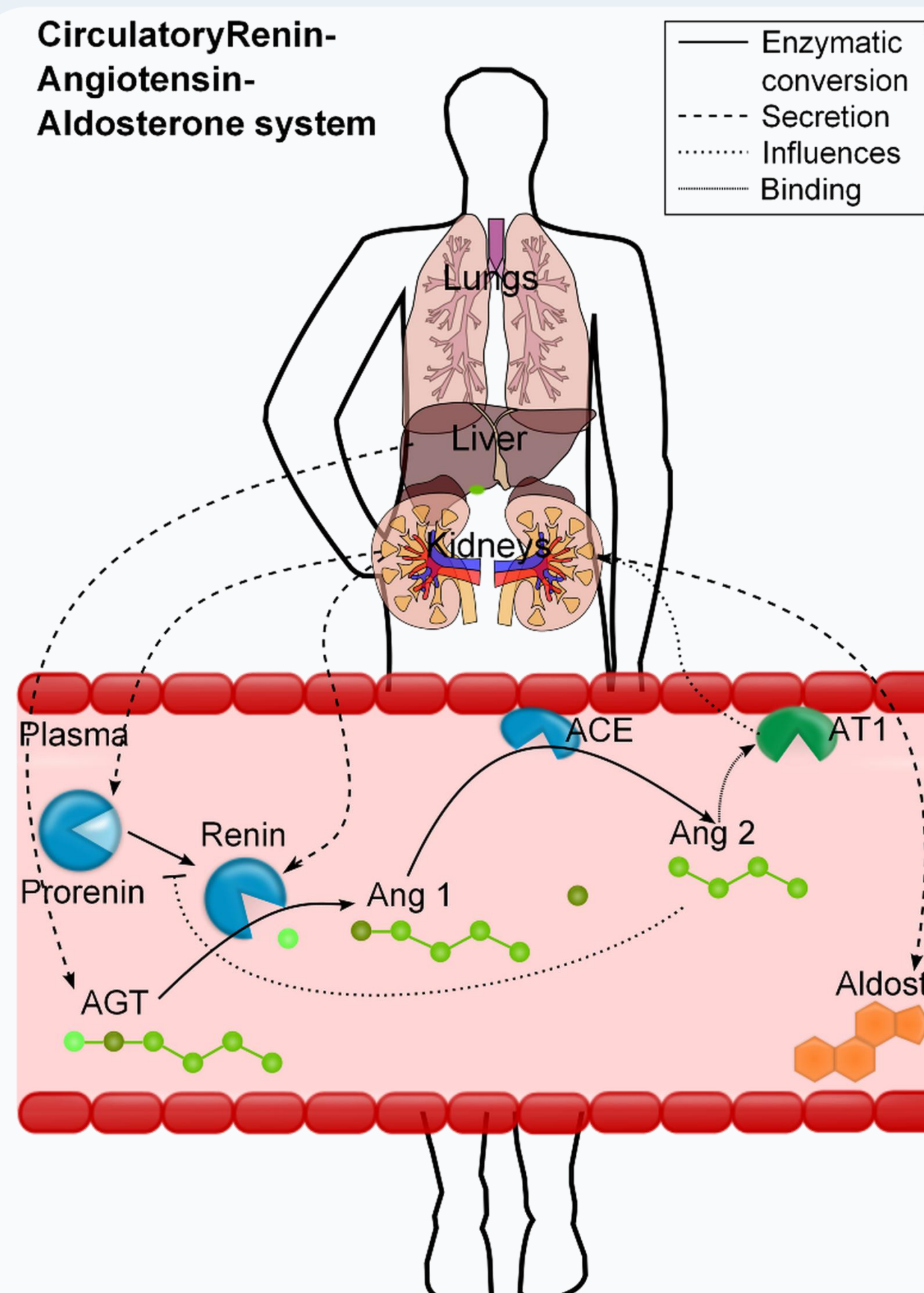


Figure 1: Schematic model of the enzymatic cascade of the RAAS. Enzymatic conversions take place in the plasma. ACE and AT1 are membrane bound. Solid arrows represent enzymatic conversions, dotted lines are secretion or binding processes as depicted in the upper right box.

Results

The two PBPK models are coupled via a hydrolytic reaction in the hepatocytes. Model parameters estimated in the separate models were kept constant. The coupled PBPK model of Ena and Enaat shows very good agreement with different experimental data as shown in [figure 2]. Additionally the Enaat plasma concentrations are accurately predicted compared to the presented experimental data.

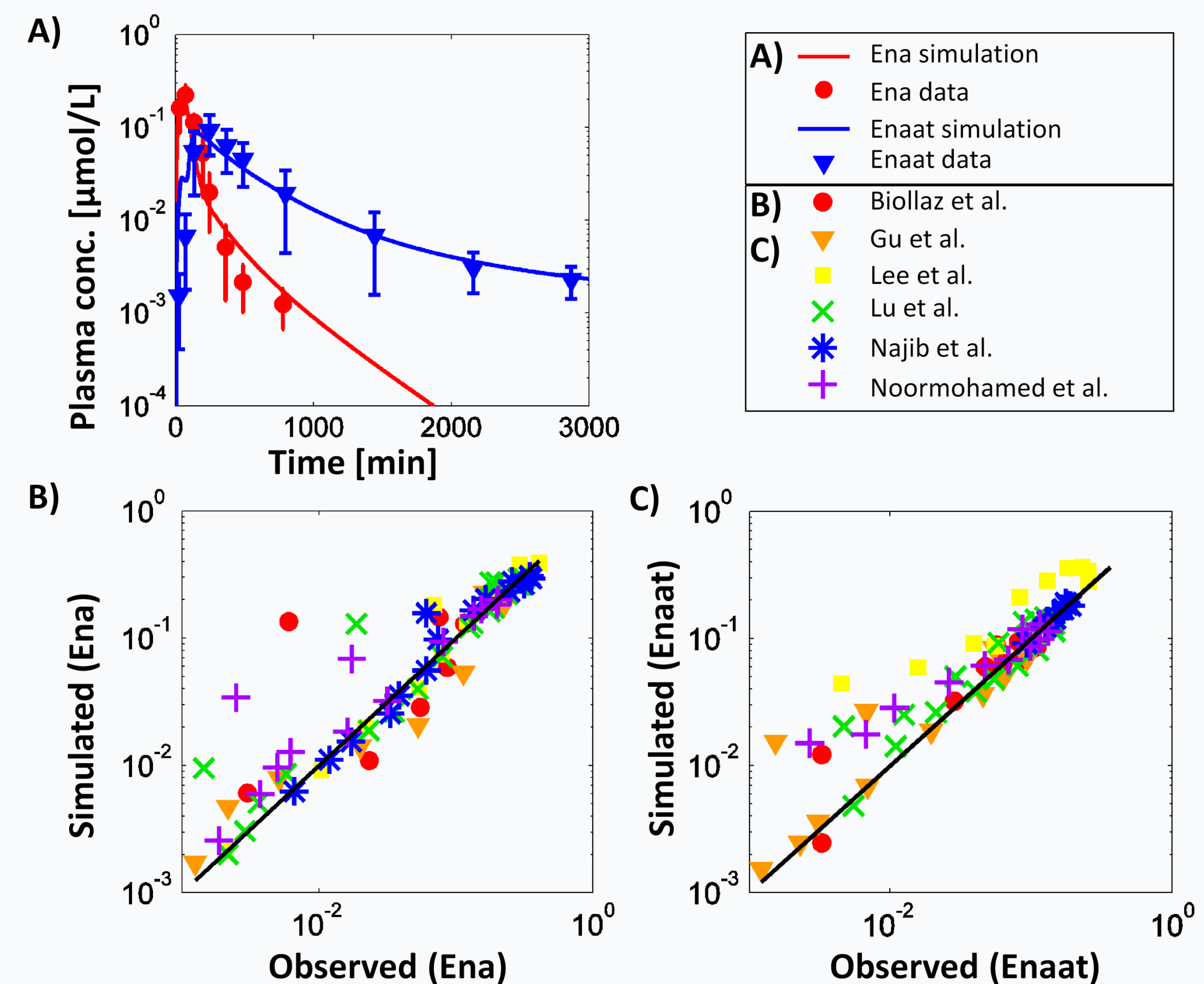


Figure 2: A) Plasma concentration-time profiles of Ena and Enaat from the coupled model, in comparison with experimental data [2]. B) Predicted versus observed plot for Ena from the coupled model, compared to the data by [1-6]. Regression line denotes the line of identity. C) Predicted versus observed plot for Enaat from the coupled model, compared to the data by [1-6]. Regression line denotes the line of identity.

Methods:

1. The Enalapril/ Enalaprilat model

Two separate PBPK models of oral Ena [figure 2] and intravenous (IV) Enaat (not shown) were developed with PK-Sim[®] and then coupled with MoBi[®] [15]. The association ($k_{\text{Association}}$) and dissociation ($k_{\text{Dissociation}}$) constants for Enaat binding to ACE were fitted with the Enaat IV model to data presented by Hocking et al. [13]. The obtained parameters were then used in the coupled model without any changes. The oral Ena model has been compared to different experimental data [1-6]. Physicochemical properties included in the two models are presented in Table 1.

Table 1: Physicochemical properties of Ena and Enaat

Property	Ena	Enaat	Unit	References
Molecular weight	376.5	348.4	g/mol	[7]
Log P	0.07	-0.740	Log Units	[8]
pKa	4.74	2.03	-	[8]
		4.03		
Plasma protein binding	55	84	%	[9]
Hepatic clearance	-	197.0	ml/min	[10]
Renal clearance	28	4.6	ml/min/kg	[10]
Clearance via feces	15.1	187.0	ml/min	[10]

The coupling of both models was realized via the following equation:

$$\frac{dC_{\text{Enaat}}}{dt} = \frac{V_{\text{MaxOrg}} \cdot C_{\text{Ena}}(t)}{C_{\text{Ena}}(t) + K_{\text{mOrg}}} \quad (1)$$

The coupled model was assessed on its ability to predict the PK of both plasma concentrations (Ena and Enaat) with different publications and experiments [1-6]. Plasma concentrations of Enaat after oral Ena administration were predicted.

2. The RAAS model:

The RAAS model consists of seven separate PBPK models for Aldost, ACE, Ang 1, Ang 2, AT1, renin and prorenin. The model includes the hormone cascade as depicted in [figure 1]. For all hormones the following rates have been included:

- production rates in the respective organ
- secretion rates from the respective organ
- decay rates from the plasma

Model structure was realized as shown in [figure 1] and corresponds directly to physiological description in literature. Couplings between the models are mediated by Michaelis-Menten kinetics as for example by:

$$\frac{dC_{\text{Hormone}}}{dt} = \frac{V_{\text{MaxOrg}} \cdot C_{\text{Enzyme}}(t) \cdot C_{\text{Prehormone}}(t)}{C_{\text{Prehormone}}(t) + K_{\text{mOrg}}} \quad (2)$$

The competitive inhibition of renin production by Ang2 conc. was mediated by:

$$\frac{dC_{\text{Renin}}}{dt} = \frac{V_{\text{MaxOrg}} \cdot C_{\text{Prorenin}}(t)}{C_{\text{Prorenin}}(t) + K_{\text{mOrg}} \left(1 + \left(\frac{C_{\text{Ang2}}(t)}{K_{\text{inhibition}}} \right) \right)} \quad (3)$$

ACE expression data were included from data source [14]: The two presented models are coupled via the following equation for Enaat binding to ACE.

$$\frac{dC_{\text{EnaatACE}}}{dt} = (k_{\text{Association}} \cdot C_{\text{ACE}} \cdot C_{\text{Enaat}}(t)) - (C_{\text{Enaat}}(t) \cdot C_{\text{ACE}}(t) \cdot k_{\text{Dissociation}}) \quad (4)$$

Abbreviations: C_{Ena} = Concentration of enalapril, C_{Enaat} = Concentration of enalaprilat, C_{ACE} = ACE concentration, C_{Enzyme} = the respective enzyme concentration, $C_{\text{Prehormone}}$ = the respective Prehormone concentration, C_{Ang2} = the Angiotensin 2 concentration, C_{ref} = reference concentration, V_{maxOrg} = Specific Vmax, K_{mOrg} = Specific Km, $k_{\text{inhibition}}$ = the inhibition constant, $k_{\text{Association}}$ = association constant, $k_{\text{Dissociation}}$ = dissociation constant

The results in [figure 3] show that the RAAS model is able to very well represent all measured circulating plasma hormone levels [11] at steady-state. The simulation of ACE-inhibitor Ena administration (administration at $t=1500$) shows, that the full dynamical behavior of ACE and the other RAAS-hormone levels can be very well represented [figure 3]. Following the hormone cascade, ACE is blocked, which decreases the conversion of Ang 1 to Ang 2. As expected renin and Ang 1 plasma levels increase after ACE inhibition, while Ang 2 and Aldost levels decrease.

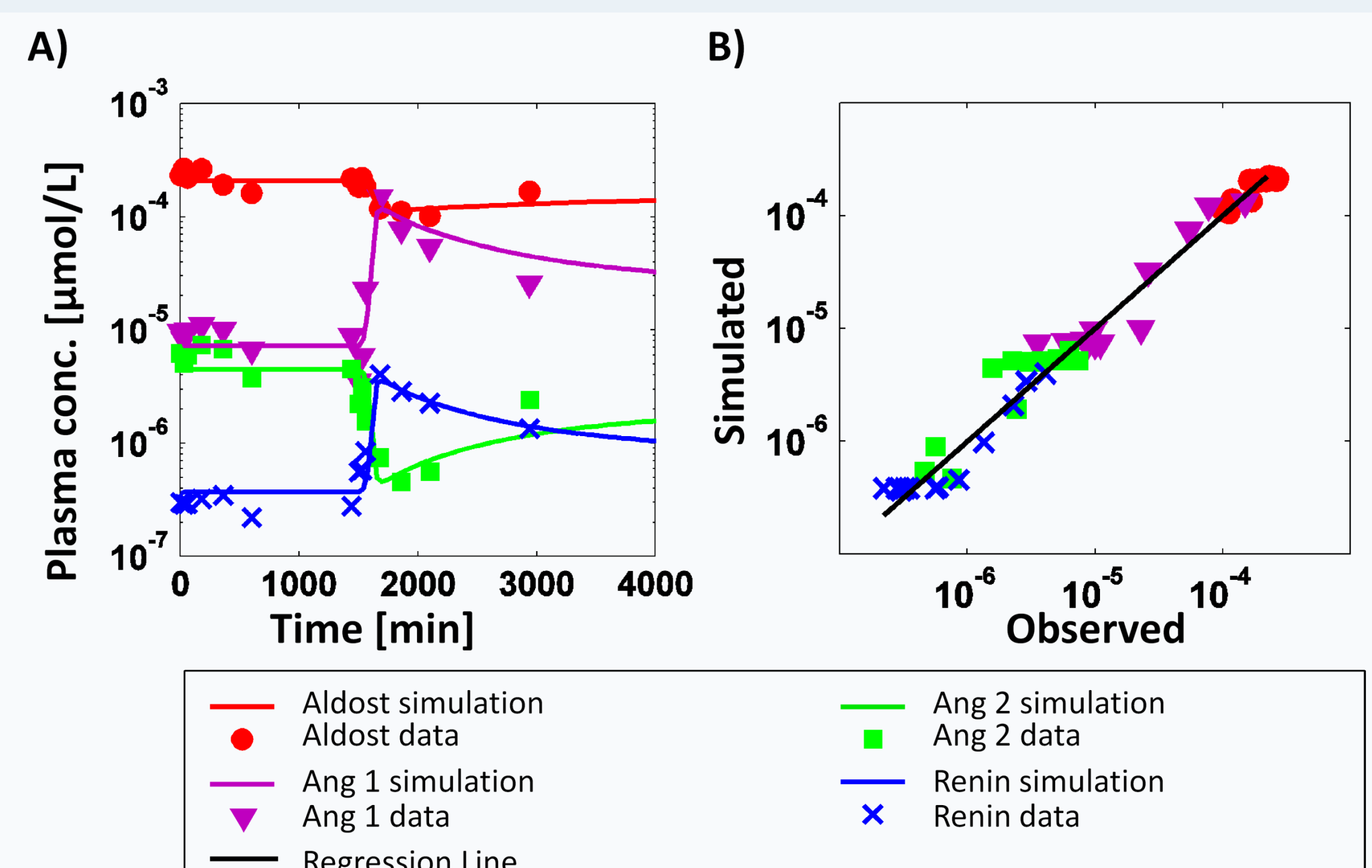


Figure 3: A) Plasma concentration-time profiles for hormones of the RAAS. Hormones are in a steady state until administration of oral Ena at $t=1500$ min. The curves then represent the hormonal changes after ACE inhibition by Ena. PK data is depicted by different symbols [11]. B) Predicted versus observed plasma concentrations of different hormones belonging to the RAAS after inhibition of ACE by Ena. Hormone data is depicted by different symbols [11]. Regression line denotes the line of identity.

Conclusions

A coupled model consisting of PBPK models for Ena and its active metabolite Enaat and full mechanistic representation of the RAAS was developed. The model is able not only to represent the pharmacokinetics of the prodrug Ena and the metabolite Enaat very well, but also the hormone cascade of RAAS in a very accurate manner, indicating a sufficient description of the underlying physiological processes. This model constitutes a first major step to establish a PBPK-PD model including the PK, the coupling to the mode of action (MoA) via RAAS and soon the PD (regulation of blood pressure). In the next step the model will be extended for detailed representation of the arterial blood pressure, which offers the opportunity to represent the relationships between blood pressure, blood volume (systemic, pulmonary, arterial, venous), heart rate, resistances and compliances. This will lead to a mechanistic representation of the PBPK-PD relationship in cardiovascular diseases and thus help to facilitate dose and dosing regimen decisions in this area.

References

- [1] Biollaz (1984), Br J Clin Pharmacol 14, 363-368.
- [2] Gu (2004), J Chromatogr B Analyt Technol Biomed Life Sci 813, 337-342.
- [3] Lee (2003), Rapid Commun Mass Spectrom 17, 1157-1162.
- [4] Lu (2009), J Pharm Biomed Anal 49, 163-167.
- [5] Najib (2003), Biopharm Drug Dispos 24, 315-320.
- [6] Noormohamed (1990), J Pharmacol Exp Ther 253, 362-368.
- [7] Wang (2012), Nucleic Acids Res 40, 2.
- [8] Remko (2007), Chemical Papers 61, 133-141.
- [9] Sirianni, (1998), Drug Metab Dispos 26, 324-331.
- [10] Dhareeswar (2007).
- [11] Nussberger, Hypertension 39, E1-8.
- [12] Juillerat, Hypertension 16, 564-572.
- [13] Hockings, (1986), Br J Clin Pharmacol 21, 341-348.
- [14] Cited in PK-Sim5, Protein expression database, Gene ID 1636; information from Unigene. www.ncbi.nlm.nih.gov/gene/1636
- [15] Eissing, (2011), Front Physiol. 2, 4.