



Muhammad W. Ashraf¹, Panu Uusalo^{1,2}, Mika Scheinin³ and Teijo I. Saari^{1,2}

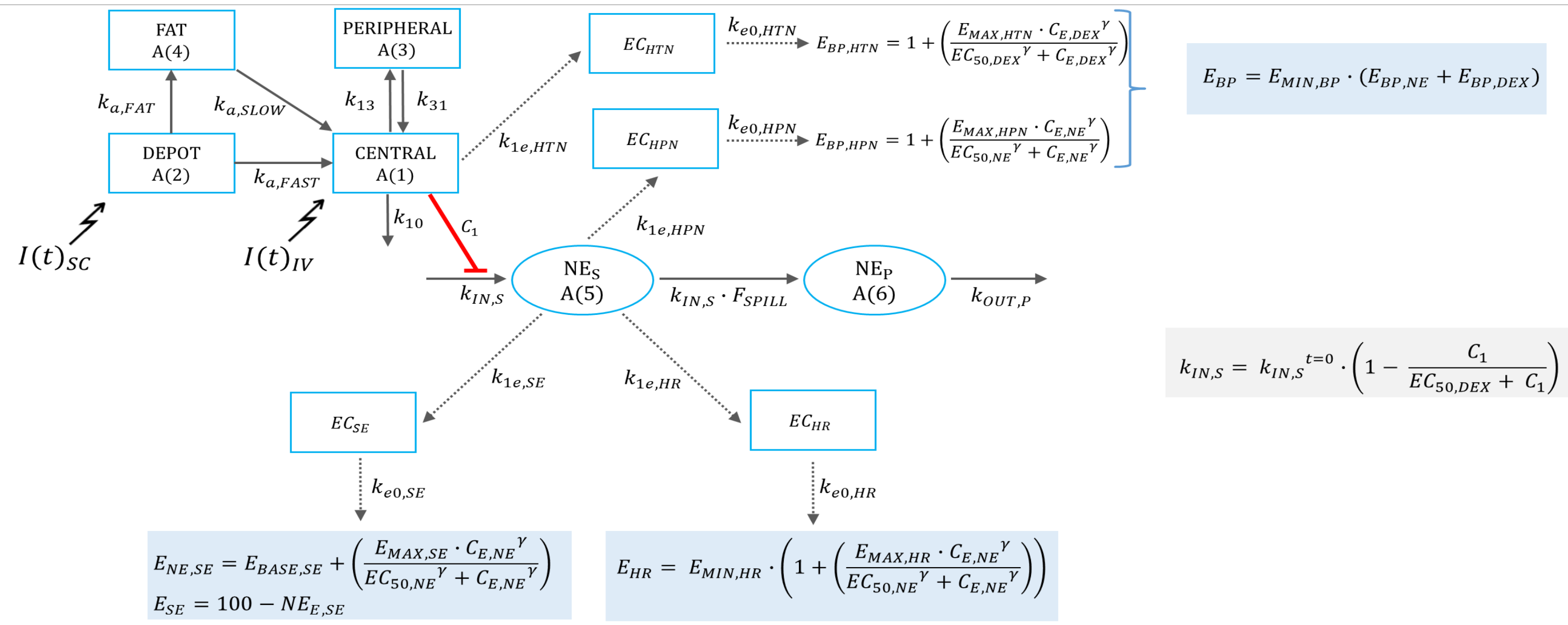
¹Department of Anesthesiology and Intensive Care, University of Turku, Turku, Finland. ²Division of Perioperative Services, Intensive Care and Pain Medicine, Turku University Hospital, Turku, Finland. ³Institute of Biomedicine, University of Turku, and Unit of Clinical Pharmacology, Turku University Hospital, Turku, Finland



- Intravenous (IV) dexmedetomidine, an α_2 -agonist, is licensed for sedation of surgical and intensive care patients. Extravascular administration of dexmedetomidine would be favored in palliative care.
- Subcutaneous (SC) infusion of dexmedetomidine could be a suitable alternative, as it provides therapeutic plasma concentrations with less unwanted effects.¹
- Our aim was to use previously collected data to develop a semimechanistic model to characterize dexmedetomidine pharmacokinetics (PK) and sympatholytic, hemodynamic and sedative effects of dexmedetomidine after IV and SC dosing.

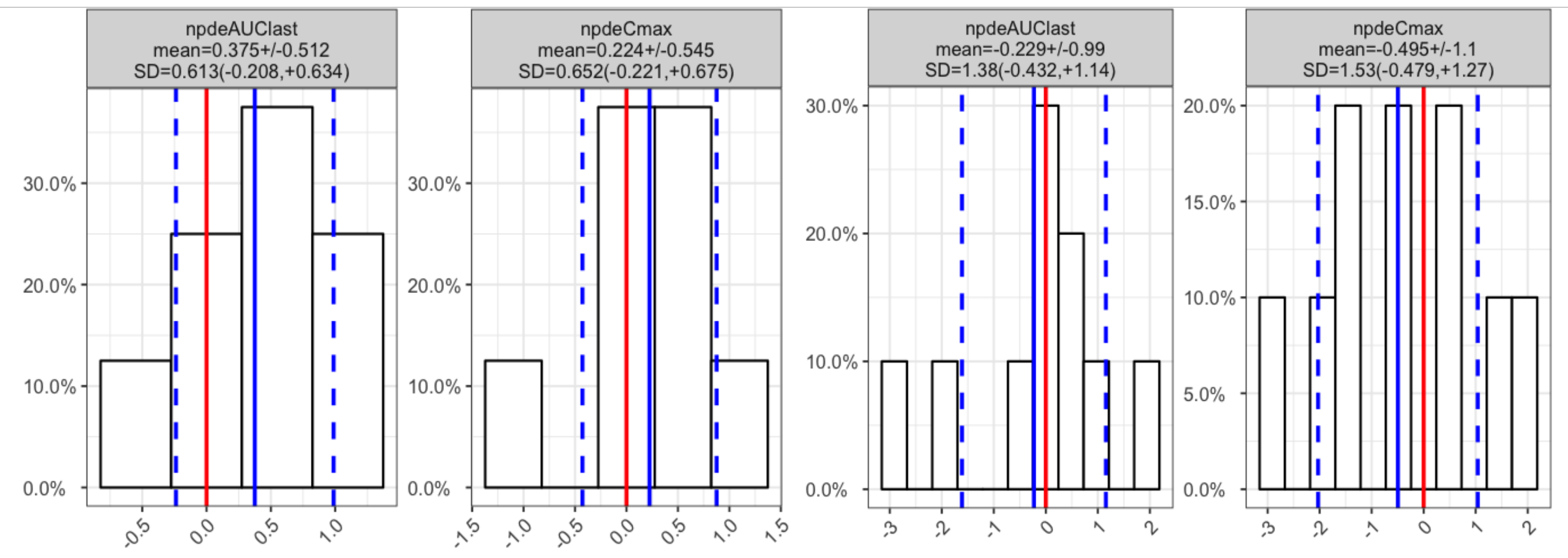
- Pharmacokinetic and –dynamic (PD) data was used from our recently published work¹
- Non-linear mixed effects modelling was conducted using **NONMEM**® (v. 7.3.0, ICON Development Solutions, Ellicott city, MD, USA)² supported by Perl-Speaks-NONMEM toolkit (**PsN**, v. 4.6.0 or above)³ for model development, execution and evaluation. **RStudio** (v. 1.0.153 or above) using R (v. 3.4.0 or above)⁴ was used for diagnostic model evaluation and graphing
- Model parameters were estimated using first order conditional estimation with interaction (**FOCE-I**), and **ADVAN13** subroutine
- **Sequential PK-PD modelling** approach was used
- Disposition model was developed with IV data, followed by absorption model for SC administration. Final PK model was validated with IV and SC data.
- PD model was developed for norepinephrine concentration-time data followed by effect models for heart rate, systolic and diastolic blood pressure, and subjective vigilance and performance were developed .
- Models were evaluated according to the recent guidance.⁵

Figure 1. Schematic representation of the final semi-mechanistic PKPD model



- Dexmedetomidine disposition kinetics was adequately accounted by a two compartment model (Fig. 1), while absorption after SC dosing was accurately predicted by biphasic absorption ($K_{A,FAST}$ and $K_{A,SLOW}$) and a fat compartment (Fig 2,3, Table 1)
- Indirect response model adequately predicted the time course of norepinephrine conc. after dexmedetomidine challenge. Epinephrine model could not be successfully developed due to abundance of below limit of quantification (BLQ) values in the data
- E_{MAX} -models could accurately predict heart rate and blood pressure (Fig.3)
- Biphasic approach for BP modelling i.e. inhibition of NE caused a hypotensive while dexmedetomidine was responsible for a dose dependent direct hypertensive effect
- Subjective effects of vigilance and performance were predicted in line with the observations (Fig. 2)
- Simulations indicate no cumulation after subcutaneous dosing (Fig. 4)

Figure 3. Histogram of the NPDE values of the NCA metrics for IV and SC dosing



- Our PK model provides a **mechanistic exploration of the absorption process and disposition after SC dexmedetomidine** with excellent precision.
- Indirect response model accurately accounted for the inhibition of NE release to control the diverse effects of the drug.
- Our model provides **accurate and clinically plausible predictions**, which can guide clinical decision in palliative care through simulating scenarios of interest.

Table 1. Parameter estimates from the final model for Dexmedetomidine and Norepinephrine

Parameter	Description	Parameter estimate Mean	Parameter estimate %RSE	Bootstrap results Median	Bootstrap results 95% CI
Dexmedetomidine					
Cl_1	Elimination clearance	44.5	15.1	43.5	[37.7, 52.4]
V_1	Volume of the central compartment	18.3	38.0	17.7	[13.8, 27.9]
Cl_2	Inter-compartmental clearance	115	4.0	115	[101, 133]
V_2	Volume of the peripheral compartment	77.6	2.2	77.6	[71.9, 83.2]
$k_{a,FAST}$	Rate constant for fast absorption	1.11	15.3	1.09	[0.652, 1.95]
$k_{a,SLOW}$	Rate constant for slow absorption	0.130	24.3	0.131	[0.054, 0.165]
$K_{f,FAT}$	Rate constant for partitioning to subcutaneous fat	3.11	20.2	3.07	[1.76, 4.99]
$\eta_{1,CL1}$	Interindividual variability on CL_1	0.266	31.2	0.243	[0.094, 0.377]
$\eta_{2,V1}$	Interindividual variability on V_1	0.570	43.2	0.532	[0.279, 0.769]
$\sigma_{PROP,IV}$	Proportional RE for intravenous dosing	0.152	5.9	0.150	[0.107, 0.183]
$\sigma_{PROP,SC}$	Proportional RE for subcutaneous dosing	0.194	7.8	0.191	[0.138, 0.231]
Norepinephrine					
E_{MAX}	Scaling factor for E_{MAX}	1 (FIXED)			
$C_{50,NE}$	DEX concentration at 50% maximal inhibition in NE production	0.310	13.2	0.310	[0.202, 0.576]
$C_{NE,0}$	Baseline NE concentration in effect compartment	0.805	19.0	0.804	[0.672, 0.989]
$k_{OUT,S}$	Rate constant for NE spill-over from synthesis compartment	9.31	16.1	9.28	[7.12, 13.9]
$f_{NE,SPILL}$	Spill-over fraction to plasma	0.15 (FIXED)			
$k_{OUT,P}$	Rate constant for NE elimination from plasma	11.3	8.5	11.3	[9.83, 15.3]
$\eta_{1,C_{E,0}}$	Interindividual variability on $C_{E,0}$	0.449	21.0	0.422	[0.203, 0.588]
$\eta_{2,k_{OUT,S}}$	Interindividual variability on $k_{OUT,S}$	0.227	36.8	0.219	[0.083, 0.404]
$\sigma_{ADD,NE}$	Additive RE for NE model	0.113	4.7	0.111	[0.093, 0.130]

Figure 2. Visual Predictive Checks (VPCs) from the final PK and PD models

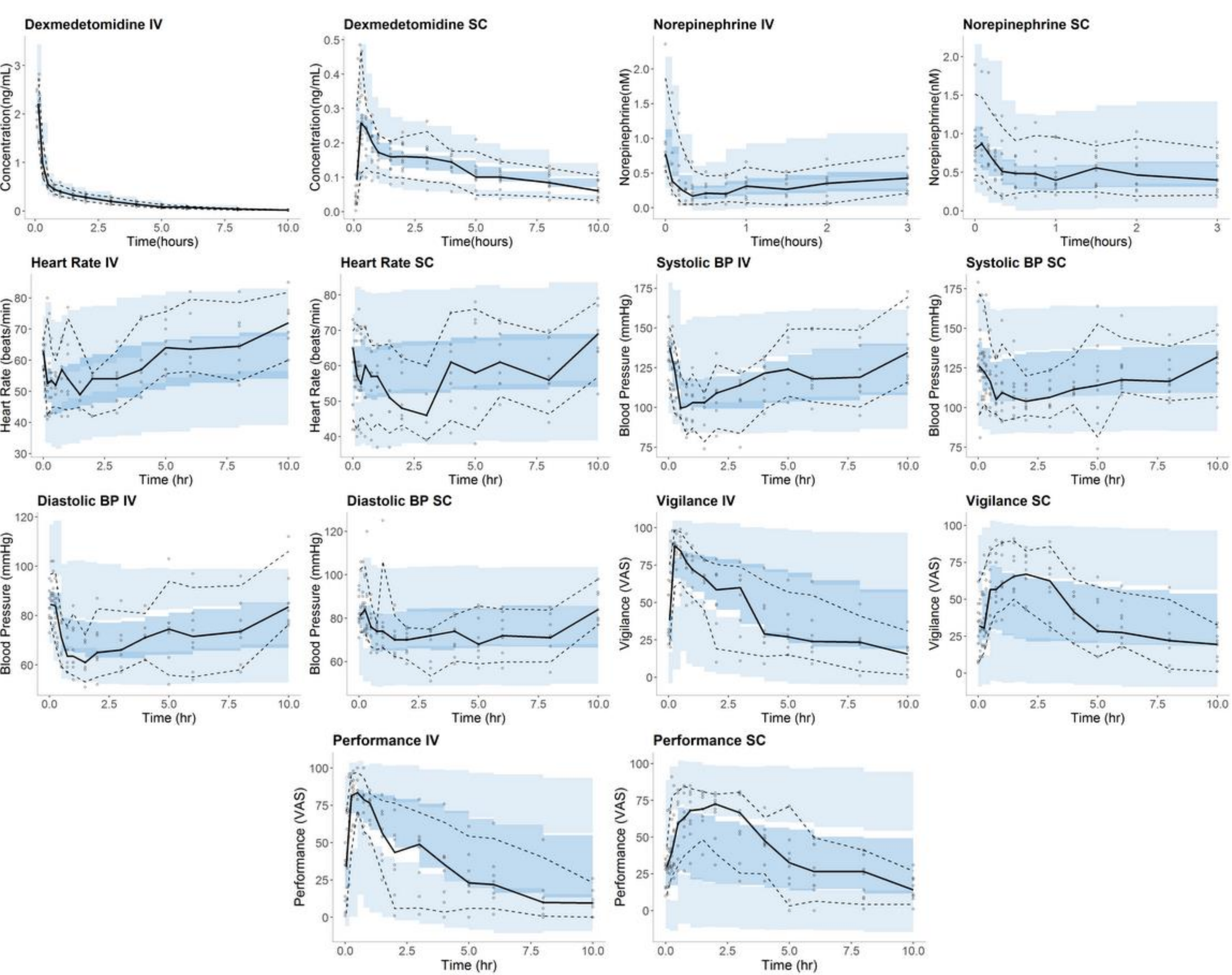
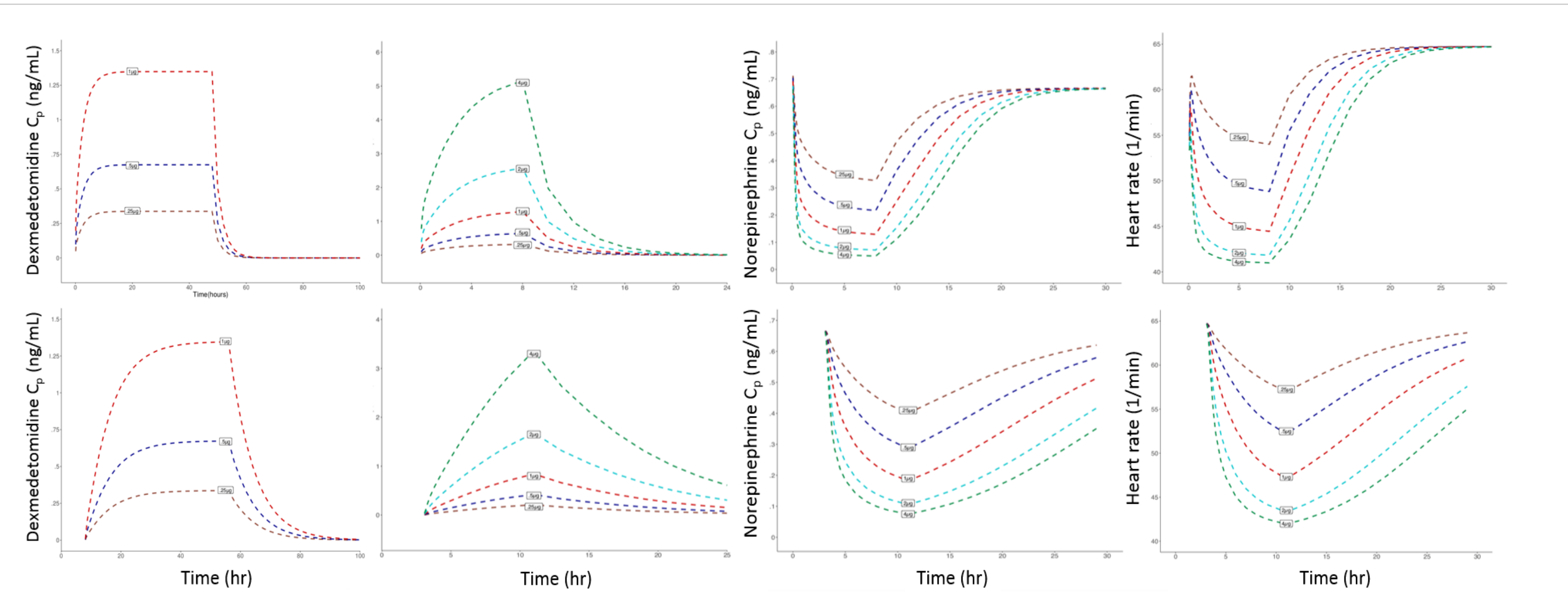


Figure 4. Simulations from the final PK model (8h/48h continuous dexmedetomidine infusions via IV and SC routes), and PD models for NE and HR (8h dexmedetomidine infusion)



Contact information:

MUHAMMAD WAQAR ASHRAF

muwaas@utu.fi, +358414833401

ORCID ID: 0000-0002-9947-1579

Web: <https://www.utu.fi/en/people/muhammad-ashraf>

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