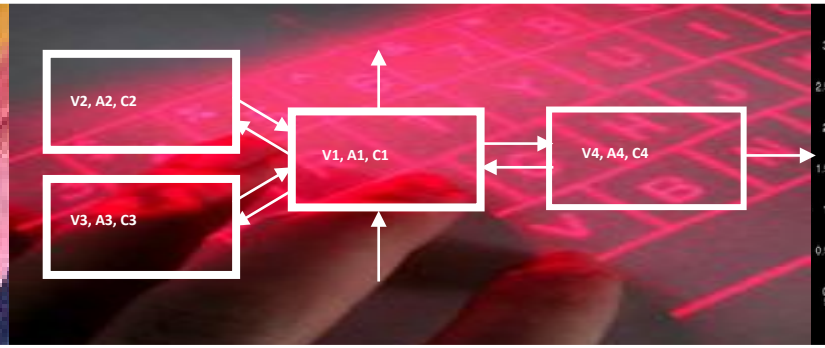

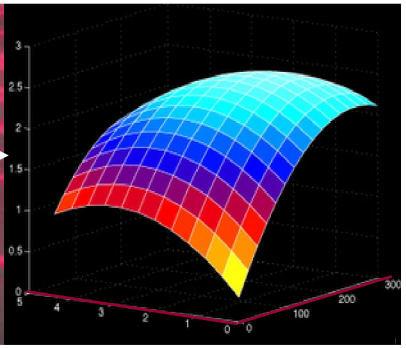

The miracle of smart data in unravelling pharmacokinetic- and pharmacodynamic relationships

Liesbeth de Lange, PhD, PharmHD, FAAPS

Professor in Predictive Pharmacology
Leiden University (ULEI)

4th General Assembly Meeting, Barcelona, 5th – 7th December 2022

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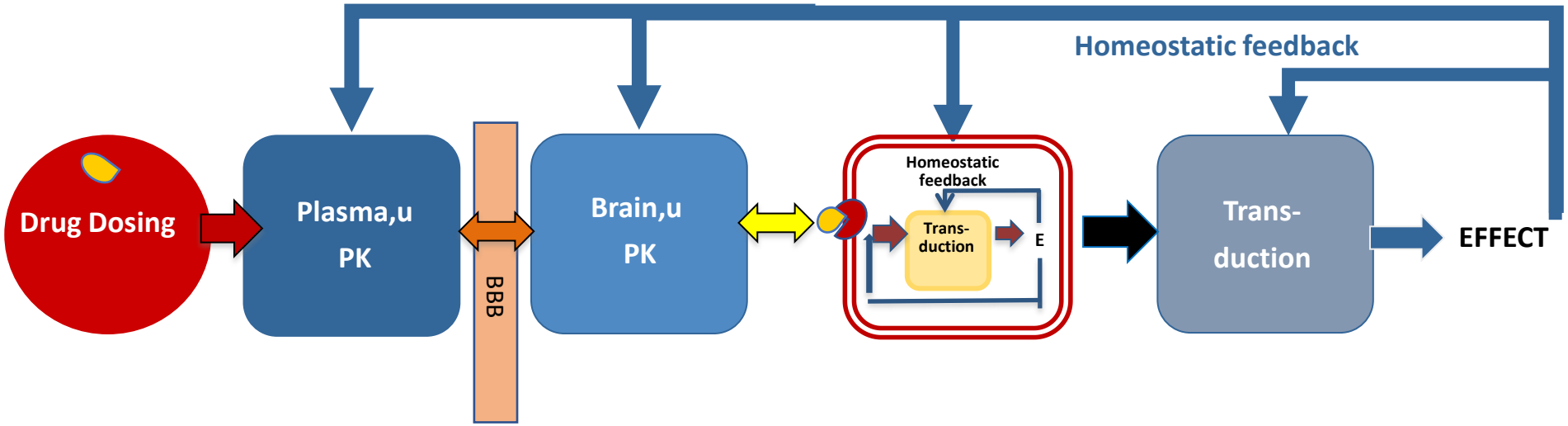
Universiteit Leiden The Netherlands

LACDR

How to predict human CNS drug effects in health and disease?

- De Lange et al. Toward the Prediction of CNS Drug Effect Profiles in Physiological and Pathological Conditions Using Microdialysis and MB PKPD Modeling. AAPSJ, 2005
- De Lange & Hammarlund-Udenaes. Translational aspects of BBB transport and CNS effects of drugs: From discovery to patients. CPT. 2015

Introduction

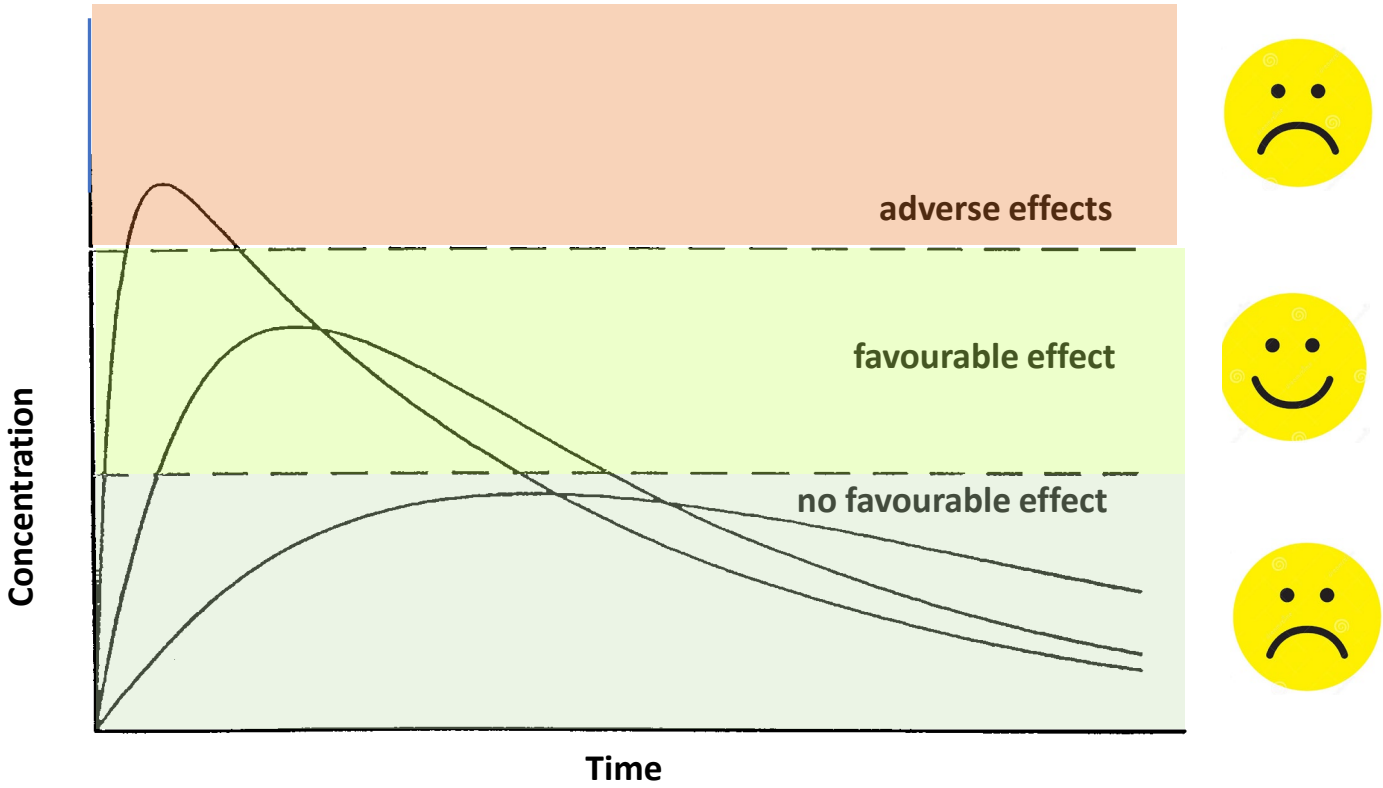


- Drug dosing
- Plasma,u PK
- BBB transport
- Brain,u PK
- Target binding kinetics (BK)
- Cellular signal transduction & homeostatic feedback
- Tissue response & homeostatic feedback
- Body response & homeostatic feedback

Pharmacokinetics (PK)-pharmacodynamics (PD)

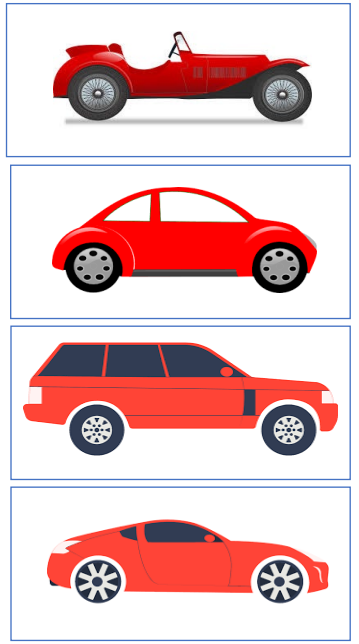
Refresh

Introduction



Interconnections and relationships

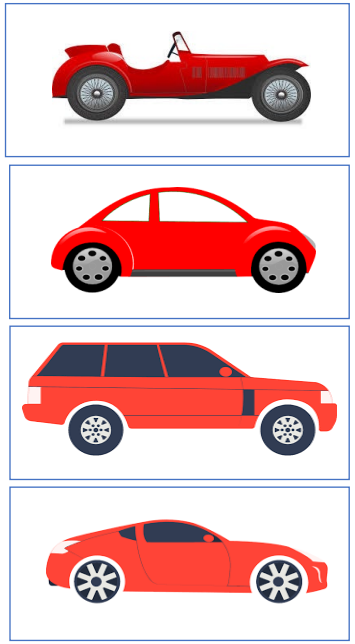
Introduction

Driver +  = Car performance

Interconnections and relationships

Introduction

Driver +

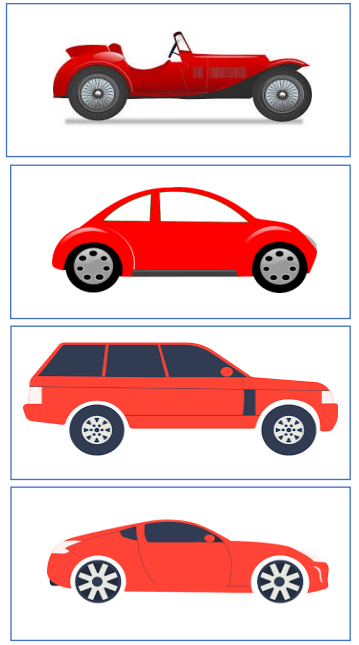


= Car performance

All components in the car are connected and contribute to the overall performance

Interconnections and relationships

Introduction

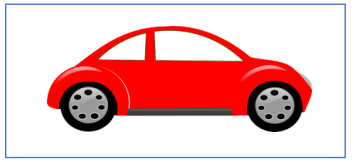
Driver +  = Car performance

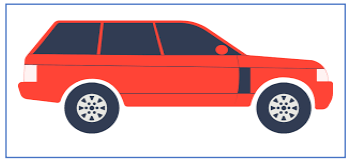
Drug +   = Pharmacokinetics (PK) + pharmacodynamics (PD)

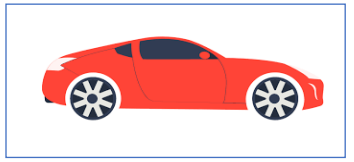
Interconnections and relationships

Introduction

Driver +







= Car performance

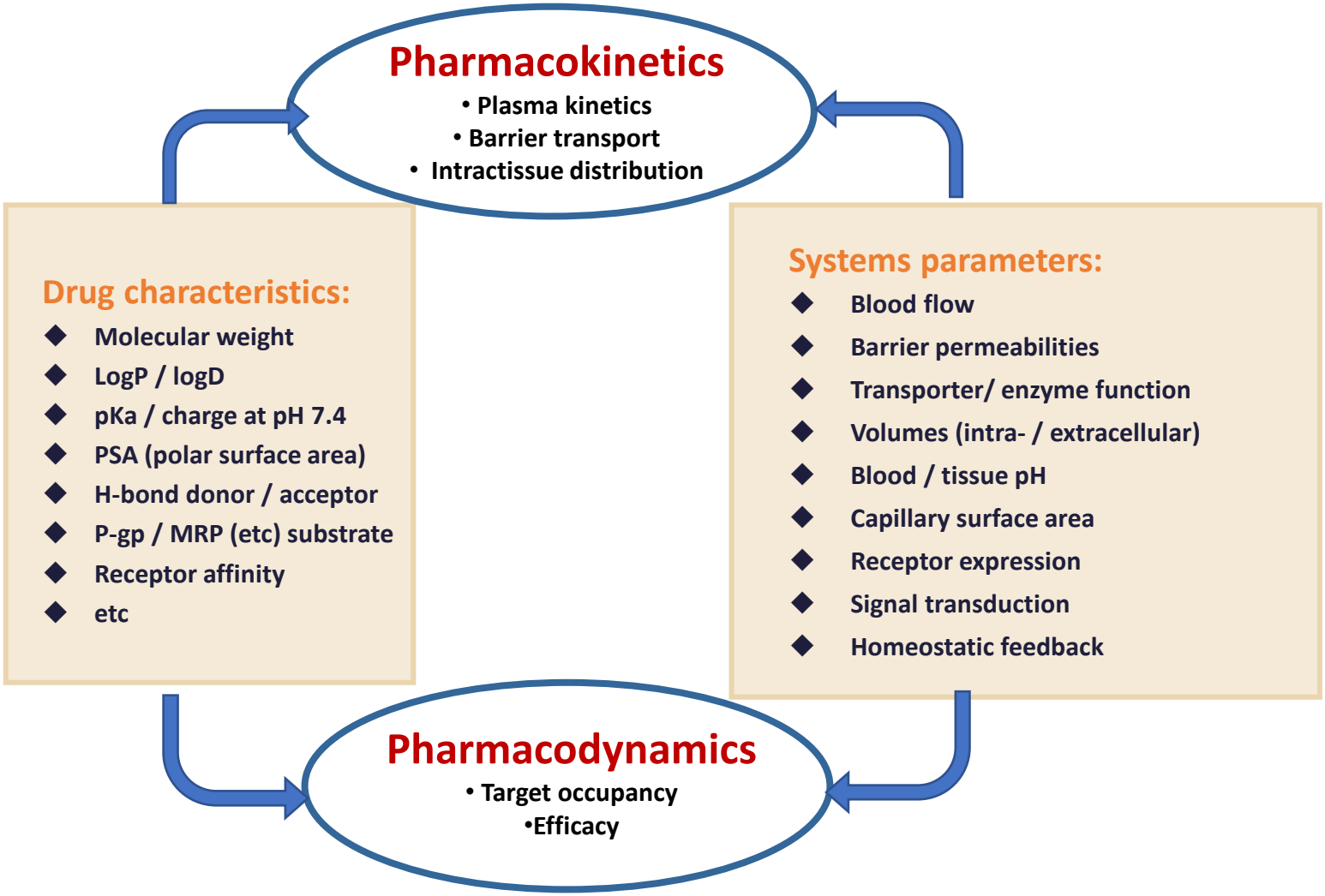
CNS processes are connected and contribute to pharmacokinetics and pharmaco-dynamics

Drug +

= Pharmacokinetics (PK) + pharmacodynamics (PD)

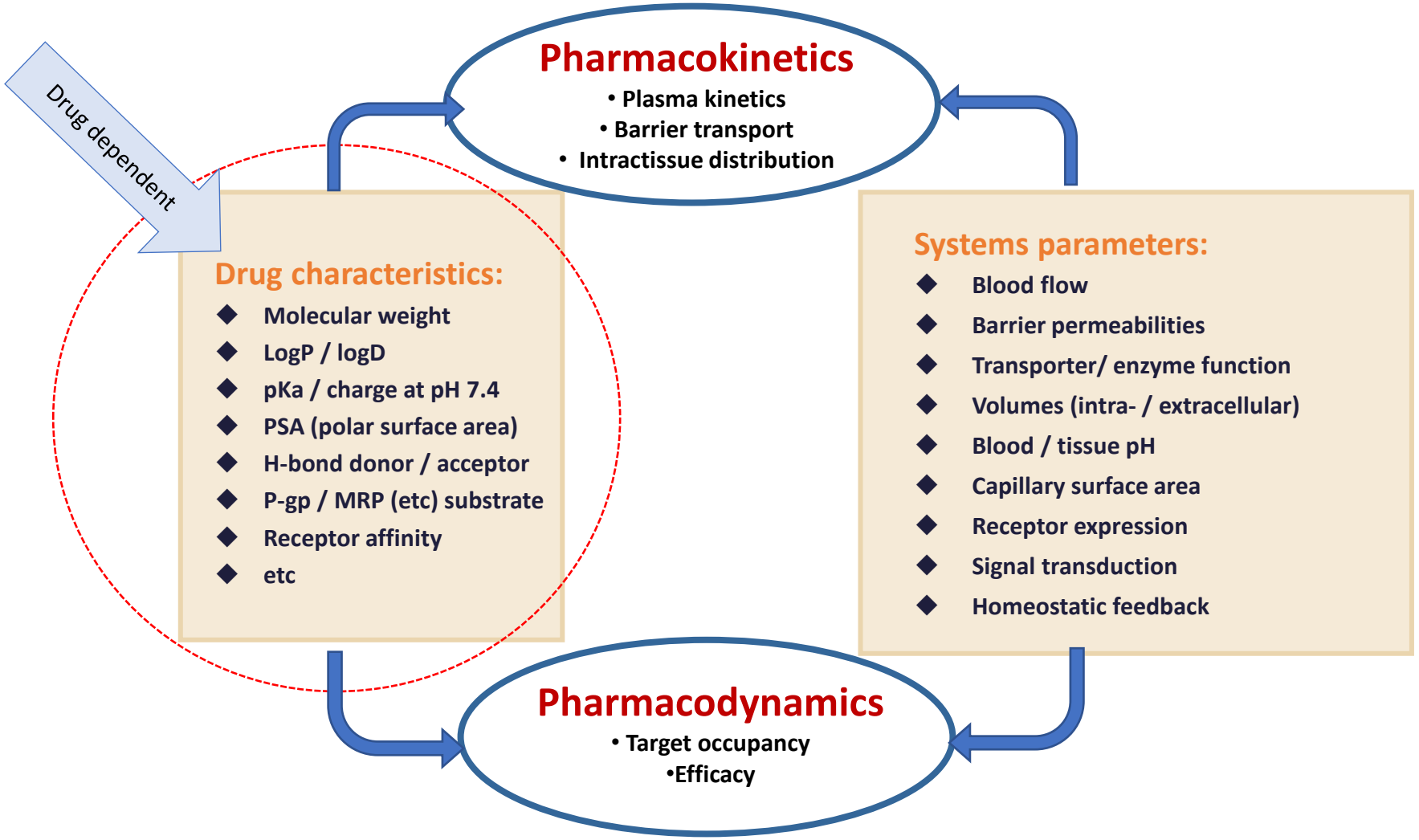
Drug versus CNS systems properties

Introduction



Drug versus CNS systems properties

Introduction



Drug versus CNS systems properties

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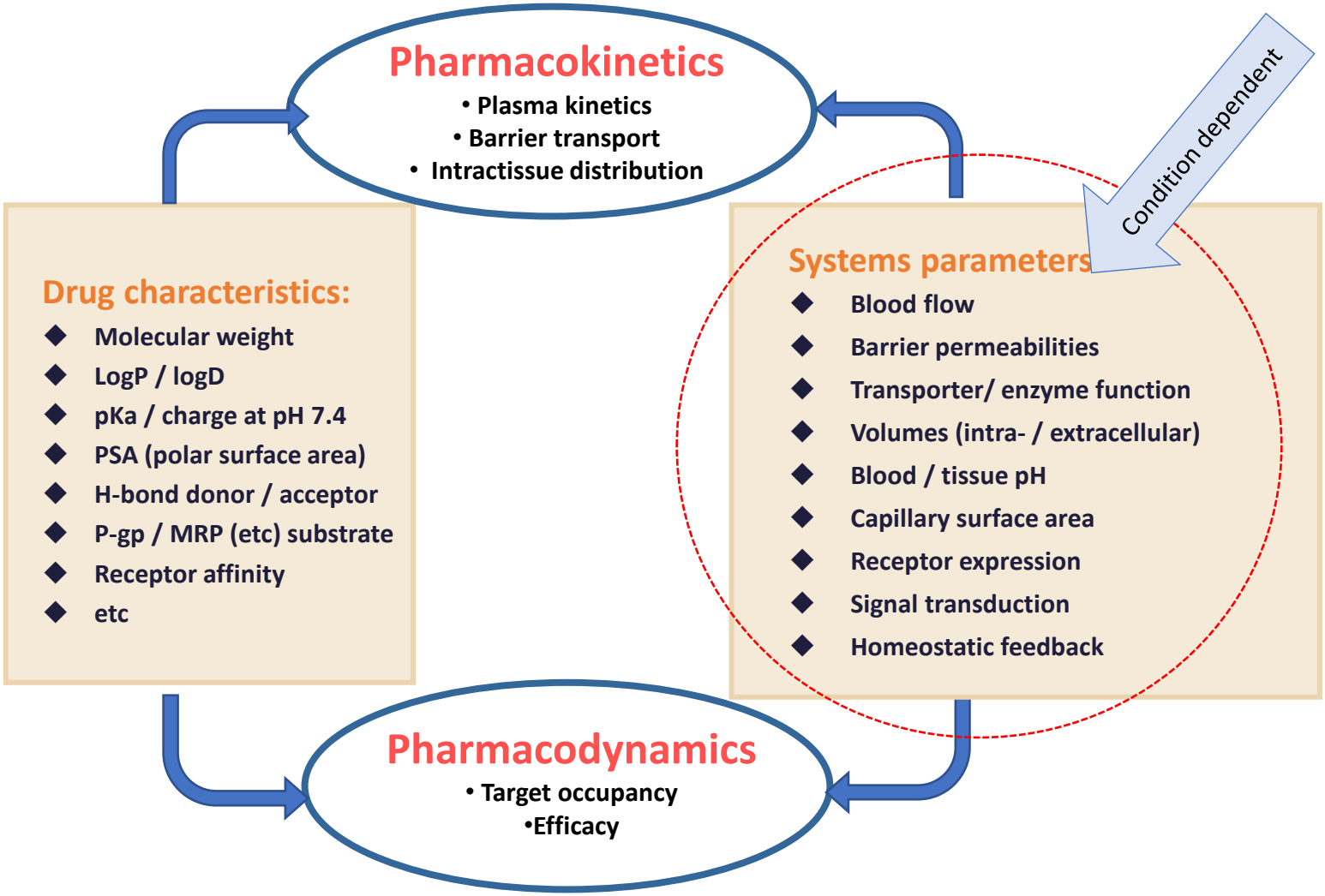

Drug versus CNS systems properties

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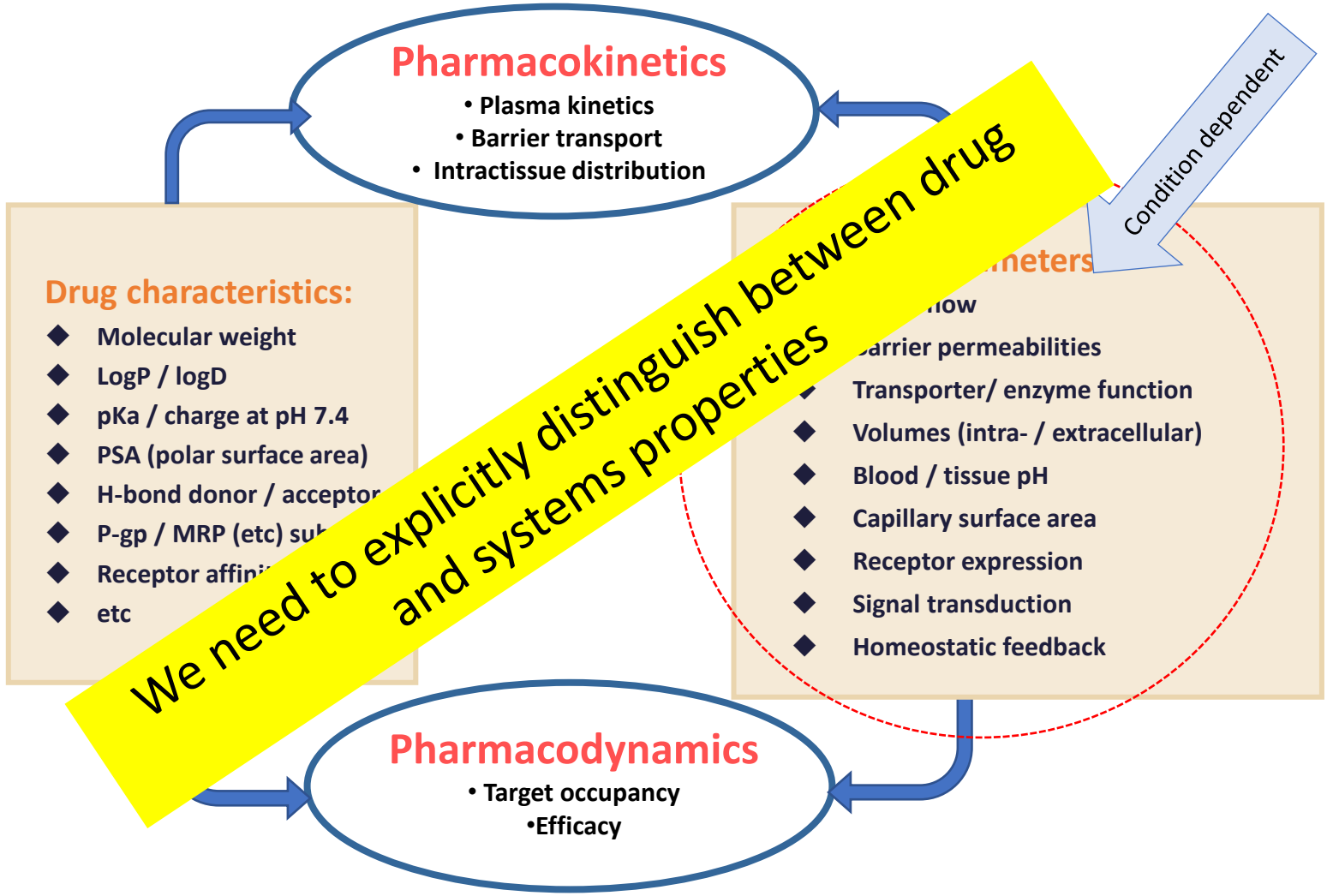
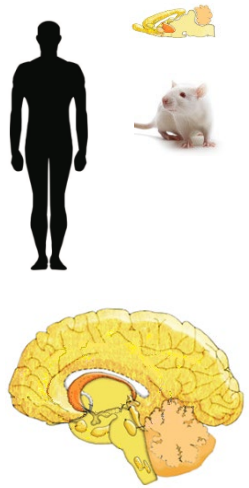
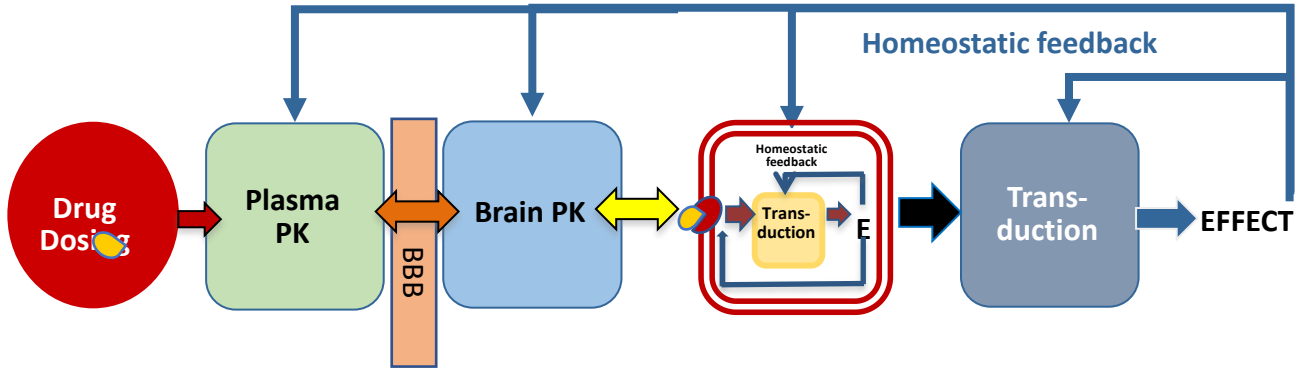




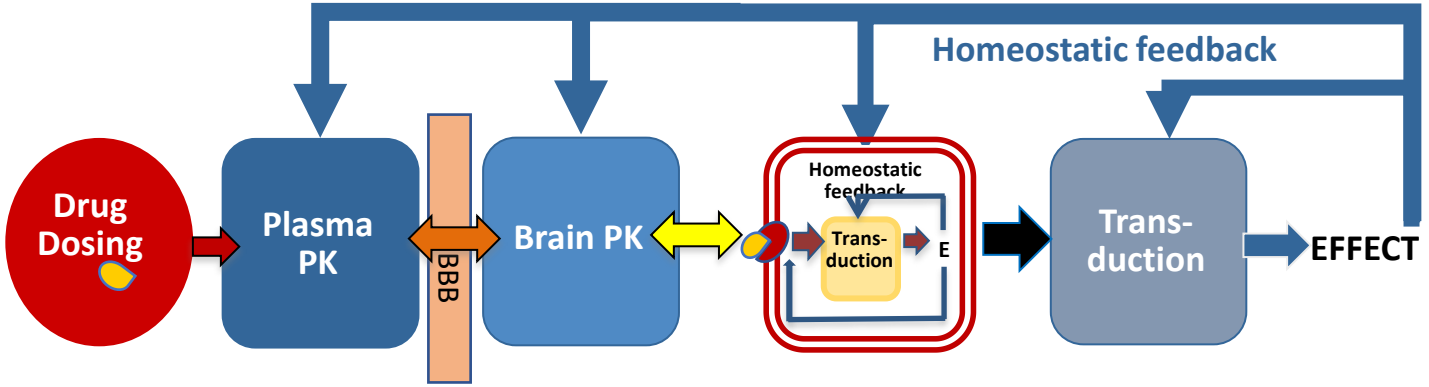
Translation- need for information on systems conditions

- Hammarlund-Udenaes et al. On the rate and extent of drug delivery to the brain. Pharm Res. 2008
- De Lange et al. Novel CNS DDD approach: model-based integration to predict neuro-PK and PD. EODD. 2017

Introduction



- Differences in systems properties (e.g sizes, areas, flows, pH….)
- Results in differences in PK, BBB transport, BK and PD processes

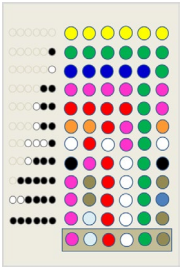


- De Lange. The mastermind approach to CNS drug therapy: translational prediction of human brain distribution, target site kinetics, and therapeutic effects. Fluids Barriers CNS. 2013

Smart data?

Approach

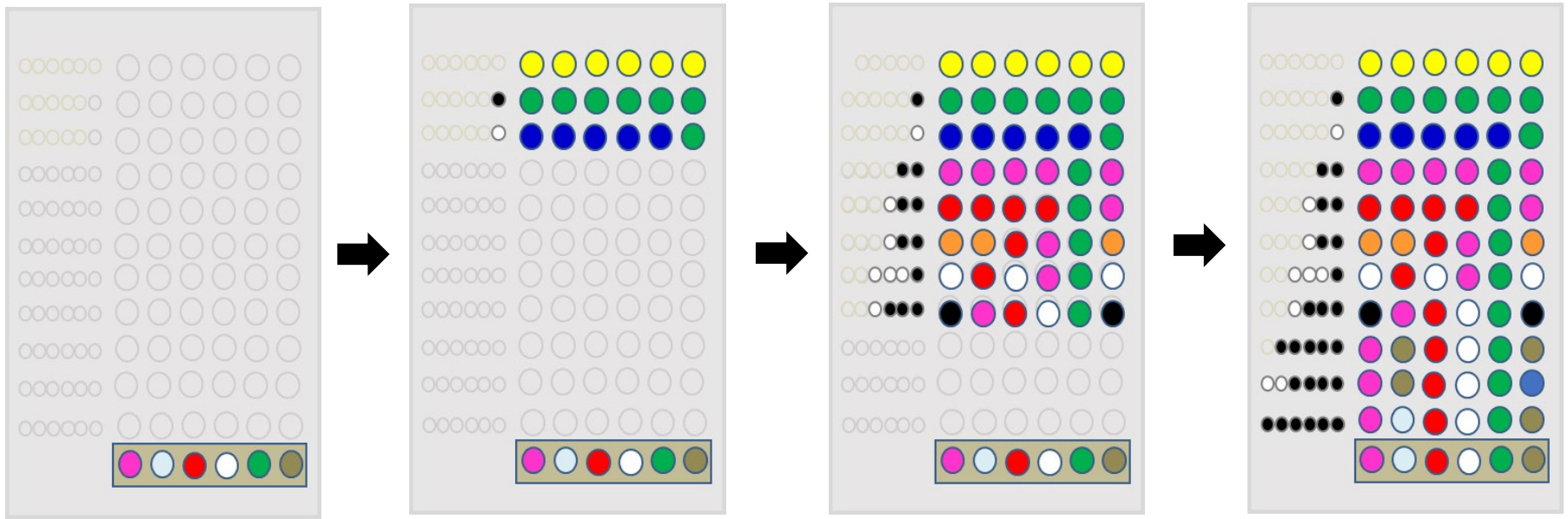
- CNS drug distribution and effects are controlled by many mechanisms.
- CNS research is complex
- We cannot sample human brain (ethics)
- We need to get information indirectly (via animals)
- The rate and extent of these mechanisms are context dependent
- Animal experiments need to be designed to unravel this context dependency as the basis for translation to human
- We need time-course from subjects at multiple levels, so we know the data is connected (Mastermind research approach)
- Connected data can be subjected to mathematical modelling to provide rate and extent of pharmacokinetics processes
- Mathematical models are needed to organize, condense, integrate and storage knowledge and understanding



Mastermind Research Approach

- De Lange. The mastermind approach to CNS drug therapy: translational prediction of human brain distribution, target site kinetics, and therapeutic effects. FBCNS. 2013
- De Lange et al. Novel CNS drug discovery and development approach: model-based integration to predict neuro-pharmacokinetics and pharmacodynamics. EODD. 2017
- De Lange et al. The physiological characteristics and transcytosis mechanisms of the blood-brain barrier (BBB). Special issue "Brain Drug Delivery Systems", in: CPD 2012

Approach

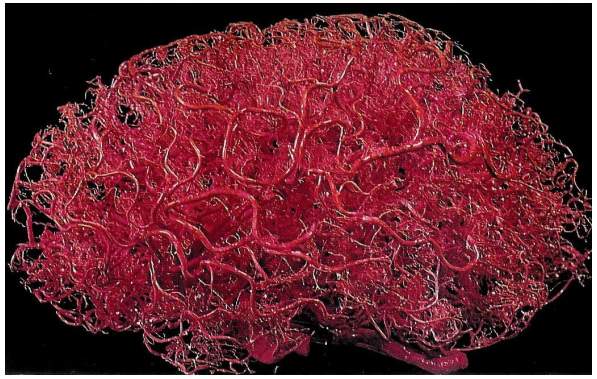


Learn and confirm

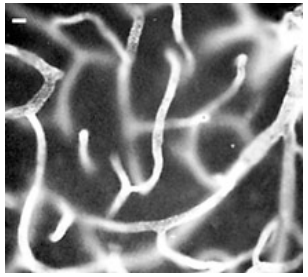
The blood-brain barrier (BBB)

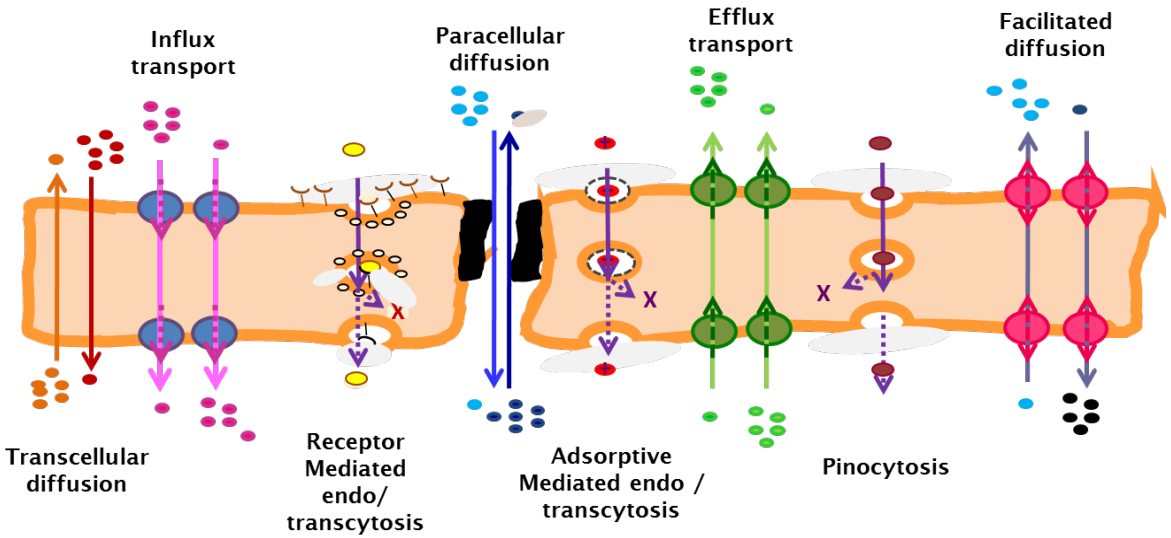
- Hammarlund-Udenaes et al. On the rate and extent of drug delivery to the brain. Pharm Res. 2008
- De Lange. Physiological characteristics and transcytosis mechanisms of the blood- brain barrier (BBB). Special issue "Brain Drug Delivery Systems", in: CPD 2012
- Abbott. BBB structure and function and the challenges for CNS drug delivery. J Inherit Metab Dis. 2013

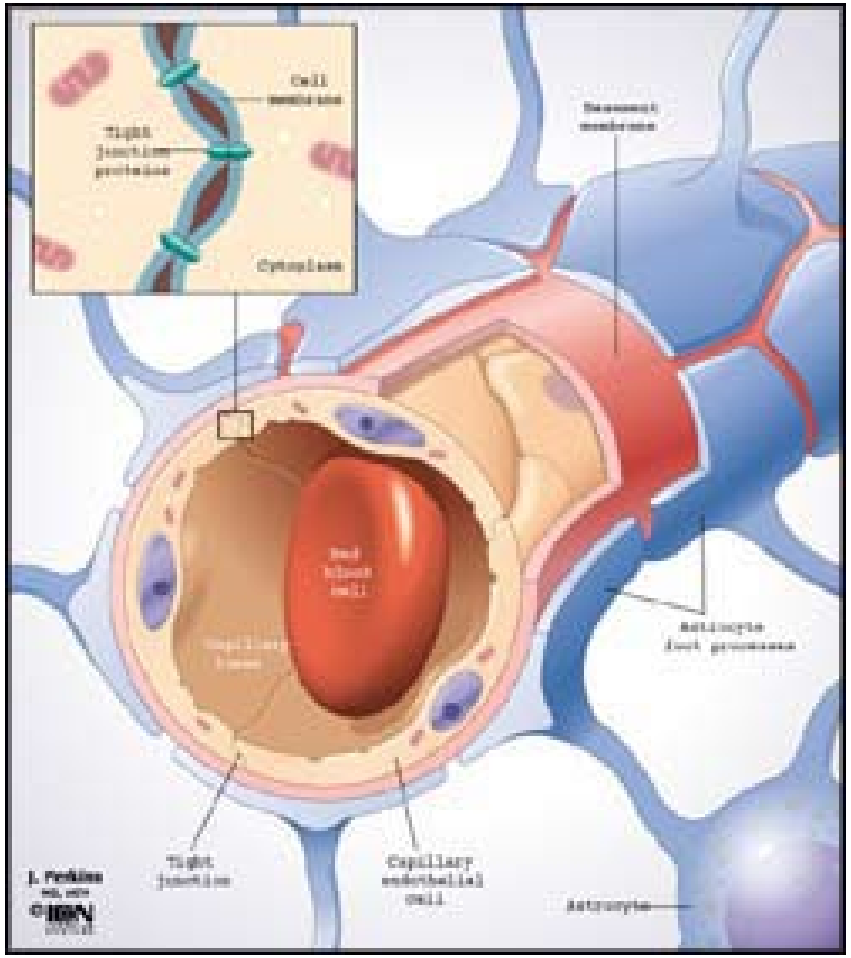
Introduction



Brain capillary network



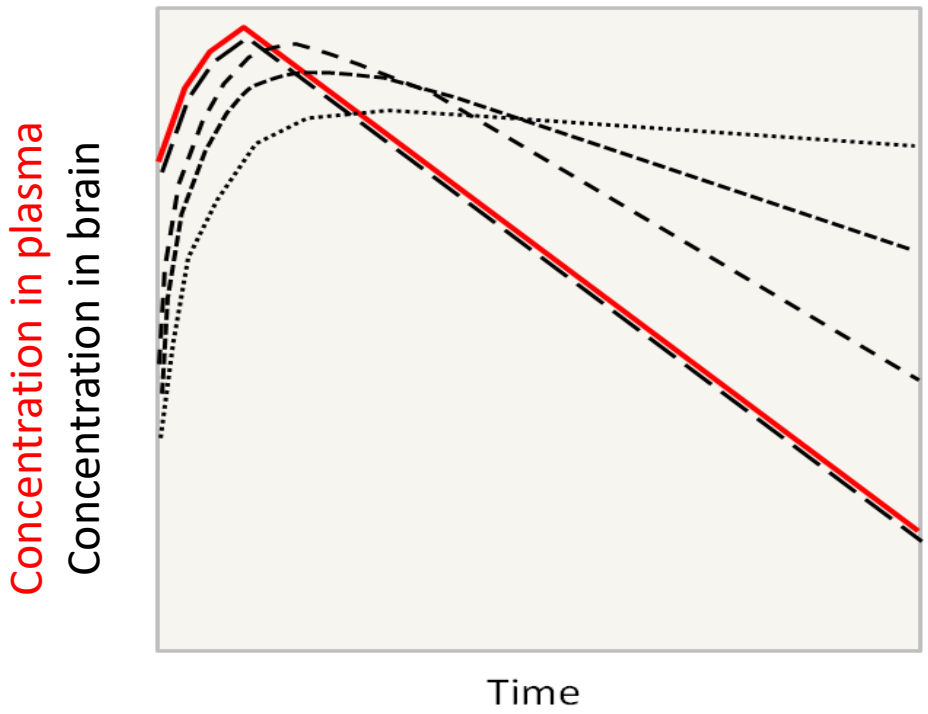




Drug distribution into the brain

- Hammarlund-Udenaes M, Paalzow LN and De Lange ECM. Drug Equilibration Across the Blood- Brain-Barrier - Pharmacokinetic Considerations Based on the Microdialysis Method. Pharm Res, 14: 128-134, 1997.

Introduction



- Slow BBB transport
- Fast BBB transport

Drug distribution into the brain

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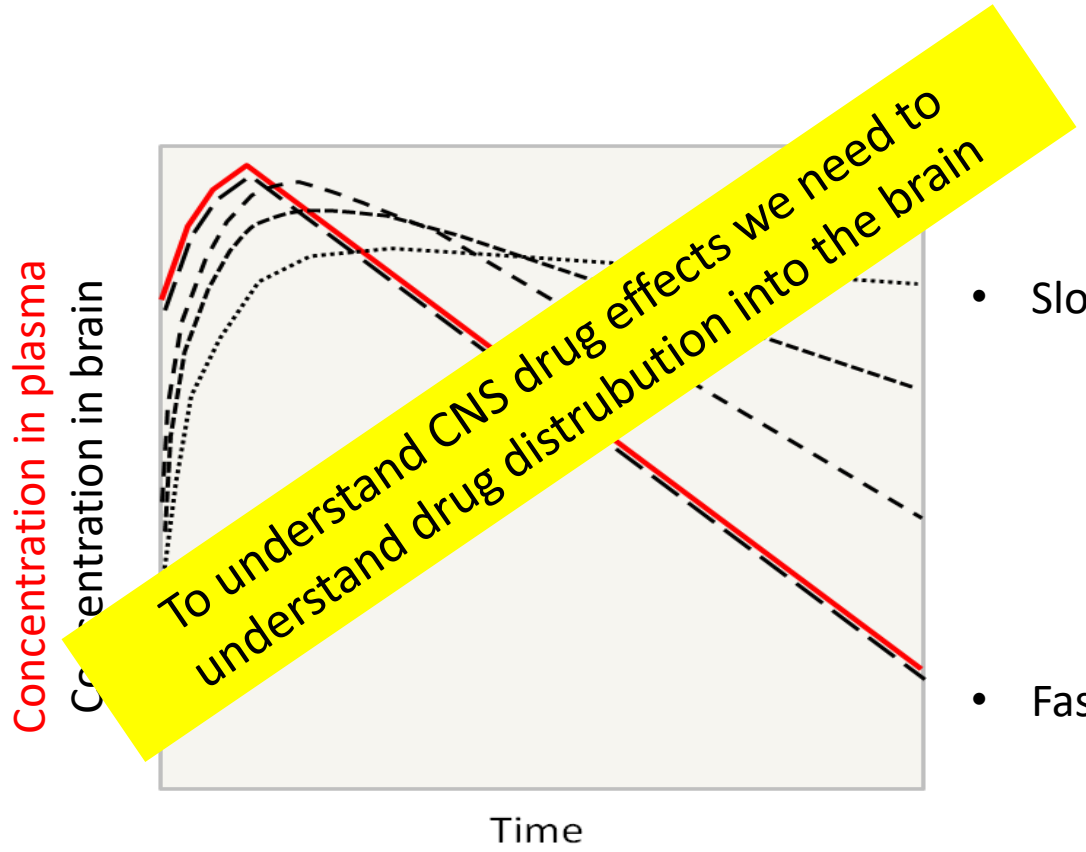


- Slow BBB transport
- Fast BBB transport

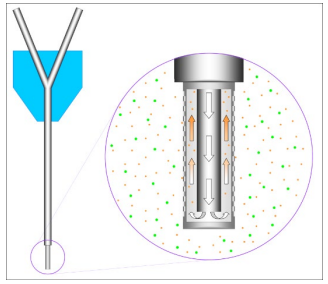
Time course and multi-level monitoring

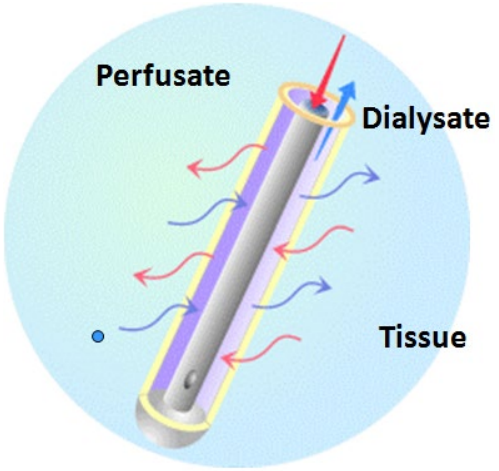
- De Lange et al .Methodological Considerations of Intracerebral Microdialysis in Pharmacokinetic Studies on BBB Transport of Drugs. Brain Res Revs, 1997
- De Lange et al. Methodological Issues in Microdialysis Sampling for Pharmacokinetic studies. Adv Drug Del Rev, 2001

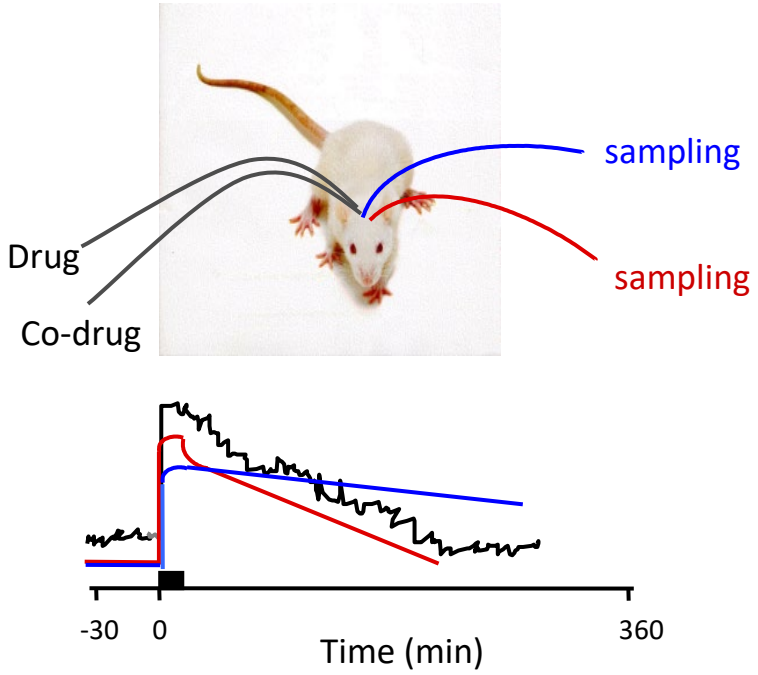
Approach

Unbound concentrations drive transport and target interaction.
Knowledge on the time course of unbound concentrations is crucial to understand the rate and extent of such processes

Microdialysis is the key technique for monitoring unbound concentrations







Unbound concentrations

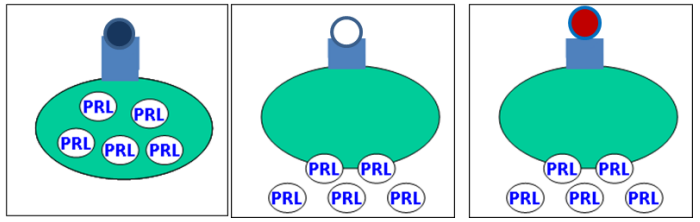
- **Drugs**
- **Biomarkers** of effect/ disease

Prediction of CNS drug effects on the DA system

- Movin-Osswald et al. Influence of the dosing interval on prolactin release after remoxipride. Br J Clin Pharmacol. 199S
- tevens et al. New rat model for preclinical studies on intranasal administration of CNS drugs, Pharm Res. 2009
- Stevens et al. MBPKPD model for the prolactin biological system response following acute dopamine inhibition challenge: quantitative extrapolation to humans. JPKPD 2012

PKPD prediction

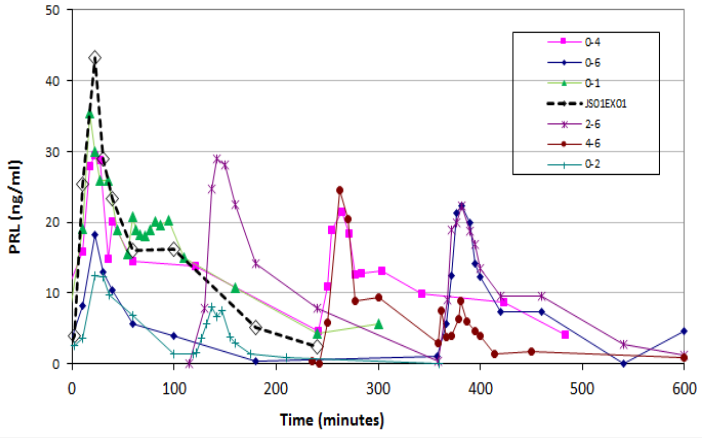
Pituitary lactotrophs release prolactin into blood



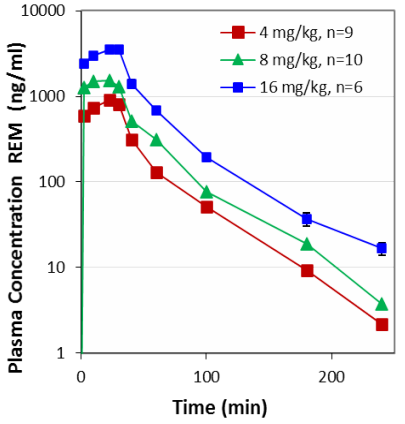
Dopamine high

Dopamine low

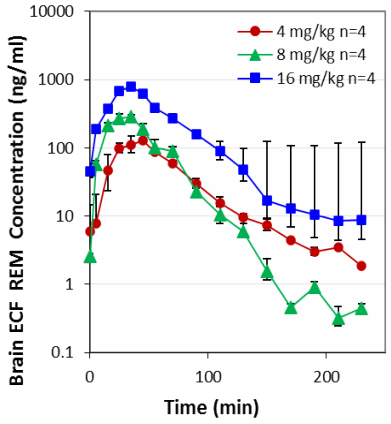
DA antagonist



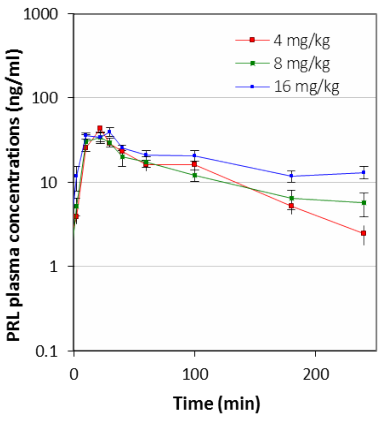
Remoxipride plasma



Remoxipride brainECF

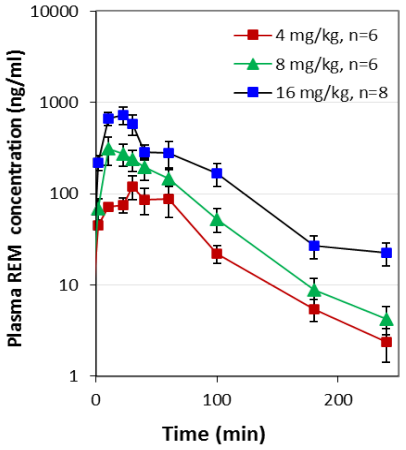


Prolactin plasma

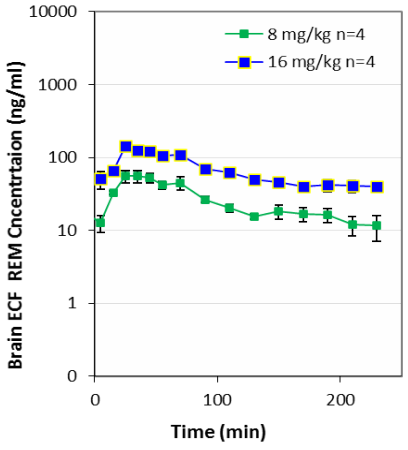


IV

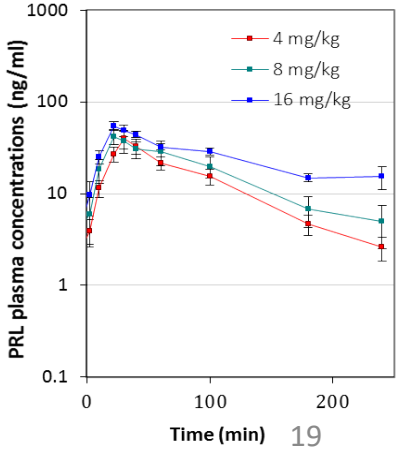
Remoxipride plasma



Remoxipride brainECF



Prolactin plasma



IN

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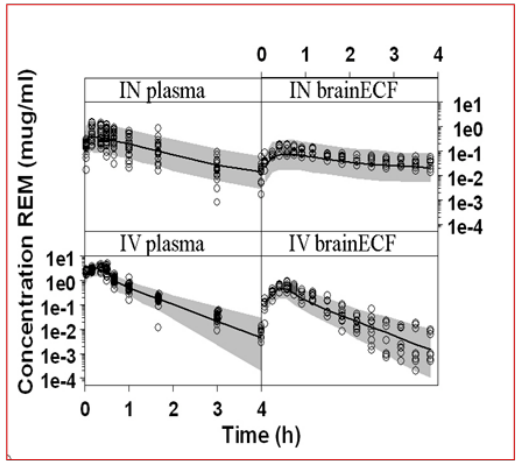
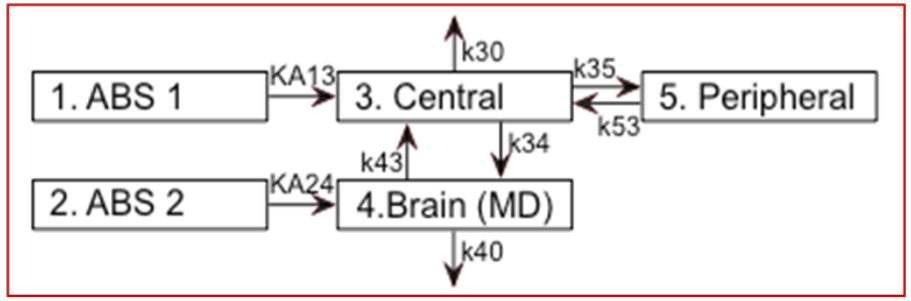
PKPD prediction

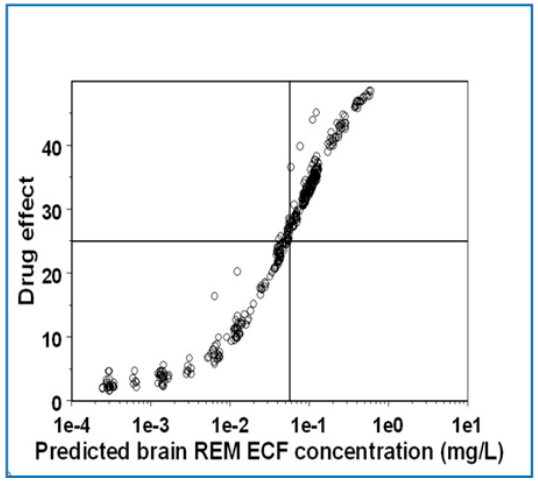
PK



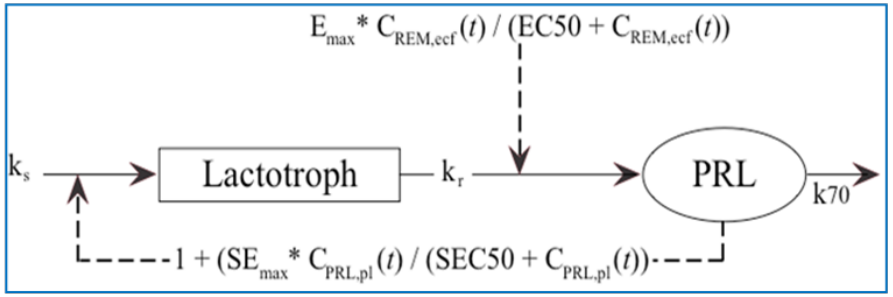
IN: Brain Distribution enhancement



PD



Rat: unbound brain PK of REM = linked to the effect



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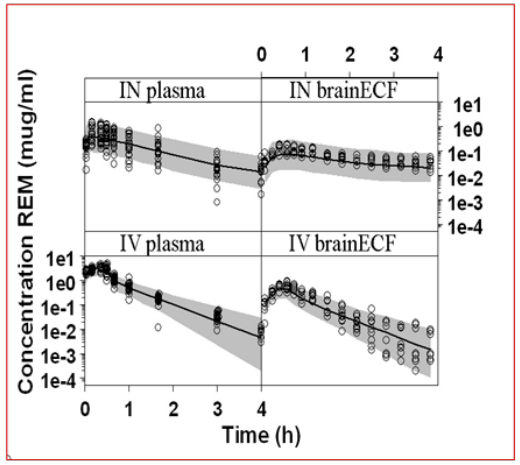
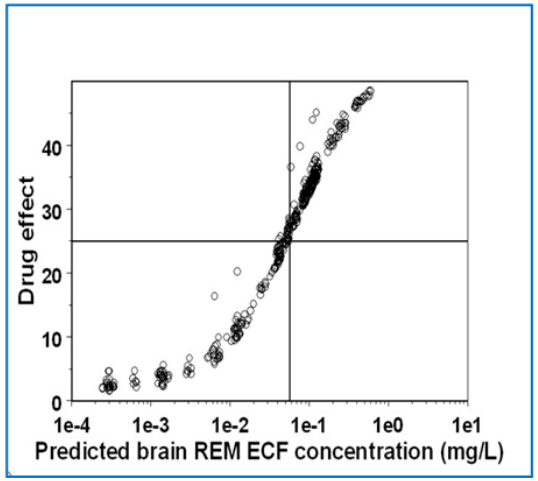
PKPD prediction

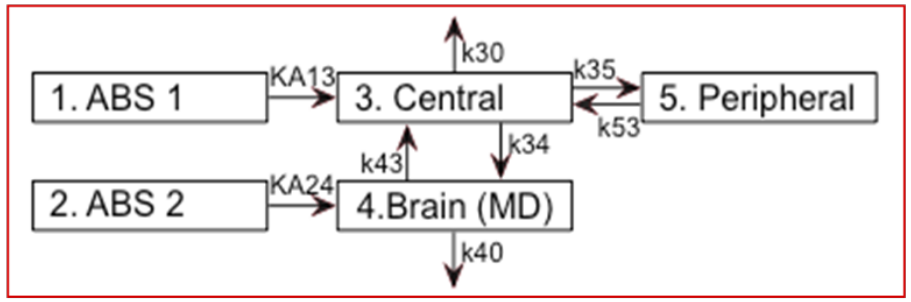
PK



PD

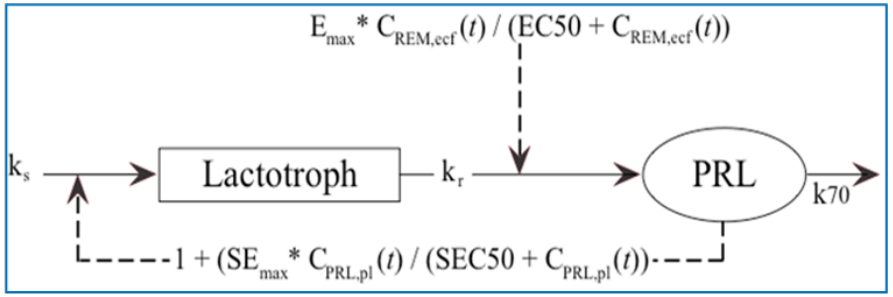


IN: Brain Distribution enhancement



IV: Same model for rat and human

Rat: unbound brain PK of REM = linked to the effect



Human: In vitro values + allometric scaling give prediction of human plasma PRL concentrations

Prediction of CNS drug effects on the DA system

- Stevens et al. New rat model for preclinical studies on intranasal administration of CNS drugs, Pharm Res. 2009
- Movin-Osswald & Hammarlund-Udenaes M. Prolactin release after remoxipride by an integrated pharmacokinetic-pharmacodynamic model with intra- and interindividual aspects. JPET 1995
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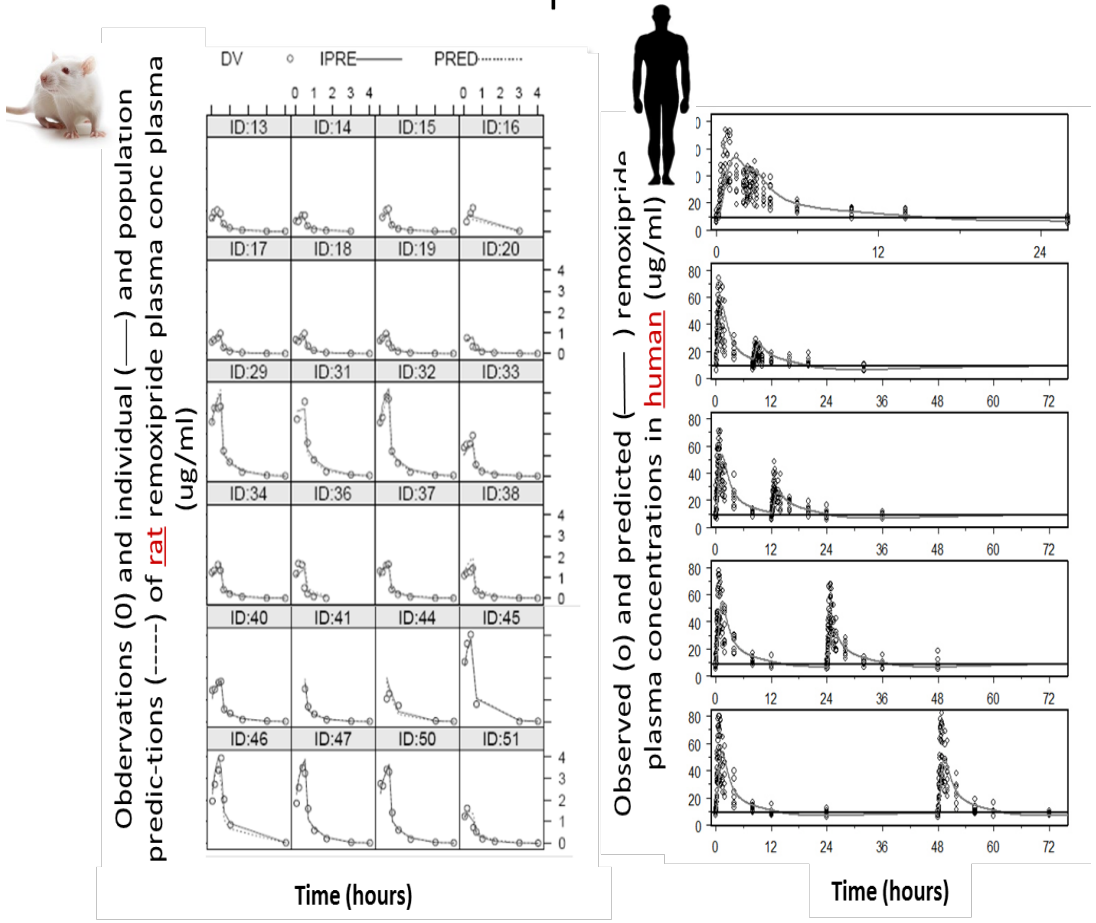
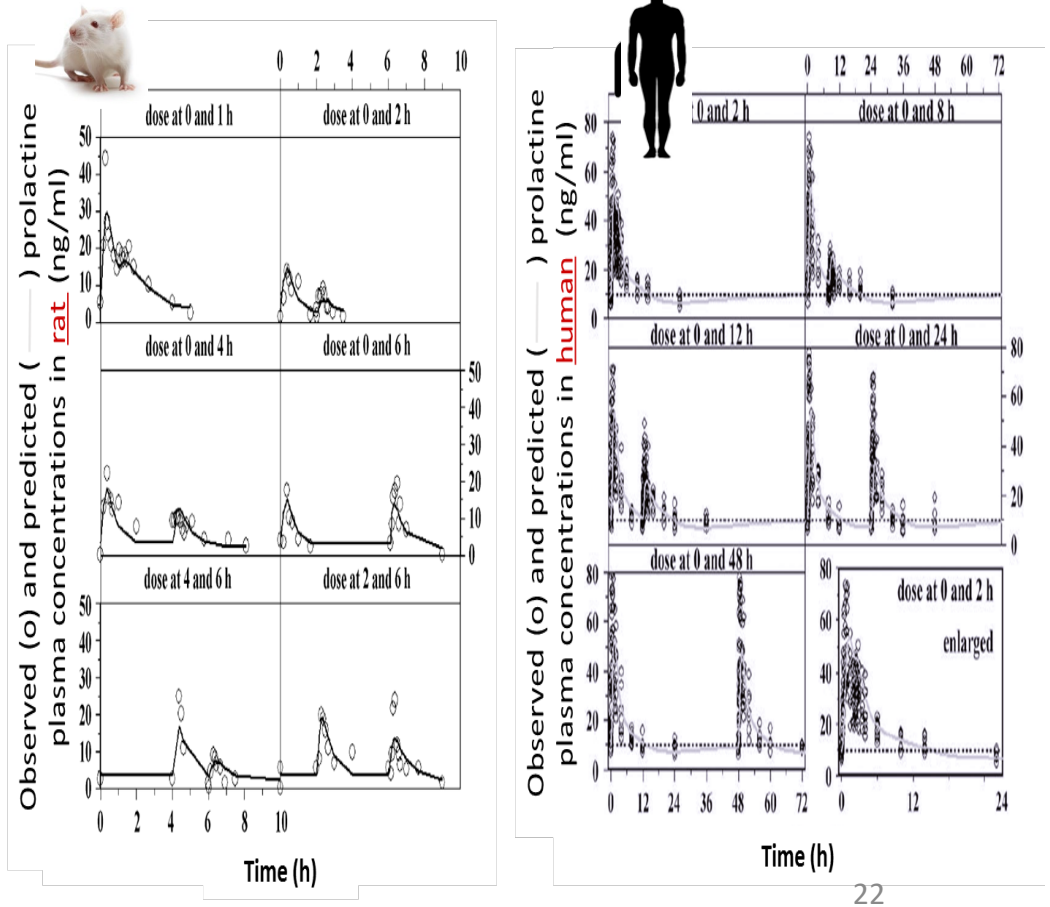
PKPD prediction

POP-PK Model of remoxipride in rat versus human



PKPD model of remoxipride and PRL



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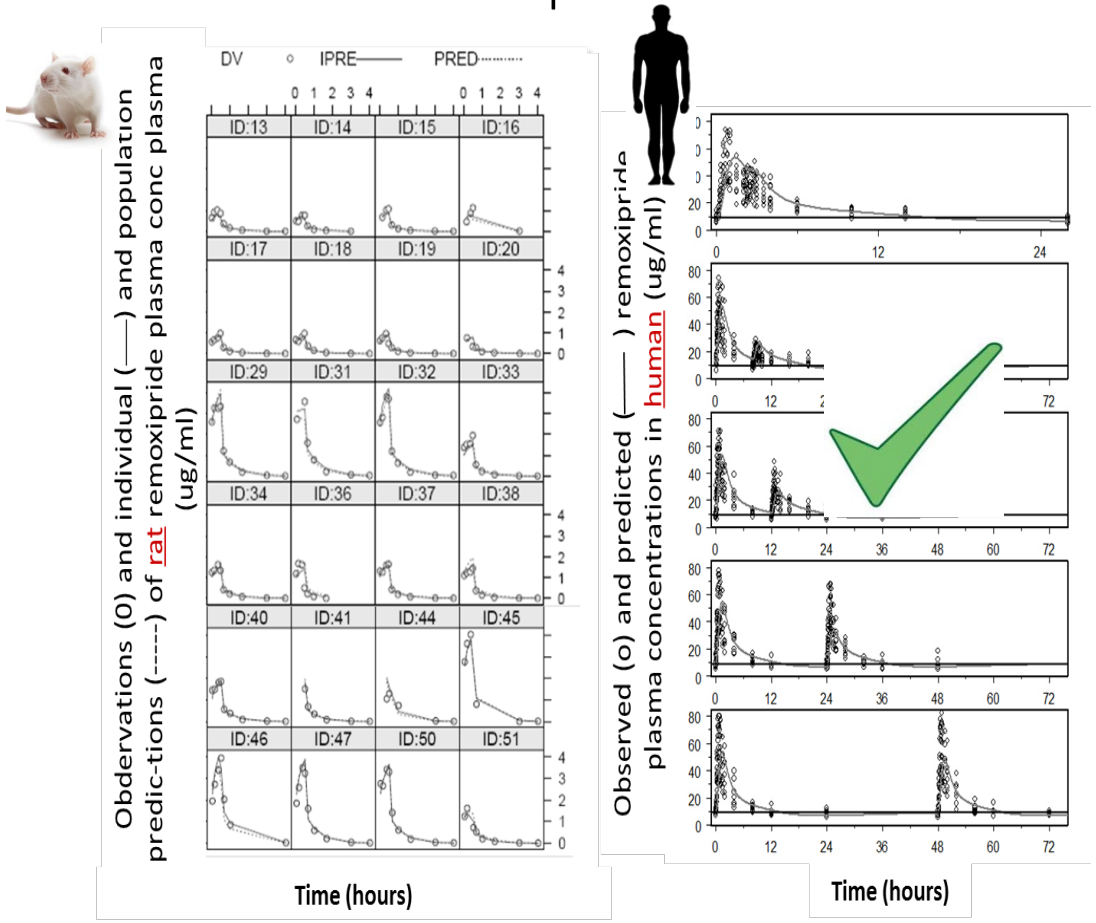
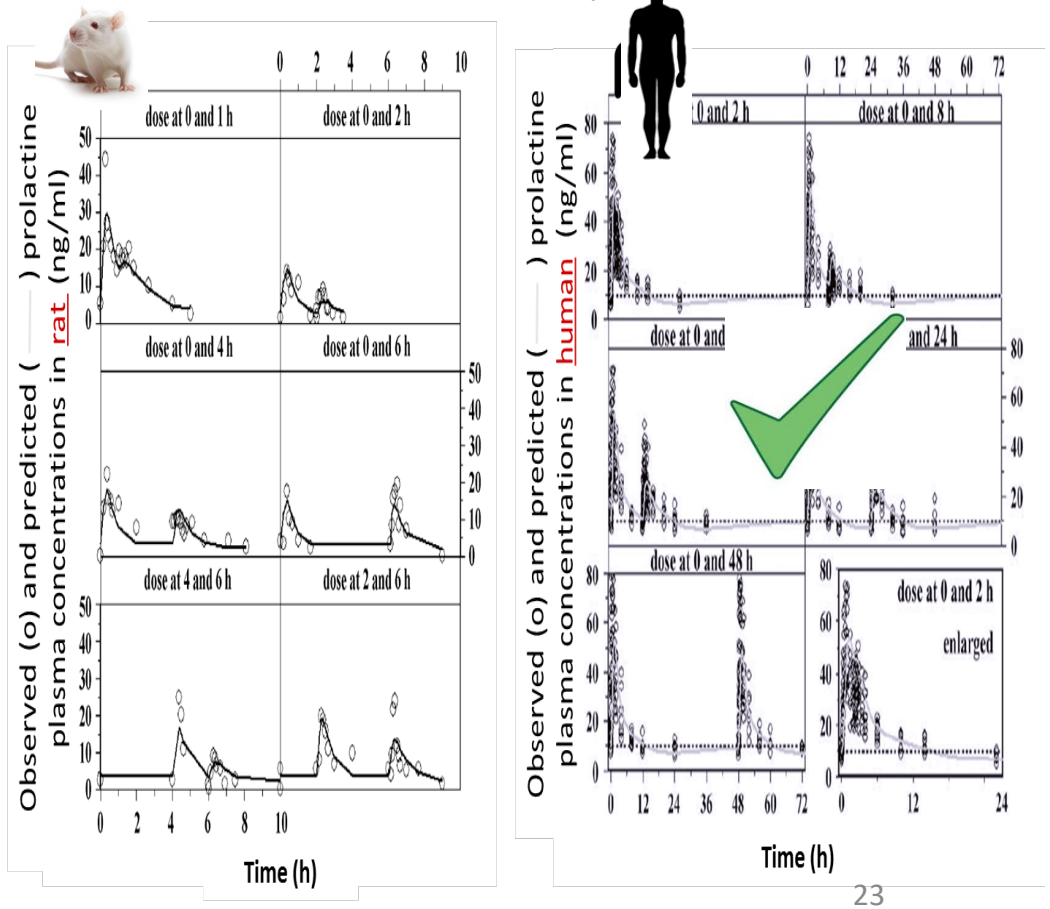
PKPD prediction

POP-PK Model of remoxipride in rat versus human



PKPD model of remoxipride and PRL

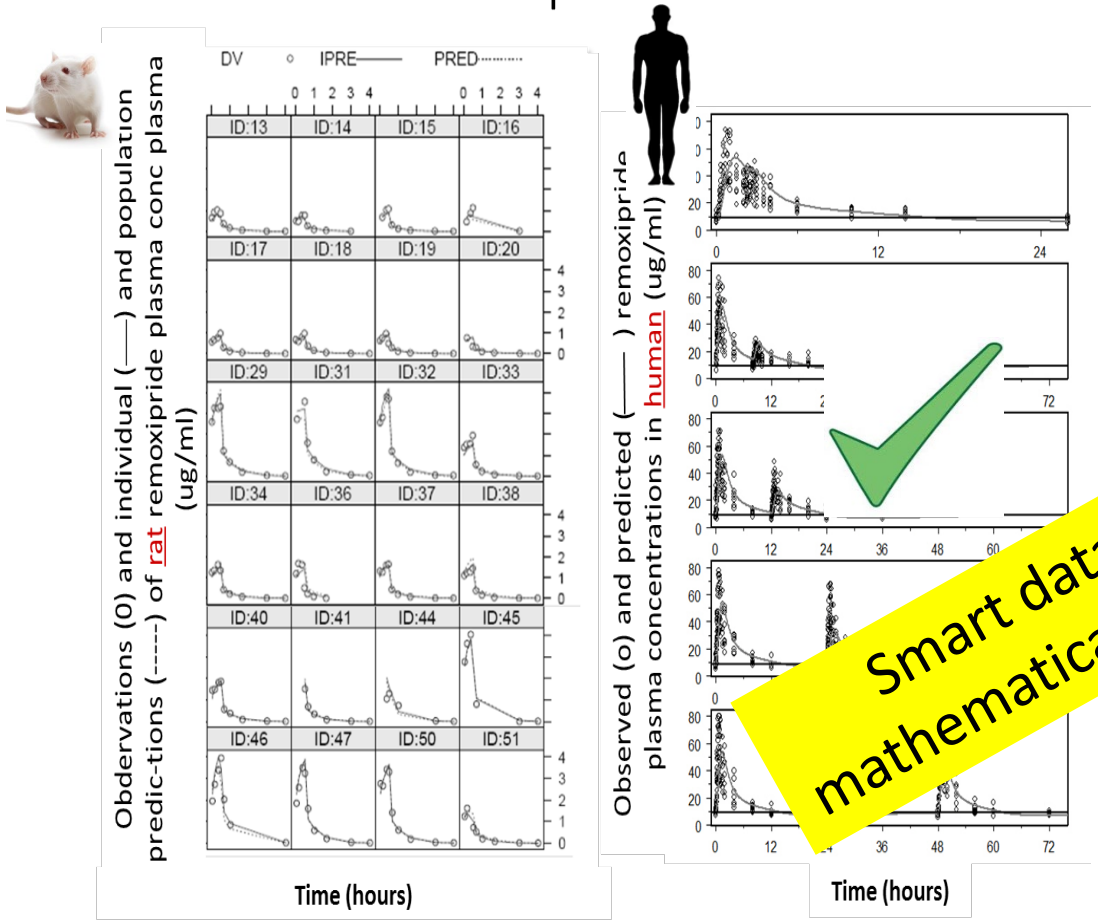


Prediction of CNS drug effects on the DA system

- Stevens et al. New rat model for preclinical studies on intranasal administration of CNS drugs, Pharm Res. 2009
- Movin-Osswald & Hammarlund-Udenaes M. Prolactin release after remoxipride by an integrated pharmacokinetic-pharmacodynamic model with intra- and interindividual aspects. JPET 1995
- Stevens et al. MBPKPD model for the prolactin biological system response following acute dopamine inhibition challenge: quantitative extrapolation to humans. JPKPD 2012

PKPD prediction

POP-PK Model of remoxipride in rat versus human



PKPD model of remoxipride and PRL

Smart data from only 23 rats and mathematical modelling could do the job

CSF PK as surrogate of brain,u PK?

- De Lange et al: Monitoring In Vivo BBB Drug Transport: CSF sampling, the Unit Impulse Response Method and, with Special Reference, Intracerebral Microdialysis. STP Pharm Sci, 1997
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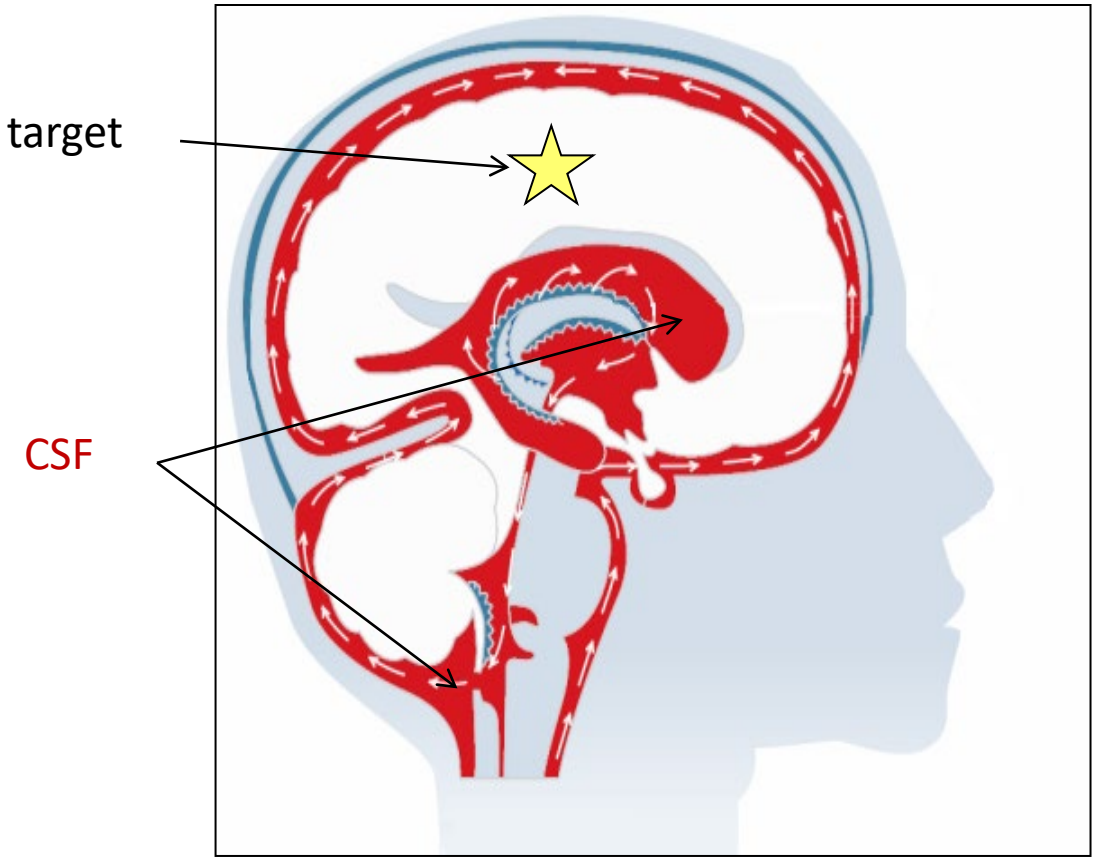
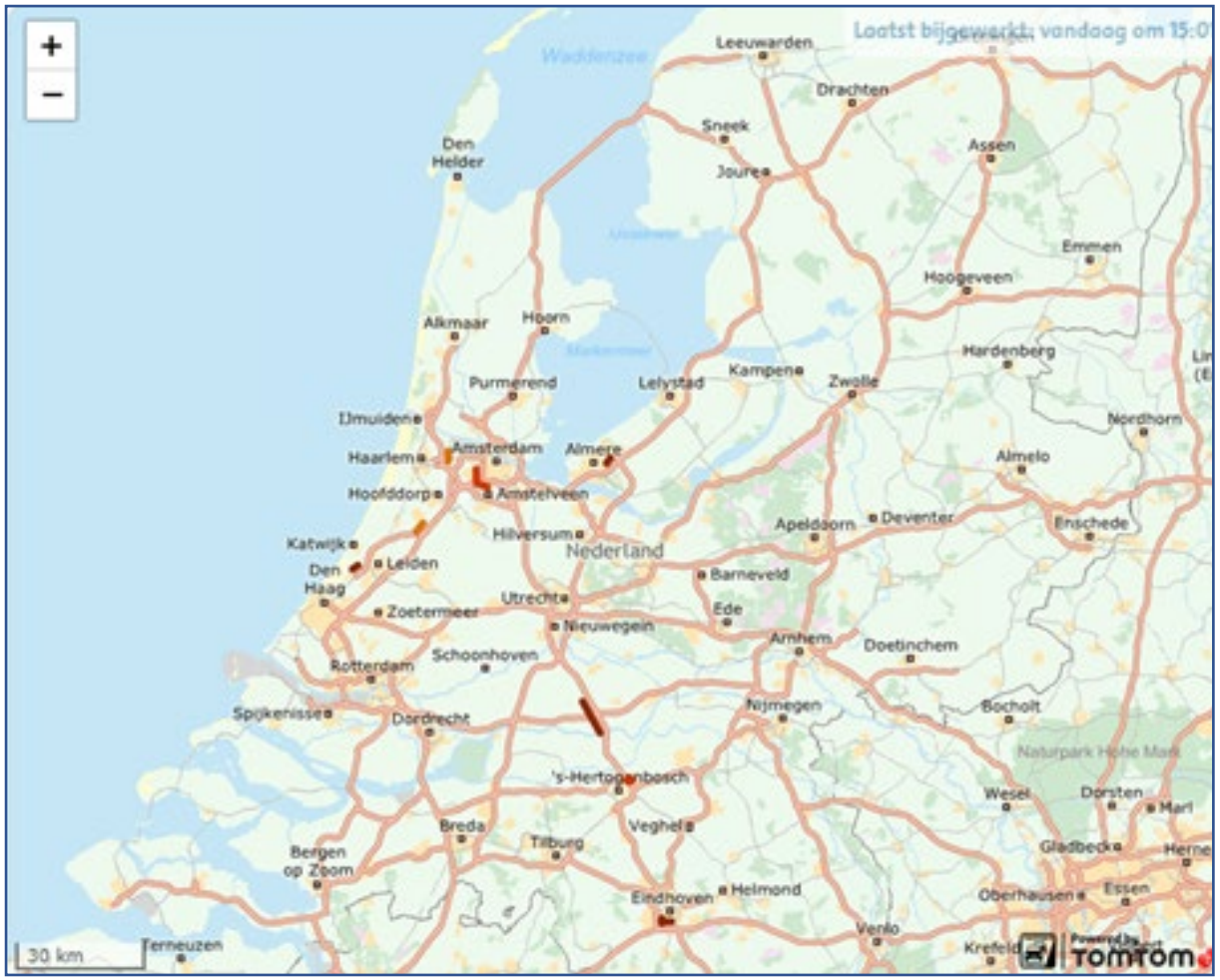
- De Lange and, Danhof. Considerations in the Use of CSF PK to Predict Brain Target Concentrations in the Clinical Setting: Implications of the Barriers between Blood and Brain. Clin. PK, 2002
- De Lange et al. Utility of cerebrospinal fluid in translational neuroscience. In: Special Issue "Translational Modeling In Neuroscience". Editor P Bonate. JPKPD. 2013

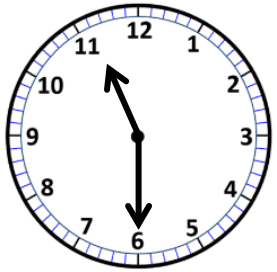
CNS PK prediction



Location and time dependency

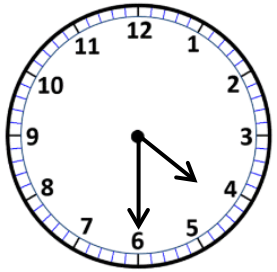
At 11.30 h



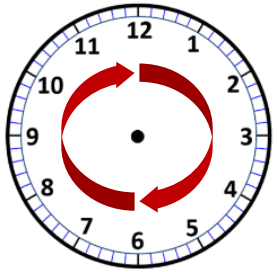


Location and time dependency

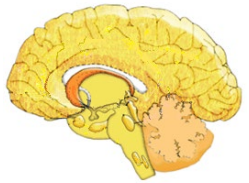
At 16.30

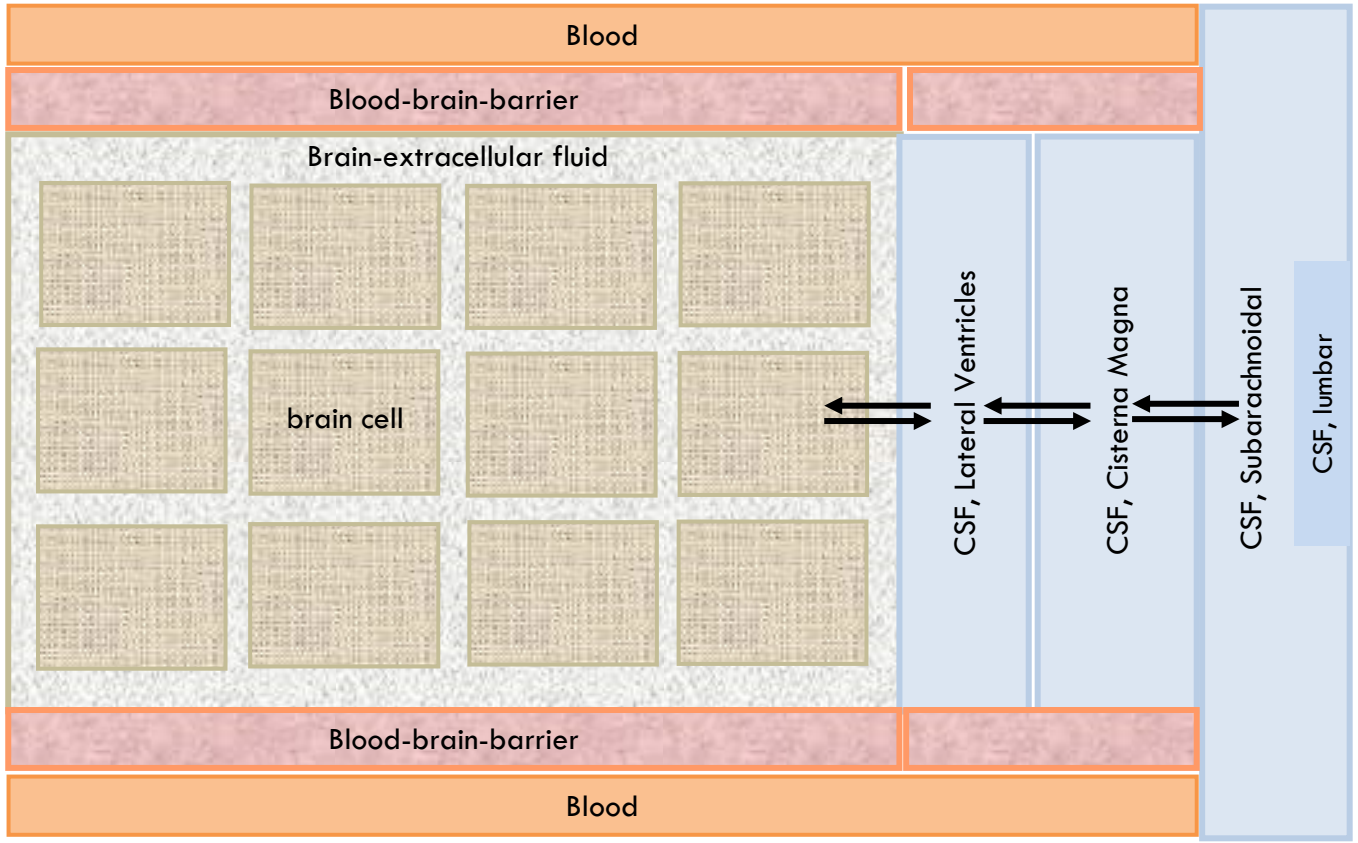


Location and time dependency



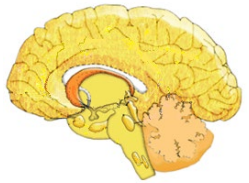
CNS properties

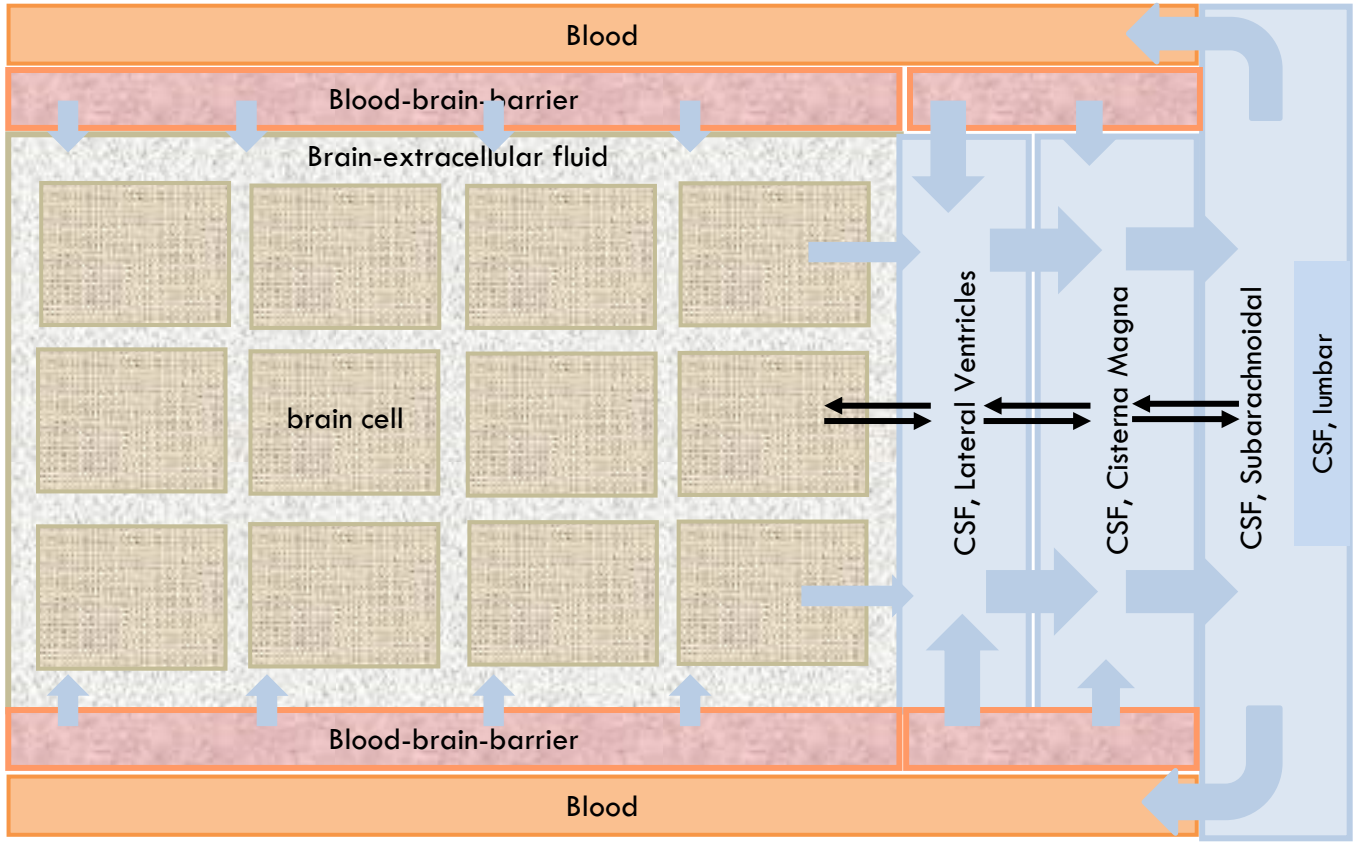




Physiological CNS compartments

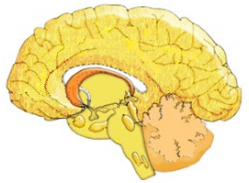
CNS properties

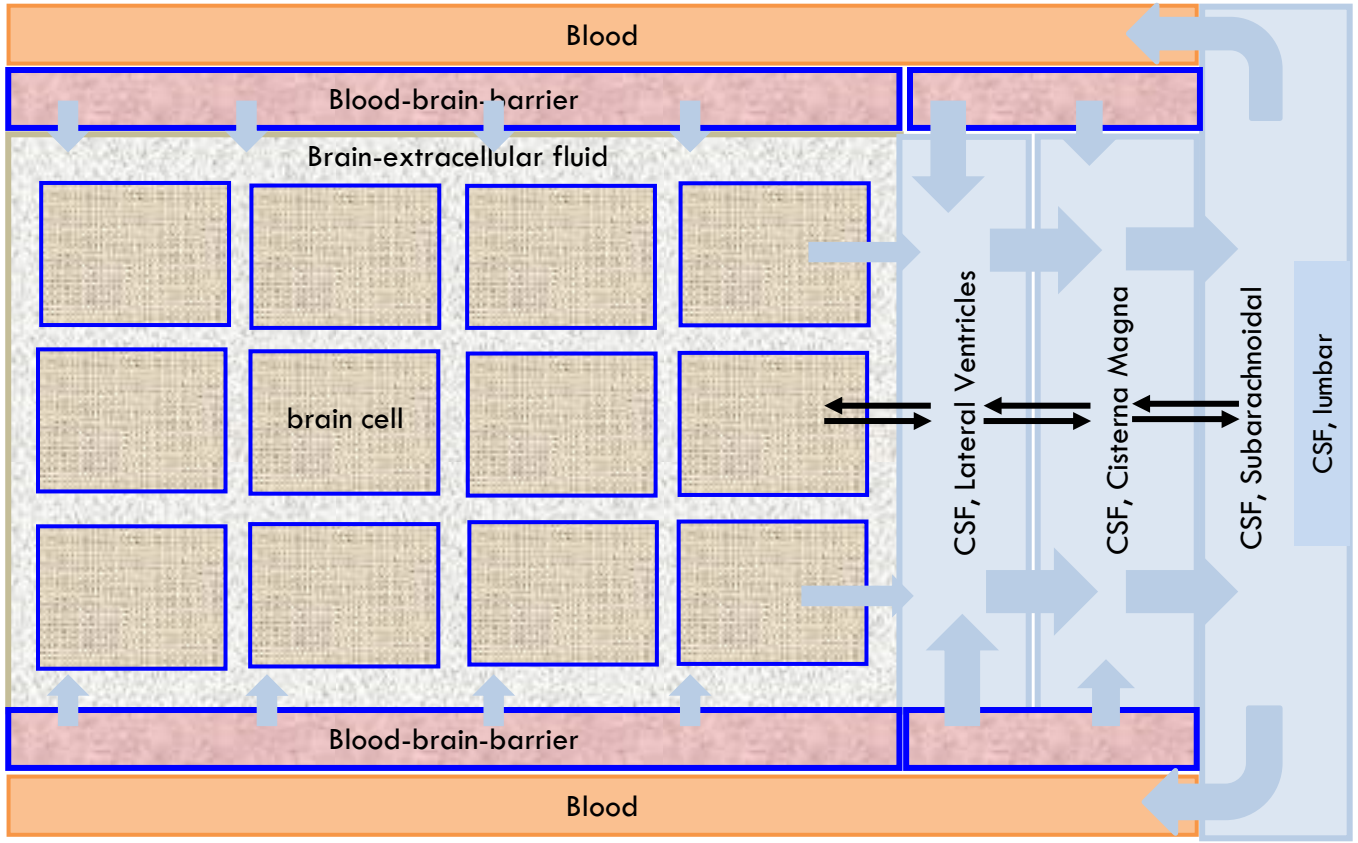




Physiological CNS compartments, Volumes, Flows

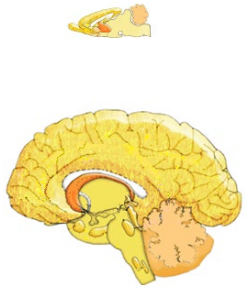
CNS properties

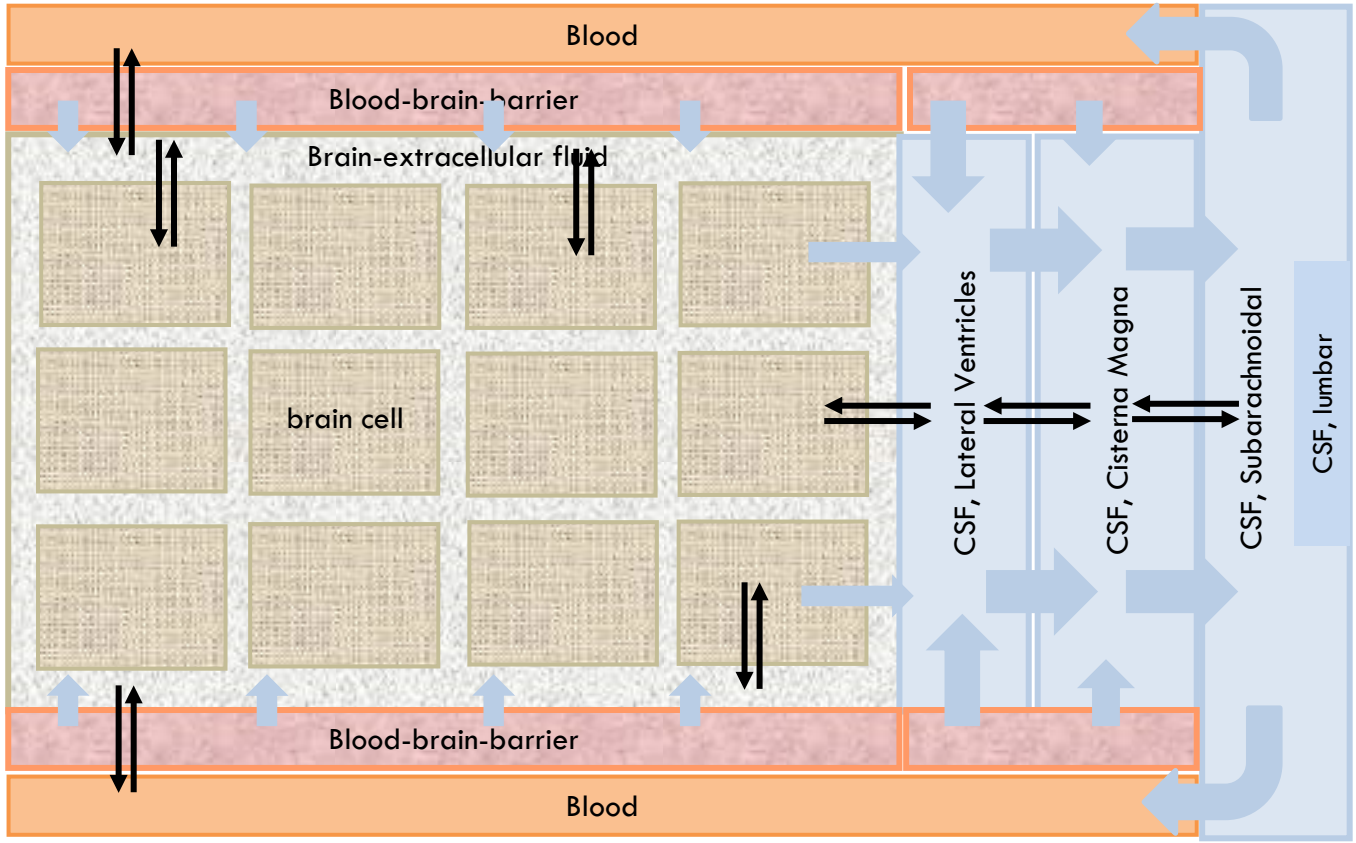




Physiological CNS compartments, Volumes, Flows, Membrane surfaces,

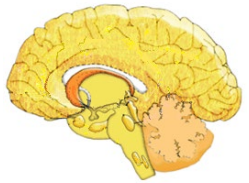
CNS properties

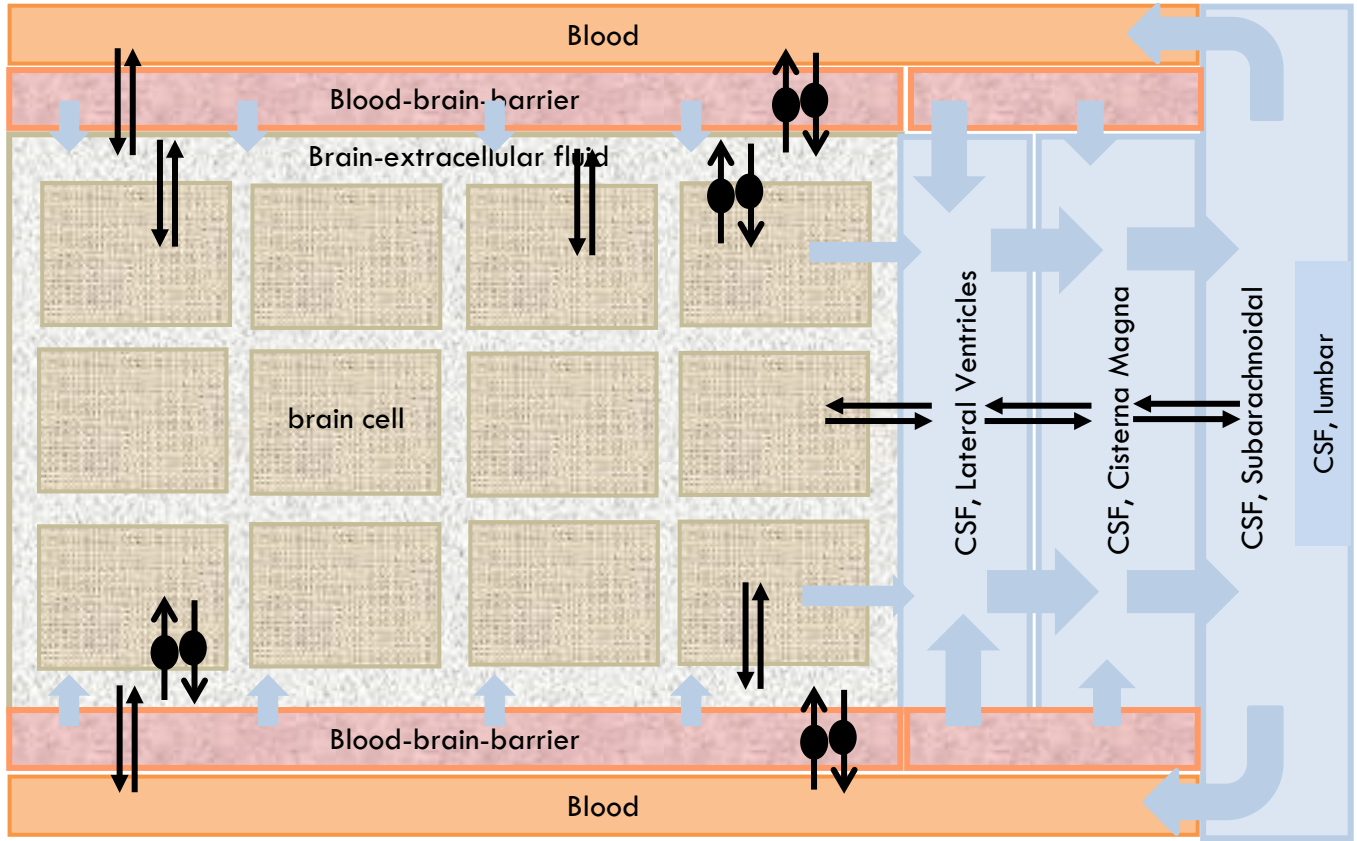




Physiological CNS compartments, Volumes, Flows, Membrane surfaces, Membrane properties

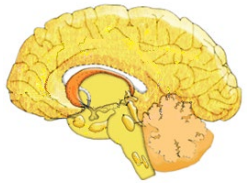
CNS properties

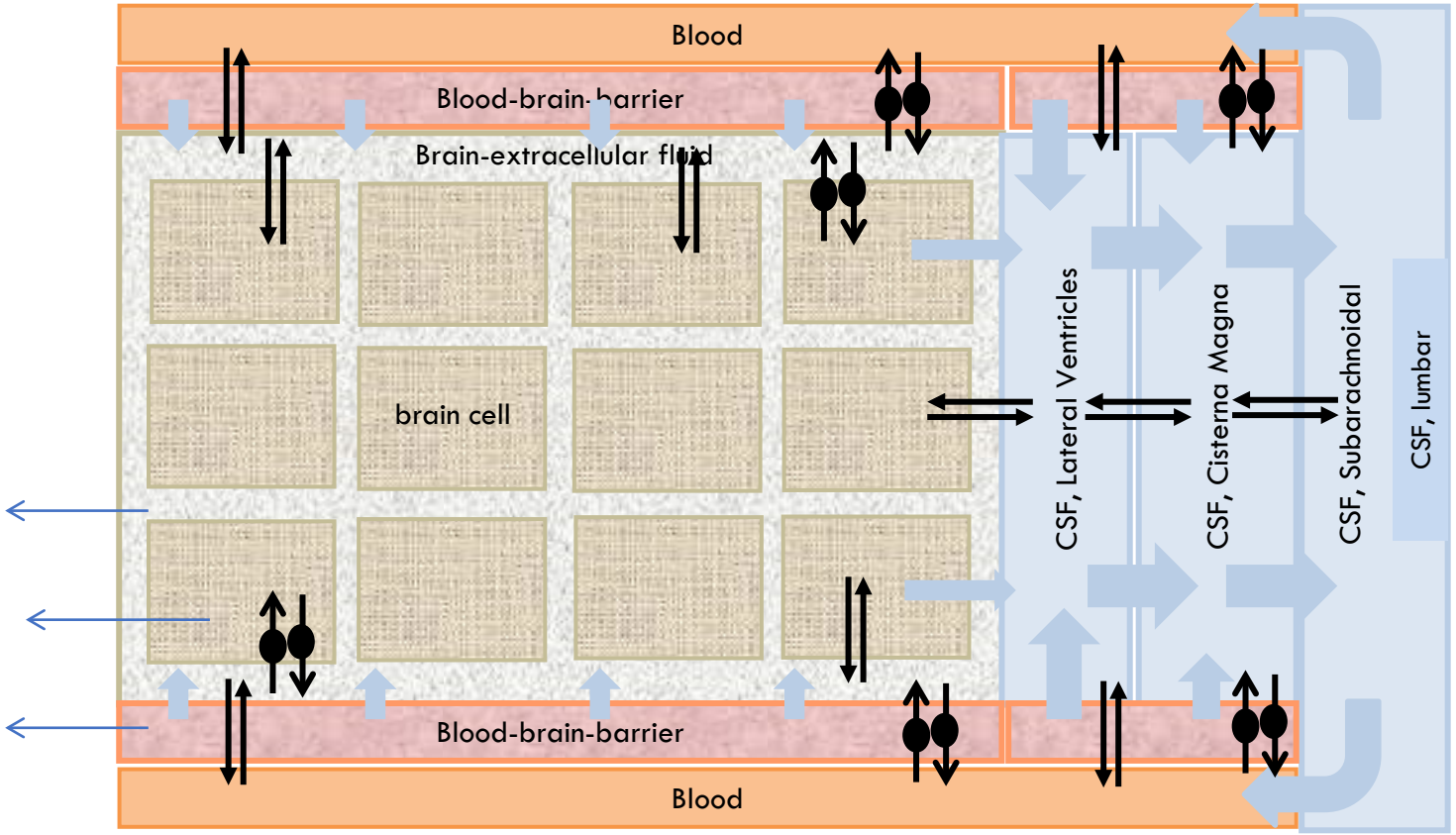




Physiological CNS compartments, Volumes, Flows, Membrane surfaces, Membrane properties, Active transporter functionalities

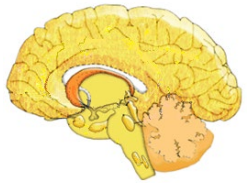
CNS properties

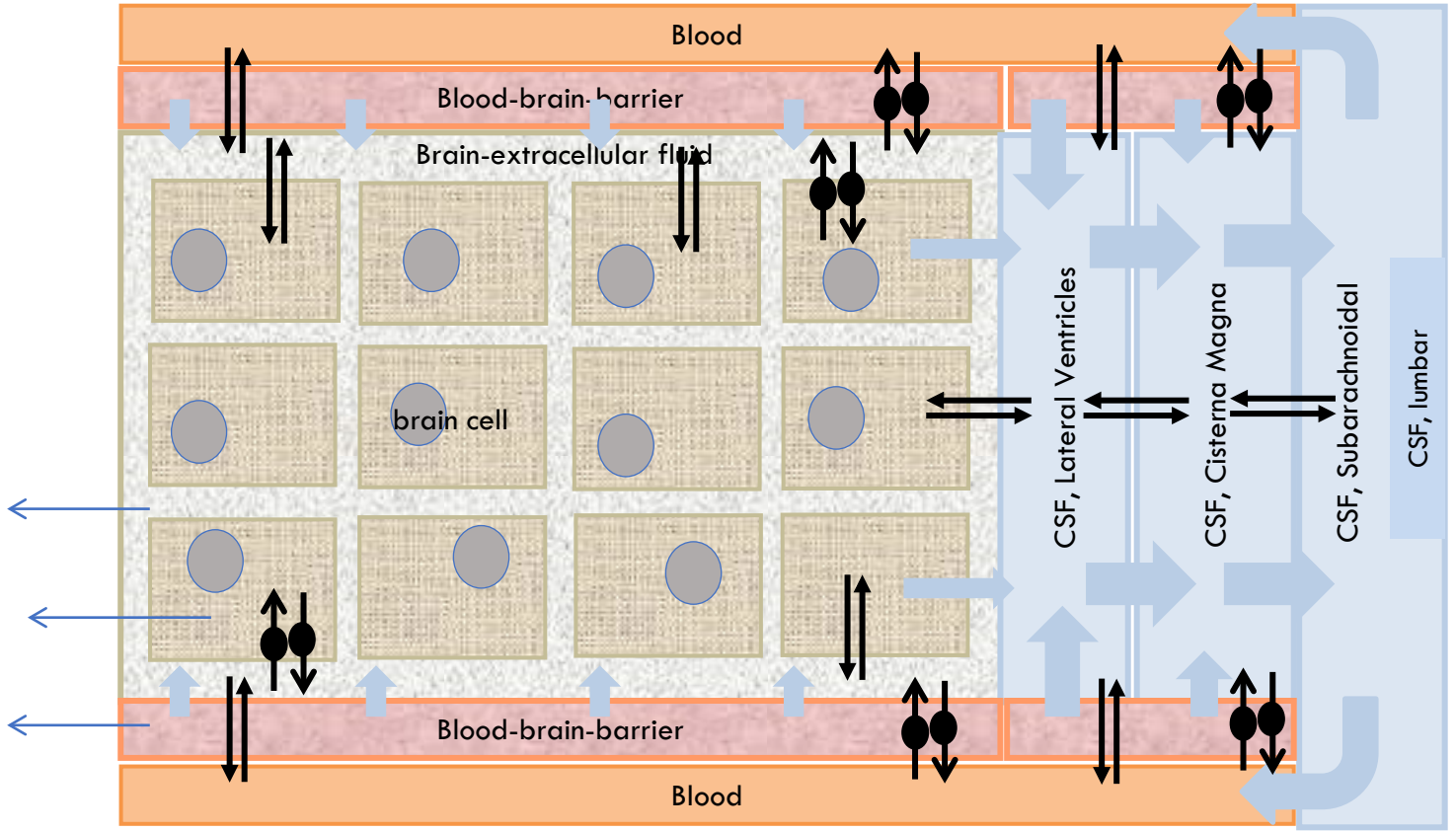




Physiological CNS compartments, Volumes, Flows, Membrane surfaces, Membrane properties, active transporter functionalities, Enzyme functionalities

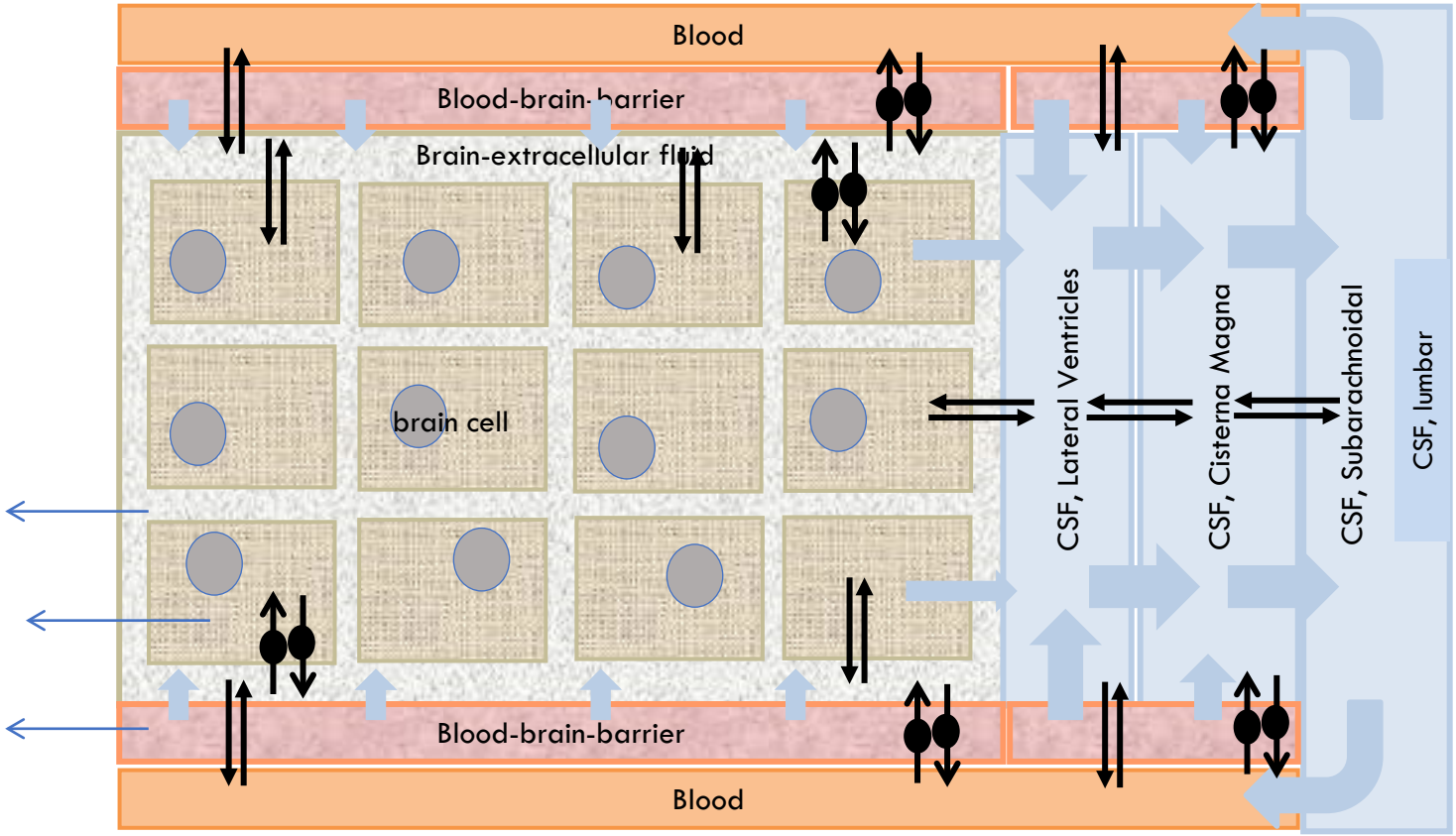
CNS properties





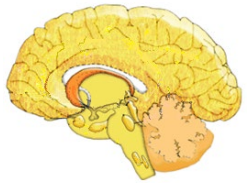
Physiological CNS compartments, Volumes, Flows, Membrane surfaces, Membrane properties, active transporter functionalities, Enzyme functionalities, Subcellular compartments,

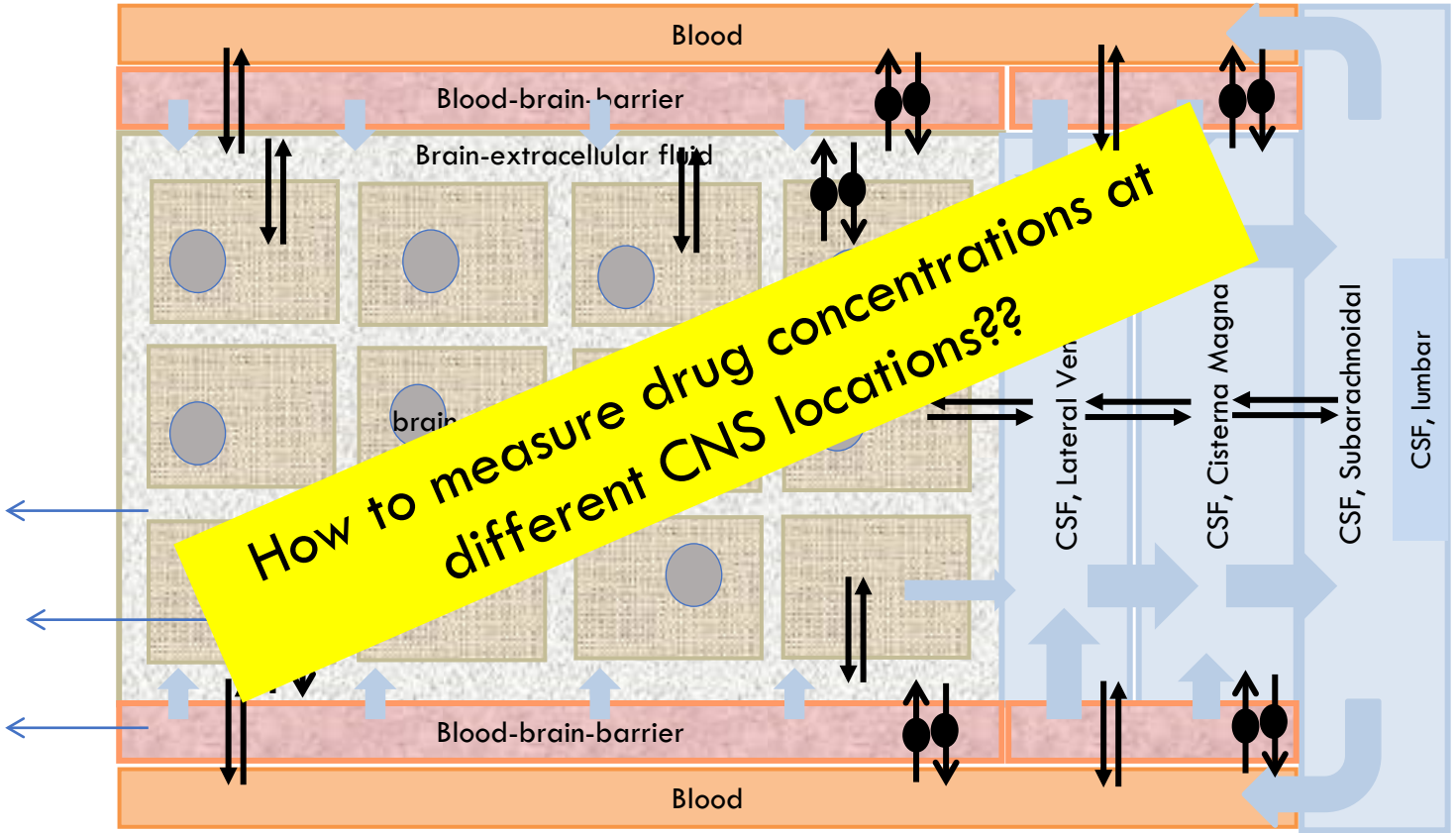
CNS properties



Physiological CNS compartments, Volumes, Flows, Membrane surfaces, Membrane properties, active transporter functionalities, Enzyme functionalities, Subcellular compartments, pH values of the fluids

CNS properties





Physiological CNS compartments, Volumes, Flows, Membrane surfaces, Membrane properties, active transporter functionalities, Enzyme functionalities, Subcellular compartments, pH values of the fluids

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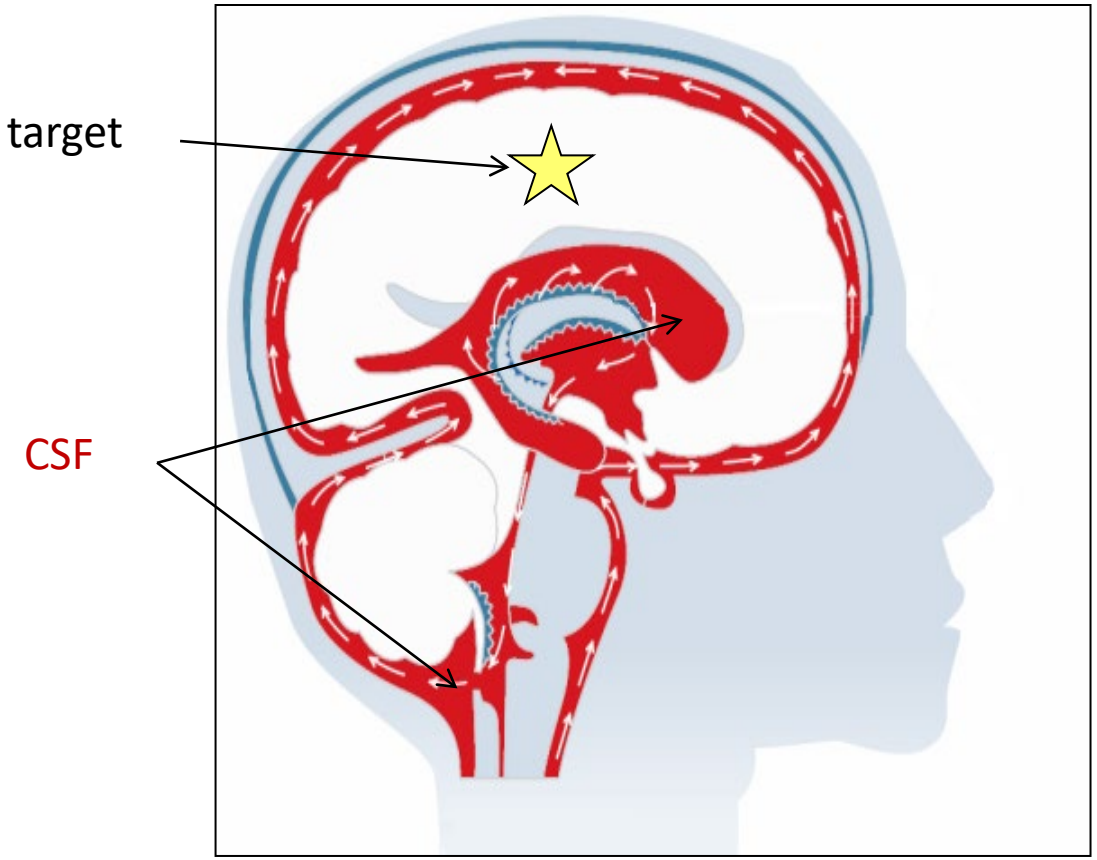
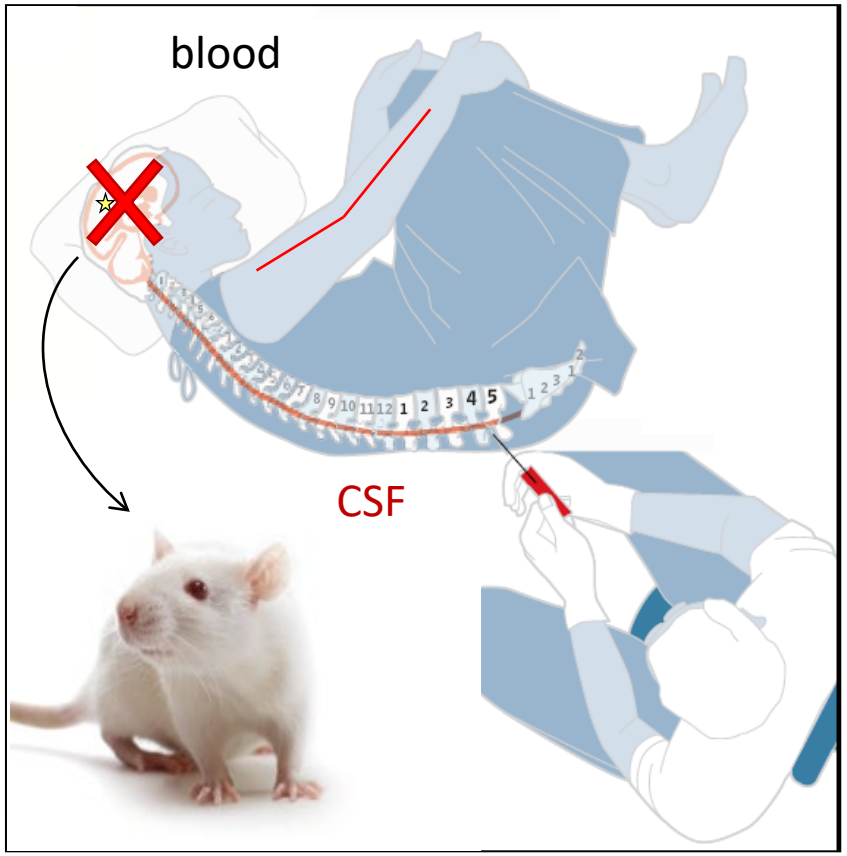
CNS PK prediction





Experimental approach

- Westerhout et al. Preclinical prediction of human brain target site concentrations: Considerations in extrapolating to the clinical setting. JPS, 2011
- Westerhout et al. Physiologically-based pharmacokinetic modeling to investigate regional brain distribution kinetics in rats. AAPSJ. 2012
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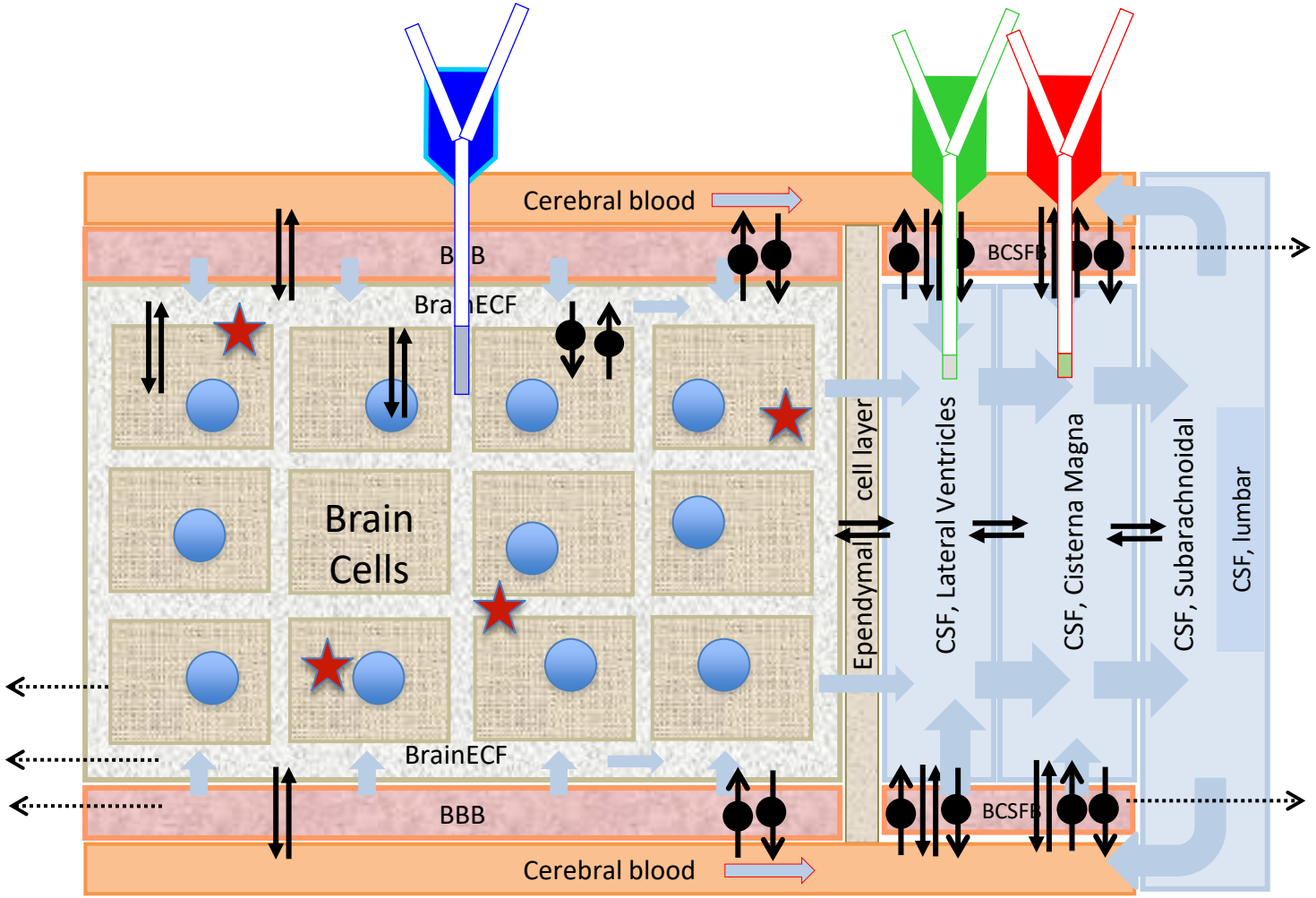
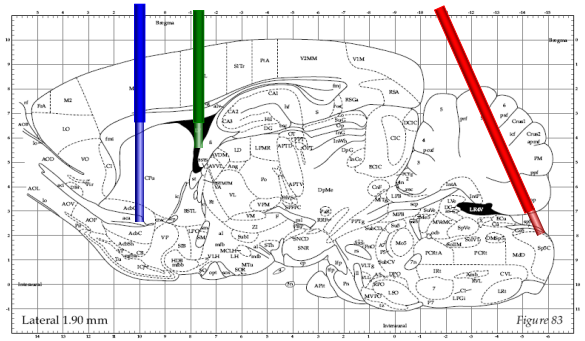
CNS PK prediction





From animal data to human prediction for acetaminophen

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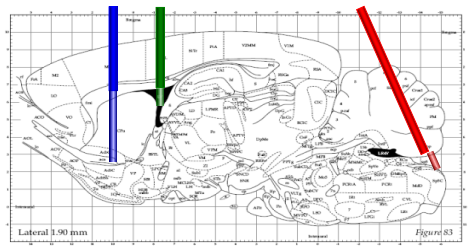
CNS PK prediction

Animal experiment



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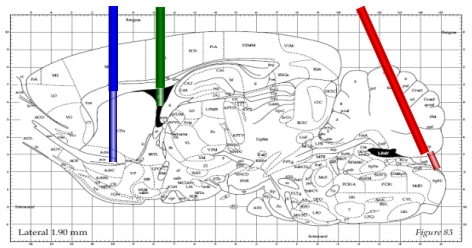
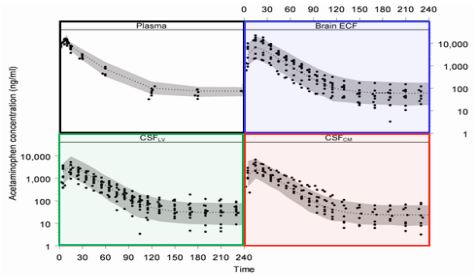
CNS PK prediction

Animal experiment



Animal PK profiles



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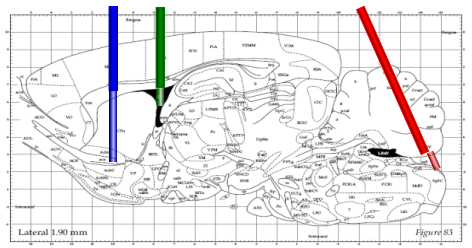
CNS PK prediction

Animal experiment



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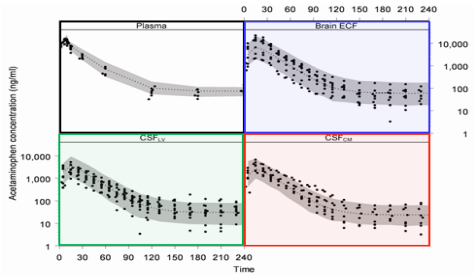
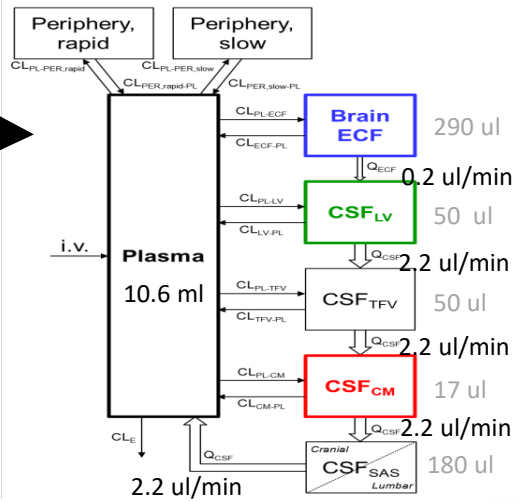


Animal PBPK model



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CNS PK prediction

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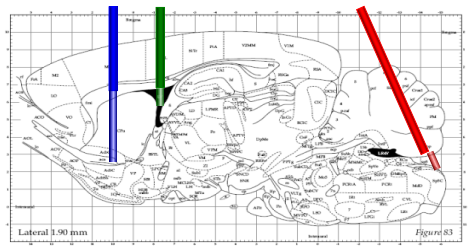

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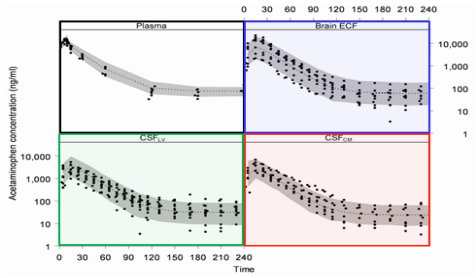

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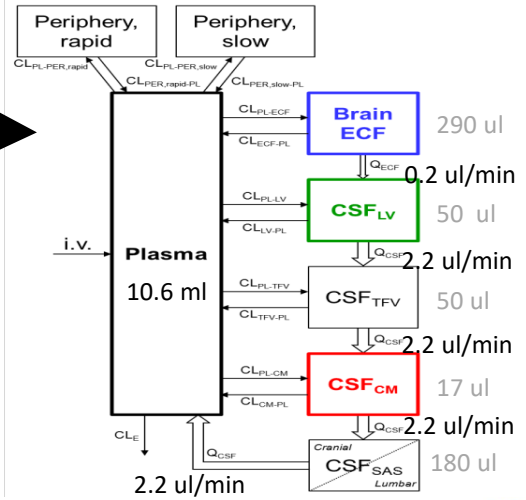

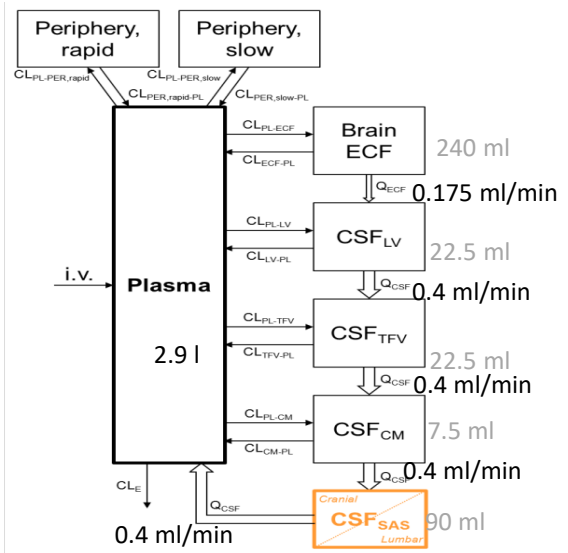

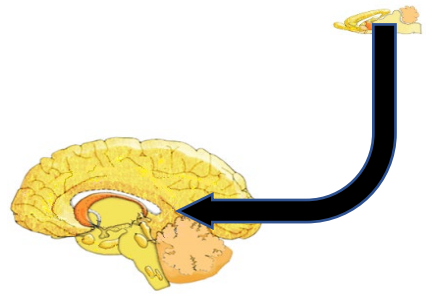

Translation to human model

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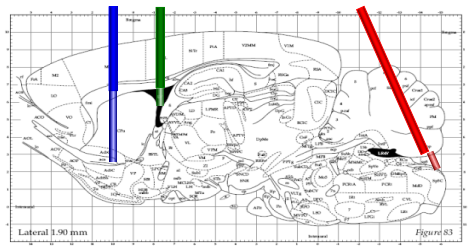
CNS PK prediction

Animal experiment



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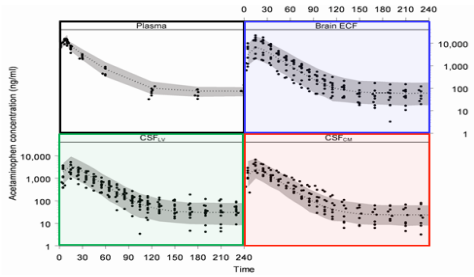
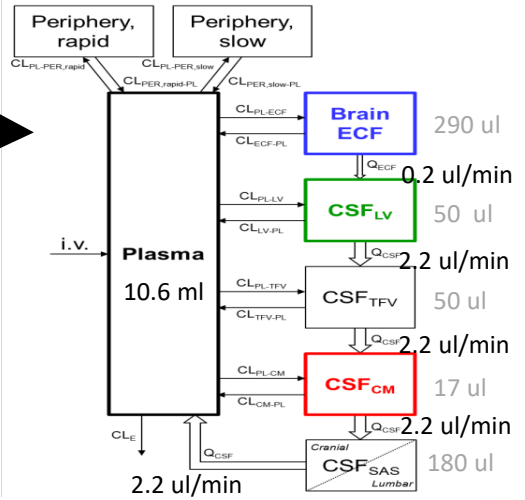
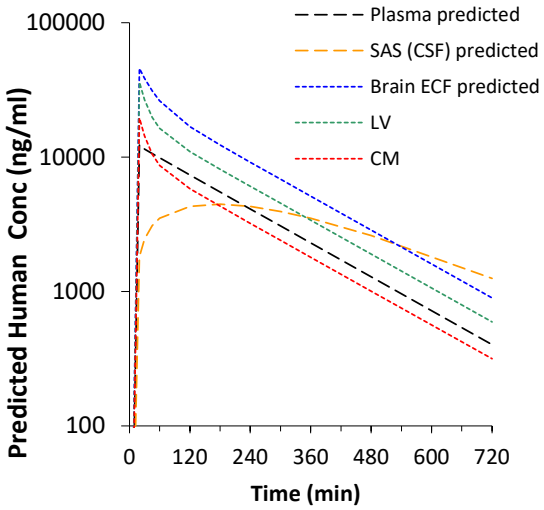
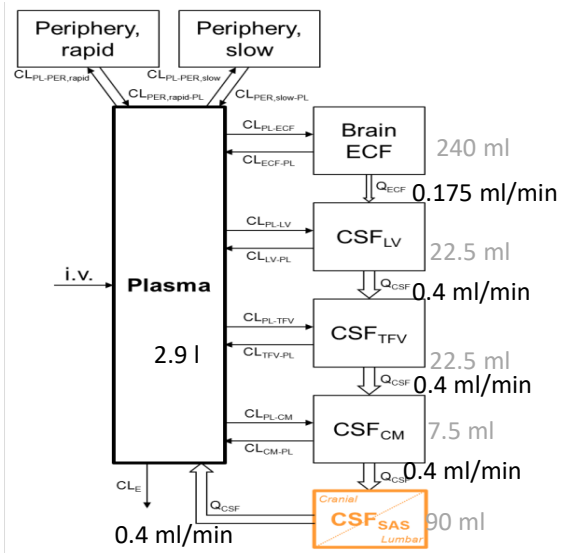


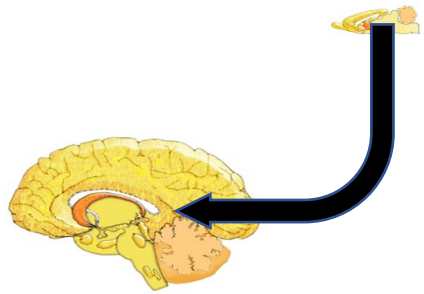
Animal PBPK model



Prediction of human data







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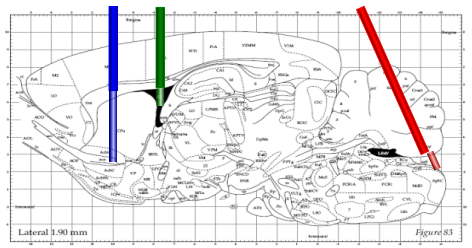
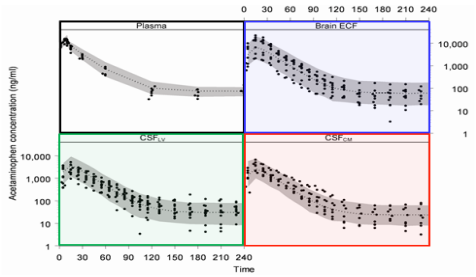
CNS PK prediction

Animal experiment



Animal PK profiles



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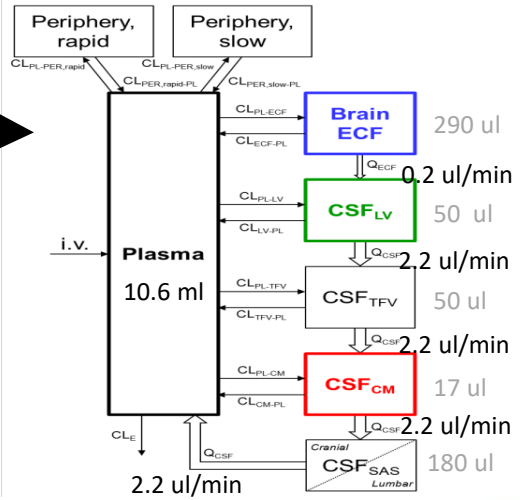
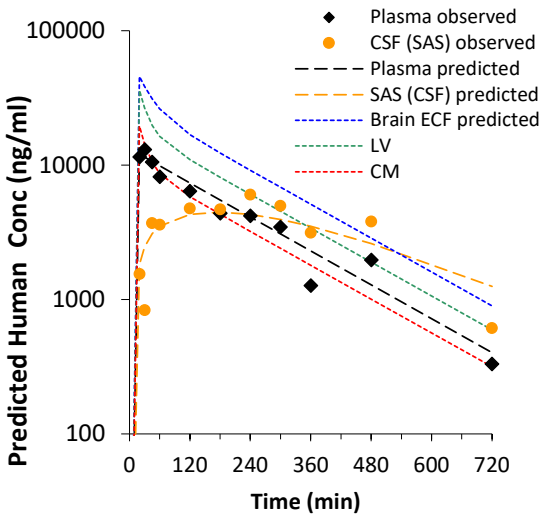
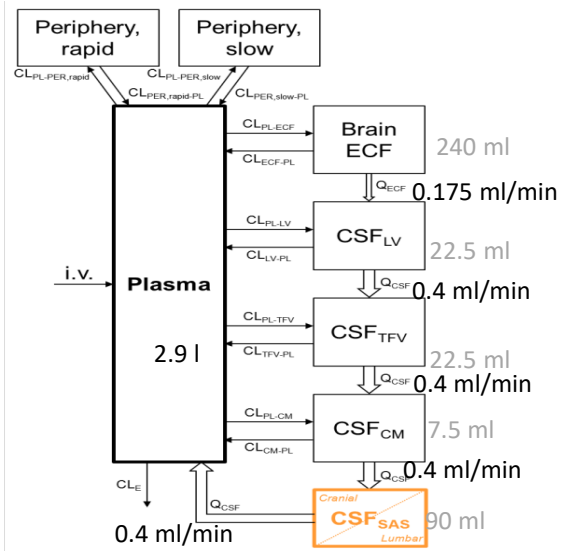
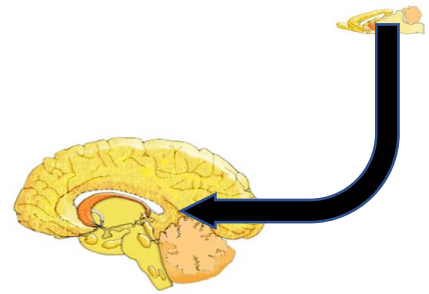


Validation on human data







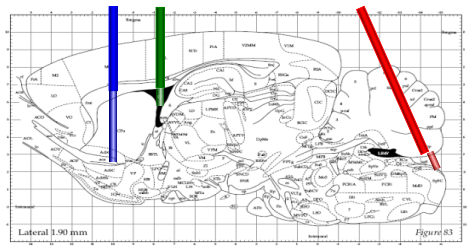
Translation to human model

From animal data to human prediction for acetaminophen

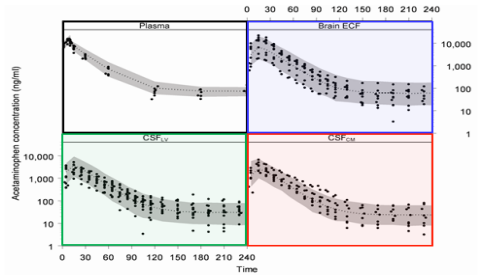
- Westerhout et al. The impact of P-gp functionality on non- steady state relationships between CSF and brain extracellular fluid. JPKPD, 2013
- Westerhout et al. Physiologically-based pharmacokinetic modeling to investigate regional brain distribution kinetics in rats. AAPSJ. 2012
- Westerhout et al. Prediction of methotrexate CNS distribution in different species - influence of disease conditions. EJPS. 2014

CNS PK prediction

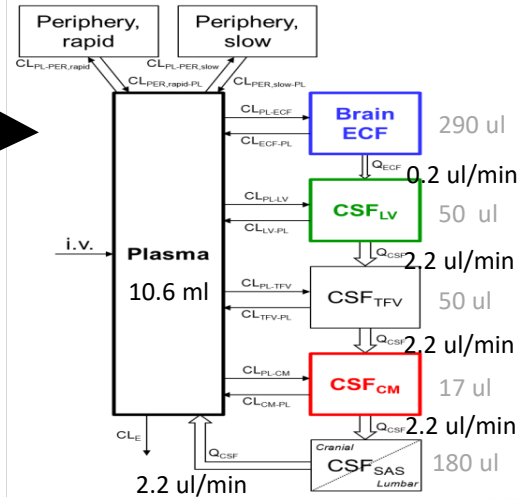
Animal experiment



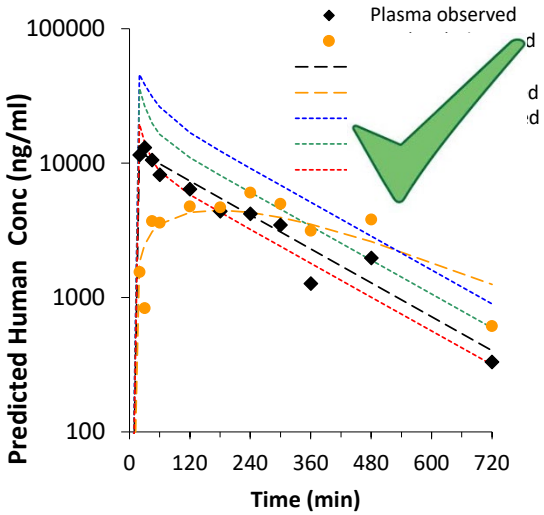
Animal PK profiles

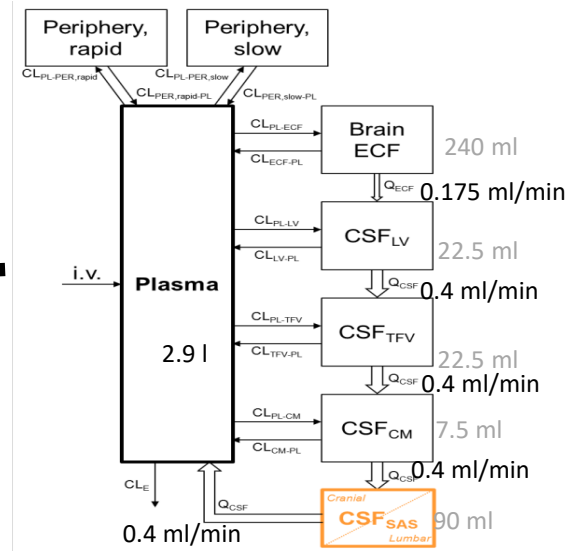


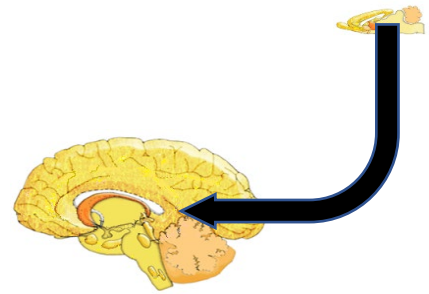
Animal PBPK model



Validation on human data







Translation to human model

Extending *in vivo* data on multiple drugs

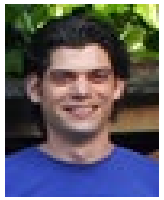
- Westerhout et al. The impact of P-gp functionality on non- steady state relationships between CSF and brain extracellular fluid. JPKPD, 2013
- Westerhout et al. Physiologically-based pharmacokinetic modeling to investigate regional brain distribution kinetics in rats. AAPSJ. 2012
- Westerhout et al. Prediction of methotrexate CNS distribution in different species - influence of disease conditions. EJPS. 2014

CNS PK prediction




	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Drug 6	Drug 7	Drug 8
Molecular weight								
Lipophilicity								
pKa								
Polar Surface Area								
H-bond donor								
H-bond accept								
Pgp substrate								
Transporter X substrate								

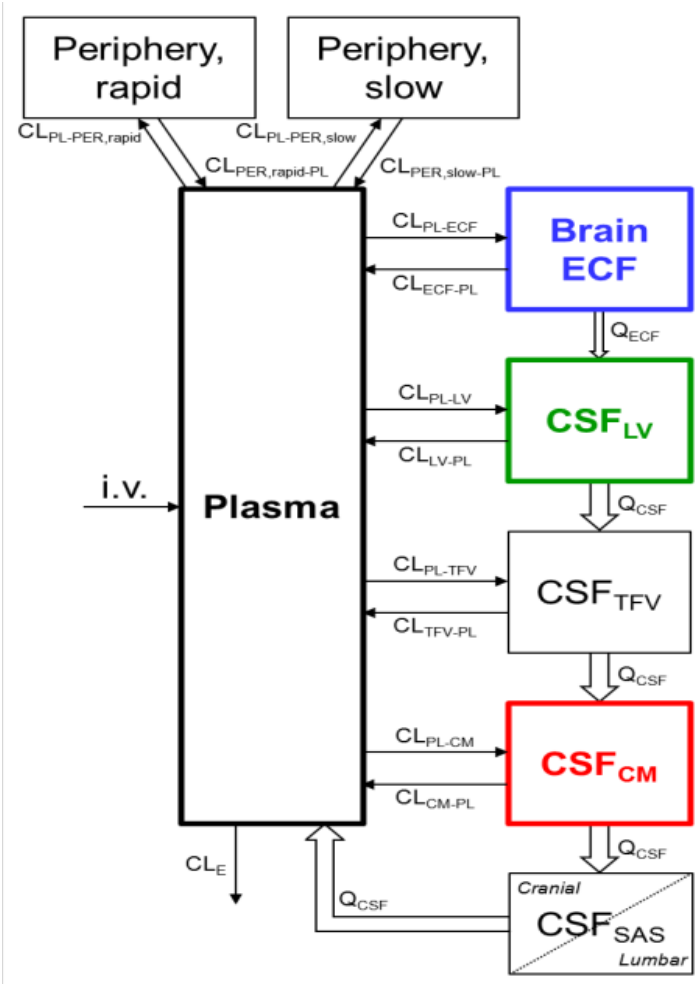


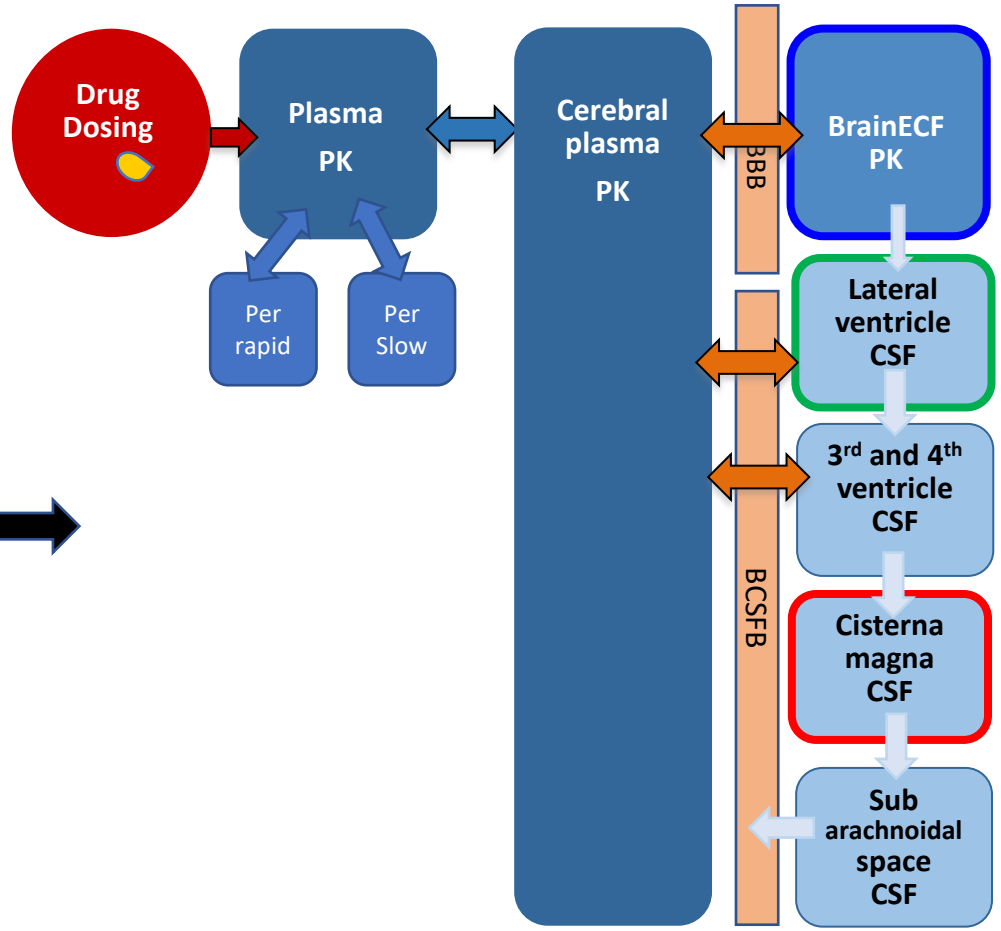



From individual drug to a generic CNS drug model

- Yamamoto et al, A generic multi-compartmental CNS distribution model structure for 9 drugs allows prediction of human brain target site concentrations. Pharm Res, 2016

CNS PK prediction

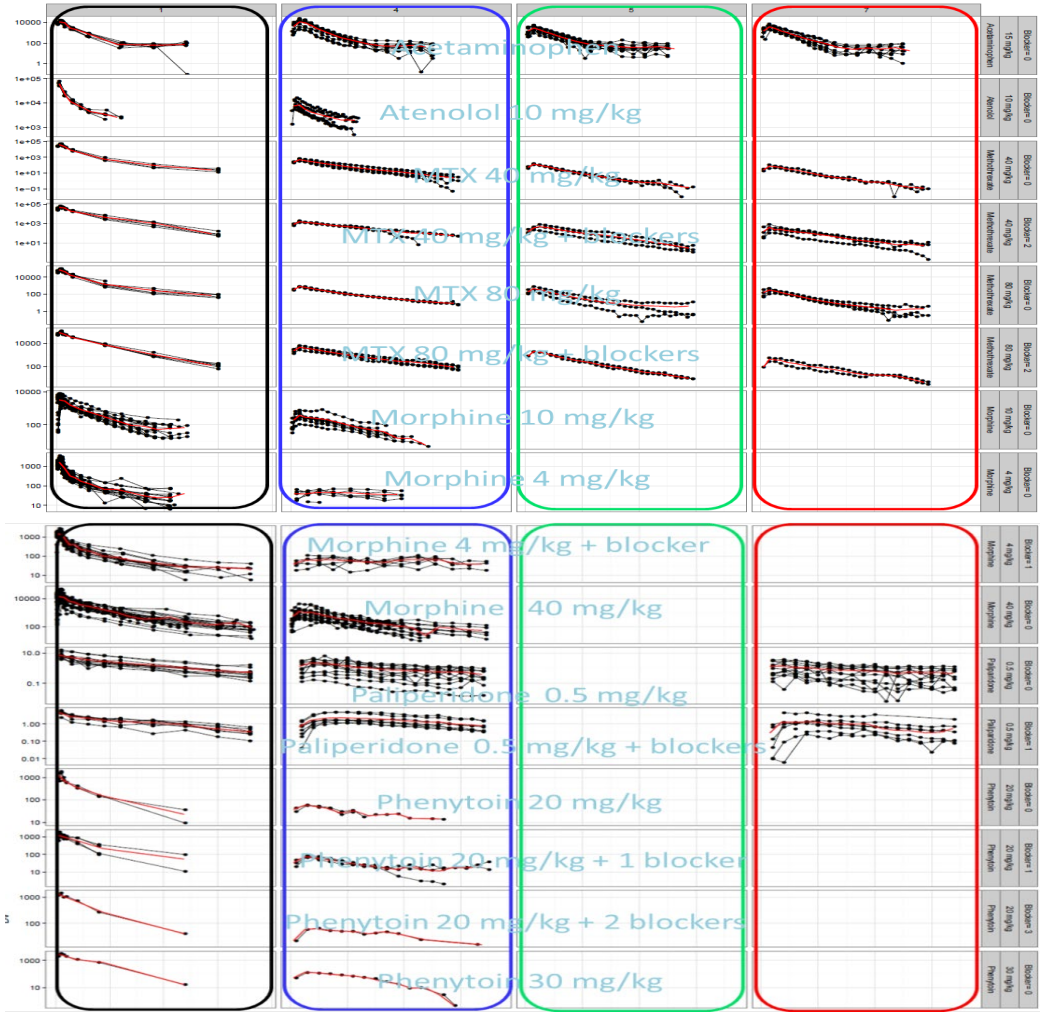


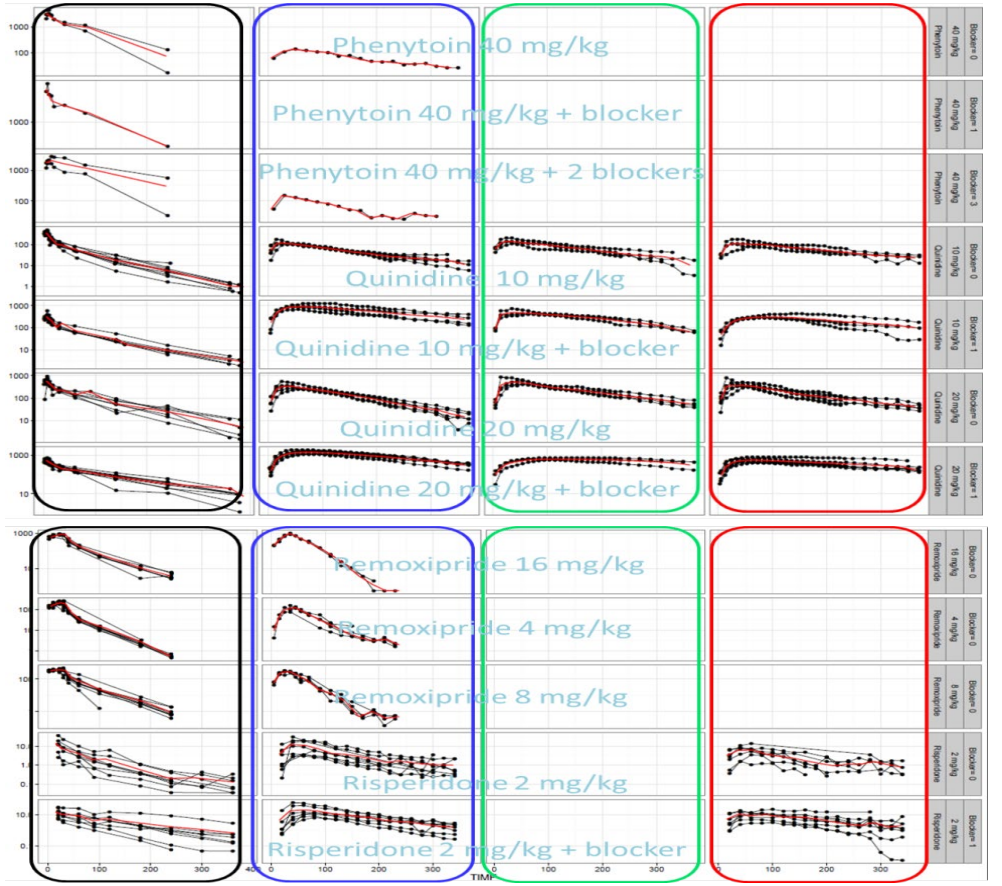


Generic CNS PK model for multiple drugs

- Yamamoto et al, A generic multi-compartmental CNS distribution model structure for 9 drugs allows prediction of human brain target site concentrations. Pharm Res, 2016

CNS PK prediction

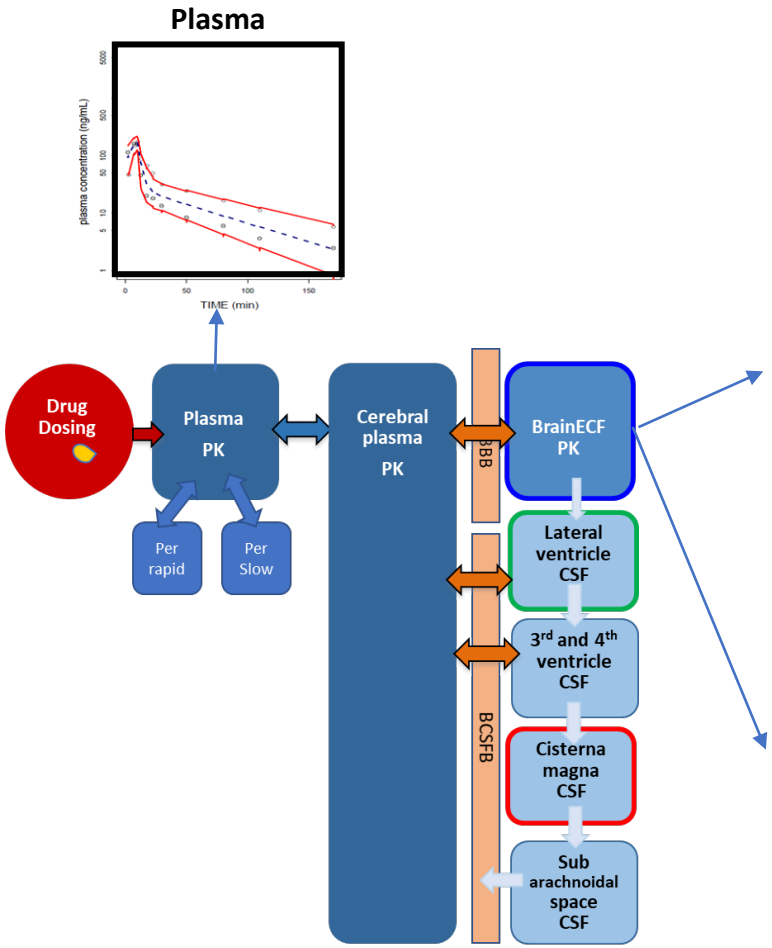


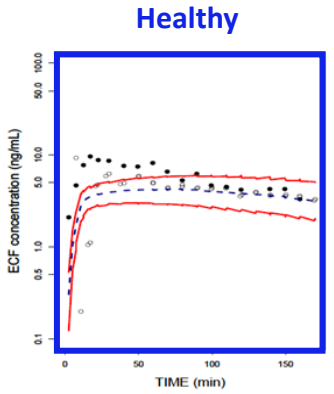


Prediction human CNS morphine- adults

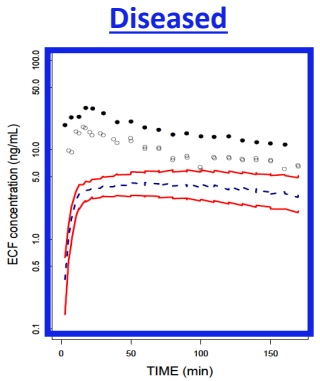
- Bouw et al. Icreased blood-brain barrier permeability of morphine in a patient with severe brain lesions as determined by microdialysis.. Acta Anaesthesiol Scand. 2001
- Ederoth et al. BBB transport of morphine in patients with severe brain trauma. Br J Clin Pharmacol 2004
- Yamamoto et al, A generic multi-compartmental CNS distribution model structure for 9 drugs allows prediction of human brain target site PK. Pharm Res, 2016

CNS PK prediction





BrainECF in Cortex tissue with normal appearance at CT scan

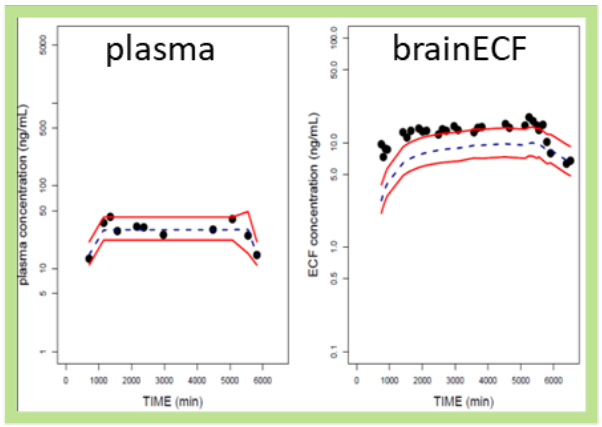


BrainECF in Penumbra zone surrounding the evacuated haematoma

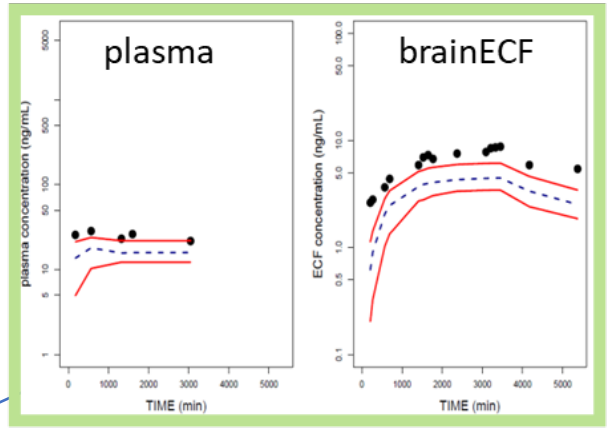
Prediction human CNS morphine- Children

- Ketharanathan et al. Combining Brain Microdialysis and Translational PK Modeling to Predict Drug Concentrations in Pediatric Severe Traumatic Brain Injury: The Next Step Toward Evidence-Based Pharmacotherapy? J Neurotrauma. 2018

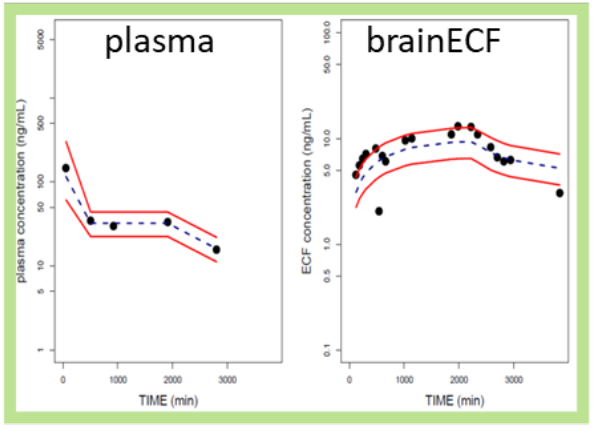
CNS PK prediction



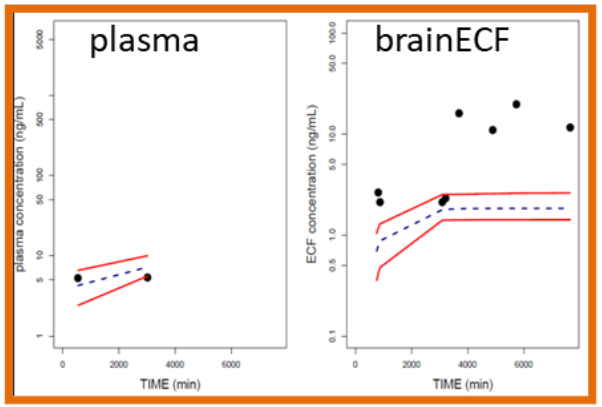
Patient 1 (focal TBI)



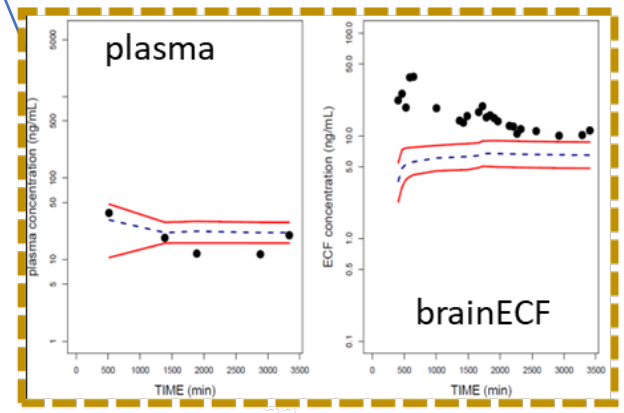
Patient 2 (Focal TBI)



Patient 4 (Focal TBI)



Patient 5 (Focal TBI, only 2 blood samples)



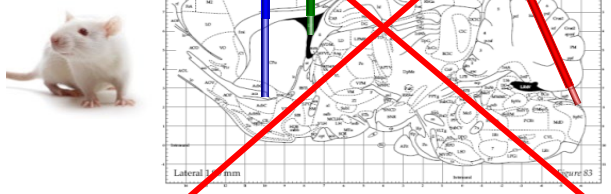
Patient 6 (Diffuse TBI)

Prediction without use of animal in vivo data?

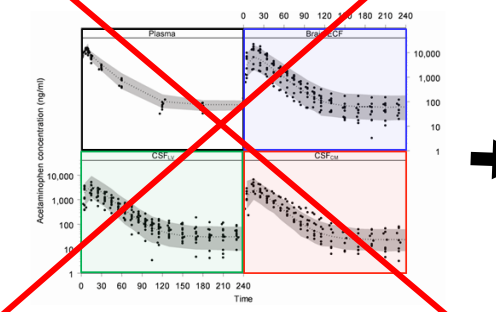
- Yamamoto et al, A generic multi-compartmental CNS distribution model structure for 9 drugs allows prediction of human brain target site concentrations. Pharm Res, 2016

CNS PK prediction

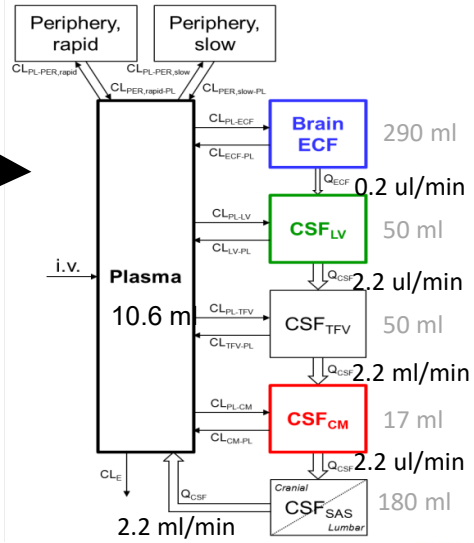
Animal experiment



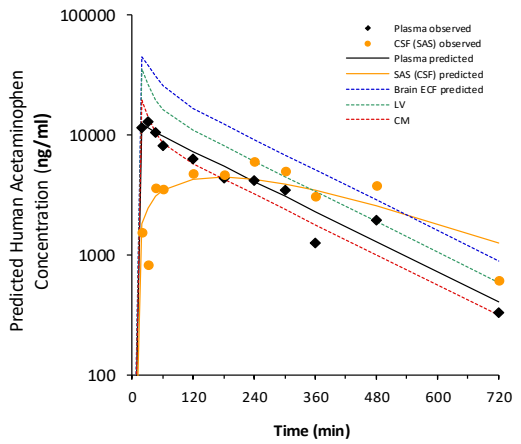
Animal PK profiles

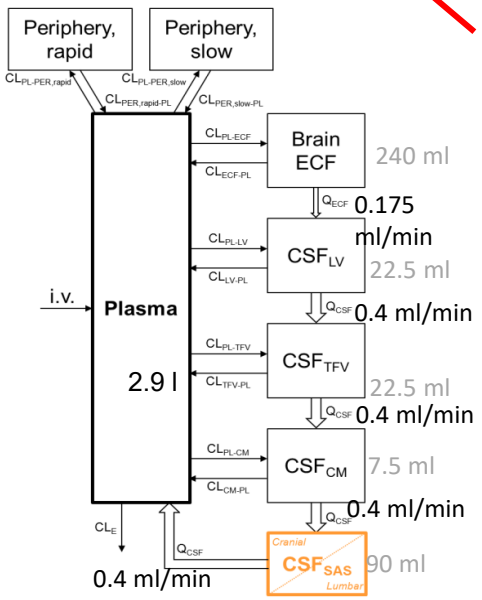


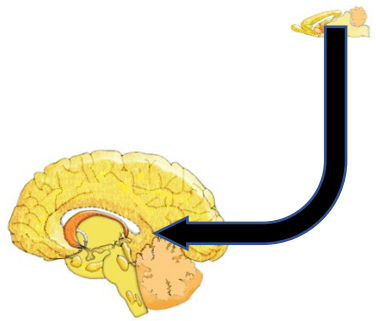
Animal PBPK model



Human prediction





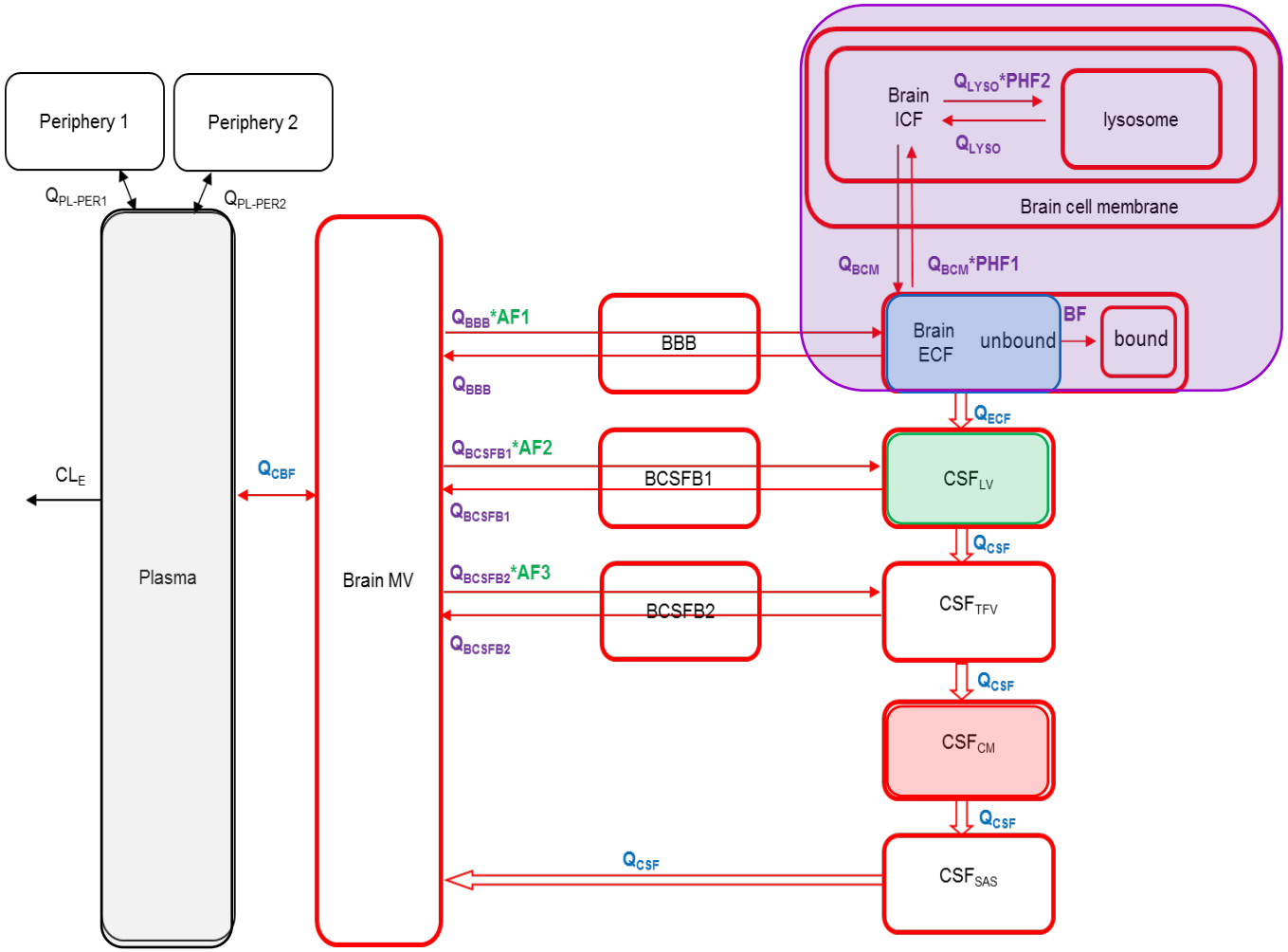


Translation to human model

CNS PBPK model prediction without using animals

- Yamamoto et al: Microdialysis: the Key to PBPK Model Prediction of Human CNS Target Site Concentrations. AAPS J. 2017
- Yamamoto et al. Predicting drug concentration-time profiles in multiple CNS compartments using a comprehensive PBPK model. CPT PSP. 2017
- Yamamoto et el. Prediction of human CNS pharmacokinetics using a PBPK modeling approach. EJPS. 2018

CNS PK prediction



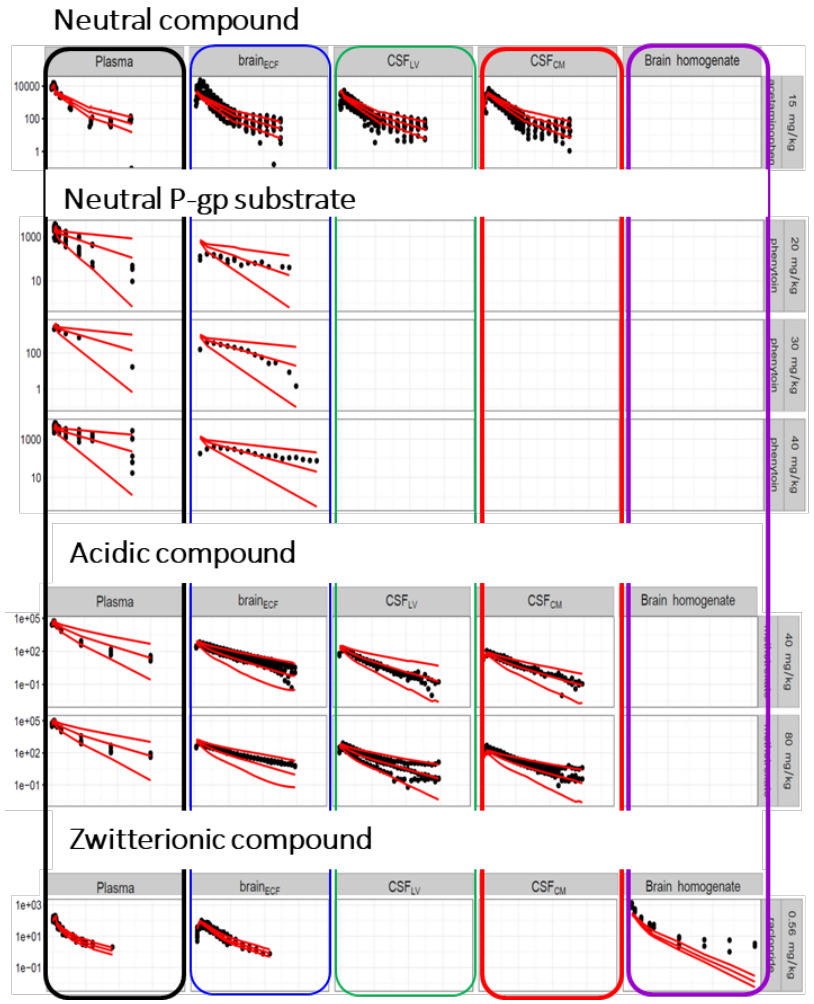
Predictions ?

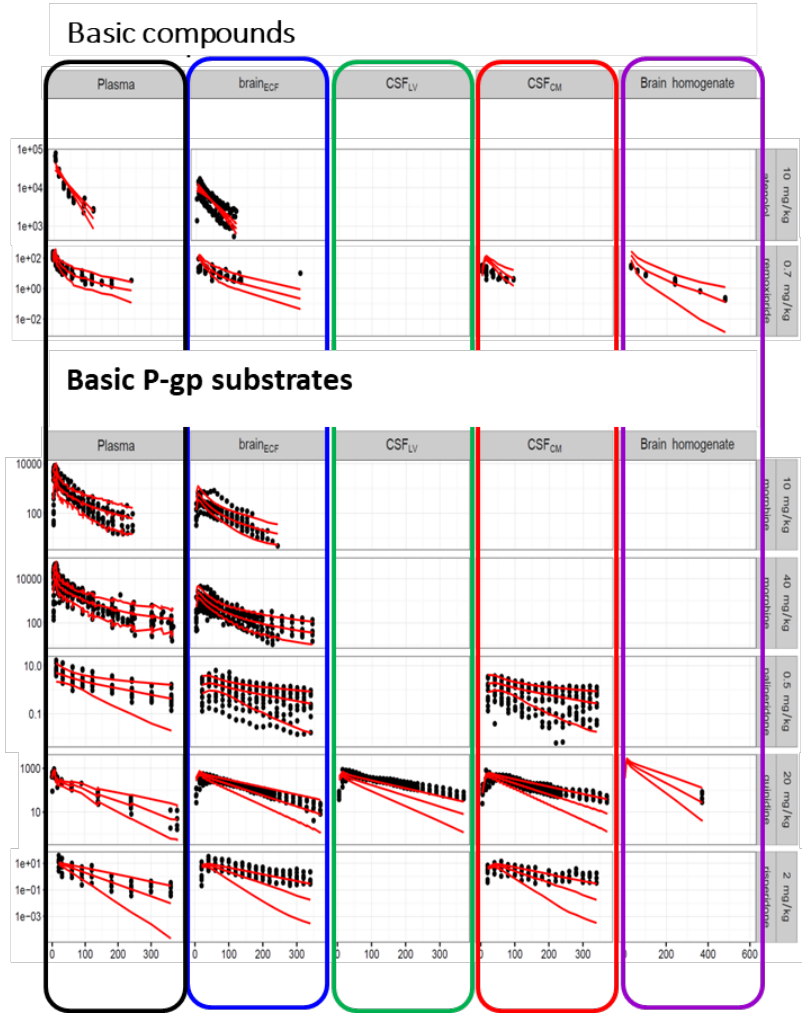
Predictions ?

CNS PK prediction without the use of animals

- Yamamoto et al. Predicting drug concentration-time profiles in multiple CNS compartments using a comprehensive PBPK model. CPT PSP. 2017

CNS PK prediction



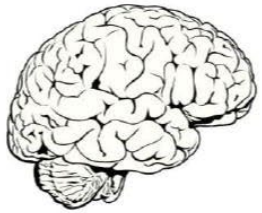


CNS PK prediction without the use of animals v1.0

- Yamamoto et al. Predicting drug concentration-time profiles in multiple CNS compartments using a comprehensive PBPK model. CPT PSP. 2017
- Yamamoto et el. Prediction of human CNS pharmacokinetics using a PBPK modeling approach. EJPS. 2018

CNS PK prediction

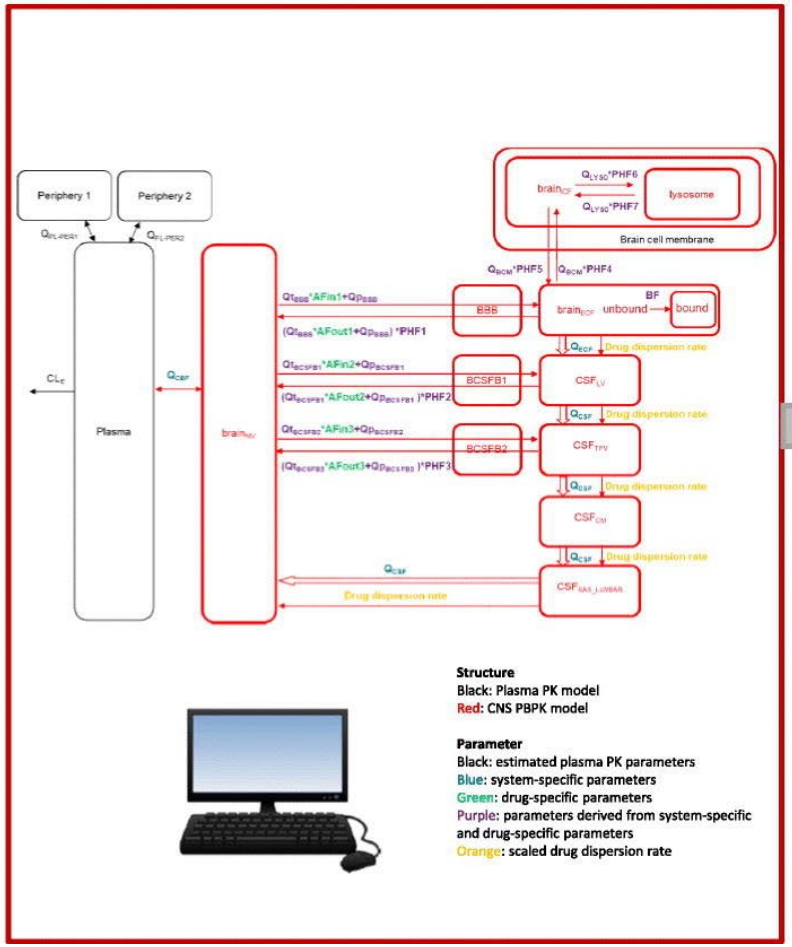
Input



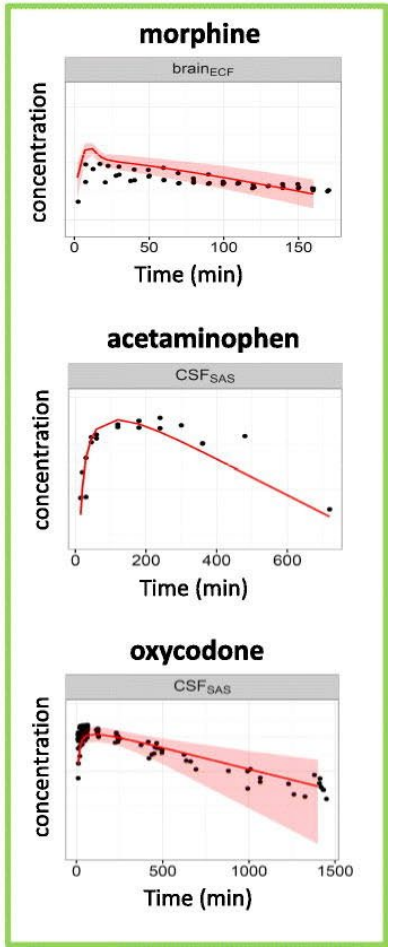
CNS Systems properties
Compartment volumes
Flows,
BBB, BCSFB
Active transporters

Drug properties
Molecular weight
Log P
pKa
Active transport

Human CNS PBPK model



Prediction



CNS PK prediction without the use of animals v1.0

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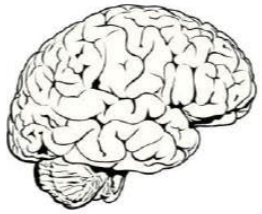
CNS PK prediction

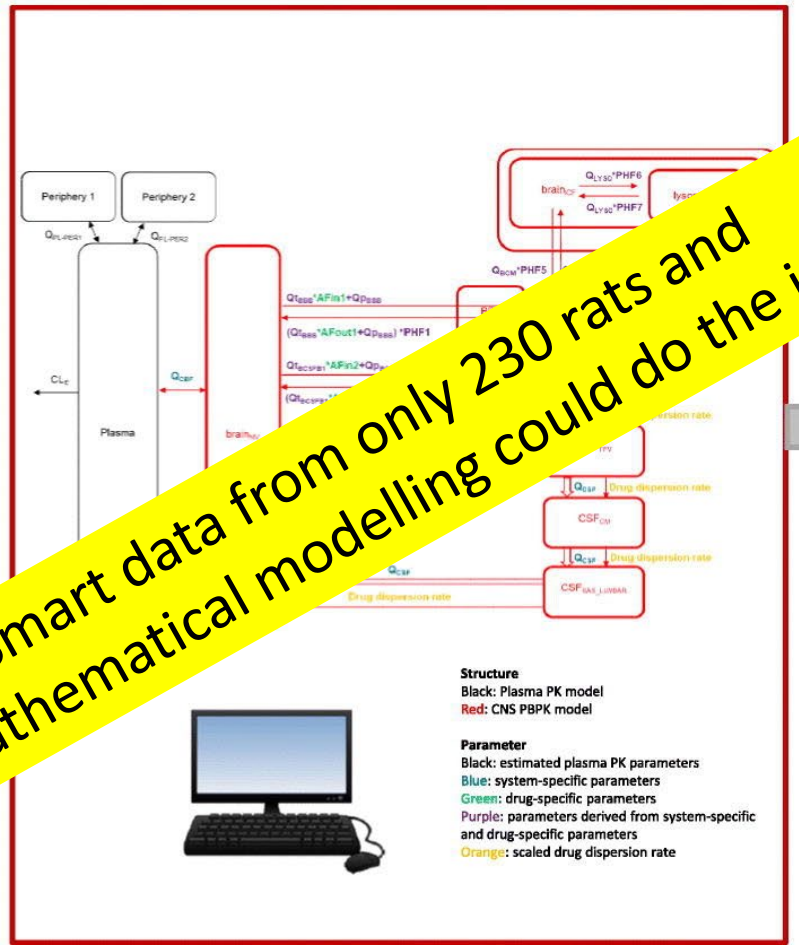
Input



CNS Systems properties
Compartment volumes
Flows,
BBB, BCSFB
Active transporters

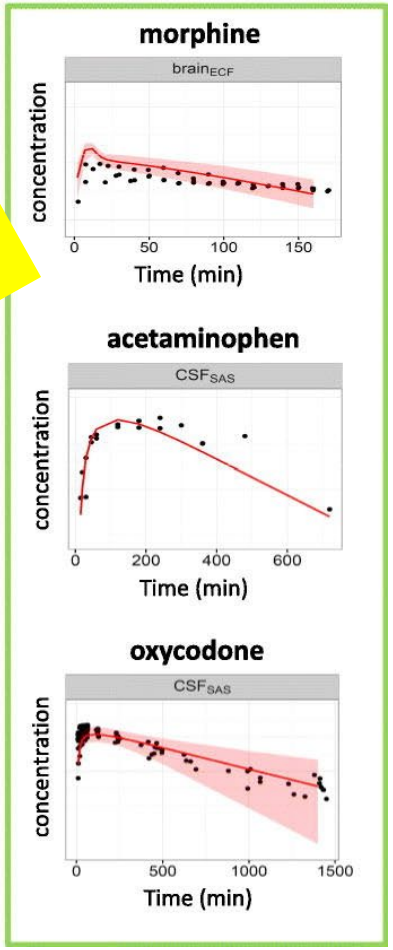
Drug properties
Molecular weight
Log P
pKa
Active transport

Human CNS PBPK model



Smart data from only 230 rats and mathematical modelling could do the job

Prediction



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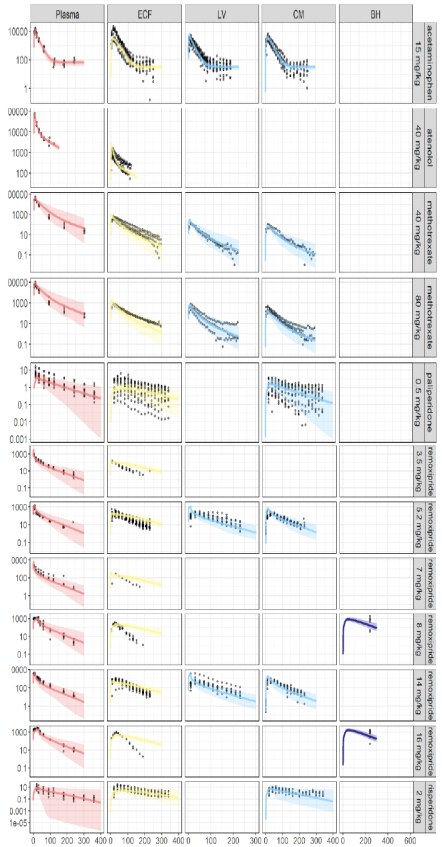
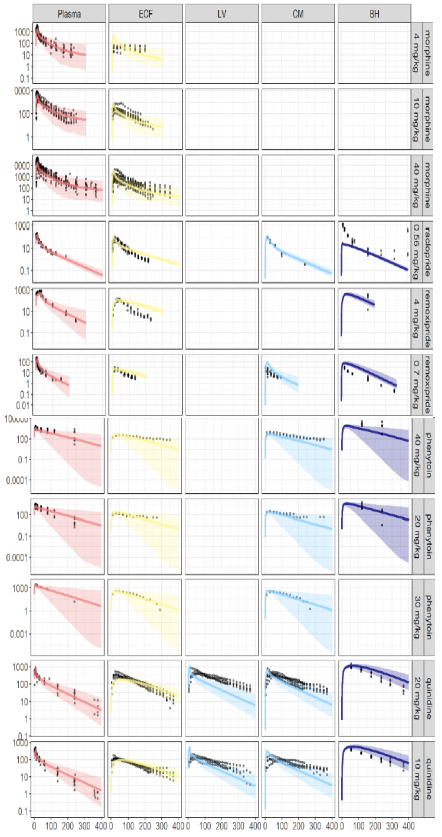
CNS PK prediction without the use of animals v3.0

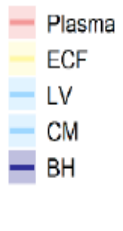
- Ederoth et al. BBB transport of morphine in patients with severe brain trauma. BJCP 2004
- Yamamoto et al. Predicting drug concentration-time profiles in multiple CNS compartments using a comprehensive PBPK model. CPT PSP. 2017
- Yamamoto et el. Prediction of human CNS pharmacokinetics using a PBPK modeling approach. EJPS. 2018
- Saleh et al. Lumbar CSF-to-brainECF fluid surrogacy is context-specific: insights from LeiCNS-PK3.0 simulations, JPKPD, 2021
- Saleh et al. Impact CNS Diseases DD to BrainECF and ICF Target Sites in Human-WHAT-IF Simulations. Pharmaceutics. 2021

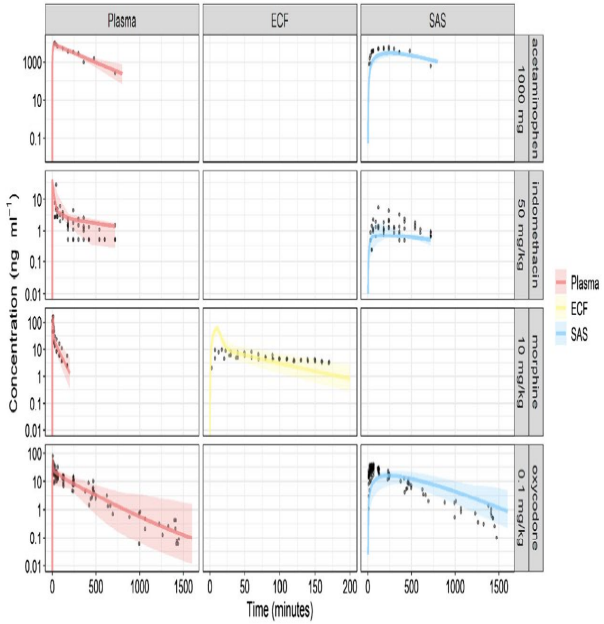
CNS PK prediction

- pH of each compartment
- Ionization of drugs in each compartment
- Distinction between neutral and charged drug molecule transport
- Explicit brain tissue binding





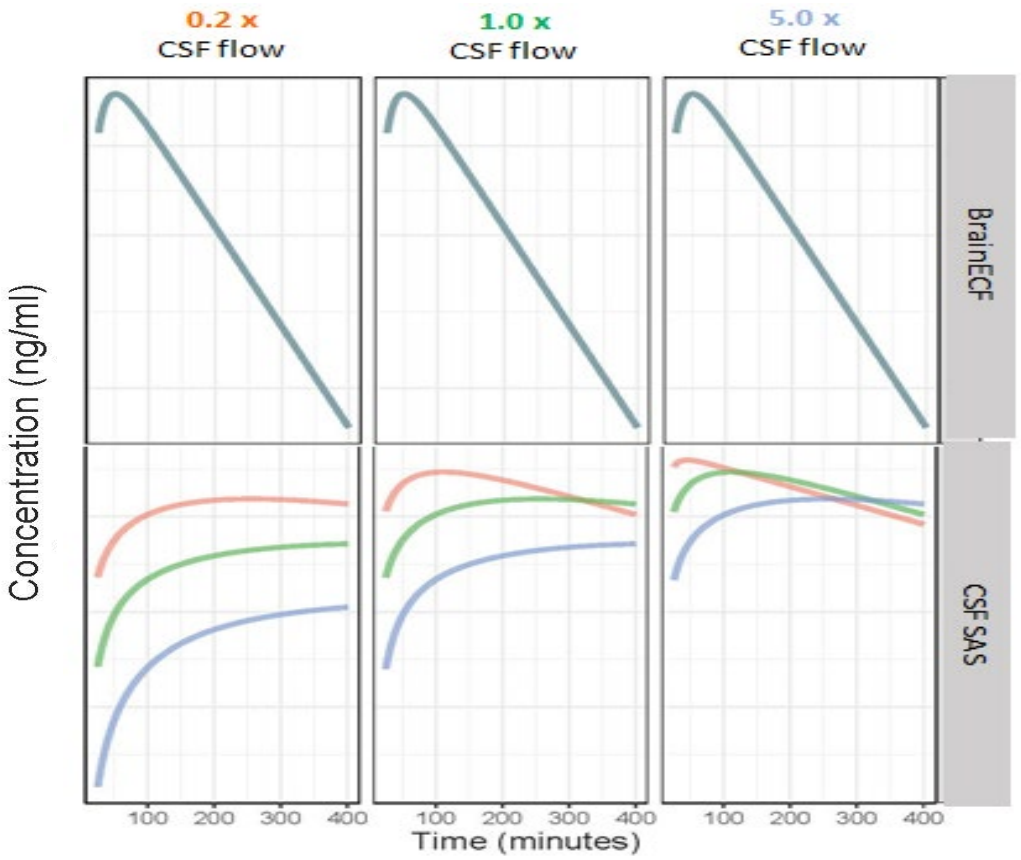




Prediction of CNS PK in (disease) conditions

- Saleh et al. Lumbar CSF-to-brainECF fluid surrogacy is context-specific: insights from LeiCNS-PK3.0 simulations, JPKPD, 2021

What if scenarios



- What if CSF flow and/or volume has changed?
- The relationship between lumbar CSF and brainECF pharmacokinetics is *CSF volume and flow dependent* for all drugs investigated

Prediction of CNS PK in (disease) conditions

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What if scenarios

Table 3. Pathophysiological changes of $para_{radius}$, pH_{ECF}, and pH_{ICF} in multiple CNS diseases.

Disease	Parameter	Value	References
Alzheimer's	BBB permeability	↔ (86–150,000 Da)	[107]
	pH_{ECF}	↓ (0.01 pH unit/decade)	[25]
	pH_{ICF}		
Brain tumors	$para_{radius}$	↑ (800%)	[114]
	pH_{ECF}	↓ (0.6 pH unit)	[115,116]
	pH_{ICF}	↑ (0.3 pH unit)	[115,116]
TBI	BBB permeability	↑ (up to 160,000 Da)	[107–109]
	pH_{ECF}	↓ (0.3 pH unit)	[22]
	pH_{ICF}	↓ (0.1 pH unit)	[106]
Ischemia	BBB permeability	↑ (up to 70,000 Da)	[117]
	pH_{ECF}	↓ (1.4 pH unit)	[118]
	pH_{ICF}	↓ (2 pH unit)	[23,24,119]
Epilepsy	BBB permeability	↑ (albumin and up to 70,000 Da)	[111]
	pH_{ECF}	↓ (0.5 pH unit)	[112]
	pH_{ICF}	↓ (0.3 pH unit)	[112]

Prediction of CNS PK in (disease) conditions

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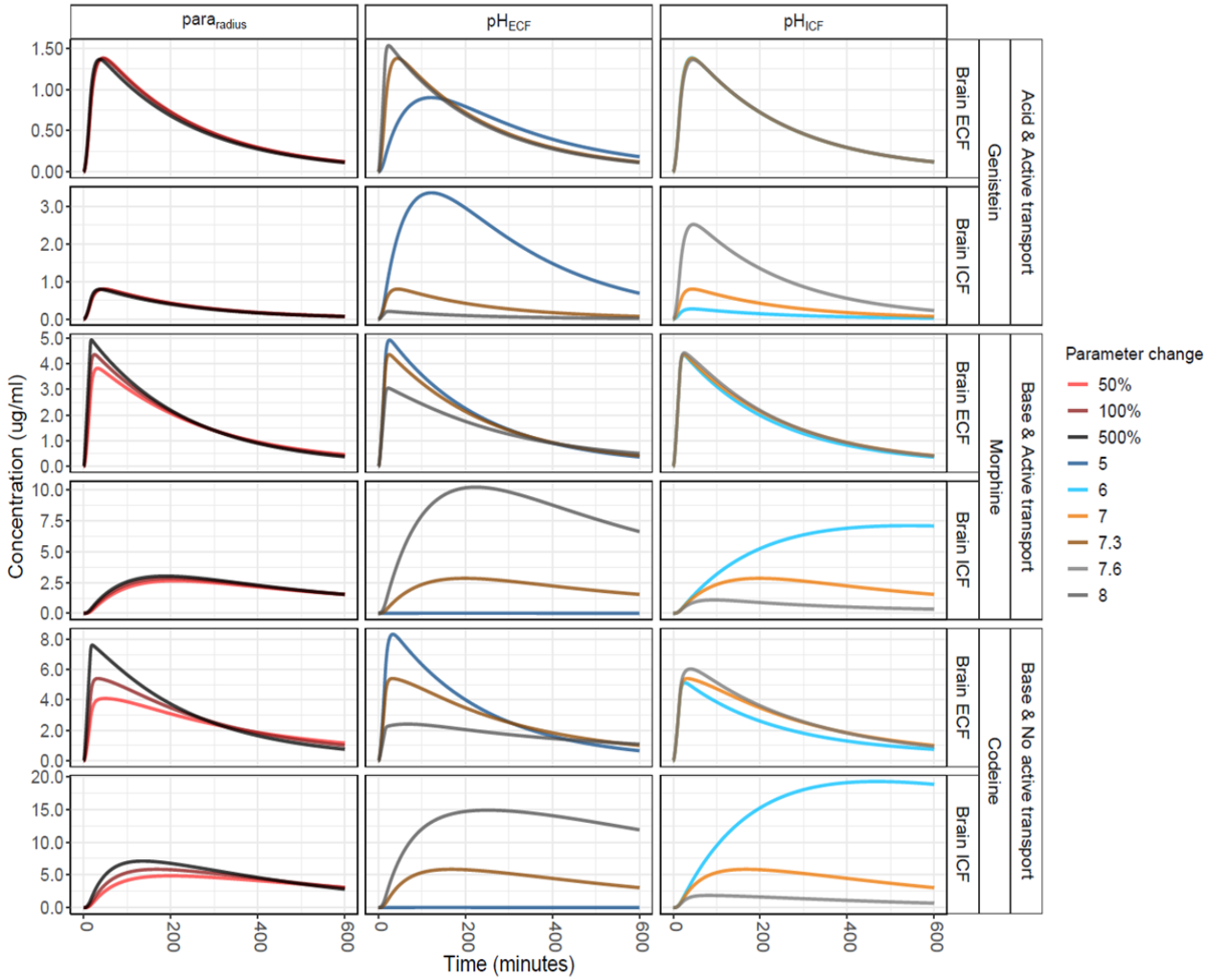
What if scenarios

WHAT IF
- Paracellular width
- pH brainECF
- pH ICF

have changed?



Prediction of CNS PK in (disease) conditions

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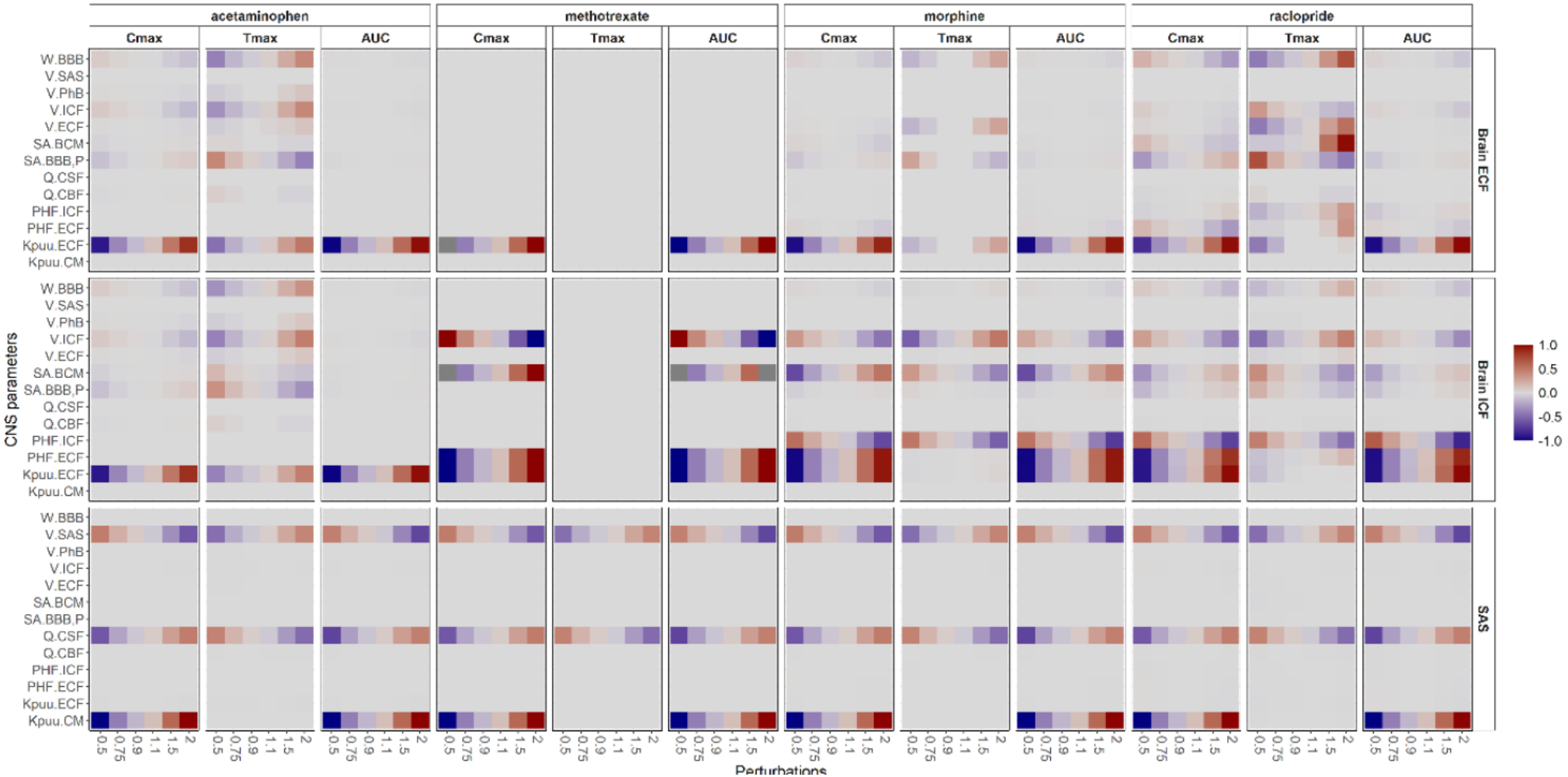
What if scenarios

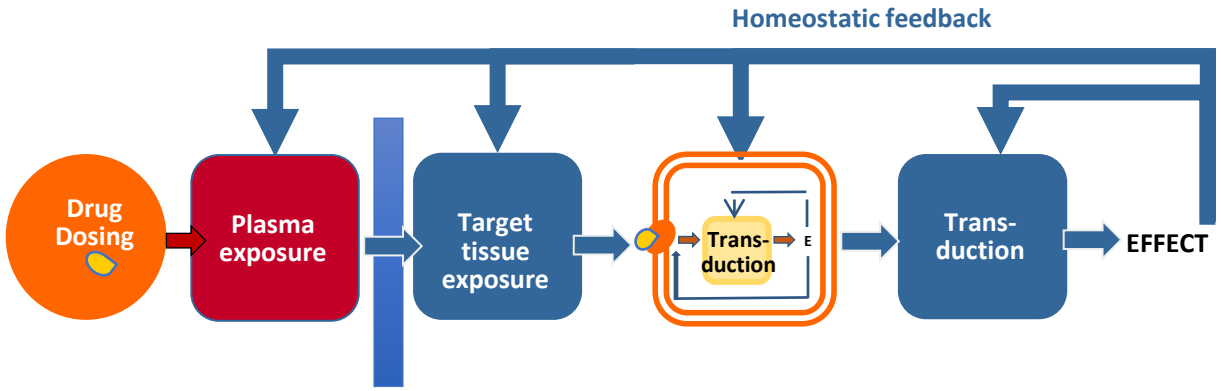


CNS PK predictor 3.0

Summary

The CNS PBPK model will help to systematically unravel and predict:

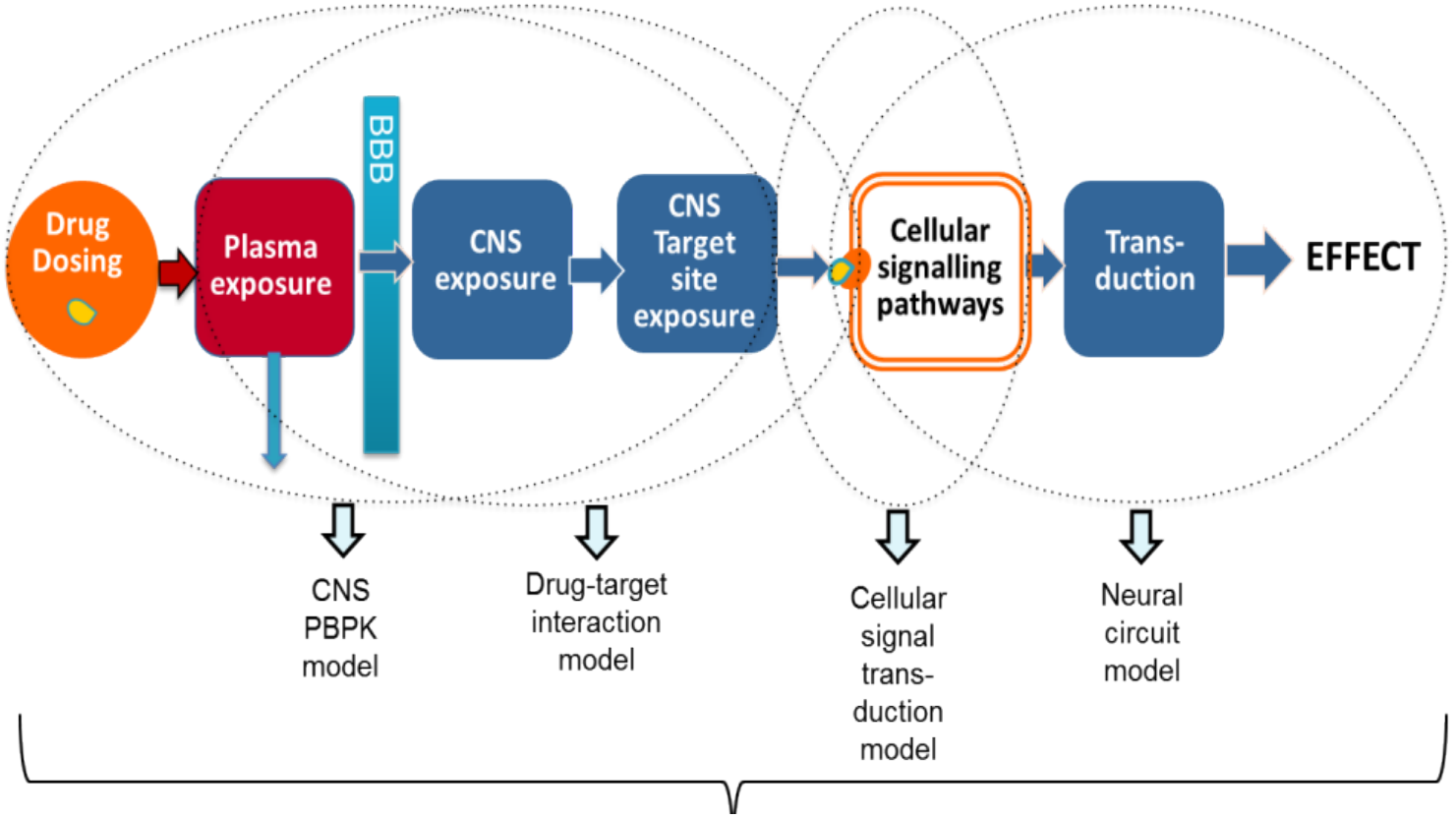
- CNS PK in multiple physiological CNS compartments
- Relationships between plasma PK, brainECF, brainICF, and CSF in lateral ventricle, cisterna magma, and lumbar region
- How this relationship can be affected by conditions, such as CNS diseases
- How this influence CNS target site concentrations
- How target site concentrations influence target occupancy (not shown in this presentation)



Effective combinational treatment of chronic pain in individual patients by an innovative QSP pain relief approach

https://qspainrelief.eu/

Chronic pain



The QSPainRelief Model platform

- To develop a model platform to evaluate drug combinations to improve analgesia, and to reduce side-effects in chronic pain patients.
- Including patient specific information
- Right place, Right time, Right concentration, for the Right person

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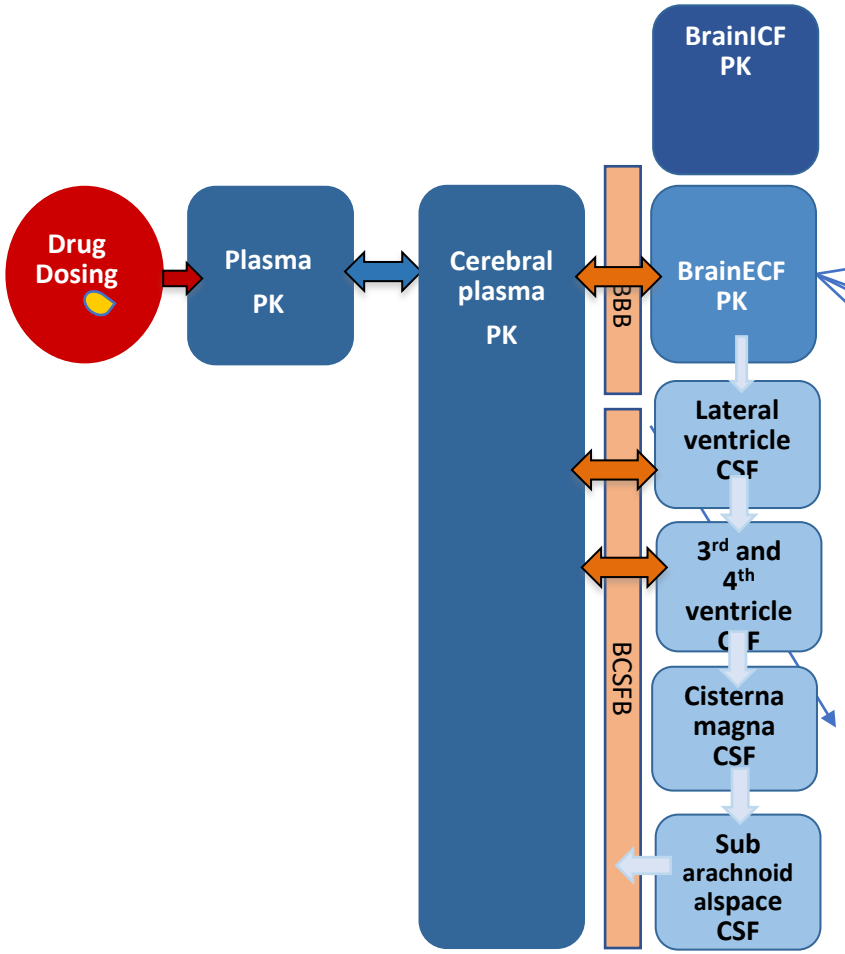
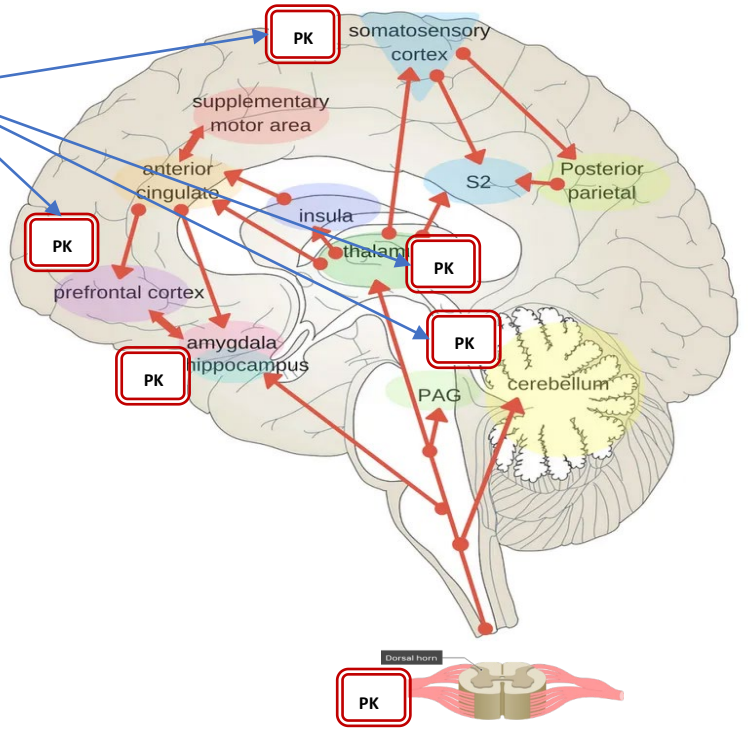
Chronic pain





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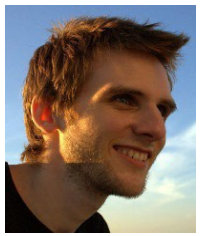
Berfin Gülave



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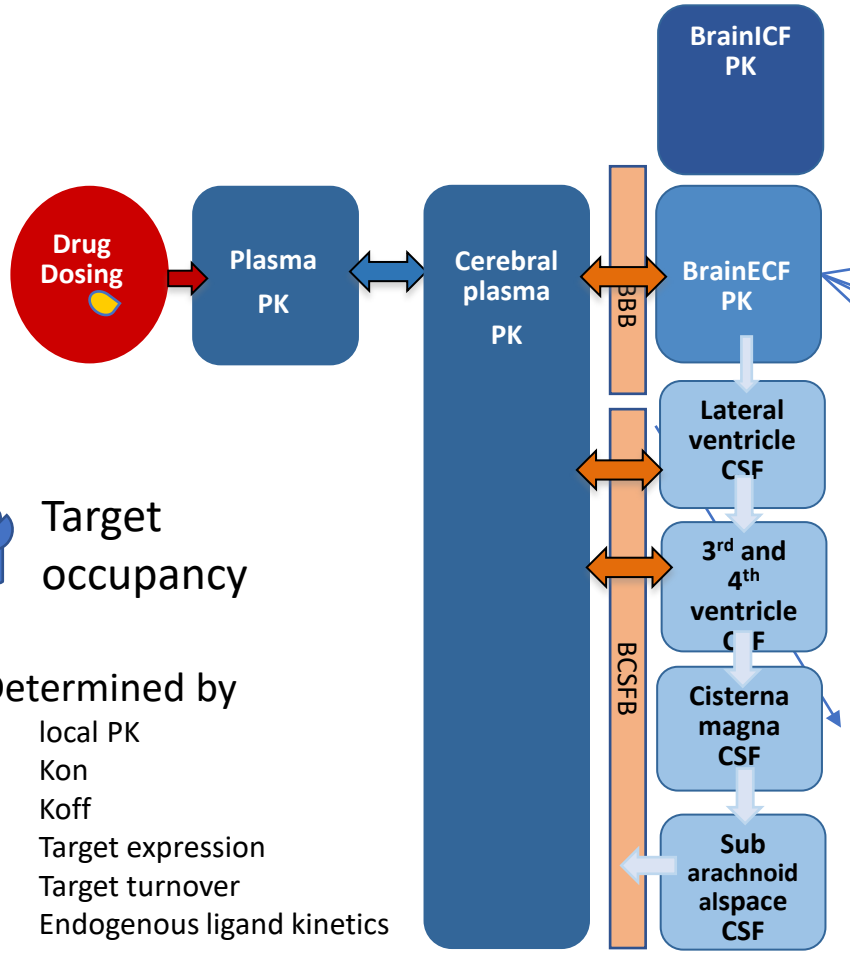
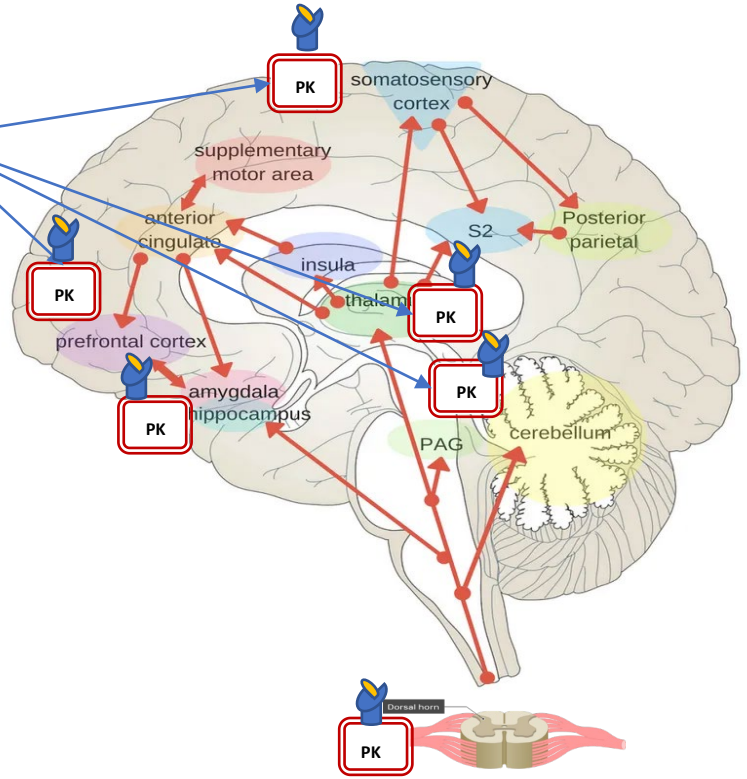


Target occupancy

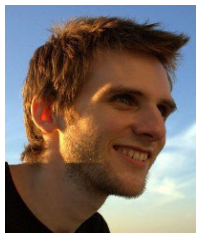
Determined by

- local PK
- Kon
- Koff
- Target expression
- Target turnover
- Endogenous ligand kinetics



https://www.google.com/search?q=brain+areas+pain&tbm=isch&ved=2ahUKEwj06LO79NTtAhXS0KQKHSZBAIsQ2-cCegQIABAA&oq=brain+areas+pain&gs_lcp=CgNpbWcQAzIECAAQEzIICAAQCBAeEBMyCAgAEAgQHhATMggIABABEB4QEzIICAAQCBAeEBMyCAgAEAgQHhATOgIIADoECAAQHlCMgANYsZIHYP6UB2gAcAB4AIABTYgBywKSAQE1mAEAoAEBqgELZ3dzLXdpei1pbWfAAQE&sclient=img&ei=qUDbX7TwKNKhkwWmgoHYCA&rlz=1C1GCEJ_enNL847NL863#imgrc=ryCm72qTB3RIKM&imgdii=nxc9WPgf1SaOdM

Divakar Budda



Coen van Hasselt

- *De Lange. The mastermind research approach to CNS Therapy. Translational prediction of brain distribution, target site concentrations, and therapeutic effect. FBCNS. 2013*

Concluding statements

Rounding off

- Complex questions cannot be answered by simple tests
- Strategically obtained preclinical PK and PD information (*smart data*), with special emphasis on microdialysis data, is key to develop predictive PKPD models for humans
- Predictive models can be used to explore *what if* scenarios and will help better design of (pre)clinical testing
- Predictive models will aid in the reduction,and replace of experimental animals

- **R**ight place
- **R**ight time
- **R**ight concentration
- **R**ight person

- **R**eduction
- **R**efinement
- **R**eplacement of experimental animals

Acknowledgements & thanks