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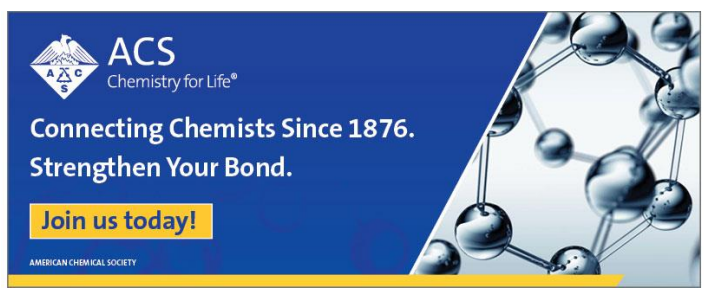

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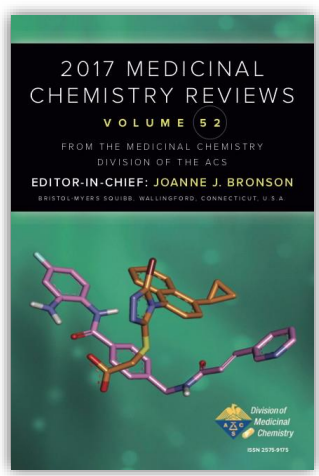

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JCIM JOURNAL OF CHEMICAL INFORMATION AND MODELING

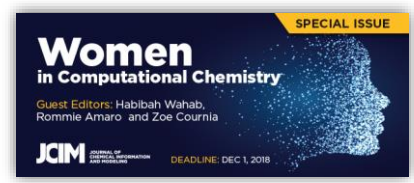
2017 Impact Factor
3.804
Total Citations
14,365

Journal Scope

The Journal of Chemical Information and Modeling publishes papers reporting new methodology and/or important applications in the fields of chemical informatics and molecular modeling.

Special Issues

Accepting Submissions!



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Chemical Entity and Biomolecule Scientific Program Tracks:

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Chemical Entity and Biomolecule Scientific Program Tracks:

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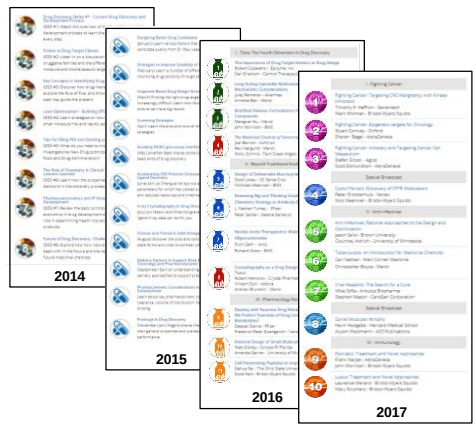

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Thursday, November 1, 2018

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Co-produced with the ACS Subdivision of Astrochemistry

Experts

Brett McGuire
National Radio Astronomy Observatory

Ryan Fortenberry
University of Mississippi

Thursday, November 8, 2018

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Experts

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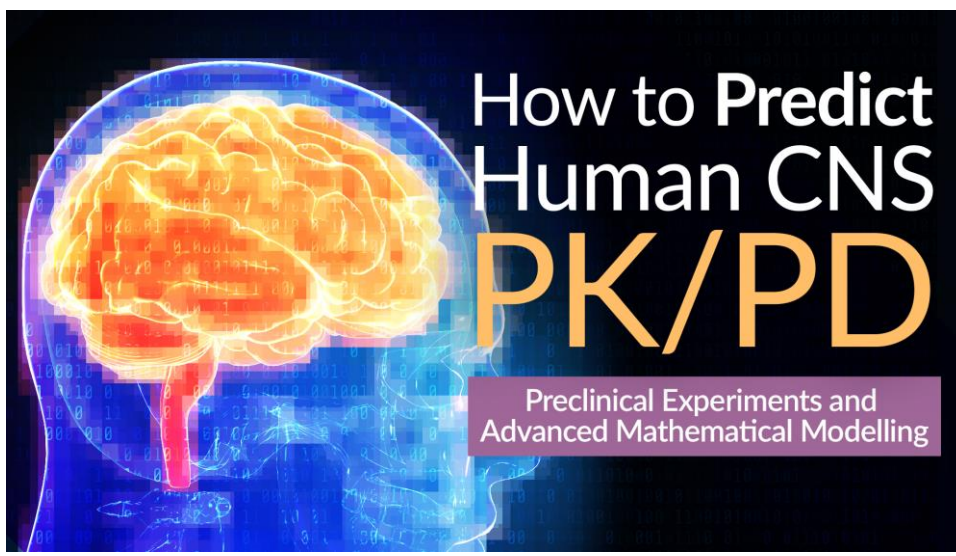

THIS ACS WEBINAR WILL BEGIN SHORTLY...

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*"**How to Predict Human CNS PK/PD:** Preclinical Experiments and Advanced Mathematical Modelling"*

Alexander Tropsha
Associate Dean for Pharmacoinformatics and Data Science, University of North Carolina

Elizabeth CM de Lange
Professor in Predictive Pharmacology, LACDR, Leiden University

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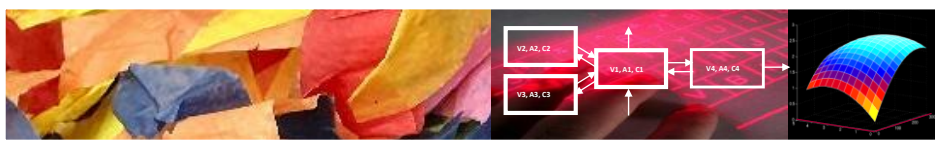

How to Predict Human CNS PK/PD: Preclinical Experiments and Advanced Mathematical Modelling

Elizabeth CM de Lange
Professor in Predictive Pharmacology, LACDR,
Leiden University, The Netherlands
ecmdelange@lacdr.leidenuniv.nl

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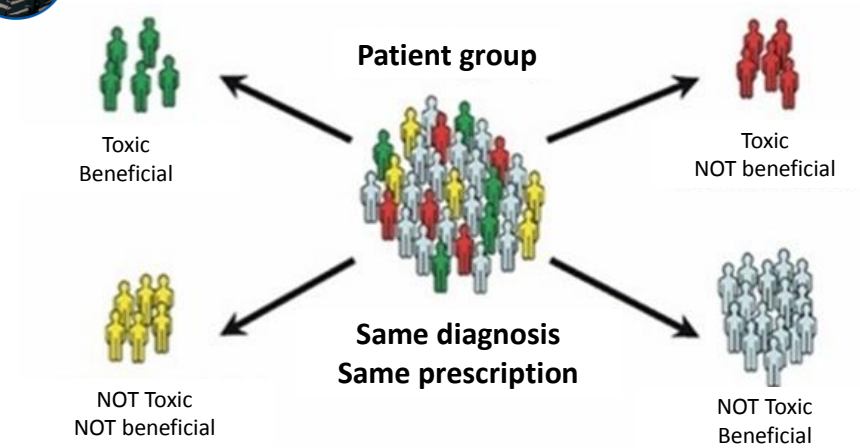
Pharmacology in Human



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Audience Challenge Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

Given patients having the same diagnosis and same drug prescription:

What is the most important reason for differences in effects among the patients?

A) Not all patients take the drug according to the instructions with regard to when and how to take the drug

B) Not all patients take the drug according to the instructions with regard to the amount: they take too little or too much

C) Not all patients are the same. Rate and extent of body processes differ, so do the drug effects

D) It is still unknown what the reason is for interindividual differences of drug effects between patients

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Outline

Interrelationships of body processes
Factors in CNS drug effects
Need for knowledge on unbound CNS conc-time profiles
Microdialysis as key technique
Mastermind Research Approach
Drug vs. systems properties
Prediction of the PKPD of a CNS drug in human
Prediction of human CNS PK for a single drug
Prediction of human CNS PK for *multiple* drugs
CNS PK prediction for *any* small drug without the need for in vivo data?

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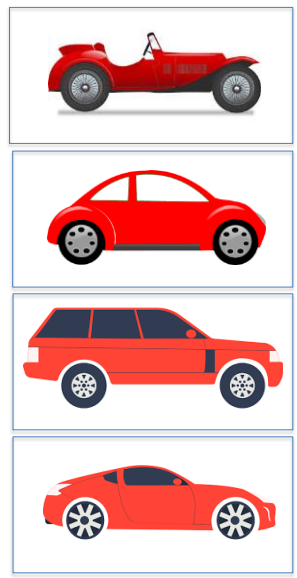
Interconnections and Relationships

Driver +  = Car Performance

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Interconnections and Relationships

Drug +  = CNS Drug Effect

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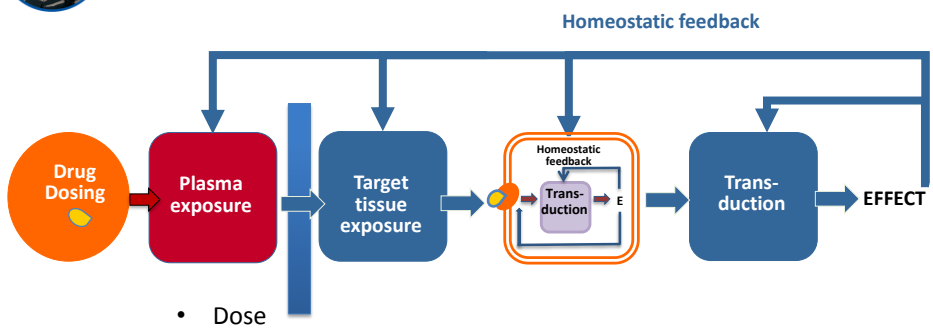
Factors in CNS Drug Effects



- Dose
- Plasma PK
- Target tissue (site) distribution
- Target binding kinetics
- Cellular response & homeotstatic feedback
- Body response & body homeostatic feedback

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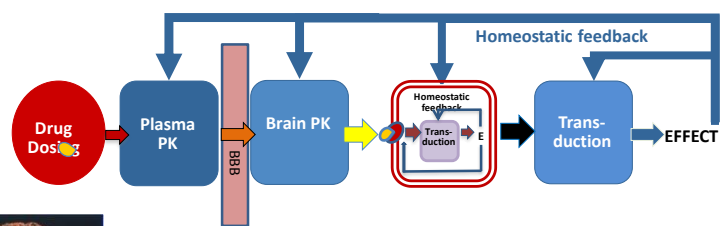
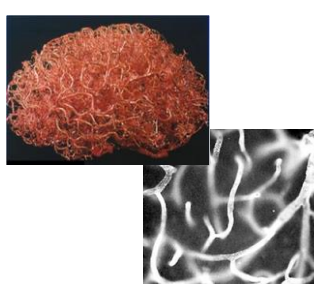
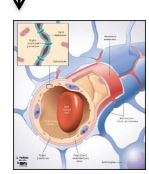
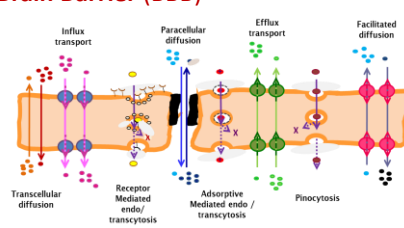
Factors in CNS Drug Effects





The Blood-Brain Barrier (BBB)





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Audience Challenge Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

BBB transport of drugs depend on:

A) The drug's properties

B) BBB transport just generally restricts transport of drugs into the brain

C) The BBB characteristics

D) Combination of drug properties and BBB characteristics

E) None of the above

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Audience Challenge Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

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C) The BBB characteristics

D) Combination of drug properties and BBB characteristics

E) None of the above

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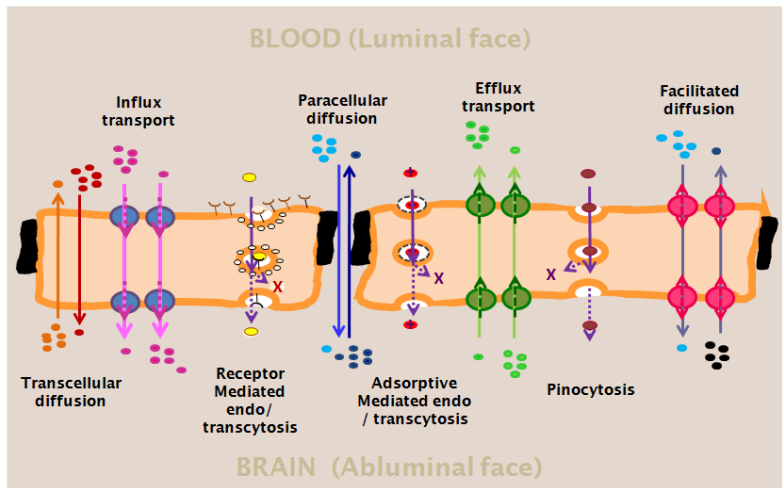
Factors in CNS Drug Effects

Blood-Brain Barrier - Modes of Transport



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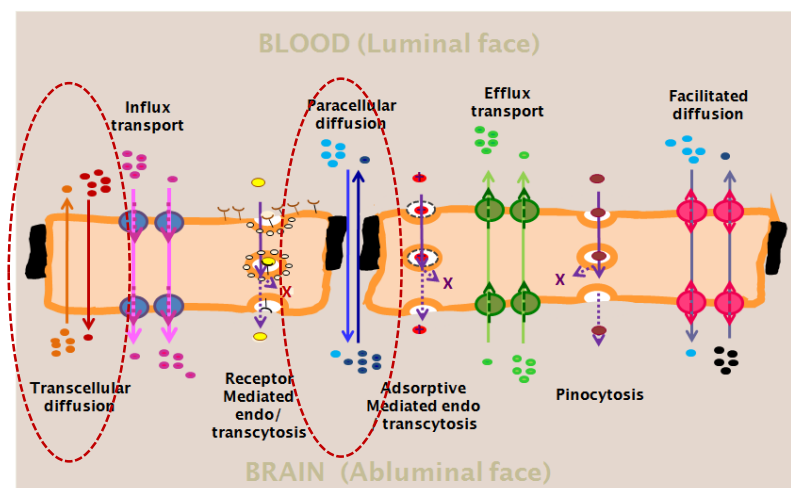
Factors in CNS Drug Effects

Blood-Brain Barrier - Simple Diffusion



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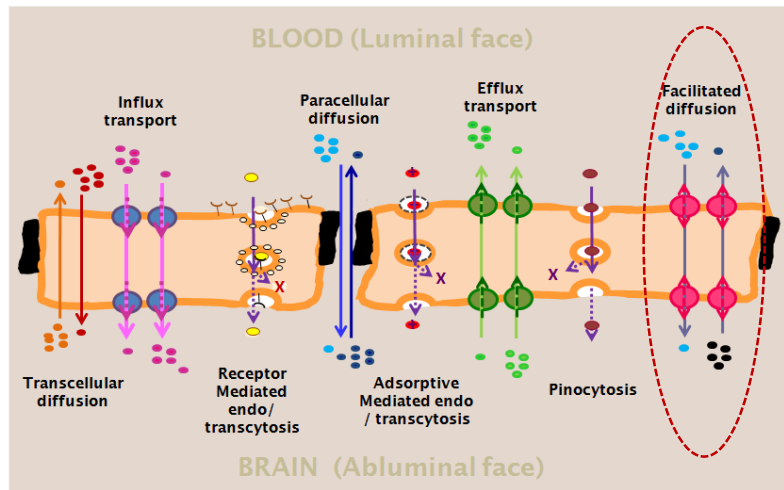
Factors in CNS Drug Effects

Blood-Brain Barrier - Facilitated Diffusion



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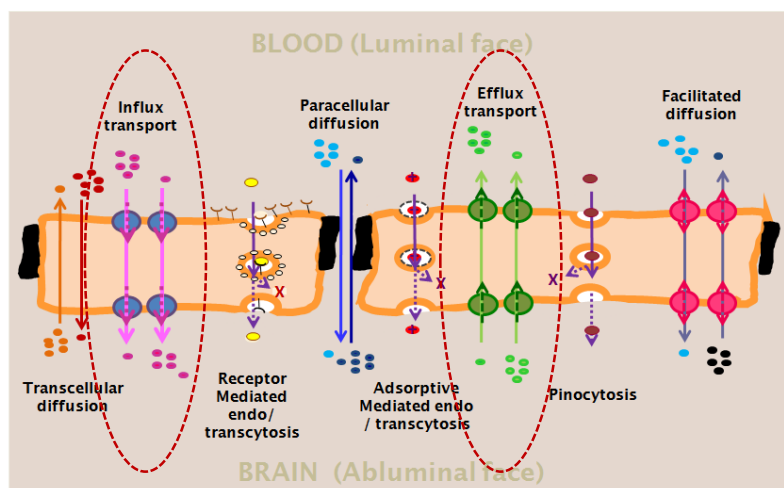
Factors in CNS Drug Effects

Blood-Brain Barrier - Active Transport



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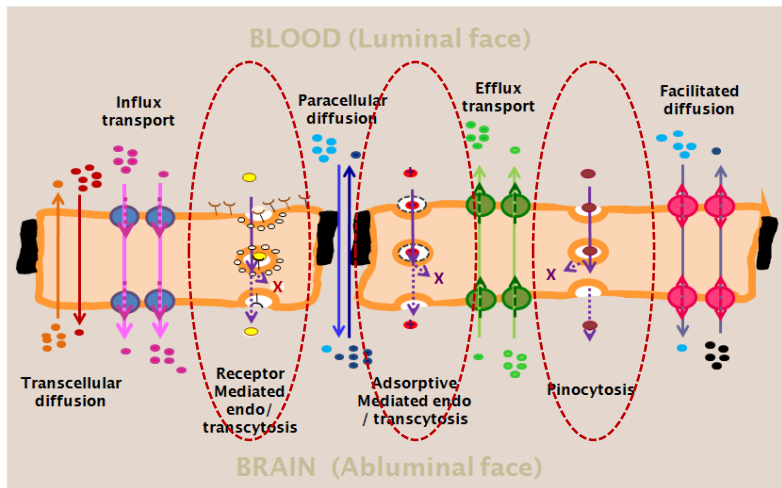
Factors in CNS Drug Effects

Blood-Brain Barrier - Vesicle Based Transport



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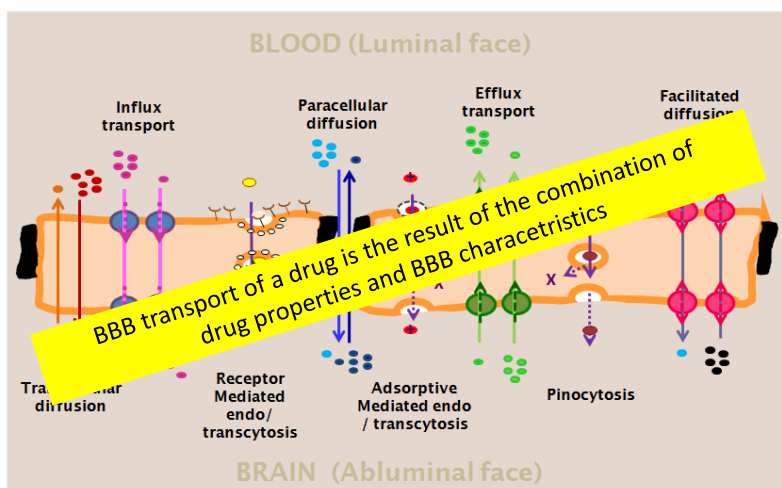
Blood-Brain Barrier - Modes of Transport



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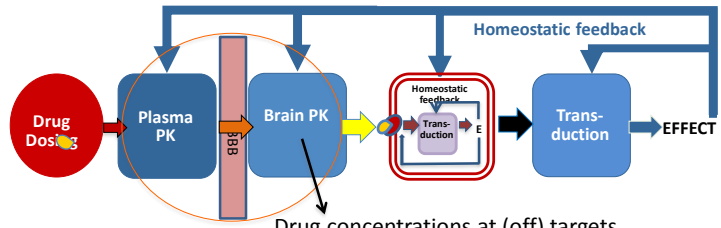
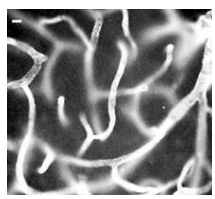
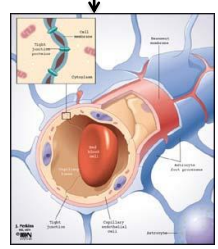
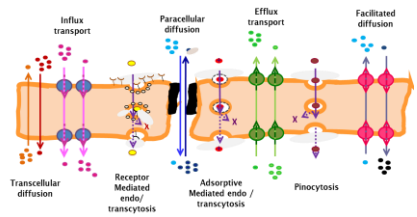


Drug concentrations at (off) targets drive the effects of the drug







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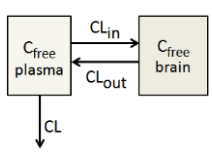
Factors in CNS Drug Effects

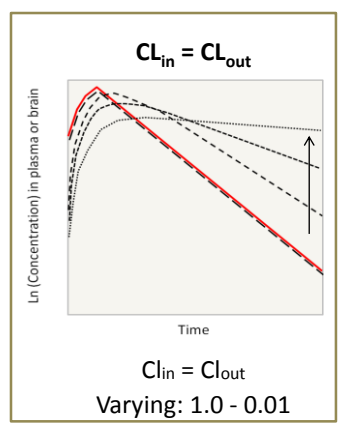
Simulations on plasma$_u$ and brain$_u$ PK

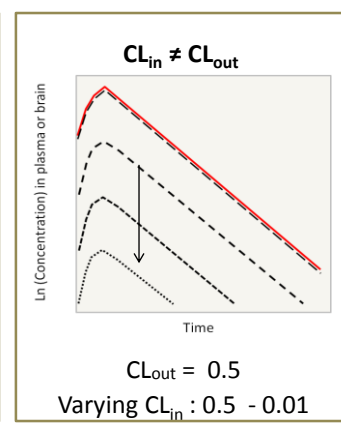
BBB transport – simple cases

Model for simulations



Hammarlund-Udenaes, Paalzow, & De Lange. Pharm Res (1997)





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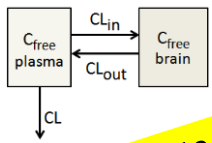
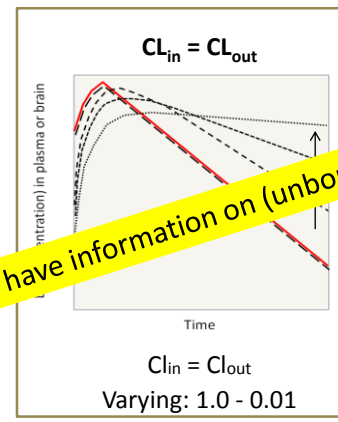
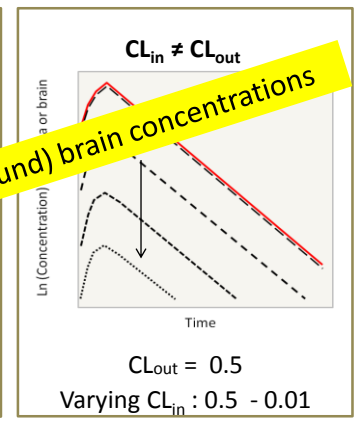


H… …ues, P… … & De Lange. Pharm Res (1997)



$Cl_{in} = Cl_{out}$

Varying: 1.0 - 0.01



CL_{out} = 0.5

Varying CL_{in} : 0.5 - 0.01

We need to have information on (unbound) brain concentrations

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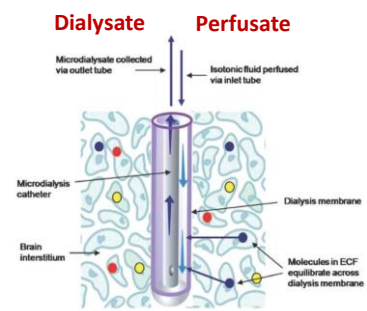
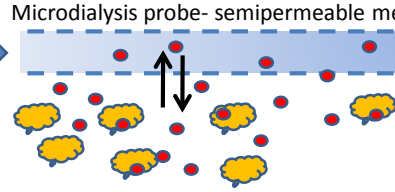
Experimental Approach

Microdialysis: a key technique



Microdialysis probe- semipermeable membrane

C_{in} Flow C_{out}



Tissue / external

Reflection of unbound Extracellular tissue concentrations

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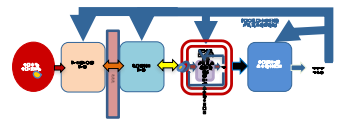
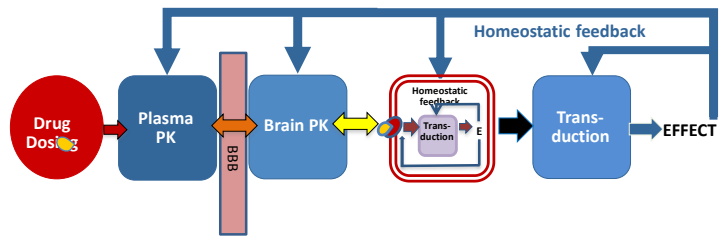
Prediction of CNS Drug Effects in Human



Differences in:

- *rate of PK and PD processes*
- *sizes, and surfaces of physiological compartments, and* flows



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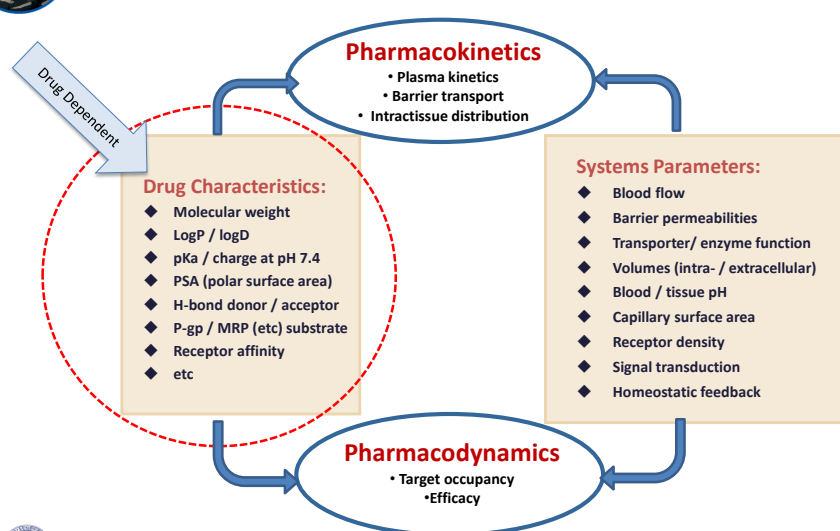
Drug vs. CNS Systems Properties



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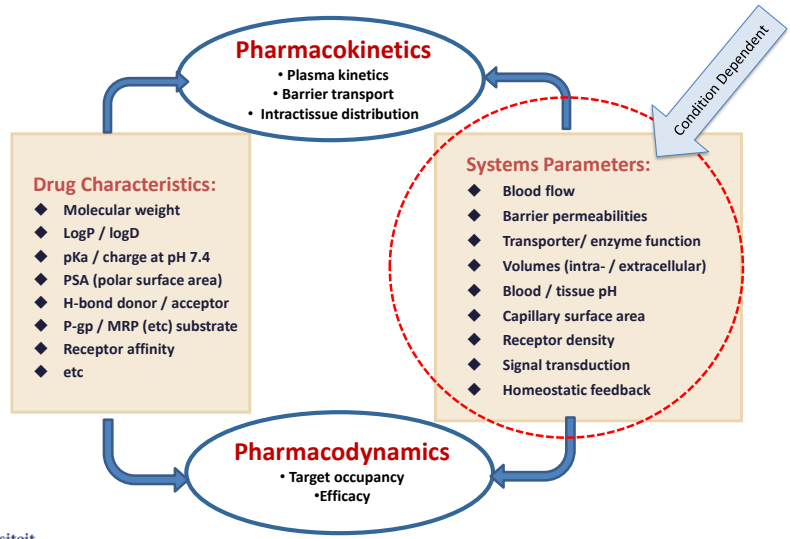

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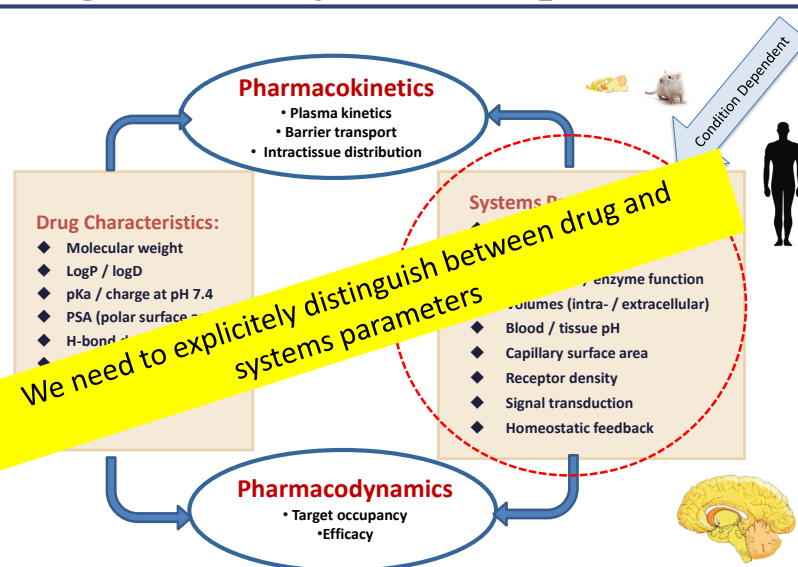
Drug vs. CNS Systems Properties



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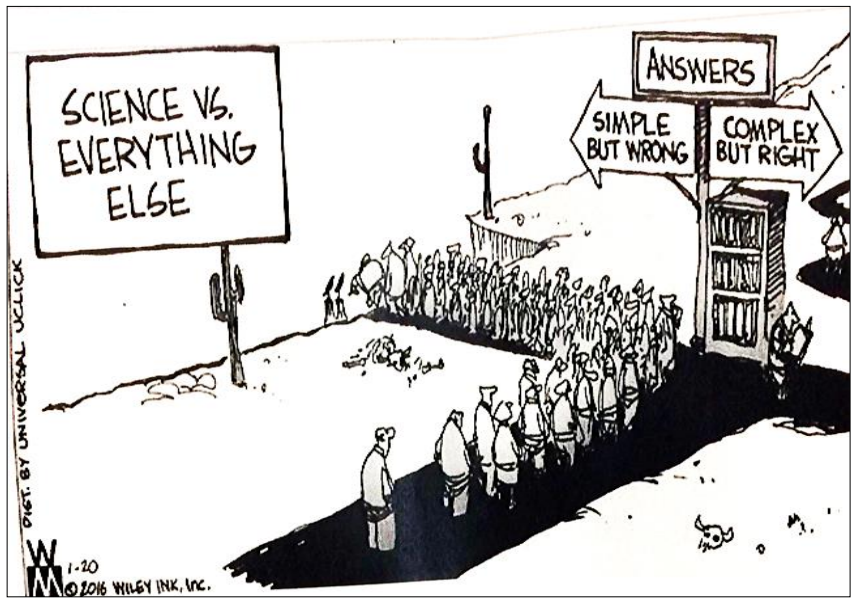

Gary Larsson

Mastermind Research Approach

To crack the code:
need for an integrated systems approach

- Move away from reductionism and face complexity
- Obtain connected data at multiple levels
- Reveal interactions & interdependency

Apply

- Cross-compare designed studies
- Advanced mathematical modeling

to dissect contributions of individual mechanisms in animals to provide information that can be used for extrapolation to the human situation.

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

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Appl…

- …signed studies
- …ed mathematical modeling

to dissect contributions of individual mechanisms in animals to provide information that can be used for extrapolation to the human situation.

Experiments using animals should include measurements:
- Measurements with time-resolution
- Measurements that reflect different processes within one single animal

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

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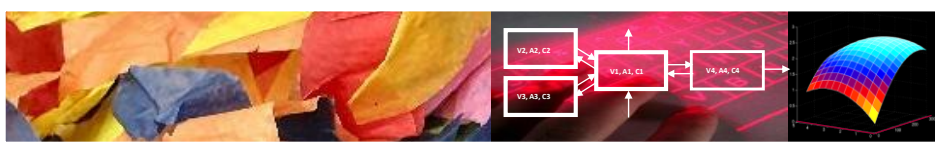

1. Prediction of PKPD of a CNS Drug in Human

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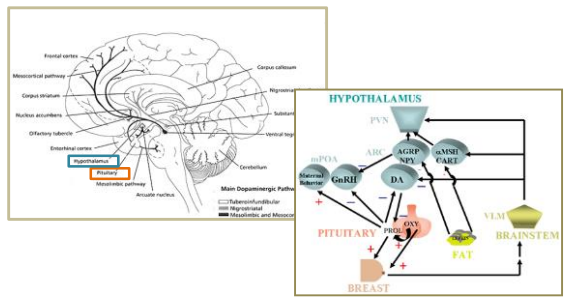
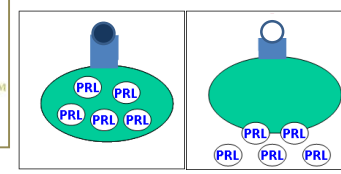
Prediction of Human PKPD of a CNS Drug

Prolactine as a translational biomarker of the dopaminergic system



Pituitary lactotrophs release prolactin into blood



- Dopamine high → inhibition of release of prolactin
- Dopamine low → induction of release of prolactin (~ use of DA antagonist)

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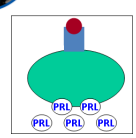
Prediction of Human PKPD of a CNS Drug

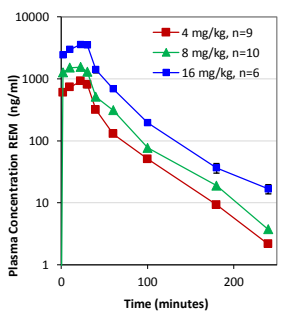
Remoxipride plasma and brain PK in the rat



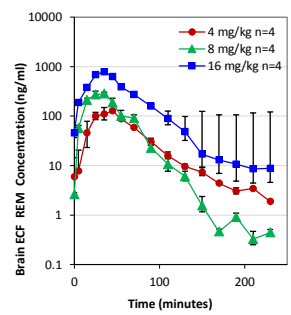
Intravenous administration

- Remoxipride = Dopamine D2 antagonist → Induces Prolactin Release

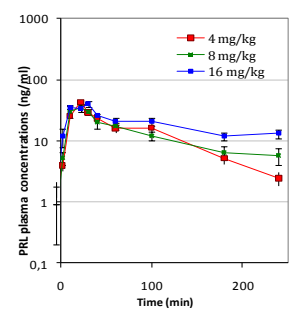
Remoxipride plasma



Remoxipride brainECF



Prolactin plasma



Stevens et al. Systemic and Direct Nose-to-Brain Transport PK Model for Remoxipride after IV and IN Administration. DMD 2011

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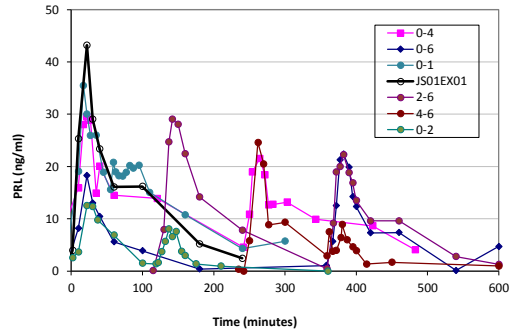
Prediction of Human PKPD of a CNS Drug

Remoxipride PD in the rat

Insight into rate of synthesis of prolactin in lactotrophs in rats

Rat plasma PRL concentrations (+/-SEM) after different interval dosing regimens of 3.8 mg/kg REM IV (IV, 30 min)



Movin-Osswald and Hammarlund-Udenaes. Prolactin release after remoxipride by an integrated PKPD model with intra- and interindividual aspects. JPET, 1995

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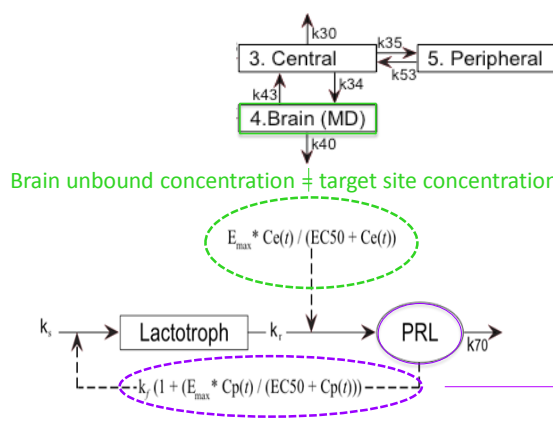
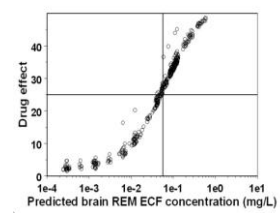
Prediction of Human PKPD of a CNS Drug

PK-PD Model Remoxipride in rat





Prolactin plasma concentrations increase synthesis rate of prolactine

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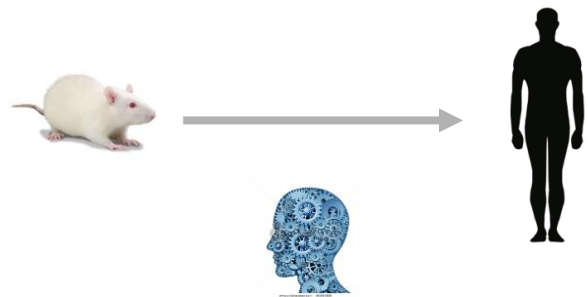
Prediction of Human PKPD of a CNS Drug

Translation on species:

Prediction of PKPD relationship of REM in human



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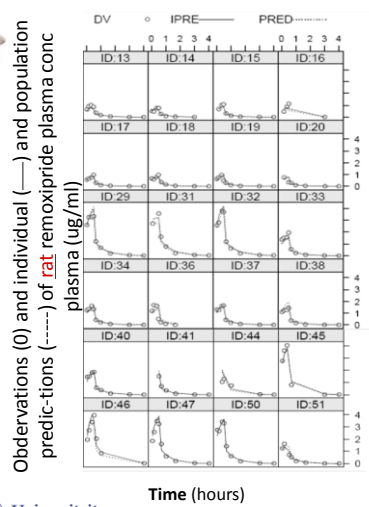
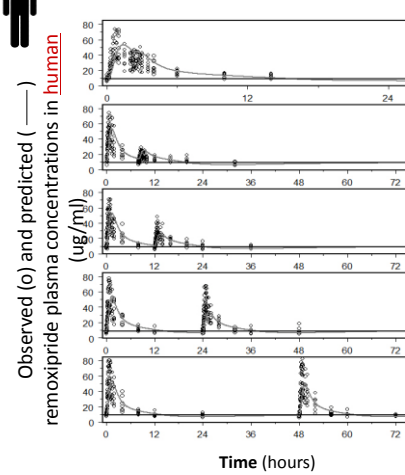
Prediction of Human PKPD of a CNS Drug

POP-PK Model of remoxipride in rat versus human





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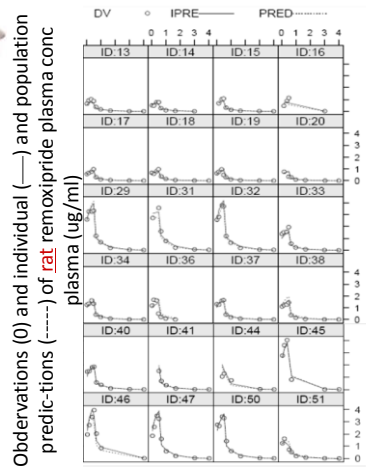

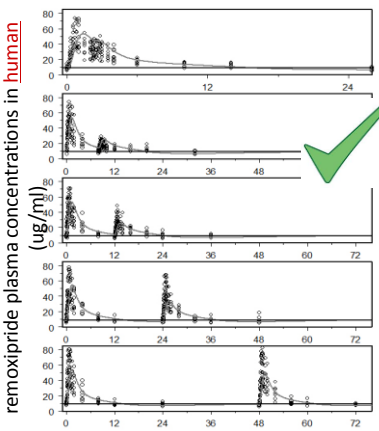

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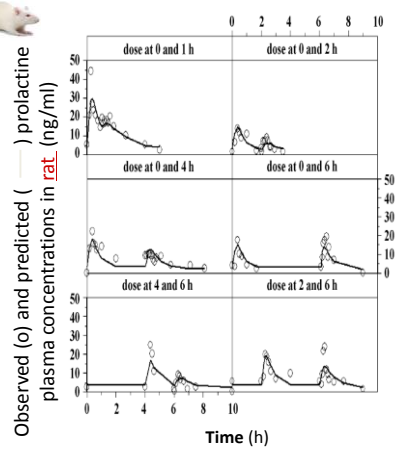
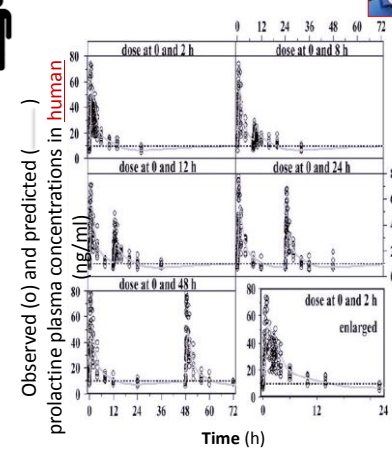
Prediction of Human PKPD of a CNS Drug

PRL human – data and translational model prediction





Stevens et al. MBPKPD model for the prolactin biological system response following acute dopamine inhibition challenge: quantitative extrapolation to humans. JPKPD 2012

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Prediction of Human PKPD of a CNS Drug

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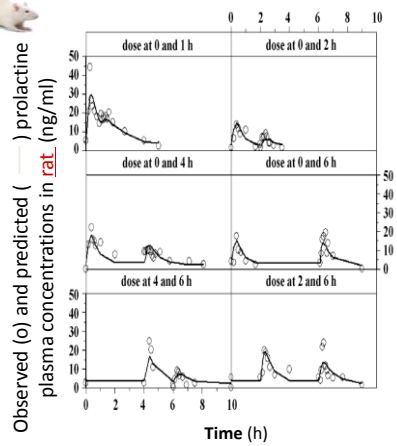

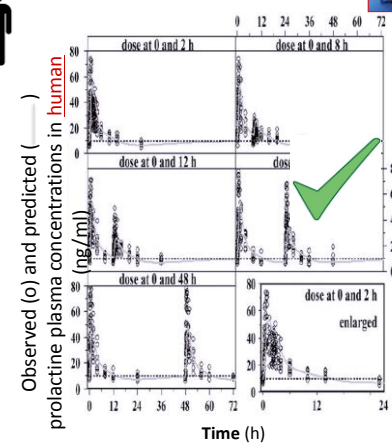

Stevens et al. MBPKPD model for the prolactin biological system response following acute dopamine inhibition challenge: quantitative extrapolation to humans. JPKPD 2012

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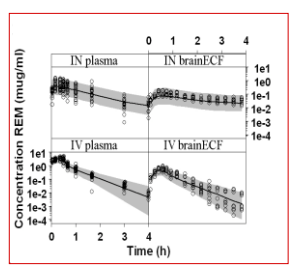
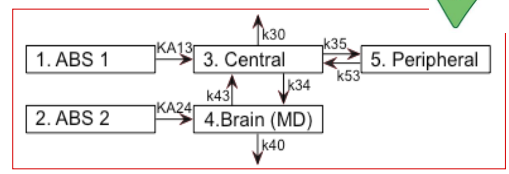
Prediction of Human PKPD of a CNS Drug

PK

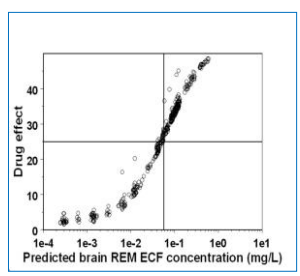


IN: Brain Distribution enhancement

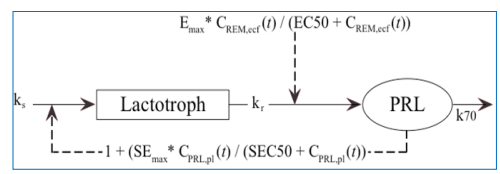


IV: Same model for rat and human

PD



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



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

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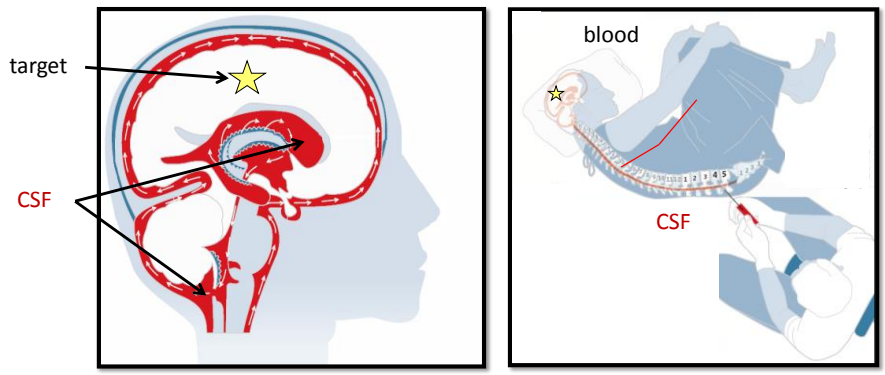
Use of CSF to predict CNS target site PK?

Which concentration in the human brain is most representative to the brain target site concentration?

What CNS sites in human are accessible to obtain information about brain PK?



De Lange. Utility of CSF in translational neuroscience. JPKPD. 2013

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Audience Challenge Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

For prediction of human CNS target site PK for a target that is facing the brainECF:

A) CSF concentrations can be used as it is in quick equilibrium with brainECF

B) We can use in vitro and animal data to build a mathematical model by which we can calculate brainECF concentrations

C) We can make direct use brainECF concentrations as measured in animals

D) CSF concentrations can be used, if taken from the ventricles in the brain, as CSF in the brain ventricles is the closest to the brainECF

E) We can make use of brainECF concentrations measured in humans

- CSF = cerebrospinal fluid
- BrainECF = brain extracellular fluid

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Audience Challenge Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

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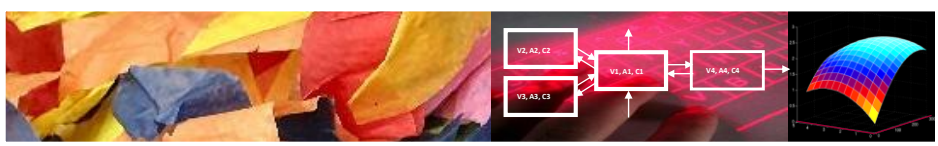

2. Prediction of Human CNS PK for a Single Drug

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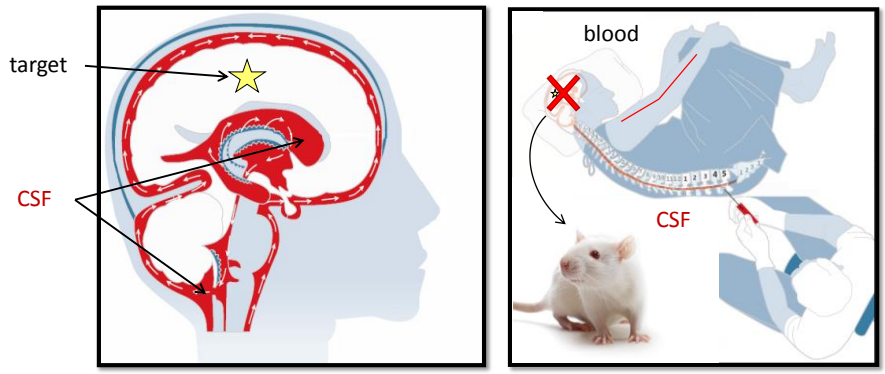

De Lange. Utility of CSF in translational neuroscience. JPKPD. 2013

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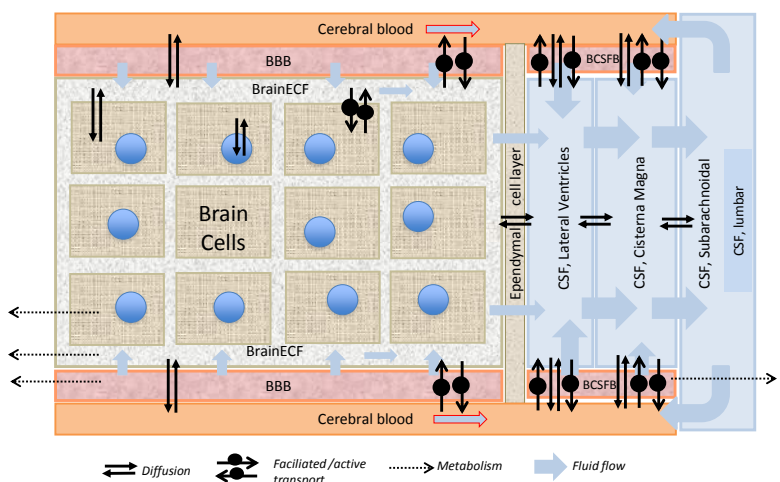
CNS Properties

Physiological brain compartments, flows, membranes, active transporters, metabolic enzymes, subcellular compartments, pH values, targets



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Experimental Approach

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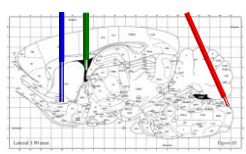
Overview- How to Predict CNS PK?

Animal experiment



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Westerhout et al. PBPK Modeling to Investigate Regional Brain Distribution Kinetics in Rats. AAPSJ. 2012

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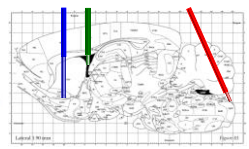
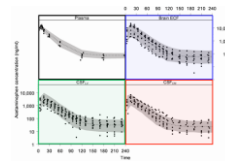
Overview- How to Predict CNS PK?

Animal experiment

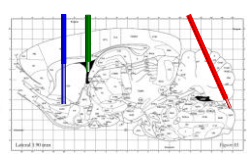


Animal PK profiles



Overview- How to Predict CNS PK?

Animal experiment



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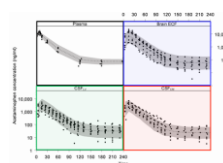
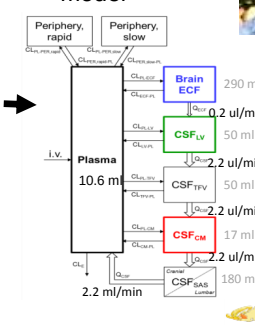
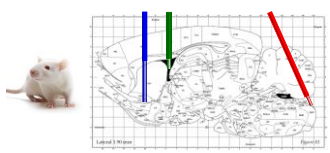


Animal PBPK model



Overview- How to Predict CNS PK?

Animal experiment



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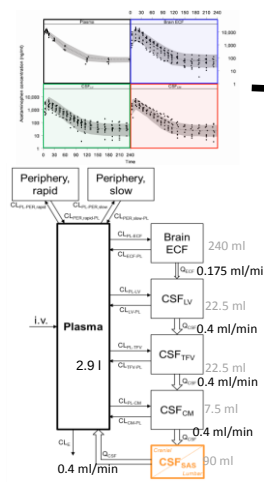
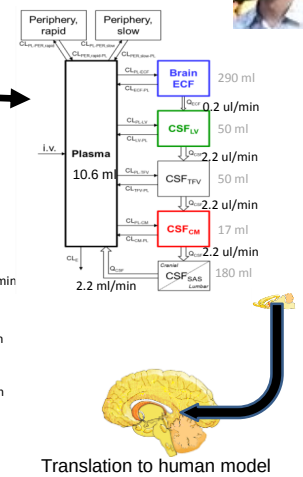


Animal PBPK model



Translation to human model

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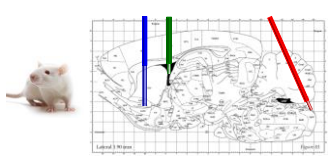
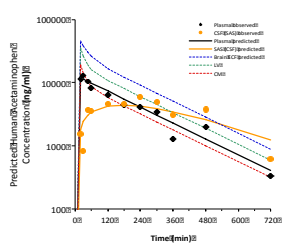
Overview- How to Predict CNS PK?

Animal experiment

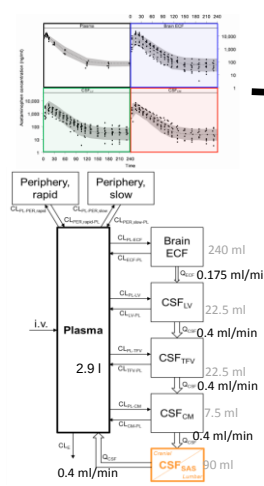


Validation on human data

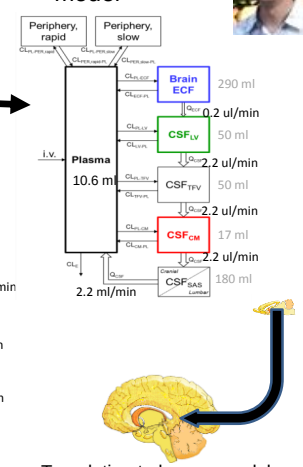


Observed (*Bannwarth et al. Br J Clin Pharmacol. 1992*) and predicted human acetaminophen concentrations in plasma (●, ...) and CSF (o, - -- -)

Animal PK profiles



Animal PBPK model



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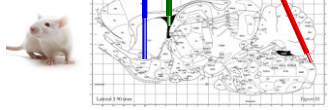
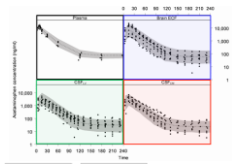
Overview- How to Predict CNS PK?

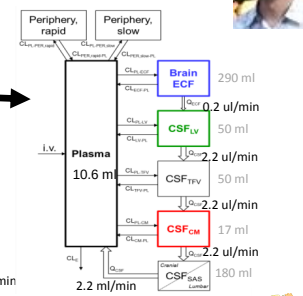
Animal experiment



Animal PK profiles



Animal PBPK model



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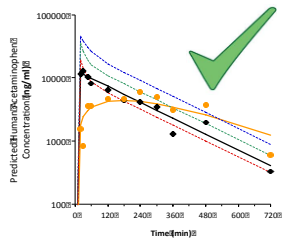

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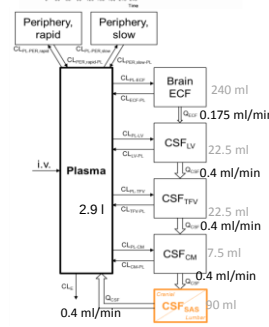

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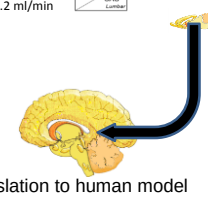

Translation to human model

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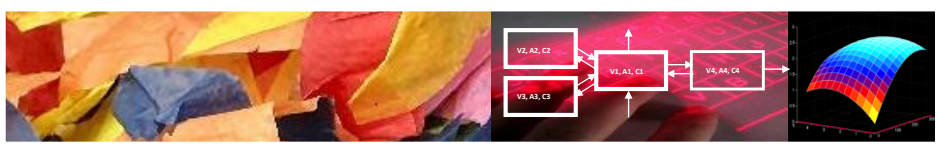

3. Prediction of Human CNS PK for *Multiple* Drugs

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Audience Challenge Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

CNS target site concentration-time profiles (PK) depends on:

A) BBB permeability (rate of crossing the BBB)

B) BBB permeability and all aspects of intra-brain distribution

C) BBB permeability and cellular accumulation (brain binding)

D) The ratio between unbound plasma and brain PK

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Audience Challenge Question

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CNS target site concentration-time profiles (PK) depends on:

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B) BBB permeability and all aspects of intra-brain distribution

C) BBB permeability and cellular accumulation (brain binding)

D) The ratio between unbound plasma and brain PK

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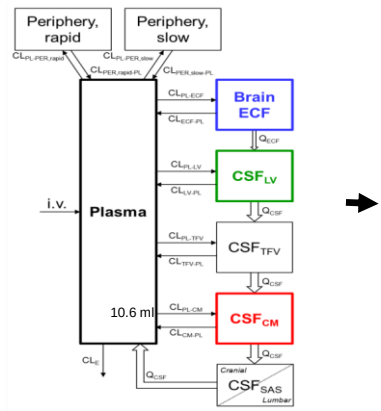
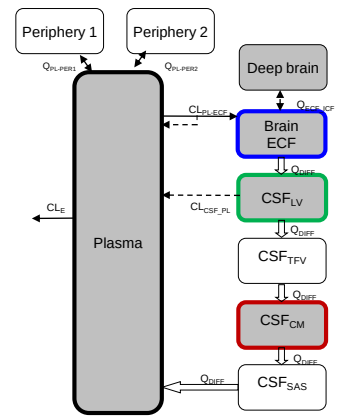
Generic Drug Modeling Approach





Individual drug translational models

Generic drug translational model (mult. drugs with distinctive phys-chem properties)

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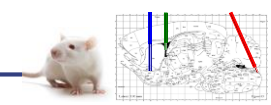
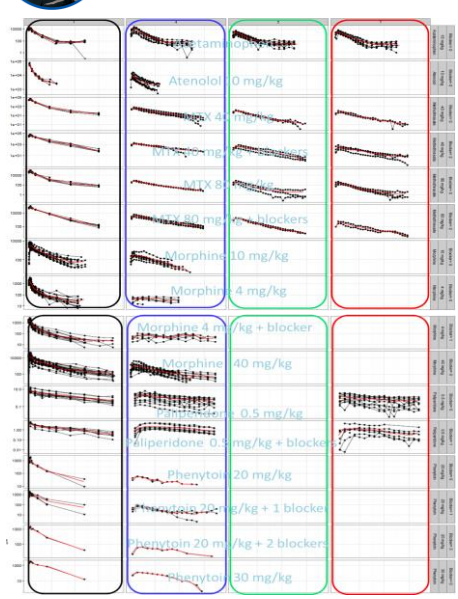
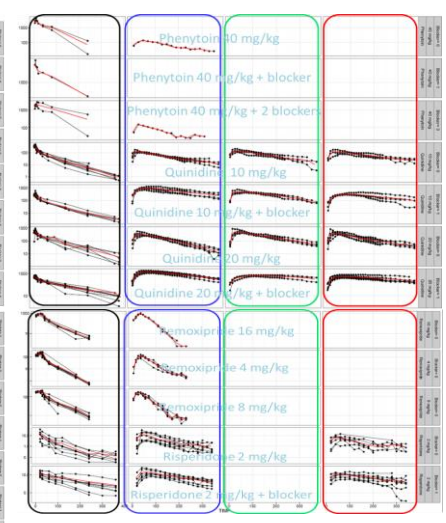
Overview Data Modeling

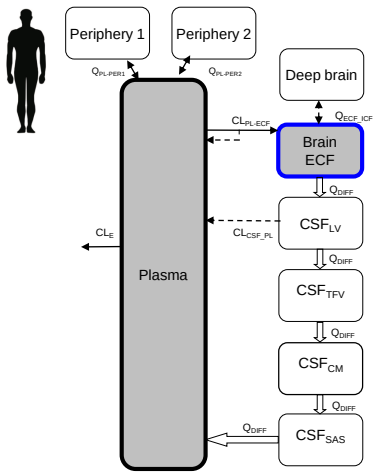


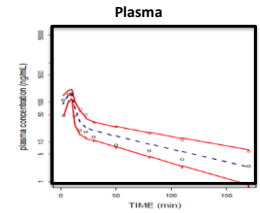


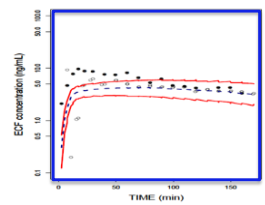


Yamamoto et al, A generic multi-compartmental CNS distribution model structure for 9 drugs allows prediction of human brain target site concentrations. Pharm Res, 2016

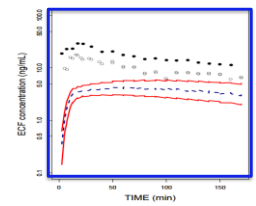
Prediction: Human CNS Morphine







Cortex tissue with normal appearance at CT scan



penumbra zone surrounding the evacuated haematoma

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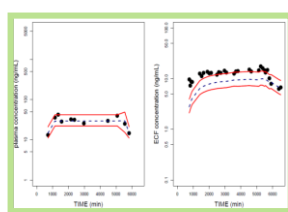
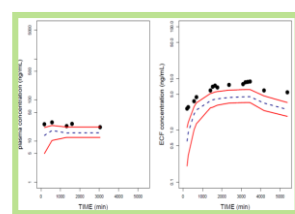
Yamamoto et al, A generic multi-compartmental CNS distribution model structure for 9 drugs allows prediction of human brain target site concentrations. Pharm Res, 2016

Prediction: Human CNS Morphine

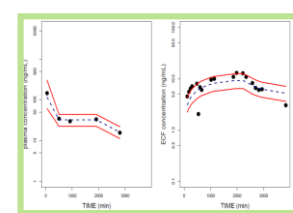
Pedriatic TBI patients

plasma brainECF plasma brainECF plasma brainECF

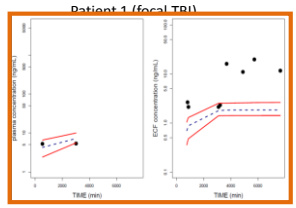




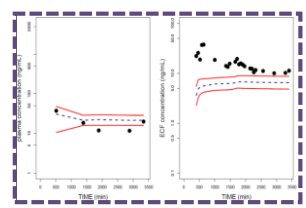
Patient 2 (Focal TBI)



Patient 4 (Focal TBI)



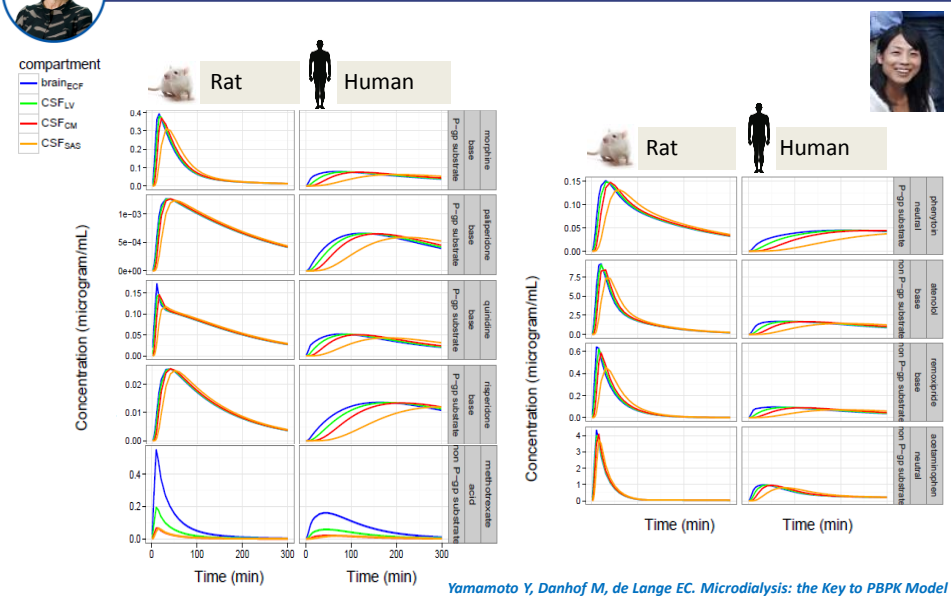
Patient 5 (Focal TBI, only 2 blood samples)



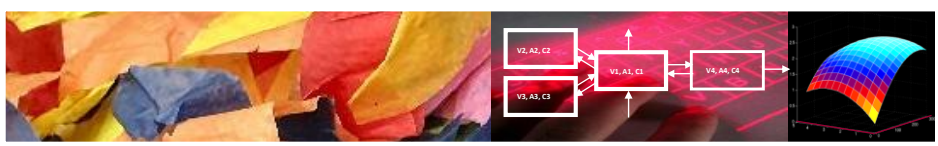
Patient 6 (Diffuse TBI)

Erasmus MC

Use of CSF to Predict CNS PK?



Yamamoto Y, Danhof M, de Lange EC. Microdialysis: the Key to PBPK Model Prediction of Human CNS Target Site Concentrations.. AAPS J. 2017



4. CNS PK prediction for *any* small drug without the need for in vivo data?

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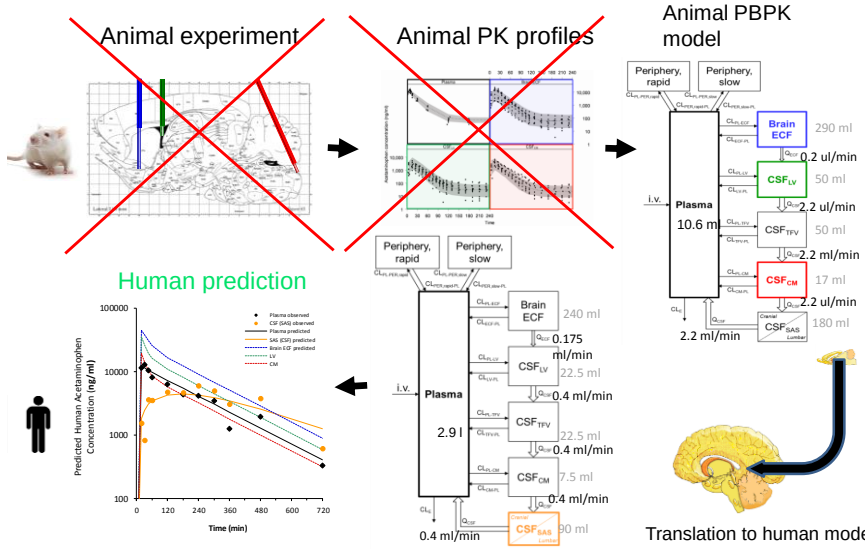
Prediction *without* in vivo data?



Full PBPK CNS Model

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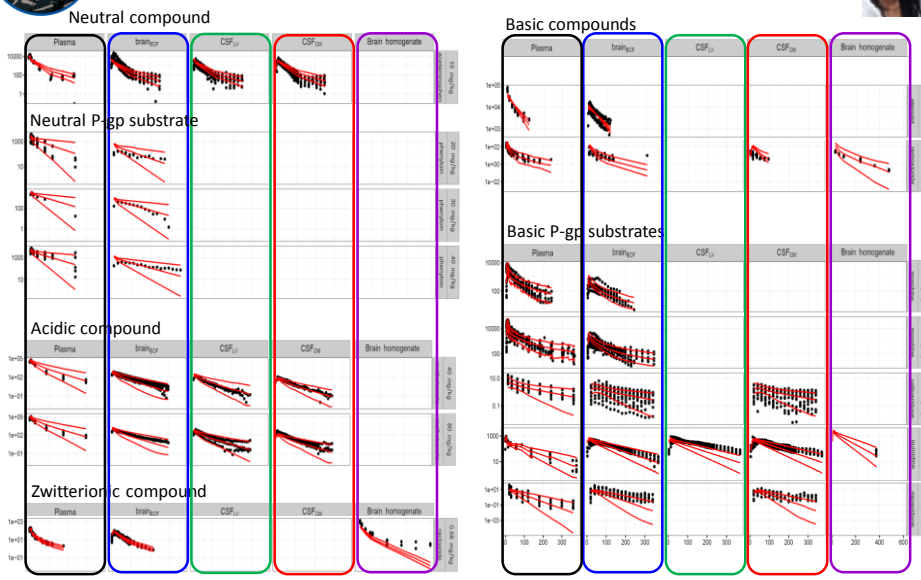
Simulations and Actual Data



Yamamoto et al, CPT: PSP, 2017; Yamamoto et al, EJPS, 2018

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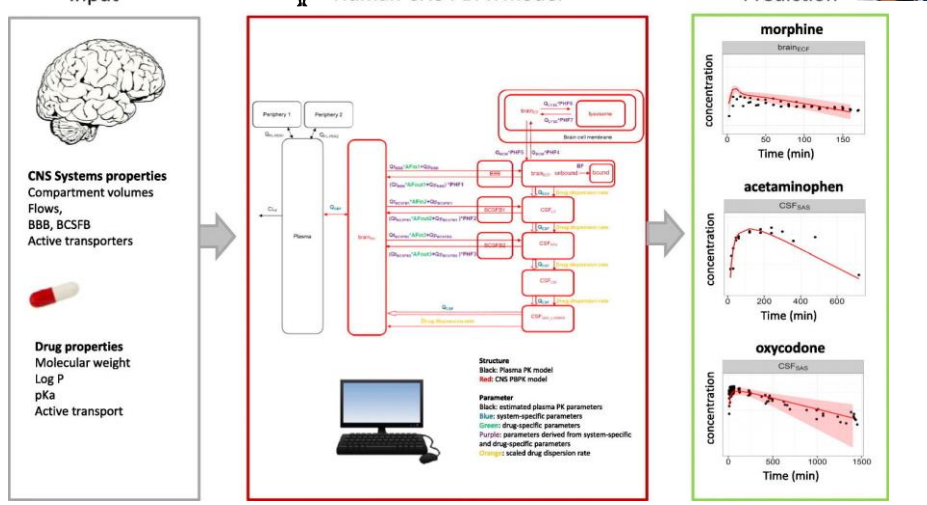
Human PBPK CNS Model



Yamamoto et al, EJPS, 2018

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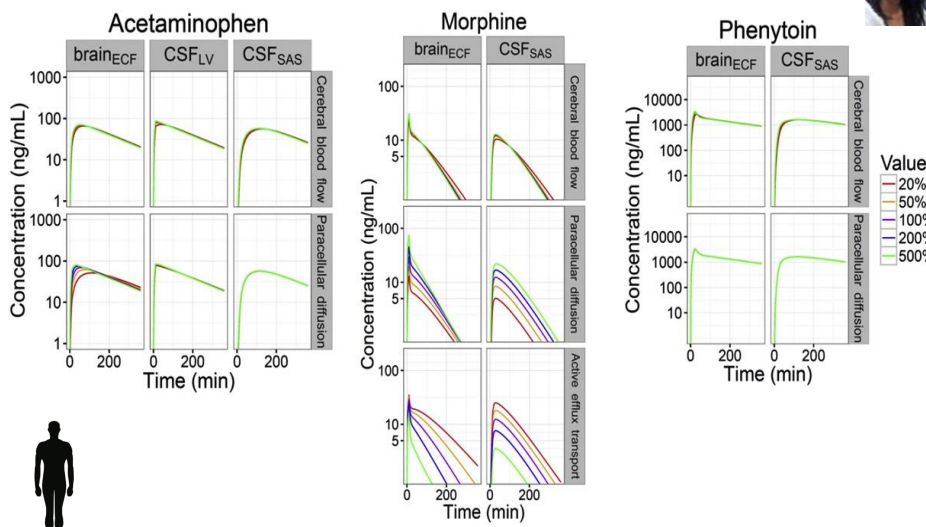
Human PBPK CNS Model

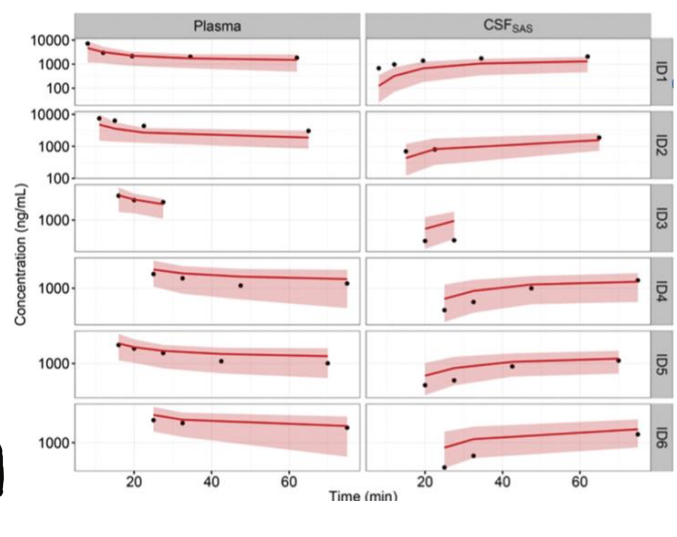
Simulations – systems changes



Yamamoto et al, EJPS, 2018

Human PBPK CNS Model

Simulations and Actual Data



Phenytoin

Yamamoto et al, EJPS, 2018

General Conclusions (1)

Can we use animal data on brainECF, and CSF and/or human CSF PK to predict human brainECF (off) target PK?

Relation between drug concentrations and their time course in brainECF, CSF in lateral ventricles, CSF in cisterna Magna, and CSF in lumbar region are

- Drug dependent 
- Species dependent 
- Time dependent 

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General Conclusions

- We need to distinguish between drug properties and system (CNS) characteristics for being able to translate between species and/or conditions
- Inter-relationships between PK and PD processes of drugs can be revealed by mathematical modelling if experiments using in individual animals include
  - Measurements with time-resolution (multiple time-points)
  - Measurements that reflect different processes within one single animal (multi-level measurements)
- Such information from animals should be stored in mathematical models, so that it provides knowledge, and reduces the need for animals in research.

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Final Food for Thought

- Reductionists approaches will not bring us further ….
- We should face the complexity of processes in the living body, and design our experiments accordingly in order to unravel interrelationships for true understanding and translation

- Medicinal chemist need to realize that many PK processes govern CNS target site PK- it is not only “BBB permeability”
- Thus, for optimization of drug properties, all aspects need to be considered
- The CNS PBPK model provides a very useful tool for investigating the relationship between drug properties and drug distribution into and within the CNS

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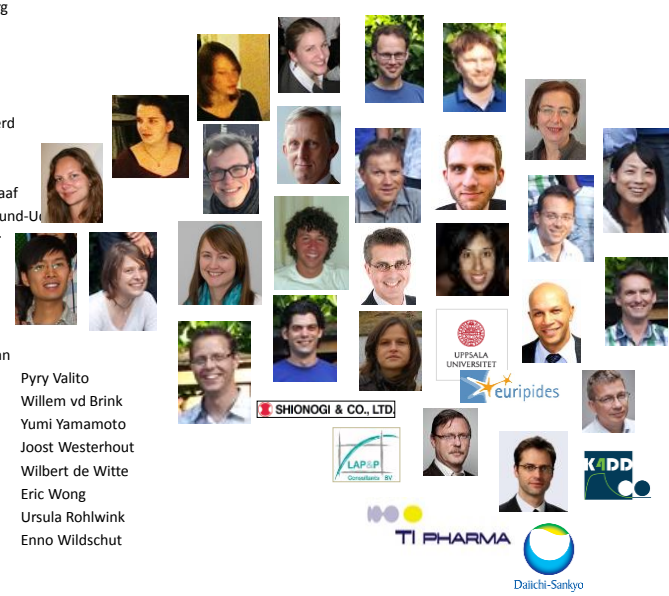

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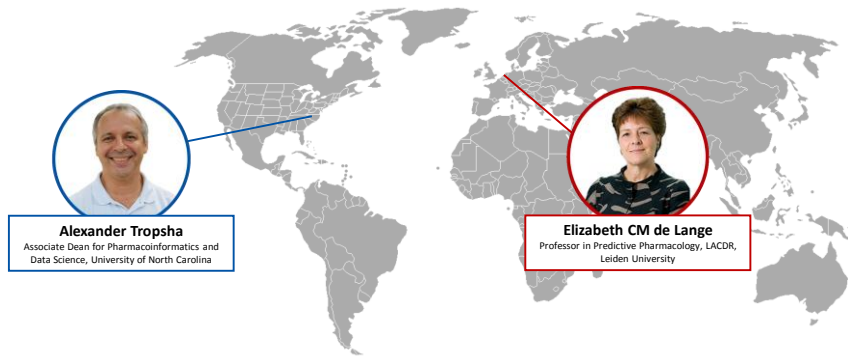

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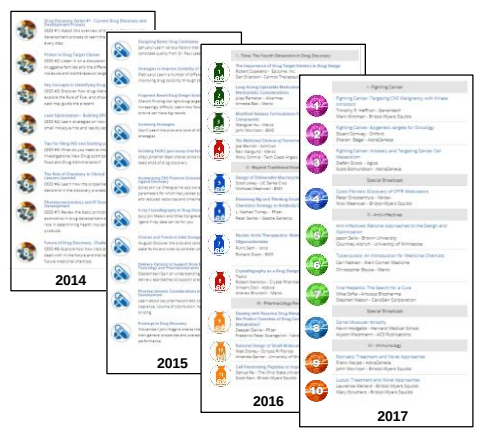

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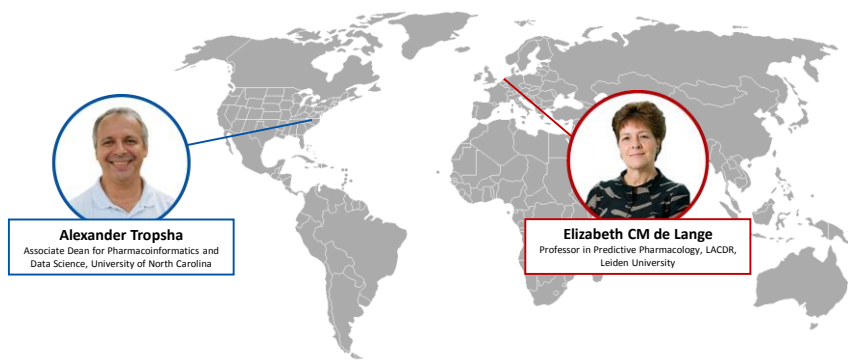

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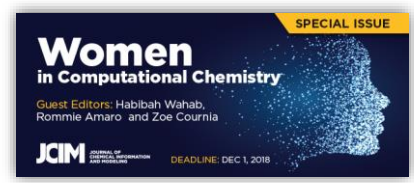

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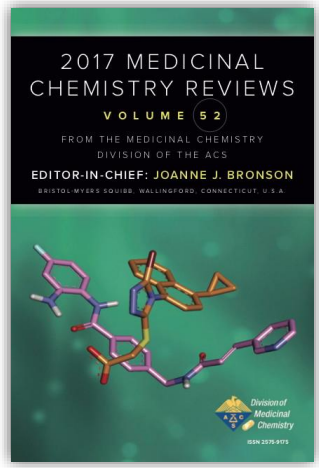

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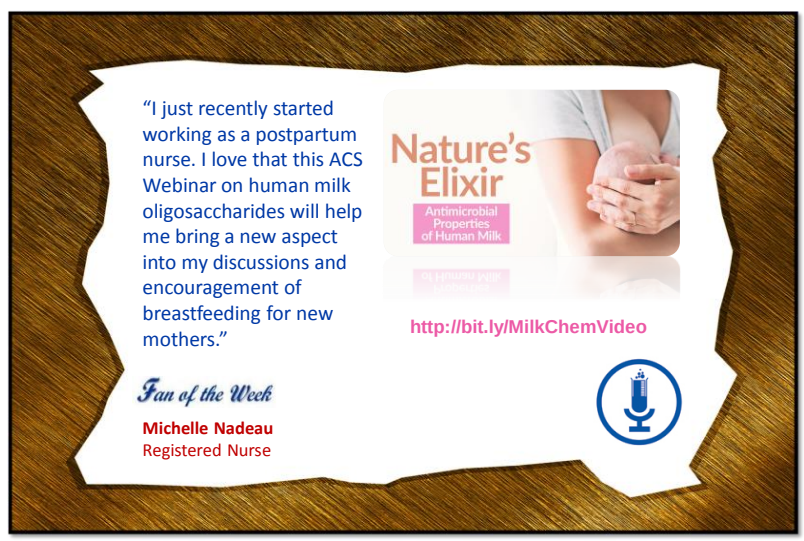

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