A USER-FRIENDLY PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) BRAIN MODEL AND ITS APPLICATION IN SIMULATING DRUG DISPOSITION IN BRAIN

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Objective

A PBPK brain model with a user-friendly interface was developed which enables a wider group of scientists to explore, via modelling, the effects of transporters within the blood-brain/cerebrospinal fluid barriers (BBB, BCSFB) on tissue drug disposition and hence pharmacological or safety related concerns. The model also acts as a repository for holding a wide range of biological (drug independent) information.

Background

Drug penetration from the circulating blood into the brain is primarily limited by the BBB/BCSFB, because of the existence of tight junctions as well as active efflux and uptake transporters at these barriers (Figure 1).

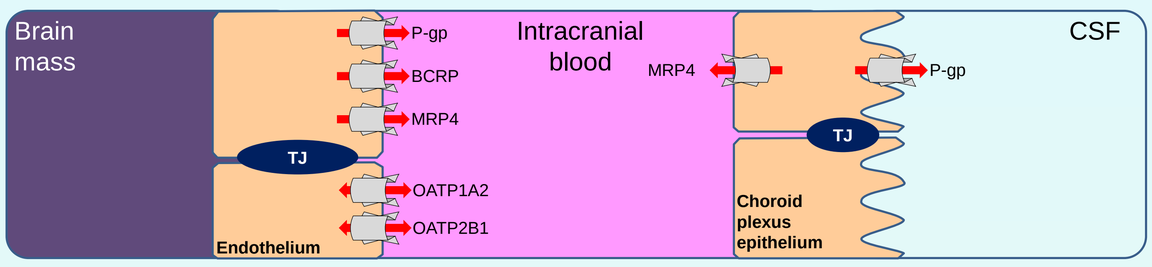


Figure 1. Major drug transporters on BBB and BCSFB

Drug disposition within the brain is further affected by CSF hydrodynamics, because the CSF is circulated within the cranial cavity, from the ventricles to subarachnoid spaces after secreted from the choroid plexus and then absorbed from the cranial and spinal sections (Figure 2).

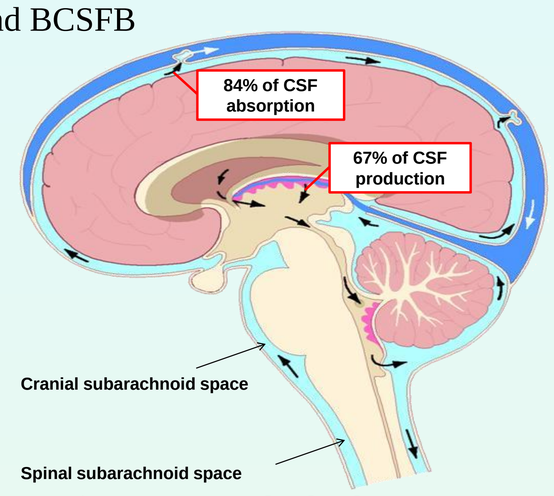
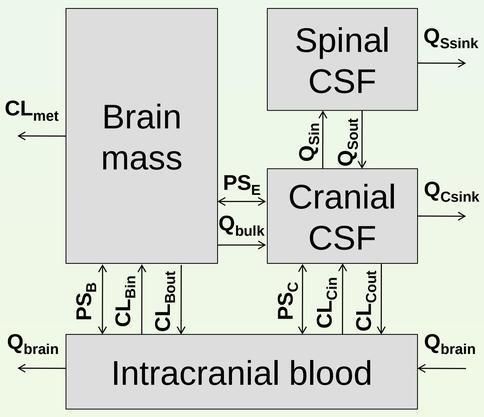


Figure 2. CSF hydrodynamics

Method

Literature was reviewed to collate brain related physiological, anatomical and biological attributes as well as any information on transporter abundance and activities on the BBB and BCSFB. A novel 4-compartment permeability-limited brain model was initially developed in Matlab Simulink® which includes the brain intracranial blood and mass and the spinal and cranial CSF compartments (Figure 3). The model also accounts for CSF hydrodynamic and incorporates transporter functionality at both BBB and BCSFB. Any associated inter-individual variability can be incorporated to simulations and they propagate into predicted drug disposition in brain compartments.

Following the prototyping phase, the model and its database were implemented within Simcyp Simulator V.11 (Simcyp Limited, Sheffield, UK).



Symbol	Description [Unit]
Q_{brain}	Cerebral blood flow [L/hr]
PS_B	Permeability-surface are product of BBB [L/hr]
PS_C	Permeability-surface are product of BCSFB [L/hr]
PS_E	Permeability-surface are product of CSF-Brain-Barrier [L/hr]
CL_{Bin}	Apparent clearance of BBB uptake transporters [L/hr]
CL_{Bout}	Apparent clearance of BBB efflux transporters [L/hr]
CL_{Cin}	Apparent clearance of BCSFB uptake transporters [L/hr]
CL_{Cout}	Apparent clearance of BBCSFB efflux transporters [L/hr]
Q_{bulk}	Bulk flow rate of CSF from brain to cranial CSF section [L/hr]
Q_{Csink}	CSF absorption rate from cranial CSF section [L/hr]
Q_{Ssink}	CSF absorption rate from spinal CSF section [L/hr]
Q_{Sin}	CSF flow rate form cranial to spinal section [L/hr]
Q_{Sin}	CSF flow rate form spinal to cranial section [L/hr]
CL_{met}	Metabolic clearance [L/hr]

Figure 3. Structure and parameters of the 4-compartmental diffusion-limited brain model

Results

The information on physiological and anatomical attributes were relatively *'rich'*, however there was a major shortcoming regarding the *'abundance'* of transporters and their *'activities'* (Tables 1 & 2).

Table 1. Parameters availability in brain model

Parameter	Intracranial blood	Brain mass	Cranial CSF	Spinal CSF
Volume	☑	☑	☑	☑
Flow rate	☑	☑	☑	☑
pH	☑	☑	☑	☑
Protein	☑		☑	☑
Enzyme	☑		☑	☑

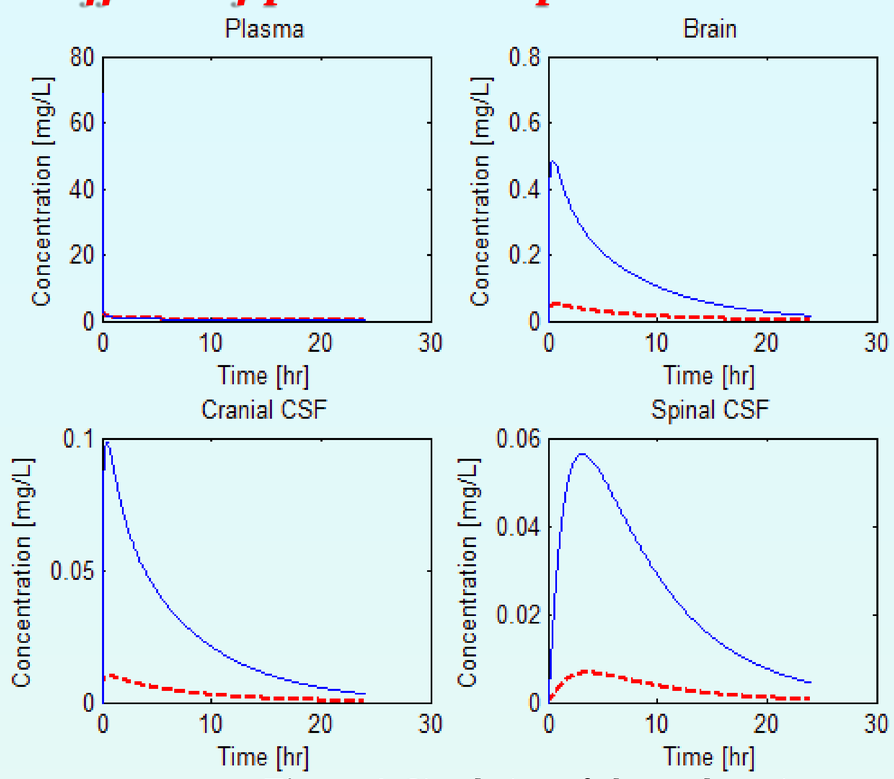
Table 2. Abundance data available for active transporters

Transporters	P-gp	MRP4	BCRP	OATP1A2	OATP2B1
BBB	☑	☑	☑	☑	☑
BCSFB					

Simulation Studies

Various scenarios were assumed to explore the possible effects of physiological functions and drug properties on the drug disposition in brain and CSF (Figures 4-6).

- Effects of passive transport



Compound X
Dose: iv, 200 mg

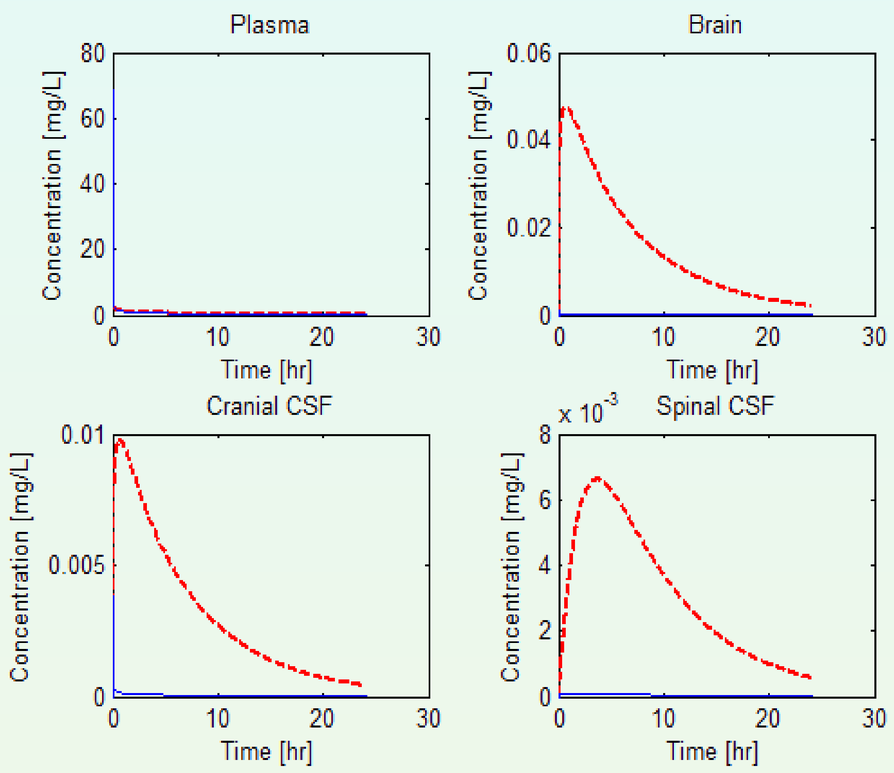
Fixed parameters:
PS_E=300 L/hr;
CL_{Bin}=0 L/hr;
CL_{Bout}=5.25 L/hr;
CL_{Cin}=0.21 L/hr;
CL_{Cout}=0.042 L/hr;
Q_{Sin}=0.014 L/hr;
Q_{Sout}=0.006 L/hr;

Floating parameters:
PS_B=0.0021 L/hr;
PS_C=0.0000021 L/hr;

PS_B=2.1 L/hr;
PS_C=0.0021 L/hr;

Figure 4. Simulation of changed passive transport

- Effects of active transporters



Compound Y
Dose: iv, 200 mg

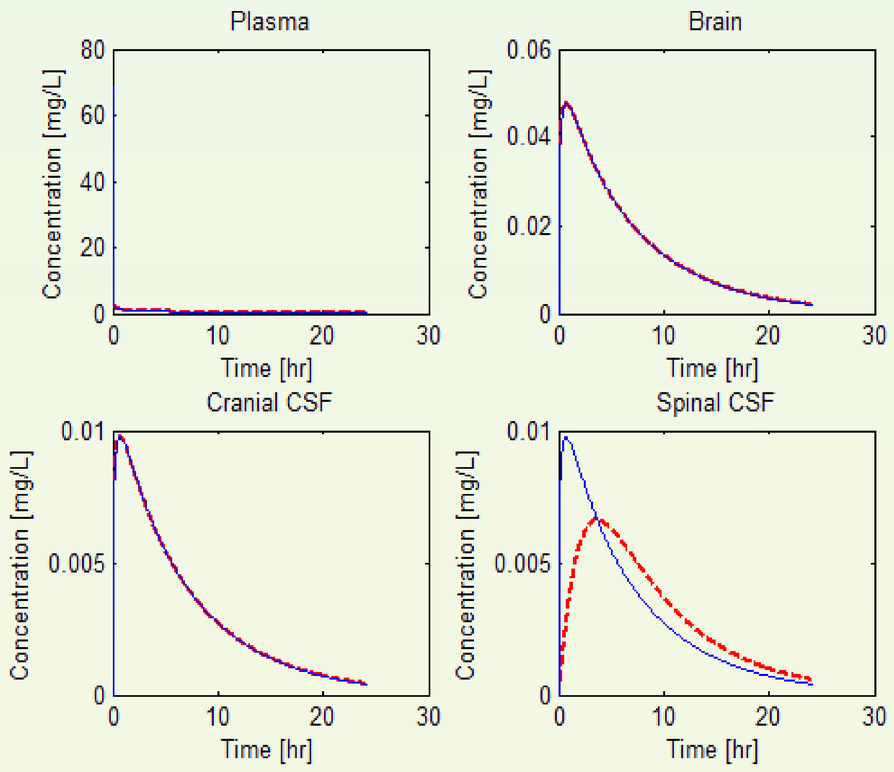
Fixed parameters:
PS_B=0.0021 L/hr;
PS_C=0.0000021 L/hr;
PS_E=300 L/hr;
CL_{Bin}=0 L/hr;
CL_{Cin}=0.21 L/hr;
Q_{Sin}=0.014 L/hr;
Q_{Sout}=0.006 L/hr;

Floating parameters:
CL_{Bout}=5.25 L/hr;
CL_{Cout}=0.042 L/hr;

CL_{Bout}=5250 L/hr;
CL_{Cout}=42 L/hr;

Figure 5. Simulation of changed active transport

- Effects of CSF hydrodynamics



Compound Z
Dose: iv, 200 mg

Fix parameters:
PS_B=0.0021 L/hr;
PS_C=0.0000021 L/hr;
PS_E=300 L/hr;
CL_{Bin}=0 L/hr;
CL_{Bout}=5.25 L/hr;
CL_{Cin}=0.21 L/hr;
CL_{Cout}=0.042 L/hr;

Floating parameters:
Q_{Sin}=0.014 L/hr;
Q_{Sout}=0.006 L/hr;

Q_{Sin}=14.427 L/hr;
Q_{Sout}=14.419 L/hr;

Figure 6. Results of various simulation scenarios

Conclusions and further development

- The user-friendly interface of the brain model can facilitate investigating effects of different drug and system parameters on the brain drug disposition.
- This paves the way for better understanding of drug actions in the Central Nerve System which is essential in "decision making" during drug development.
- Future extensions of the current model may include investigating the effect of transporters- and enzyme-mediated drug-drug interactions.

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