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

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Objective

The aim of this study is to develop a PBPK brain model to explore the effects of various physiological functions, particularly the active transporters present within the blood-brain/cerebrospinal fluid barriers (BBB/BCSFB), on drug disposition in brain.

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).

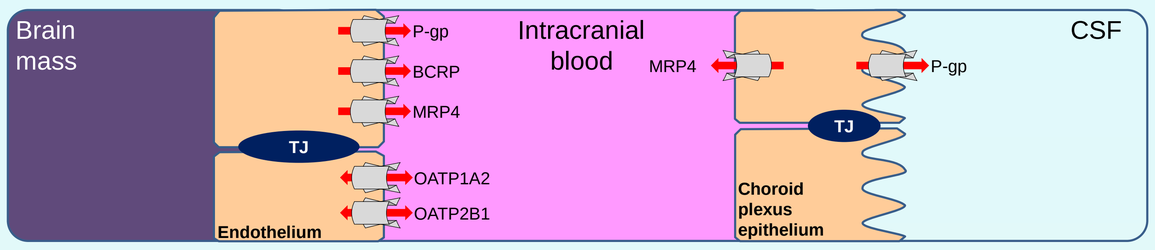


Figure 1. Major drug transporters on BBB and BCSFB

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).

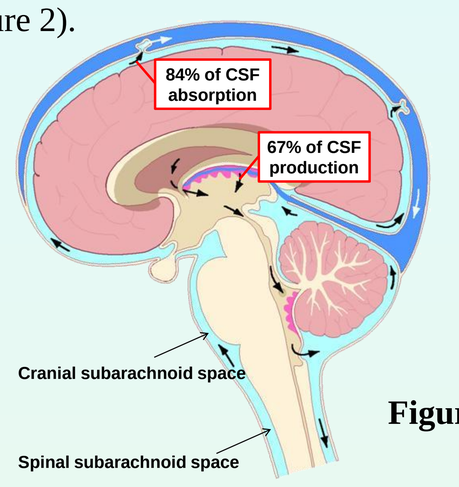


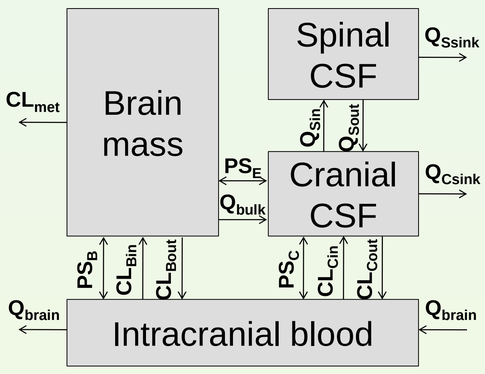
Figure 2. CSF hydrodynamics

Method

Literature were reviewed to collate brain physiological and anatomical attributes as well as any information on transporter abundance and activities on the BBB and BCSFB.

A 4-compartment diffusion-limited brain model was developed and implemented in Matlab Simulink®. The model divides CSF into 2 compartments namely cranial and spinal sections (Figure 3). The brain model was combined with a whole-body PBPK model, which has been established in the Simcyp Simulator.

Using the model, several scenarios were investigated to explore the effects of various physiological functions, particularly, the effects of transporters, on drug disposition in brain and CSF.



Symbol	Meaning [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 of 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	☑		☑	☑

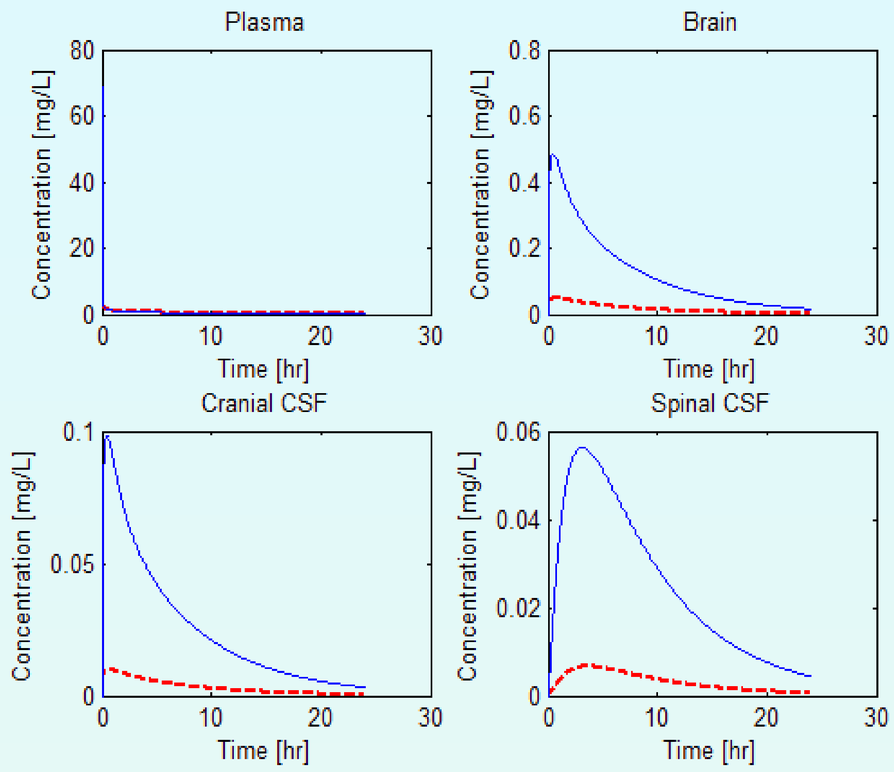
Table 2. Abundance of active transporters

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

Simulation outcome

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

- Effects of passive transport



Compound: Quinidine
Dose: iv, 200 mg

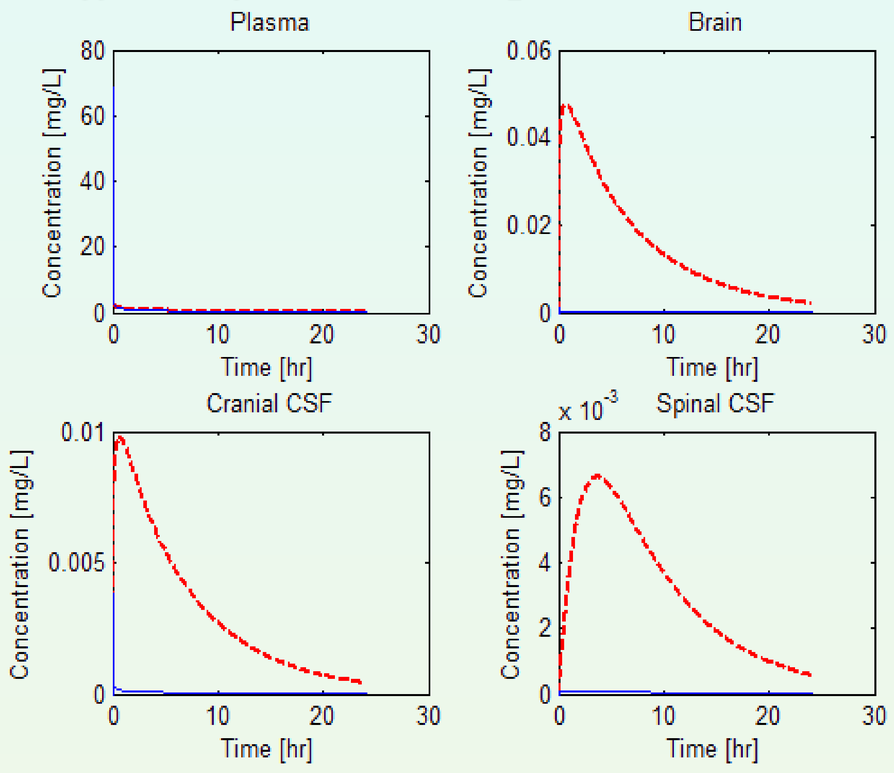
Fixed parameters:
PS_E=300 L/hr;
CL_{Bin}=0 L/hr;
CL_{Bout}=5.25 L/hr;
CL_{Cin}=0.21 L/hr;
CL_{Cout}=0.042 L/hr;
Q_{Sin}=0.014 L/hr;
Q_{Sout}=0.006 L/hr;

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: Quinidine
Dose: iv, 200 mg

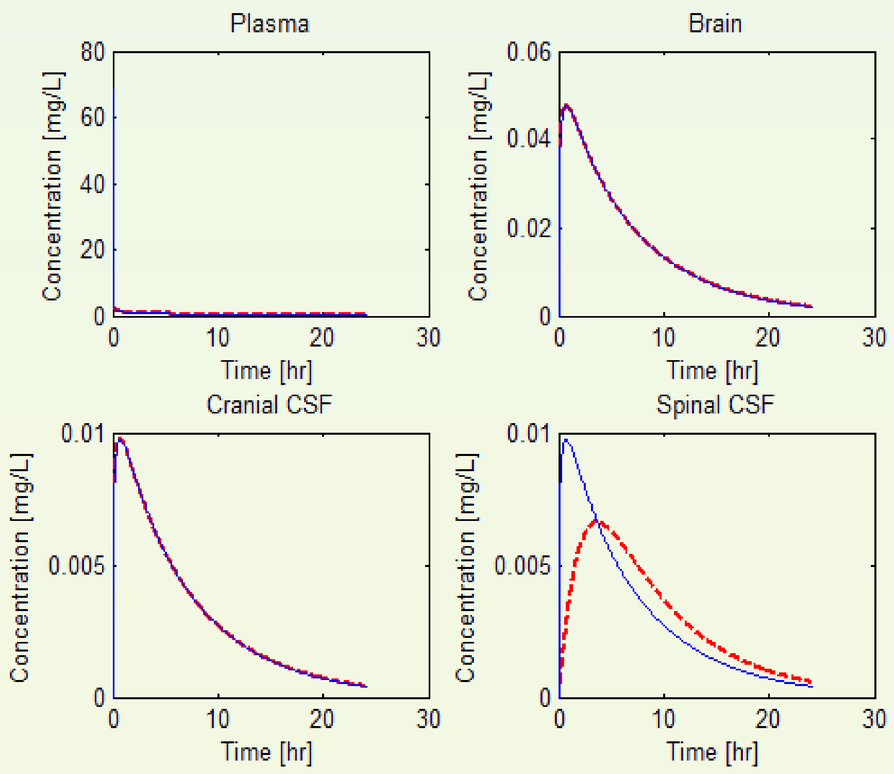
Fixed parameters:
PS_B=0.0021 L/hr;
PS_C=0.0000021 L/hr;
PS_E=300 L/hr;
CL_{Bin}=0 L/hr;
CL_{Cin}=0.21 L/hr;
Q_{Sin}=0.014 L/hr;
Q_{Sout}=0.006 L/hr;

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: Quinidine
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. Simulation of changed CSF hydrodynamics

Conclusions and further development

- Consistent with reported clinical studies, the model was able to show the disparities in drug concentration-time profiles in blood (or plasma), brain mass, cranial and spinal CSF which was related to drug properties, particularly transporter affinities.
- On the basis of observations, the 4-compartmental diffusion-limited brain model is now being incorporated within the Simcyp Population-based Simulator.

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