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Towards a spatial drug distribution model of the brain

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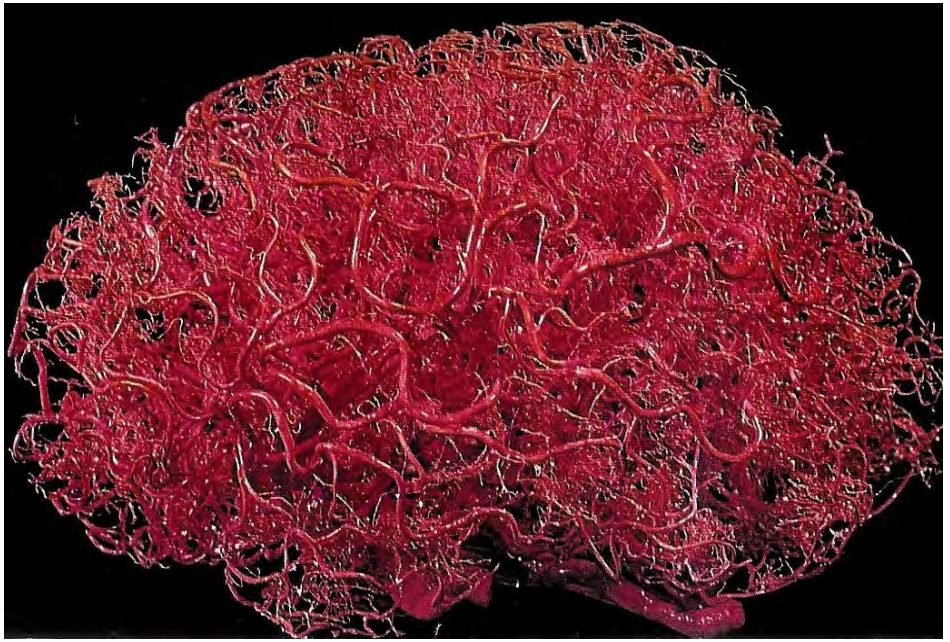
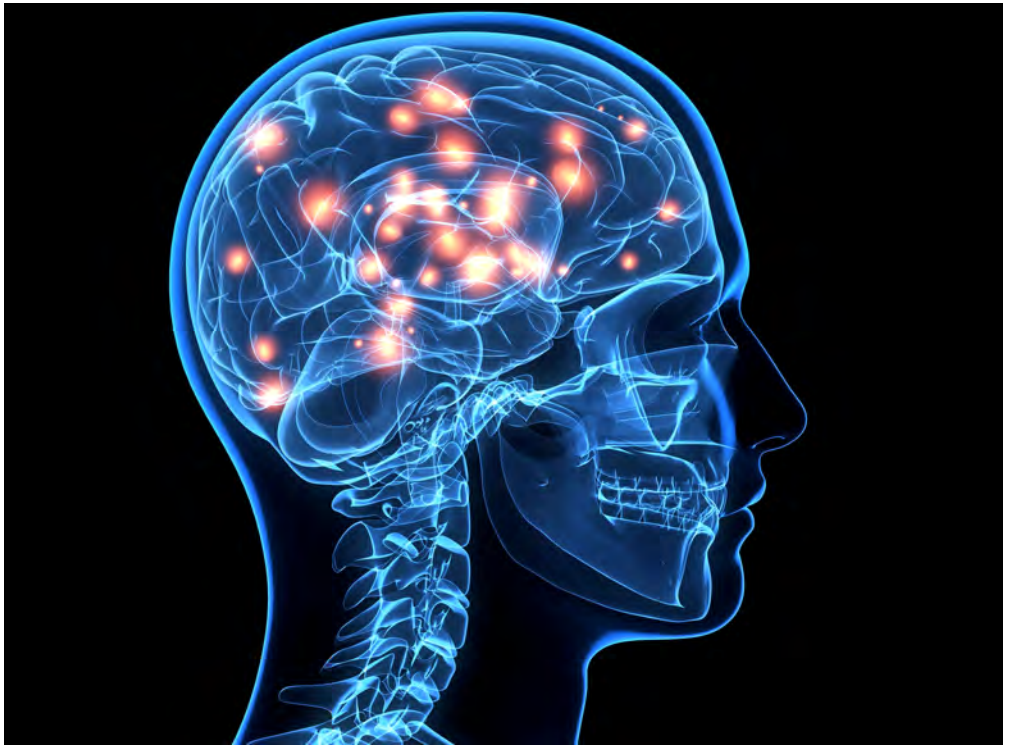
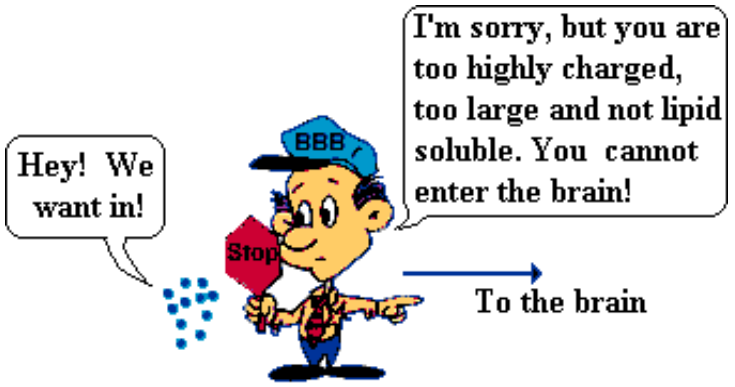
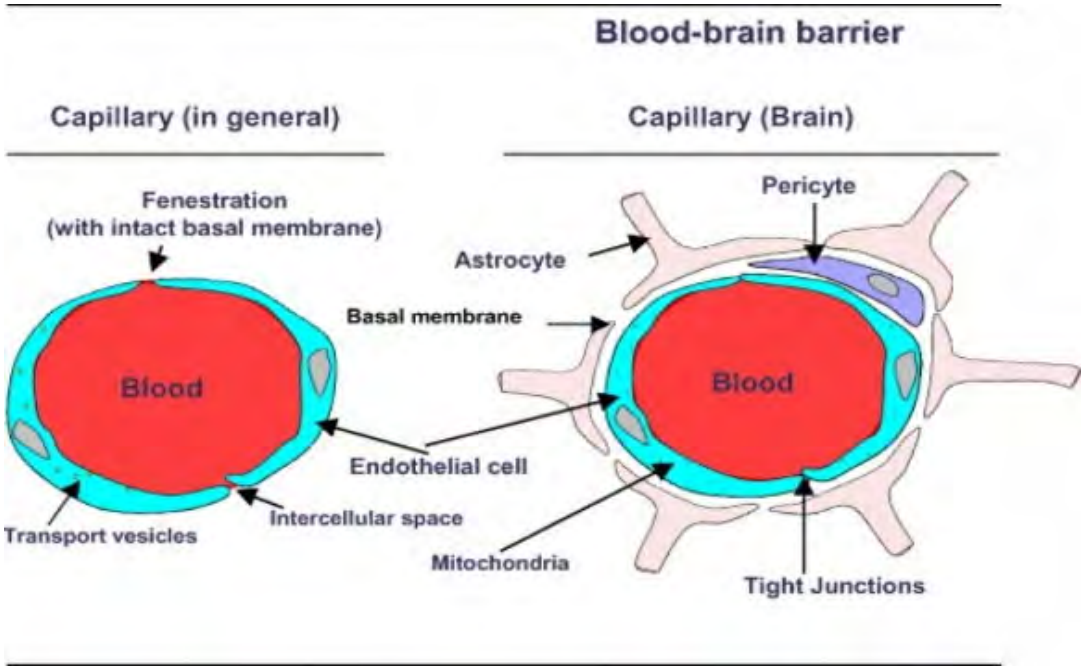
The prediction of drug distribution in the brain is challenging



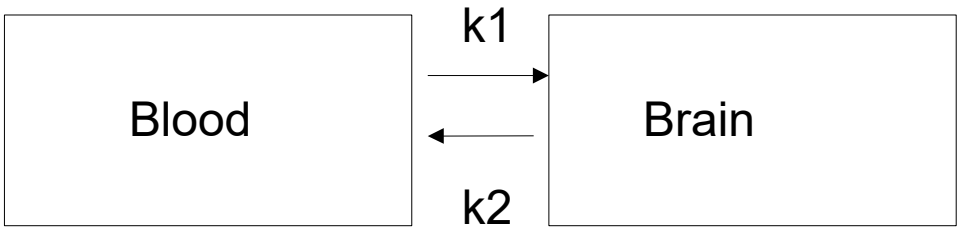


Blood brain barrier (BBB)





Esparza 2015, Standford



BBB

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But there is more than the BBB...

..and many other factors **within** the brain

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Drug distribution within the brain

Spatial variability
Drug distribution over time and space

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Setting up spatial drug distribution model of the brain

Goal:

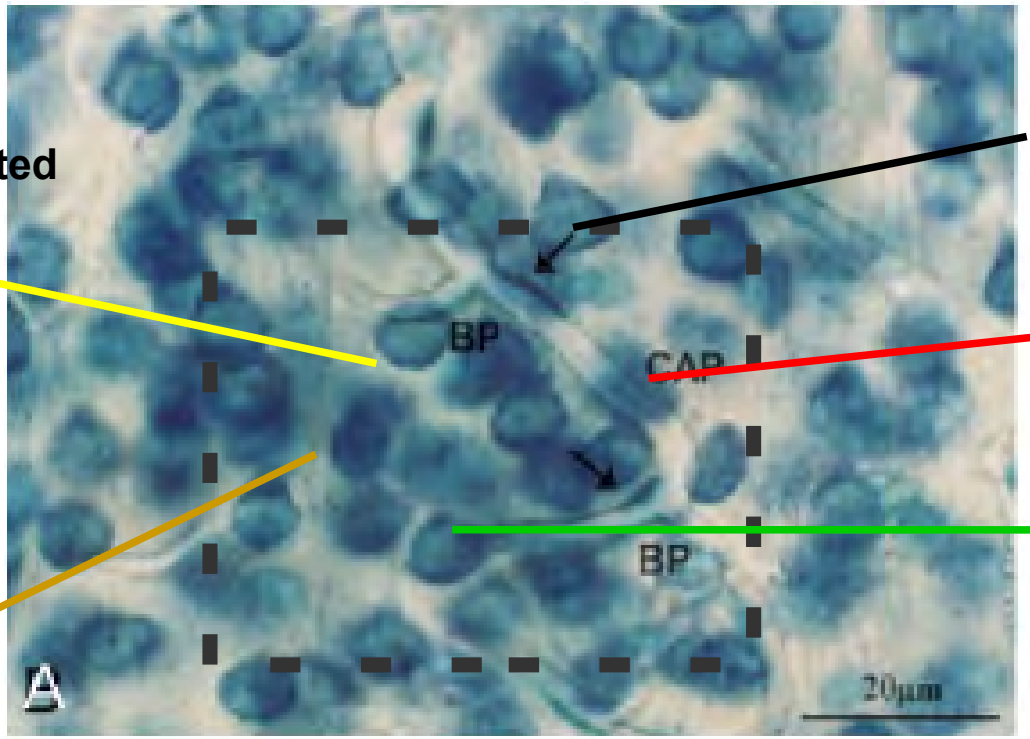
- Understand the **spatial behaviour** of drugs through the brain
- Understand how the **local drug concentration profile** is influenced by which factors

What do we want to model?

Focus on **drug distribution** in **the brain extracellular fluid (ECF):**
1. **Drug transport** in the brain ECF by diffusion and bulk flow
2. **Drug binding** to specific and non-specific binding sites

Unit: smallest building block of the brain in terms of drug distribution

Brain ECF
in which drug is **transported**
by diffusion and bulk flow



Physiological unit.
Approx. 50 x 50 um

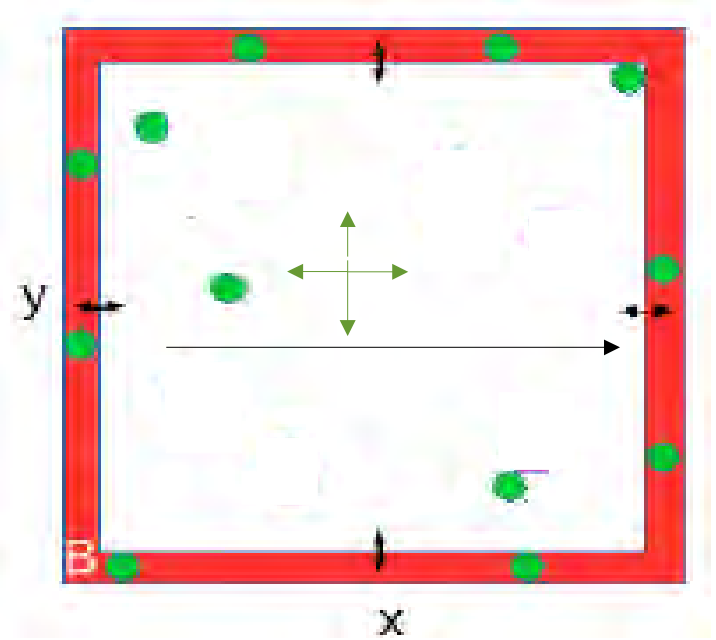
Capillary

Cells, **hinder diffusion** and contain **binding sites**

Blood-brain barrier

A modelled unit – Drug transport

Drug



ECF

BBB

Blood

ECF bulk flow

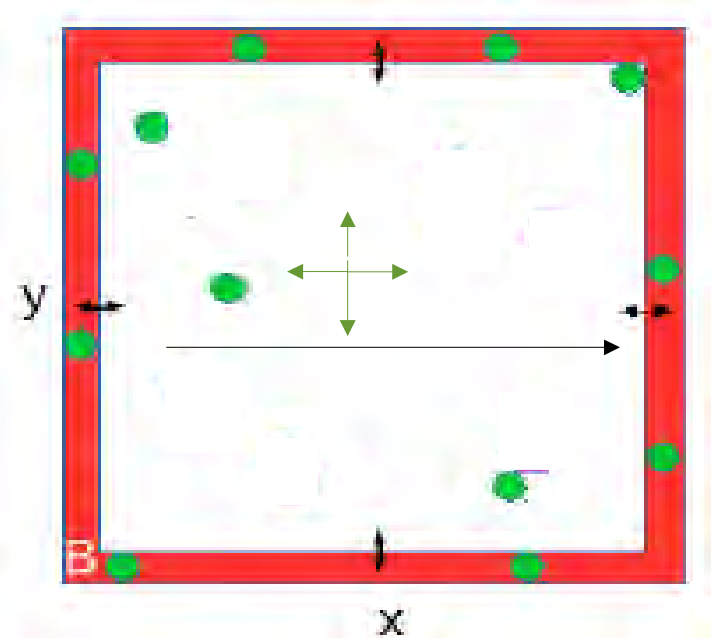
Diffusion

In one unit:

1. Drug is transported in the brain ECF by **diffusion** and **bulk flow**
   Diffusion through the ECF is hindered by **cells,** which are not **explicitly** modelled
   Cells are not explicitly modelled but implicitly as they hinder diffusion
2. Drug distributes by **binding** to specific and non-specific binding sites (see next slide)
   that are **distributed evenly** over the unit
   Cells are not explicitly modelled but implicitly as they contain binding sites

A modelled unit – Drug transport

Drug



ECF

BBB

Blood

ECF bulk flow

Diffusion

$$\frac{\partial C_{ECF}}{\partial t} = \frac{D}{\lambda^2}\nabla^2 C_{ECF} - v\nabla C_{ECF}$$

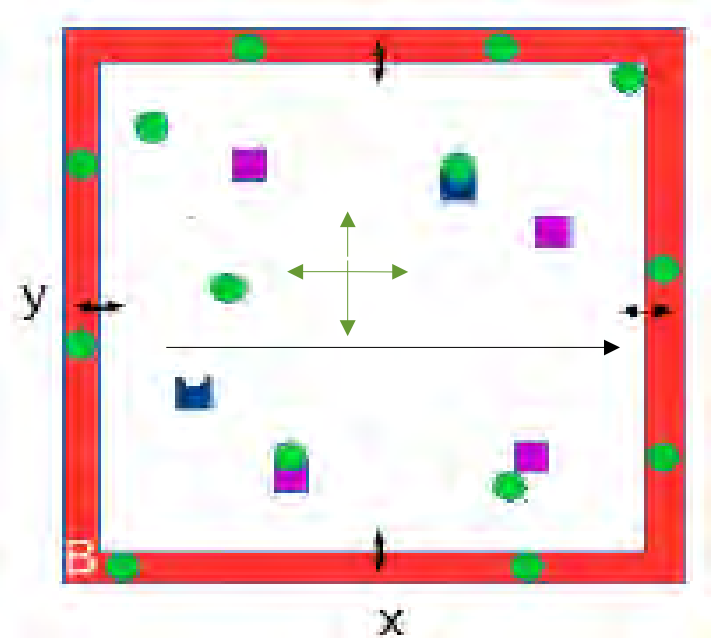
λ = tortuosity = hindrance imposed on diffusion in ECF

A modelled unit – Drug binding

Drug

Receptor

Non-specific binding site



ECF

BBB

Blood

ECF bulk flow

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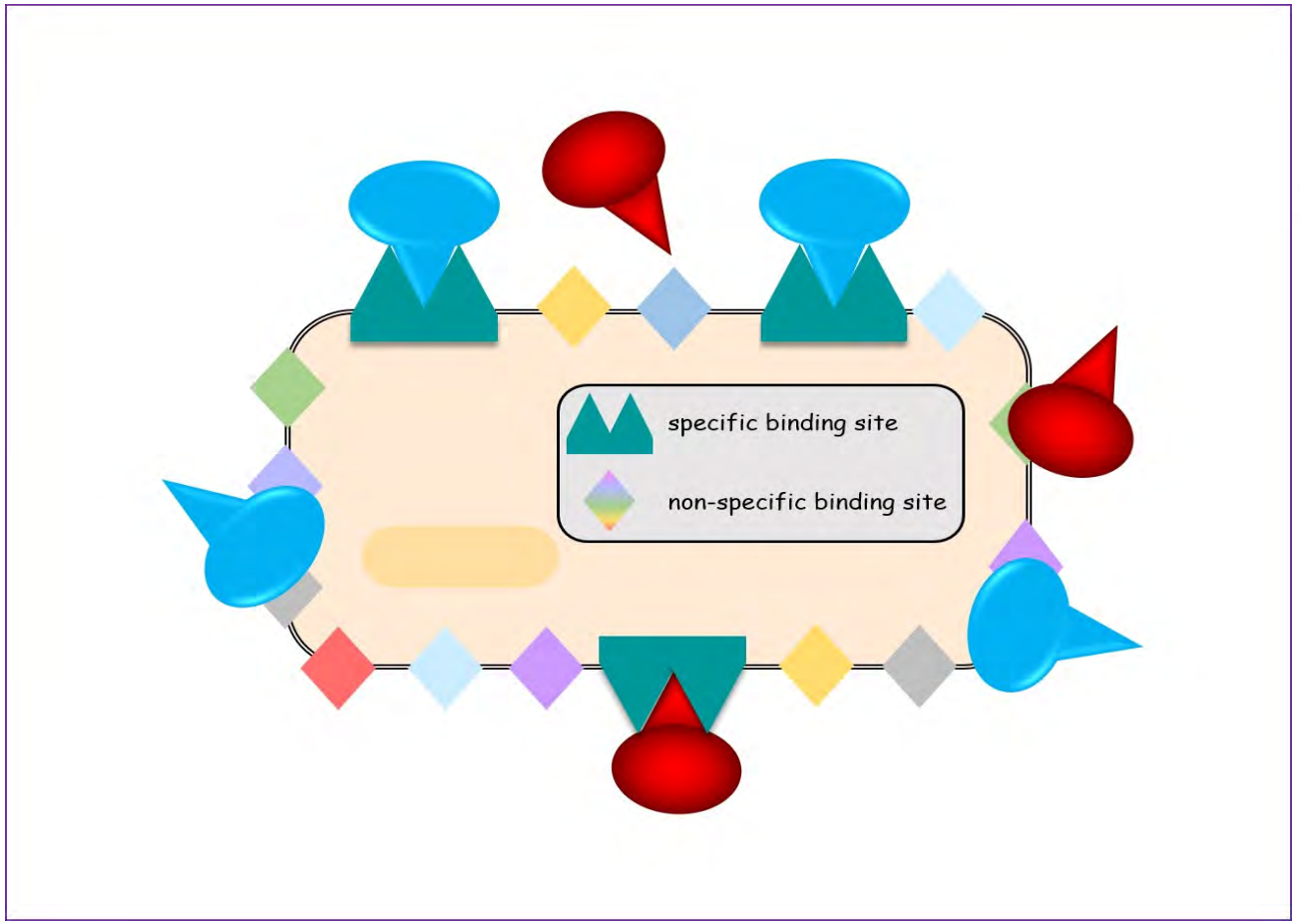
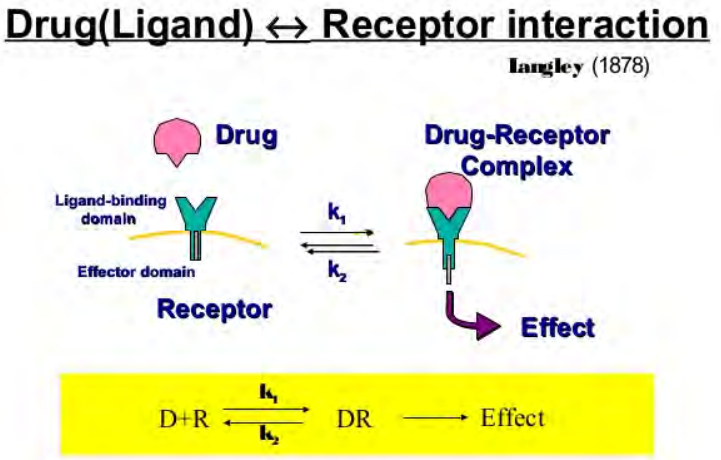
Drug binding in the ECF

- Drug may bind to and unbind from **targets** that are distributed throughout the ECF
- These targets may be **specific** (wanted) or **non-specific** (unwanted)





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Extending the equation with drug binding

Extend PDE and introduce 2 additional **ODEs** that describe:

1. Concentration change of drug bound to receptors (B_1)
2. Concentration change of drug bound to non-specific binding sites (B_2)

Based on the affinity (association and dissociation constants **K_{on}** and **K_{off}**) of the drug for specific (1) or non-specific (2) binding sites

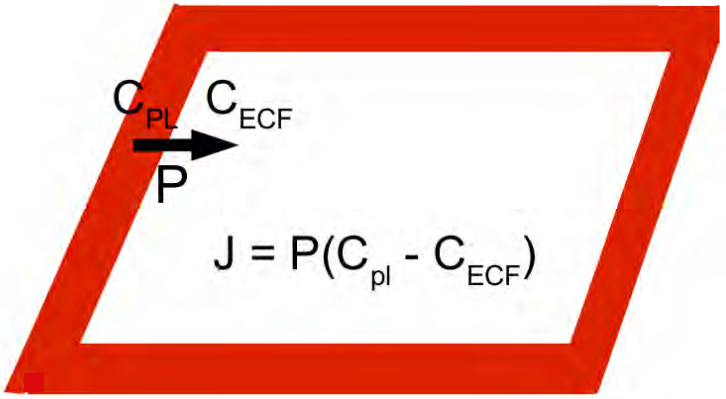
$$\partial \frac{C_{ECF}}{\partial t} = \frac{D}{\lambda^2}\nabla^2 C_{ECF} - v\nabla C_{ECF} - k_{1on}C_{ECF}(B_1^{max} - B_1) + k_{1off}B_1 \\ -k_{2on}C_{ECF}(B_2^{max} - B_2) + k_{2off}B_2 \quad (3)$$

$$\frac{\partial B_1}{\partial t} = k_{1on}C_{ECF}(B_1^{max} - B_1) - k_{1off}B_1 \quad (4)$$

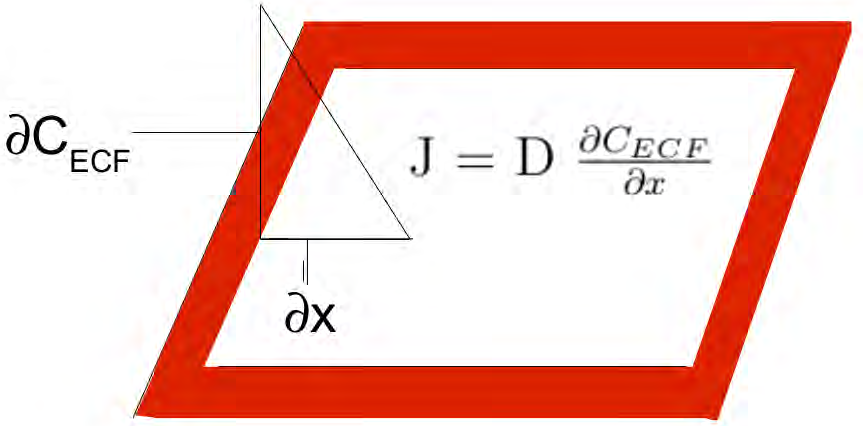
$$\frac{\partial B_2}{\partial t} = k_{2on}C_{ECF}(B_2^{max} - B_1) - k_{2off}B_2, \quad (5)$$

Drug transport through the BBB

Drug enters and leaves the brain extracellular fluid (ECF) from the blood through the BBB, which is described in the **permeability (P)**



Permeability (P)



Fick's law of diffusion

$$D\frac{\partial C_{ECF}}{\partial x} = P(C_{pl} - C_{ECF})$$

for x=0 and x=x_r

$$D\frac{\partial C_{ECF}}{\partial y} = P(C_{pl} - C_{ECF})$$

for y=0 and y=y_l

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Implementation of the model

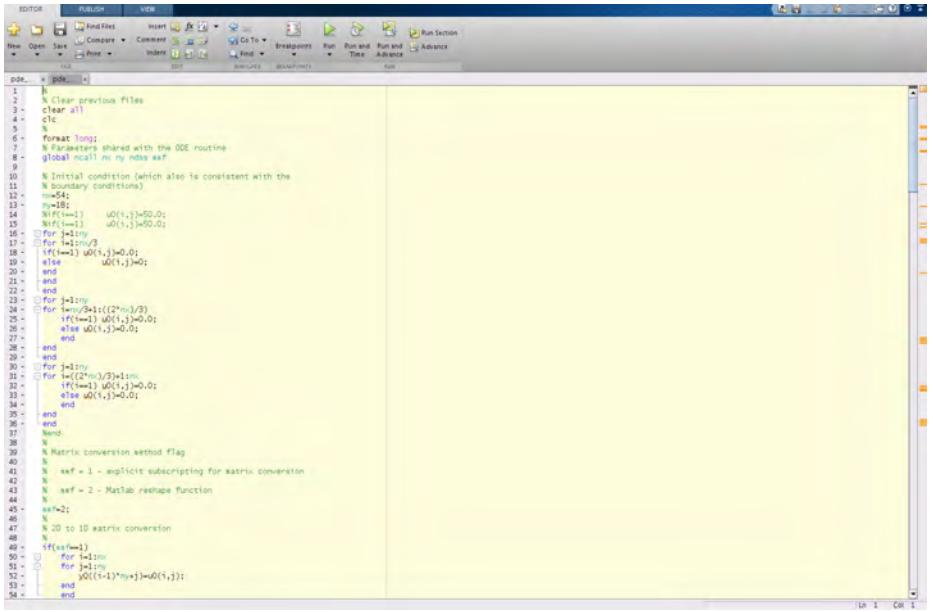
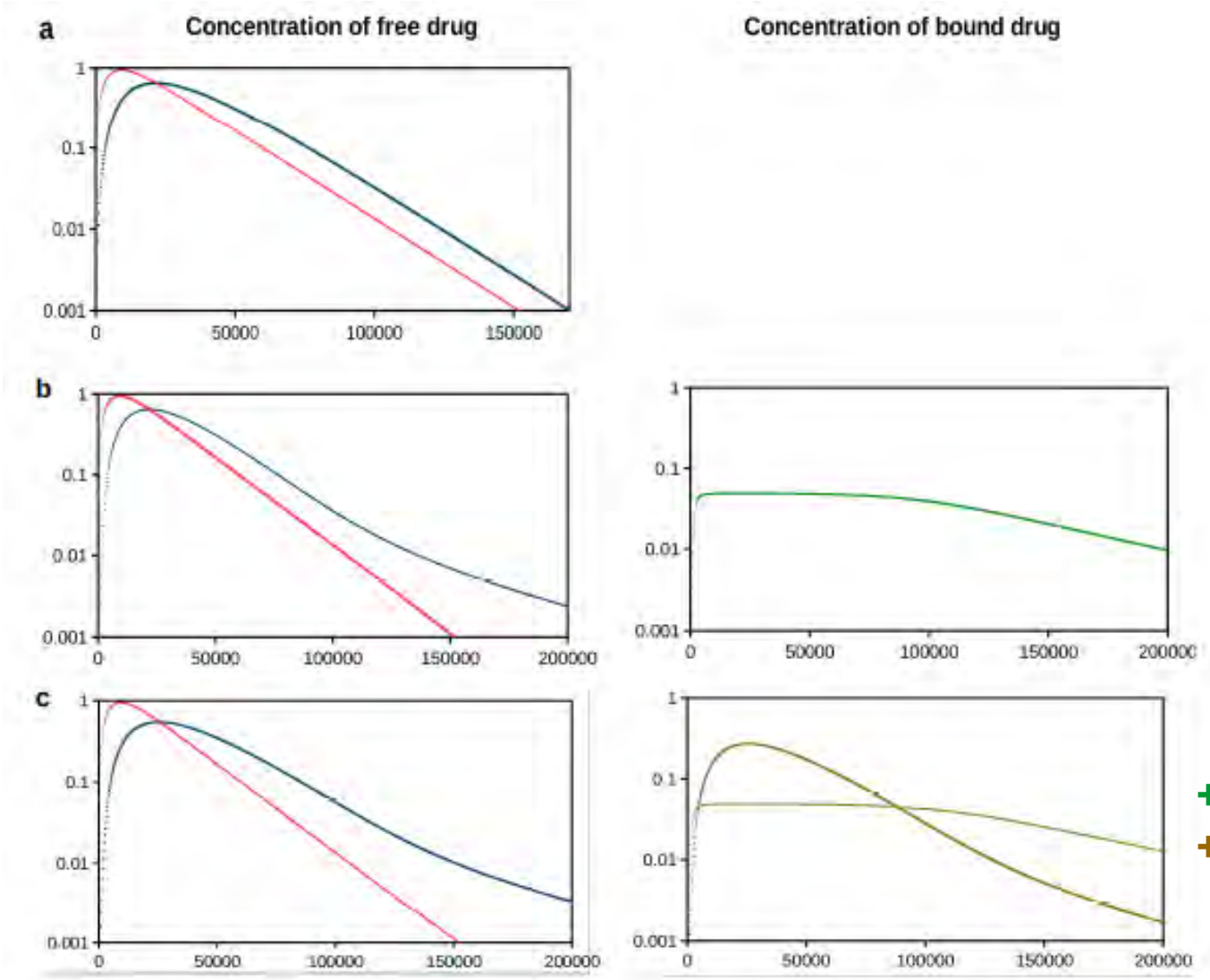


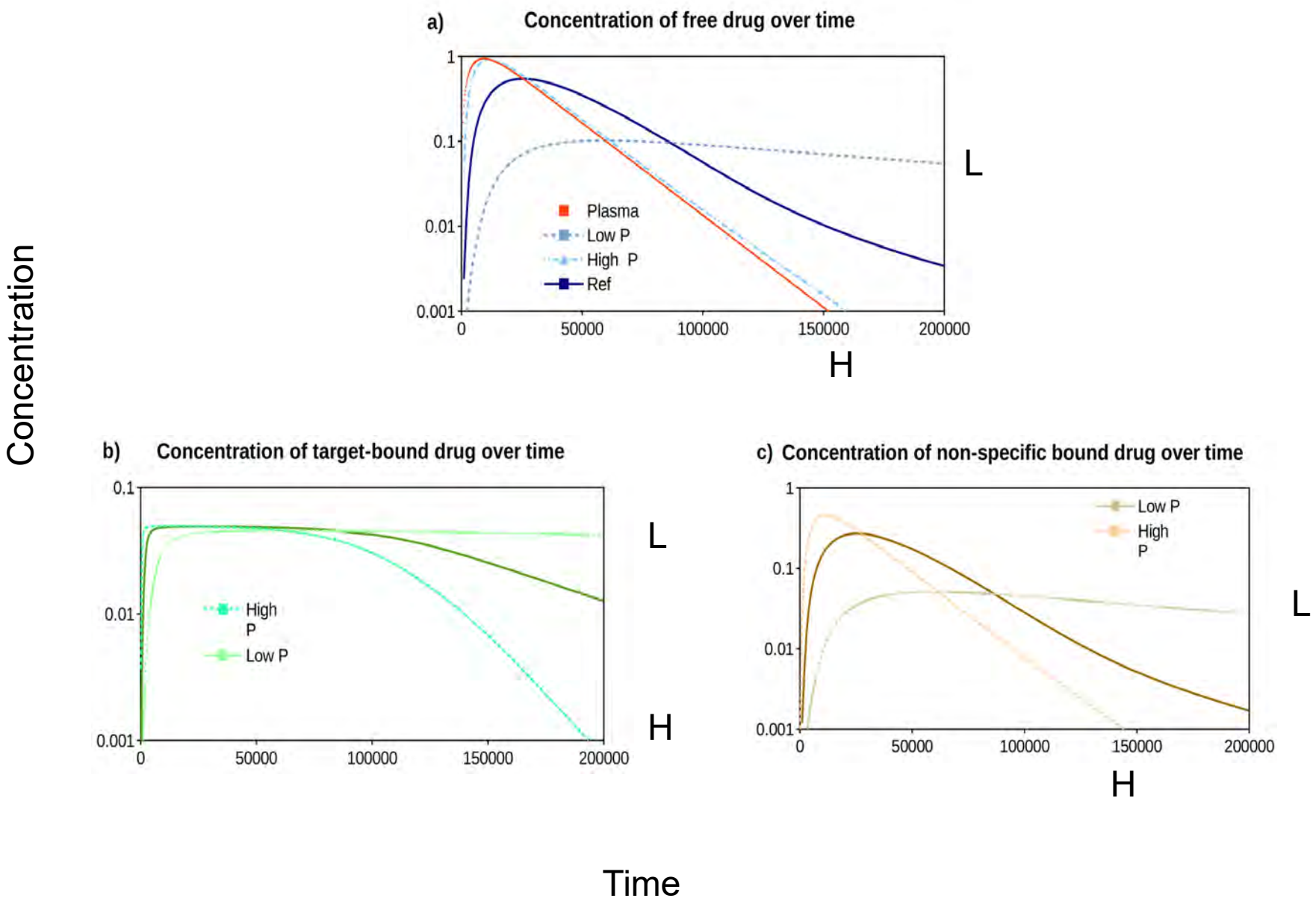
Table 1: Model values

Quantity	Unit	Magnitude	References
Time(t)	s	1	-
Distance(x)	m	$50 \cdot 10^{-6}$	[9, 26, 29, 18, 6]
Distance(y)	m	$50 \cdot 10^{-6}$	[9, 26, 29, 18, 6]
Concentration in ECF (C_{ECF}(x,y,t))	μM	0-100	[22]
Diffusion coefficient (D)	$m^2 s^{-1}$	0.1 - $1 \cdot 10^{-10}$ (0.5)	[17]
Tortuosity (λ)	-	1.44 - 3.5	[17, 15]
Flow velocity (v)	ms^{-1}	0.05-5 $\cdot 10^{-6}$	[23]
Concentration in plasma (C_{pl})	μM	0-100	[22]
Permeability (P)	ms^{-1}	0.1-1000 $\cdot 10^{-}8$	[32]
Total concentration receptors(B_1^{max})	μM	0.001-0.5	[31]
Receptor association constant (k_{1on})	$\mu M^{-1} s^{-1}$	10^{-1} - 10^{3} (10^{0})	[31]
Receptor dissociation constant (k_{1off})	s^{-1}	10^{-6} - 10^{-2}	[31]
Total non-specific binding sites (B_2^{max})	μM	1-500	[30, 10, 11]
NS association constant (k_{2on})	$\mu M^{-1} s^{-1}$	10^{-5} - 10^{1}	[10]
NS dissociation constant (k_{2off})	s^{-1}	10^{0}	[10]
Bioavailability (F)	-	0-1	[22]
Dose	μmol	0.1-5000	[22]
Absorption rate constant (k_a)	s^{-1}	0-2 $\cdot 10^{-3}$	[22]
Elimination rate constant (k_e)	s^{-1}	0.1-5 $\cdot 10^{-3}$	[22]

Influence of drug binding



Influence of permeability



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Spatial distribution

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Spatial distribution - Free drug in the ECF

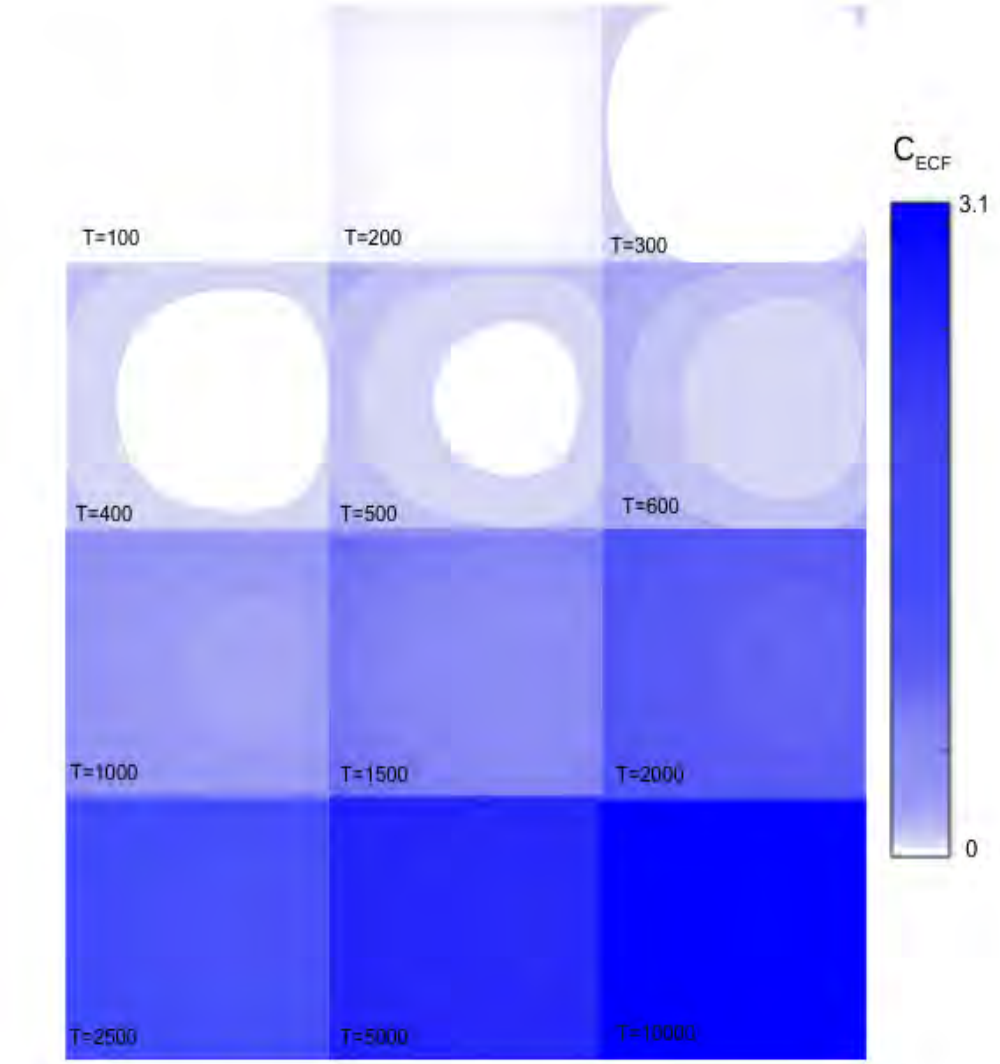

Fig. 7: **Spatial distribution of free drug in the ECF (C_{ECF}).** The concentration time profile of C_{ECF} is shown including the local distribution of C_{ECF} within one unit. The concentration is indicated by the shades of the color bar. The concentration at the top of the color bar is the peak concentration of the simulation.

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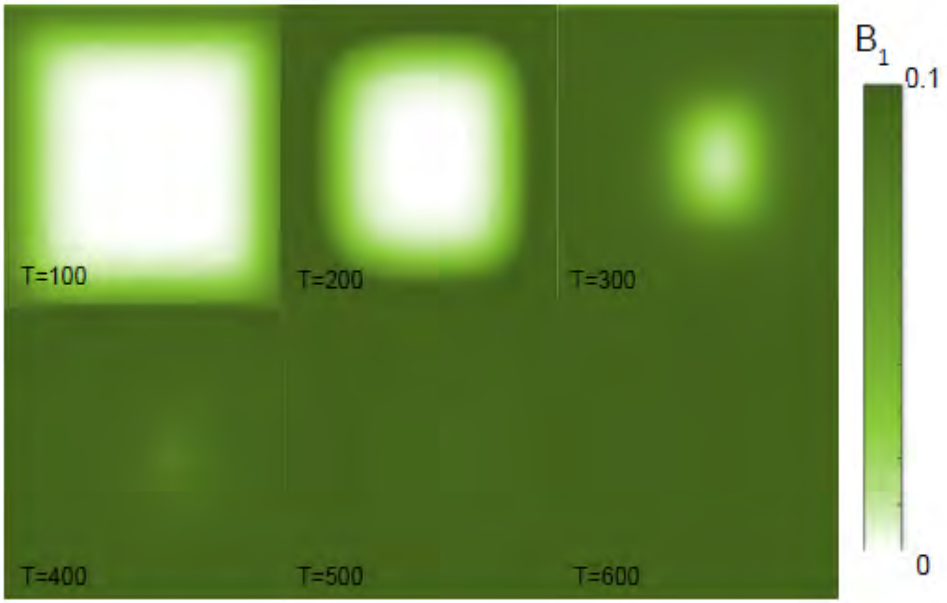
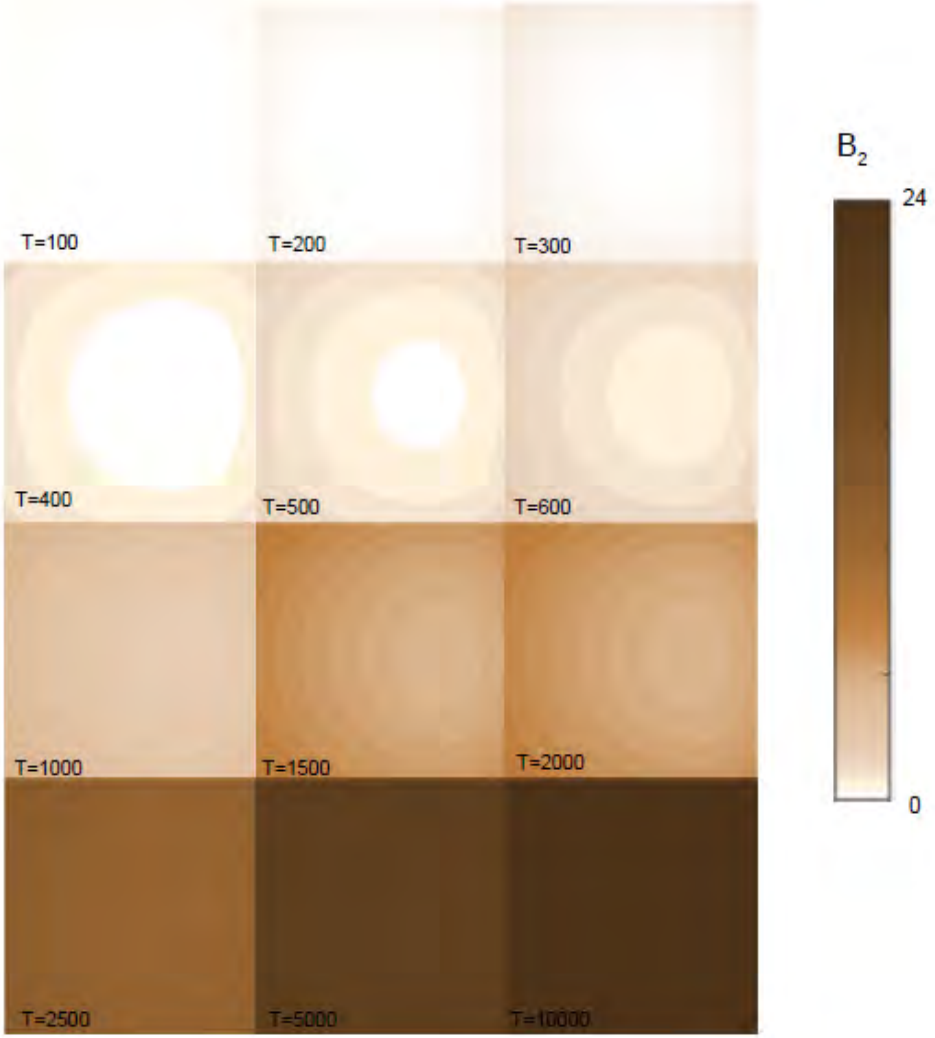
Spatial distribution – Bound drug in the ECF

Specific-bound drug



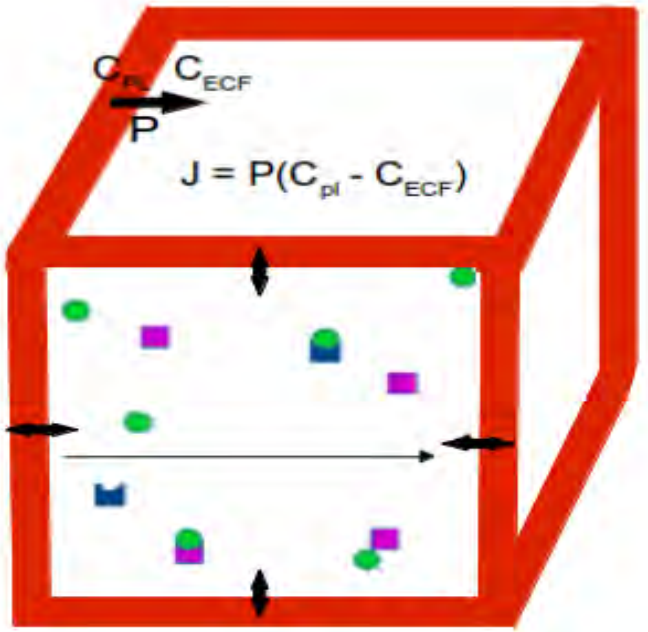
Non-specific bound drug



Next steps and future

- Get into 3D!

- Extend the **permeability** with additional info:
  - distinction between paracellular and transcellular transport
  - distinction between passive and active transport



- **Ultimate aim:** integrate both drug distribution and target interaction kinetics
  - in a 3D manner to improve the prediction of drug action in the brain

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