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)

I'm sorry, but you are too highly charged, too large and not lipid soluble. You cannot enter the brain!

Hey! We want in!

To the brain

Blood |
| k1 |
| k2 |

Brain

BBB

Esparza 2015, Standford
But there is more than the BBB...

..and many other factors within the brain
Drug distribution within the brain

Spatial variability
Drug distribution over time and space

Brain fluid flow
Cerebral blood flow
Target site distribution
Drug binding
Drug diffusion
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
- **Blood-brain barrier**
- **Physiological unit**: Approx. 50 x 50 um
- **Capillary**
- **Cells**, hinder diffusion and contain **binding sites**
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

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

$$\lambda = \text{tortuosity} = \text{hindrance imposed on diffusion in ECF}$$
A modelled unit – Drug binding

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.
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)
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

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

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

\[
\frac{\partial B_2}{\partial t} = k_{2on} C_{ECF} (B_2^{max} - B_2) - k_{2off} B_2, \tag{5}
\]
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 \( P \)

\[
J = P(C_{pl} - C_{ECF})
\]

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 \( y=y_t \)
Implementation of the model

Table 1: Model values

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Unit</th>
<th>Magnitude</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time(t)</td>
<td>s</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Distance(x)</td>
<td>m</td>
<td>50 - 10^-6</td>
<td>[9, 26, 29, 18, 6]</td>
</tr>
<tr>
<td>Distance(y)</td>
<td>m</td>
<td>50 - 10^-6</td>
<td>[9, 26, 29, 18, 6]</td>
</tr>
<tr>
<td>Concentration in ECF (C_{ECF}(x,y,t))</td>
<td>μM</td>
<td>0-100</td>
<td>[22]</td>
</tr>
<tr>
<td>Diffusion coefficient (D)</td>
<td>m^2s^-1</td>
<td>0.1 - 10^-10 (0.5)</td>
<td>[17]</td>
</tr>
<tr>
<td>Tortuosity (λ)</td>
<td>-</td>
<td>1.44 - 3.5</td>
<td>[17, 15]</td>
</tr>
<tr>
<td>Flow velocity (v)</td>
<td>ms^-1</td>
<td>0.05-5 - 10^-6</td>
<td>[23]</td>
</tr>
<tr>
<td>Concentration in plasma (C_{pl})</td>
<td>μM</td>
<td>0-100</td>
<td>[22]</td>
</tr>
<tr>
<td>Permeability (P)</td>
<td>ms^-1</td>
<td>0.1-1000 - 10^-8</td>
<td>[32]</td>
</tr>
<tr>
<td>Total concentration receptors (B_{1max})</td>
<td>μM</td>
<td>0.001-0.5</td>
<td>[31]</td>
</tr>
<tr>
<td>Receptor association constant (k_{1on})</td>
<td>μM^-1s^-1</td>
<td>10^-1 - 10^3</td>
<td>[31]</td>
</tr>
<tr>
<td>Receptor dissociation constant (k_{1off})</td>
<td>s^-1</td>
<td>10^-6 - 10^-2</td>
<td>[31]</td>
</tr>
<tr>
<td>Total non-specific binding sites (B_{2max})</td>
<td>μM</td>
<td>1-500</td>
<td>[30, 10, 11]</td>
</tr>
<tr>
<td>NS association constant (k_{2on})</td>
<td>μM^-1s^-1</td>
<td>10^-5 - 10^1</td>
<td>[10]</td>
</tr>
<tr>
<td>NS dissociation constant (k_{2off})</td>
<td>s^-1</td>
<td>10^5</td>
<td>[10]</td>
</tr>
<tr>
<td>Bioavailability (F)</td>
<td>-</td>
<td>0-1</td>
<td>[22]</td>
</tr>
<tr>
<td>Dose</td>
<td>μmol</td>
<td>0.1-5000</td>
<td>[22]</td>
</tr>
<tr>
<td>Absorption rate constant (k_a)</td>
<td>s^-1</td>
<td>0.2 - 10^-3</td>
<td>[22]</td>
</tr>
<tr>
<td>Elimination rate constant (k_e)</td>
<td>s^-1</td>
<td>0.1-5 - 10^-3</td>
<td>[22]</td>
</tr>
</tbody>
</table>
Influence of drug binding

- Blood plasma
- Brain ECF
- Specific binding sites
- Non-specific binding sites

Concentration of free drug
Concentration of bound drug

Time
Influence of permeability

a) Concentration of free drug over time

b) Concentration of target-bound drug over time

c) Concentration of non-specific bound drug over time
Spatial distribution
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.
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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