Kinetics of Proteins in the Blood Brain Barrier

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Introduction: The delivery of chemotherapy into the central nervous system remains a challenge. Here, I look at the environment of the blood brain barrier, in particular transport proteins. Then, I create a COMSOL model to describe and predict behavior at the blood-brain barrier (BBB) with respect to one pharmaceutical agent.

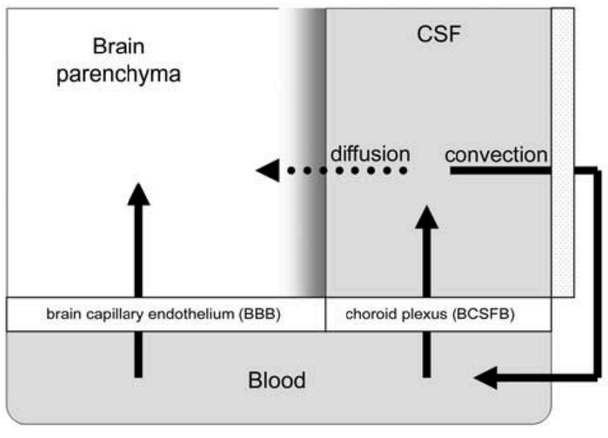

Figure 1. CNS Transport Schematic [3]

Computational Methods: I created a model of concentration of pharmaceutical across the BBB. I used experimentally determined partition coefficients (K_p) and diffusivity. I used K_p to create a linear model of flux across the membrane.

$$K_p = C1final/C2final$$

$$\text{Inward Flux to C1} = \text{Constant} * (C1 - K_p*C2) \ (mol/m^2 * s)$$

Below is a table of K_p values.

Variable	Erlotinib	Flavopiridol
Wild-type	1.00	1.00
Bcrp knockout	1.29	1.27
P-gy knockout	2.95	3.49
Double Knockout	8.52	14.2

Table 1. K_p values for Erlotonib and Flavopiridol [1]

Results: A computer-aided design (CAD) can be used to better study the concentration gradient. CAD can more accurately predict and describe the gradient, with respect to table-based data.

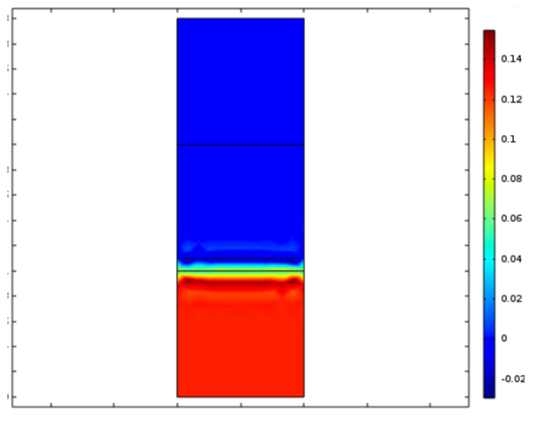

Figure 2. Wild type, t=0

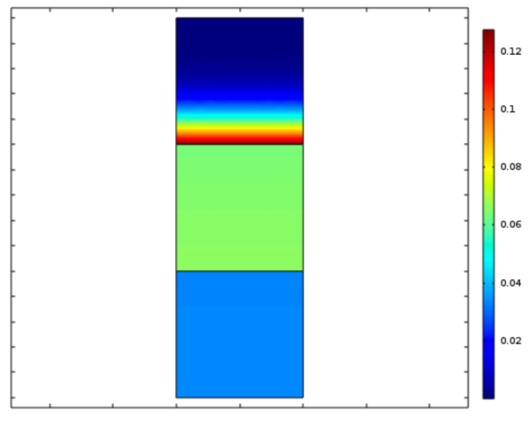

Figure 3. Wild type, t=1

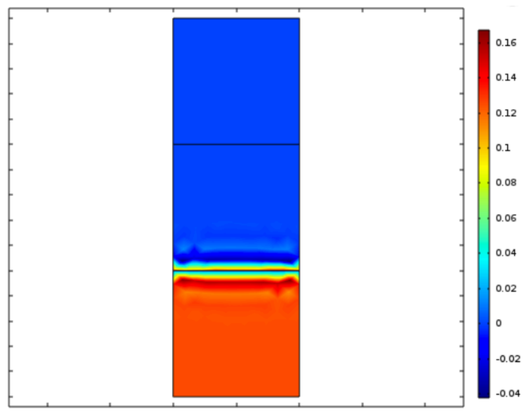

Figure 4. Knock-out, t=0

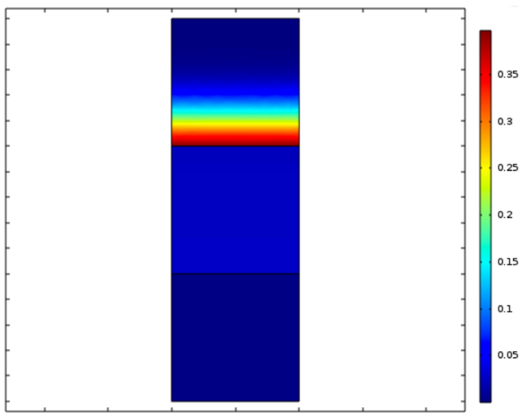

Figure 5. Knock-out, t=1

Conclusions: COMSOL or CAD models can be used to study transport kinetics. They may more effectively communicate data. Also, they may be used to further interpret data.

References:
1. Kodaira H, et. al., Kinetic Analysis of the Cooperation of P-Glycoprotein and Breast Cancer Resistance Protein in Erlotinib, Flavopiridol, and Mitoxantrone, The Journal of Pharmacology and Experimental Therapeutics, Vol. 333, 788-796 (2010)
2. Adachi Y, et. al., Comparative Studies on in Vitro Methods for Evaluating in Vivo Function of MDR1 P-Glycoprotein, Pharmaceutical Research, Vol. 18, 1660-1668 (2001)
3. Pardrige, W, Drug Transport Across the Blood-Brain Barrier, Journal of Cerebral Blood Flow & Metabolism, Vol. 23, 1959-1972 (2012)