National Institute of Environmental Health Sciences
Division of Translational Toxicology

PBPK Modeling to Predict Chemical Distribution in Brain and Adipose Tissues

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Poster P221

Introduction

- Physiologically based pharmacokinetic (PBPK) models represent absorption, distribution, metabolism, and excretion (ADME) processes to help predict concentrations of chemicals in relevant tissues. PBPK models are based on various assumptions and simplifications to make them computationally tractable.
- Here we build upon the existing generic PBPK model included in the U.S. Environmental Protection Agency's (EPA's) httk package (version 2.2.2) [1] to estimate chemical concentrations in brain and adipose compartments of the body. The httk R package is open-source and can accommodate integration of new models.

Workflow

- The workflow represented below was used to develop a perfusion-limited model that facilitated parameterization with limited data and assumed linear clearance. This model is getting revised to incorporate blood–brain barrier activity, which would make the brain a diffusion-limited compartment, thus aiding in predicting brain tissue distribution of chemicals from capillary blood.

IDENTIFY
- **Model structure**
- **Model equations**
- **Model parameters**

GENERATE
- **File representing a description of the model.**
- **C translation file created using GNU MCSim simulation package [2].**
- **R programming functions for model information, chemical-specific parameters, and model simulation.**

EXECUTE
- **Model building**
- **Model output**
- **Model evaluation**

Conclusion

- By expanding the existing open-source PBPK modeling approach, this work can refine the quantification of chemical distribution in specific toxicologically relevant body compartments for human and other species.
- Incorporation of a brain compartment can support the assessment of drug efficacy and potential to induce neurotoxicity. Determining the concentration of chemicals distributed to adipose tissue can provide valuable information on a chemical's likelihood of bioaccumulation.
- The model output includes time series dynamic concentration graphs representing chemical distribution and disposition in these compartments. For acetaminophen, both simple and complex brain models provided acceptable estimates of experimental brain Cmax, with the complex brain model showing slightly superior performance.
- The alignment between the model's predictions to both predictions from a commercial model and experimental data for a subset of chemicals indicates the robustness of the expanded httk models and its applicability in various aspects of drug development.
- Further comparisons using pharmacokinetic time series data from additional chemicals will help provide greater confidence in these models.

References

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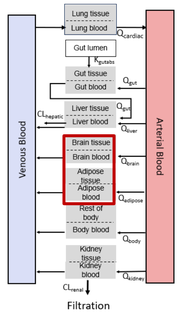
Perfusion-Limited Model With Brain and Adipose Compartments (Simple Model)

Model Structure



Physiological Parameters Specific for Brain and Adipose Model

Parameter	Description	Value	Source
Qbrainf	Fraction of cardiac output flowing to the brain tissue	0.125	[1]
Vbrainc	Volume fraction of the brain tissue per kg body weight	0.02	[1,3]
Qadiposef	Fraction of cardiac output flowing to the adipose tissue	0.05	[4]
Vadiposec	Volume fraction of the adipose tissue per kg body weight	0.21	[1, 4]

Equations for Brain and Adipose Model

$$\frac{dA_{brain}}{dt} = Q_{brain}\left(C_{art} - \frac{C_{brain} \cdot R_{b2p}}{K_{brain2pu} \cdot f_{up}}\right) \qquad \frac{dA_{adipose}}{dt} = Q_{adipose}\left(C_{art} - \frac{C_{adipose} \cdot R_{b2p}}{K_{adipose2pu} \cdot f_{up}}\right)$$

$$Q_{tissue} = Q_{cardiac} \cdot Q_{tissuef} \qquad V_{tissue} = V_{c\,tissue} \cdot BW$$

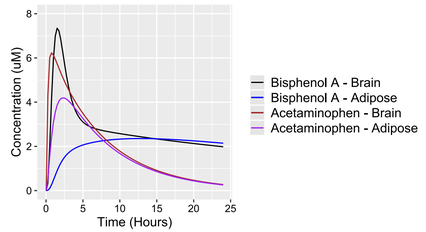
A_i : amount in tissue i
Q_i : blood flow to tissue i
V_i : volume of tissue I
BW: body weight

f_{up}: unbound fraction in plasma
R_{b2p}: blood to plasma concentration ratio
$K_{tissue2pu}$: the tissue to plasma partition coefficient
$Q_{tissuef}$: fraction of blood flow to tissue out of total cardiac output

Example Brain and Adipose Compartment Outputs

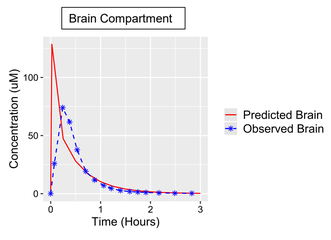
Chemical	Cmax*, µM		Tmax*, Hours	
	Brain	Adipose	Brain	Adipose
Acetaminophen	6.1	4.2	1	2.5
Bisphenol A	7.4	2.7	1.5	12

Cmax* – Maximum chemical concentration in the compartment
Tmax* – Time when the maximum chemical concentration in the compartment is reached

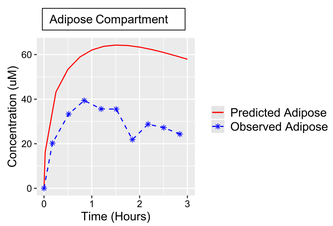


Model concentration vs. time (CvT) output using a generic dosing regimen of 1 mg/kg daily dose in human through oral route showed higher accumulation in bisphenol A than acetaminophen.

Acetaminophen Comparison with Observed



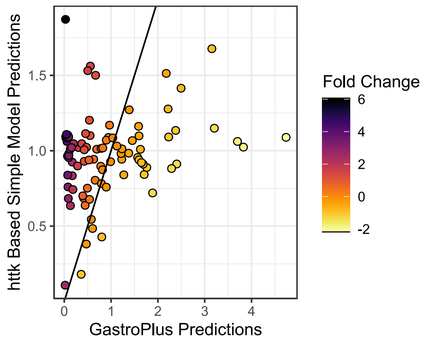
Dosing regimen: daily dose = 16 mg/kg, days = 1, doses per day = 1, species = rat, route = IV



Dosing regimen: daily dose = 14.2 mg/kg, days = 1, doses per day = 1, species = human, route = IV

For acetaminophen, predictions for both brain and adipose compartments shows general concordance with the observed data. The observed data also suggests certain degree of accumulation in the adipose tissue.

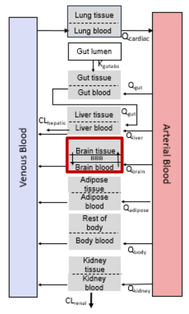
Comparison to GastroPlus®



For 91 potential developmental neurotoxicants, predictions of brain Cmax generated by the simple model were within 10-fold of those generated by the commercial GastroPlus® model.

Diffusion-Limited Model Considering Blood Brain Barrier (Complex Model)

Model Structure



Equations for Complex Brain Model

Movement of chemicals from capillary blood to the cellular matrix of the brain tissue is proportional to the permeability-area product. This can be expressed as a proportion of the blood flow Q_{brain} due to the blood-brain barrier effect represented by K_{pbbb}, assuming the surface area is proportional to the regional blood flow.

$$\frac{d}{dt}A_{brain,b} = Q_{brain} \cdot (C_{art} - C_{brain,b}) - K_{pbbb} \cdot Q_{brain} \cdot (C_{brain,b} - \frac{C_{brain} \cdot R_{b2p}}{K_{brain2pu} \cdot f_{uP}})$$

$$\frac{d}{dt}A_{brain} = K_{pbbb} \cdot Q_{brain} \cdot \left(C_{brain,b} - \frac{C_{brain} \cdot R_{b2p}}{K_{brain2pu} \cdot f_{up}}\right)$$

$$K_{pbbb} = min((P_e \cdot Area_{brain})/Q_{brain}, 1)$$

$A_{brain,b}$: amount of chemicals in capillary blood of brain
C_{brain}: concentration of chemical in brain tissue
$C_{brain,b}$: concentration of chemicals in the capillary blood of brain
K_{pbbb}: permeability coefficient between capillary blood and brain

Parameters Specific for Complex Brain Model

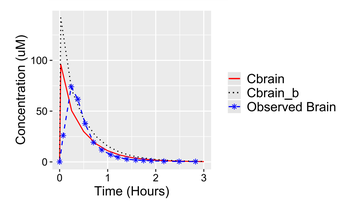
Parameter	Value
Qbrainf	0.125
Vbrainc	0.018
Vbrain_bc	0.002

Example Model Outputs for Complex Brain

Chemical	Cmax*, µM		Tmax*, Hours	
	Brain	Brain_b	Brain	Brain_b
Acetaminophen	6.0	5.2	0.9	0.7
Bisphenol A	6.5	0.7	1.9	1.4

Acetaminophen - Hydrophilic

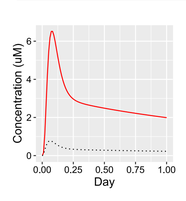
Complex Brain with K_{pbbb} = 1 Compared to Observed Brain



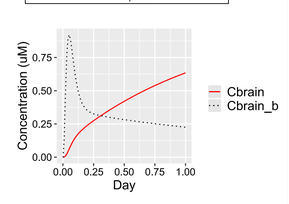
Dosing regimen: daily dose = 16 mg/kg, days = 1, doses per day = 1, species = rat, route = IV

Bisphenol A - Lipophilic

Brain Tissue and Brain Capillary Blood with K_{pbbb} = 1



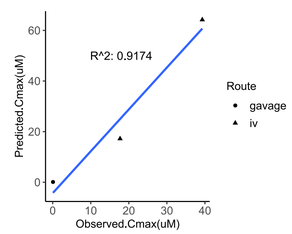
Brain Tissue and Brain Capillary Blood with K_{pbbb} = 0.003



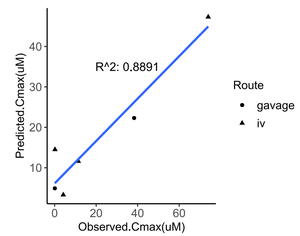
Generic dosing regimen: daily dose = 1 mg/kg, days = 1, doses per day = 1, species = human, route = oral

Prediction Comparison with Observed Data for Both Models

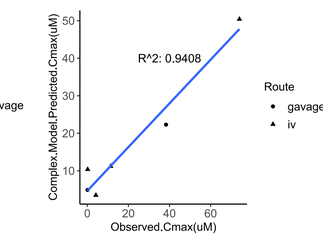
Simple Model Predicted Adipose Cmax vs Observed Data



Simple Model Predicted Brain Cmax vs Observed Data



Complex Model Predicted Brain Cmax vs Observed Data



- To check the effectiveness of the models, predictions of Cmax were compared with observed data for a few chemicals including benzo[a]pyrene, diazepam, trichloroethylene, deltamethrin, acetaminophen, bisphenol A and dieldrin.
- The prediction results were compared with available pharmacokinetic time series data derived from literature sources and CvT [9] database, which showed overall low disparity between predicted and observed data.
- The complex model made it possible to simulate the rate of permeability of chemicals to brain tissue.