Article

Interspecies Brain PBPK Modeling Platform to Predict Passive Transport through the Blood-Brain Barrier and Assess Target-Site Disposition

Supplementary Materials

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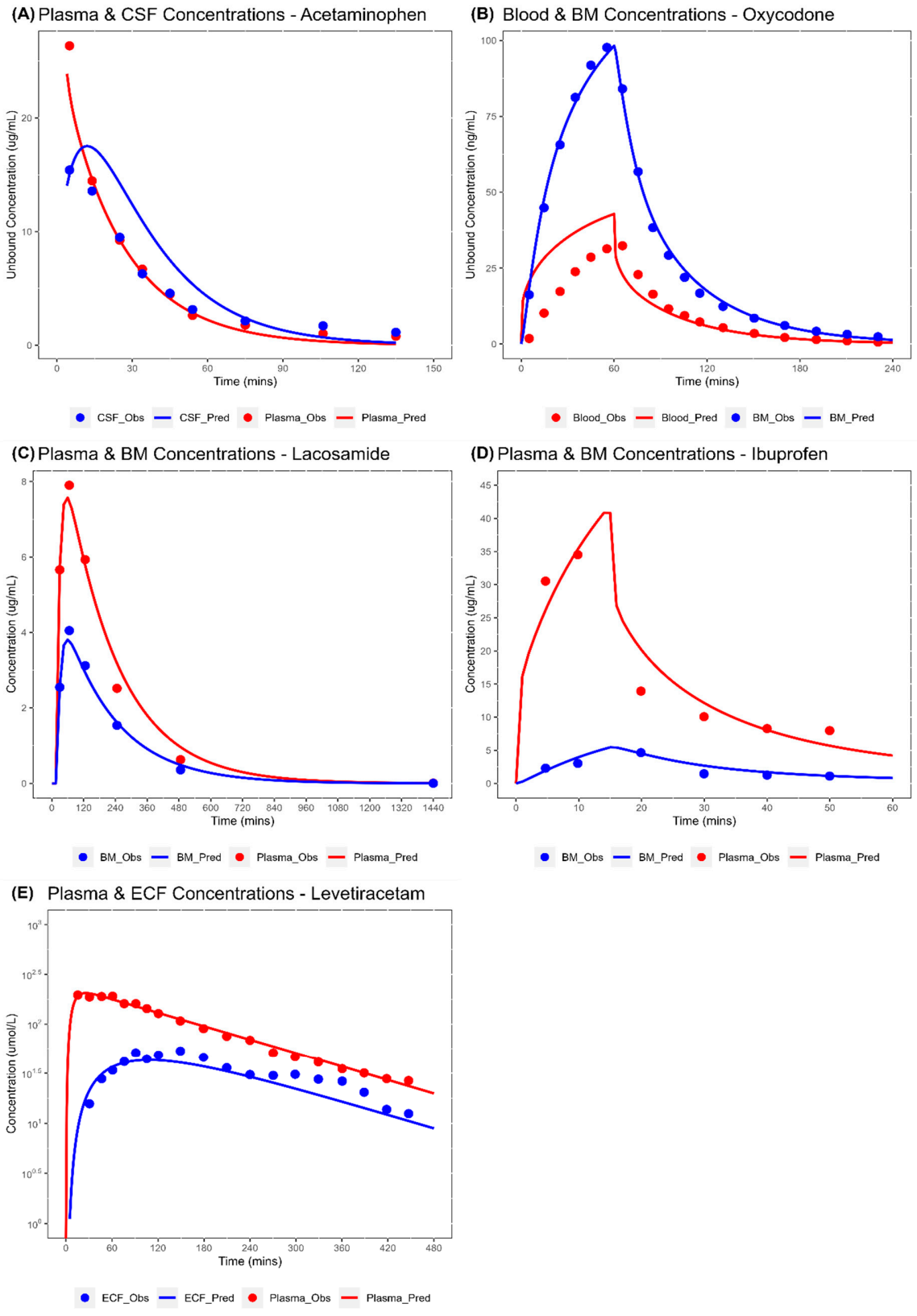
(A) Plasma & CSF Concentrations - Acetaminophen
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CSF_Obs
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Figure S1. Simulated versus observed concentration profiles for plasma and CNS in rats.

Panel A: Red solid line represents the simulated unbound plasma concentrations and blue solid line represents the unbound simulated CSF concentrations for the drug acetaminophen. Red and blue dots represent the observed plasma and CSF concentrations respectively, from Sauernheimer et al [40]

Panel B: Red solid line represents the simulated unbound blood concentrations and blue solid line represents the unbound simulated Brain Mass (BM) concentrations for the drug oxycodone. Red and blue dots represent the observed blood and BM concentrations respectively, from Ball et al [8]

Panel C: Red solid line represents the simulated plasma concentrations and blue solid line represents the simulated BM concentrations for the drug lacosamide. Red and blue dots represent the observed plasma and BM concentrations respectively, from Koo et al [42]

Panel D: Red solid line represents the simulated plasma concentrations and blue solid line represents the simulated BM concentrations for the drug ibuprofen. Red and blue dots represent the observed plasma and BM concentrations respectively, from Talhoni et al [44]

Panel E: Red solid line represents the simulated plasma concentrations and blue solid line represents the simulated ECF concentrations for the drug levetiracetam - 40mg/kg. Red and blue dots represent the observed plasma and ECF concentrations respectively, from Tong et al [34]

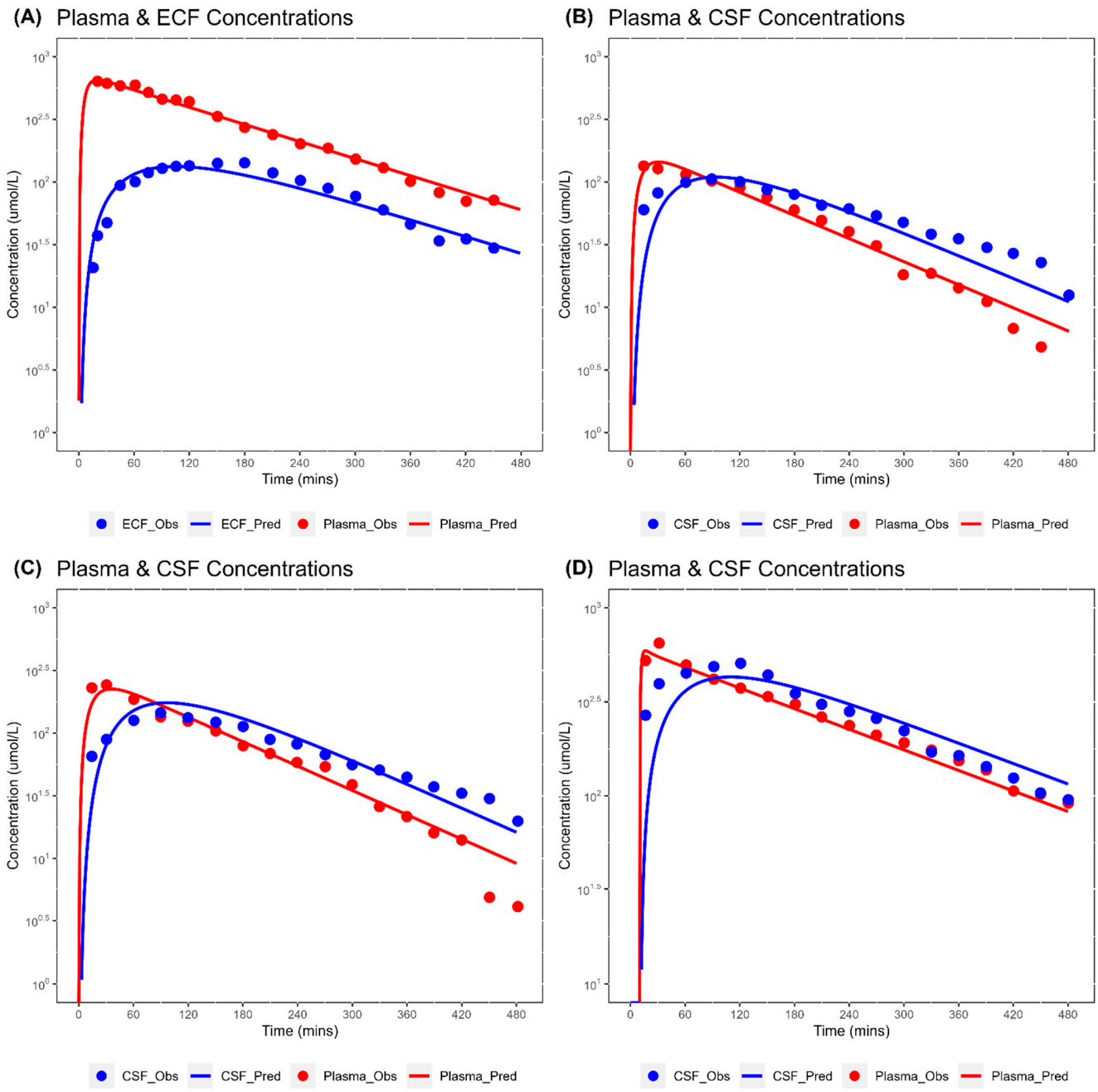

Figure S2. Simulated versus observed concentration profiles in rats. Panel A: Red solid line represents the simulated plasma concentrations and blue solid line represents the simulated ECF concentrations for the drug levetiracetam - 80mg/kg doses from a study by Tong et al. [34]. Red and blue dots represent observed plasma and CSF concentrations, respectively from a study by Tong et al. [34]. Panel B, C & D: Red solid line represents the simulated plasma concentrations and blue solid line represents the simulated CSF concentrations for the drug levetiracetam for the 20mg/kg (B), 40mg/kg (C) and 80mg/kg (D) doses respectively from a study by Doheny et al. [46]. Red and blue dots represent observed plasma and CSF concentrations, respectively for the 20mg/kg (B), 40mg/kg (C) and 80mg/kg (D) doses respectively from a study by Doheny et al. [46].

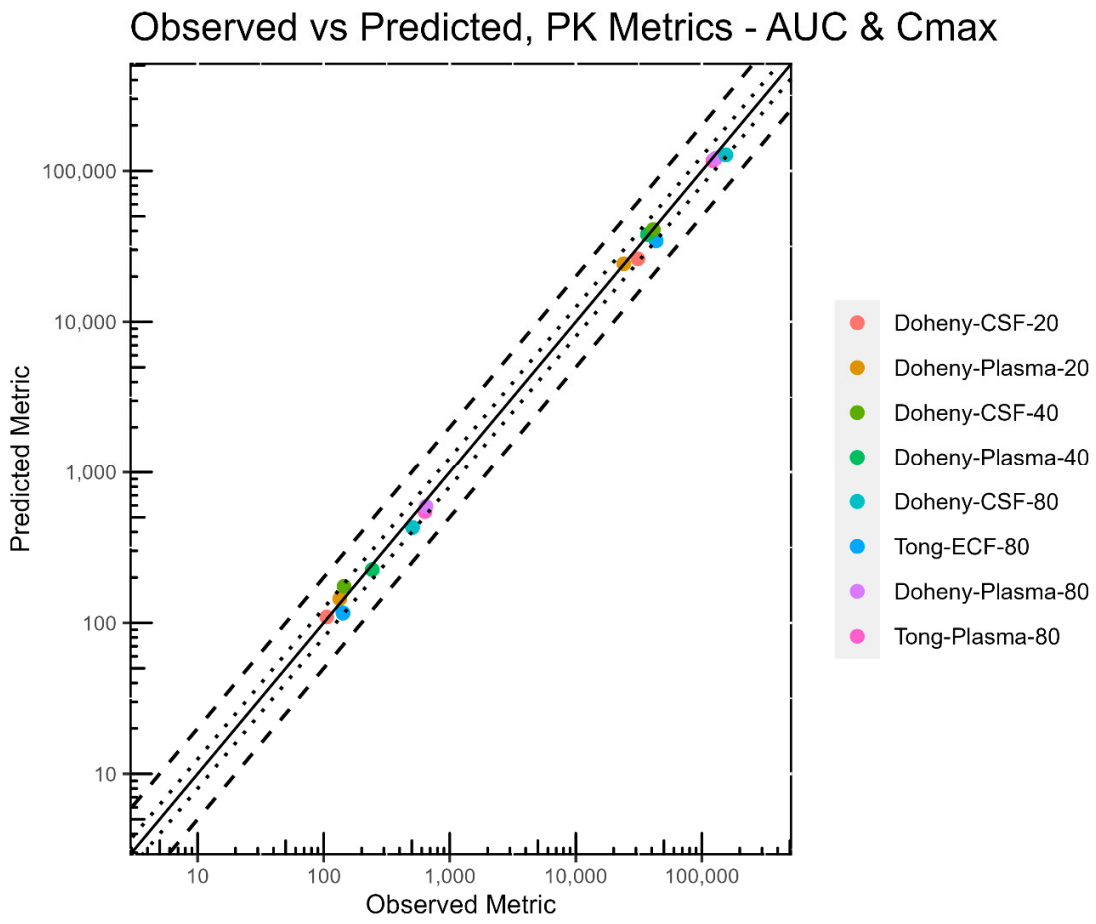

Figure S3. Goodness-of-fit plots of predicted vs observed pharmacokinetic metrics (AUC & Cmax) in plasma and CSF/ECF in rats. The line of identity is shown as a solid line; 1.25-fold deviation is shown as a dotted line; 2-fold deviation is shown as a dashed line. The observed data are from both the above studies Doheny [46], Tong [34].

Table S1. Physiological parameters - Rat PBPK model

Parameter	Equation / Value	Reference
Hematocrit	0.439	[52]
Rat Serum Albumin (g/L)	31.14	[52]
Weight (g)	250	[34]
Volumes (mL)		
Parameter	**Equation / Value**	**Reference**
Other Organ Compartments:		
Vlung	1.24	[52]
Vadipose	16.66	[52]
Vbone	15.68	[52]
Vheart	1.05	[52]
Vkidney	2.19	[52]
Vmuscle	116.13	[52]
Vskin	39.41	[52]
Vspleen	0.57	[52]
Vgut	6.19	[52]
Vliver	8.57	[52]
Vbla	6.8	[91]
Vblv	13.6	[91]
Vrest	1.3	[91]
Brain Compartments:		
Vbrain total	1.24	[52]
Vbrain blood	$0.0310 * Vbtotal$	[52]
Vccsf	$0.144 * Vbtotal$	[52]
Vscsf	$0.18750 * Vccsf$	[52]
Vecf	0.29	[8,52]
Vbrain mass	$Vbtotal - Vccsf - Vscsf$	
Fluid flow rates (mL/min)		
Parameter	**Equation / Value**	**Reference**
Other organ Compartments:		
Qcarout	80	[52]
Qlung	80	[52]
Qadipose	$5.9 * Qcarout$	[52]
Qbone	$10.1 * Qcarout$	[52]
Qheart	$4 * Qcarout$	[52]
Qkidney	$14.5 * Qcarout$	[52]
Qmuscle	$23.7 * Qcarout$	[52]
Qskin	$5.1 * Qcarout$	[52]
Qspleen	$1.1 * Qcarout$	[52]
Qgut	$10.1 * Qcarout$	[52]
Qha	$1.6 * Qcarout$	[91,52]
Qliver	$Qgut + Qspleen + Qha$	[52]
Qrestflow	1	[52]
Brain Compartment:		
Qbrain	1.12	[52]
Qproductionrate	0.0026	[52]

Qbulk	$0.085 * Qproductionrate$			[52]
Qssink	$0.37 * (0.75 * Qproductionrate + Qbulk)$			[52]
Qsout	$0.9 * Qssink$			[52]
Qsin	$(Qssink + Qsout)$			[52]
Qcsink	$(0.75 * Qproductionrate + Qbulk - Qsin + Qsout)$			[52]
Tissue Composition (fraction)				
Parameter	**Rowdgers and Rowland**	**Poulin and Theil**	**Berezhkovskiy**	**Reference**
Adipose	EW = 0.135 IW = 0.017 NL = 0.846 NP = 0.0016 AP = 0.4 AR = 0.049 LR = 0.068	FW = 0.152 NL = 0.846 NP = 0.0016 pH = 7	FW = 0.152 NL = 0.846 NP = 0.0016 pH = 7	[53,56,57]
Bone	EW = 0.10 IW = 0.346 NL = 0.017 NP = 0.0017 AP = 0.67 AR = 0.1 LR = 0.05	FW = 0.446 IW = 0.346 NL = 0.017 NP = 0.0017 pH = 6.7	FW = 0.446 IW = 0.346 NL = 0.017 NP = 0.0017 pH = 6.7	[53,56,57]
Gut	EW = 0.282 IW = 0.475 NL = 0.038 NP = 0.0125 AP = 2.41 AR = 0.158 LR = 0.141	FW = 0.757 NL = 0.038 NP = 0.0125 pH = 7.16	FW = 0.757 NL = 0.038 NP = 0.0125 pH = 7.16	[53,56,57]
Heart	EW = 0.32 IW = 0.456 NL = 0.014 NP = 0.0111 AP = 2.25 AR = 0.157 LR = 0.16	FW = 0.776 NL = 0.014 NP = 0.0111 pH = 7.13	FW = 0.776 NL = 0.014 NP = 0.0111 pH = 7.13	[53,56,57]
Kidney	EW = 0.273 IW = 0.483 NL = 0.012 NP = 0.0242 AP = 5.03 AR = 0.13 LR = 0.137	FW = 0.756 NL = 0.012 NP = 0.0242 pH = 7.31	FW = 0.756 NL = 0.012 NP = 0.0242 pH = 7.31	[53,56,57]
Liver	EW = 0.161 IW = 0.573 NL = 0.014 NP = 0.024 AP = 4.56 AR = 0.086 LR = 0.161	FW = 0.734 NL = 0.0138 NP = 0.024 pH = 7.03	FW = 0.734 NL = 0.0138 NP = 0.024 pH = 7.03	[53,56,57]
Lung	EW = 0.336 IW = 0.446	FW = 0.782 NL = 0.0219	FW = 0.782 NL = 0.0219	[53,56,57]

	NL = 0.022 NP = 0.0128 AP = 3.91 AR = 0.212 LR = 0.168	NP = 0.0128 pH = 7.36	NP = 0.0128 pH = 7.36	
Muscle	EW = 0.118 IW = 0.63 NL = 0.01 NP = 0.0072 AP = 1.53 AR = 0.064 LR = 0.059	FW = 0.748 NL = 0.01 NP = 0.0072 pH = 6.27	FW = 0.748 NL = 0.01 NP = 0.0072 pH = 6.27	[53,56,57]
Skin	EW = 0.382 IW = 0.291 NL = 0.06 NP = 0.0044 AP = 1.32 AR = 0.277 LR = 0.096	FW = 0.673 NL = 0.06 NP = 0.0044 pH = 6.27	FW = 0.673 NL = 0.06 NP = 0.0044 pH = 6.27	[53,56,57]
Spleen	EW = 0.207 IW = 0.579 NL = 0.0077 NP = 0.0113 AP = 3.18 AR = 0.097 LR = 0.207	FW = 0.786 NL = 0.0077 NP = 0.0113 pH = 6.27	FW = 0.786 NL = 0.0077 NP = 0.0113 pH = 6.27	[53,56,57]
Plasma	EW = 0.945 IW = 0.0 NL = 0.0023 NP = 0.0013 AP = 0.057 AR = NA LR = NA	FW = 0.945 NL = 0.0023 NP = 0.0013 pH = 7.4	FW = 0.945 NL = 0.0023 NP = 0.0013 pH = 7.4	[53,56,57]

EW: Extracellular Water, **IW:** Intracellular Water, **NL:** Neutral Lipids, **NP:** Neutral Phospholipids, **AP:** Acidic Phospholipids, **AR:** Albumin ratio, **LR:** lipoprotein ratio

Table S2. Physiological parameters - Human PBPK model

Parameter	Equation / Value		Reference
Hematocrit	Male: 0.43, CV (%): 6.5 Female: 0.38, CV (%): 7.1		[52]
Human Serum Albumin (g/L)	45		[52]
Height	Male: $175.32 + 0.1113 * age - 0.0025 * age^2$ CV (%): 3.9 Female: $161.66 + 0.1319 * age - 0.0027 * age^2$ CV (%): 3.9		[28,52]
Weight	Male: $\exp(2.643 + 0.0099 * Height)$ CV (%): 15 Female: $\exp(2.7383 + 0.0091 * Height)$ CV (%): 18.8		[28,52]
Body Surface Area	$0.007184 * Height\text{^}0.725 * Weight\text{^}0.425$		[28,52]
Volumes (L)			
Parameter	**Equation / Value**	**Notes**	**Reference**
Other Organ Compartments:			
Vlung	Male:$((29.08 * (Height/100) * Weight\text{^}0.5 + 11.06 + 35.47 * (Height/100) * Weight\text{^}0.5 + 5.53)/1000)/1.05$ Female:$((31.46 * (Height/100) * Weight\text{^}0.5 + 1.43 + 35.3 * (Height/100) * Weight\text{^}0.5 + 1.53)/1000)/1.05$		[28,52]
Vadipose	Male: $(1.36 * Weight)/(Height/100) - 42$ Female: $(1.61 * Weight)/(Height/100) - 38.3$		[28,52]
Vbone	Male:$((Weight - Vadipose * 0.92)/1.3 * 0.058)$ Female:$((Weight - Vadipose * 0.92)/1.3 * 0.051)$		[28,52]
Vheart	Male:$((155.18 * (BSA)\text{^}1.29)/1000)/1.05$ Female:$((124.13 * (BSA)\text{^}1.242)/1000)/1.05$		[28,52]
Vkidney	$((15.4 + 2.04 * Weight + 51.8 * (Height/100)\text{^}2)/1000)/1.05$		[28,52]
Vmuscle	Male:$(0.244 * Weight + 7.8 * (Height/100) - 0.098 * age + 3.3)/1.04$ Female:$(0.244 * Weight + 7.8 * (Height/100) - 0.098 * age - 3.3)/1.04$		[28,52]
Vskin	$(BSA/1000) * 45.655 + (BSA/1000) * 1240$	Skin thickness was derived from SimCYP simulator	[28,52]
Vspleen	$(6.516 * Weight\text{^}0.797)/1000$		[28,52]
Vgut	Male: $0.021 * (Weight - Vadipose * 0.92)/1.05$ Female: $0.027 * (Weight - Vadipose * 0.92)/1.05$		[28,52]
Vliver	$(1072.8 * (BSA) - 345.7)/1000$		[28,52]
Vbla	Male: $(((13.1 * Height + 18.05 * Weight - 480)/0.5723)/1000)/2$ Female: $(((35.5 * Height + 2.27 * Weight - 3382)/0.6178)/1000)/2$		[28,52]
Vblv	Male: $(((13.1 * Height + 18.05 * Weight - 480)/0.5723)/1000)/2$		[28,52]

	Female: $(((35.5 * Height + 2.27 * Weight - 3382)/0.6178)/1000)/2$		
Vrest	$Weight - Vblv - Vbla - Vliver - Vgut - Vspleen - Vskin - Vmuscle - Vkidney - Vheart - Vbone - Vadipose - Vlung - Vbrain$	Body density of 1 kg/L assumed	-
Brain Compartments:			
Vbrain total	$(1.449 - 3.62/BW)/1.04$		[28,52]
Vbrain blood	$0.05 * Vbraintotal$		[28,52]
Vccsf	Male: $Vbrainmale * 0.105 * 0.8$ Female: $Vbrainfemale * 0.092 * 0.8$		[28,52]
Vscsf	Male: $Vbrainmale * 0.105 * 0.2$ Female: $Vbrainfemale * 0.092 * 0.2$	Vscsf capped at 20% of the total csf	[28,52]
Vendothelial mass	$Vbrainmale * 0.005$		[28,52]
Vbrain mass	$Vbrain - Vbrainendo - Vbb - Vccsf - Vscsf$		[28,52]
Fluid flow rates (L/hr)			
Parameter	**Equation / Value**	**Notes**	**Reference**
Other organ Compartments:			
Qcarout	$BSA * 60 * (3 - 0.01 * (age - 20))$	Cardiac output * fractional tissue flow	[28,52]
Qlung	$Qcarout * 1$		[28,52]
Qadipose	Male: $Qcarout * 0.05$ Female: $Qcarout * 0.085$		[28,52]
Qbone	$Qcarout * 0.05$		[28,52]
Qheart	Male: $Qcarout * 0.04$ Female: $Qcarout * 0.05$		[28,52]
Qkidney	Male: $Qcarout * 0.19$ Female: $Qcarout * 0.17$		[28,52]
Qmuscle	Male: $Qcarout * 0.17$ Female: $Qcarout * 0.12$		[28,52]
Qskin	$Qcarout * 0.05$		[28,52]
Qspleen	Male: $Qcarout * 0.02$ Female: $Qcarout * 0.03$		[28,52]
Qgut	Male: $Qcarout * 0.15$ Female: $Qcarout * 0.17$		[28,52]
Qha	$Qcarout * 0.065$		[28,52]
Qliver	Male: $Qcarout * 0.235$ Female: $Qcarout * 0.265$		[28,52]
Qrestflow	Male: $Qcarout * 0.095$ Female: $Qcarout * 0.09$	Qcarout – organ flows	[28,52]
Brain Compartment:			
Qbrain	$Qcarout * 0.12$	Cardiac output * fractional tissue flow	[52,59]
Qproductionrate	0.021, CV (%): 10		[52,59]
Qbulk	$0.25 * Qproductionrate$, CV (%): 8	Assumed: Relative CSF flows (as part of Qcsfproduction rate)	[52,59]
Qssink	$0.38 * (0.75 * Qproductionrate + Qbulk)$, CV (%): 30		[52,59]
Qsout	$0.9 * Qssink$, CV (%): 100%		[52,59]
Qsin	$(Qssink + Qsout)$		[52,59]
Qcsink	$(0.75 * Qproductionrate + Qbulk - Qsin + Qsout)$		[52,59]
Tissue Composition (fraction)			

Parameter	**Rowdgers and Rowland**	**Poulin and Theil**	**Berezhkovskiy**	**Reference**
Adipose	EW = 0.141 IW = 0.039 NL = 0.79 NP = 0.002 AP = 0.4 AR = 0.037 LR = 0.068	FW = 0.18 NL = 0.79 NP = 0.002 pH = 7	FW = 0.18 NL = 0.79 NP = 0.002 pH = 7	[53,56,57]
Bone	EW = 0.098 IW = 0.341 NL = 0.074 NP = 0.0011 AP = 0.67 AR = 0.1 LR = 0.05	FW = 0.439 NL = 0.074 NP = 0.0011 pH = 7	FW = 0.439 NL = 0.074 NP = 0.0011 pH = 7	[53,56,57]
Gut	EW = 0.267 IW = 0.451 NL = 0.0487 NP = 0.0163 AP = 2.84 AR = 0.158 LR = 0.141	FW = 0.718 NL = 0.0487 NP = 0.0163 pH = 7	FW = 0.718 NL = 0.0487 NP = 0.0163 pH = 7	[53,56,57]
Heart	EW = 0.313 IW = 0.445 NL = 0.0115 NP = 0.0166 AP = 3.07 AR = 0.157 LR = 0.16	FW = 0.758 NL = 0.0115 NP = 0.0166 pH = 7	FW = 0.758 NL = 0.0115 NP = 0.0166 pH = 7	[53,56,57]
Kidney	EW = 0.283 IW = 0.50 NL = 0.0207 NP = 0.0162 AP = 2.48 AR = 0.13 LR = 0.137	FW = 0.783 NL = 0.0207 NP = 0.0162 pH = 7.2	FW = 0.783 NL = 0.0207 NP = 0.0162 pH = 7.2	[53,56,57]
Liver	EW = 0.165 IW = 0.586 NL = 0.0348 NP = 0.0252 AP = 5.09 AR = 0.086 LR = 0.161	FW = 0.751 NL = 0.0348 NP = 0.0252 pH = 7	FW = 0.751 NL = 0.0348 NP = 0.0252 pH = 7	[53,56,57]
Lung	EW = 0.348 IW = 0.463 NL = 0.003 NP = 0.009 AP = 0.5 AR = 0.212 LR = 0.168	FW = 0.811 NL = 0.003 NP = 0.009 pH = 6.7	FW = 0.811 NL = 0.003 NP = 0.009 pH = 6.7	[53,56,57]
Muscle	EW = 0.091 IW = 0.669 NL = 0.0238 NP = 0.0072 AP = 2.49 AR = 0.034 LR = 0.059	FW = 0.76 NL = 0.0238 NP = 0.0072 pH = 7	FW = 0.76 NL = 0.0238 NP = 0.0072 pH = 7	[53,56,57]
Skin	EW = 0.623 IW = 0.0947 NL = 0.0284	FW = 0.7177 NL = 0.0284 NP = 0.0111	FW = 0.7177 NL = 0.0284 NP = 0.0111	[53,56,57]

	NP = 0.0111 AP = 1.32 AR = 0.277 LR = 0.096	pH = 7	pH = 7	
Spleen	EW = 0.208 IW = 0.579 NL = 0.0201 NP = 0.0198 AP = 2.81 AR = 0.097 LR = 0.207	FW = 0.787 NL = 0.0201 NP = 0.0198 pH = 7	FW = 0.787 NL = 0.0201 NP = 0.0198 pH = 7	[53,56,57]
Plasma	EW = 0.945 IW = 0 NL = 0.0035 NP = 0.0023 AP = 0.04 AR = NA LR = NA	FW = 0.945 NL = 0.0035 NP = 0.0023 pH = 7.4	FW = 0.945 NL = 0.0035 NP = 0.0023 pH = 7.4	[53,56,57]

EW: Extracellular Water, **IW:** Intracellular Water, **NL:** Neutral Lipids, **NP:** Neutral Phospholipids, **AP:** Acidic Phospholipids, **AR:** Albumin ratio, **LR:** lipoprotein ratio

Table S3. Physicochemical and Drug Specific Parameters for Acetaminophen, Oxycodone, Lacosamide, Ibuprofen & Levetiracetam.

Drug		Acetaminophen		Oxycodone		Lacosamide		Ibuprofen		Levetiracetam	
		Parameter	**Ref.**	**Parameter**	**Ref.**	**Parameter**	**Ref.**	**Parameter**	**Ref.**	**Parameter**	**Ref.**
Molecular weight (g/mol)		151.2	[28,59]	315.4	[31]	250.3	[31]	206.285	[92]	170.21	[93]
Log P		0.46	[28,59]	1.2	[31]	0.3	[31]	3.97	[92]	-0.67	[94]
Pka		9.38	[28,59]	8.53	[31]	12.4	[31]	4.91	[92]	15.74	[94]
Compound Type		Monoprotic acid	[28,59]	Monoprotic base	[31]	Neutral	[31]	Monoprotic acid	[92]	Neutral	[58]
Kp Method		Rodgers & Rowland [59]		Poulin & Theil		Rodgers & Rowland [31]		Berezhkovskiy		Rodgers & Rowland	
BCS Classification		III	[95]	I or III	[96]	I	[97]	II	[98]	I	[99]
CL - Human (L/hr)		22.8 CV(%):35.4	[59]	49.2 CV (%):30	[31]	2.13 CV (%):30	[31]	3.88 CV (%):30	[38]	3.96 CV(%):42	[93]
CL-scalar		-	-	0.8	#	0.8	#	-	-	-	-
BP	Rats	1	[100]	1.3	[8]	1	[42]	0.55	[101]	1.05	[34]
	Humans	1.09	[28,59]	1.3	[31]	1	[31]	1	[31]	0.85	[102]
Fupl	Rats	0.88	[100]	0.56	[8]	0.96	[42]	0.04	[103]	0.9-1	[104]
	Humans	0.855	[28,59]	0.59	[31]	1	[31]	(0.00567+ 0.0107)/2	[105,106]	0.95	[104]
Fubm	Rats	0.83	[107]	0.39	[8]	0.899	[108]	0.3117 - Assumed same as human		0.98	[46]
	Humans	0.747	[107]	0.45	[8]	0.899 - Assumed same as rats		0.3117	[109]	0.98	γ
Fuccsf		1	*	1	*	1	*	1	*	1	*
Fuscsf		1	**	1	**	1	**	1	**	1	**
P_{BBB} (cm/sec)		11.11×10^{-6}	#	26.79×10^{-6}	#	18.8×10^{-6}	#	35.138×10^{-6}	#	1.5295×10^{-6}	#
PS_B	Rats (ml/min)	0.179	#	0.434	#	0.305	#	0.569	#	0.02456	#
	Humans (L/hr)	5.98	#	14.47	#	10.15	#	18.97	#	0.8187	#
PS_E (Brain-CCSF)	Rats (ml/min)	80	##	80	##	80	##	80	##	80	##
	Humans (L/hr)	300	##	300	##	300	##	300	##	300	##
PSc (BCSFB)	Rats (ml/min)	0.0179	[59], β	0.0434	[59], β	0.0305	[59], β	0.0569	[59], β	0.002456	[59], β
	Humans (L/hr)	0.598	[59], β	1.447	[59], β	1.015	[59], β	1.897	[59], β	0.08187	[59], β

PS_B, PS_C and PS_E: permeability surface area products between brain blood and brain mass, brain blood and cranial CSF respectively; **Fubm, Fupl, Fuccsf, Fuscsf**: Fraction unbound in brain mass, plasma, cranial CSF and spinal CSF respectively; **CL:** clearance; **BP:** Blood to plasma ratio; **BCS:** Biopharmaceutical classification system

γ Assumed (low conc. of protein than plasma)
* Assumed (low conc. of protein in Cranial-CSF);
** Assumed (low conc. of protein in Spinal-CSF);
# Optimized using Rat PBPK Model / Human PBPK Model,
Assumed to be no barrier
β Assumed to be 1/10th of PS_B.