pharmaceutics

Supplementary Materials: Impact of CNS Diseases on Drug Delivery to Brain Extracellular and Intracellular Target Sites in Human: A "WHAT-IF" Simulation Study

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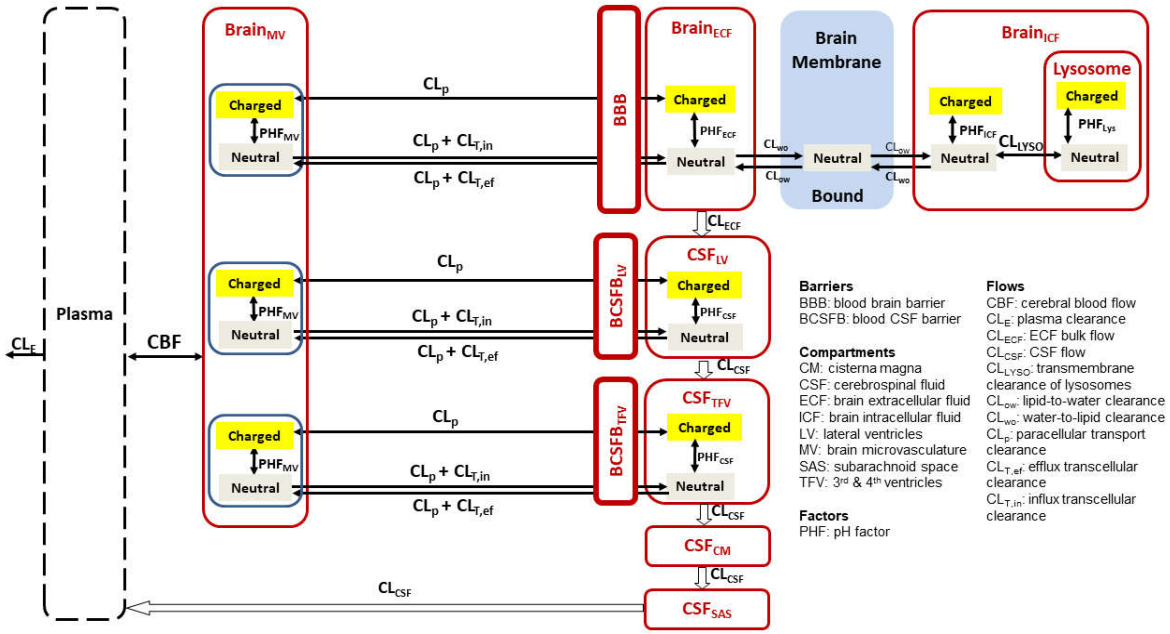


Figure S1. Detailed mathematical structure of LeiCNS-PK3.0.

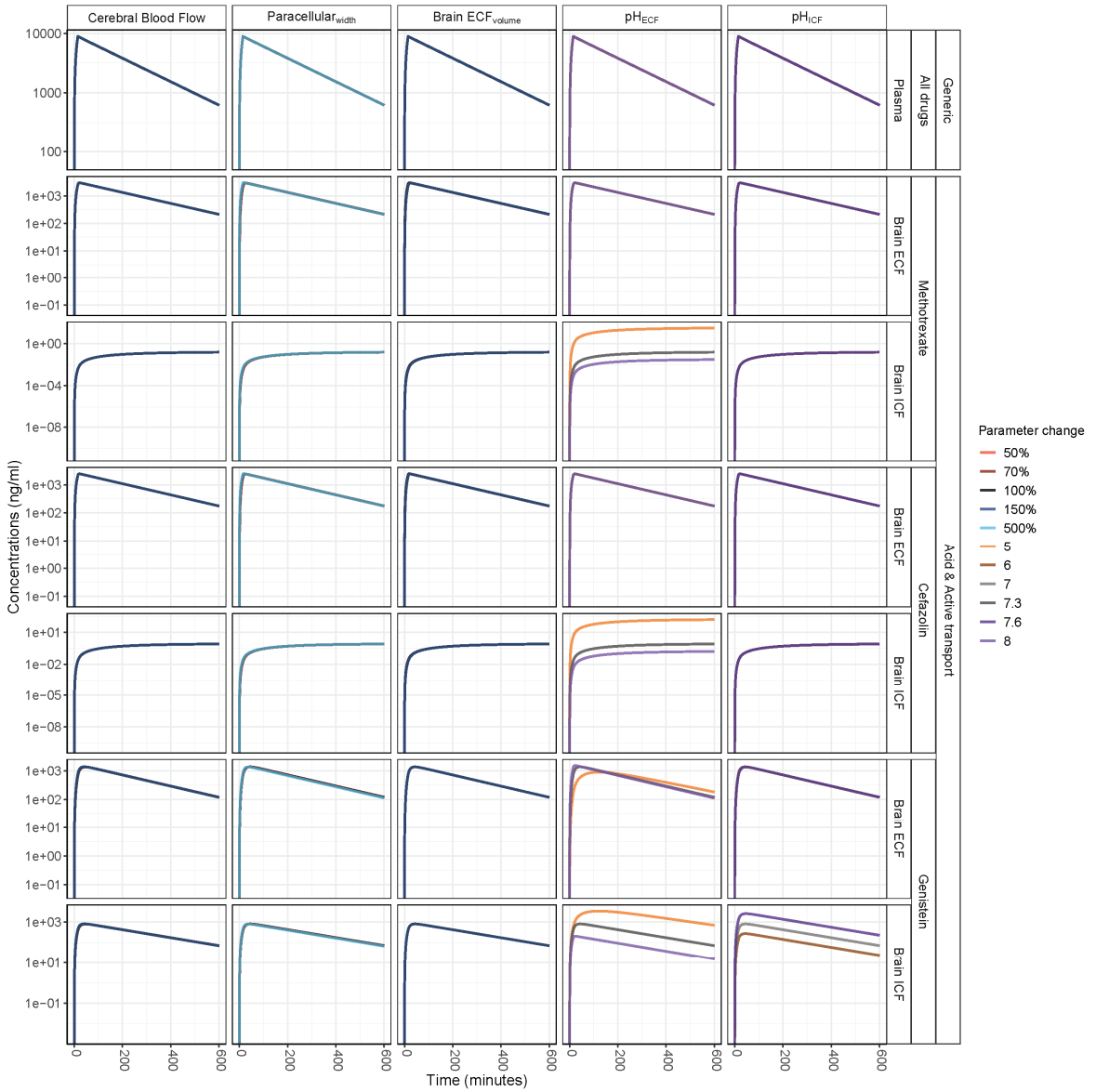
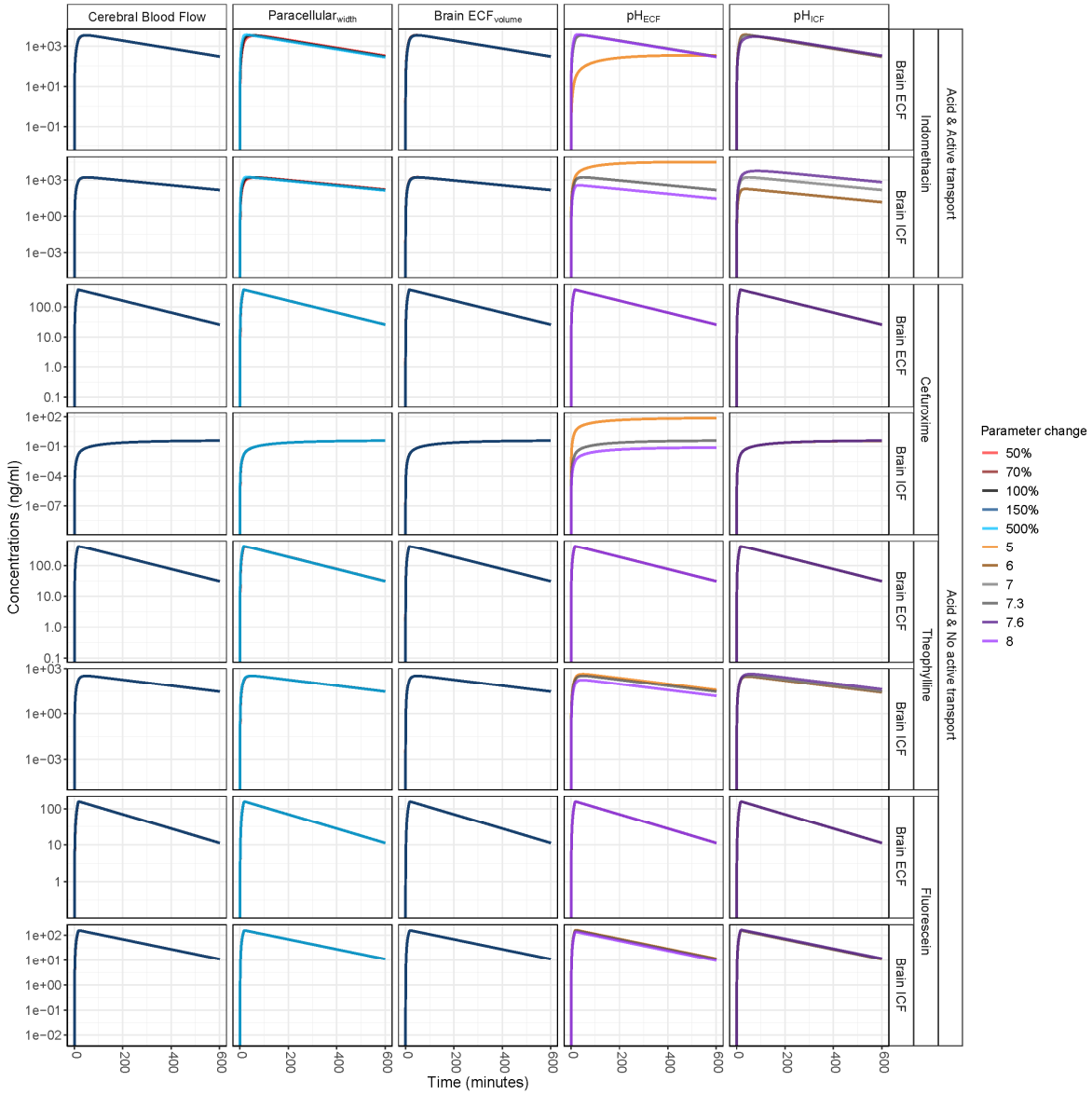


Figure S2. Simulated concentration-time profiles of all 46 drugs at physiological and pathophysiological values of CBF, para$_{radius}$ (paracellular$_{width}$), brain$_{ECF}$ volume, pH$_{ECF}$, and pH$_{ICF}$.

Figure S2. Continued



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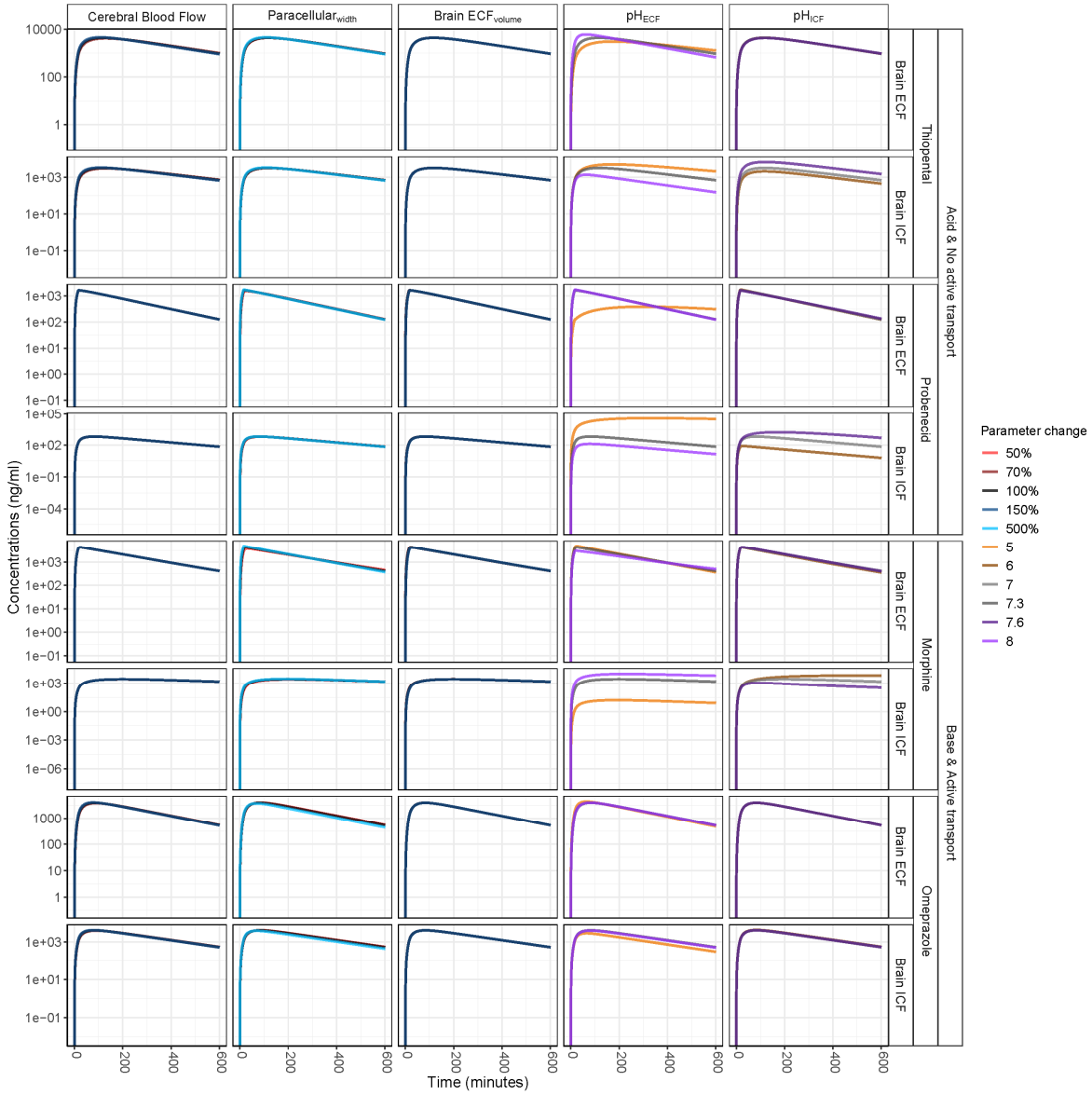

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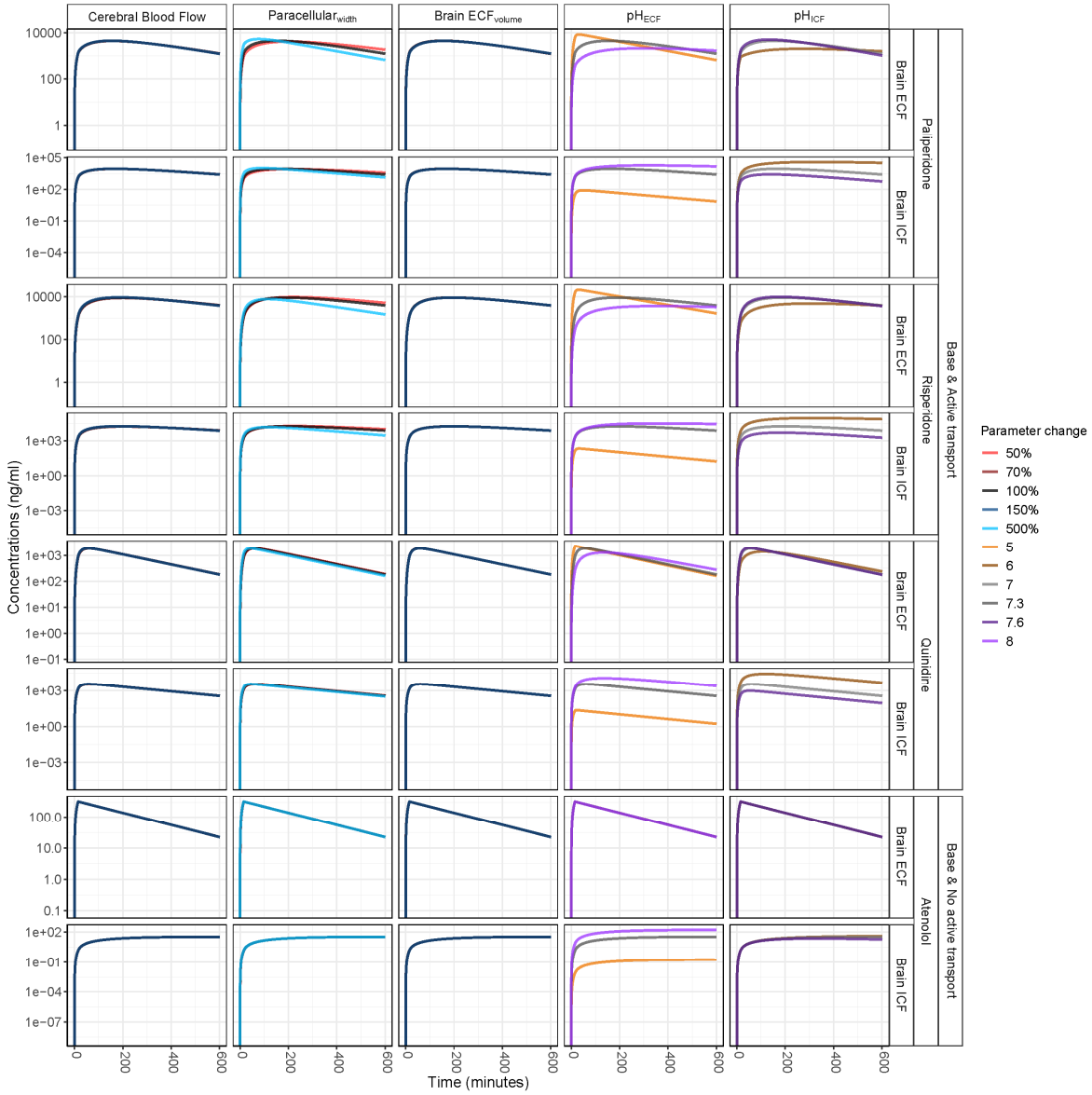

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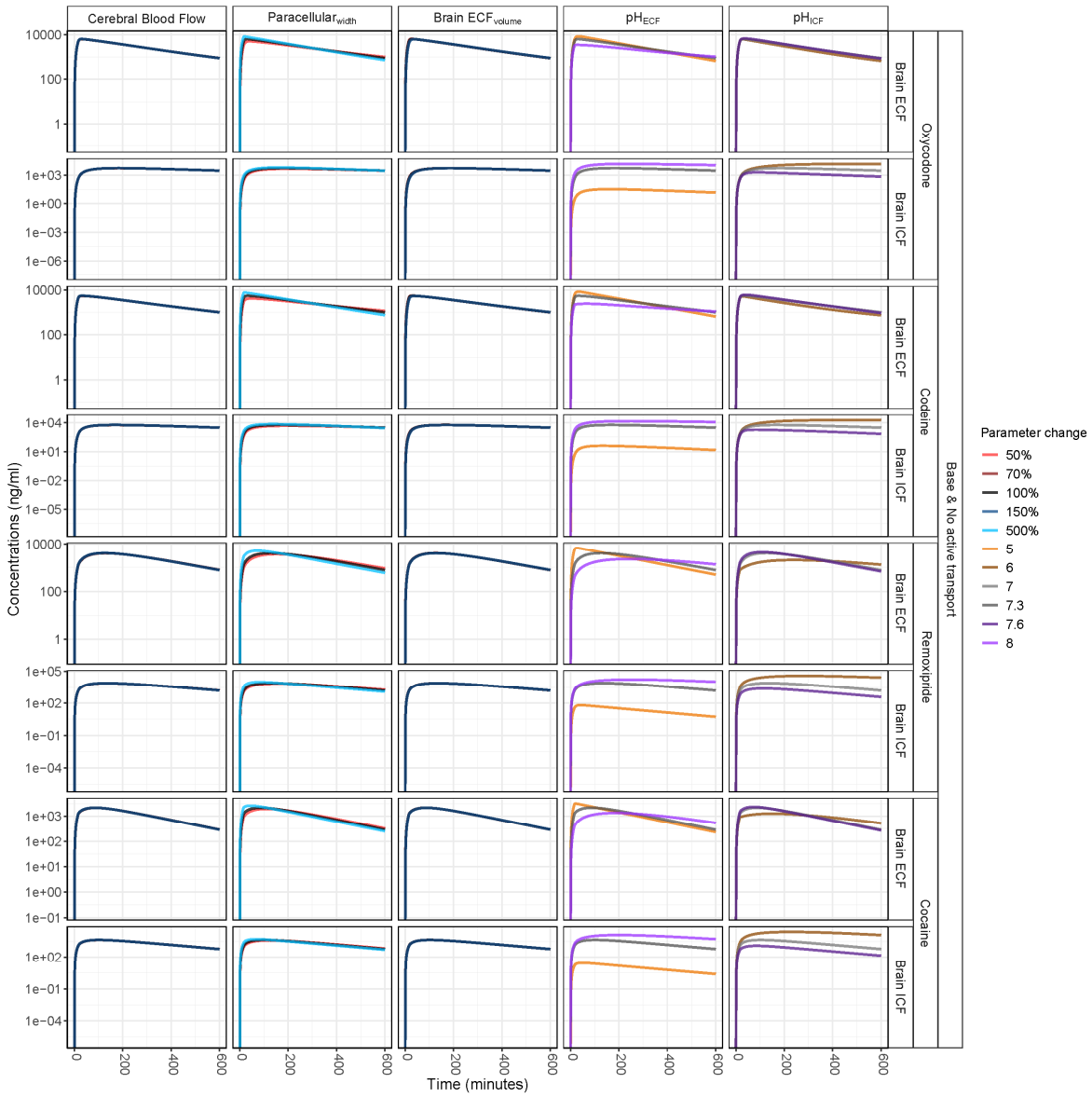

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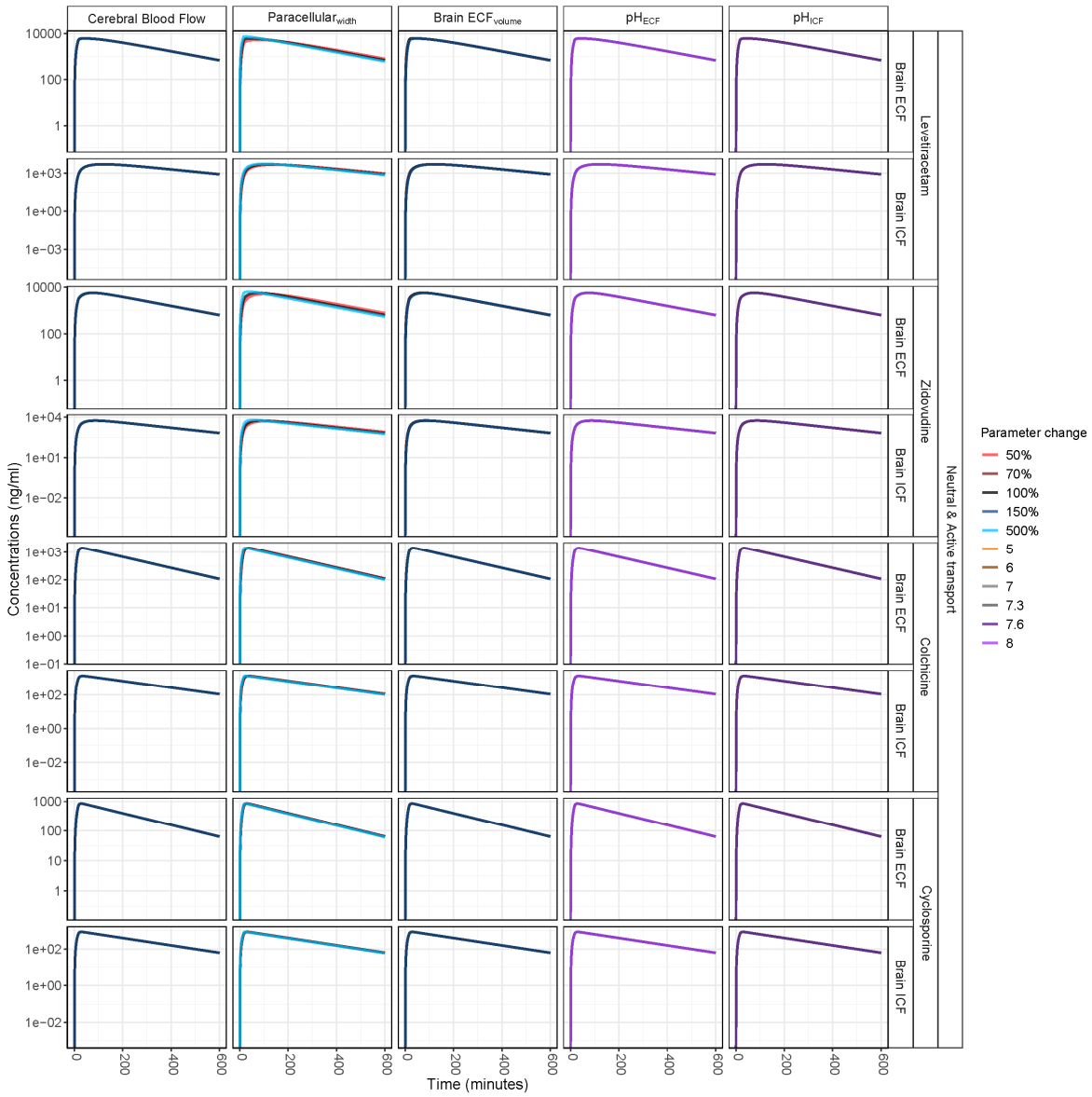

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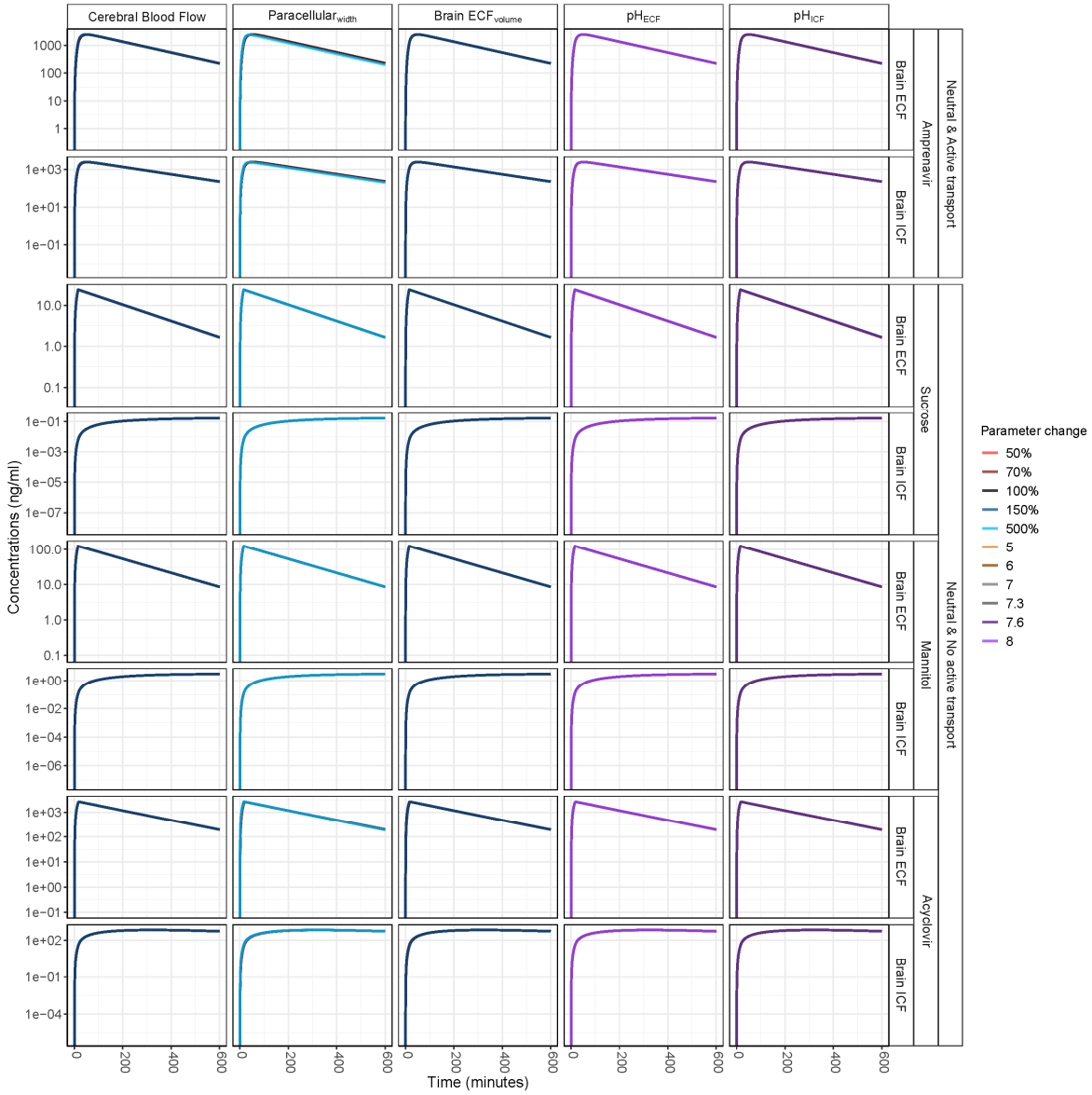

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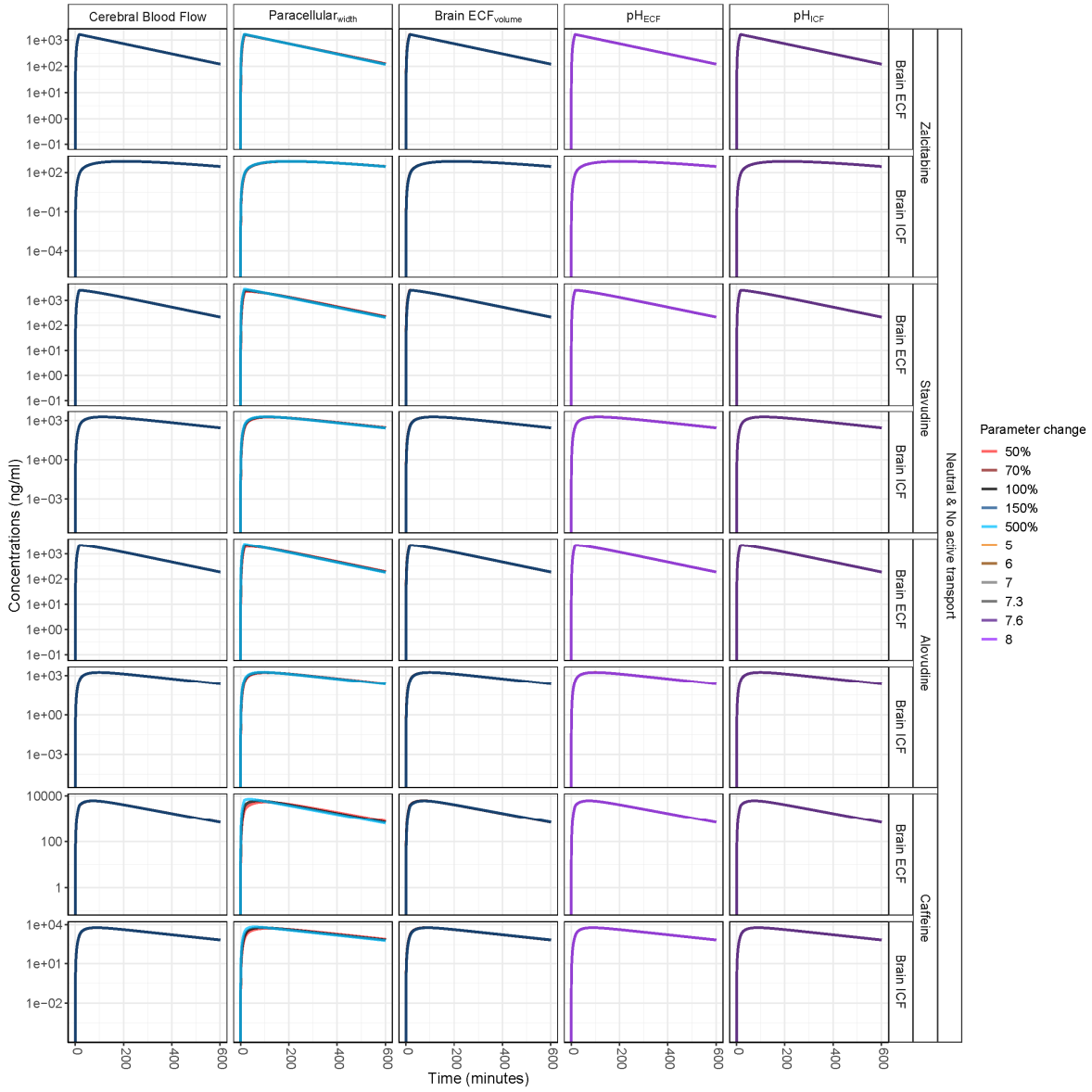

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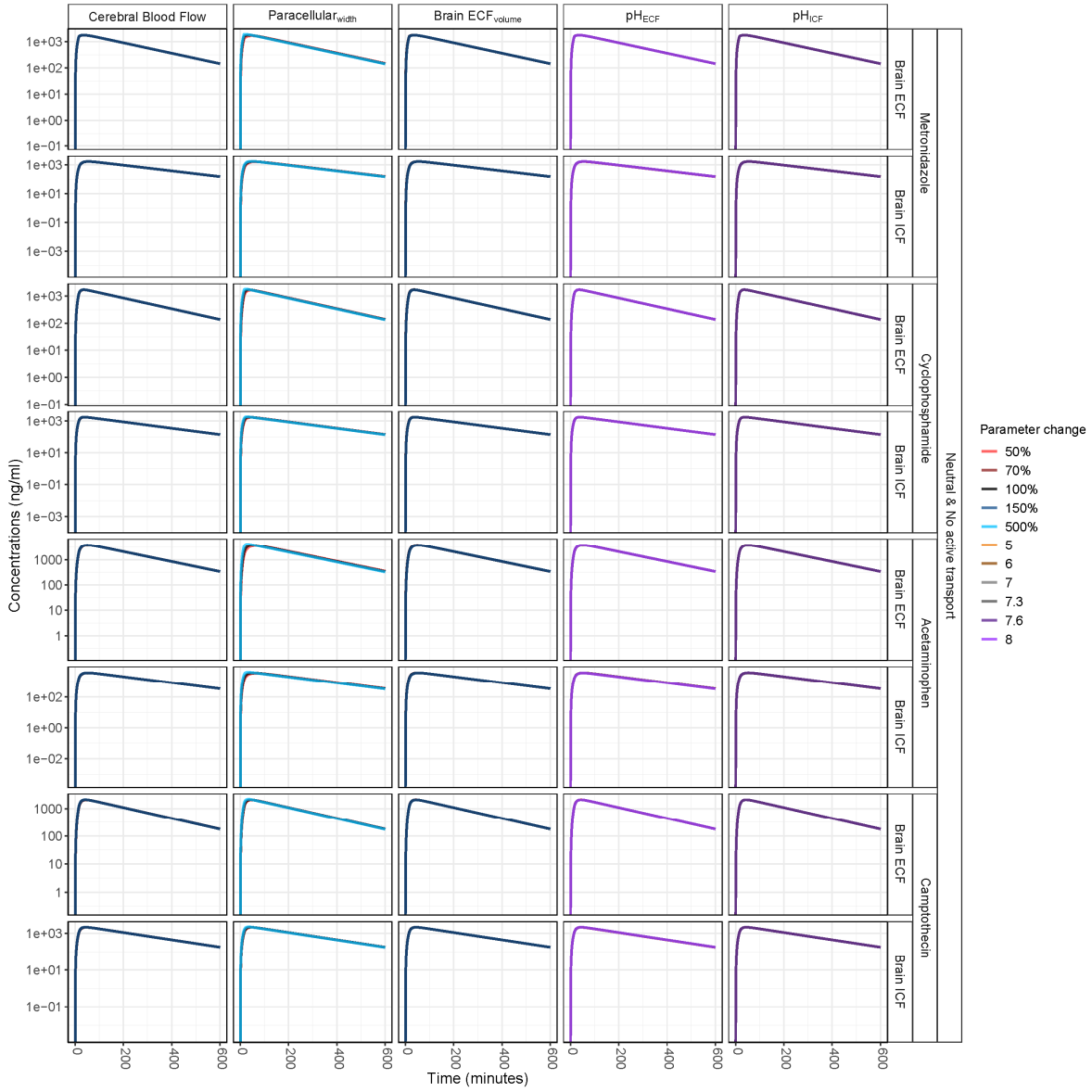

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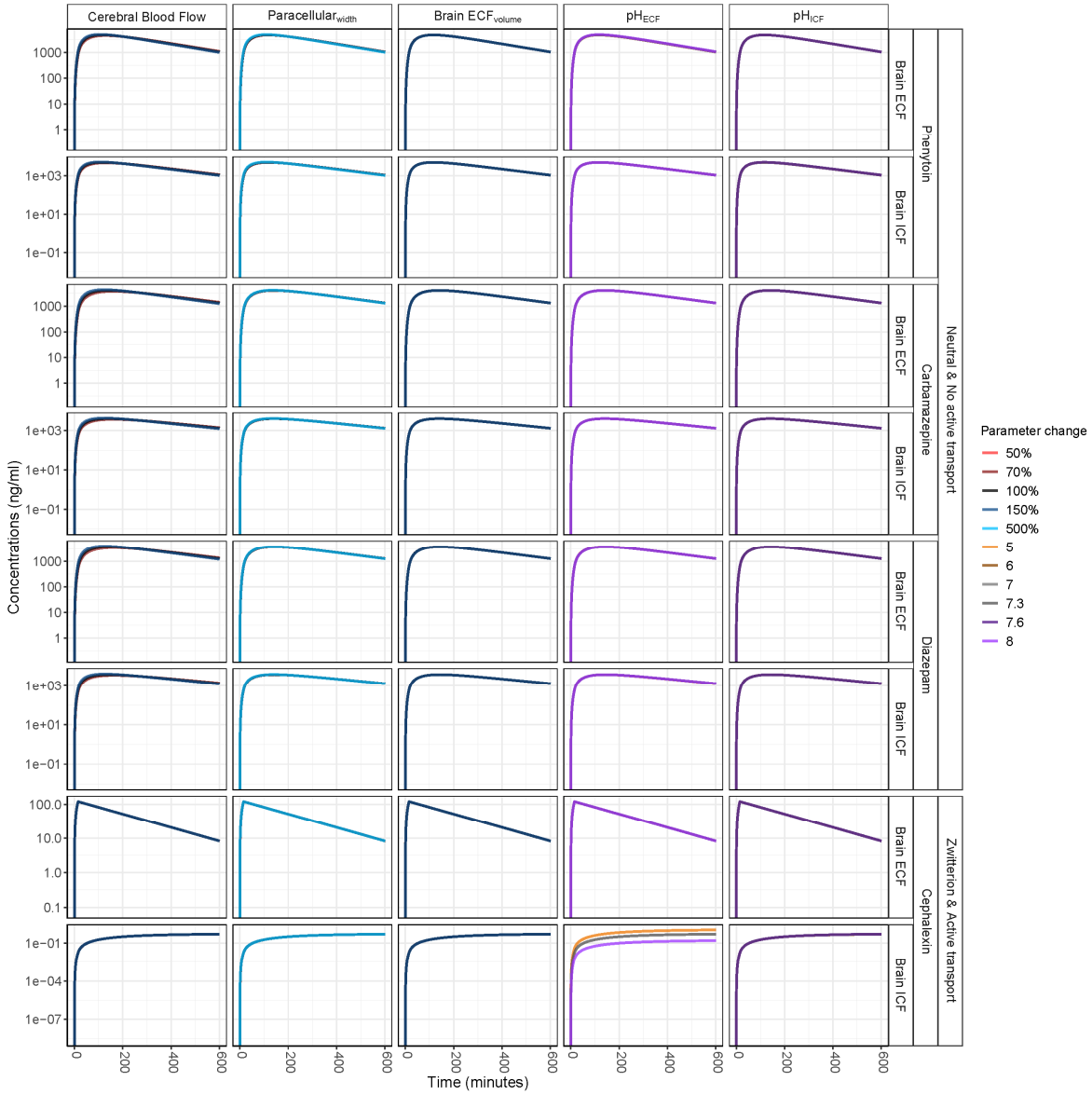

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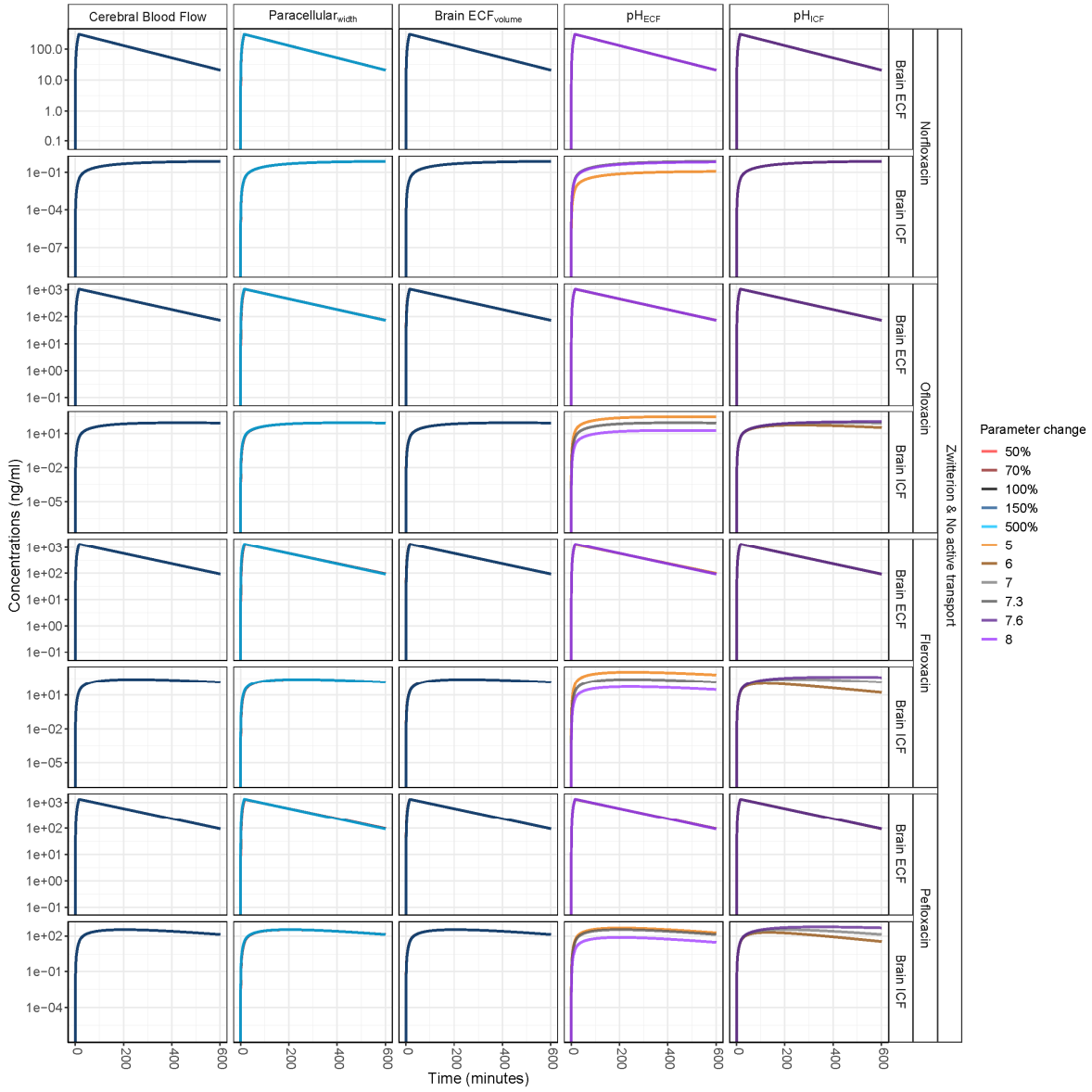

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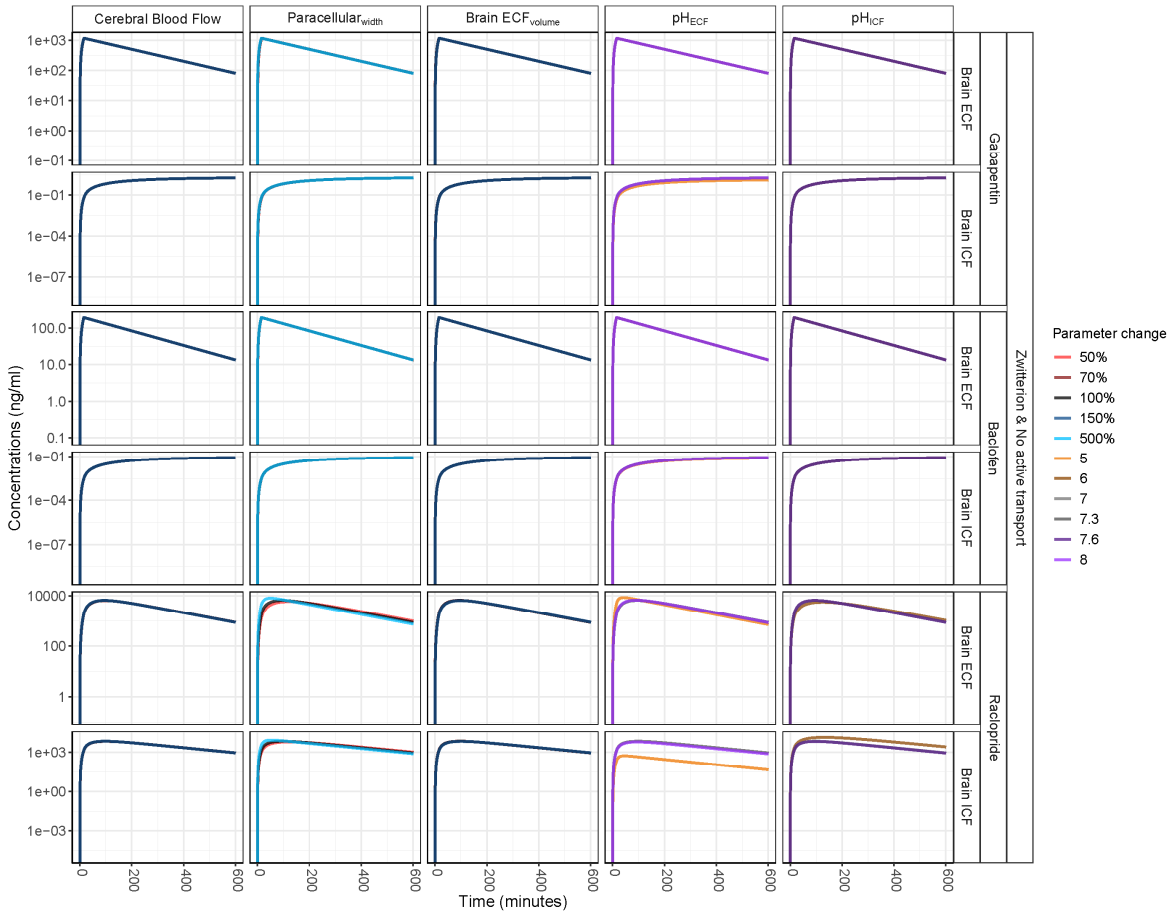


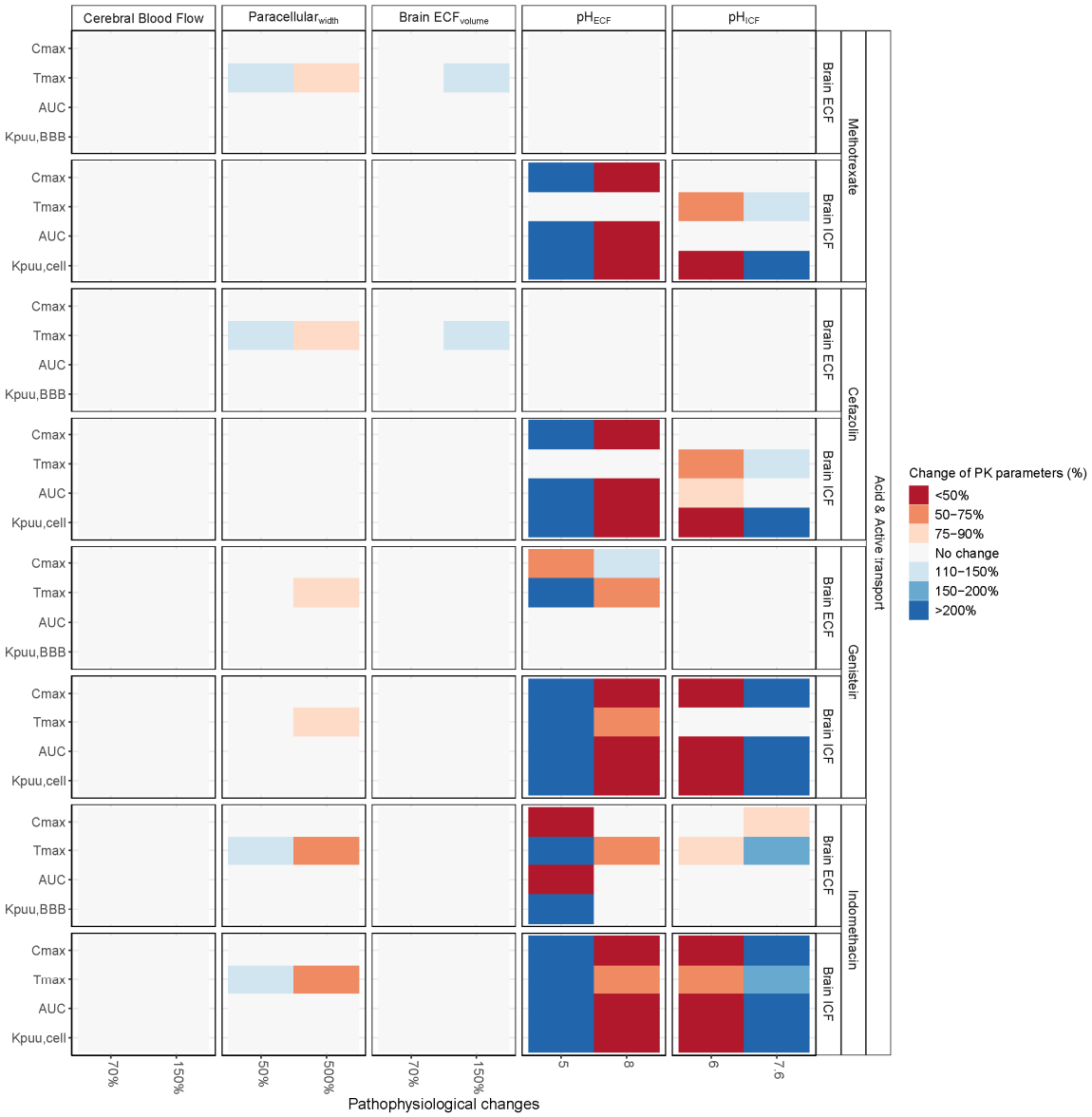
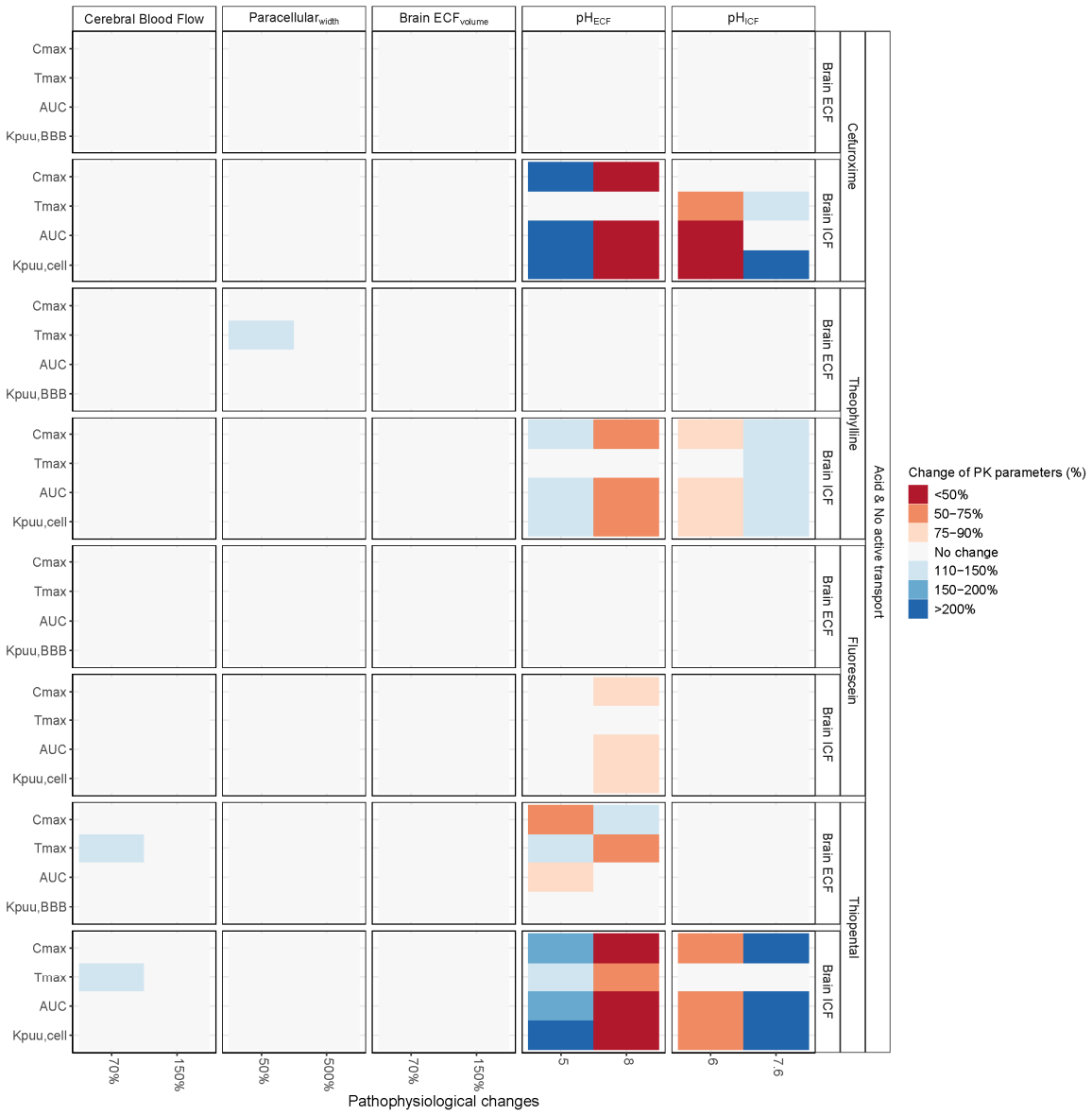


Figure S3. Heatmaps summarizing the effect of pathophysiological changes of CBF, para$_{radius}$ (paracellular$_{width}$), brain$_{ECF}$ volume, pH$_{ECF}$, and pH$_{ICF}$ on brain pharmacokinetics parameters: C_{max}, T_{max}, AUC, $Kp_{uu,ECF}$, and $Kp_{uu,cell}$.

Figure S3. (Continued)



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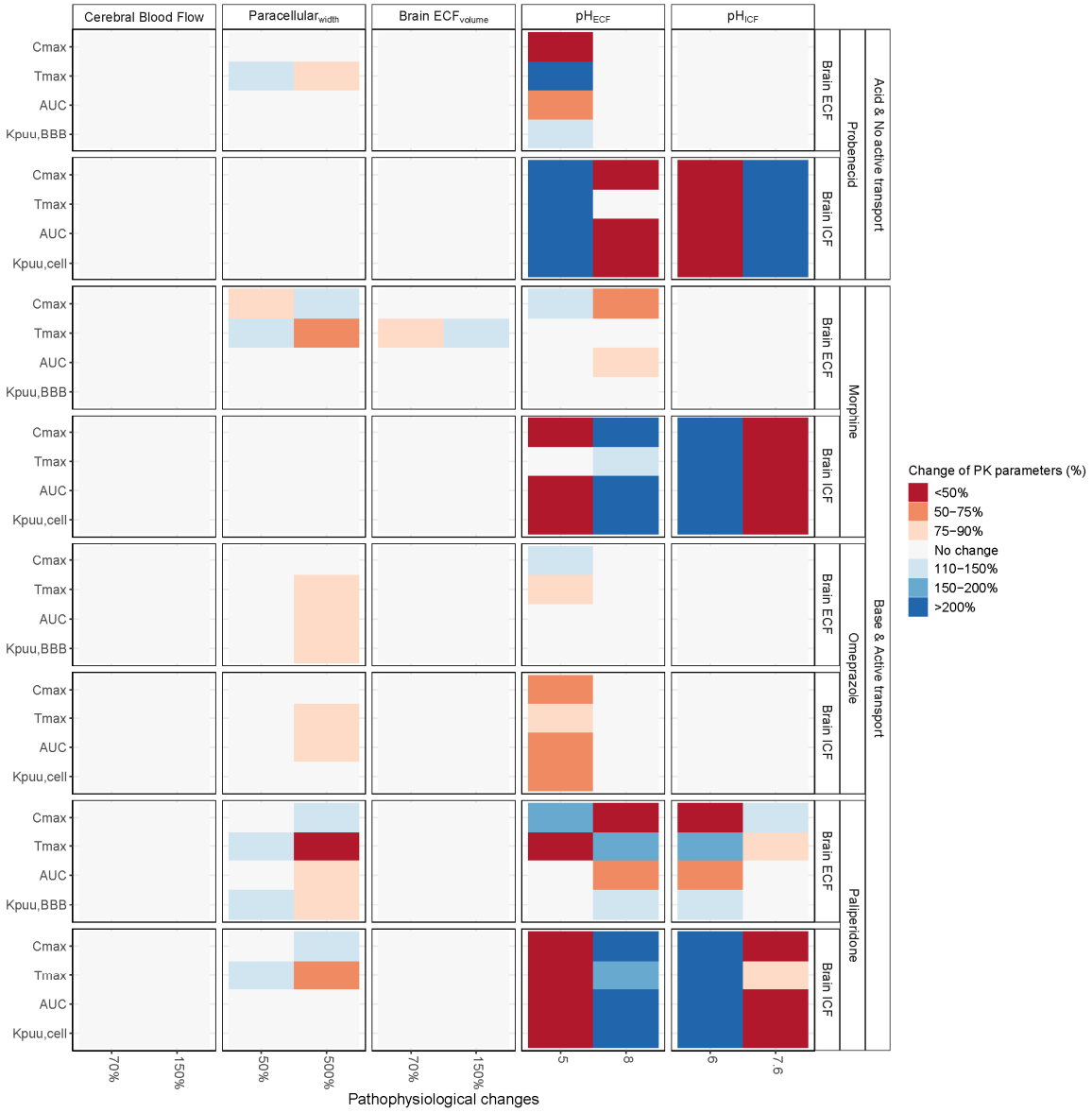

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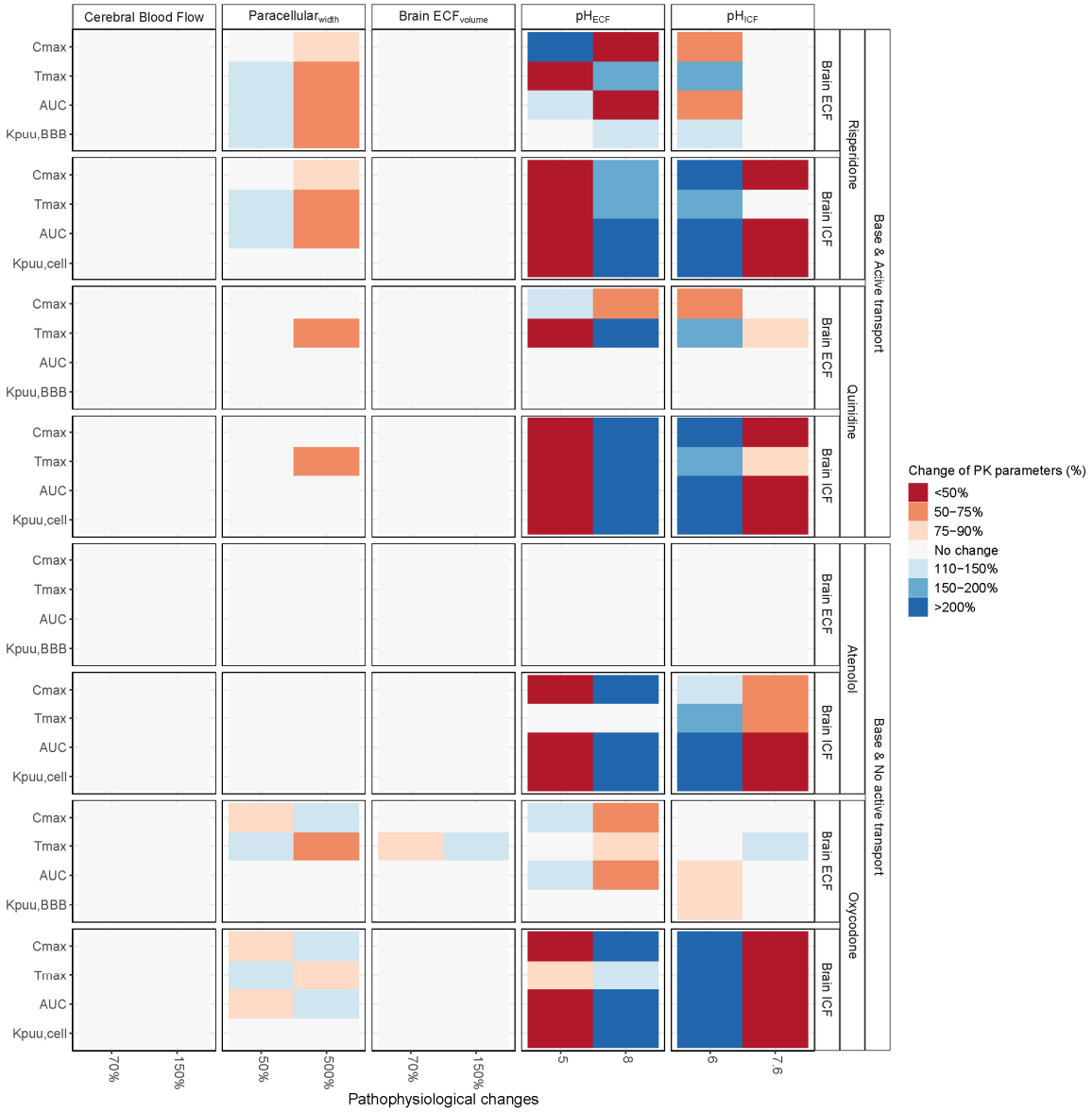

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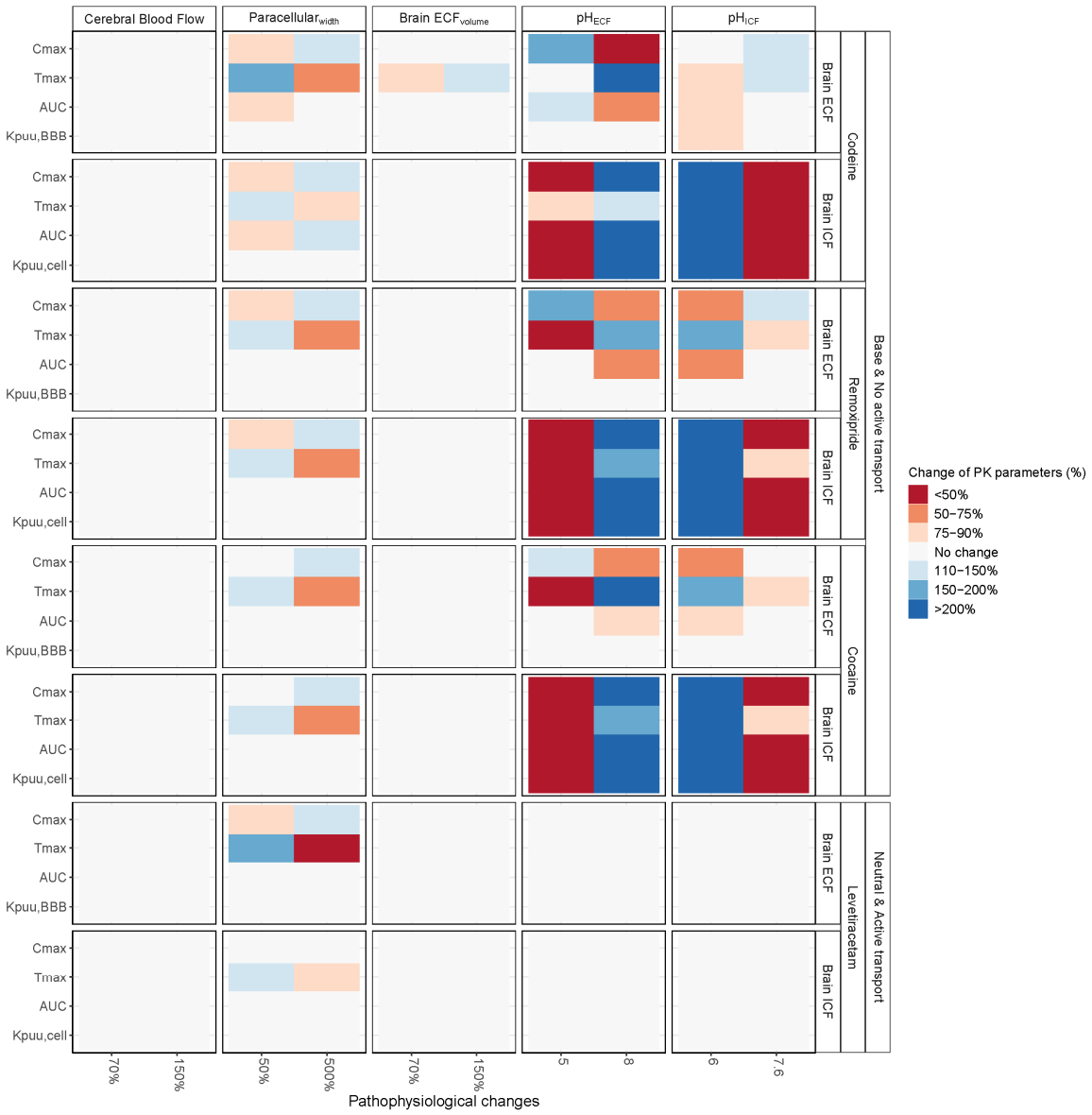

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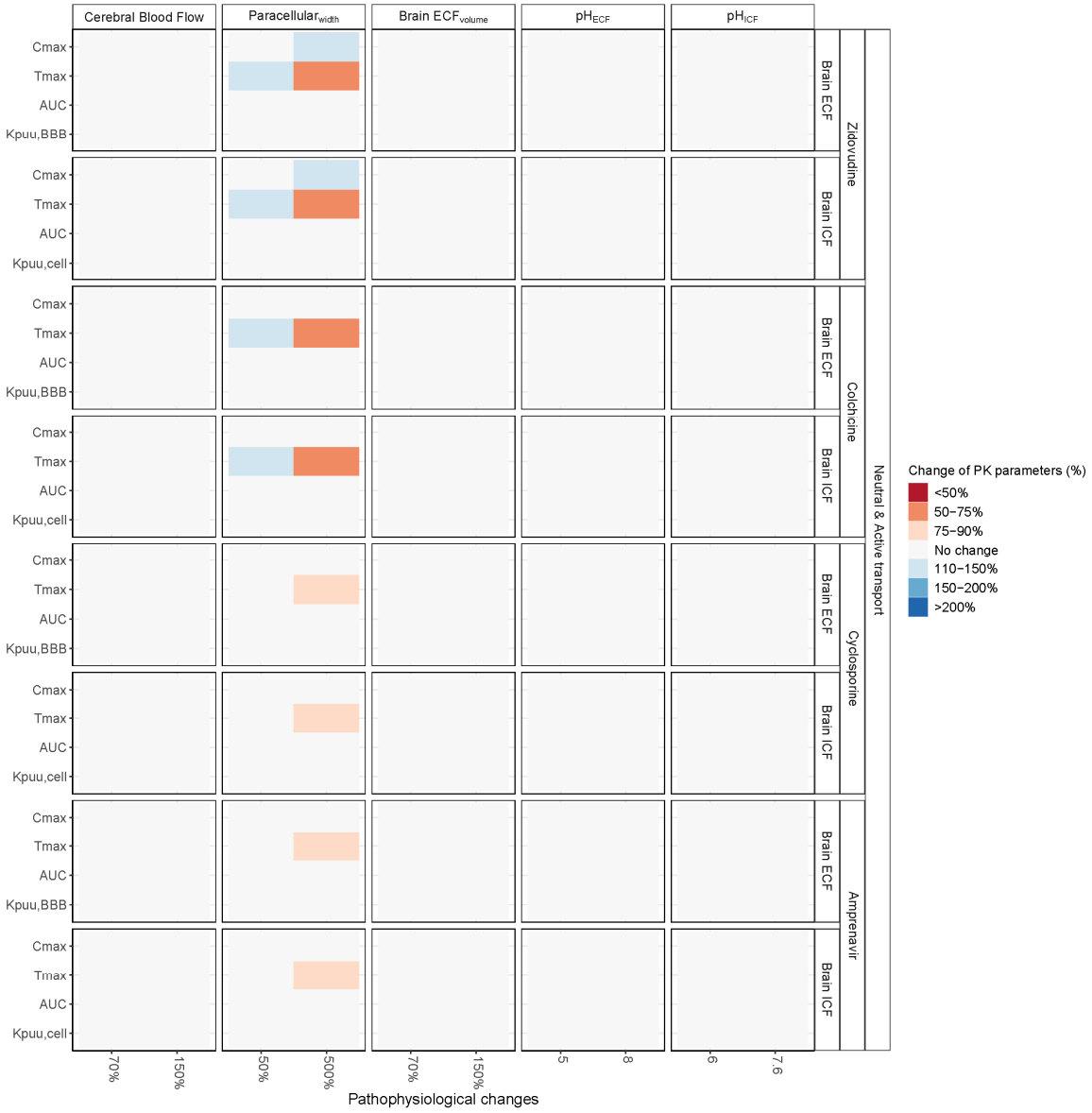

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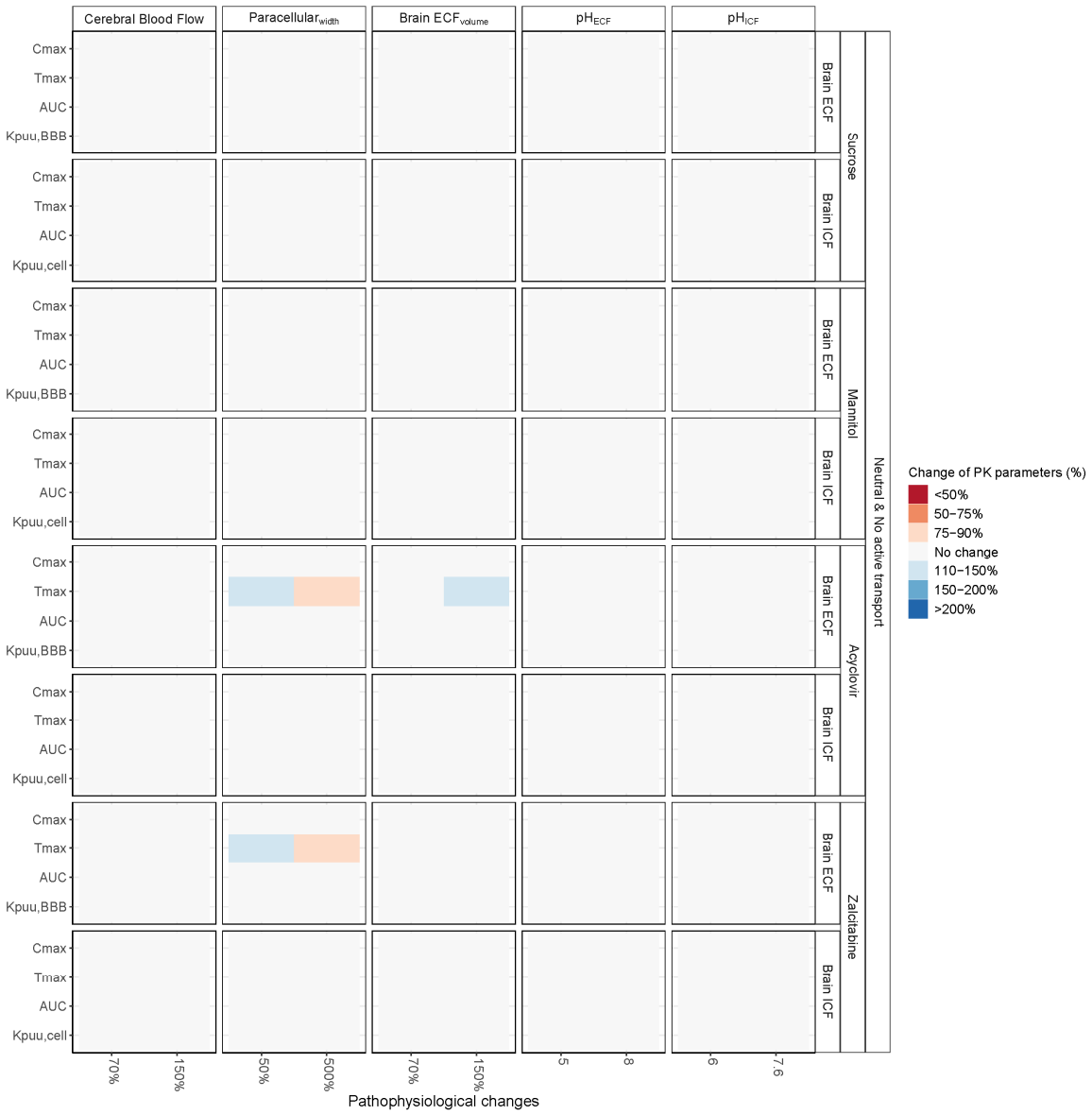

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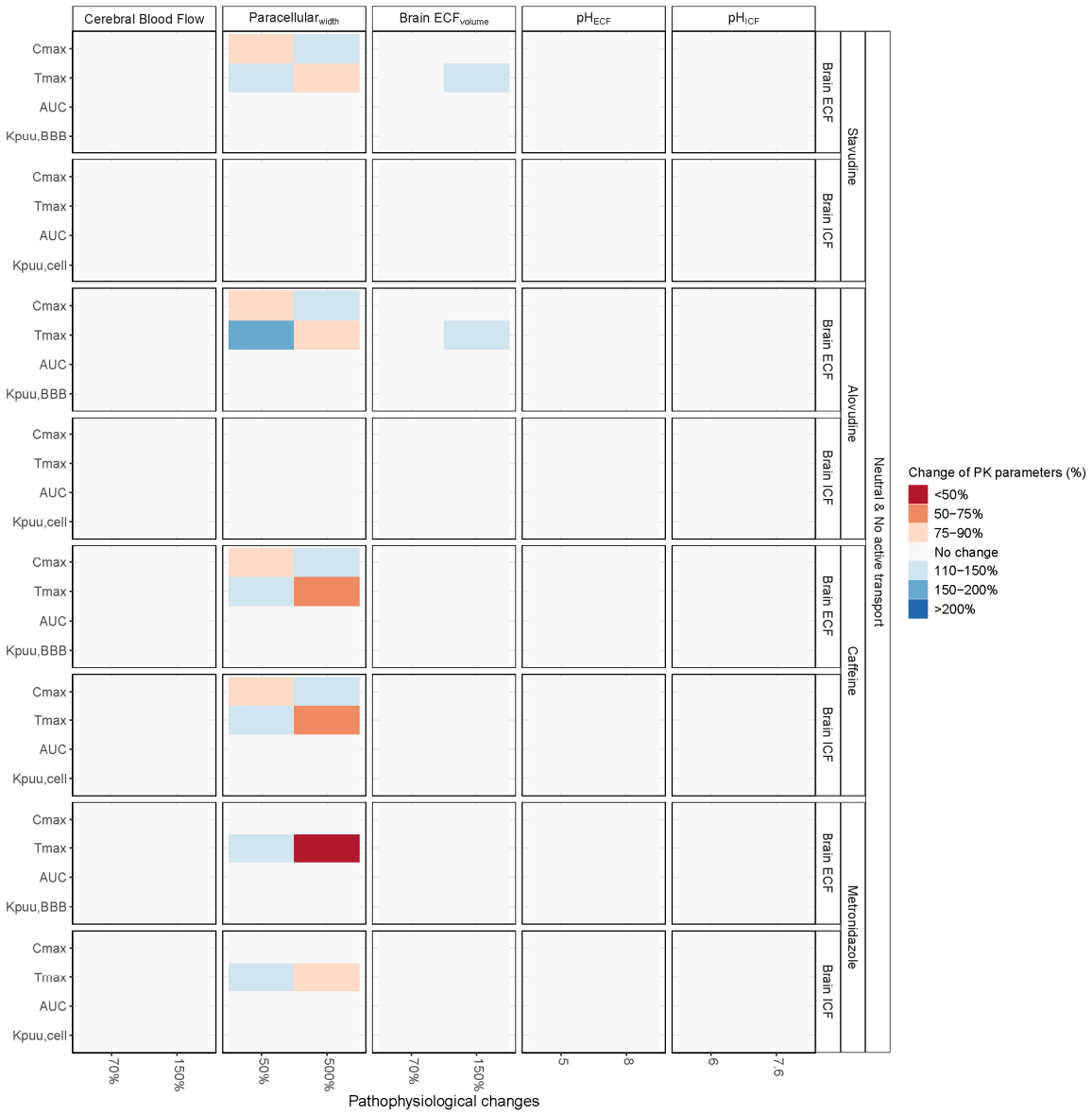

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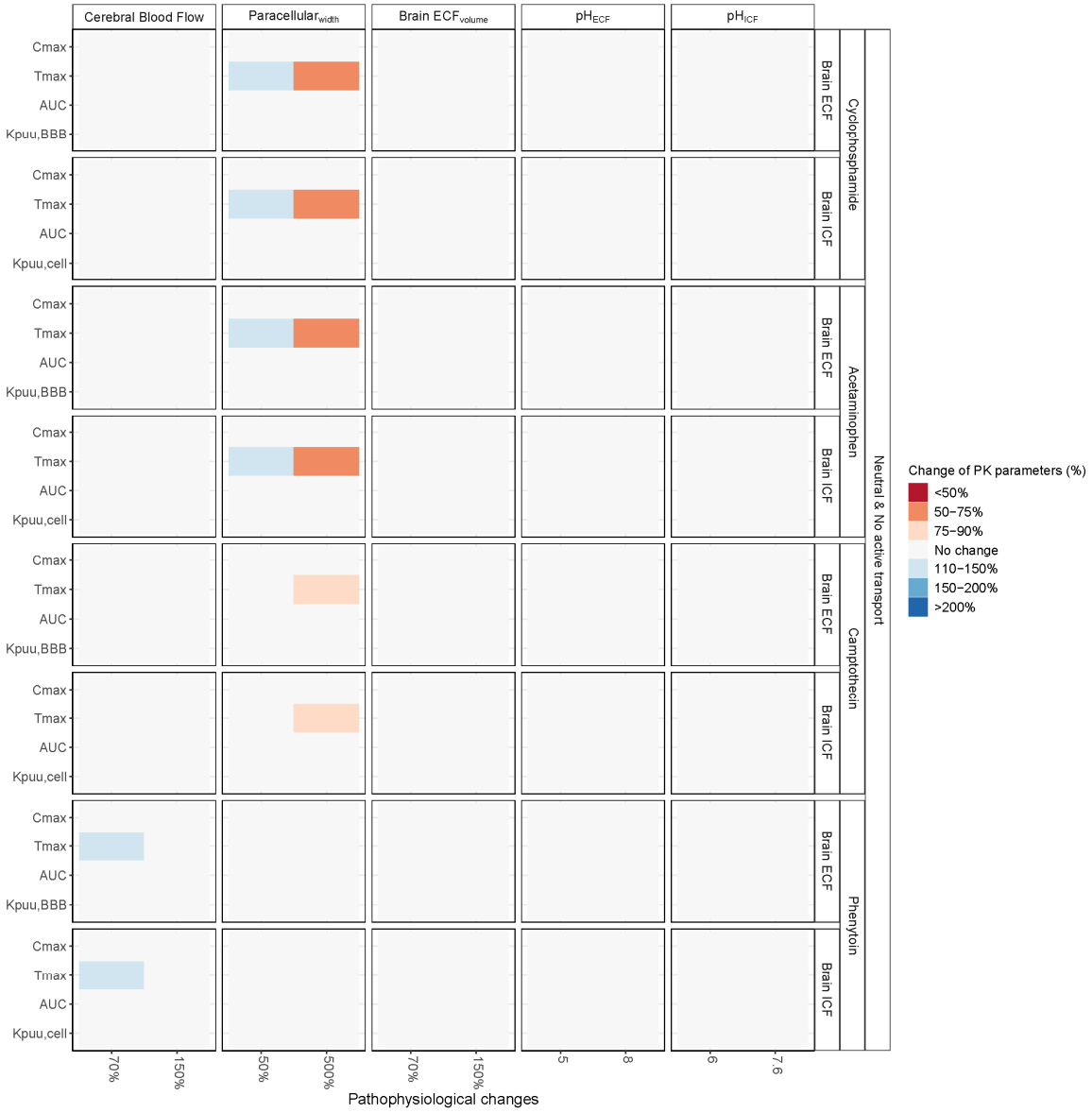

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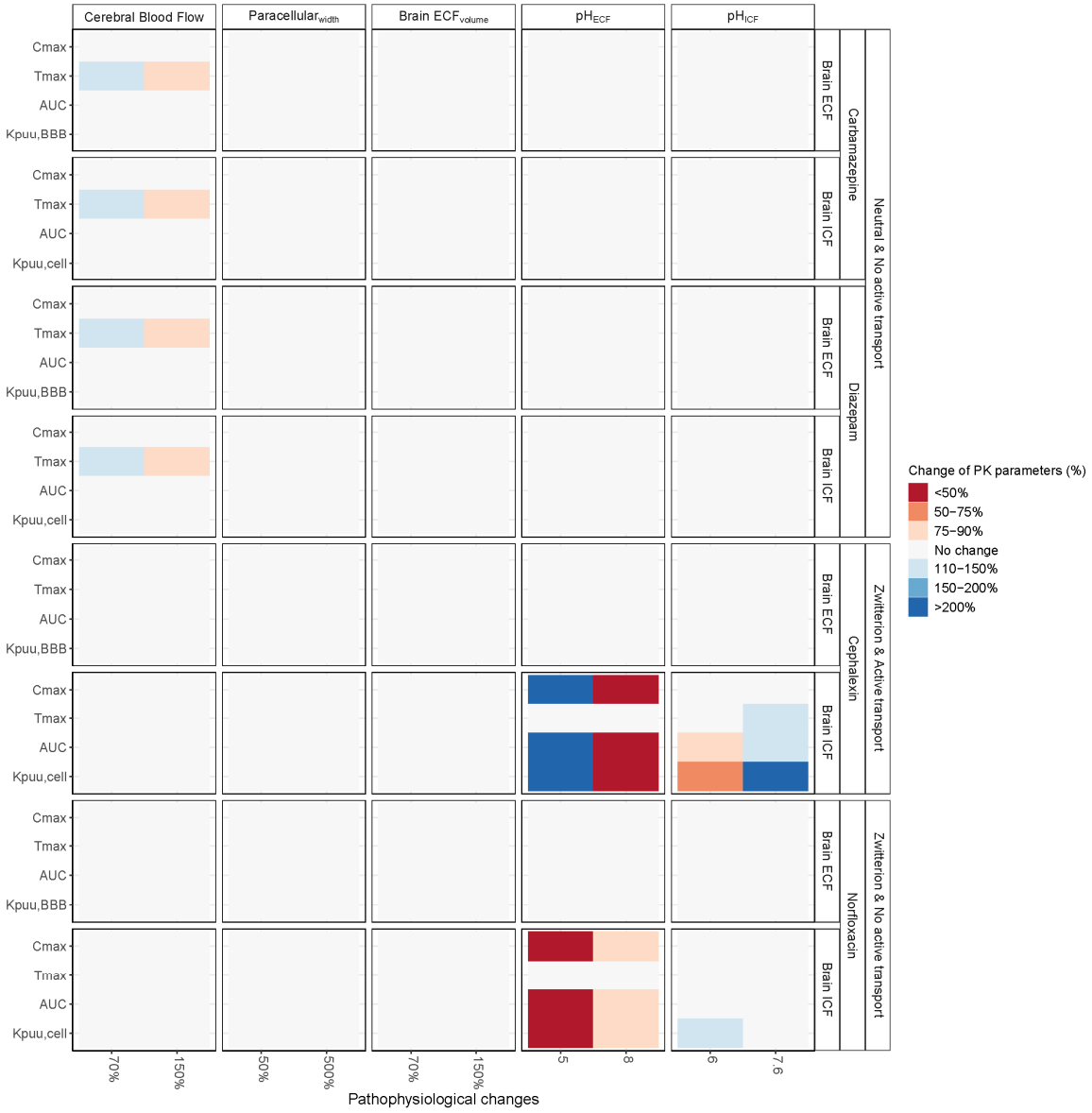

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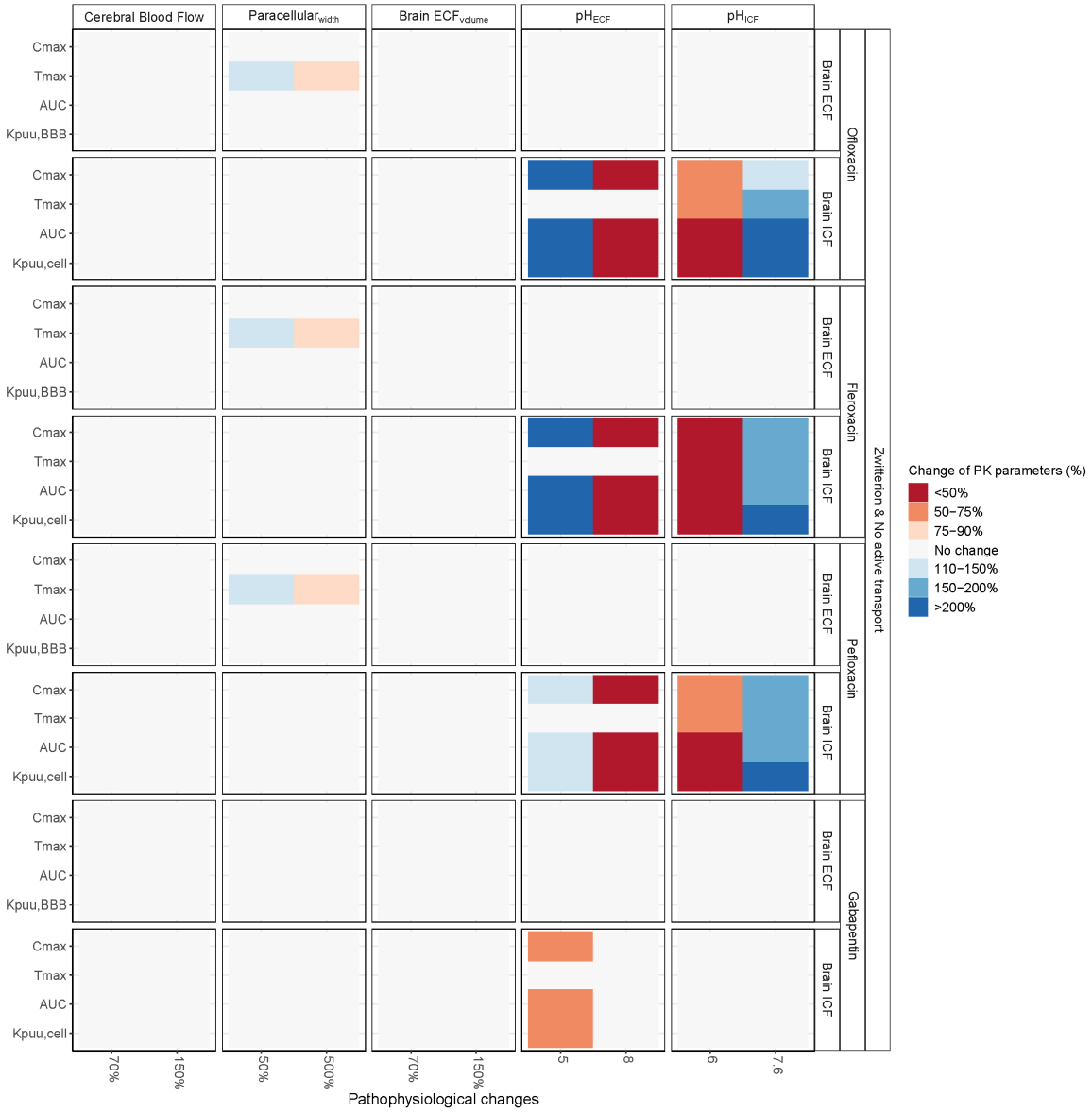

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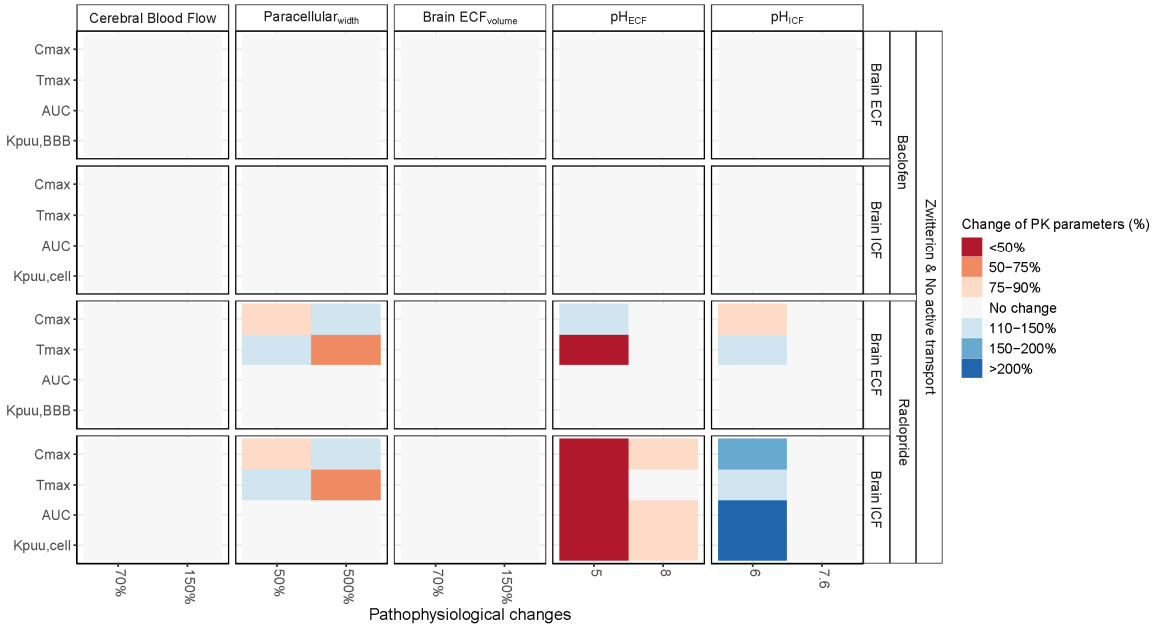

Table S1. Physicochemical properties, active transporter affinities, and BBB transport clearances of all 46 drugs.

Drug	Mwt	logP	Drug Ion Class	pk_a	pk_b	$Kp_{uu,ECF}$	$Kp_{uu,LV}$	$Kp_{uu,CM}$	BCRP	p-gp	OAT3	MRP4	CL_p	$CL_{T,ef}$	$CL_{T,in}$
Acetaminophen	151.2	0.91	Neutral	9.46	−4.4	0.51 [1]	0.51 [1]	0.51 [1]	-	-	-	-	54.93	91.03	19.64
Acyclovir	225.2	−1.76	Neutral	11.98	3.02	0.3 [2]	0.3 [2]	0.3 [2]	-	-	-	-	45.71	106.64	0.06
Alovudine	244.2	−0.6	Neutral	10.11	−3	0.29 [2]	0.29 [2]	0.29 [2]	-	-	-	-	44.04	110.19	0.76
Amprenavir	505.6	1.85	Neutral	13.61	2.39	0.076 [2]	0.076 [2]	0.076 [2]	-	X	-	-	31.49	517.39	151.18
Atenolol	266.3	0.16	Base	14.08	9.67	0.037 [1]	0.037 [1]	0.037 [1]	-	-	-	-	42.31	1101.56	0.02
Baclofen	213.7	1.3	Zwitterion	3.89	9.79	0.022 [2]	0.022 [2]	0.022 [2]	-	-	-	-	46.83	2081.76	<0.01
Caffeine	194.2	−0.07	Neutral	NA	−0.92	0.96 [2]	0.96 [2]	0.96 [2]	X	-	-	-	48.94	4.28	2.38
Camptothecin	348.4	1.74	Neutral	11.71	3.07	0.27 [2]	0.27 [2]	0.27 [2]	-	-	-	-	37.39	542.15	119.17
Carbamazepine	236.3	2.77	Neutral	15.96	−3.8	1.02 [2]	1.02 [2]	1.02 [2]	-	-	-	-	44.71	1105.03	1128.96
Cefazolin	454.5	−0.58	Acid	3.03	0.26	0.06 [2]	0.06 [2]	0.06 [2]	-	-	X	X	33.07	83.64	<0.01
Cefuroxime	424.4	−0.16	Acid	3.15	−1.1	0.042 [2]	0.042 [2]	0.042 [2]	-	-	-	-	34.13	778.38	<0.01
Cephalexin	347.4	0.65	Zwitterion	3.26	7.23	0.015 [2]	0.015 [2]	0.015 [2]	-	-	X	-	37.43	2735.53	<0.01
Cocaine	303.4	2.3	Base	NA	8.85	0.37 [2]	0.37 [2]	0.37 [2]	-	-	-	-	39.85	104.66	13.71
Codeine	299.4	1.39	Base	13.78	9.19	1 [2]	1 [2]	1 [2]	-	-	-	-	40.09	0.71	0.89
Colchicine	399.4	1.07	Neutral	15.06	−0.038	0.04 [2]	0.04 [2]	0.04 [2]	-	X	-	-	35.10	336.40	27.99
Cyclophosphamide	261.1	0.8	Neutral	12.78	−0.57	0.216 [3]	0.216 [3]	0.216 [3]	-	-	-	-	42.70	227.04	15.61
Cyclosporine	1202.6	1.4	Neutral	11.83	−2.4	0.023 [4]	0.023 [4]	0.023 [4]	-	X	-	-	21.12	743.86	57.14

Mwt: molecular weight (g/mol); logP: octanol-water partition coefficient; pK_a: acid dissociation coefficient; pK_b: base dissociation coefficient; $CL_{T,ef}$: transcellulr efflux clearance (in ml/min) at BBB; $CL_{T,in}$: transcellulr influx clearance (in ml/min) at BBB; CL_P: paracellular passive BBB clearance (in ml/min); X: active transporter substrate; p-gp: P-glycoprotein, MRP4: multi-drug-resistant protein-4, BCRP: breast cancer resistance protein, OAT3: organic anionic transporter 3. $CL_{T,ef}$, $CL_{T,in}$, and CL_P are calculated as described in [12,13].

[1] Saleh et al. Submitted. British Journal of Clinical Pharmacology. 2020. [6]

[2] Summerfield et al. The Journal of Pharmacology and Experimental Therapeutics. 2007. [7]

[3] Campagne et al. Journal of Pharmacy and Pharmaceutical Sciences. 2019. [8]

[4] Legg et al. Journal of Pharmacy and Pharmacology. 1987, Brophy et al. Journal of Neurotrauma. 2013, Zaghloul et al. Journal of Clinical Pharmacology. 1987. [9–11]

Drug	Mwt	logP	Drug Ion Class	pk_a	pk_b	$Kp_{uu,ECF}$	$Kp_{uu,LV}$	$Kp_{uu,CM}$	BCRP	p-gp	OAT3	MRP4	CL_p	$CL_{T,ef}$	$CL_{T,in}$
Diazepam	284.7	2.82	Neutral	NA	2.92	0.98 [2]	0.98 [2]	0.98 [2]	-	-	-	-	41.03	1256.12	1231.14
Fleroxacin	369.3	0.24	Zwitterion	5.44	6.06	0.15 [2]	0.15 [2]	0.15 [2]	-	-	-	-	36.39	206.32	0.05
Fluorescein	332.3	2.64	Acid	8.72	−3.7	0.018 [2]	0.018 [2]	0.018 [2]	-	-	-	-	38.21	46314.68	796.16
Gabapentin	171.2	1.25	Zwitterion	4.63	9.91	0.13 [2]	0.13 [2]	0.13 [2]	-	-	-	-	51.86	346.86	<0.01
Genistein	270.2	3.04	Acid	6.55	−5.3	0.04 [2]	0.04 [2]	0.04 [2]	X	X	-	-	42.03	1557.22	245.20
Indomethacin	357.8	4.27	Acid	3.79	−2.9	0.11 [1]	0.17 [1]	0.17 [1]	-	-	X	X	36.93	58.41	6.95
Levetiracetam	170.2	−0.64	Neutral	16.09	−1.6	0.31 [2]	0.31 [2]	0.31 [2]	-	X	-	X	52.01	3.73	0.69
Mannitol	182.2	−3.1	Neutral	12.59	−3	0.014 [2]	0.014 [2]	0.014 [2]	-	-	-	-	50.41	3549.99	<0.01
Methotrexate	454.4	−1.85	Acid	3.41	2.81	0.018 [1]	0.0066 [1]	0.0024 [1]	X	X	X	X	33.08	63.57	<0.01
Metronidazole	171.2	−0.02	Neutral	15.44	3.09	0.23 [2]	0.23 [2]	0.23 [2]	-	-	-	-	51.88	184.96	2.65
Morphine	285.3	0.87	Base	10.26	9.12	0.23 [1]	0.23 [1]	0.23 [1]	-	X	-	-	40.99	30.21	0.34
Norfloxacin	319.3	−1.03	Zwitterion	5.77	8. 68	0.034 [2]	0.034 [2]	0.034 [2]	-	-	-	-	38.92	1105.46	<0.01
Ofloxacin	361.4	−0.39	Zwitterion	5.45	6.2	0.12 [2]	0.12 [2]	0.12 [2]	-	-	-	-	36.76	269.45	0.01
Omeprazole	345.4	2.23	Base	9.29	4.77	0.15 [2]	0.15 [2]	0.15 [2]	X	X	-	-	37.53	538.80	338.64
Oxycodone	315.4	0.7	Base	13.57	8.77	1.03 [1]	0.65 [1]	0.65 [1]	-	-	-	-	39.14	0.41	1.82
Paliperidone	426.5	2.3	Base	13.74	8.76	0.5 [1]	0.5 [1]	0.5 [1]	-	X	-	-	34.06	14.68	16.73
Pefloxacin	333.4	0.27	Zwitterion	5.66	6.47	0.15 [2]	0.15 [2]	0.15 [2]	-	-	-	-	38.15	216.50	0.08
Phenytoin	252.3	2.47	Neutral	9.47	−9	1 [1]	1 [1]	1 [1]	-	-	-	-	43.38	573.78	572.79
Probenecid	285.4	3.21	Acid	3.53	NA	0.2 [2]	0.2 [2]	0.2 [2]	-	-	-	-	40.99	165.65	0.39
Quinidine	324.4	3.44	Base	13.89	9.05	0.0674 [5]	0.0678 [5]	0.0678 [5]	-	X	X	-	38.63	500.77	103.01
Raclopride	347.2	3.19	Zwitterion	6.26	8.47	1.1 [1]	1.1 [1]	1.1 [1]	-	-	-	-	37.44	14.50	19.96
Remoxipride	371.3	2.1	Base	13.06	8.4	0.8 [1]	0.8 [1]	0.8 [1]	-	-	-	-	36.30	38.33	23.60
Risperidone	410.5	3.27	Base	NA	8.76	0.97 [1]	0.97 [1]	0.97 [1]	-	X	-	-	34.66	30.81	136.24

[5] Nagaya et al. Drug Metabolism and Pharmacokinetic. 2016. [12]

Drug	Mwt	logP	Drug Ion Class	pk_a	pk_b	$Kp_{uu,ECF}$	$Kp_{uu,LV}$	$Kp_{uu,CM}$	BCRP	p-gp	OAT3	MRP4	CL_p	$CL_{T,ef}$	$CL_{T,in}$
Stavudine	224.2	−0.72	Neutral	9.95	−3	0.33 [2]	0.33 [2]	0.33 [2]	-	-	-	-	45.80	94.53	0.58
Sucrose	342.3	−3.7	Neutral	11.84	−3	0.0027 [2]	0.0027 [2]	0.0027 [2]	-	-	-	-	37.69	13921.70	<0.01
Theophylline	180.2	−0.02	Acid	7.82	−0.78	0.05 [2]	0.05 [2]	0.05 [2]	-	-	-	-	50.66	1000.80	1.92
Thiopental	242.3	2.85	Acid	7.2	−3	0.9 [2]	0.9 [2]	0.9 [2]	-	-	-	-	44.19	569.06	508.22
Zalcitabine	211.2	−1.3	Neutral	14.67	0.18	0.19 [2]	0.19 [2]	0.19 [2]	-	-	-	-	47.08	201.37	0.17
Zidovudine	267.2	0.05	Neutral	9.96	−3	0.15 [2]	0.15 [2]	0.15 [2]	X	X	X	X	42.24	9.15	3.08

Table S2. Mean protein expression levels [1] (in fmol/μg total protein) of relevant transporters at the BBB.

	Human	References	Rat	References	Human:rat
p-gp	4.21	[1–3]	19.28	[4,5]	0.22
MRP4	0.25	[2,3]	1.74	[4,5]	0.15
BCRP	5.50	[1–3]	4.95	[5]	1.11
OAT3	0.27	[1]	2.13	[5]	0.13

[1] Experimentally-measured Kp_{uu} values from rats were used to account for active transport at the blood-brain barrier. These were translated to predict human BBB active transport using the difference in expression between rats and humans of the four main transporters (p-gp, BCRP, MRP4, OAT3) at the BBB. Information on drug affinities to the four transporters were available from Drugbank database and were manually checked. This translation procedure is described in more details in [13]. Transporters functionality were assumed the same between rats and humans.

References

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