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Evaluating the Impact of Estimated Partition Coefficients by Different Methods Using a Unified PBPK Model

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Acknowledgements

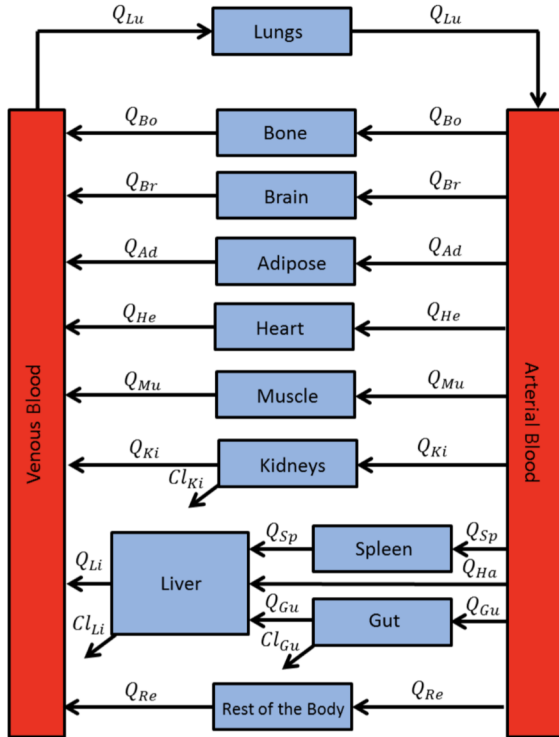
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Role of Partition Coefficients (PC) in PBPK Models



$$\frac{dA_T}{dt} = Q_T \cdot \left(C_{art} - \frac{C_T}{\frac{K_{pT}}{B:P}} \right)$$

A red arrow points to the $\frac{C_T}{\frac{K_{pT}}{B:P}}$ term in the equation.

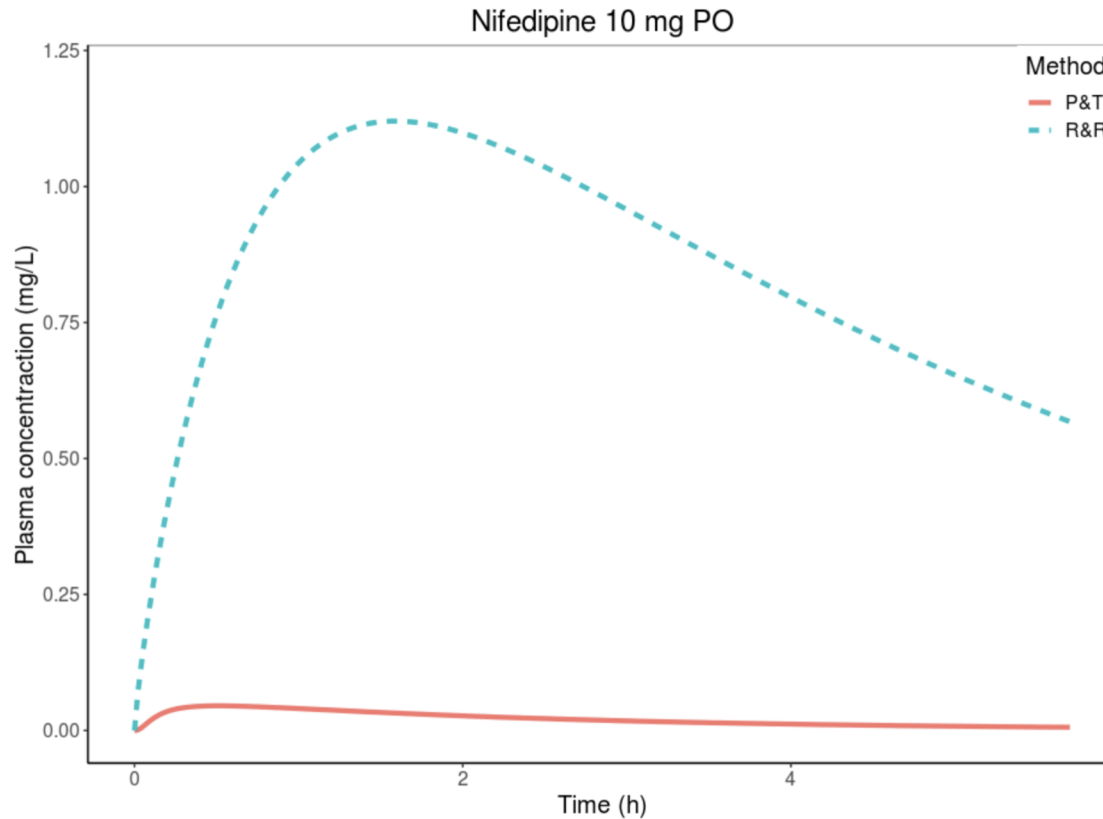
Calculation of PC

In silico methods:

- Inputs:
 - Compound's physicochemical properties (lipophilicity, pKa, etc...)
 - Tissue composition (water fraction, lipid fraction, etc...)
- Examples:
 - Poulin and Theil <https://www.ncbi.nlm.nih.gov/pubmed/11782904>
 - Berezhkovskiy <https://www.ncbi.nlm.nih.gov/pubmed/15124219>
 - Rodgers and Rowland <https://www.ncbi.nlm.nih.gov/pubmed/15858854> and <https://www.ncbi.nlm.nih.gov/pubmed/16639716>
 - Schmitt <https://www.ncbi.nlm.nih.gov/pubmed/17981004>
 - PK-Sim Standard <https://www.ncbi.nlm.nih.gov/pubmed/16922658>

<https://github.com/Open-Systems-Pharmacology>

Impact of Using Different PC Calculation Methods on PBPK Model Prediction



Different PC Calculation Methods Use Different Tissue Compositions!!

Tissues	Neutral Lipid
Adipose	0.79
Bone	0.074
Brain	0.051
Gut	0.0487
Heart	0.0115
Kidney	0.0207
Liver	0.0348
Lung	0.003
Muscle	0.0238

Tissue	Neutral Lipid
Adipose	0.853
Bone ^e	0.017
Brain ^f	0.039
Gut	0.038
Heart	0.014
Kidney	0.012
Liver	0.014
Lung	0.022
Muscle	0.010

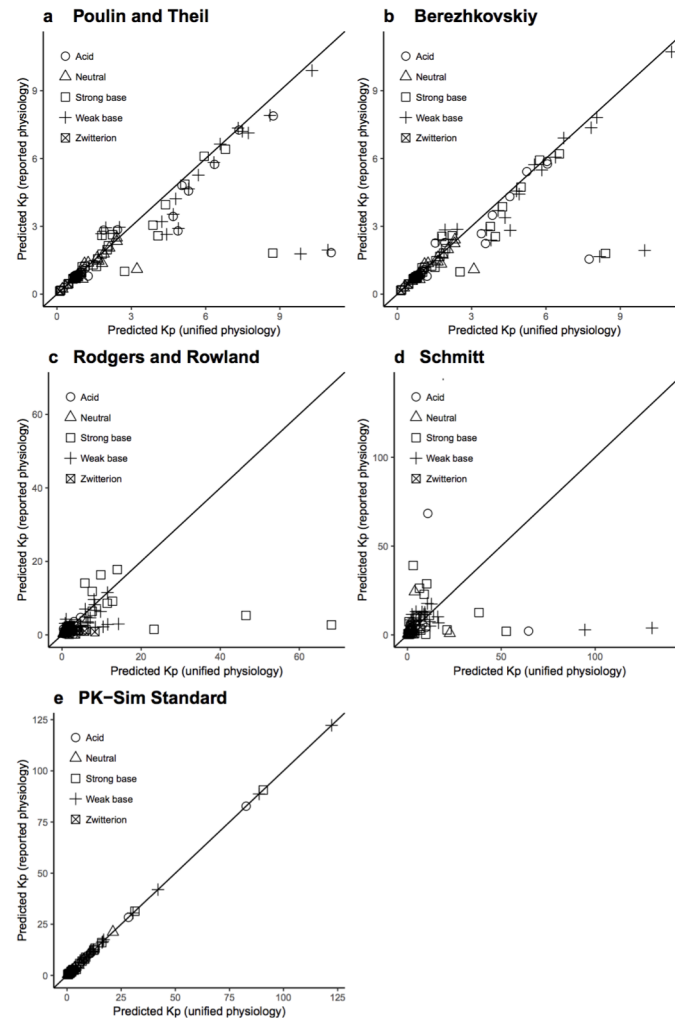
Towards a Unified Tissue Composition

Tissue	flipid	fprotein	fpl	fnl	fnpl	fapl	pH	few	fiw	AR	LR
Bone	0.268	0.268	0.0011	0.074	0.0016	8E-04	7	0.100	0.346	0.100	0.050
Brain	0.107	0.08	0.0565	0.045	0.0553	0.02022	7.1	0.162	0.620	0.048	0.041
Adipose	0.800	0.05	0.002	0.798	0.0478	0.00670	7.10	1.35	0.017	0.049	0.069
Heart	0.100	0.17	0.0166	0.089	0.0079	0.00309	7.1	0.320	0.456	0.157	0.160
Kidney	0.052	0.17	0.0162	0.036	0.0166	0.00387	7.22	0.273	0.483	0.130	0.137
Gut	0.062	0.133	0.0163	0.0487	0.0124	3.5E-03	7.4	0.282	0.475	0.158	0.141
Liver	0.067	0.18	0.0252	0.037	0.0115	0.00258	7.23	0.161	0.573	0.086	0.161
Lung	0.010	0.18	0.009	0.0030	0.0056	0.0014	6.6	0.336	0.446	0.212	0.168
Muscle	0.019	0.17	0.0072	0.013	0.0092	0.0019	6.81	0.118	0.630	0.064	0.059
Skin	0.100	0.29	0.0111	0.036	0.0502	0.01382	7.0	0.382	0.291	0.277	0.096
Spleen	0.028	0.19	0.0198	0.014	0.0103	0.00191	7.0	0.207	0.579	0.097	0.207
Plasma	0.009	0.07	0.00225	0.003	0.0050	0.00097	7.3	NA	NA	0.029	0.0006
RBCs	0.005	0.33	NA	0.002	0.0025	0.0005	7.2	NA	0.603	NA	NA

Sources:

- flipid, fprotein, fpl, fnl, fnpl and pH for adipose, liver, muscle, lung, kidney, brain, heart, RBCs, plasma, spleen, and skin (Ruark et al. 2014; human data).
- fnl for bone and gut (P. Poulin, Schoenlein, and Theil 2001; human data).
- fpl for all tissues (P. Poulin, Schoenlein, and Theil 2001; human data).
- few, fiw, AR, and LR for all tissues (Rodgers, Leahy, and Rowland 2005; rat data).
- fnpl for bone and gut (Rodgers and Rowland 2006; rat data).
- flipid and fprotein for bone and gut from PK-Sim standard method in PK-Sim.
- fapl for bone and gut from Schmitt method in PK-Sim.

Comparing PC Predictions Using Unified vs Reported Tissue Composition



Thank you