PhysChem Forum

PCF2024, Jealott's Hill

Closing the loop - measuring, modelling and predicting physicochemical properties

Surrogation of biological properties by physicochemical parameters

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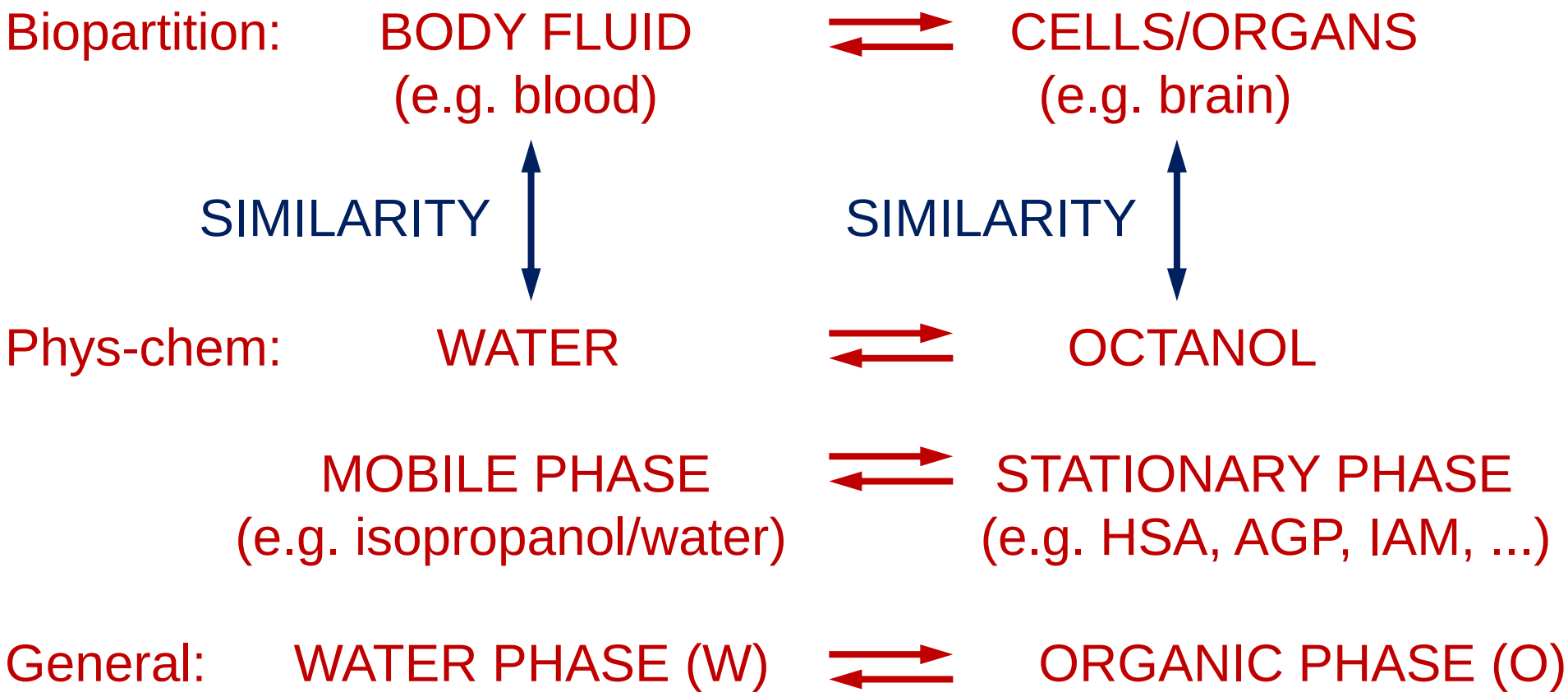
Hypotesis of similarity of biopartition and phys-chem processes



$\log P = \log (S_O/S_W) = \log S_O - \log S_W$ Similarity of differences !

Evaluated by the same QSAR – QSPR model

Abraham Linear Free Energy Relationships Model

M.H. Abraham
1931-2021

$$\Delta G^0_{process} = \sum \Delta G^0_{molecular\ interactions} \qquad \Delta G^0 = -RT \ln K$$

$$\log SP = c + e\,E + s\,S + a\,A + b\,B + v\,V$$

SOLUTE DESCRIPTORS		SOLVENT COEFFICIENTS (SP-MP)	
V:	McGowan molar volume ($cm^3mol^{-1}/100$)	v:	Cohesiveness (hydrophobicity)
B:	Overall hydrogen bond basicity	b:	Hydrogen bond acidity
A:	Overall hydrogen bond acidity	a:	Hydrogen bond basicity
S:	Dipolarity/polarizability	s:	Polarity
E:	Excess molar refractivity	e:	n and π interactions

Abraham database: 9000 solutes partially or totally (≈ 4000) characterized

Software: ACD/Percepta. Advanced Chemistry Development (ACD/Labs). http:// www.acdlabs.com
UFZ-LSER database v 3.2, http://www.ufz.de/lserd

Abraham equations

Biopartitions

System	*c*	*e*	*s*	*a*	*b*	*v*
Blood-brain	0.547	0.221	−0.604	−0.641	−0.681	0.635
Blood-muscle	0.082	−0.059	0.010	−0.248	0.028	0.110
Blood-liver	0.292	0.000	−0.296	−0.334	0.181	0.337
Blood-lung	0.269	0.000	−0.523	−0.723	0.000	0.720.
Blood-kidney	0.494	−0.067	−0.426	−0.367	0.232	0.410
Blood-heart	0.132	−0.039	−0.394	−0.376	0.009	0.527
Blood-skin	−0.105	−0.117	0.034	0.000	−0.681	0.756
Blood-fat	0.077	0.249	−0.215	−0.902	−1.523	1.234
Water-skin	0.523	0.101	−0.076	−0.022	−1.951	1.652
Skin perm	−5.420	−0.102	−0.457	−0.324	−2.680	2.066

Plus intestinal absorption, toxicities, soil-water partition, etc.

Physico-chemical partitions

More than 100 water/solvent partitions (including octanol/water) characterized by Abraham, Acree, and others.

Many HPLC and EKC (micelles, microemulsions, liposomes) systems characterized by Poole, Rosés, and others.

Surrogation of biological systems

$$log\ SP_{bio} = c_{bio} + e_{bio}E + s_{bio}S + a_{bio}A + b_{bio}B + v_{bio}V$$

$$log\ k_{chrom} = c_{chrom} + e_{chrom}E + s_{chrom}S + a_{chrom}A + b_{chrom}B + v_{chrom}V$$

$$log\ SP_{bio} = c_{bio} + l_{bio}(e_{u,bio}E + s_{u,bio}S + a_{u,bio}A + b_{u,bio}B + v_{u,bio}V)$$

$$log\ k_{chrom}$$

$$= c_{chrom} + l_{chrom}(e_{u,chrom}E + s_{u,chrom}S + a_{u,chrom}A + b_{u,chrom}B + v_{u,chrom}V)$$

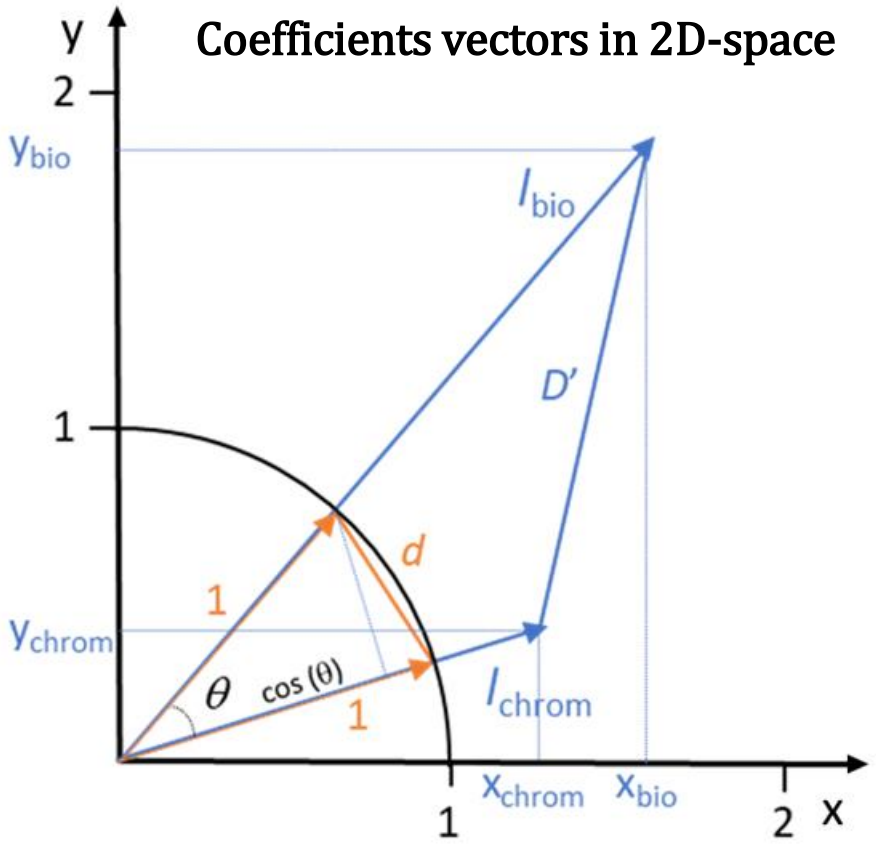
$$l = \sqrt{e^2 + s^2 + a^2 + b^2 + v^2} \qquad x_u = \frac{x}{l}$$

$$(e_{u,bio}E + s_{u,bio}S + a_{u,bio}A + b_{u,bio}B + v_{u,bio}V)$$

$$= (e_{u,chrom}E + s_{u,chrom}S + a_{u,chrom}A + b_{u,chrom}B + v_{u,chrom}V)$$

$$log\ SP_{bio} = \frac{l_{chrom}c_{bio} - l_{bio}c_{chrom}}{l_{chrom}} + \frac{l_{bio}}{l_{chrom}}\ log\ k_{chrom}$$

Coefficients vectors in 2D-space

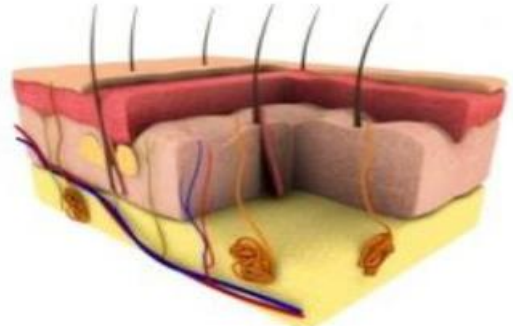


$d = 0$ $(d < 0.25)$

$$d = \sqrt{(e_{u,bio} - e_{u,chrom})^2 + (s_{u,bio} - s_{u,chrom})^2 + (a_{u,bio} - a_{u,chrom})^2 + (b_{u,bio} - b_{u,chrom})^2 + (v_{u,bio} - v_{u,chrom})^2}$$

Surrogation of skin permeation: Characterized systems

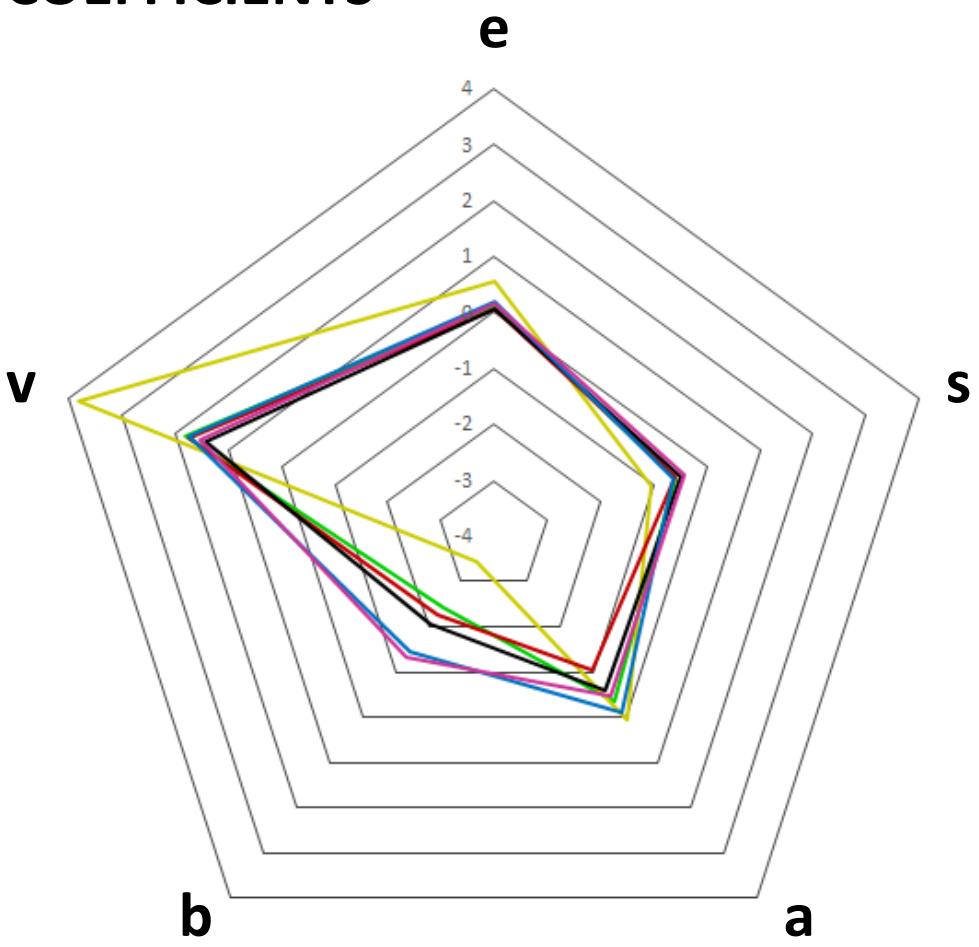
$$\log SP = c + e\,E + s\,S + a\,A + b\,B + v\,V$$



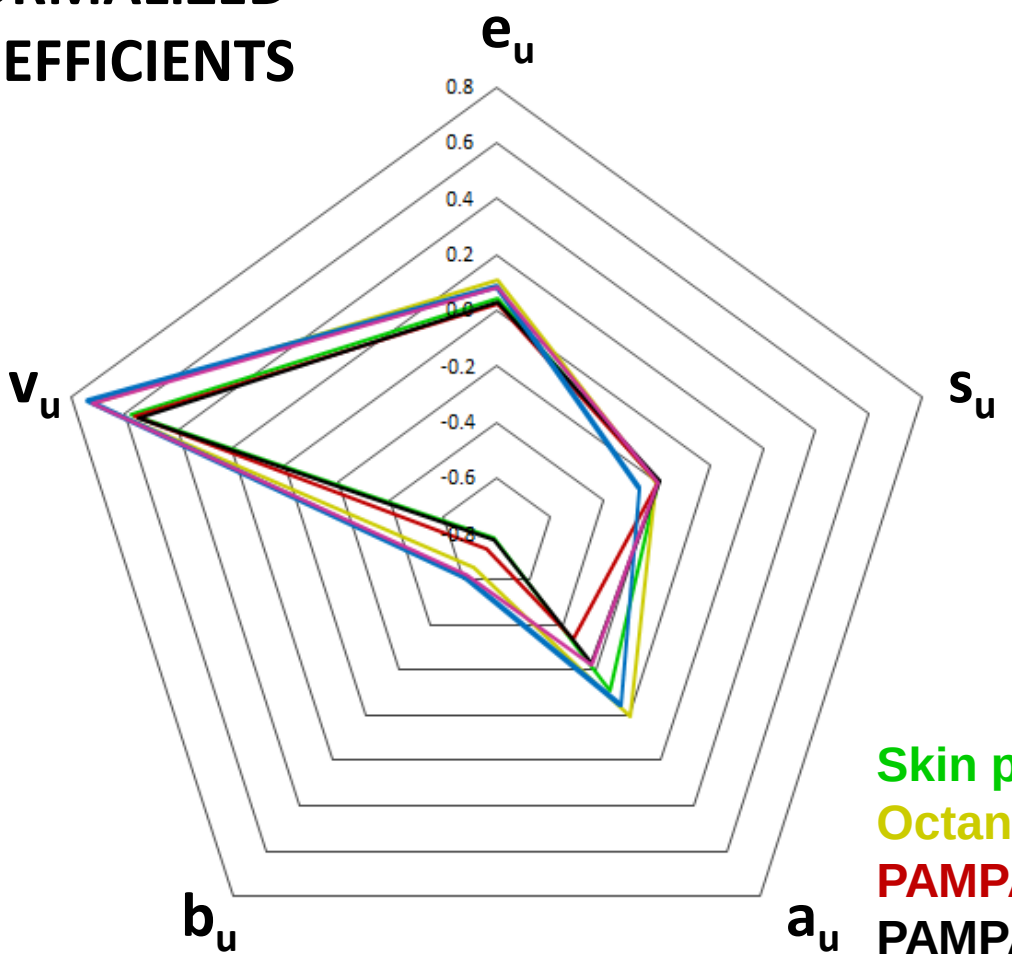
System	log *SP*	*c*	*e*	*s*	*a*	*b*	*v*	R^2	*SD*	*n*	Ref
Skin permeation	log K_p	-5.33	0.14	-0.60	-0.34	-2.43	1.80	0.866	0.43	247	Abraham et al. 2004
Octanol/water	log $P_{o/w}$	0.09	0.56	-1.05	0.03	-3.46	3.81	0.995	0.12	613	Abraham et al. 1994
PAMPA-Certramides	log P_e	-4.18	0.06	-0.59	-1.04	-2.27	1.73	0.906	0.25	52	Rosés, Fuguet et al. 2023
PAMPA-IPM	log P_e	-4.20	0.08	-0.50	-0.60	-2.04	1.44	0.835	0.30	27	Rosés, Fuguet et al. 2023
Cerasome-LEKC	log *k*	-1.92	0.20	-0.63	-0.11	-1.45	1.76	0.814	0.29	71	Liu, Abraham et al. 2011
C-18 HPLC	log *k*	-0.48	0.18	-0.41	-0.48	-1.32	1.55	0.927	0.16	116	Rosés, Fuguet et al. 2021

Comparison of systems: Radial plots of coefficients

COEFFICIENTS

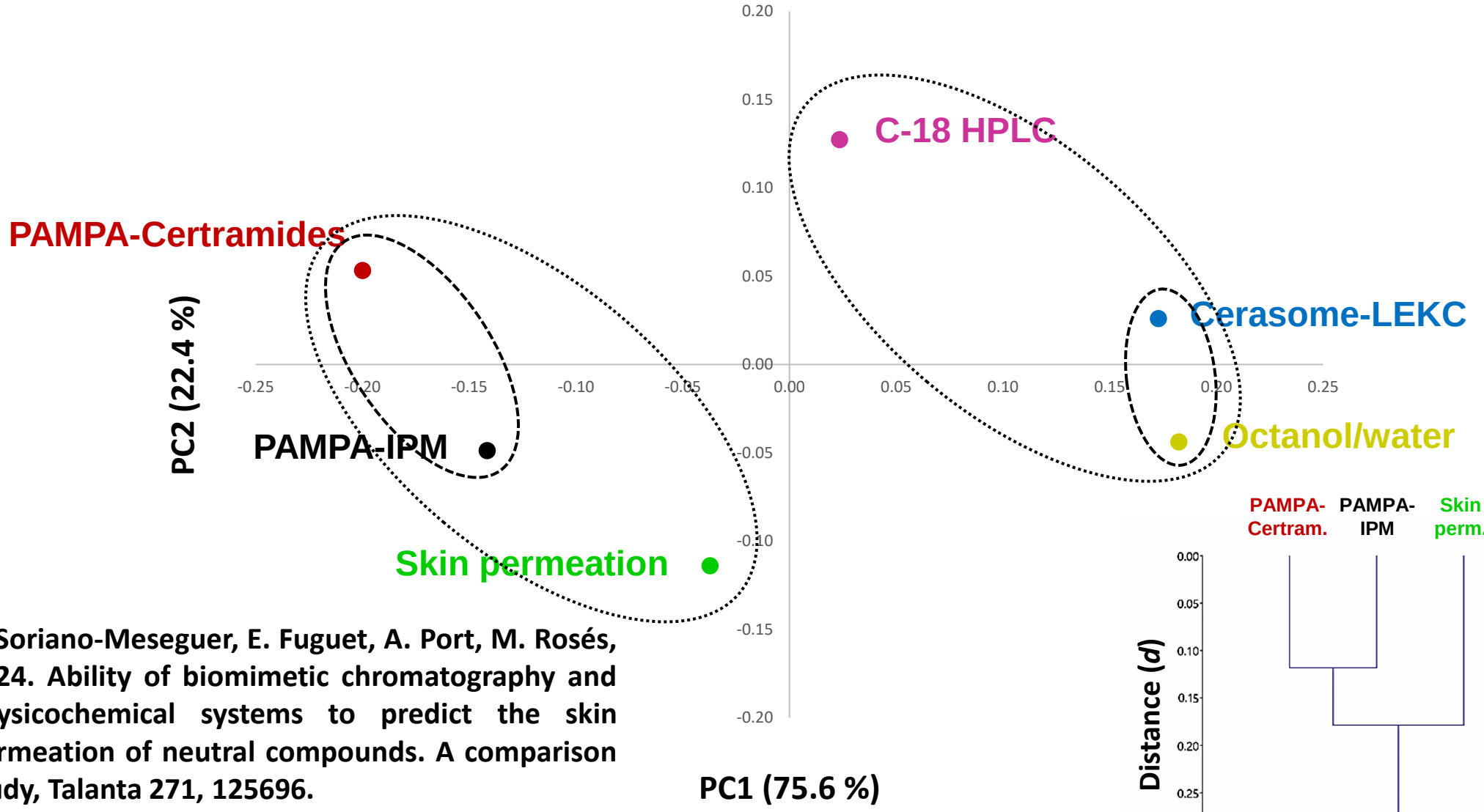


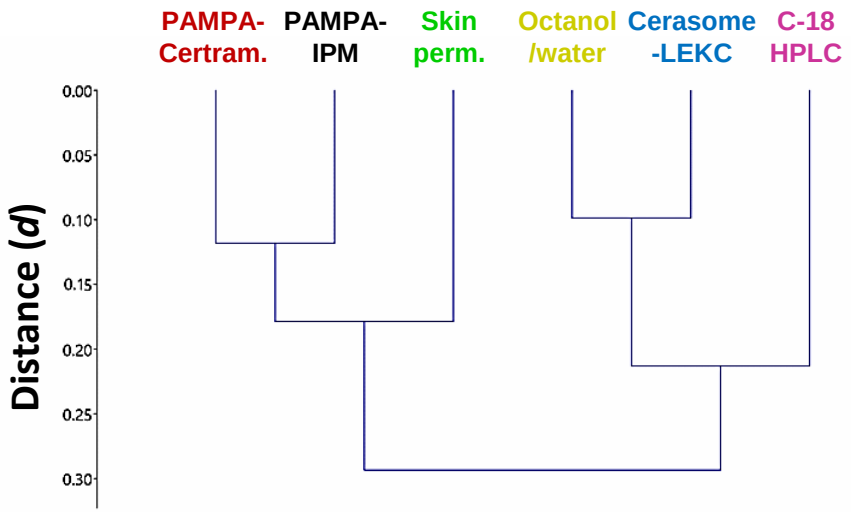
NORMALIZED COEFFICIENTS



Skin permeation
Octanol/water
PAMPA-Certramides
PAMPA-IPM
Cerasome-LEKC
C-18 HPLC

Dendrogram and PCA (normalized coefficients)

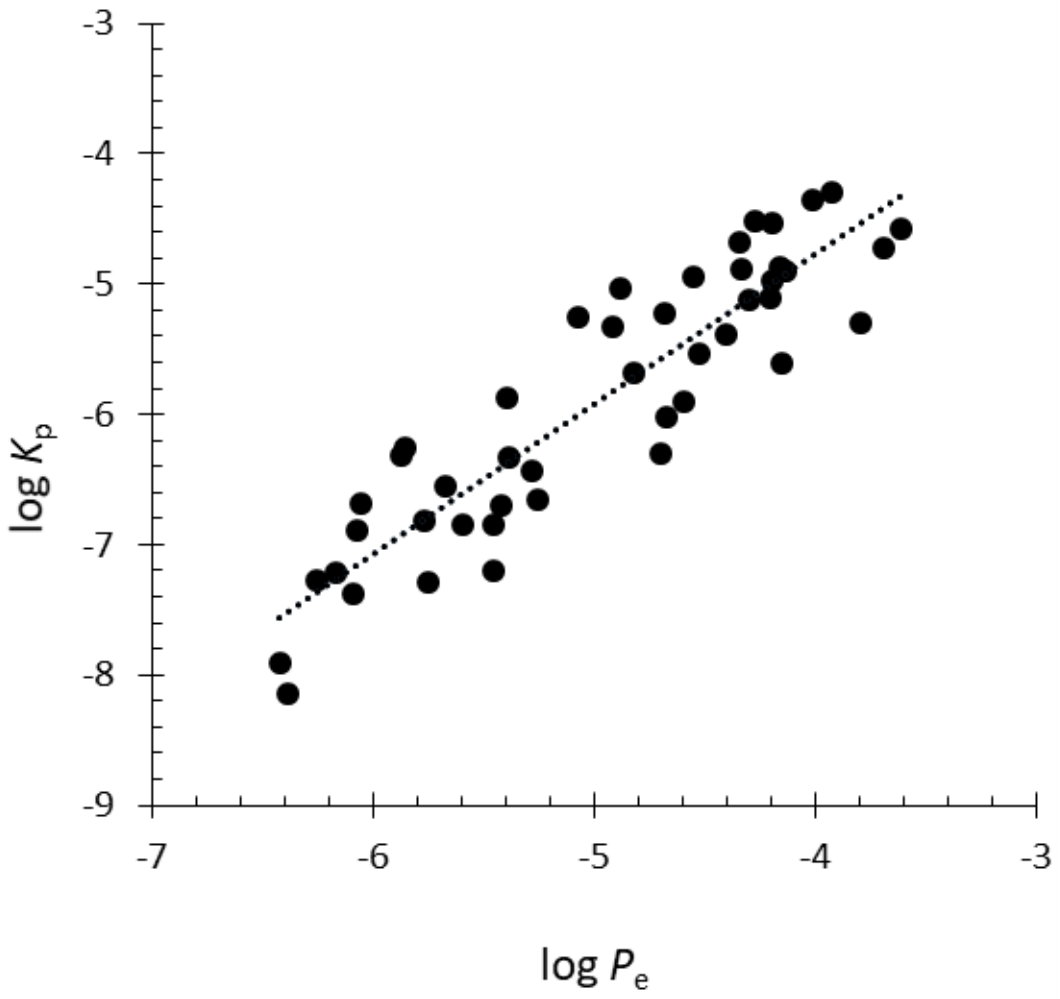




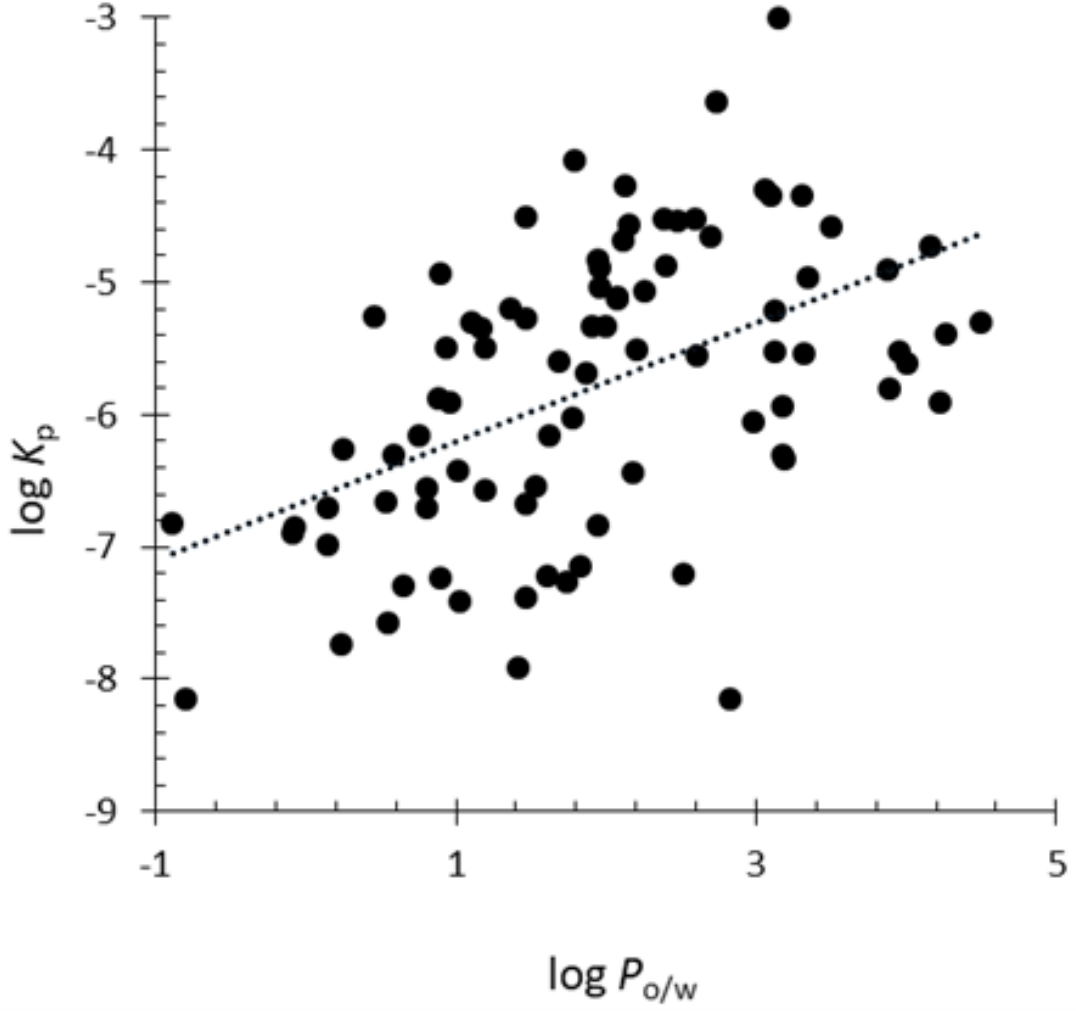
S. Soriano-Meseguer, E. Fuguet, A. Port, M. Rosés, 2024. Ability of biomimetic chromatography and physicochemical systems to predict the skin permeation of neutral compounds. A comparison study, Talanta 271, 125696. https://doi.org/10.1016/j.talanta.2024.125696.

Surrogation of skin permeation: Experimental correlations

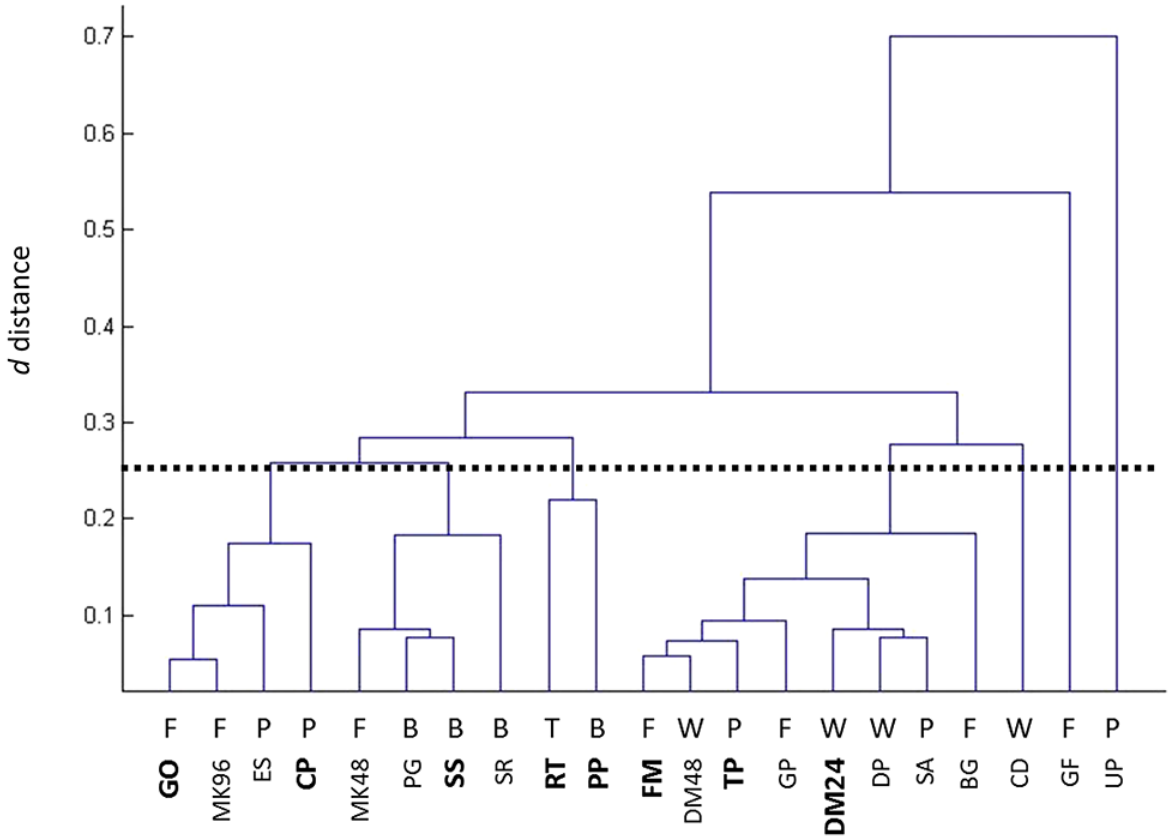
PAMPA-Certramides (Pion)

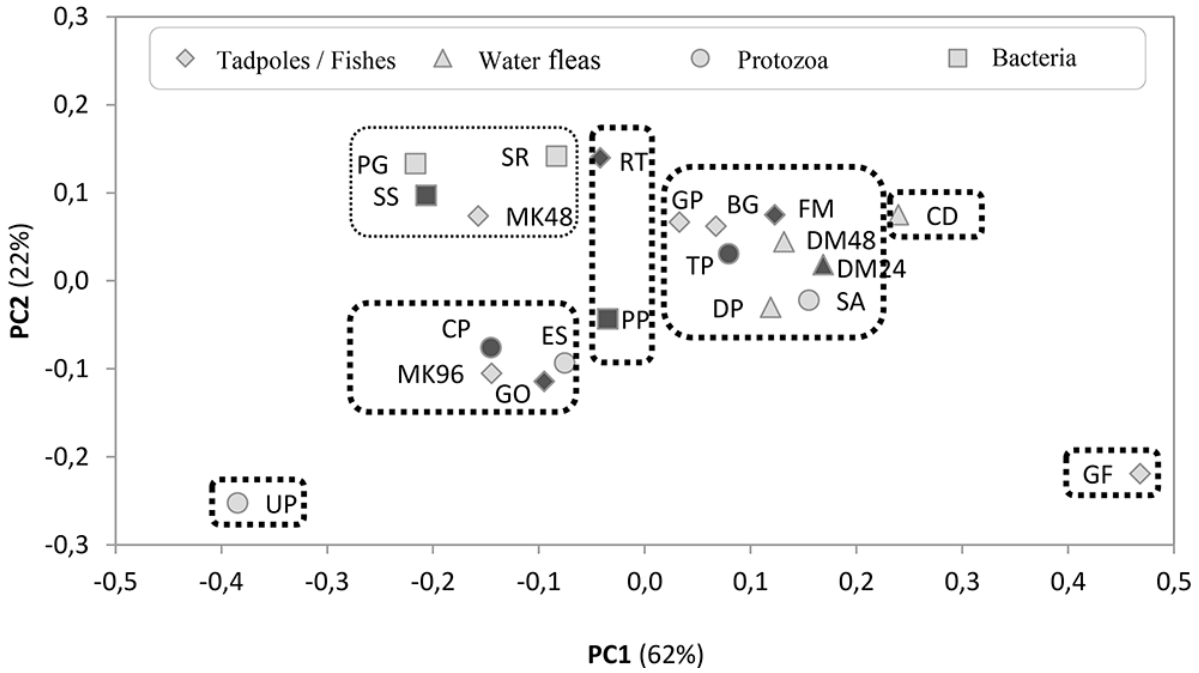


Octanol/water



Comparison of aquatic toxicity systems

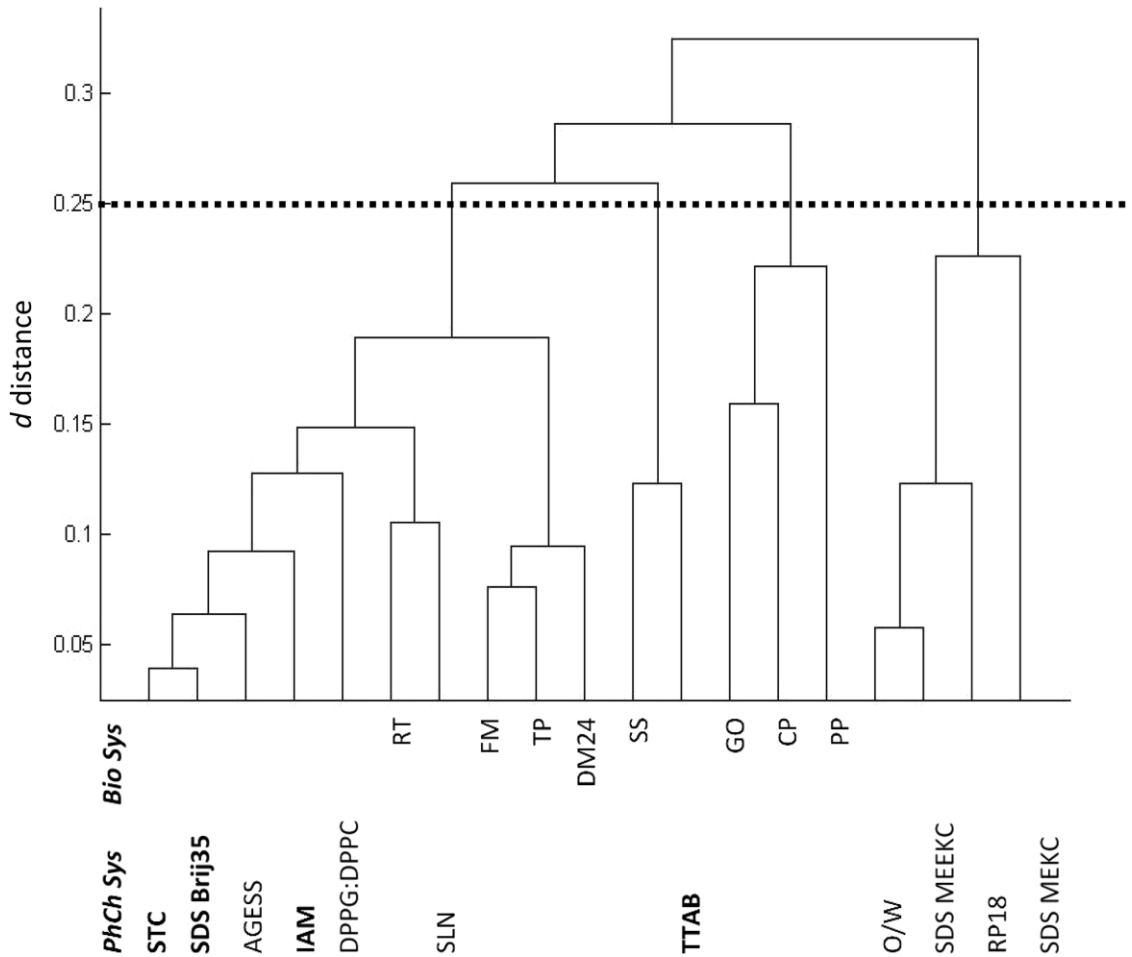


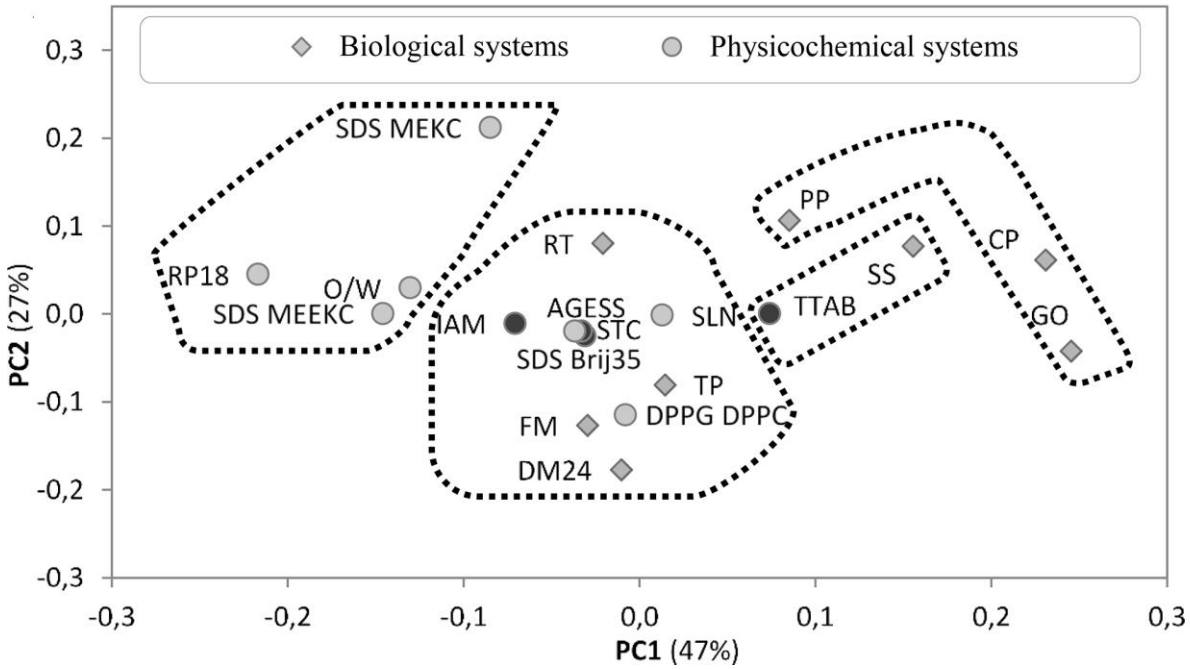


A. Fernández-Pumarega, S. Amézqueta, S. Farré, L. Muñoz-Pascual. M. H. Abraham, E. Fuguet, M. Rosés. Modeling Aquatic Toxicity through Chromatographic Systems. Analytical Chemistry 89 (2017) 7996–8003.
https://doi.org/10.1021/acs.analchem.7b01301.

RT: *Rana tadpoles* (-log C_{nar}), FM: *Fathead minnow* (-log LC50), GP: *Guppy* (-log LC50), BG: *Bluegill* (-log LC50), GO: *Golden orfe* (-log LC50), GF: *Goldfish* (-log LC50), MK48: *Medaka high-eyes* (-log LC50 in 48 h), MK96: *Medaka high-eyes* (-log LC50 in 96 h), DM24: *Daphnia magna* (-log LC50 in 24 h), DM48: *Daphnia magna* (-log LC50 in 48 h), CD: *Ceriodaphnia dubia* (-log LC50), DP: *Daphnia pulex* (-log LC50), TP: *Tetrahymena pyriformis* (-log IGC50), SA: *Spirostomum ambiguum* (-log LC50), ES: *Entosiphon sulcantum* (-log IGC), UP: *Uronema parduczi* (-log IGC), CP: *Chilomonas paramecium* (-log IGC), PP: *Pseudomonas putida* (-log IGC), PG: *Porphyromonas gingivalis* (-log MIC), SR: *Selenomonas artemidis* (-log MIC), SS: *Streptococcus sobrinus* (-log MIC).

Comparison of aquatic toxicity systems





HPLC: RP18: C18 (40% MeCN); IAM: IAM (40% MeCN)
MECK: SDS MEKC: sodium dodecyl sulfate; SLN: sodium N-lauroyl-sarcosinate; STC: sodium taurocholate; TTAB: tetradecyltrimethyl-ammonium bromide; SDS Brij 35: sodium dodecyl sulfate + polyoxy-ethylene(23)dodecyl ether; DPPG DPPC: dipalmitoylphosphatidyl glycerol + dipalmitoylphosphatidyl choline; AGESS: dodecane allyl glycidyl ether sulfite-modified siloxane.
SDS MEEKC: MEEKC with sodium dodecyl sulfate.
O/W: octanol/water partition (log $P_{o/w}$).

Effect of additional descriptors: Volume correction

$$\log SP_{bio} = c_{bio} + l_{bio}(e_{u,bio}E + s_{u,bio}S + a_{u,bio}A + b_{u,bio}B + v_{u,bio}V)$$

$$\log k_{chrom} = c_{chrom} + l_{chrom}(e_{u,chrom}E + s_{u,chrom}S + a_{u,chrom}A + b_{u,chrom}B + v_{u,chrom}V)$$

$$(e_{u,bio}E + s_{u,bio}S + a_{u,bio}A + b_{u,bio}B) = f(e_{u,chrom}E + s_{u,chrom}S + a_{u,chrom}A + b_{u,chrom}B)$$

$$f = \sqrt{\frac{{e_{u,bio}}^2 + {s_{u,bio}}^2 + {a_{u,bio}}^2 + {b_{u,bio}}^2}{{e_{u,chrom}}^2 + {s_{u,chrom}}^2 + {a_{u,chrom}}^2 + {b_{u,chrom}}^2}}$$

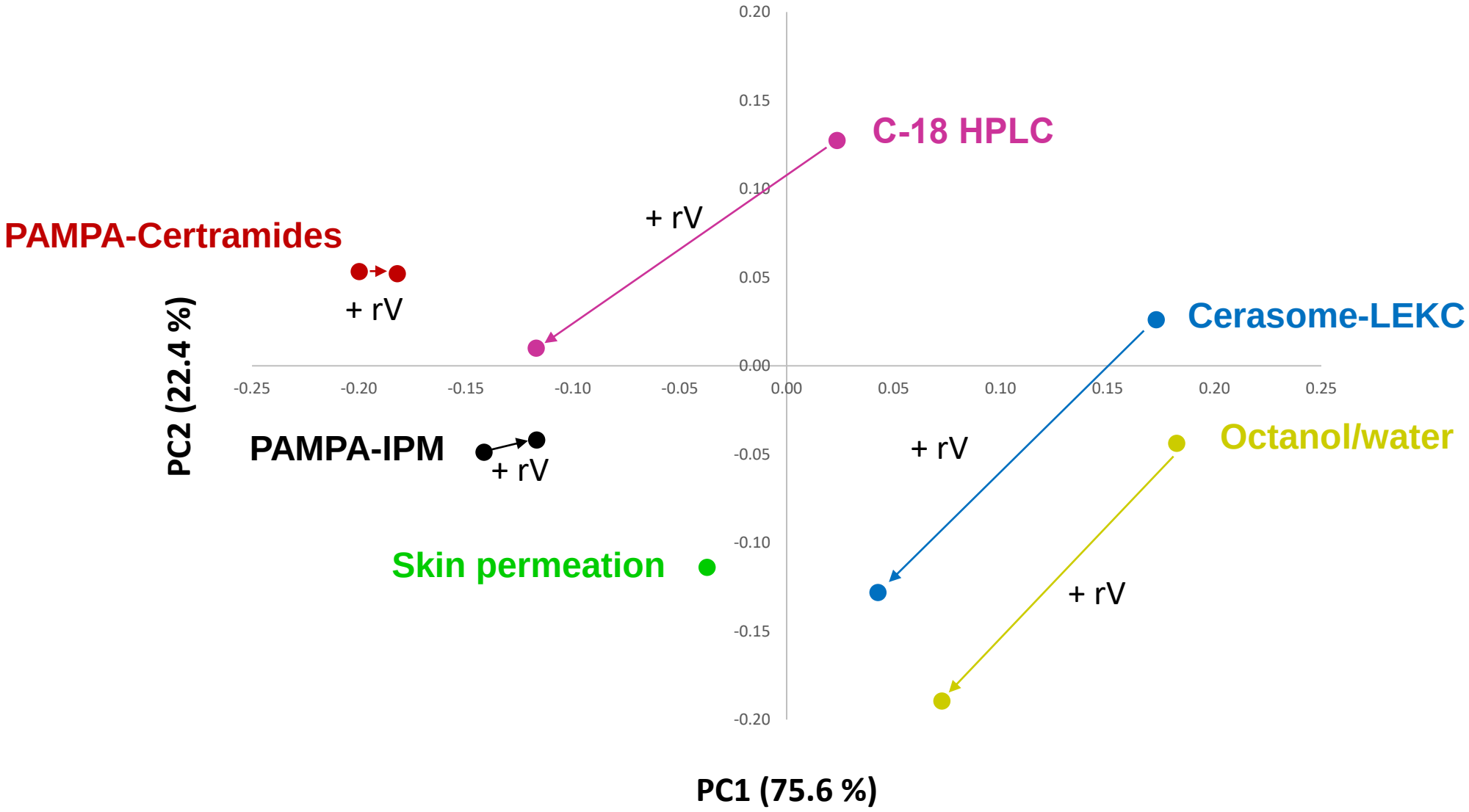
$$\log SP_{bio} = c_{bio} + l_{bio}\,(e_{u,bio}E + s_{u,bio}S + a_{u,bio}A + b_{u,bio}B) + l_{bio}v_{u,bio}V$$

$$\log k_{chrom} = c_{chrom} + l_{chrom}\,(e_{u,chrom}E + s_{u,chrom}S + a_{u,chrom}A + b_{u,chrom}B) + l_{chrom}v_{u,chrom}V$$

$$\log SP_{bio} = q + p\log k_{chrom} + rV \qquad \log SP_{bio} = q + p(\log k_{chrom} + \frac{r}{p}V)$$

$$q = \frac{l_{chrom}c_{bio} - f l_{bio}c_{chrom}}{l_{chrom}} \qquad p = \frac{f l_{bio}}{l_{chrom}} \qquad r = l_{bio}(v_{u,bio} - f v_{u,chrom})$$

Comparison of systems: Effect of volume correction



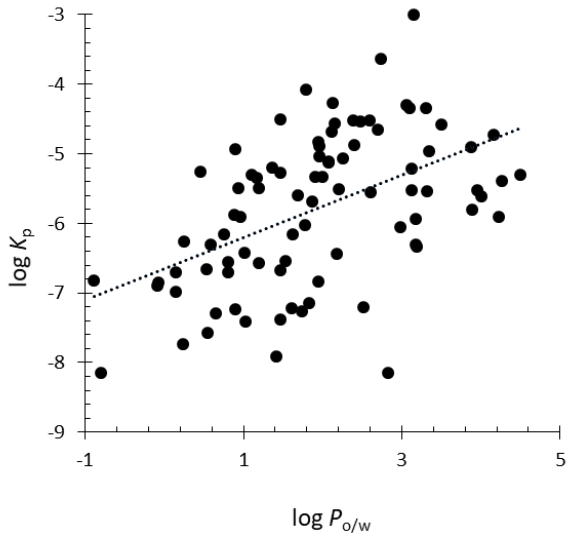
Fitting surrogation parameters: Predicted vs experimental

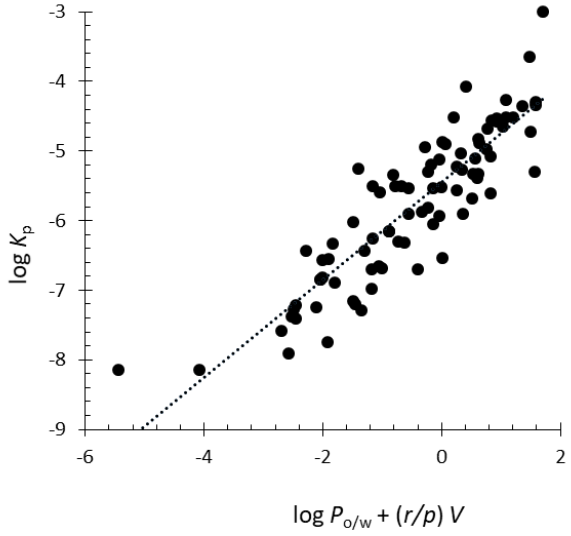
$$log\, SP_{bio} = q + p\, log\, k_{chrom} + rV$$

		Predicted from equations				Experimental correlation			
System	*d*	*f*	*q*	*p*	*r*	*q*	*p*	*r*	R^2
Octanol/Water	0.23	1.00	-5.38	0.59	-	-6.65	0.45	-	0.25
PAMPA-Certramides	0.23	1.00	-1.14	1.00	-	-0.13	1.16	-	0.82
PAMPA-IPM	0.12	1.00	-0.35	1.18	-	0.57	1.35	-	0.77
Cerasome-LEKC	0.26	1.00	-2.82	1.31	-	-4.29	1.34	-	0.12
C-18 HPLC	0.25	1.00	-4.63	1.45	-	-5.83	1.05	-	0.29
Octanol/Water + rV	0.15	1.18	-5.39	0.69	-0.84	-5.44	0.70	-1.02	0.78
PAMPA-Certramides + rV	0.23	0.98	-1.21	0.99	0.09	-0.13	1.07	-0.25	0.87
PAMPA-IPM + rV	0.12	0.98	-0.47	1.16	0.13	0.55	1.31	-0.11	0.78
Cerasome-LEKC + rV	0.16	1.21	-2.29	1.58	-0.98	-2.52	1.41	-0.91	0.77
C-18 HPLC + rV	0.18	1.18	-4.50	1.71	-0.85	-3.90	1.71	-1.23	0.87

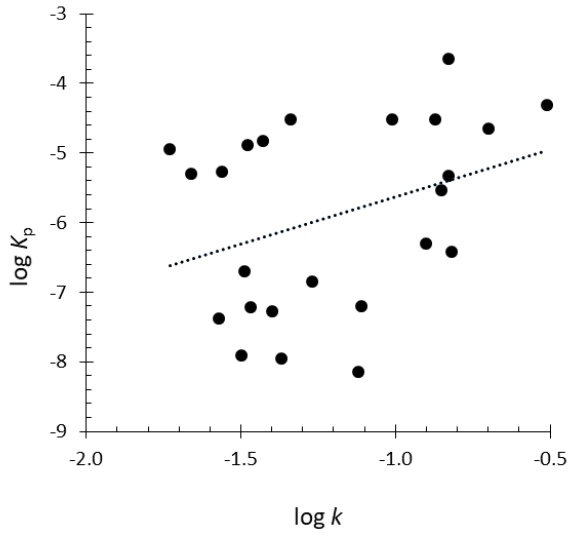
Surrogation of skin permeation: Experimental correlations

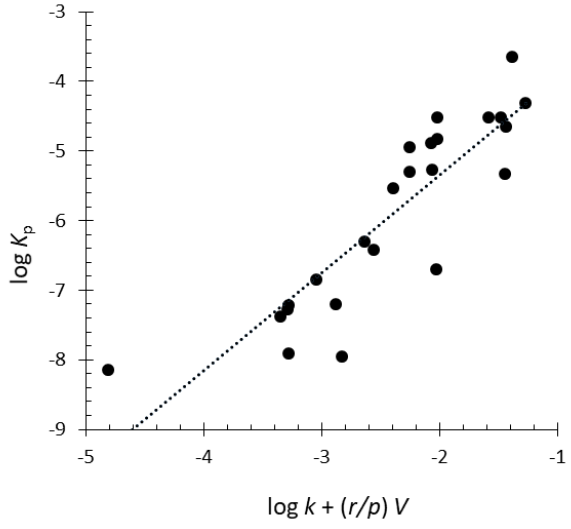
Octanol/water



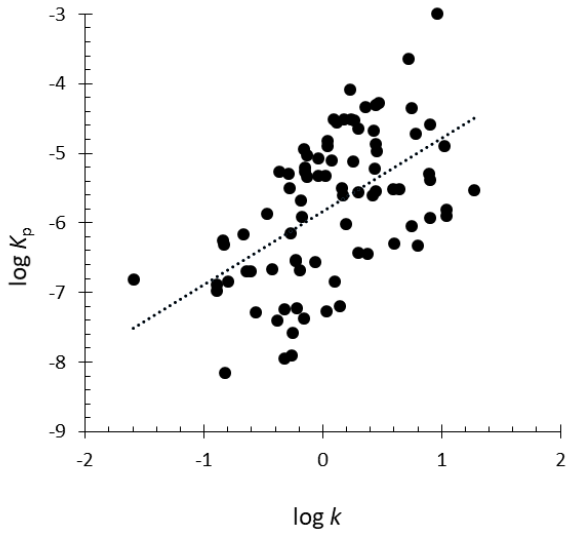


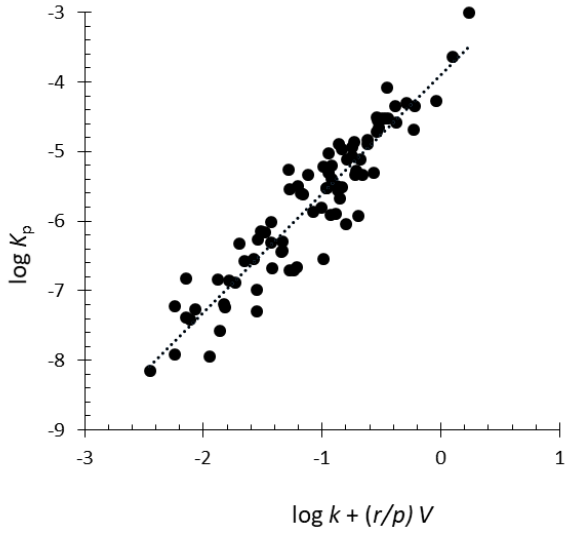
Cerasome-LEKC





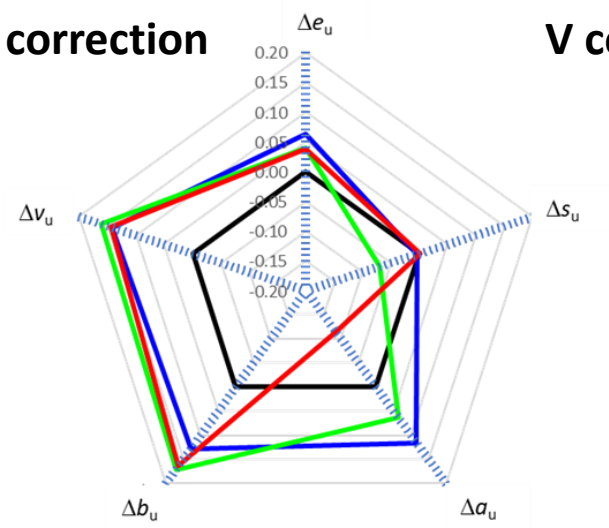
C-18 HPLC



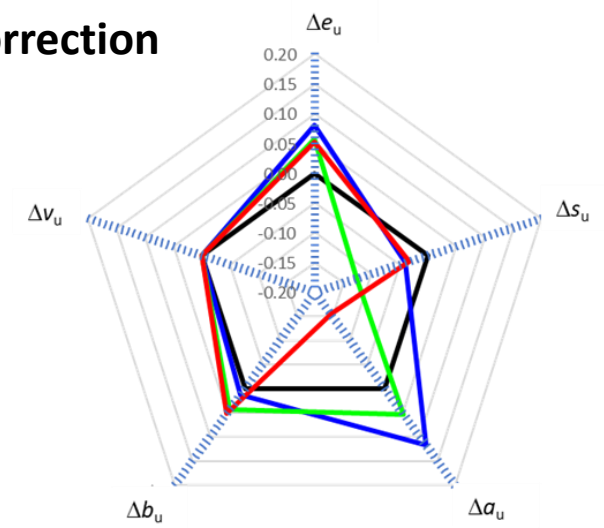


Correction of factors: Radial plots of coefficient differences and PCA

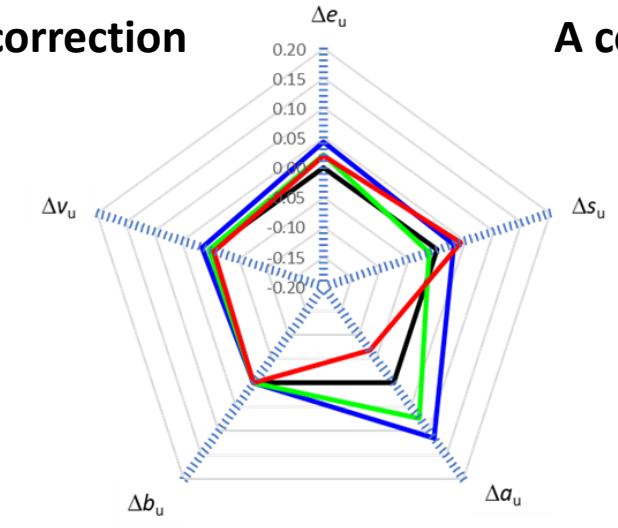
No correction



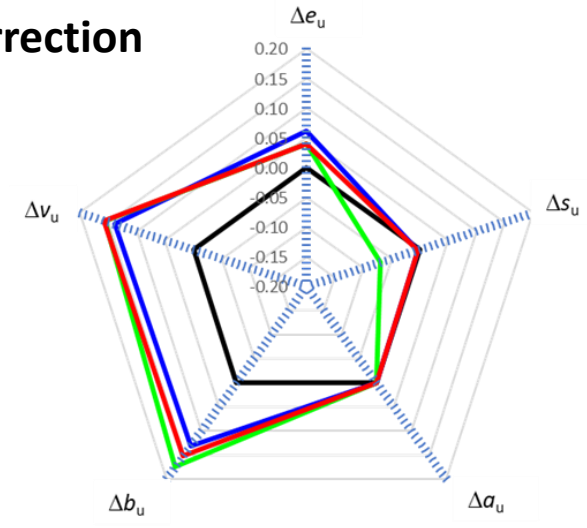
V correction

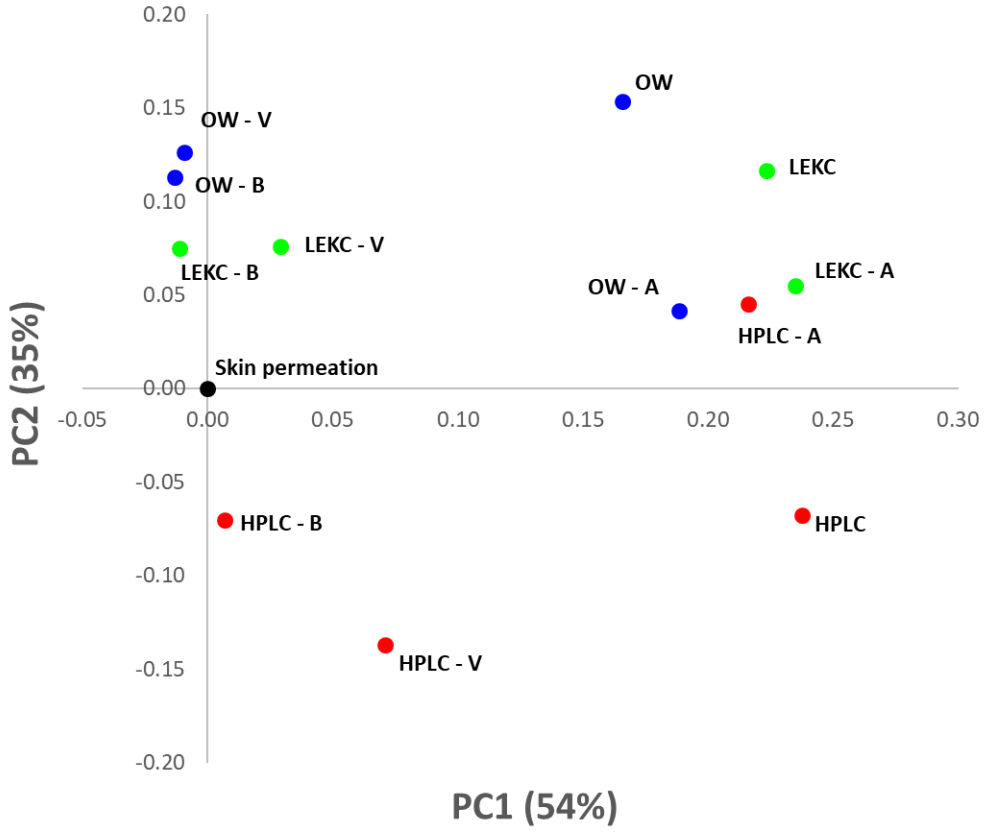


B correction



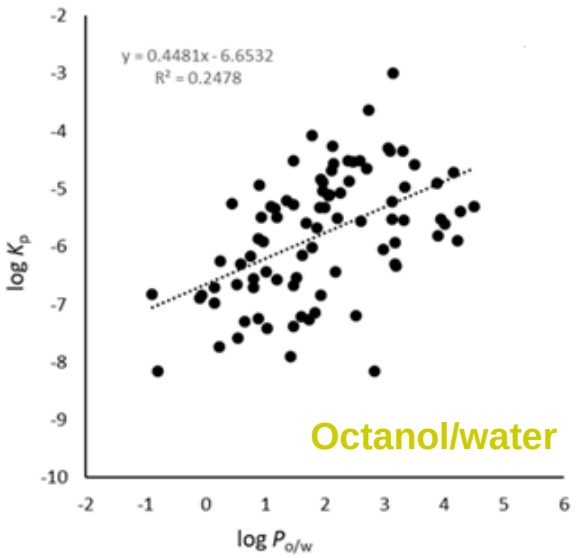
A correction

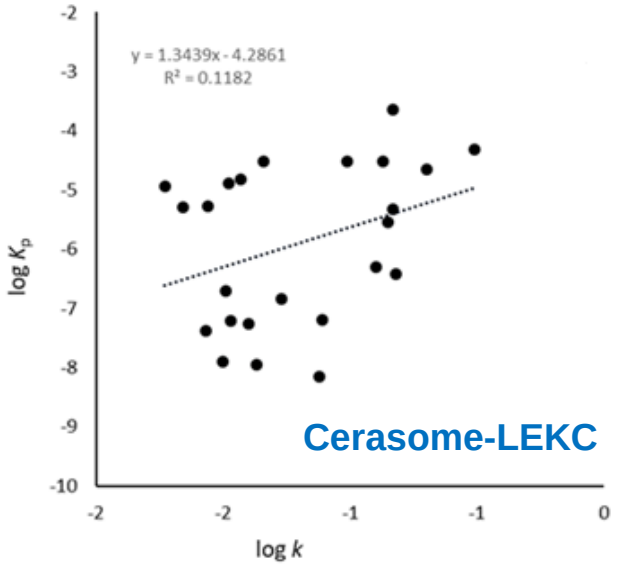


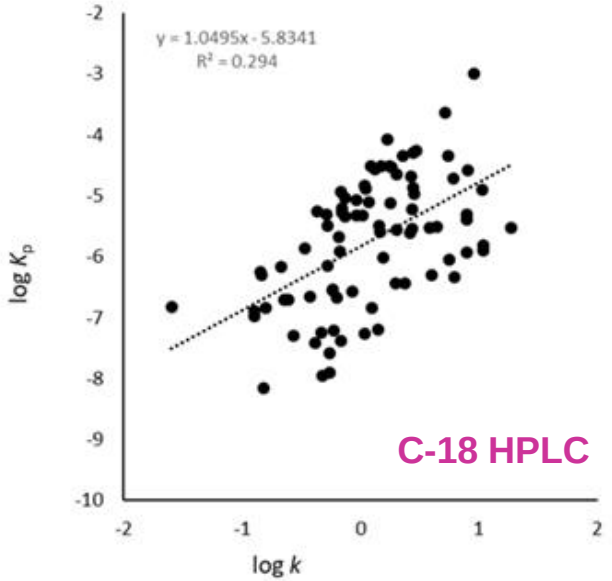


E. Fuguet and M. Rosés, 2024. Tutorial on modelling chromatographic surrogation of biological, Journal of Chromatography Open, submitted.

Correction of factors: Experimental correlations







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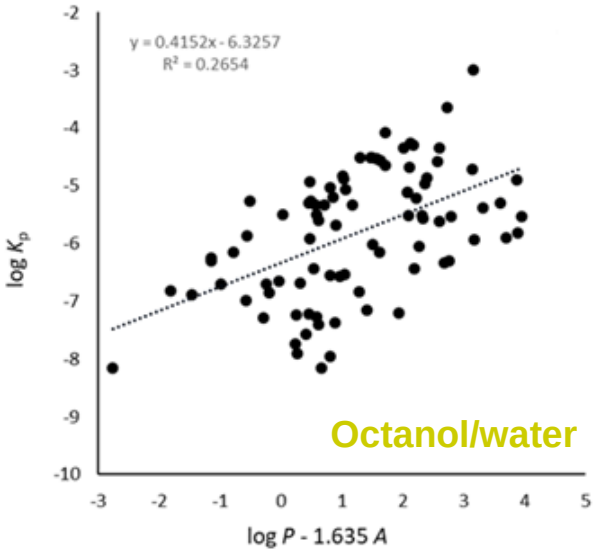
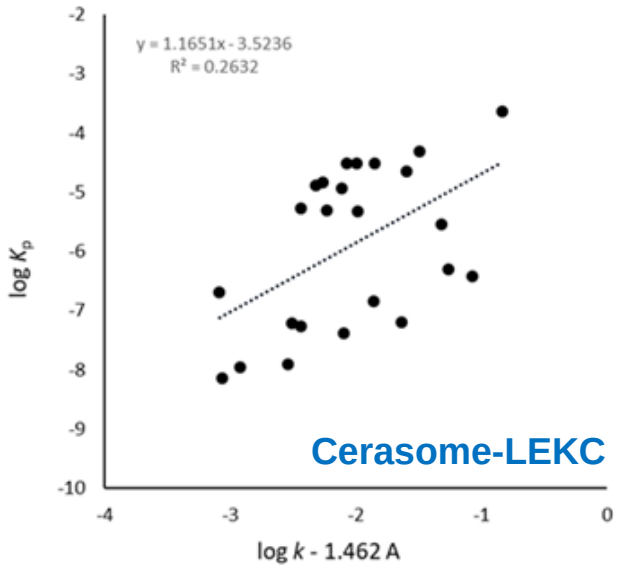
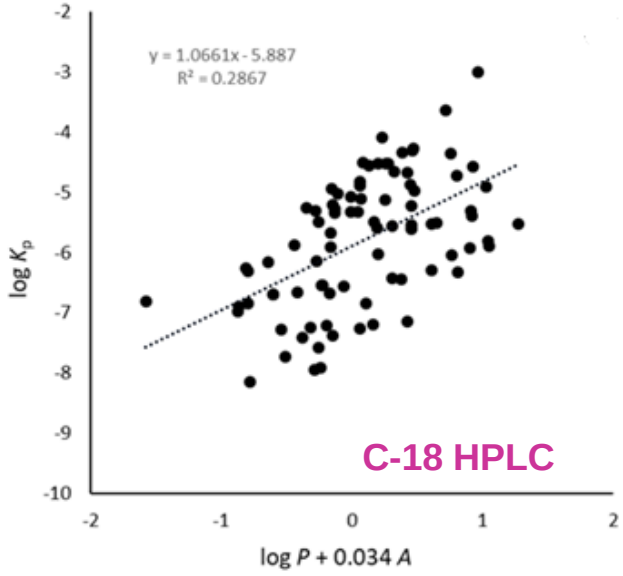
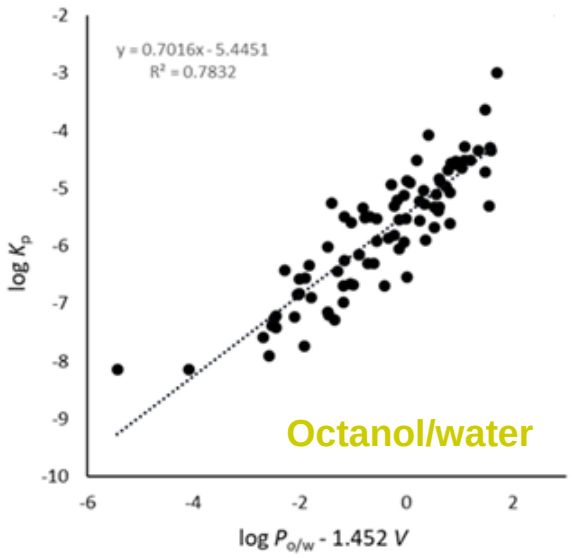


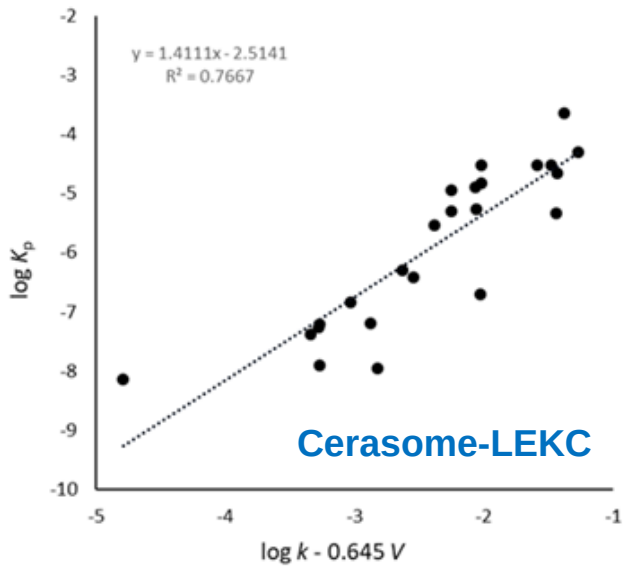


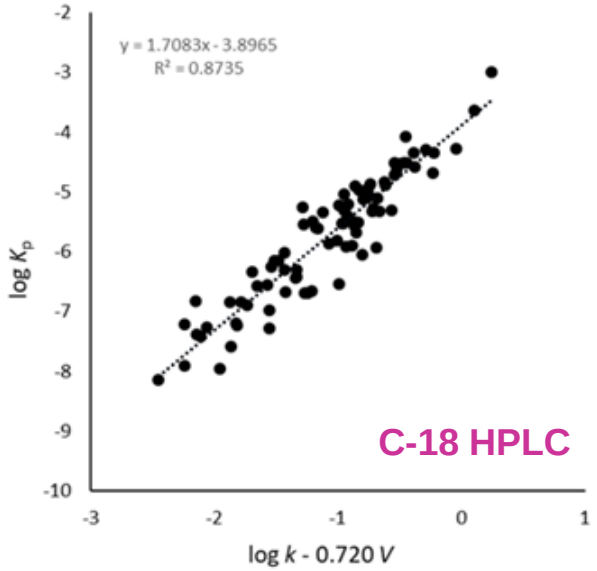


A correction

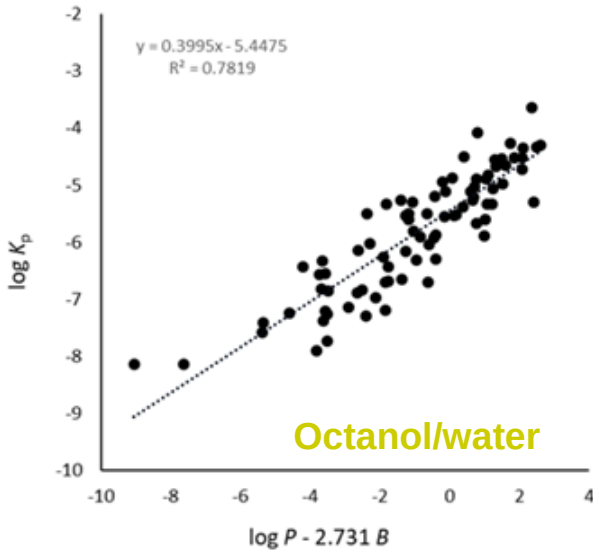
Correction of factors: Experimental correlations

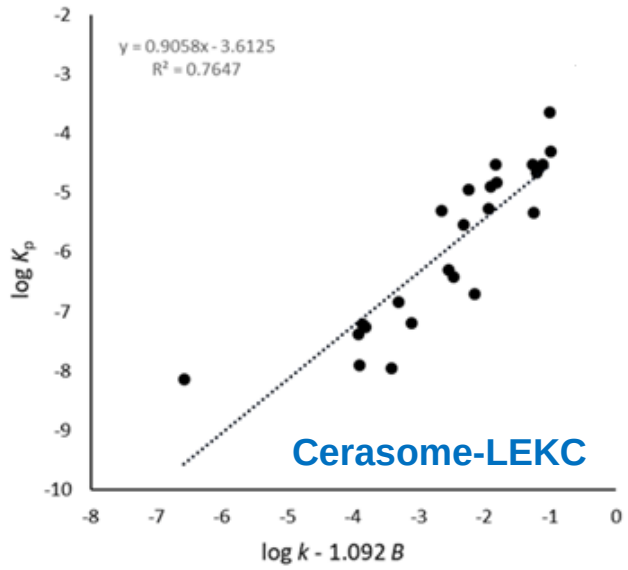


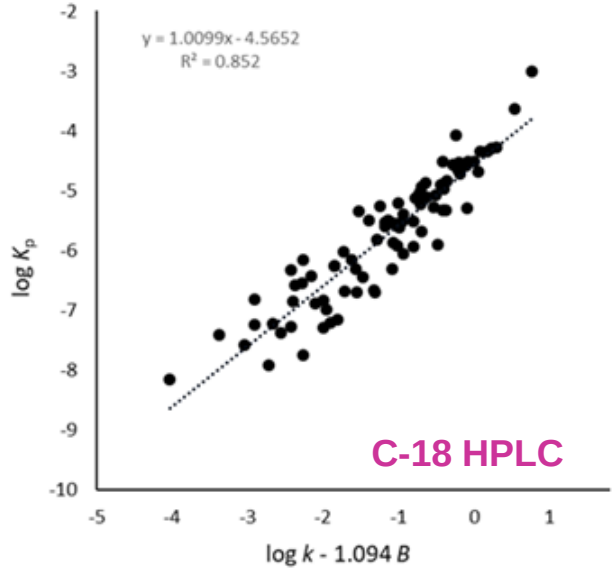




V correction







B correction

Current and future research

- **Characterization of green solvents for surrogation of poorly sustainable HPLC mobile phases (MeCN, THF).**
- **Characterization of common biomimetic columns (HSA, AGP, IAM) for surrogation of biological properties.**
- **Preparation and characterization of biomimetic new protein bonded stationary phases.**
- **Preparation and characterization of artificial parallel membranes for biomimetic microfluidic systems.**

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