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Tutorial on modelling chromatographic surrogation of biological processes

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ABSTRACT

The accurate emulation of biological partition systems through physicochemical models is crucial in pharmacology, toxicology, and environmental science for understanding the ADMET profiles of substances. Direct experimentation on biological systems can be long, expensive, and ethically and practically challenging, so developing reliable physicochemical models is essential. These models help predict compound behaviour in organisms, reduce animal testing, and streamline drug discovery and risk assessment. Chromatographic systems are of particular interest to mimic biological or environmental processes because of its versatility, as they provide a large number of different partition systems only by changing the nature of the mobile and stationary or pseudostationary phases. The effectiveness of any physicochemical system in emulating biological processes is usually evaluated through empirical correlation with biological data. However, the characterization of physicochemical and biological systems using a common model, such as Abraham's solvation model, allows to identify the best physicochemical systems to surrogate particular biological or environmental processes, only by comparison of the system constants of the models. This tutorial demonstrates how to compare, predict, and improve the efficiency of physicochemical systems to surrogate biological or environmental ones without the need for previous empirical correlations. Skin permeation is presented as example of chromatographic surrogation and case study.

1. Introduction

The accurate emulation of biological partition systems through physicochemical partition models is a critical pursuit in various scientific disciplines, particularly in pharmacology, toxicology, and environmental science. Biological partitioning, which involves the distribution of compounds between different biological phases such as tissues, cells, and membranes, is fundamental to understanding the absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles of substances. However, direct experimentation on biological systems can be ethically challenging, time-consuming, and resource-intensive. Consequently, the development and validation of physicochemical partition systems that closely mimic biological partitioning is essential. These models provide practical and efficient means to predict how compounds behave in living organisms, facilitating drug discovery, risk assessment, and the evaluation of environmental contaminants. By employing robust physicochemical models, researchers can reduce the reliance on animal testing, enhance the accuracy of in silico predictions, and streamline the process of bringing safe and effective compounds to market. Therefore, establishing reliable and predictive physicochemical partition systems is not only a scientific necessity but also a step towards more ethical and sustainable research practices.

Among the different physicochemical systems that may surrogate biological partition, those based in liquid chromatography can be highlighted because of their numerous advantages [1–11]. Liquid chromatography is a versatile, sensitive, highly automatized, and high throughput separation technique present in almost any analytical or pharmaceutical laboratory, which requires low amounts of reagents without the need of high purity. In high-performance liquid chromatography (HPLC), there is a diversity of stationary and mobile phases with varied selectivity that offer different possibilities to mimic biological systems. Recent advances have led to biomimetic chromatography where phospholipids and proteins are bonded to HPLC supports in order to emulate cell permeation and biological drug transport processes [8,9,12–20]. Diverse types of micelles, microemulsions and liposomes can be used as pseudo-stationary phases in electrokinetic chromatography (EKC) mimicking some biological processes too [21–26]. For all these advantages, systems based on liquid chromatography are usually

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the preferred physicochemical systems to surrogate biopartitions and other biological and environmental processes.

The goodness of any physicochemical system, chromatographic or not, to surrogate a biological one is often based on the empiric correlation between the physicochemical and the biological data. Although these comparisons provide direct evidence of the quality of the emulation, they have a main drawback, as partition data in the evaluated systems is needed in advance for a representative number of compounds. However, a prediction of the ability of different physicochemical systems to model a given biological or environmental process can be easily done in advance, if all the compared systems are evaluated with a common model.

Once different systems (physicochemical and biological) are characterized through the same model, reliable comparison methods can be used and determine whether physicochemical partition systems can accurately emulate biological partition systems. Such comparative methods enable researchers to assess the predictive ability of physicochemical systems without the need for direct correlation of partition data for a common set of compounds. By rigorously comparing these models, strengths and limitations of each system can be identified, and model parameters can be corrected, to enhance, in this way, the predictive ability.

The present tutorial is focused on showing the different ways in which chromatographic (and in general physicochemical) and biological systems, all characterized through the same common model (Abraham's solvation model in our case), can be compared with the aim of predicting which physicochemical systems are the best options to surrogate biological or environmental processes, without the need for empirical correlations.

2. Solvation model of Abraham

In the early 1990s, Michael H. Abraham developed a solvation model [27–30], based in Linear Free Energy Relationships (LFERs), which has been widely used to parametrize and interpret a wide variety of physicochemical and biological processes mainly ruled by solute-solvent interactions. As in all LFERs models, the overall free energy change of a solvation process is decomposed as a sum of the free energy changes of the individual solute-solvent interactions. In Abraham's LFER model, each solute-solvent contribution is taken as the product of a solute (solute descriptor, written in capital letters) and a solvent (system constant, written in lower case letters) parameters. Since the Gibbs free energy variation of the process is directly related to the logarithm of the constant or solvent property (*SP*) ruling the process (or a related thermodynamic parameter, such as retention factor in liquid chromatography), the Abraham model for solvation of neutral solutes takes the form of Eq. (1).

$$\log SP = c + eE + sS + aA + bB + vV \quad (1)$$

The $e{\cdot}E$ term models polarizability contributions from solute *n*- and π- electrons; $s{\cdot}S$ accounts for general dipolarity/polarizability interactions; $a{\cdot}A$ represents the hydrogen bonding donation from solute to solvent and $b{\cdot}B$ from solvent to solute; and $v{\cdot}V$ is related to the energy of formation of the solute cavity in the solvent together with some Van der Waals residual interactions. The constant term (*c*) accounts for system factors that are not dependent of the solute-solvent interactions (normalization of solute descriptors or property, change of property units, property conversion factors, such as phase ratio in liquid chromatography, etc.). E, S, A, B, and V are the solute molecular descriptors of excess molar refraction (in reference to a linear alkane of similar molecular size), dipolarity/polarizability, hydrogen bond acidity, hydrogen bond basicity, and McGowan's characteristic volume (in $cm^3{\cdot}mol^{-1}$ /100), respectively. And *e, s, a, b*, and *v* are the systems constants accounting for the complementary solvent properties that interact with those of the solute: capability of the solvent to interact with electron lone pairs as the result of loosely bound solute *n*- and π-electrons; dipole-type interactions (orientation and induction); hydrogen-bond acceptor basicity; hydrogen-bond donor acidity; and easiness of formation of a cavity to accommodate the solute, respectively. In partition processes, which imply solute distribution between two solvents (e.g., mobile and stationary phase, blood and brain, …) system constants measure the difference between the interactions of the solute with the two solvents or phases. The sign and magnitude of the system constants determine tendency and extent of the solutes to partition in one or the other solvent or phase. For instance, a positive coefficient in chromatographic retention processes (being the retention factor *k* the measured *SP* property) indicates that an increase in the corresponding solute property (or solute descriptor value) favours partition to the stationary phase and thus solute retention. On the contrary, a negative coefficient favours solute elution. Therefore, system constants characterize the biological or chromatographic process, and they are usually determined by multiple linear regression of the measured property (e.g., *k*) for a set of adequate solutes with very well-known and diverse descriptors. Free and payment databases and calculation software are available to obtain the descriptors [31–34].

An excellent tutorial for the application of the model to separation systems has been published by Poole [35], who also coined the term "solvation parameter model" for the application of Abraham's solvation model to these systems. A simplification of the regression method to obtain good estimates of the system constants with a much lower set of solutes and experimental work has been recently published too [36].

This model can be also used to estimate biopartition properties if the coefficients of the system and the descriptors are known for the compounds of interest. However, some descriptors (*S, A* and *B*) are not easily determined experimentally, and often need to be estimated. The main advantage of chromatographic surrogate systems lies in the fact that there is no need to know all the descriptors involved in the model to predict the biological property. This is especially useful for estimating the properties of new compounds, particularly in the pharmaceutical field, where a high number of compounds are synthesized to find those with the most suitable characteristics for a given application.

The Abraham LSER model, with some variations, has been developed to characterize a large diversity of physicochemical and biological processes, such as liquid/liquid [37–40] and gas/liquid partitions [37, 41–43], biopartitions [44–49], kinetic processes [37,48,50], toxicities [7,51,52], etc. On one hand, Abraham and co-workers did a thoughtful characterization of many biological and environmental processes by his model [53], including blood-brain and other blood-organ or tissue distributions [44–46], intestinal-absorption [47], skin permeation [46,48, 49], and aquatic toxicities [7,51,52]. On the other hand, the Abraham model has been used from the decade of the 90 s [54–56] to characterize many HPLC and EKC systems and there are extensive literature reviews, compilations, and tutorials [24,25,35,57–60]. The Abraham's model is by far the most common model used for characterization of both biological and chromatographic processes. Therefore, the high availability of characterized biological and liquid chromatography systems allows comparison of the system constants of both sets of data in order to select liquid chromatography systems with similar solute-solvent interactions to those of a particular biological/environmental system and predict the feasibility of biological surrogation.

3. Comparison of models

Since the sign and magnitude of the system constants of the Abraham's solvation model defined by the coefficients of Eq. (1) measure the effect and significance of the solute-solvent interactions in the chromatographic and biological systems, comparison of the values of these coefficients should led to identification of the best chromatographic systems to surrogate a particular biological or environmental process.

Different rigorous numerical parameters have been proposed to compare Abraham models and measure their similarity. All of them are geometrical angles or distances between the five system constants of the

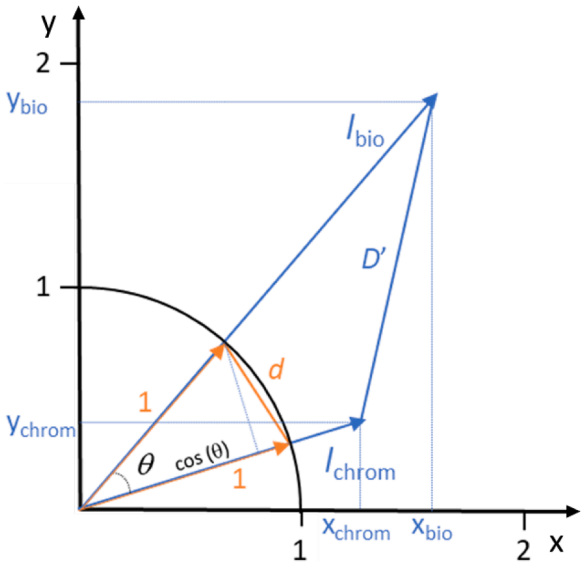

Fig. 1. Relationships between *D*', *d*, and θ in a two-dimensions space. Adapted from [9].

Abraham equations plotted as vectors in a 5-D space. A schematic representation of the implied vectors, angle and distances is presented in Fig. 1 for a hypothetical comparison of two simplified Abraham equations with only two systems constants (x and y coefficients in a 2-D plotting space).

Application of the Abraham equation to a biological *SP* measured property (subscript *bio*) and a surrogation chromatographic property (subscript *chrom*), which usually is the retention factor *k*, gives the following Eqs. (2) and (3).

$$\log SP_{bio} = c_{bio} + e_{bio}E + s_{bio}S + a_{bio}A + b_{bio}B + v_{bio}V \tag{2}$$

$$\log k_{chrom} = c_{chrom} + e_{chrom}E + s_{chrom}S + a_{chrom}A + b_{chrom}B + v_{chrom}V \tag{3}$$

It is useful to write Eqs. (2) and (3) in terms of normalized coefficients (or system constants of the unitary vectors, subscript *u*) according to Eqs. (4) and (5):

$$\log SP_{bio} = c_{bio} + l_{bio}\left(e_{u,bio}E + s_{u,bio}S + a_{u,bio}A + b_{u,bio}B + v_{u,bio}V\right) \tag{4}$$

$$\log k_{chrom} = c_{chrom} + l_{chrom}\left(e_{u,chrom}E + s_{u,chrom}S + a_{u,chrom}A + b_{u,chrom}B + v_{u,chrom}V\right) \tag{5}$$

where *l* is the length of any Abraham vector easily calculated from the system constants through Eq. (6). Each one of the normalized coefficients can be easily calculated dividing the system constants by the length of the vector.

$$l = \sqrt{e^2 + s^2 + a^2 + b^2 + v^2} \tag{6}$$

First measure of similarity was proposed by Ishihama and Asakawa [61] as the angle θ (or cos θ as a better numerical parameter) between the 5 Abraham coefficients vectors as shown in Fig. 1 (for two coefficients) and numerically calculated by Eq. (7). The lower the θ value or the closer cos θ to 1, the more similar the two systems are.

$$\cos\theta = \frac{e_{bio}e_{chrom} + s_{bio}s_{chrom} + a_{bio}a_{chrom} + b_{bio}b_{chrom} + v_{bio}v_{chrom}}{\sqrt{{e_{bio}}^2 + {s_{bio}}^2 + {a_{bio}}^2 + {b_{bio}}^2 + {v_{bio}}^2}\sqrt{{e_{chom}}^2 + {s_{chrom}}^2 + {a_{chrom}}^2 + {b_{chrom}}^2 + {v_{chrom}}^2}} \tag{7}$$

Later, Abraham and Martins [48] proposed the use of the Euclidean distance (*D*') between the system constants (Eq. (8)) as a simpler measure of the similarity between the two systems. The lower the *D*', the more similar the two systems are. They suggested that a *D*' value below 0.8 indicated similarity enough between the two compared systems.

$$D' = \sqrt{(e_{bio} - e_{chrom})^2 + (s_{bio} - s_{chrom})^2 + (a_{bio} - a_{chrom})^2 + (b_{bio} - b_{chrom})^2 + (v_{bio} - v_{chrom})^2} \tag{8}$$

It turns out that this similarity measure depends on the length of the Abraham coefficients vector, regardless that the Ishihama-Asakawa vector angle θ is not dependent (see Fig. 1). Then, Rosés, Abraham and coworkers proposed a variation of this parameter [8] by using the unitary system constants instead of the direct Abraham coefficients. The Rosés-Abraham *d* distance parameter is calculated by means of Eq. (9).

$$d = \sqrt{\left(e_{u,bio} - e_{u,chrom}\right)^2 + \left(s_{u,bio} - s_{u,chrom}\right)^2 + \left(a_{u,bio} - a_{u,chrom}\right)^2 + \left(b_{u,bio} - b_{u,chrom}\right)^2 + \left(v_{u,bio} - v_{u,chrom}\right)^2} \quad (9)$$

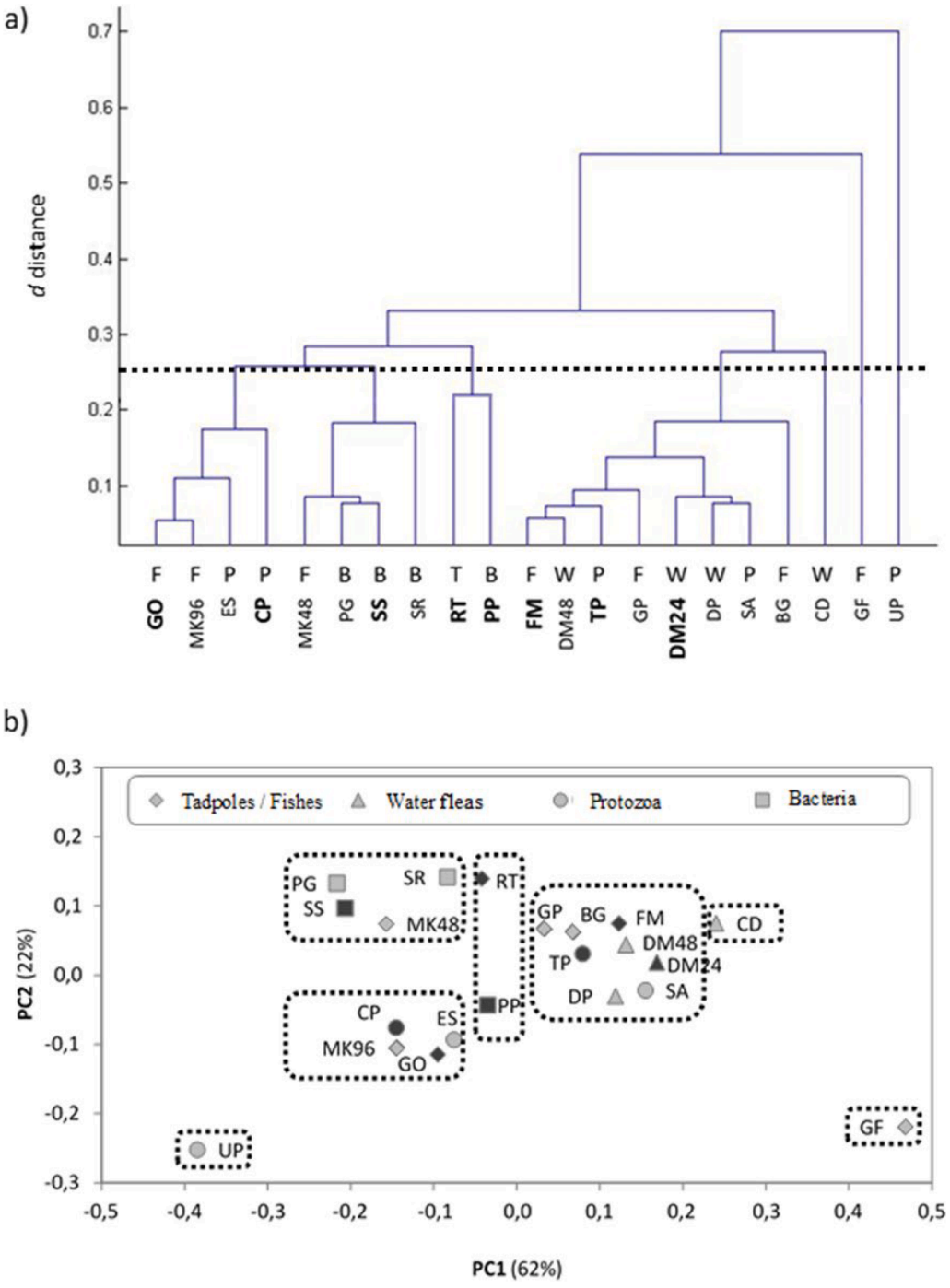

Fig. 2. a) Dendrogram plot of aquatic toxicity biological systems in tadpoles (T), fishes (F), water fleas (W), protozoans (P), and bacteria (B). RT: *Rana tadpoles* (-log C_{nar}), FM: *Fathead minnow* (-log LC50), GP: *Guppy* (-log LC50), BG: *Bluegill* (-log LC50), GO: *Golden orfe* (-log LC50), GF: *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), C_{nar}: narcosis concentration, LC50: median lethal concentration (50 %), IGC50: median inhibitory growth concentration (50 %), IGC: inhibitory growth concentration, MIC: minimum inhibitory concentration towards bacterial growth. Selected representative systems are shown in boldface. b) PCA scores plot of the aquatic toxicity biological systems. Selected representative systems are shown in dark grey. Reprinted with permission from [7]. Copyright 2017 American Chemical Society.

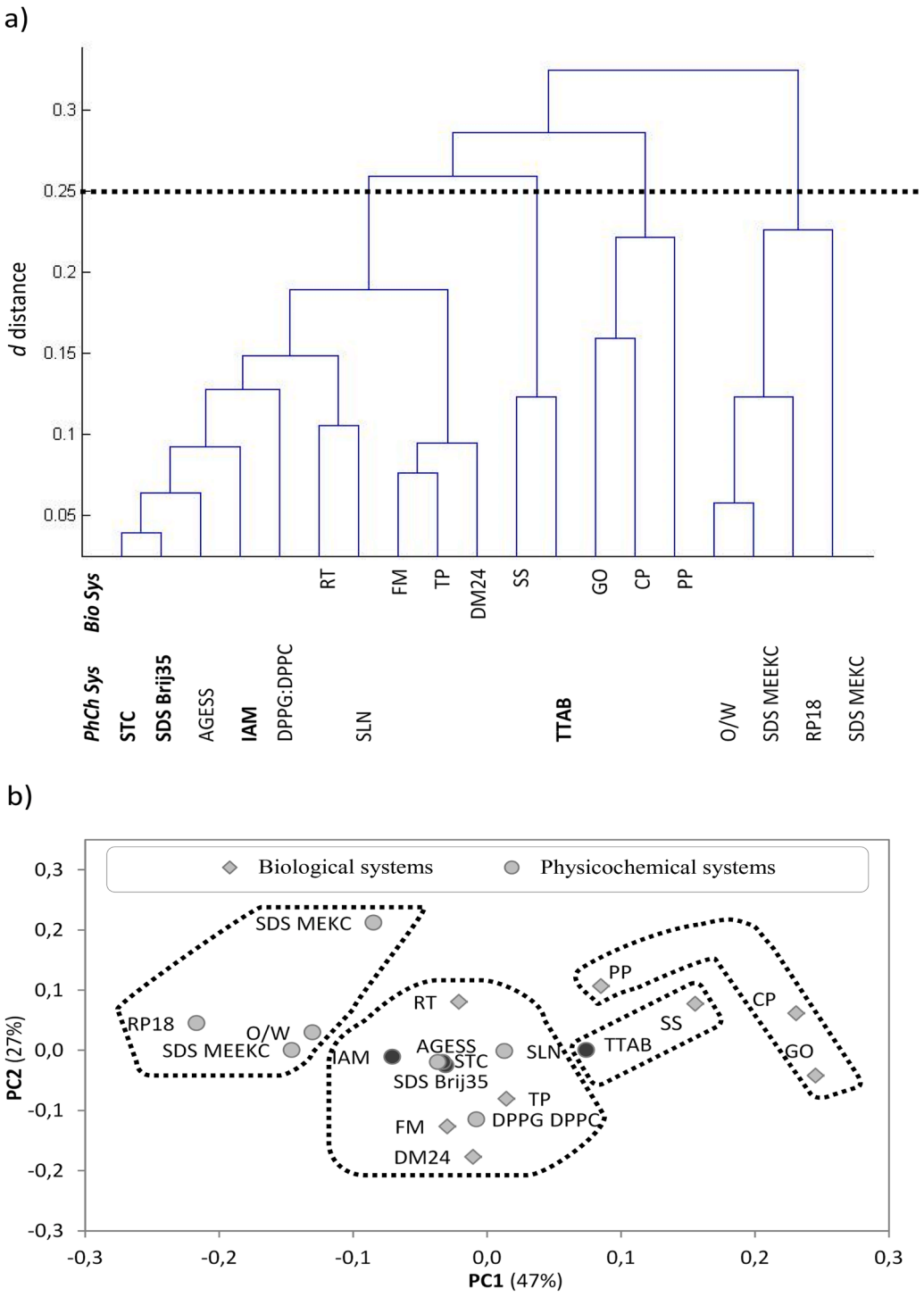

Fig. 3. a) Dendrogram plot of the selected aquatic toxicity biological systems and of the surrogating chromatographic and octanol/water systems. RP18: RPLC in a C18 column (40 % acetonitrile); IAM: RPLC in an immobilized artificial membrane column (40 % acetonitrile); SDS MEKC: MEKC with sodium dodecyl sulfate; SDS MEEKC: MEEKC with sodium dodecyl sulfate; SLN: MEKC with sodium N-lauroylsarcosinate; STC: MEKC with sodium taurocholate; TTAB: MEKC with tetradecyltrimethylammonium bromide; SDS Brij 35: MEKC with a mixture of sodium dodecyl sulfate and polyoxyethylene(23)dodecyl ether; DPPG DPPC: MEKC with a mixture of dipalmitoylphosphatidyl glycerol and dipalmitoylphosphatidyl choline; AGESS: MEKC with dodecane allyl glycidyl ether sulfite-modified siloxane; O/W: octanol/water partition (log $P_{o/w}$). Abbreviations of biological systems as in Fig. 2. b) PCA scores plot of the eight selected biological systems (circle) and the eleven surrogating physicochemical systems (diamond) evaluated. Reprinted with permission from [7]. Copyright 2017 American Chemical Society.

Table 1
Unitary system constants of skin permeation and the surrogate physicochemical systems, module of the non-normalized coefficients' vector (l) and Euclidean distance (d) to skin permeation. K_p: skin-water permeability coefficient (cm s^{-1}), $P_{o/w}$: octanol-water partition coefficient, P_0: PAMPA permeability (cm s^{-1}).

System	log *SP*	c	e_u	s_u	a_u	b_u	v_u	l	d
Skin permeation	log K_p	−5.328	0.044	−0.195	−0.109	−0.783	0.579	3.10	0.00
Octanol/water	log $P_{o/w}$	0.088	0.106	−0.199	0.006	−0.655	0.721	5.29	0.23
PAMPA-Certramides	log P_0	−4.180	0.021	−0.192	−0.335	−0.733	0.559	3.09	0.23
PAMPA-IPM	log P_0	−4.200	0.031	−0.191	−0.228	−0.780	0.550	2.62	0.12
Cerasome-LEKC	log k	−1.922	0.084	−0.265	−0.046	−0.611	0.740	2.37	0.26
C-18 HPLC	log k	−0.386	0.082	−0.193	−0.223	−0.618	0.724	2.14	0.25

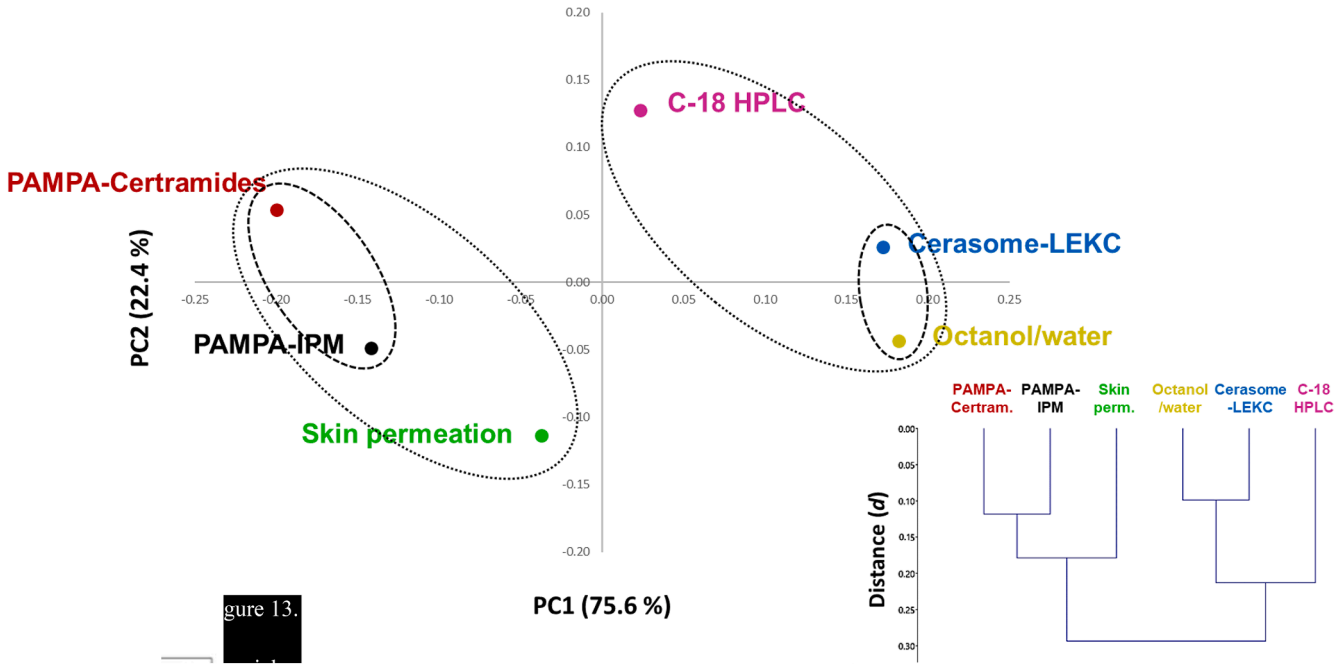

Fig. 4. Principal component analysis and dendrogram of d distances of the skin permeation and the evaluated surrogate physicochemical systems according to their normalized system constants. Clusters: —— $d < 0.15$; ····· $d < 0.25$. Reprinted from [9], with permission from Elsevier.

An approximated d value of 0.25 or less was suggested as indicator of close similarity between the two compared systems.

It can be easily derived that d and θ are geometrically related by Eq. (10).

$$\theta = 2\arcsin\left(\frac{d}{2}\right) \tag{10}$$

Notice that although the different parameters can be related, they measure different similarities and improper use may lead to wrong conclusions. Whereas θ and d are directly related by Eq. (10), relationship with D' is more complex and depends on the length of the vectors. For instance, two coefficient vectors very close in the 5-D space will have a very low θ angle and a very low d distance, which would indicate a close similarity. However, the D' distance can be large, indicating poor similarity, if they have quite different lengths.

The angle and distance parameters can be used for rigorous estimation of the similarity between the biological and the chromatographic systems. When several biological and/or chromatographic systems are going to be compared, a table of distances (or angles) between the different systems should be constructed and some graphical methods may help to compare the systems. Dendrograms and principal component analysis (PCA) can be particularly useful for clustering the systems according to their similarity.

Dendrogram are diagrams plotted using hierarchical clustering algorithms that show the distances between pairs of sequentially merged classes. The height of the dendrogram indicates the order in which the clusters are joined. The algorithm to do a dendrogram repeatedly executes the following two steps: (1) identify the two clusters that are closest together, and (2) merge the two most similar clusters. This iterative process continues until all the clusters are merged together. Identification of the closest clusters is done by means of different distance metrics. The most common are Euclidean distances, such as D' or d. Linkage of the clusters can be done by different criteria too: from the two closest items of the clusters, from the two farthest ones, from the center of the cluster, and many others. As with distance metrics, the choice of linkage criteria should be made based on theoretical considerations. For our purpose of similarity checking, d distance from the center of the formed clusters can be a good option.

Principal components analysis is a chemometric tool used to transform the input data in a multivariate space (5-D in our case) to a new multivariate space (principal components (PCs) space) whose axes are uncorrelated and rotated with respect to the original space. The number of PCs is equal to the number of original variables and the first PCs are those that more explain the system variance. Thus, a 2-D plot of PC2 vs PC1 will keep most of the distance information between the original 5-D system constants plot. However, some loss of information is always expected, as much as lower is the variance explained by PC1 and PC2. In some cases, more PCs should be considered.

An example is presented in Figs. 2 and 3 for comparison and surrogation of aquatic toxicity [7]. Many different aquatic systems, based in tadpoles, fishes, water flea, protozoan and bacteria, are used to measure aquatic toxicities (expressed as Narcosis concentration, Lethal Dosis,

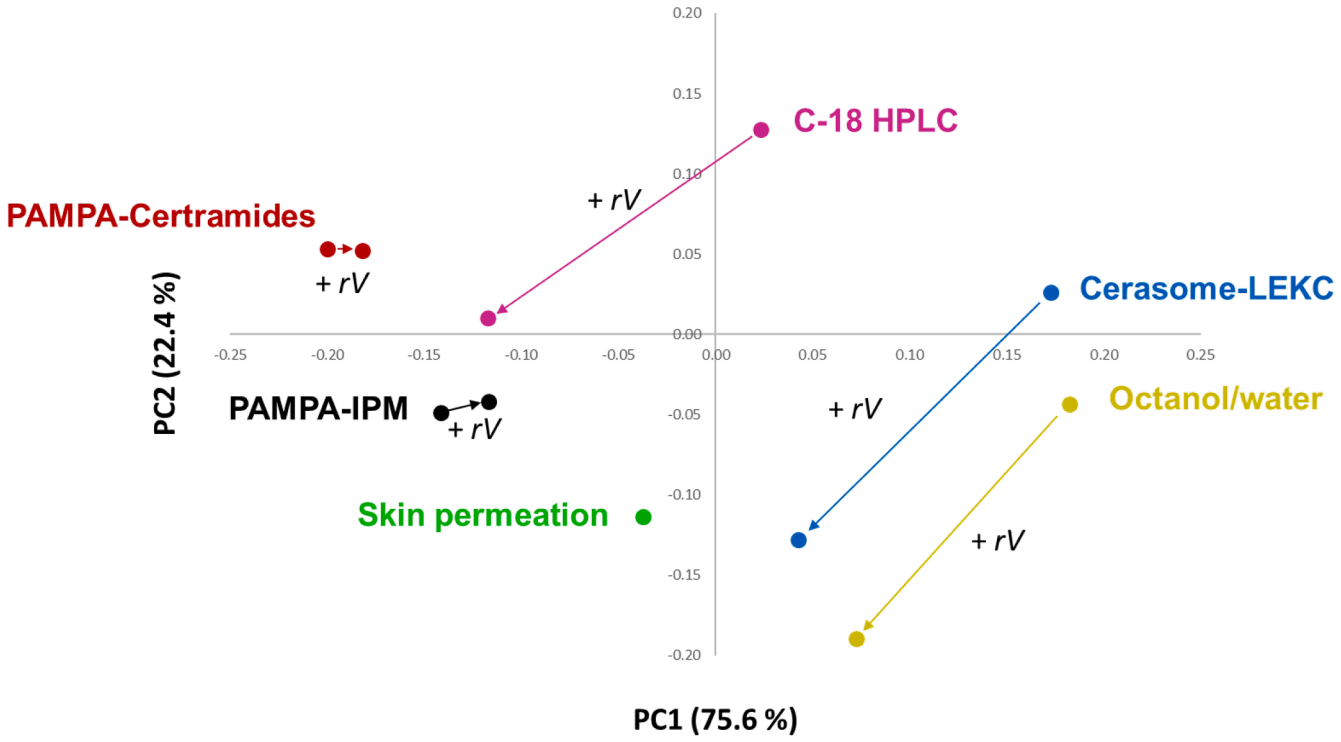

Fig. 5. Principal component analysis of the skin permeation and the evaluated surrogate systems according to their normalized system constants (as in Fig. 4) plus addition of the same systems with volume correction effect (+ *rV*). Reprinted from [9], with permission from Elsevier.

Inhibition Growth Concentration, or Minimum Inhibition Concentration). Fig. 2 presents the dendrogram (Fig. 2a) and the two first PCs (Fig. 2b) of the studied toxicity systems. The unitary system constants and the Euclidean *d* distance are used for clustering the systems (numerical data given in the original publication). Cutting the dendrogram height at $d = 0.25$, seven clusters are formed (three of them with only one element) which are also shown in the PCA plot. Since all elements in one cluster are supposed to behave similarly, some biological systems in the main clusters were selected as representative systems.

The *d* distances between the selected biological systems and several HPLC and electrokinetic chromatographic systems, together with the traditional octanol-water partition system, are plotted in the dendrogram and PCA of Fig. 3. Four clusters are observed. One cluster contains the chromatographic systems of RP18 column, micellar and microemulsion EKC with SDS surfactant, and octanol-water partition and none of the toxicity systems. Thus, these chromatographic systems are not expected to be good surrogates for aquatic toxicity. On the other side of the PCA plot, there is a cluster with three toxicity systems (PP, CP, and GO). None of the studied chromatographic systems is in the cluster and therefore they are not expected to be surrogated. Another cluster is formed by the TTAB MECK system and the SS biological system. Therefore, TTAB is expected to be a good surrogate for SS and for the systems of the SS cluster in Fig. 2 (PG, SR, and MK48). The last cluster includes the toxicity systems of RT, FM, TP, and DM24 and several chromatographic systems of HPLC with IAM column and EKC systems with different surfactants (STC, SDS-Brij mixtures), liposomes (DPPG-DPPC) and a polymer (AGESS). Of course, the conclusions from dendrograms and PCA plots are merely indicative because of the loss of information in clustering and principal components reduction. Rigorous comparison of systems should be done by the distance or angle parameters.

4. Direct surrogation of biological processes

For surrogation of biological processes by chromatographic systems, one expects to obtain good linear relationships between the measured free energy parameters of the biological process (log SP_{bio}) and the surrogate chromatographic parameter (log k_{chrom}). The expected linear equation can be easily obtained if the two systems have been characterized by the same model (Abraham solvation model in our case) and a short distance parameter between the two systems is obtained. In the best case, the *d* distance is equal to zero, and then, according to Eq. (9), the coefficients of both systems are equal, which implies that Eq. (11) holds for any solute.

$$\left(e_{u,bio}E + s_{u,bio}S + a_{u,bio}A + b_{u,bio}B + v_{u,bio}V\right) = \left(e_{u,chrom}E + s_{u,chrom}S + a_{u,chrom}A + b_{u,chrom}B + v_{u,chrom}V\right) \quad (11)$$

Applying this equality to Eqs. (4) and (5), linear Eq. (12) is obtained.

$$\log SP_{bio} = \frac{l_{chrom}c_{bio} - l_{bio}c_{chrom}}{l_{chrom}} + \frac{l_{bio}}{l_{chrom}}\ log\ k_{chrom} \quad (12)$$

The expected slope of the biological-chromatographic correlation equals to the ratio of the lengths of the two vectors, and the intercept, a combination of vector lengths and correlation constants of the model.

Notice that the requirement for a good correlation between a biological parameter and a chromatographic one is similarity of the normalized coefficients of the two models (measured by *d* distance), and not of the non-normalized correlation coefficients of the models (measured by *D*'). In the latter case, equality of the non-normalized coefficients would imply the length of the two vectors to be the same and the correlation equation between the two systems would simply be a shift of the biological parameter from the chromatographic one according to the difference of the correlation constants of the models.

5. Surrogation of biological processes by chromatographic retention and additional descriptors

Direct surrogation of biological processes by chromatography implies a very good similarity of the normalized system constants of both processes, which is seldom accomplished. Therefore, many surrogation

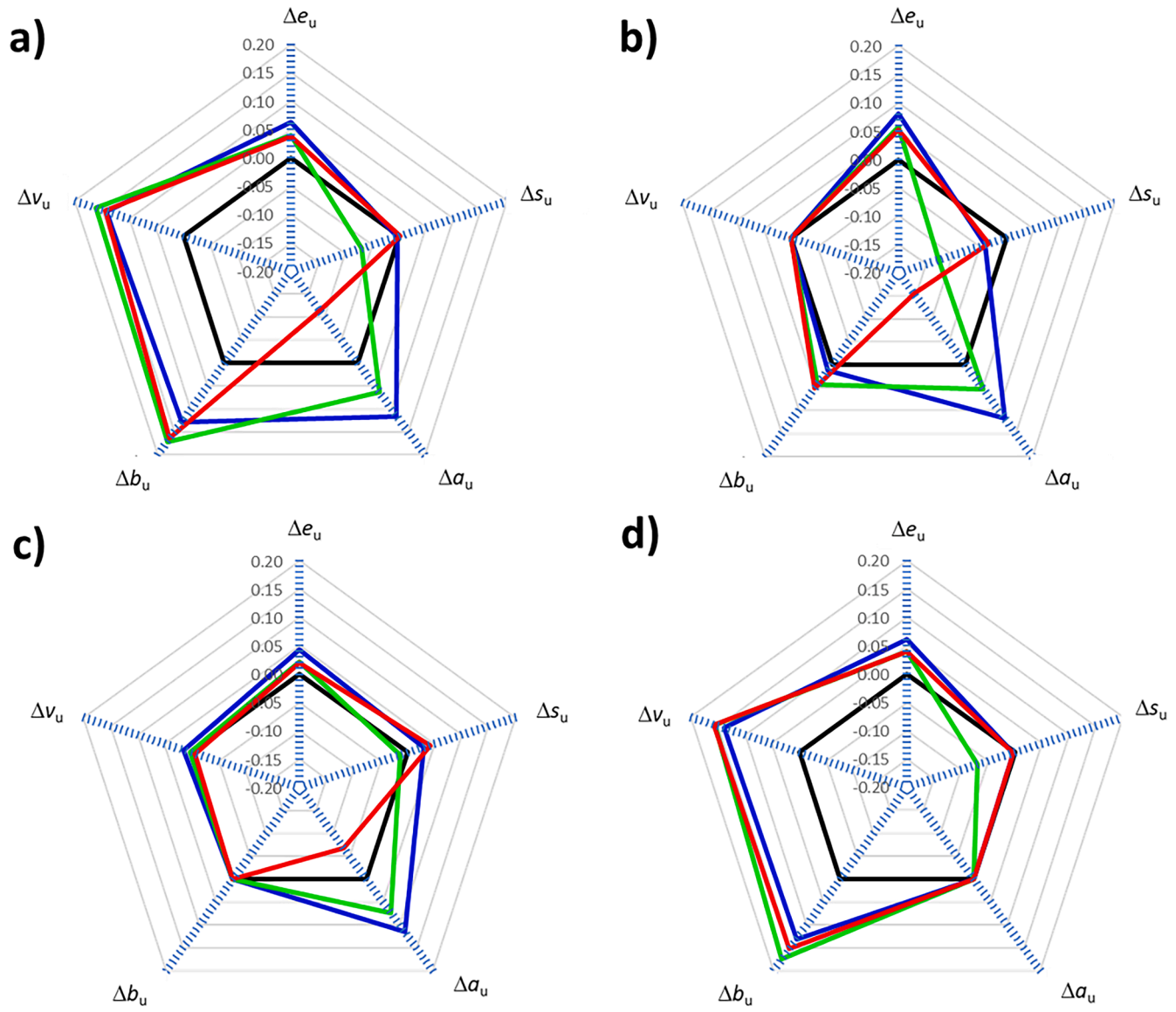

Fig. 6. Radial plots of the system constants differences between the skin permeation and the physicochemical surrogate systems. a) No parameter correction; b) Solute volume (*V*) correction; c) Solute hydrogen bond basicity (*B*) correction; d) Solute hydrogen bond acidity (*A*) correction. Systems: — skin permeation, — octanol-water partition, — cerasome-LEKC, — C18-HPLC.

Table 2
Predicted unitary system constants with correction parameters and Euclidean *d* distances.

System	e_u	s_u	a_u	b_u	v_u	*f*	*q*	*p*	*r*	*d*
Skin permeation	0.044	−0.195	−0.109	−0.783	0.579					
V correction										
Octanol-water partition	0.125	−0.235	0.008	−0.770	0.579	1.177	−5.39	0.69	−0.84	0.15
Cerasome-LEKC	0.102	−0.321	−0.056	−0.740	0.579	1.212	−2.29	1.58	−0.98	0.15
C18-HPLC	0.097	−0.228	−0.264	−0.730	0.579	1.181	−4.50	1.71	−0.85	0.18
B correction										
Octanol-water partition	0.088	−0.164	0.005	−0.783	0.594	0.823	−5.37	0.48	−0.76	0.13
Cerasome-LEKC	0.066	−0.208	−0.036	−0.783	0.582	0.786	−3.35	1.03	−0.94	0.08
C18-HPLC	0.065	−0.153	−0.177	−0.783	0.573	0.792	−4.77	1.15	−0.91	0.08
A correction										
Octanol-water partition	0.106	−0.198	−0.109	−0.651	0.717	0.994	−5.38	0.58	−0.36	0.20
Cerasome-LEKC	0.084	−0.264	−0.109	−0.608	0.736	0.995	−2.83	1.30	−0.20	0.25
C18-HPLC	0.084	−0.197	−0.109	−0.631	0.738	1.020	−4.61	1.48	0.37	0.22

models rely on the addition of complementary descriptors that improve the correlations [13]. Very often, these complementary descriptors are calculated in silico by many different estimation parameters and algorithms which empirically select the ones that best fit the correlation. Thus, experimental chromatographic and computed in silico descriptors are combined to create hybrid models for a better biological surrogation.

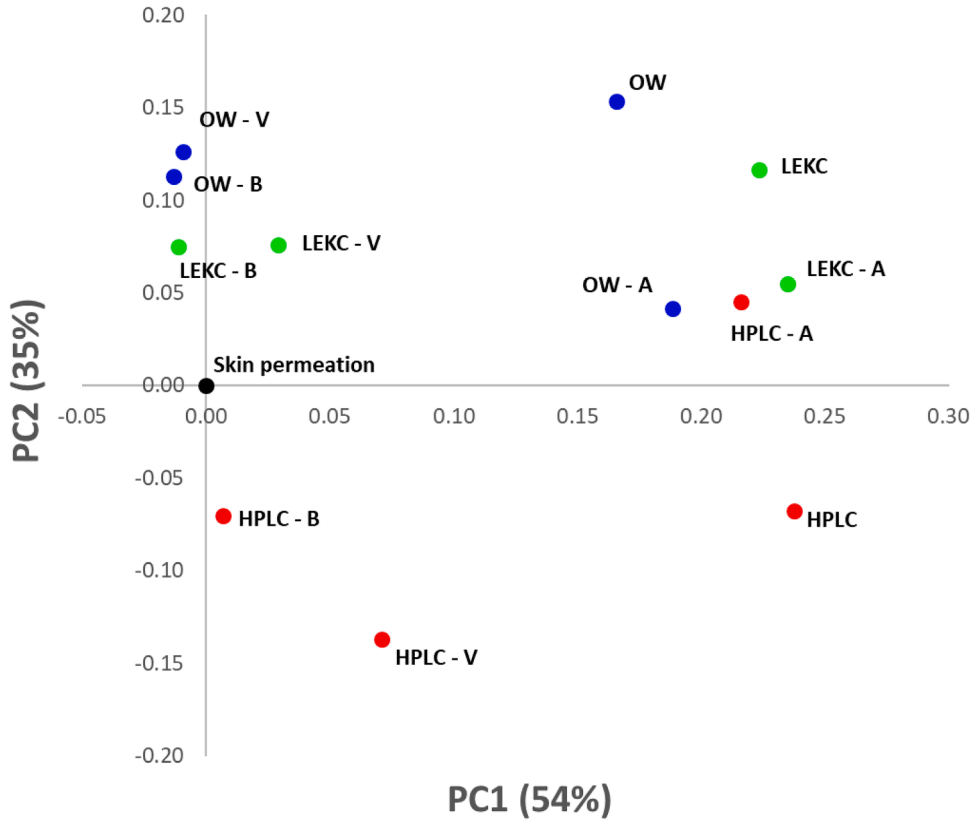

Fig. 7. Principal component analysis of the skin permeation and the evaluated surrogate systems according to their normalized system constants, and the same physicochemical systems with volume (*V*), basicity (*B*) and acidity (*A*) correction.

A close inspection of the similarity of the individual normalized Abraham coefficients of the two systems can help to foresee what type of descriptors (mainly descriptors related to solute volume, hydrogen bond, and/or polarity/polarizability properties) should improve the correlation and even to estimate the degree of improvement.

If the normalized system constants of the biological and chromatographic Abraham correlations are very similar except one, the difference in the contributions of the dissimilar interaction can be subtracted from the correlation and used as a correction factor. As an example, we shall derive the correction for the solute volume interaction (vV), which is one of the most significant for many chromatographic and biological processes, although the same derivation can be applied to any other interaction [9].

Since the length of the vector of the normalized coefficients must be always one, equality of Eq. (11) cannot be fulfilled if the v_u coefficients of biological and chromatographic systems are different. But a proportionality between the other 4 coefficients (Eq. (13)) is enough to fulfil the requirement of linear regression between the biological parameter (corrected by solute volume) and the surrogating chromatographic parameter.

$$\begin{aligned}&\left(e_{u,bio}E+s_{u,bio}S+a_{u,bio}A+b_{u,bio}B\right)\\&=f\left(e_{u,chrom}E+s_{u,chrom}S+a_{u,chrom}A+b_{u,chrom}B\right)\end{aligned} \tag{13}$$

This proportionality coefficient (f) is the ratio between the length of the 4 non-corrected coefficients vectors, which are obtained from the normalized coefficients of the systems, excluding the coefficient to be corrected, v_u in this case. Therefore, the f correction factor can be calculated by Eq. (14).

$$f=\sqrt{\frac{{e_{u,bio}}^2+{s_{u,bio}}^2+{a_{u,bio}}^2+{b_{u,bio}}^2}{{e_{u,chrom}}^2+{s_{u,chrom}}^2+{a_{u,chrom}}^2+{b_{u,chrom}}^2}} \tag{14}$$

Eqs. (4) and (5) can then be written as Eqs. (15) and (16):

$$\log SP_{bio}=c_{bio}+l_{bio}\left(e_{u,bio}E+s_{u,bio}S+a_{u,bio}A+b_{u,bio}B\right)+l_{bio}v_{u,bio}V \tag{15}$$

$$\begin{aligned}\log k_{chrom}=&\,c_{chrom}+l_{chrom}\left(e_{u,chrom}E+s_{u,chrom}S+a_{u,chrom}A+b_{u,chrom}B\right)\\&+l_{chrom}v_{u,chrom}V\end{aligned} \tag{16}$$

And combining them with Eq. (13), arranging terms, and isolating $\log SP_{bio}$, a bilinear correlation between the biological parameter and the retention factor and volume of the solutes is obtained according to Eq. (17).

$$\log SP_{bio}=q+p\log k_{chrom}+rV \tag{17}$$

where

$$q=\frac{l_{chrom}c_{bio}-fl_{bio}c_{chrom}}{l_{chrom}} \tag{18}$$

$$p=\frac{fl_{bio}}{l_{chrom}} \tag{19}$$

$$r=l_{bio}\left(v_{u,bio}-fv_{u,chrom}\right) \tag{20}$$

Alternatively, Eq. (17) can be written as a linear correlation of the biological parameter from the physicochemical parameter corrected by the volume of the solute, such as Eq. (21) shows.

$$\log SP_{bio}=q+p\left(\log k_{chrom}+\frac{r}{p}V\right) \tag{21}$$

Notice that Eq. (12) is equivalent to Eqs. (17)–(21) when there is no volume correction, i.e., considering that $f=1$ and $r=0$.

In fact, correction of one of the system constants of the chromatographic model to assimilate it to the one of the biological model, provides a new chromatographic unitary vector with the corrected system constant equal to the one of the biological system (e.g., $v_{u,chrom}$=$v_{u,bio}$)

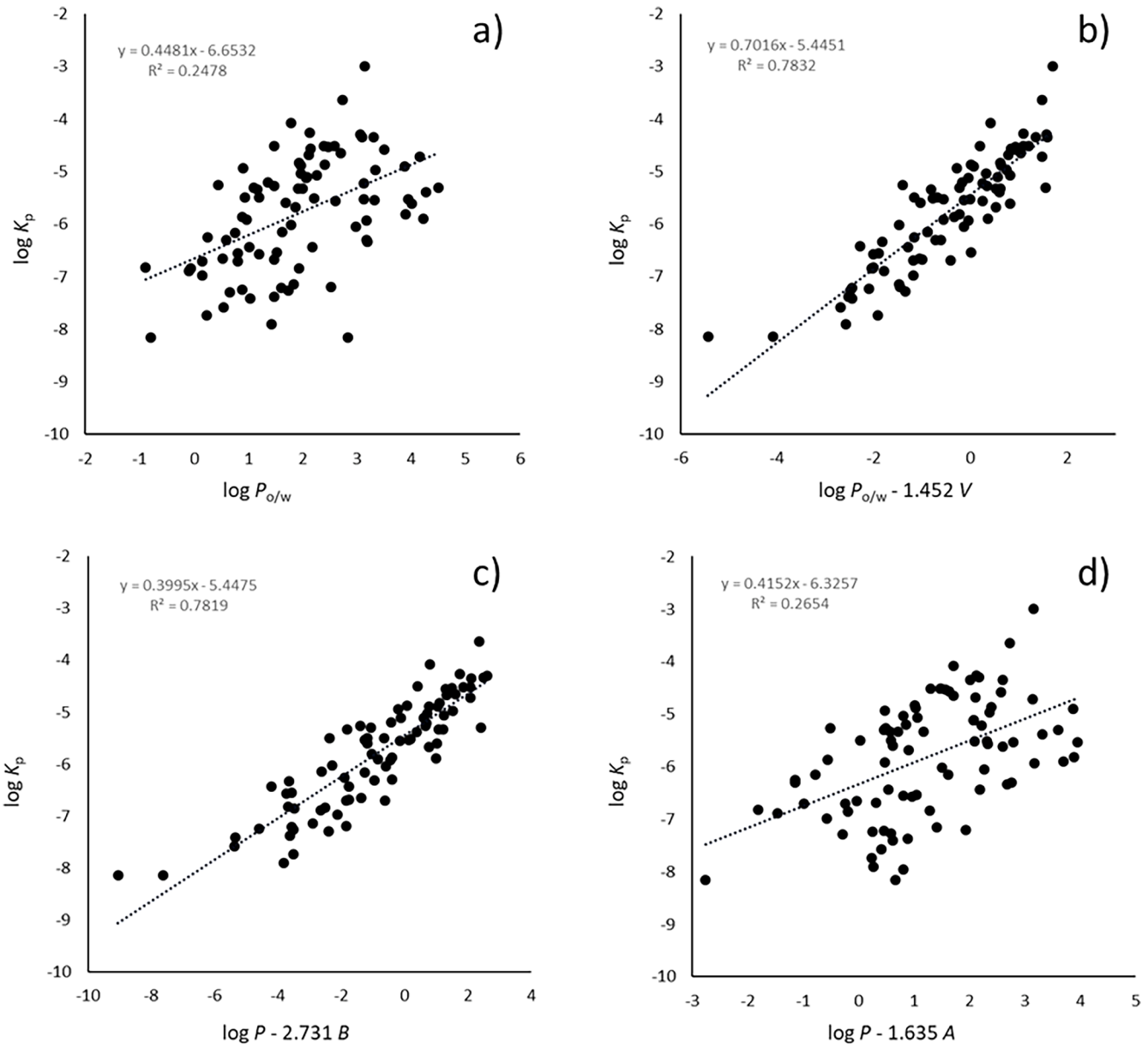

Fig. 8. Experimental correlation for the surrogation of skin permeation by octanol-water partition. a) No parameter correction; b) Solute volume (*V*) correction; c) Solute hydrogen bond basicity (*B*) correction; d) Solute hydrogen bond acidity (*A*) correction.

and the other chromatographic unitary system constants equal to the initial ones multiplied by the *f* parameter (i.e., $fe_{u,chrom}$, $fs_{u,chrom}$, $fa_{u,chrom}$, and $fb_{u,chrom}$,). New *d* distances between the chromatographic and biological models can be then calculated using the new chromatographic system constants and the biological ones by Eq. (9), which should be shorter than the uncorrected previous distances.

6. Skin permeation: a case of study

An illustrative example of the improvement of chromatographic surrogation for skin permeation [9] by one system constant correction is proposed. Permeation of bioactive compounds through the skin is a truly relevant process in fields like drug development, cosmetics, or toxicity studies. Nevertheless, the in vivo measurement of skin permeation implies a long and complex procedure, ethically questionable in some cases [62]. The standard in vitro method, based in permeation of compounds through skin membranes placed in Franz cells is very long too, and requires human (or surrogating animals) skin membranes [63–65]. Therefore, development of good surrogate physicochemical systems is very desirable.

We compared six surrogate physicochemical systems in a recent publication [9]. Two based on parallel artificial membrane permeation assays (PAMPA) with specific artificial membranes with certramides (PAMPA-Certramides) and isopropyl myristate (PAMPA-IPM) that simulate the *stratum corneum* of the epidermis [66–68]; the classical octanol-water partition [69], used for estimation of many biological parameters; and two liquid chromatography systems. One of the chromatography systems, developed by Liu, Abraham, and coworkers [26,70], was based on liposome EKC with a pseudo-stationary phase of cerasomes that emulate the *stratum corneum* lipids (Cerasome-LEKC). The last one was a simple HPLC system with a common C18 column and an acetonitrile-water (60:40, v/v) mobile phase that was proved to give good correlations with skin permeation especially if a size correction factor (solute volume or molecular weight) was added [10,11,71,72].

The normalized coefficients of all these systems together with that of skin permeation [49] are presented in Table 1. Distances from the

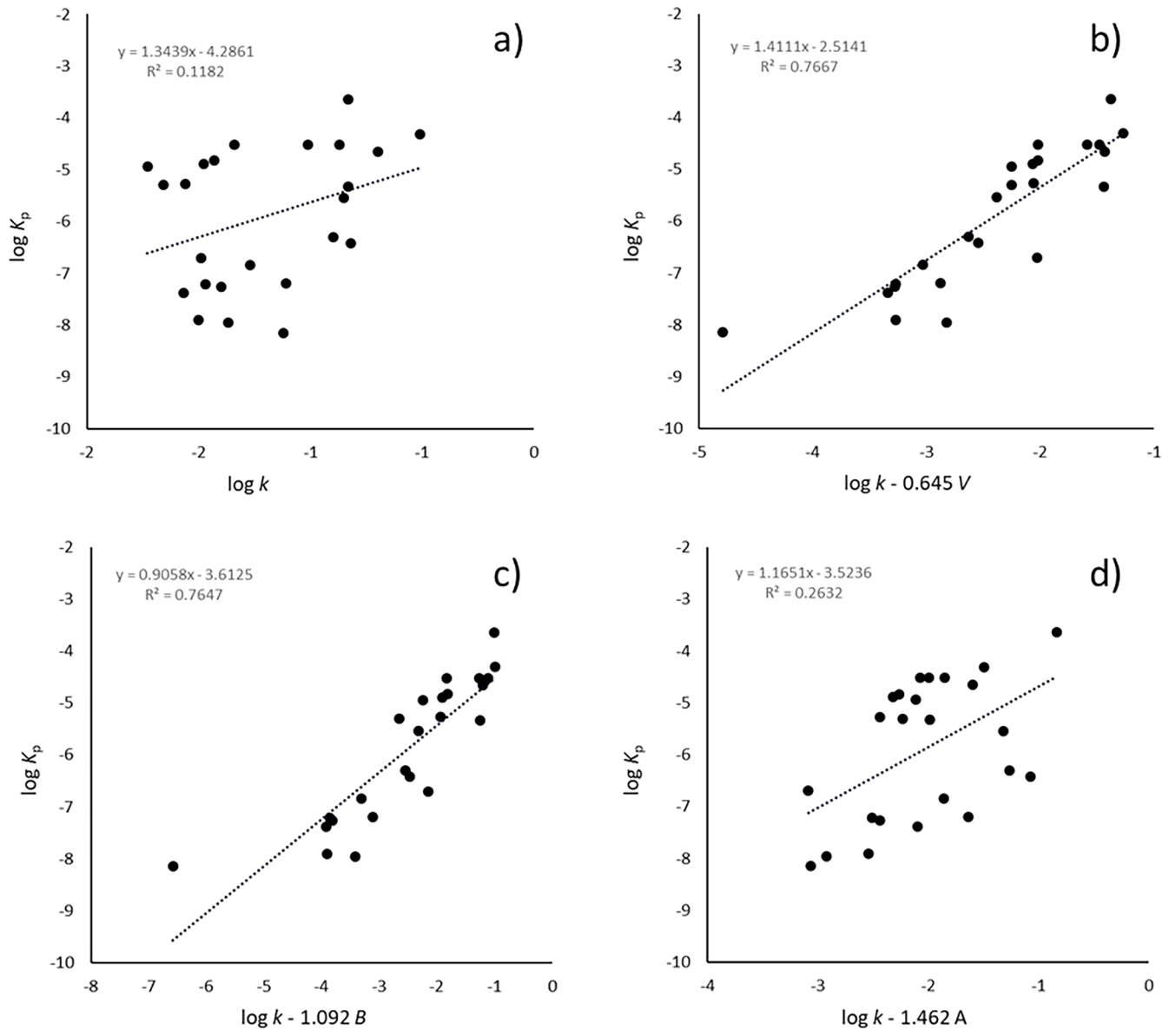

Fig. 9. Experimental correlation for the surrogation of skin permeation by cerasome-LEKC. a) No parameter correction; b) Solute volume (V) correction; c) Solute hydrogen bond basicity (B) correction; d) Solute hydrogen bond acidity (A) correction.

different surrogate systems to skin permeation are presented in the Table too. From the inspection of these distances, it is clear that only PAMPA-IPM could be a good surrogate of skin permeation ($d << 0.25$). All the other systems are in the verge of surrogation ($d \approx 0.25$). Fig. 4 presents the clustering of these systems. The corresponding dendrogram shows that the two PAMPA systems form a cluster at $d < 0.15$. This cluster joints skin permeation at d between 0.15 and 0.20 (distance from skin permeation to the center of the two PAMPAs' cluster). Another cluster at $d \approx 0.10$ is formed by octanol/water partition and cerasome-LEKC, which points out that the later could be used as surrogate system for octanol-water partition better than for skin permeation. These two systems form another cluster with C-18 HPLC at $0.20 < d < 0.25$, but they are not related to the skin permeation cluster until a d value close to 0.30. Regarding principal components analysis, PC2 vs PC1 plot represents practically all data variability (98 %, 75.6 % in PC1 and 22.4 % in PC2) and thus, systems and clusters distances in the bidimensional plot are very representative of the original ones in the five-dimensional space.

Solute volume correction significantly improves the similarity of the chromatographic and octanol-water systems to skin permeation by shortening the distance between systems as Fig. 5 shows [9]. In this Figure, PC1 and PC2 of the surrogate systems have been calculated after volume correction ($+rV$) and plotted in the same diagram of Fig. 4. It can be observed that volume correction practically does not change the position of PAMPA systems because their v system constants are very similar to that of skin permeation (see Table 1). Volume system constants of the other surrogate systems differ from that of skin permeation in more than 0.1 units, then effect of volume correction is notable. In fact, close inspection of Table 1 reveals that there are remarkable differences of other system constants between skin permeation and some of the surrogate systems, mainly b and a system constants, in addition to v (and s for cerasome-LEKC). Therefore, parameter correction by B or A should improve surrogation too. Radial plots of the system constants or their differences may help to visualize what corrections may work.

Fig. 6a presents the radial plots of the differences between the system constants of the surrogate chromatographic and octanol-water systems and skin permeation. PAMPA systems are not considered. Skin permeation, the surrogated system, is represented by the regular black

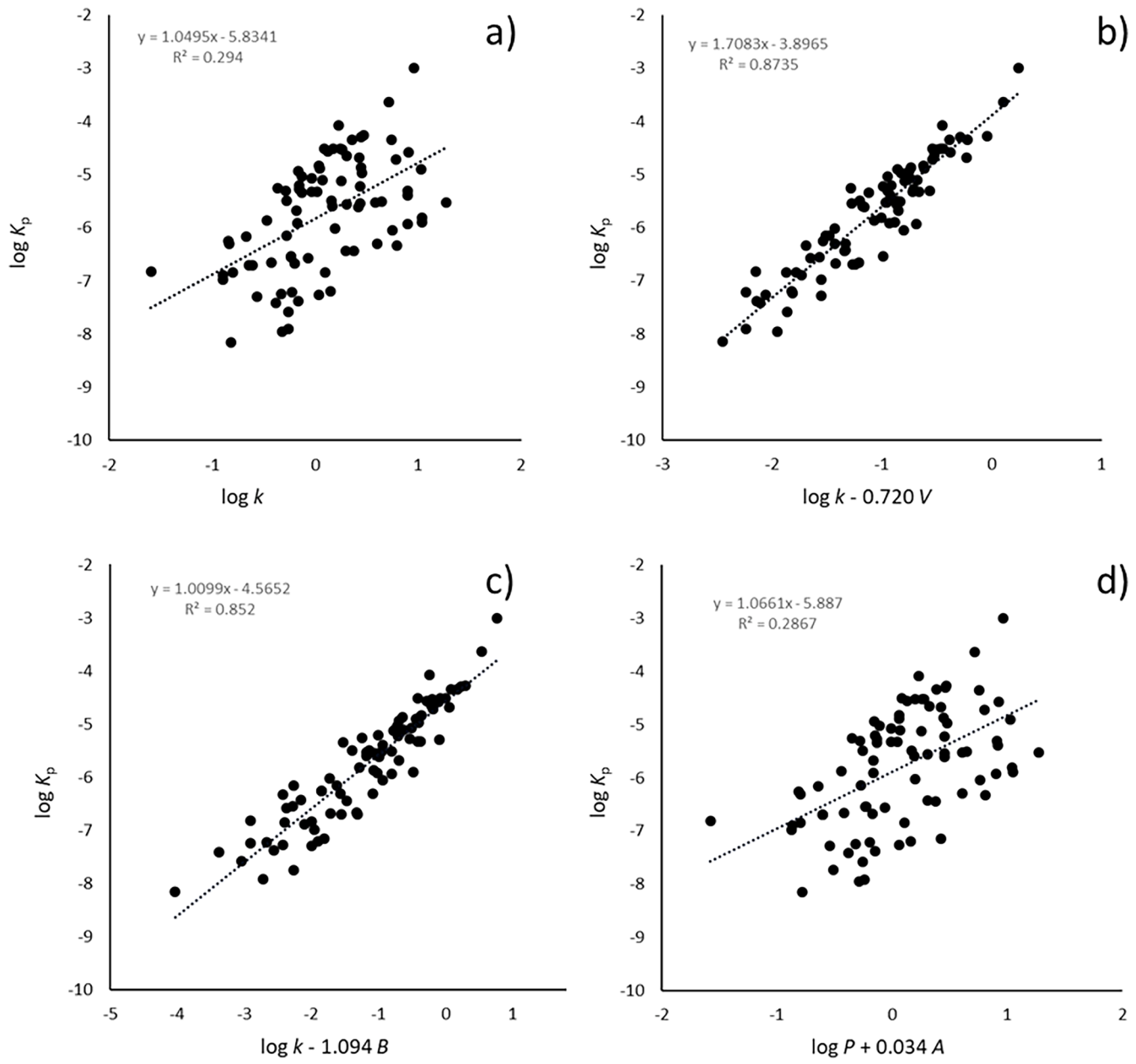

Fig. 10. Experimental correlation for the surrogation of skin permeation by C18-HPLC. a) No parameter correction; b) Solute volume (V) correction; c) Solute hydrogen bond basicity (B) correction; d) Solute hydrogen bond acidity (A) correction.

pentagon drawn at 0 intercepts of the axes, each one representing a particular system constant difference. The irregular pentagon of each physicochemical surrogate system is marked by a distinct colour. Large positive differences are observed for v_u and b_u system constants of all surrogate systems, and smaller for a_u (positive for octanol-water and cerasome-LEKC and negative for C18-HPLC). Differences for e_u and especially s_u are very small for all systems. Then, we can conclude that the best parameter corrections should be for V and B corrections, followed by A corrections. S and E corrections are not expected to improve the surrogation significantly.

We have tested the expected main corrections, by V, B, and A solute parameters, by calculation of the new unitary system constants, their distances to skin permeation, the proportionality f and correction r parameters (Eqs. (14) and (20)), and the predicted slope and intercept of the biological vs. chromatography correlation for skin permeation (q and p parameters of Eqs. (18) and (19)). The obtained parameters are presented in Table 2 and the radial plots of the differences to skin permeation after parameter corrections are presented in Fig. 6 (b, c and d subfigures). Notice that when one parameter is corrected, the corresponding parameter system constant is set up equal to that of the surrogated system, but that the shift moves the rest of the surrogate system constants modifying the differences. For instance, corrections by V (Fig. 6b) increase differences in s_u (which were almost zero in the no corrected system constants, Fig. 6a), although it decreases very much the differences in b_u. Similarly, correction by B increases s_u differences and almost cancels differences in v_u. However, correction by A (Fig. 6d) almost does not change the rest of the system constants.

Comparison of the different radial plots shows that V (Fig. 6b) and B (Fig. 6c) corrections become in system constants much more similar to those of skin permeation than those without correction (Fig. 6a), and therefore it is expected that these corrections significantly improve surrogation. However, system constants of Fig. 6d are similar to those of Fig. 6a, except for a_u, and therefore, A correction is expected to improve surrogation in a much lower degree.

Visual conclusions from radial plots are confirmed by calculation of the *d* distances to the skin permeation, presented in Table 2 too. Correction by solute volume (*V*) decreases distances from about 0.25 (Table 1) to 0.15 - 0.18, and correction by solute hydrogen bond basicity (*B*) even more to 0.08 – 0.13. However, the improvement of the correction by *A* is very low, only from 0.23 to 0.20 (octanol-water partition), from 0.26 to 0.25 (cerasome-LEKC), and from 0.25 to 0.22 (C18-HPLC).

The effect of the solute corrections can be visually observed by PCA plots too. Fig. 7 presents the PC2 (35 % of variance explained) vs. PC1 (54 % of variance explained) plot for all the evaluated systems, with and without corrections. In this case, we have centered the plot to the skin permeation system to better visualize the distances. The variance explained by the two first PCs (89 %) is less than in Figs. 4 and 5 and some more information is lost in PCs 3–5. Even so, it can be observed that A correction does not decrease distance to the center. It lows PC2 but slightly increases PC1. However, there is a big decrease of PC1 for *V* and *B* corrections, giving PC1 values very close to the 0 value of skin permeation. There is also a small improvement in PC2, at least for octanol-water partition and Cerasome-LEKC. It is noteworthy that the loadings of PC1 are mostly *v* and *b* system constants, whereas loading of PC2 is mostly the *a* system constant. The main loading of PC3 (10 % of variance) is *s*, PC4 (2 % of variance) *e*, and PC5 (almost 0 % of variance) *b* and *v* again. Therefore, changes in *v* and *b* system constants are mainly observed in PC1, and *a* changes in PC2.

7. Checking by experimental data correlations

Tools and procedures developed in the previous sections should allow to predict the performance of different chromatographic systems to surrogate a specific biological system if the same model characterizes all of them. Thus, the best surrogate systems and additional descriptors can be selected to be experimentally evaluated, without need to get experimental data for the worst surrogate systems. Experimental tests are usually done by plotting the biological data against the surrogating chromatographic data, corrected or not, and checking the goodness of the linear correlation by statistical parameters (*sd,* R^2, *F*, or others).

As an example, in Figs. 8, 9 and 10 we show the experimental correlations with the available data obtained between skin-water permeability coefficient (log K_p) and the surrogating octanol-water partition (log $P_{o/w}$), and cerasome-LEKC and C18-HPLC retentions (log *k*), respectively. The effect of additional correction by solute volume (subfigure a), hydrogen bond basicity (subfigure b), or hydrogen bond acidity (subfigure c) is also presented. Experimental data is shown in Table S1 of the Supplementary information.

As expected, direct correlations of skin permeation with octanol-water partition, cerasome-LEKC and C18-HPLC retentions are not very good ($R^2 < 0.3$). Solute hydrogen bonding acidity (*A*) correction does not improve the correlations, but solute volume (*V*) and hydrogen bond basicity (*B*) significantly improve them to the level expected for biological vs. physicochemical correlations ($R^2 \approx 0.8$).

8. Conclusions

Characterization of solute-solvent interactions in biological and chromatographic systems by the same model, e.g., Abraham's solvation model, allows to predict the ability of different chromatographic systems to surrogate the biological one. Model characterization provides the constants of the modelled systems which define the sign and extent of the solute-solvent interactions in each surrogated or surrogating system. Calculation of Euclidean distances (*d*) between the system constants of the biological and surrogate chromatographic systems measures the similarity of the systems, which can be effectively visualized and clustered by means of dendrograms and principal component analysis plots. Low distances between surrogating and surrogated systems indicates good surrogation for the biological system. In this case, the slope and intercept of a good linear regression between the biological property and the measured surrogate chromatographic retention can be predicted.

If the similarity between biological and chromatographic systems is not good enough, the correction by the inclusion of additional descriptors in the biological vs. chromatographic correlation can be modelled, and their effect in the improvement of the surrogation, predicted. Thus, the best additional descriptors to improve the surrogation can be selected. These descriptors can be easily obtained from the available data bases or calculated by commercial or free estimation software of Abraham descriptors to be directly used in the surrogation. If other Quantitative Structures Activity Relationships, different from Abraham model, want to be tried, the procedure can be useful to indicate the type of descriptors (size, hydrogen-bonding, dipolarity-polarizability) that can be adequate to test before being experimentally measured or in silico calculated.

Modelling the surrogation of biological processes by chromatography should allow to select the best surrogate chromatographic systems for a particular biological process with no need of experimental measurement of the retention of the test compounds in a wide set of chromatographic systems, which is certainly needed for the selection of good surrogates by empirical correlations.

The use of chromatographic systems has the advantage of being a fast, highly automated, sustainable, and ethical way to determine biopartition or environmental properties. Moreover, unlike *in silico* models, it is not necessary to know the value of the compounds' descriptors in order to predict the property of interest. The different types of chromatographic systems, with a wide variety of stationary phases, offer a broad range of partition systems. Moreover, the comparison between physicochemical and biological/environmental systems allows for the detection of which coefficients are more similar and which are not, making it possible to modify the nature of the chromatographic stationary phases (especially in electrokinetic chromatography) to create ad-hoc phases that can emulate the system of interest. Therefore, retention in chromatographic systems, either alone or in combination with additional descriptors, represents a highly versatile and powerful alternative for emulating biological or environmental partitioning processes.

CRediT authorship contribution statement

Elisabet Fuguet: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Martí Rosés:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Table with the Abraham descriptors and experimental literature data for skin-water permeability coefficient (log K_p), octanol-water partition

coefficient (log $P_{o/w}$), cerasome-LEKC and C18-HPLC retentions factor (log k) of the solutes used in Figures 5–10.

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcoa.2024.100189.

Data availability

Data will be made available on request.

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