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An assessment of experimental methods and computational tools to determine membrane-water partition coefficients for surfactants

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1 Abstract

Background: Due to their complex physico-chemical properties, surfactants can present challenges in standard environmental tests which can lead to uncertainty, particularly concerning partitioning behaviour. The speciation-corrected membrane-water distribution coefficient, log D_{MW}, is a promising alternative chemical descriptor for surfactants to circumvent high uncertainty pertaining to the octanol-water partition coefficient (log K_{OW}) and is gaining some acceptance within regulatory frameworks. Log D_{MW} relates to partitioning into a critical cellular component and accounts for ionic interactions. Whereas dissolved unilamellar liposomes are considered the 'benchmark' to measure D_{MW}, consistent sets of D_{MW} values for a variety of surfactants have been measured predominantly using silica bead-supported lipid membranes (SSLM). Also computational approaches have become available to derive log D_{MW} for ionisable chemicals. The overall aim of this study was to systematically evaluate three experimental methods and several computational approaches to determine log D_{MW} for a diverse set of non-ionic, anionic, cationic, and zwitterionic surfactants.

Results: Using D_{MW} measurements for 12 surfactants, we confirmed that results from SSLM align with the benchmark dissolved unilamellar liposomes based on dialysis systems. Liquid chromatography columns with immobilized phospholipid monolayers provide useful estimates for anionic and cationic surfactants although they showed deviations for ethoxylated non-ionic and zwitterionic surfactants. Alongside existing log D_{MW} data, the data set allowed for calibration of available molecular computational methods. The coarse-grained molecular dynamics calculations aligned well with experimental values for most surfactants, except for several ionisable amines. Recalibration of the membrane potential in COSMOtherm improved predictions but leaves significant uncertainties for zwitterions. Fragment-based and descriptor-based approaches worked well within limited domains of applicability.

Conclusions: We increased confidence in log D_{MW} determination for surfactants, demonstrating that SSLM provides a robust and efficient alternative to benchmark liposome methods across major surfactant classes. Computational approaches can complement experimental methods, particularly for complex mixtures and technically challenging substances, although performance and applicability depend on surfactant class and chemical domain. Together, these complementary approaches enable membrane-water partitioning to be assessed across a broad range of surfactant chemistries. Further standardisation, including consideration for OECD guidance or test guidelines development, would further support consistent generation and regulatory use of log D_{MW} values.

2 Background

Surfactants are chemicals with surface-active properties, which share the common structural characteristics of a hydrophilic head group and one or more hydrophobic tails. Due to these amphiphilic properties, surfactants are used in a broad range of industrial processes and consumer products. The structural diversity of surfactants is very large, including non-ionic, anionic, cationic and zwitterionic molecules. Even though most surfactants used in home and personal care products are rapidly degradable, their significant market volumes mean that a fraction may nonetheless enter environmental systems through treated wastewater systems. An adequate understanding of the potential environmental impacts is, therefore, important. In Europe, chemicals are regulated under the European REACH legislation (registration, evaluation, authorization and restriction of chemical substances on the European Market) [1], and many other chemical regulations are in place worldwide to protect human and environmental health by assessing intrinsic chemical properties and exposure [2, 3]. One important property of organic chemicals commonly used to help determine the environmental distribution and potential toxicity is the octanol–water partition ratio K_{OW}, or for ionisable chemicals the pH-dependent octanol–water distribution ratio, D_{OW} (more commonly referred to in their logarithmic form of log K_{OW} and log D_{OW} respectively). For most neutral organic chemicals the affinity for octanol compared to water is a representative metric of the affinity to bind to organic matter fractions in soils and sediments [4], as well as to lipid phases in tissues of exposed aquatic organisms [5]. Understanding partitioning behaviour of chemicals, usually using a synonymous descriptor such as K_{OW}/D_{OW}, is a mandatory requirement for many legislative global frameworks such as REACH in the EU, TSCA in the US and Measures for Environmental Management Registration of New Chemical Substances (MEE Order No. 12) in China [6, 7]. However, OECD guidelines on K_{OW} measurements [8-10] indicate that surface active agents are outside the applicability domain. Due to their amphiphilic properties, surfactants accumulate at the interface of hydrophobic and hydrophilic phases, and emulsify both phases, making the measurement and calculation of

K_{OW}/D_{OW} challenging [11-14]. Additionally, the *n*-octanol-water system does not account for the strong interaction of ionic surfactants with zwitterionic phospholipid molecules present in biological cell membranes, whereas ionic surfactants interact only weakly with storage lipids [15]. The membrane–water partition ratio K_{MW} for neutral surfactants, or the pH-dependent membrane–water distribution coefficient D_{MW} for partially/fully ionisable structures (from here on, we refer only to its corresponding logarithmic form, log D_{MW}), is increasingly being considered as a more biologically relevant and methodologically defensible alternative to K_{OW}/D_{OW} for these types of chemicals. For example, REACH Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7c and the Ecological Risk Classification of Organic Substances, Version 2.0 (ERC2), developed by Environment and Climate Change Canada (ECCC) as part of Canada's Chemicals Management Plan (CMP), both reference opportunities for applying log D_{MW} [16, 17]. Also log D_{MW} has been shown to be a valuable descriptor for understanding membrane-related toxicity mechanisms [18].

Currently, several experimental and computational approaches are available for determination of log D_{MW}. Experimental methods include: (1) batch sorption studies with liposomes as unilamellar bilayer vesicles, using for example dialysis systems to sample the equilibrated freely dissolved concentrations [19-24], (2) batch sorption studies with solid-supported lipid membranes (SSLM) with bilayers non-covalently covering silica particles, requiring only centrifugation to sample equilibrated freely-dissolved concentrations [15, 25-29], and (3) chromatographic column retention measurements using silica coated with a monolayer of immobilised artificial membrane phospholipids (IAM-HPLC), where the logarithmic retention capacity factor is proportional to log D_{MW} [30-36]. Bilayer vesicles are considered the benchmark *in vitro* phase to assess log D_{MW} [37] although there is still some work to do to standardise various aspects of the method including extrusion protocol and selection of phospholipid starting materials. The commercially available SSLM assay has so far been most widely applied for

surfactant research, as reviewed in 2021 [15], but has had limited evaluation compared to liposomal data [24].

The common computational approaches that are not dependent on surfactant log K_{OW} data are: (1) Molecular Dynamics (MD) simulations, which use Newton's equations of motion to sample solute-membrane interactions [38-40], (2) the 'COSMOmic' module within COSMOtherm — proprietary software which extends the COnductor-like Screening MOdel for Realistic Solvation (COSMO-RS) to describe anisotropic systems [41-43], (3) 'COSMOplex' — the newest release from COSMOtherm which includes a more dynamic representation of the bilayer [44], (4) fragment-based approaches, where structural properties of a set of homologues are related to log D_{MW} via an empirically fitted linear equation [15], and (5) polyparameter linear free energy relationships (pp-LFERs), which use a standard set of solute descriptors for the neutral form to predict log D_{MW} via a linear equation, which can be corrected for ionisation [15, 45-47].

The Environmental Risk Assessment of Surfactants Management (ERASM) "Membrane Water partitioning of Surfactants (MWPS)" Task Force has conducted a project in which these eight experimental and computational methods are evaluated for a set of twelve surfactants (three each from non-ionic, anionic, cationic and amphoteric surfactant classes). Here we report the data for all methods and surfactants and evaluate the accuracy, variability and ease of use for all methods, with the aim of providing clear recommendations on the most appropriate method to determine log D_{MW} for a given class of surfactant.

3 Methods

3.1 Compound selection

To maximise continuity with previous work, eight of the twelve selected surfactants for this work were taken from a study on octanol-water distribution coefficients [14] (See Table 1). The remaining four choices were also based on the octanol-water study but were substituted as follows. The anion C_{12}-SO_4^- is omnipresent in lab materials causing high background contamination issues and was replaced by C_{12}-SO_3^-. The quaternary ammonium cations C_{16}-trimethylammonium (C_{16}-$TMAC^+$) and C_{18}-benzalkonium (C_{18}-$TMAC^+$) were expected to sorb too strongly to membranes and, therefore, to be outside the experimental feasibility domain. Instead, we selected the primary amine cation C_{12}-NH_3^+ and the analogue dihexylamine C_6-NH_2^+-C_6 (both pK_a>10). Also, the pure zwitterion C_{12}-betaine was purchased instead of using the technical (C_{12-16}) mixture. See Table S1 for additional details.

The pK_a of ionisable surfactants is such that the fraction of the neutral form (f_N) is present at sufficiently low levels (<0.1%) not to influence the overall distribution ratio (D_{MW}) at the tested medium pH, according to:

$$f_N = \left[1 + 10^{\alpha(\mathrm{pH}-\mathrm{p}K_a)}\right]^{-1}; \quad \text{Eq.1}$$

where $\alpha = 1$ if the neutral species is an acid and $\alpha = -1$ if it is a base;

$$D_{MW} = f_N\, K_{MW,N} + (1 - f_N) K_{MW,ion} \quad \text{Eq.2}$$

For most of the selected ionic surfactants, the large difference between test pH and pK_a meant that the neutral form was present at negligible levels, and the measured or calculated membrane-water partitioning could, therefore, be expressed directly as D_{MW} (see Section 5.3.2). The two reference non-surfactant chemicals were the acid pentachlorophenol (pK_a = 4.7) and the relatively large and polar fungicide azoxystrobin ($C_{22}H_{17}N_3O_5$, log K_{OW} = 2.5). All surfactants were high-purity test samples obtained from commercial sources, except for C_{12}-EO_4-SO_4^- which was

from the same batch supplied by P&G, as used in the previous octanol-water study [14]. Stock solutions were prepared in methanol (details in Supplementary Information (SI) Table S1 and Section S1.1).

3.2 Experimental methods summary

3.2.1 Liposome dialysis assay

Liposome solution batches were custom-prepared at the Institute for Risk Assessment Sciences (IRAS), Utrecht University, The Netherlands (details in SI Section 2.1.1.1). For each test chemical, two specific dilutions were prepared with the aim of achieving approximately 50% and 80% sorbed fractions, using pH 7.5 buffered ammonium acetate (150 mM) solution in MilliQ water. The liposome dialysis experiments were performed at room temperature (20 °C) with 2 × 1.0 mL dialysis sets (PTFE Fast Micro-Equilibrium Dialyzer, Harvard Bioscience, Holliston, MA, USA), using polycarbonate membranes of 0.05 µm pore size (SP1 7415-PC05, Harvard Bioscience). Pilot studies measured the equilibration time needed to evenly distribute surfactants over the membrane to both compartments (details in SI Section 2.1.1.2), which included mass balance checks on recovery and adsorptive loss to the dialysis system. In brief, one compartment contained 0.95 mL of liposome solution, the other compartment clean buffer to which 10 µL stock solution was added. Solutions were shaken for 48 h, after which 0.5 mL of the clean buffer was sampled and mixed with 0.5 mL methanol for chemical analysis. A mass balance approach was used to calculate the liposome sorbed concentration, except for C_{12}-NH_3^+ and C_{12}-$TMAC^+$ (see SI Section 2.1.1.3), after which D_{MW} was derived.

3.2.2 Solid Supported Lipid Membranes (SSLM) in sorbent dilution series

The SSLM assay was performed with material from 96-well Intestinal Absorption kits (Sovicell GmbH, Germany). Specific recommendations for surfactants as described in SSLM studies with surfactants were followed [15, 27, 28], deviating from the supplier's protocol. In brief, the sorbent doses from the well plate series were transferred into 1.5 mL glass HPLC vials, and the original

PBS buffer was replaced with a 150 mM ammonium acetate solution (pH 7.5) in three supernatant exchange steps. Three buffer control reference vials (no lipid) and two methanol controls (no adsorptive loss to glass walls) were spiked with the same amount as the sorbent dilution series. The low-density plate series (LD) ranged 0.048–0.9 µL lipid per vial, high-density plate series (HD) 0.61–11.5 µL lipid (step factor 1.8). A mass balance approach was used to calculate the lipid bilayer sorbed concentration from analysed supernatant samples and controls, in order to derive D_{MW} (details in SI Section 2.2.1).

3.2.3 Immobilized Artificial Membrane chromatography (IAM-HPLC)

The IAM-HPLC column and pre-column were provided by Regis Technologies Inc. (Morton Grove, IL, USA), respectively 10 cm and 1cm (10 µm silica) IAM-PC-DD2. Injected concentrations varied between 0.1–1 mg/L. As recommended for cations [35] and for anions [28], a series of fully aqueous eluents with different pH (5.0–7.5) were prepared at two different ionic strengths of ammonium acetate (5 and 100 mM) (details in SI Section 2.3.1). For each buffer, column retention was determined for a reference organic anion (C_7-SO_3^-) and a reference organic cation (C_8-$TMAC^+$) (see SI Section 2.3.1). The optimum eluent pH for C_7-SO_3^- was used for anionic and zwitterionic surfactants, and reference chemicals, the optimum pH for C_8-$TMAC^+$ was used for cationic and non-ionic surfactants. Retention capacity factors (k_{iam}^0) at fully aqueous eluent were derived from series of solvent/buffer eluents as recommended before [28, 35]. Multiplying k_{iam}^0 with the IAM-PC-DD2 column specific phase ratio (ϕ = 1/0.053 = 18.9) gives the intrinsic sorption coefficient (K_{IAM}) between water and the IAM-monolayer [48].

3.2.4 Chemical analysis

Samples from the dialysis method and SSLM method were analysed for most chemicals on an Agilent 1260 HPLC system connected with an Agilent Ultivo QQQ mass detector and AJS ESI ion source, while an Agilent 1260 HPLC system connected to Agilent 6460 QQQ mass detector was used for some chemical requiring lower detection limits. For IAM-HPLC, the Ultivo QQQ was

used. Column details and elution programs and detection details are in SI Section 1.2 and Table S2.

3.3 Computational methods summary

3.3.1 Coarse-Grained Molecular Dynamics

MD simulations are computationally costly or even unfeasible when all atoms are explicitly represented. To reduce the cost of calculating log D_{MW} by MD, small groups of atoms can be represented by coarse-grained (CG) "beads". Here, we deployed version 3 of the Martini CG forcefield, which has been developed with biological systems in mind [49], but has also been used in materials applications [50]. All parameters in Martini 3 are published and freely available online [51]. The tool cg_param automates both the mapping (grouping) of atoms into beads and parameterisation of bead-bead interactions [52]. cg_param is designed for high-throughput modelling starting from SMILES codes and is freely available [20, 38, 53]. Parametrisation of neutral, non-bonded bead-bead interactions in cg_param is based on octanol-water partitioning, while charged groups either follow the Martini developers' recommended assignments (see the SI of [54]), or have been refined on experimental membrane-water data for simple analogues in our previous publications [20, 53], as is the case for sulfonate groups. Once the CG model has been assembled from its fragments, MD simulation then samples the collective behaviour of the molecule, allowing its conformation to respond dynamically to the local environment.

Martini CG models produced by cg_param have been validated for membrane-water partitioning of small neutral [38] and charged molecules [53]. Here, we further benchmark cg_param without further adjustment, except for the reference compound PCP and the alkylethoxyethers. PCP has no analogue in our previous work, and we have made assignments based on imidazoles as recommended by the Martini developers. For alkylethoxyethers, previous experience has shown that a different parameterisation is required for more than four ether units [53]. Full details of specific CG-MD parameterisations can be found in SI Section 3.1.

3.3.2 COSMOmic

BIOVIA COSMOsuite software V25 was used for the selected set of surfactants (Dassault Systèmes SE, Vélizy-Villacoublay, France), alongside Turbomole version 21. BIOVIA COSMOsuite V23, COSMOthermX19 and COSMOthermX15 were used for additional literature data comparisons. COSMO-RS is the COnductor-like Screening Model for Realistic Solvents (available under licence), which treats solutions as a dielectric continuum with a solute disturbing it [41]. The property estimation module COSMOmic applies this approach to anisotropic membranes. To capture the behaviour of ionic solutes, a sigmoidal membrane potential curve needs to be added [55]. Using an experimental D_{MW} dataset, Bittermann *et al.* (2014) [55] fitted the curve parameters as potential height (326 meV, or 7.516 kcal/mol), width of the sloping region (8.866 Å) and position of the curve's centre (17.0796 Å) as the distance from the bilayer interior centre.

As set out in more detail in SI Section 3.2, we could not reproduce the D_{MW} output reported by Bitterman *et al.* [55] with the identical bilayer file and membrane potential curve settings. Earlier studies already noted incorrect predictions of chain length contributions for anionic surfactants [28], which are critical for all surfactants. To circumvent the apparent parameterisation issues between different software versions, we created a new lamellar DMPC bilayer structure using the COSMOplex toolkit, using the same TZVP-level DMPC phospholipid molecule as applied in previous COSMOmic calculations [55], and mostly default settings (see SI Section 3.2.2). This procedure can now be repeated by any user of COSMOthermX V25. To calibrate the sigmoidal membrane potential curve parameters for this new bilayer, we first aligned COSMOmic to measured D_{MW} for a series of C_4-C_{10} anions [28], in order to correctly calculate the chain length increments for all anionic surfactants (see SI Figure S13). Based on the newly optimised membrane potential settings (450 meV, width 1 Å, centre position 22 Å), all other anionic surfactants and non-surfactant anions scattered around the experimental data, and no further adjustments were made (the RMSE for all 60 anions is 0.83). Selecting POPC instead of DMPC as a bilayer system may further influence calculated D_{MW} outcomes, but was not further explored as

an optimisation step (Figure S15). The COSMOmic D_{MW} predictions for cationic surfactants, however, were on average 2.57 log units lower (n = 26, SI Table S11) than experimental D_{MW} data. Although this suggests that further optimisation and evaluation of the membrane potential within the COSMOmic approach is warranted, it was decided to apply this empirical +2.6 correction factor for now for cations, as it seemed to align all types of cationic surfactants and organic cations (RMSE = 0.59 for all 34 cations). No decision was made on further attempts to align zwitterionic or non-ionic surfactants.

3.3.3 pp-LFER

The online UFZ-LSER freely accessible database (https://www.ufz.de/lserd accessed December 2024) was checked for the selected chemicals for recommended solute descriptors for the Abraham pp-LFER equation. This included experimental values for polarity descriptor S, hydrogen bond acceptor A, hydrogen bond donor B, and calculated values for McGowans Volume V_x and excess molar refractivity E. Bittermann et al. [56] used a reviewed set of D_{MW} data on anions and cations to modify the pp-LFER equation coefficients for organic ions by including J^- and J^+ as additional solute descriptors that account for anion- and cation-specific ionic interactions respectively; details of these pp-LFER calculations are provided in SI Section 3.4). Given the high uncertainty associated with deriving pp-LFER descriptors for ionic chemical forms, descriptors were calculated for the neutral forms of the surfactants, where applicable, using the Absolv module of ACD/Labs Percepta V25 software, since experimental descriptors were unavailable for most substances. This approach could, therefore, be applied to non-ionic surfactants and to ionisable surfactants for which a neutral form could be represented. However, descriptors could not be calculated for surfactants containing permanently charged quaternary ammonium cation groups, including the three zwitterions, because the Absolv module calculates descriptors for neutral chemical forms and does not support these quaternary ammonium structures. We applied fixed scaling factors between the neutral and ionic form for membrane-water partition coefficients (Δ_{MW}), which were derived for different types of ionisable compounds [57]: –0.75 for

299 phenolics, –2 for carboxylic and sulfonic acids, –1.25 for tertiary amines, –0.5 for secondary
300 amines, –0.3 for primary amines.

301 ### 3.3.4 Octanol-water partition coefficients

302 The experimental log K_{OW} values from the slow-stirring method with water at pH 7 from Hodges *et*
303 *al.* (2019) were used for comparison, as this method is considered to minimise confounding
304 factors of octanol-water test systems, such as emulsification . Log D_{MW} values using this method
305 were not calculated for the remaining three surfactants C_{12}-SO_3^-, C_{12}-NH_3^+ and C_6- NH_2^+-C_6 in the
306 absence of a reliable and comparable log K_{OW} value. For the reference chemical azoxystrobin, the
307 log K_{OW} is 2.50 [58]. The single parameter equation relating K_{MW} to K_{OW} from Endo *et al*. (2011) was
308 applied to all surfactants and reference chemicals where a reliable log K_{OW} value was available
309 (log K_{MW} = 1.01 log K_{OW} + 0.12), although this was calibrated with neutral chemicals only (n = 156.
310 SD = 0.426, R^2 = 0.948) [22].

311 ### 3.3.5 Surfactant Fragments approach

312 Müller *et al*. (1999) used their own liposomal K_{MW} data set for non-ionic alcohol ethoxylates
313 (AEOs) to derive a specific fragment-based K_{MW} model (see SI Section 3.5) [21]. Based on the
314 reviewed set of log D_{MW} values in 2021, including their own measured SSLM D_{MW} data, Droge *et al.*
315 (2021) derived two fragment-based log D_{MW} models [15], for anionic and cationic surfactants, with
316 fragments accounting for chain length, features of the hydrophobic region and different types of
317 charged hydrophilic moieties (see SI Section 3.5). No fragment model is available yet for
318 zwitterionic surfactants.

319 ### 3.3.6 Additional calculations for reviewed surfactant D_{MW} data

320 Since only three surfactants per headgroup type were selected for testing all methods,
321 comparison between computational approaches and experimental data remained limited to
322 confirm the applicability range. Therefore, the log D_{MW} data set for (non-fluorinated) surfactants
323 (reviewed in 2021 [15]) was extended with several surfactants from recent studies [20, 29] and

compared with additional calculations from CG-MD, the COSMOmic/COSMOplex approach, and the surfactant fragment approach [15].

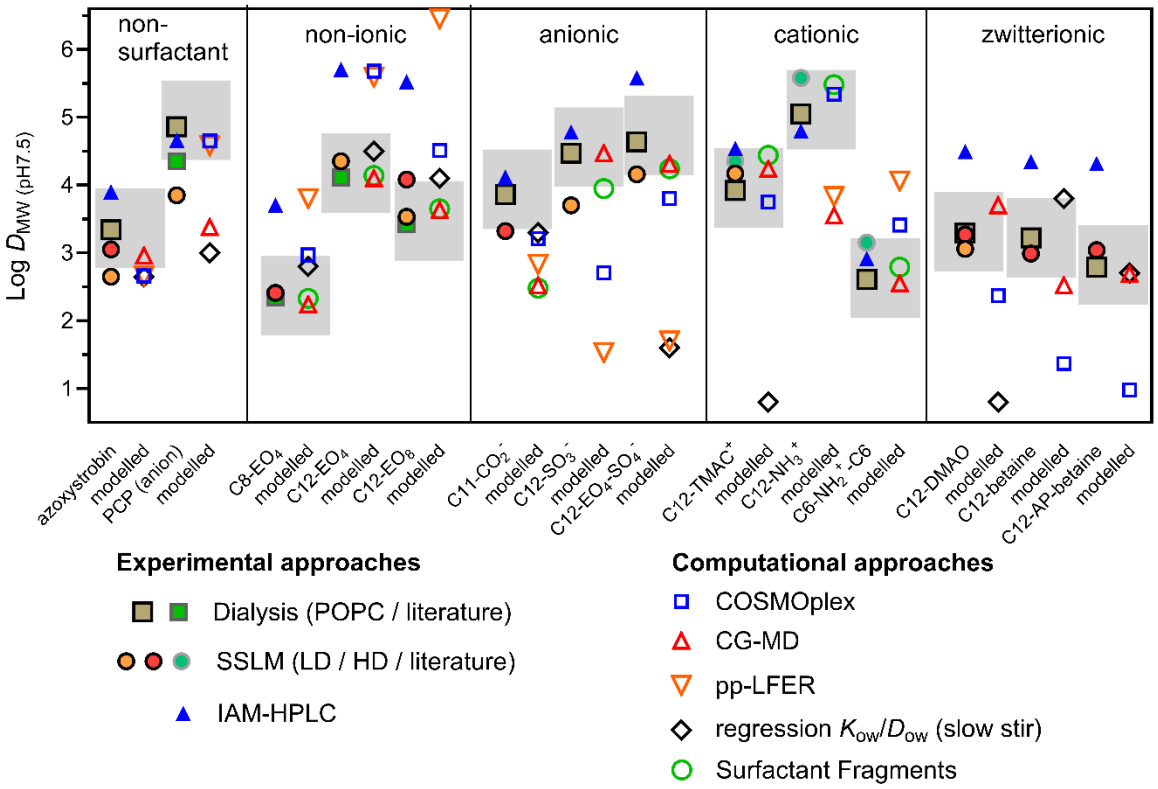


Figure 1. Overview of experimental (closed symbols) and computational / modelled (open symbols) log D_{MW} values for the surfactants and reference chemicals selected in this study. Grey bands of ±0.5 log units (a factor of ±3) around the benchmark liposome values represent the margin to qualify other assay results as 'comparable' or substantially deviating from the benchmark log D_{MW} method. Log K_{OW} / D_{OW} values obtained with the slow stir method were not available for C_{12}-SO_3^-, C_{12}-NH_3^+ and C_6-NH_2^+-C_6. pp-LFER predictions could not be made for C_{12}-TMAC$^+$ and the zwitterionic surfactants. No Surfactant Fragments approach was available for zwitterionic surfactants.

4 Results

A summary of the resulting log D_{MW} values for each approach is listed in Table 1. The key observations from the experimental and computational approaches are briefly discussed per surfactant type in sections 4.1-4.4. Figure 1 plots the clusters of experimental and computational results together, with a grey bandwidth of ±0.5 log units surrounding the log D_{MW} value obtained with the 'benchmark' liposome dialysis approach for each chemical. Details on the data from which D_{MW} values were obtained, with description per test chemical, number of samples and uncertainty margins, are presented in sections for each assay in SI Section S2 (experimental approaches) and Section S3 (computational approaches).

Table 1. Membrane-water partition coefficients for tested chemicals (as log D_{MW}, in L/kg) using various approaches.

	Experimental approaches			**Computational approaches**				
Chemical	**Liposome Dialysis**	**SSLM (high/low density)**	**IAM-HPLC (log K_{IAM}^0)**	**COSMO-plex V25 DMPC**	**CG-MD**	**pp-LFER +Δ_{MW}**	**log K_{OW} [c] regression**	**Surfactant fragments [d]**
Reference chemical								
Azoxystrobin (neutral)	3.29	2.65 (LD) 3.05 (HD)	3.91	2.66	2.96	2.66	2.6	NA [e]
Pentachlorophenol (anion, pK_a = 4.75)	4.94 4.89	3.85 (LD)	4.66	4.65	3.38	4.58	3.0	NA
Non-ionic surfactants								
C_8-EO_4	(2.3 [a])	2.41 (HD)	3.70	2.97	2.24	3.80	2.8	2.33
C_{12}-EO_4	(4.1 [a])	4.35 (LD)	5.70	5.68	4.10	5.59	4.5	4.13
C_{12}-EO_8	(3.4 [a])	3.53 (LD) 4.08 (HD)	5.52	4.51	3.63	6.45	4.1	3.65
Anionic surfactants								
C_{11}-CO_2^- [e]	3.96 3.79	3.32 (HD)	4.12	3.21	2.52	2.83	3.3	2.48
C_{12}-SO_3^-	4.64 4.48	3.70 (LD)	4.78	2.70	4.47	1.53	NA	3.95
C_{12}-EO_4-SO_4^-	4.98 4.86	4.16 (LD)	5.58	3.80	4.31	1.70	1.6	4.24
Cationic surfactants								
C_{12}-$TMAC^+$	4.04 3.79	4.17 (LD)	4.54	3.75	4.24	NA	0.8	4.44
C_{12}-NH_3^+	5.05	(5.58 [b])	4.80	5.34	3.55	3.83	NA	5.48
C_6- NH_2^+-C_6	2.59	(3.15 [b])	2.91	3.41	2.55	4.06	NA	2.79
Zwitterionic surfactants								
C_{12}-DAO	3.48 3.28	3.06 (LD) 3.27 (HD)	4.49	2.37	3.70	NA	0.8	NA
C_{12}-betaine	3.28 3.24	2.80 (LD) 3.04 (HD)	4.34	1.37	2.52	NA	3.8	NA
C_{12}-AP-betaine	2.81 2.81	2.99 (HD)	4.32	0.98	3.23	NA	2.7	NA

[a] Literature data [21]; [b] Literature data [27]; [c] Using log K_{OW} data from slow-stir assays [14], except for azoxystrobin from EFSA (2010) [58]; [d] Fragments and coefficients for anions and cations as reported in Droge *et al.* 2021[15], fragments for AEOs are reported in Müller *et al.* 2001 [21], no fragment based regression was possible for zwitterions. [e]0.3% neutral at pH 7.5. NA = Not Applicable.

4.1 Non-surfactant reference chemicals

4.1.1 Experimental results

As shown in Figure 1, for the neutral compound azoxystrobin, the results from the three assays cluster around the liposome dialysis value within the ±0.5 log unit range, with a noticeable difference between the two SSLM plate types. The anionic reference chemical pentachlorophenol (PCP) showed a 0.5 log unit higher log D_{MW} with liposome dialysis compared to literature values, a close overlap with IAM-HPLC, but substantial deviation from the tenfold (1 log unit) lower log D_{MW} with SSLM. These reference chemicals illustrate the expected variation between different assays as well as variability relative to literature data for the benchmark dialysis method.

4.1.2 Computational results

For azoxystrobin the predictions of both COSMOmic (using the new COSMOplex DMPC) and CG-MD align well with the experimental log D_{MW} values. Also, the values derived using the pp-LFER and K_{OW} regression methods only slightly underpredicted the liposome value. For the anionic PCP, only COSMOmic and pp-LFER aligned with the experimental log D_{MW}, CG-MD and K_{OW}-regression showed substantial underestimations. The underestimations are similar to the change expected in log K_{OW} upon ionisation, with Escher and Schwarzenbach reporting a Δ_{OW} of 3.65 (difference between log K for neutral and ionic form) in comparison with Δ_{MW} of 1.38 [13]. The substantial charge delocalisation over the phenol ring may be a specific feature that CG-MD experiences problems with in accurately calculating log $D_{MW.}$

4.2 Non-ionic surfactants

4.2.1 Experimental results

The liposomal log $K_{MW,N}$ values for AEOs based on both ultracentrifugation and dialysis experiments [21] were considered high quality reference values. Every approach showed that log $K_{MW,N}$ increases ~1 log unit per C_2H_4 unit, and decreases ~0.1-0.2 log units per EO unit, indicating that the basic interactions with the phospholipid system are well captured. Similar to findings by Müller *et al.* (1999), our liposome dialysis pilot studies indicated that long chain AEOs may show mass balance deficits in the dialysis tests (right vertical axis in Figure S2), while C_8-EO_4 sorbed too weakly for liposome testing. A dialysis experiment was performed with an intermediate AEO, C_{10}-EO_5, which showed only 25% adsorptive loss and 81% recovery. The average log $K_{MW,N}$ value of 3.5 was only marginally higher (approximately 0.5 log unit (factor of 3)) than the value reported with egg-yolk based POPC [21]. The SSLM sorbent dilution series for the AEOs showed good fit with a log-linear curve with slope of 1 (Figure S3). The eluent series with different solvent fractions resulted in IAM-HPLC measurements with small uncertainty margins for the extrapolated retention capacity factors k_{iam}^0 (Figure S6). When converted to IAM-surface partition coefficients (log K_{IAM}^0, See SI), values for all three AEOs that were more than one order of magnitude higher than the other experimental methods.

4.2.2 Computational results

Whereas CG-MD performed well compared to experimental data due to optimisation of ethoxy-beads, COSMOmic generally overestimated the log D_{MW}. The long polar chains of the non-ionic surfactants result in many conformers being generated and high variation in output per conformer was noted. The uncertainty remains regarding how the different conformers are weighted in the calculation of the averaged output value. For CG simulation, longer simulation times were required to sample a representative set of conformers, due to the larger number of conformations for bigger molecules (SI Section 3.7). pp-LFER values strongly deviated from experimental data.

393 The slow-stir based log K_{OW} values for AEOs are accurate predictors of the log D_{MW} using the well-
394 calibrated K_{OW}-regression for neutral chemicals [22]. The fragment approach values are also
395 within 0.5 log units of the benchmark log D_{MW} values (although these values were used in the
396 calibration of the fragment approach).

397 4.3 Anionic surfactants

398 4.3.1 Experimental results

399 Liposome dialysis systems showed minimal adsorptive losses and high recovery for C_{11}-CO_2^- and
400 C_{12}-SO_3^-. In contrast, C_{12}-EO_4-SO_4^- showed high adsorptive loss (34%), but 77% recovery when
401 including the methanol rinse fraction. The average log D_{MW} for C_{12}-SO_3^- was 4.48, and slightly
402 higher (4.92) for C_{12}-EO_4-SO_4. The log D_{MW} for C_{11}-CO_2^- (99.7% anionic at pH 7.5) was 3.89 and, to
403 best of our knowledge, this is the first time it has been measured using liposomes. SSLM-based
404 log D_{MW} values for the three anions were about threefold lower than those obtained with the
405 liposome dialysis method.[59] IAM-HPLC K_{IAM}^0 values for two anionic surfactants agreed with two
406 liposome dialysis values, but for the ethoxylated anion C_{12}-EO_4-SO_4^- K_{IAM}^0 was substantially
407 higher.

408 4.3.2 Computational results

409 CG-MD predictions are accurate for C_{12}-SO_3^- and C_{12}-EO_4-SO_4^-. For C_{11}-CO_2^-, both charged and
410 neutral forms are present in significant concentration. Simulations on the anionic form alone lead
411 to a log D_{MW} value of 2.52, which is lower than from liposome dialysis and SSLM measurements
412 by 1.38 and 0.78, respectively. To account for the two charged states approximately, simulations
413 can be used to calculate the partitioning for each state separately. The results are then combined
414 to give the overall distribution coefficient log D_{MW} as in Eq. 2. This only marginally improves the
415 resulting log D_{MW} value (2.91) and is discussed further in Section 5.3.2. For COSMOmic, the newly
416 calibrated COSMOplex DMPC resulted in a 1.8 log unit underprediction for C_{12}-SO_3^-, but values
417 closer to experimental data (0.6 and 0.8 units lower respectively) for both C_{11}-CO_2^- and C_{12}-EO_4-

418 SO_4^-. Optimisation of the membrane potential curve by using PFAS anions may have been
419 insufficient for non-fluorinated surfactants, although the majority of organic anions scatter
420 between ±1.0 log unit overall (RMSE = 0.83, n = 60, Figure S14).

421 pp-LFER values were orders of magnitude lower than experimental log D_{MW} values for C_{12}-SO_3^-
422 and C_{12}-EO_4-SO_4^-, but only 1 log unit below the liposome value of $C_{11}CO_2^-$ (0.5 log units below the
423 SSLM value). The K_{OW} regression method prediction matches well with experimental data for
424 $C_{11}CO_2^-$, but results in 3 log unit lower predictions for C_{12}-EO_4-SO_4^-. The log D_{OW} value was
425 unavailable for $C_{12}SO_3^-$. The fragment method performs well for the sulfonate and sulfate species
426 C_{12}-SO_3^- and C_{12}-EO_4-SO_4^-. In contrast, the fragment for the CO_2^- unit was derived from
427 perfluorinated carboxylates resulting in strong underprediction of the log D_{MW} for $C_{11}CO_2^-$.

428 ## 4.4 Cationic surfactants

429 ### 4.4.1 Experimental results

430 Dihexylamine showed a comparable log D_{MW} (2.6) in our POPC liposome dialysis as well as to the
431 POPC based 96-well RED dialysis systems (2.4) [20], showing high consistency. The primary
432 amine C_{12}-NH_3^+ is a singlechain analogue to dihexylamine, but showed three hundred times
433 higher D_{MW} (log D_{MW} = 5.05), based on sampling of both dialysis compartments (SPE recovery
434 91%). The quaternary ammonium cation analogue C_{12}-TMAC$^+$ showed a tenfold lower affinity
435 (log D_{MW} = 3.92) than the primary amine. A comparable difference between the three analogue
436 cations was observed for both SSLM log D_{MW} values and IAM-HPLC log K_{IAM}^0 values. The
437 membrane characteristics in each assay are thus well reflected in how they influence sorption of
438 cationic surfactants. For all three cations, SSLM log D_{MW} values were within a factor 3 (0.5 log
439 units) higher than for the POPC liposomes. As noted for anions above, this is in line with the
440 hypothesis of a negative surface charge operating on SSLM bilayers. This factor of 3-4 (0.5-0.6 log
441 units) difference, attributable to membrane surface charge falls within the range reported in other
442 studies involving different phospholipid compositions and ionisable chemicals [60].

4.4.2 Computational results

CG-MD performs well for C_{12}-TMAC$^+$ and correctly predicts the low log D_{MW} for dihexylamine. In contrast, $C_{12}NH_3^+$ was more than an order of magnitude underpredicted by CG-MD compared to both SSLM and liposome values. Accounting for the contribution of the neutral species at pH 7.5 (to calculate log D_{MW}) increased the value for this cation only 0.02 log units (Table S8). COSMOplex-COSMOmic predictions of log D_{MW} include the empirical cation offset factor, which was based on calibration with 26 cationic surfactants including the three selected surfactants. Nonetheless, also without the offset the correct differences between the three analogues were calculated by COSMOmic using the conformer sets of quantum-chemically optimized 3D input structures. The mechanistic basis of the (high) offset factor warrants further investigation. however, COSMOplex appears well suited for cationic surfactants.

pp-LFER was not available for C_{12}-TMAC$^+$, and erroneously predicted a similar log D_{MW} value for C_{12}-NH_3^+ and dihexylamine. K_{OW}-regression was only possible for C_{12}-TMAC$^+$ which underpredicts log D_{MW} by 3 log units. All three cations were included in the training set of the fragment approach, and accordingly, all predictions fall within a factor 2 (0.3 log units) of the liposome and SSLM data.

4.5 Zwitterionic surfactants

4.5.1 Experimental results

The average of the two dialysis experiments for the zwitterion C_{12}-DAO showed a log D_{MW} of 3.38, comparable to 3.4 reported for the POPC based 96-well RED dialysis systems [20]. The average of the two C_{12}-betaine values showed a liposomal log D_{MW} of 3.26, threefold higher than that of C_{12}-AP-betaine (log D_{MW} = 2.81). It was anticipated that the additional amidopropyl moiety would allow the alkyl chain of C_{12}-AP-betaine to protrude deeper in the bilayer's hydrophobic core and result in a higher log D_{MW}, but apparently the additional polarity of the amido unit results in an overall lower log D_{MW}. The three log D_{MW} values from SSLM were well within 0.3 log units of the

liposome assay. The log D_{MW} values derived using IAM-HPLC data, however, deviated with more than one log unit.

4.5.2 Computational results

CG-MD performs best from all available computational approaches. The amine oxide C_{12}-DAO prediction is slightly higher than experimental data, C_{12}-betaine a factor of 5 lower (0.74 log units), while C_{12}-AP-betaine is predicted to be close to C_{12}-betaine, as observed in experimental results. Previous issues in the Martini force field have been identified in molecules with proximate charged groups, due to so-called 'superinteraction' sites, where two beads approach so closely that their interactions are unphysical [61]. This makes zwitterions potentially challenging species for CG-MD, but overall, it performs well. The COSMOplex/COSMOmic calculations strongly underpredict C_{12}-DAO and even more so for the betaines. The cationic moiety in these zwitterionic surfactants was not accounted for using an offset, as was done for the purely cationic compounds, since there was no extensive database to validate this approach. K_{OW} regression underestimates the log D_{MW} for C_{12}-DAO by three orders of magnitude, while it only slightly overestimates the value for C_{12}-betaine and provides an accurate estimate for C_{12}-AP-betaine. This inconsistency suggests that log K_{OW} is an unreliable predictor for all zwitterionic surfactants. The pp-LFER and fragment approaches are currently not suitable for zwitterionic surfactants.

5 Discussion

Whereas the results section presented the different log D_{MW} outcomes per surfactant type, this discussion will focus more on the merits and shortcomings of the different assays. Our dataset provides a first clarification on whether liposomes are a suitable benchmark assay result, since the majority of the log D_{MW} data for the surfactants in our dataset are already available from SSLM assay results. The benchmark log D_{MW} dataset allows an illustration of the inapt use of octanol-water partition data for risk assessment of different types of surfactants. The assay evaluations

and semi-quantified scoring table of each assay per type of surfactant should allow interested stakeholders to decide on the most appropriate method of experiments to be conducted to determine the hydrophobicity of a surfactant.

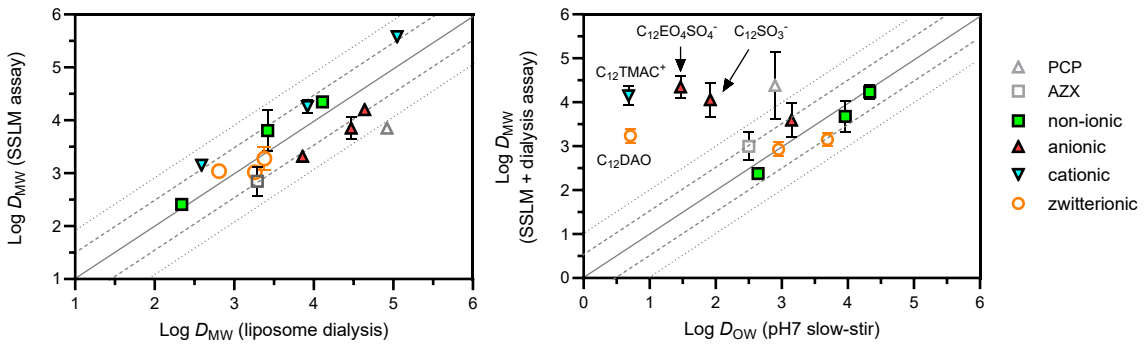


Figure 2. (left) Alignment of the SSLM approach and liposome dialysis approach to measure log D_{MW} values for different types of surfactants and the two non-surfactant reference chemicals; (right) Comparison between bilayer measurements (average of SSLM and liposome studies) of log D_{MW} and octanol-water distribution coefficients obtained with the slow-stir method [14] for the surfactants and reference chemicals. In both graphs, dotted lines indicate a factor 10 difference (1 log unit), the broken line 0.5 log unit. The deviating compounds in the right graph are identified according to Table 1.

5.1 SSLM bilayers are representative of liposome dialysis results and biomembranes.

Whereas a large database of log D_{MW} values is available for surfactants using SSLM [15], log D_{MW} values have only been scarcely measured by liposome dialysis. The currently measured series forms the largest set of surfactants studied with liposomes. For three surfactants the log D_{MW} values from POPC liposomes in Teflon dialysis systems are within a factor of four of reported values, including a non-ionic ($C_{10}EO_5$) [21], as well as cationic (dihexylamine) and zwitterion (C12-DAO). This range is expected to cover differences in handling, equipment and phospholipid material, and is comparable to the overlap for a series of perfluorinated anions [24, 28]. The

current dataset on log D_{MW} from liposome dialysis and SSLM, complemented with dialysis data for AEOs [21] and SSLM data for cations [27], is plotted in the left graph of Figure 2. Both approaches show good agreement, particularly for the non-ionic compounds and zwitterions, with an average difference of 0.3 log units across all surfactants. Where both SSLM plate types were evaluated, log D_{MW} values obtained with the HD series were consistently slightly higher than those obtained with the LD series, although the magnitude of the difference varied between test substances and the underlying cause remains unclear. In contrast, values for anionic surfactants are higher in POPC liposomes than SSLM bilayers by a factor of 3 (0.5 log units), while cationic surfactants show lower values. The large SSLM data set could thus be considered as representative for POPC liposome data for all surfactant types and used as a key descriptor to predict sorption of surfactants to actual cell membranes. Although this difference is within a common range of experimental uncertainty, it is noted that the egg-yolk based POPC likely contains anionic phospholipids (4% anionic phosphatidylinositols in addition to predominantly zwitterionic lipids: 74.4% phosphatidylcholines, 19.4% phosphatidylethanolamines, and 2% sphingomyelin, see [62, 63]) that result in negative surface charge. In contrast, the POPC used in liposome dialysis contains pure zwitterionic POPC, resulting in no net surface charge. As eukaryote cell membranes contain substantial fractions of anionic phospholipids [59], particularly in the inner leaflet, there may be more weight of evidence on setting SSLM values as benchmark cell membrane binding values rather than liposome data based on pure POPC [62, 63]. Measurements with SSLM bilayers therefore reflect the influence of anionic phospholipids on log D_{MW} of ionic surfactants. The SSLM approach has other clear advantages over suspended unilamellar liposomes by (i) attaining rapid equilibration in 1 h instead of 2-3 days for dialysis, (ii) requiring only mild centrifugation to obtain clear supernatant in case ultracentrifugation is used, (iii) being packaged in sorbent dilution series which facilitates setting an appropriate lipid level that significantly decreases freely dissolved concentrations.

The experimental methods using bilayer membranes have limits to their feasibility for surfactants, and other approaches are required to derive log D_{MW} values for chemicals that cannot be tested experimentally. Surfactants that exhibit high adsorptive losses to laboratory equipment are less suitable for the typical mass balance calculations in SSLM and dialysis systems. However, sampling of both freely dissolved and lipid suspended concentrations remains feasible, as shown for cationic surfactants in this study. However, using the 2 mol% criterion for membrane sorbed concentrations (e.g., 5 g/kg for lipid Mw of 800 and surfactant Mw of 200) does generate detection limit challenges for surfactants with log $D_{MW} > 6$, as this would require aqueous concentration (C_{aq}) measurements <5 µg/L. Quantification of C_{aq} furthermore depends on availability of analytical standards, and complexity of chemical composition in technical mixtures of many surfactant formulations. The IAM-HPLC based K_{IAM}^{0} value has been demonstrated to be a valuable indicator of log D_{MW} for anionic and cationic surfactants. It does not rely on adsorptive losses of test solutions, and the peak retention time is sufficient without further quantification. In addition the method is appropriate for mixtures of chain lengths present in surfactants since peaks are substantially separated or identified by specific m/z signals. However, also for this method, if K_{IAM} is too strong, retention time at even 30% solvent will be in the range of several hours, and the required solvent series to extrapolate to fully aqueous eluent becomes increasingly uncertain. For ethoxylated surfactants, as well as all tested zwitterionic surfactants, IAM-HPLC appears to be strongly overestimating the log D_{MW}, rendering this experimental approach ineffective. It is hypothesised that bare silica surfaces of the IAM-particles create additional IAM retention, as the ethoxylate chains are known to enhance affinity to clay surfaces [64], which may have also influence the ethoxylated anion C_{12}-EO_4-SO_4^-. Well-calibrated computational approaches could serve as a desired alternative in such cases.

5.2 Can octanol-water values be used to predict membrane water distribution coefficients for surfactants?

Log D_{OW} is commonly used as a metric of hydrophobicity. The current dataset allows a detailed comparison of log D_{OW} and log D_{MW} for various surfactant classes. As shown previously [14], for most surfactant types the various available experimental and computational approaches display high uncertainty margins. The surface-active properties of surfactants result in difficulties of obtaining accurate log D_{OW} values with existing experimental approaches (shake-flask method, HPLC method, maximum solubility ratios), while the ionic properties result in high uncertainty for model predictions. Nevertheless, the slow stir method can be used to minimise emulsification of octanol in water. If it can be shown that the surfactant–water–octanol system reaches equilibrium, a sufficiently sensitive analytical method is available, and micelle formation and adsorption are prevented, the method can produce high quality log K_{OW} measurements for non-ionic surfactants, as well as reasonable estimates for a range of ionisable surfactants. The right-hand panel of Figure 2 shows the average of bilayer based experimental log D_{MW} values (SSLM and liposomes) plotted against the most reliable log D_{OW} measurements based on slow-stir experiments. Log K_{OW} values are suitable descriptors for deriving log $K_{MW,N}$ non-ionic AEOs, but for all other surfactant classes there are clear examples where log D_{OW} underestimates log D_{MW} by several orders of magnitude. More advanced computational approaches are, therefore, required that adequately account for hydrophilic/electrostatic interactions between the (partially hydrated) outer-membrane headgroups and the ionic moieties of surfactants, which are not represented by the octanol-water system.

5.3 Advanced computational approaches to account for ionic interactions between membrane lipids and surfactants

5.3.1 Literature comparison

The nine ionic surfactants in the current study showed consistent underestimation when applying recent versions of COSMO-RS (V23, V25) and its module COSMOmic, whereas the CG-MD umbrella sampling approach showed variable agreement of predicted log D_{MW} values with measured data. A new COSMOplex approach was evaluated with a first attempt at establishing membrane potential curve parameters that correctly align ionic chemicals with different molecular features. As the current study established that log D_{MW} values obtained by SSLM do not show clear deviations from liposomal partition data for any surfactant type, all SSLM reported values for surfactants can be compared with the predictions from both approaches, to form a more detailed view on the chemical applicability domain. Figure 3 compares the CG-MD, COSMOmic and fragment method calculations with experimental data for 10 non-ionic AEOs, 3 zwitterions, 24 cationics, and 20 anionic surfactants. For many surfactants, CG-MD shows very good agreement with the experimental data. For example, the average difference (±stdev) is 0.1 (0.37) log unit for AEOs and –0.3 (0.55) log units for zwitterions. Notable exceptions include a substantial underestimation for alkylamines (primary, secondary and tertiary alkylamines) and overestimation for several linear alkylbenzosulfonate (LAS) anions. In contrast, quaternary ammonium cations show good agreement with an average deviation is only 0.17 (0.43) log units (n = 13).

COSMOmic with the recommended membrane potential curve [55] showed an overall poor agreement across all surfactant types, yielding log D_{MW} values that contradict earlier COSMOmic versions that evaluated cationic surfactants [27] (see SI Section 3.2.2). COSMOmic issues with unrealistically small carbon chain increments had been noted previously [28]. A more transparent way of deriving a DMPC membrane bilayer input structure was possible using the

606 COSMOplex tool. This allowed for a first attempt to recalibrate the membrane potential curve
607 parameters, focusing on alignment of a series of perfluorinated anionic surfactants. As a result,
608 non-fluorinated anionic surfactants were mostly underestimated, but varying the parameters
609 would have resulted in slightly more favourable predictions for some, while worse predictions for
610 others. Overall, for a large set of anionic surfactants and non-surfactant anions, the RMSE was
611 0.83 (n = 60), which given the diversity of chemical structures is a reasonable result as also
612 observed for only neutral chemicals [44]. With a single offset factor derived for cationic
613 surfactants, all other non-surfactant cations showed good alignment as well. How to handle
614 zwitterionic surfactants remains to be explored further.

615 The available surfactant fragment models showed close alignment for most surfactants, largely
616 because the majority of these chemicals were included in the calibration of the respective
617 fragment values, as reported for AEOs [21] and various anions and cations [15]. Exceptions are
618 the carboxylate anions C_7-CO_2^- and C_{11}-CO_2^-, for which the carboxylate fragment was derived
619 from a series of perfluorinated carboxylates. It is notable that only C_{11}-CO_2^- appears as an outlier.
620 The overestimated predictions for benzalkonium, morpholine and dialkylimidazolium
621 compounds are based on a study of ionic liquids [29], which used a 96 well plate SSLM system
622 without transfer into glass vials and medium renewal. This experimental setup may have led to
623 an underestimation of D_{MW} for these strongly adsorptive surfactants.

624 For cationic surfactants, previous literature results showed that COSMOmic produces good
625 results for this surfactant class [27, 28, 65], provided that the membrane potential curve is
626 correctly parameterised, as it is critical for meaningful predictions. The COSMOplex approach
627 presented here represents a first step to provide a transparent and reproducible protocol that
628 can be refined and further optimised.

629 More experimental log D_{MW} data on zwitterionic surfactants would allow for more careful
630 calibration of COSMOmic, perhaps even a shared offset with cationic chemicals. This would

631 also allow for the construction of extended surfactant fragment models. The anion and cation
632 fragment models have been trained on many different types of surfactants already, but
633 predictions for new surfactant types may first need to be explored with experimental data. CG-
634 MD performs well for linear quaternary ammonium species and secondary ammonium species.
635 For C_{12}-NH_3^+ and other primary ammonium species, pp-LFER or the fragment method are the
636 best available computational approaches.

637 ### 5.3.2 Computational calculation of log D_{MW}

638 Due to the low presence of the neutral species for variably ionisable surfactants in this study at
639 pH 7.5, calculated partitioning coefficients for the fully ionised forms in CG-MD and COSMOplex
640 have been considered to be equivalent to distribution coefficients, log D_{MW}. An attempt has been
641 made to account for the neutral fraction by interpolating between the neutral and ionised
642 versions of the solutes based on their percentage ionisation at the experimental pH using Eq. 1
643 and Eq. 2. Values for COSMOplex and CG-MD are reported in SI Tables S10 and S8, respectively.
644 Zwitterions in their unionised form were treated as cationic, as they contain permanently ionised
645 quaternary ammonium groups (see SI section S3.4). The combined log D_{MW} shows minimal
646 changes for most species, with the exception of C_{11}-CO_2^- and C_6-NH_2^+-C_6 for CG-MD. C_{11}-CO_2^- is
647 99.2 % ionised at pH 7.5 and shows an increase of 0.45 for CG-MD and 0.44 for COSMOplex when
648 combined with the neutral species. With a pK_a of 5.3, C_{11}-CO_2^- has the pK_a closest to the
649 experimental pH (7.5) among all surfactants in the test set. Dihexylamine is a 99.992 % ionised
650 base, yet shows a small but significant shift in log $D_{MW.}$ An increase of 0.15 occurs for CG-MD,
651 though COSMOplex results in a less significant change due to the smaller differences between
652 the neutral and ionised values. Although the pK_a values for most surfactants differ by several units
653 from the typical cellular pH, we advise caution when assigning log D_{MW} values calculated at a pH
654 within 3 log units of the pK_a.

655

5.3.3 Simulation time requirements

From a practical perspective, the time taken to generate data via the simulation methods is important. pp-LFER, the surfactant fragment method and K_{OW}-regression take trivial amounts of time to calculate for a new compound, once the models have been trained on the existing experimental data. However, as Table 1 shows, the applicability domain of these methods is limited by the chemical space covered in the training set.

COSMOplex calculations are fast, taking under a minute per molecule. However, the conformer optimisation stage that feeds into COSMOplex is slow for molecules with long chains, taking up to a week for C_{12}-EO_8 (37 heavy atoms) on a typical PC (although this time can be reduced with High Performance Computing infrastructure). Similarly, generation of coarse-grained models using cg_param takes under a minute, even for molecules with long chains, but umbrella sampling simulations of the models are the main time-consuming part of the CG-MD procedure. For the standard protocol with 100 simulation windows, the typical computing time is one day on a desktop PC, or two for zwitterions due to the additional charged group.

SI Table S15 presents indicative simulation times for umbrella sampling in CG-MD and conformer generation in COSMOplex. COSMOplex is faster for the shorter-chain surfactants. However, the cost of CG-MD scales more gradually with molecular size and this method becomes faster than COSMOplex after around 20 heavy atoms. CG-MD is particularly suited for non-ionic surfactants where there are no charge interactions to calculate. CG-MD is free and open source, while COSMOtherm is proprietary software, with associated licencing costs.

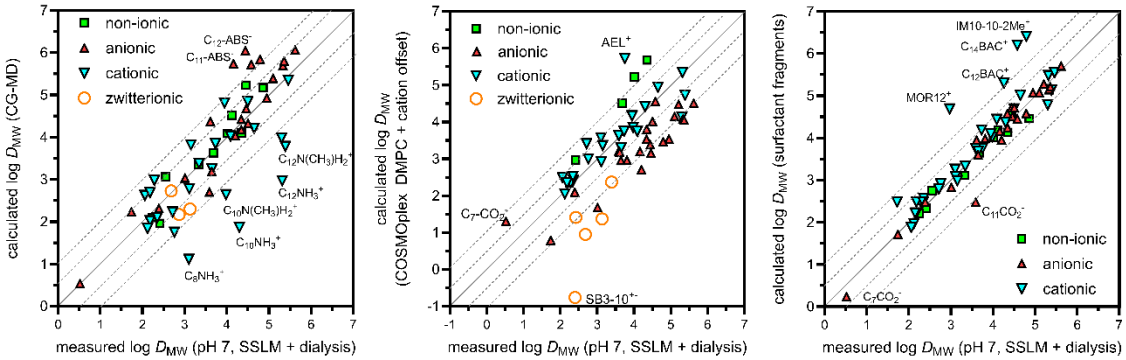


Figure 3. Comparison for larger series of surfactant structures of experimental D_{MW} from literature and D_{MW} computations with CG-MD (left), COSMOplex/COSMOmic (middle), and specific surfactant fragment models (without zwitterions, right). Broken lines indicate 1 log unit, and 0.5 log unit deviation from experimental D_{MW} values. Several examples outside these boundaries are indicated by abbreviated name (see SI section 3.2.5 Tables S11 and S14 for literature labels).

5.4 Summary of results

Overall, the evaluation shows that method performance for determining log D_{MW} is dependent on surfactant class. In order to facilitate easier use in regulatory applications and to support selection of the most appropriate method, the relative performance and confidence of experimental and computational approaches were compared across surfactant types. The resulting synthesis, summarised in Table 3, provides a practical basis for method selection by comparing results determined using the various experimental and computational methods against those obtained using liposome dialysis.

692 **Table 3.** Summary table for determination of membrane-water distribution coefficients for tested
693 chemicals using various approaches, and quantified measures of confidence compared with liposome
694 dialysis results.

	Surfactant type	Non-ionic	Anionic	Cationic	Zwitterionic
		Measures of confidence [a]			
Experimental approach	SSLM	++ (0.2/0.2, 3)	+ (-0.7/0.1, 3)	+ (0.5/0.2, 3)	++ (-0.1/0.3, 3)
	IAM-HPLC	- (1.7/0.4, 3)	++ (0.4/0.3, 3)	++ (0.2/0.4, 3)	- (1.2/0.3, 3)
Practical recommen-dations	• Liposomes: Robust benchmark method, particularly valuable for confirmation, but less practical for routine testing. • SSLM: Preferred routine experimental approach across surfactant classes, combining robust measurements with good practical efficiency • IAM-HPLC: Useful screening approach for anionic and cationic surfactants, but not recommended for ethoxylated or zwitterionic surfactants without further validation.				
Computational approach	CG-MD	++ (0.1/0.1, 3)	+ (-0.7/0.7, 3)	+ (-0.4/0.9, 3)	++ (-0.2/0.5, 3)
	COSMOmic-COSMOplex (V25)	- (1.0/0.4, 3)	+ (-0.8/0.5, 3)	++ (0.1/0.4, 3)	- (-1.6/0.5, 3)
	pp-LFER + Δmw	-- (-2.0/0.9, 3)	-- (-2.4/1.2, 3)	-- (0.1/1.9, 3)	NA
	K_{OW} - regression	++ (0.4/0.2, 3)	-- (-2.1/1.9, 2)	-- (-3.2/NA, 1)	-- (-0.9/1.7, 3)
	Fragment models	++ (0.1/0.1, 3)	+ (-0.9/0.5, 3)	++ (0.4/0.2, 3)	NA
Practical recommen-dations	• CG-MD: Open source approach that performs well for most non-ionic, anionic, zwitterionic and quaternary ammonium surfactants, but primary amines remain a priority for further development. • COSMOmic-COSMOplex: Mechanistically useful predictive approach, but performance is strongly dependent on parameterisation and surfactant class; further validation is needed for routine application; a new COSMOplex bilayer and recalibrated potential only results in accurate predictions for cations and rough estimate for anions • pp-LFER: due to scarce experimental descriptors has limited current applicability to surfactants; requires further development for ionic surfactant classes. • K_{OW}-regression: Potentially useful for neutral/non-ionic surfactants, but not recommended as a general predictor for ionic surfactants. • Fragment models: Are useful where the surfactant falls within a well supported training domain; current best approach for primary amine species.				

695 a) Measures of confidence classes (mean difference from liposome dialysis values/standard deviation of the
696 difference, number of surfactants): ++ = average difference between method values and liposome dialysis deviates
697 <0.5 for 3 surfactants, and standard deviation of the difference <0.5; + = average difference between method values
698 and liposome dialysis deviates 0.5-1 for 3 surfactants, and standard deviation of the difference <1; - = average
699 difference between method values and liposome dialysis deviates >1 for 3 surfactants, and standard deviation of the
700 difference <1; -- = average difference between method values and liposome dialysis deviates >0.5 for 3 surfactants,
701 and standard deviation of the difference >1. NA = Not Applicable.

702

703 Experimental liposomal data from this study show good agreement with previously reported
704 liposomal values for different surfactant types, indicating a high level of consistency. An extensive

comparison between the pure POPC liposomal assay and egg-yolk based SSLM assay indicates a high consistency between values generated by both methods, with only a minor influence of cell membrane charge affecting anionic and cationic surfactants. Since cell membranes predominantly contain negatively charged phospholipids, the SSLM assay might be the most representative assay to yield benchmark log D_{MW} values for ionic surfactants. Despite a high consistency and efficiency, the chromatographic IAM-HPLC method is flawed by sometimes unpredictable confounding sorption effects due to the packing material holding the membrane monolayer. Nevertheless, for both cationic and anionic surfactants, the method can be considered an effective screening tool under optimal eluent conditions.

Previous literature results show that COSMOmic can produce good results [27, 28, 65], and specifically takes charged moieties' 3D structuring into account with calculations. The effects of complex features such as branching and polar (spacer/side) groups complicates the accuracy as the model needs simplified assumptions on bilayer structuring and charge distribution. The surfactant fragment method is based on empirical findings and performs well but has limited chemical domain so its applicability should rely on molecules on which it was trained, for example for extrapolations to increments of different chain lengths, or to compare the impact of different chemical moieties on log D_{MW}. CG-MD performs well for most non-ionic, anionic, zwitterion species as well as for linear quaternary ammonium and secondary amine species but shows poorer performance for primary amine species. For C_{12}-NH_3^+ and other primary amine species, the fragment method currently represents the most suitable computational approach.

5.5 Conclusion

Overall, this study demonstrates that membrane-water partitioning can provide a robust and practically applicable measure of surfactant hydrophobicity across the major surfactant classes. In particular, the SSLM and liposome-based experimental approaches provide a strong experimental basis for determining log D_{MW}, while overcoming many of the methodological

challenges associated with determining log K_{ow}/ D_{ow} for surface-active substances. The close correspondence between the two membrane-based experimental approaches provides further confidence that membrane-water partitioning can be measured reproducibly across chemically diverse surfactants.

The computational evaluation provides a more nuanced outcome. Performance is dependent on surfactant class and chemical domain, and no individual computational approach performs optimally across all surfactant classes. Nevertheless, complementary computational methods are available such that robust estimates can be obtained across all the surfactant classes investigated. Computational approaches can also complement experimental methods where adsorption, analytical sensitivity, high membrane affinity or complex technical composition makes direct measurement difficult. Some chemical-domain limitations remain, including primary amines, as priorities for further development. Importantly, computational models can be progressively refined and extended as additional information becomes available.

Alongside scientific performance and applicability domain, practical resource requirements should be considered when selecting an approach. SSLM offers substantial practical efficiencies compared with liposome dialysis, particularly through shorter equilibration times and simpler sample handling, while retaining the advantages of an experimental membrane-based system. Computational approaches can further reduce experimental requirements, but their resource demands vary substantially. Fragment-based and descriptor approaches require minimal computational resource once established, whereas CG-MD and COSMOtherm/COSMOmic require greater computational investment. CG-MD is freely available and open source, while COSMOtherm is proprietary with associated licensing costs. Consequently, the most appropriate method should reflect a balance between scientific robustness, applicability domain, resource requirement and the intended regulatory application.

Taken together, these findings provide a basis for moving from method evaluation towards wider regulatory acceptance and standardisation of membrane-water partitioning as a descriptor for surfactants such as in supporting bioaccumulation assessment or replacement of log D_{ow} in adaptations/waivers under REACH. This direction is consistent with ECHA's identification of membrane–water partitioning as a regulatory research priority for improving the prediction and assessment of bioaccumulation of ionisable chemicals, including surfactants [66]. A key next step should be to establish which experimental and computational approaches are sufficiently mature for formal recognition and to develop internationally harmonised standards, for example through appropriate OECD guidance or test guidelines. This would provide a more consistent basis for the generation and regulatory use of log D_{MW} values for surfactants.

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Supporting information files

Include (1) a zip-file with (a) TZVP COSMO-structures for the key surfactants used in Table 1, (b) TZVP COSMO-structures for the representative DMPC phospholipid, and (c) mic file for a DMPC bilayer from COSMOplex; (2) a DITP files for CGMD; (3) Supporting information document with section on chemical analysis, details for each experimental approach, details for each computational approach, Figures and Tables.

List of abbreviations

K_{MW}: membrane-water partition coefficient; D_{MW}: speciation-corrected membrane-water distribution coefficient; K_{OW}: n-octanol/water partition coefficient; D_{OW}: n-octanol/water distribution coefficient; REACH: Registration, Evaluation, Authorisation and restriction of CHemicals; OSPAR: Oslo-Paris Convention for the Protection of the Marine Environment of the North-East Atlantic OECD: Organisation for Economic Co-operation and Development; ECHA: European CHemicals Agency; ERASM: Environmental Risk Assessment of Surfactants Management; AEO: alcohol ethoxylate; C_8EO_4: tetraethylene glycol monooctyl ether; C_{12}-EO_4: tetraethylene glycol monododecyl ether; C_{12}-EO_8: octaethylene glycol monododecyl ether; $C_{12}SO_3^-$: anionic dodecyl sulfonate; C_{12}-EO_4-SO_4^-: anionic tetraethylene glycol monododecyl ether sulphate; C_{12}-CO_2^-: anionic dodecanoate; C_{12}-$TMAC^+$: cationic dodecyltrimethyl ammonium; C_{12}-NH_3^+: cationic dodecylamine; C_{12}–betaine: zwitterionic lauryldimethylbetaine; C_{12}-AP-betaine:

zwitterionic (3-lauramidopropyl) dimethylbetaine; C_{12}-DAO: zwitterionic dodecyldimethyl N-oxide; AZX: azoxystrobin; PCP: pentachlorophenol; HPLC: high performance liquid chromatography; IAM: immobilised artificial membranes; k_{iam}: IAM-column retention capacity factor; k_{iam}^0: IAM retention capacity factor at fully aqueous eluent; K_{IAM}: sorption coefficient between eluent and the IAM-monolayer; K_{IAM}^0: sorption coefficient between water and the IAM-monolayer; SSLM: solid-supported phospholipid membranes; pp-LFER: polyparameter linear free energy relationship; quantitative structure–property relationship; CG-MD: coarse-grained molecular dynamics; COSMO-RS: COnductor like Screening MOdel for Realistic Solvents; SMILES: simplified molecular input line entry system; pK_a: negative logarithm (base 10) of the acid dissociation constant (K_a) of a solution; LC–MS: liquid chromatography mass spectrometry; WoE: weight of evidence

Declarations

- **Ethics approval and consent to participate:** Not applicable
- **Consent for publication:** Not applicable
- **Availability of data and material:** Data generated or analysed during this study are included in this published article [and its supplementary information files].
- **Competing interests:** The authors declare that they have no competing interests.
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- **Authors' contributions:** STJD, NJ, GH, LKB, DS, JB, JD, SW developed the experimental testing scheme, ELB, EMK, MAM, STJD developed the computational testing scheme. STJD, ELB, EMK, MAM drafted the manuscript. All authors read and approved the final manuscript.
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- **Authors' information:** GH, MG, LKB, DS, JB, JD, SW, KC, ELB are members of the ERASM Membrane Water Partitioning of Surfactants Task Force

Supplementary Files

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