The importance of the accuracy of the experimental data for the prediction of solubility

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Abstract: Aqueous solubility is an important factor influencing several aspects of the pharmacokinetic profile of a drug. Numerous publications present different methodologies for the development of reliable computational models for the prediction of solubility from structure. The quality of such models can be significantly affected by the accuracy of the employed experimental solubility data. In this work, the importance of the accuracy of the experimental solubility data used for model training was investigated. Three data sets were used as training sets – data set 1, containing solubility data collected from various literature sources using a few criteria ($n = 319$), data set 2, created by substituting 28 values from data set 1 with uniformly determined experimental data from one laboratory ($n = 319$), and data set 3, created by including 56 additional components, for which the solubility was also determined under uniform conditions in the same laboratory, in the data set 2 ($n = 375$). The selection of the most significant descriptors was performed by the heuristic method, using one-parameter and multi-parameter analysis. The correlations between the most significant descriptors and solubility were established using multi-linear regression analysis (MLR) for all three investigated data sets. Notable differences were observed between the equations corresponding to different data sets, suggesting that models updated with new experimental data need to be additionally optimized. It was successfully shown that the inclusion of uniform experimental data consistently leads to an improvement in the correlation coefficients. These findings contribute to an emerging consensus that improving the reliability of solubility prediction requires the inclusion of many diverse compounds for which solubility was measured under standardized conditions in the data set.

Keywords: aqueous solubility prediction; experimental data; model training; heuristic method.

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INTRODUCTION

The solubility of drugs and drug-like com pounds has been the su bject of extensive studies aimed at finding a way to predict solubility from molecular structure. The aqueous solubility of a drug is an i mportant factor that influences its absorption by, distributi on in and elim ination from the bod y.[1] Since poor pharmacokinetics is one of the major causes for late stage drug development failures,[2] it is clear that properties such as solubility need to be considered very early in the drug discovery process. Therefore, a reli able tool for the prediction of solubility from structure alone would be of great im portance to help in t he elim ination of unsuitable candidates and reduction of overall development attrition rates.

A considerable num ber of *in silico* m odels for the prediction of solubilit y have been proposed ov er the past decade. [3–22] These utilize an ever-growing va riety of approaches that dif fer in the way structure is represented, in the nature of the descriptors or properties that ar e derived from molecular structure and in th e regression methods used. The sheer volume of publications on novel methods for the prediction of solubilit y seems to indicat e that none of the exi sting models is fully satisfact ory.[23] Co nsistent with this , ver y few of the pro posed m odels for prediction of solubilit y have found pra ctical i mplications in the drug discover y process, probably due to low prediction re liability. Whilst most of the publis hed models perform satisfactorily with the test sets used for their validation, their performance with more diverse data plummet considerably.[24]

While significant progress has been made in developing new modelling techniques, there is, nevertheless, an e merging consens us that moving forward will require focusing on altogether different i ssues affecting the performance of existing models. Most of the recent reviews on solubility prediction indicate that solubility m odelling efforts have suffered from some basic faults, su ch as training sets that are not drug-like, unknown or high experimental error, lack of structural diversity, inc orrect tautomers or structures, neglect of ionization, no conside ra tion of salt a nd/or comm on io n issues, avoidance of crystal packing effects and range of solubility data that is not pharmaceutically relevant.[25]

One of the issues is that the design of a good qualit y trainin g set is so me thing often overlooked.[26] It is worth noting that an y model is only as good as th e data used for its generation. A training set codifies the relationship between the relevant property and che mical structu re; therefore, the applicabilit y dom ain as well as model reliability will depend he avily upon the choice of t he training set. The most limiting factor in the choice of a proper training set is the accur acy of the experimental solubilit y data. Katritzky *et al.* de monstrated that the average standard deviation for solubility measurements originating from different sources is as high as $0.6\log S$ units.[27] Occasionally, the solubi lity values reported for one compound may differ by 2–3 log units; this large di fference may originate from different experimental pro tocols. There are differ ences in sa mple concentration,

co-solvent presence, co-solvent concentration, incubation times, thermodynamic methods, kinetic methods, *etc*.[28] In addition, inclusion of values that were not distinctly reported, such as those for intrinsic solubility, and other unintentional errors all contribute significantly to the overall experimental error that can plague a data set.[29,30] In a recent work by Taskinen and Norinder, in which over 30 models from the literature were reviewed, it was concluded that improving the accuracy and applicability will "require more consideration of the consistency of the experimental solubility data and the training set composition".[24] Other authors also stressed that further development will require large, diverse sets of high-quality, uniformly determined experimental data.[30,31]

Despite the importance of this issue, there are very few published works dealing primarily with proposing carefully designed training sets. In one aspect this is understandable – consistent solubility data are not widely available and determining them for a "QSPR-significant" number of compounds would be a time--consuming, laborious and expensive endeavour. On the other hand, addressing the issue of a more selective collection of data from the literature is feasible. One such example is the data set proposed by Rytting *et al*., who set out clear criteria for the inclusion of experimental data.[32]

Increasing interest in the importance of high-quality experimental data for modelling purposes was perhaps best exemplified in a recent paper by Llinas *et al*., in which researchers where challenged to develop a model based on 100 reliable solubility measurements and to use it to predict the solubility of 32 additional molecules provided.[33] As the authors remarked, the findings of the challenge provided an overall perspective as to the current ability to estimate aqueous solubility.[34]

Based on the importance of this issue, the aim of this study was to investigate whether the implementation of solubility data obtained under standardized experimental conditions can make a significant contribution to the process of establishing new or optimizing existing QSPR models for the prediction of solubility.

<div align="center">EXPERIMENTAL</div>

Data sets

The set of 322 structurally diverse "drug-like" molecules proposed by Rytting *et al*.[32] served as the basis for the first set used in this study (data set 1). The solubility data originated from various literature sources and were collected following several criteria: (*i*) the given compound is a drug or drug-like molecule, solid at room temperature; (*ii*) the reported value is that of the intrinsic solubility at around 25 °C; (*iii*) for solubility measurement, the equilibrium must have been achieved over time, excess solid must be present at the end of testing and acceptable analytical methods must have been used for quantification. Due to geometrical optimisation issues, three molecules were excluded from the Rytting set; hence, data set 1 consisted of 319 compounds. For the investigation of the implementation of experimental solubility data obtained under the uniform experimental conditions, the Sirius data set, [35]

consisting of 8 4 diverse drug molecules for which the sol ubility was deter mined u sing th e Sirius CheqSol technique,[36] was used. This pot entiometric method for the measurement of intrinsic solubility is very accurate and allows for rapid equilibration of the experiment and collection of the precipitate during the experiment for characterization.[37]

Data set 2 was created by sub stituting 28 solubility values fro m dat a set 1 with those from the Sirius data set. Data set 3 wa s creat ed by adding the re maining 56 molecules fr om the Sirius data set to data set 2 (Table I). The Table with structures of all components included in the Sirius data set can be obtained on request.[35]

Table I. Data sets composition

Data set	Solubility values of compounds
1	319 from ref. 32
2	291 from ref. 32 and 28 from ref. 35
3	291 from ref. 32 and 84 from ref. 35

Structure optimisation and descriptor calculation

All structure s were con structed usi ng Sp artan soft ware.[38] Geometry o ptimisation w as performed by the A M1 semi-empirical method i mplemented in the Sp artan software. Calculation of descriptors was performed using the Codessa programme (comprehensive descriptors for structural and statistical analysis).[39] A total of 728 de scriptors were calculated and divided into five groups: constitutional, topological, geometrical, electrostatic and quantum-chemical.

Correlation analysis

The heuristic method implemented in the Cod essa software w as used for the selection of the most si gnificant descriptors for the prediction of solubil ity. The m ost significant de s-criptors were se lected in each g roup of descriptors using the he uristic method. Heuristic 5-pa-rameter analysis was also used for sel ection of the fiv e most significant descriptors among all descriptors cal culated, which w ere then used for establi shing a QSPR (qua ntitative structure––property relationship) equation for each of the sets using the multiple linear regression (MLR) method. Prior to this, de scriptor intercorrela tion analy sis was perfor med, so that no two d es-criptors appearing in the final equations have an intercorrelation coefficient larger than 0.5.

RESULTS AND DISCUSSION

The potential limit of the accuracy of ex perimental data on the predictability of solubilit y models should be addressed before turning to t he purely com puta-tional methods, therefore the Sirius data set wa s used to investigate the extent to which the i mplementation of solubility data measured under the sam e standard-dized method may influence the quality of the potent ial model training. The cre-ation of data sets 1, 2 and 3 are described in the Experimental section.

The heuristic method was applied for the selection of the most significant descriptors for the prediction of solubility to all three data sets. Th e most signi-ficant descriptors for all t hree sets fro m each of the groups of descriptors ob-tained by the heuristic method are presented in Table II. The m ost highly corre-lated descriptor in all data sets was the partition coefficient (log *P*). Most of the selected elect rostatic and quantum -chemical des criptors are derived from mole-

cular surface areas   (H-donor/acceptor surface areas) and relativ e el ectrostatic charges. This would indicate that the descriptors selected using the heuristic method proved to be related to the solvation mechanism of the molecules.

Table II. The most significant descriptors among the five groups of descriptors, selected using the heuristic method

Descriptor[a]	Data set 1		Data set 2		Data set 3	
	R^2	F	R^2	F	R^2	F
Constitutional descriptors						
log P	0.5013	318.67	0.5337	362.77	0.5479	451.95
N_{BR}	0.3848	198.28	0.4116	221.73	0.4390	291.88
R_C	0.3587	177.33	0.3562	175.41	0.3289	182.81
R_{BR}	0.3133	144.65	0.3184	148.09	0.2978	158.16
N_C	0.3013	136.71	0.3294	155.70	0.3639	213.34
N_R	0.2651	114.34	0.2675	115.74	0.2765	142.53
N_{AB}	0.1885	73.63	0.2062	82.36	0.2686	136.97
R_N	0.1526	57.08	0.1570	59.05	–	–
GI_{all}	0.1351	49.53	0.1479	55.04	0.2051	96.23
MW	0.1283	46.65	0.1409	51.97	0.1962	91.05
Topological descriptors						
^{0}ABIC	0.2833	125.31	0.2943	132.19	0.2526	126.06
^{0}ACIC	0.2478	104.41	0.2661	114.94	0.2640	133.81
^{1}ACIC	0.2196	89.22	0.2339	96.76	–	–
^{1}ABIC	0.2072	82.83	0.2147	86.68	–	–
^{2}ACIC	0.1949	76.73	0.2089	83.72	–	–
^{3}Randic	0.1926	75.62	0.2038	81.12	0.2446	120.76
^{2}CIC	0.1895	74.14	0.2224	90.68	0.2254	108.54
^{1}K&H	0.1884	73.59	0.2061	82.31	0.2576	129.40
^{1}Randic	0.1829	70.96	0.2023	80.39	0.2580	129.72
^{2}Randic	–	–	0.1938	76.19	0.2426	119.49
^{0}K&H	–	–	–	–	0.2327	113.13
^{2}K&H	–	–	–	–	0.2199	105.16
Geometrical descriptors						
MSA	0.2312	95.31	0.2565	109.36	0.3125	169.57
XY Shadow	0.2259	92.50	0.2495	105.38	0.2978	158.17
I_C	0.2176	88.19	0.2289	94.11	0.2550	127.69
I_B	0.1778	68.55	0.1868	72.80	0.2142	101.66
MV	0.1613	60.99	0.1829	70.95	0.2378	116.35
I_A	0.1407	51.92	0.1500	55.93	0.1719	81.36
ZX Shadow		32.46	0.1104	39.34	0.1685	75.56
Electrostatic descriptors						
^{e}FPSA-3	0.2603	111.56	0.2676	115.80	0.2759	142.10
^{ed}HDSA-1/TMSA	0.2590	110.81	0.2678	115.96	0.2649	134.42
^{ed}HDSA-2/TMSA	0.2555	108.82	0.2621	112.62	0.2554	127.93
^{e}HASA-2/TMSA	0.2282	93.74	0.2401	100.17	0.2454	121.31
^{e}HACA-2/TMSA	0.2189	88.82	0.2279	93.56	0.2333	113.48
^{ed}HDSA-2/SQRT	0.2001	79.32	0.2037	81.09	–	–

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TABLE II. Continued

Descriptor[a]	Data set 1		Data set 2		Data set 3	
	R^2	F	R^2	F	R^2	F
Electrostatic descriptors						
^{ed}HDCA-1/TMSA	0.1984	78.48	0.2072	82.86	0.2091	98.60
^{ed}HDCA-2/TMSA	0.1979	79.20	0.2040	81.22	0.2040	95.57
^{e}HASA-2/SQRT	0.1935	76.06	0.2035	81.01	–	–
^{e}HASA-1/TMSA	0.1905	74.59	0.2026	80.54	0.2164	103.01
^{ew}WNSA-1	–	–	–	–	0.2497	124.17
^{e}TMSA	–	–	–	–	0.2437	120.18
Quantum-chemical descriptors						
ALFA-pol	0.2657	114.70	0.2873	127.79	0.3458	197.12
^{qd}HDSA-1/TMSA	0.2579	110.18	0.2673	115.67	0.2642	133.95
^{qd}HDSA-2/TMSA	0.2574	109.85	0.2645	113.99	0.2579	129.64
^{q}HASA-2/TMSA	0.2282	93.74	0.2401	100.17	0.2454	121.31
^{q}RNCG	0.2281	93.69	0.2393	99.72	0.2433	119.23
PMI_C	0.2176	88.19	0.2289	94.11	0.2550	127.31
^{qd}HDSA-2/SQRT	0.2005	79.52	0.2047	81.60	–	–
^{q}HASA-2/SQRT	0.1935	76.06	0.2035	81.01	–	–
^{q}HASA-1/TMSA	0.1905	74.59	0.2026	80.54	–	–
PMI_C/#	0.1892	73.99	–	–	–	–
^{q}TMSA	–	–	–	–	0.2437	120.16
$Etot_{2\text{-c ex}}$	–	–	–	–	0.2385	116.80
^{qw}WNSA-1	–	–	–	–	0.2274	109.80

[a]Symbols of descriptors used; **constitutional**: N_{BR} – number of benzene rings, N_C – number of C atoms, R_{BR} – relative number of benzene rings, R_C – relative number of C atoms, R_N – relative number of N atoms, N_R – number of rings, N_{AB} – number of aromatic bonds, GI_{all} – gravitational index (all bonds), MW – molecular weight; **topological**: ^{0}ACIC – average complementary information content (order 0), ^{1}ACIC – average complementary information content (order 1), ^{2}ACIC – average complementary information content (order 2), ^{0}ABIC – average bonding information content (order 0), ^{1}ABIC – average bonding information content (order 1), ^{2}CIC – complementary information content (order 2), ^{1}Randic – Randic index (order 1), ^{2}Randic – Randic index (order 2), ^{3}Randic – Randic index (order 3), ^{0}K&H – Kier & Hall index (order 0), ^{1}K&H – Kier & Hall index (order 1), ^{2}K&H – Kier & Hall index (order 2); **geometrical**: XY Shadow – area of the shadow of the molecule projected on a plane defined by X and Y axes, ZX Shadow - area of the shadow of the molecule projected on a plane defined by Z and X axes, MSA – molecular surface area, MV – molecular volume, I_A – moment of inertia A, I_B – moment of inertia B, I_C – moment of inertia C; **electrostatic** (Zefirov's PC): ^{e}FPSA-3 – FPSA-3 fractional PPSA (PPSA-3/TMSA), ^{ed}HDSA-1/TMSA – HA dependent HDSA-1/TMSA, ^{ed}HDSA-2/TMSA – HA dependent HDSA-2/TMSA, ^{ed}HDSA-2/SQRT – HA dependent HDSA-2/SQRT(TMSA), ^{ed}HDCA-1/TMSA – HA dependent HDCA-1/TMSA, ^{ed}HDCA-2/TMSA – HA dependent HDCA-2/TMSA, ^{e}HASA-1/TMSA – HASA-1/TMSA, ^{e}HASA-2/TMSA – HASA-2/TMSA, ^{e}HASA-2/SQRT – HASA-2/SQRT(TMSA); ^{e}HACA-2/TMSA – HACA-2/TMSA, ^{e}TMSA – TMSA total molecular surface area, ^{ew}WNSA-1 – WNSA-1 weighted PNSA (PNSA1*TMSA/1000); **quantum-chemical**: ALFA-pol – ALFA polarizability (DIP), ^{qd}HDSA-1/TMSA – HA dependent HDSA-1/TMSA [Semi-MO PC], ^{qd}HDSA-2/TMSA – HA dependent HDSA-2/TMSA (semi-MO PC), ^{qd}HDSA-2/SQRT – HA dependent HDSA-2/SQRT(TMSA) (semi-MO PC), ^{q}HASA-1/TMSA – HASA-1/TMSA (semi-MO PC), ^{q}HASA-2/TMSA – HASA-2/TMSA (semi-MO PC), ^{q}HASA-2/SQRT – HASA-2/SQRT(TMSA) (semi-MO PC), PMI_C – principal moment of inertia C, PMI_C/# – principal moment of inertia C/# of atoms, ^{q}RNCG – RNCG relative negative charge (QMNEG/QTMINUS) (semi-MO PC), $Etot_{2\text{-c ex}}$ – total molecular 2-center exchange energy, ^{q}TMSA – TMSA total molecular surface area (semi-MO PC).

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Comparing data sets 1 and 2, which differ only in the solubility values of 28 compounds, the order of the most significant descriptors selected by the heuristic method in the one-parameter correlation among each of the five groups of descriptors remained relatively unchanged. However, there was an increase in the correlation coefficient in all the descriptors involved. Comparing data sets 1 and 3, the order of the descriptors was slightly changed. Although the correlations of the individual descriptors decreased in a small number of instances, there was an overall improvement of the correlation in all descriptor groups. This would suggest that if no additional components are included in the set, with just the experimental data being altered, individual descriptors could retain their respective capacities for describing the correlation between solubility and structure. This does not hold true, however, when establishing a multi-parameter correlation, as is later demonstrated.

Inclusion of additional components in data set 3 increased the diversity of the set. This can result in a change of relative importance of different molecular properties governing solubility (within a set), which in turn affects the significance of selected molecular descriptors. In the present case, this was reflected in the reordering of closely related descriptors among each group of descriptors.

The present observations showed that changing the experimental data in multi-parameter correlations tended to have even a greater impact. A five-parameter heuristic correlation analysis and subsequent MLR yielded the following QSPR equations for data sets 1, 2 and 3, respectively:

$$\log S = -0.63647 \log P - 0.01454 qHBCA + 24.65157 I_{C} + 0.010761 {}_2AIC - 19.7268 R_{NR}, \quad n = 319, \quad R^2 = 0.6616 \tag{1}$$

$$\log S = -0.42352 \log P + 0.559774 E\text{tot}_{2\text{-c ex}}/\# - 0.00756 qDPSA\text{-}3 + 9.912633 qRNCG + 0.197134 \min(\#HA, \#HD), \quad n = 319, \quad R^2 = 0.6689 \tag{2}$$

$$\log S = -0.60863 \log P - 0.04033 N_{AB} - 14.2527 R_{NR} - 0.01145 qDPSA\text{-}3 + 2.020366 eRNCG, \quad n = 375, \quad R^2 = 0.7045 \tag{3}$$

where: $\log P$ – partition coefficient;

qHBCA – HBCA H-bonding charged surface area (semi-MO PC);

I_C – moment of inertia C;

$_2AIC$ – average information content (order 2);

R_{NR} – relative number of rings;

$Etot2\text{-}c\ ex/\#$ – total molecular 2-center exchange energy/# of atoms;

qDPSA-3 – DPSA-3 difference in CPSAs (PPSA3-PNSA3) (semi-MO PC);

qRNCG – RNCG relative negative charge (QMNEG/QTMINUS) (semi-MO PC);

min(#HA, #HD)- minimum number of H-acceptors/donors;

N_{AB} – number of aromatic bonds;

R_{NR} – relative number of rings;

qDPSA-3– DPSA-3 difference in CPSAs (PPSA3-PNSA3) (semi-MO PC);

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eRNCG - RNCG Relative negative charge (QMNEG/QTMINUS).

The plots of the experimental *vs.* the predicted solubilit y values using t hese three equations for the three training sets are shown in Figs. 1–3.
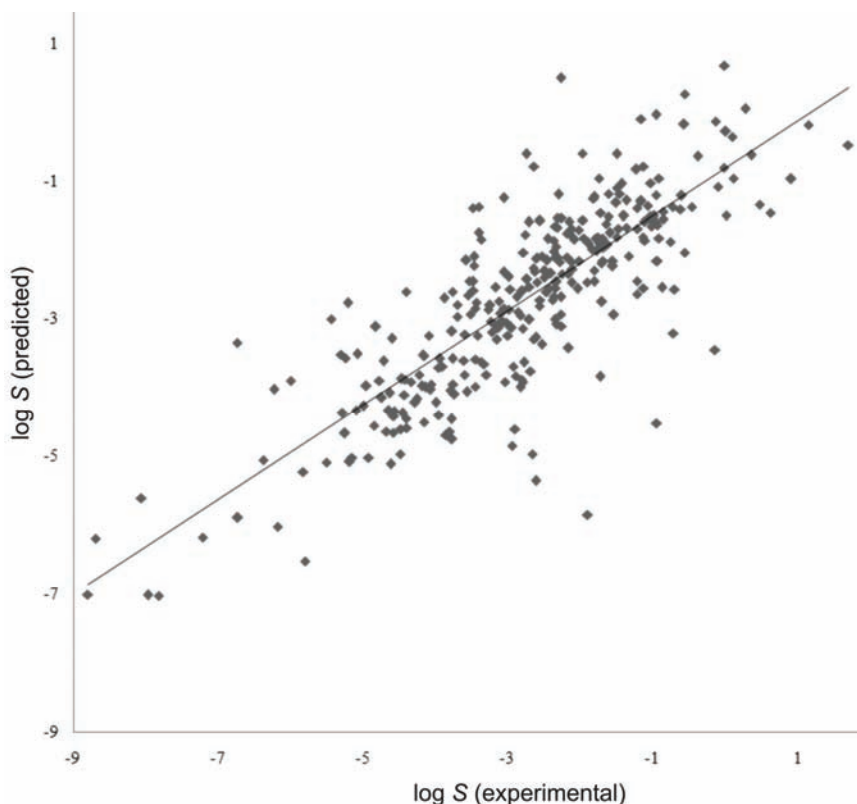

Fig. 1. The correlation between the experimental and predicted log *S* values
for data set 1 ($n = 319$, $R^2 = 0.6616$).

Equation (1), derived from data set 1 ($n = 319$), has t he smallest correlation coefficient of the three ($R^2 = 0.6616$, $RMSE = 0.9641$). In com parison, Eq. (2) shows a somewhat improved performance, with a slightly better correlation coefficient and a remarkable reduction in the root mean squared error ($n = 319$, $R^2 = 0.6689$, $RMSE = 0.8623$). Equation (3), derived from the supplemented set ($n = 375$), has the best correlation coe fficient and a slightl y reduced *RMSE*, compared to Eq. (1) ($R^2 = 0.7045$, $RMSE = 0.9382$). Introductio n o f uniform ex - perimental d ata consist ently leads to an increase in the correlati on coefficient. This can be attributed t o both the correction of outli ers and the i mprovement of overall data consistency.
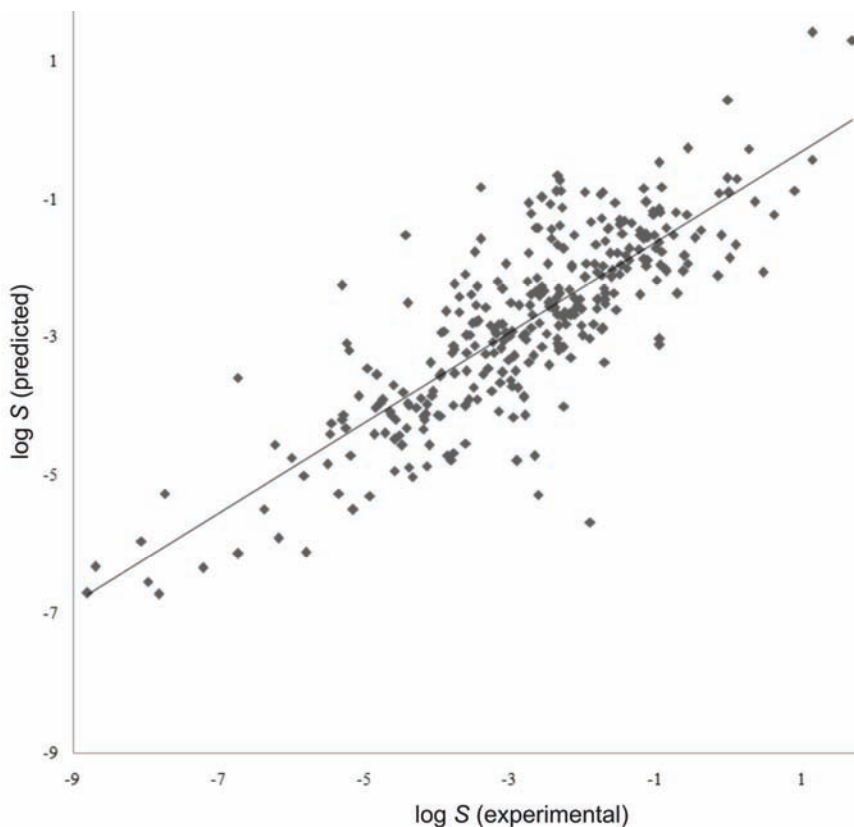
Fig. 2. The correlation between the experimental and predicted log *S* values
for data set 2 (*n* = 319, R^2 = 0.6689).

Moving from single to multi-parameter correlations, the difference in selection of the m ost significant descriptors us ing the three data se ts beca me more evident. The equation corresponding to data set 1 is composed of 2 constitutional, 1 geom etrical, 1 t opological and 1 quantum -chemical descriptor. On the ot her hand, Eq. (2) was established using 1 constitutional and 4 quantum-chemical descriptors, which toget her account for several aspects of the solvation process, especially polar interactions and the possibilit y of H-bond form ation. Thus, while the R^2 values for Eqs. (1) and (2) are simila r, the interpretability of these equations is significantly affected by the changes in the solubility values of the data set. On average, these values for the 28 substitutions made between data set 1 and 2 (Table III) differ by 0.57log *S*. Thi s is largely consistent wi th observations made by Katritzky *et al*.[27] Differenc es in excess of 1.5log *S* are also present in some instances, *e.g*., phenylbutazone, propranolol, sulfamerazine and notably ter-fenadine, for which the values differ by 3log *S*. Such large-sc ale di fferences can clearly affect the selection of the most significant descriptors. Data Set 3 is struc-

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turally m ore diverse than the previous two, thus t he correspondin g Eq. (3) als o features a different combination of descriptors. It is composed of 3 constitutional and 2 quantu m-chemical descriptors. Th ese de scriptors en compass mol ecular pro - perties that relate to hy drophobicity as we ll as those that facilitate solvation. In summary, both the structural diversity of the training set and the standardized ex- perimental solubility data included in the training significantly influence not just the statistical performance but also the interpretability of a prospective model.
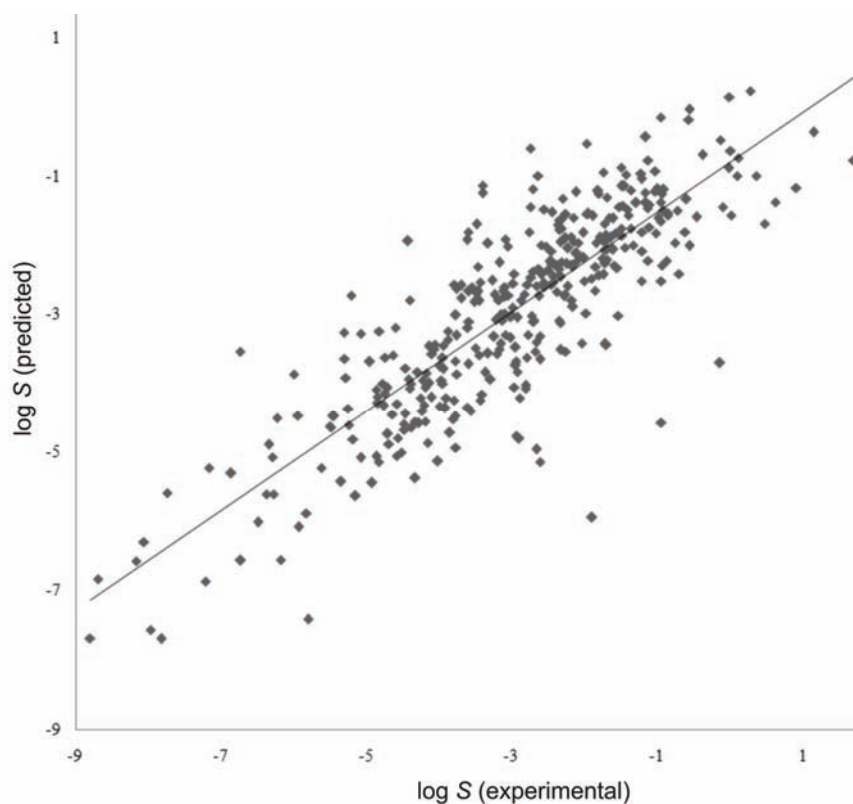

Fig. 3. The correlation between the experimental and predicted log *S* values for data set 3 ($n = 375$, $R^2 = 0.7045$).

TABLE III. Rytting s olubility data us ed in data set 1, substituted with Sirius solubility data used in data Set 2 (No. of compounds: 28)

Compound	log *S*	
	Rytting (data set 1)	Sirius (data set 2)
Amitriptyline –4.4560		–4.3900
Benzocaine –2.6160		–2.2300
Benzoic acid	–1.5550	–1.6100
Chlorzoxazone –2.8310		–2.6100

TABLE III. Continued

Compound	log S	
	Rytting (data set 1)	Sirius (data set 2)
Diclofenac –5.0970		–5.4500
Flufenamic acid	–4.6230	–5.3500
Flurbiprofen –3.7400		–4.1100
Folic acid	–5.4410	–5.3100
Haloperidol –4.4290		–5.4700
Hydrochlorothiazide –2.6890		–2.6800
Ibuprofen –3.4200		–3.6100
Lidocaine –1.7680		–1.8500
Metoclopramide –3.1760		–3.5900
Nadolol –1.0080		–1.5700
Naproxen	–4.1550	–4.1400
Nitrofurantoin –3.4770		–3.3300
Norfloxacin	–3.0570	–2.7500
Paracetamol	–1.0740	–1.0000
Phenobarbital –2.3660		–2.2800
Phenylbutazone	–2.6440	–4.3900
Prochlorperazine	–4.3980	–4.8700
Promethazine –4.2600		–4.1900
Propranolol	–0.7140	–3.5000
Quinine	–2.7900	–2.8100
Sulfamerazine –1.2180		–3.1000
Sulfathiazole	–2.8050	–2.7000
Sulindac	–5.0000	–4.5200
Terfenadine –4.6740		–7.7400

CONCLUSIONS

Solubility is a difficult property to predict, and one reason for this is the absence of a high-quality data set of reliable and reproducible solubility measurements. Hopefully, by measuring many compounds under standardized conditions, current predictive models can be improved. In this work, an attempt was made to demonstrate the importance of implementing such data to improve the confidence of the training of the models.

It was successfully shown that the usage of uniform experimental data can significantly improve the correlation in the training set. The results also showed that updating existing data sets with such data leads to changes in the selection of the most significant descriptor, which would require the given model to be additionally optimized. Continuously updated models would be a valuable tool for preliminary solubility screening and could be developed alongside solubility measurement devices as added value software.

И З В О Д

ВАЖНОСТ ПРЕЦИЗНОСТИ ЕКСПЕРИМЕНТАЛНИХ ПОДАТАКА
ЗА ПРОЦЕНУ РАСТВОРЉИВОСТИ

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Растворљивост лека у води је значајан фактор који утиче на више аспеката његовог фармакокинетичког профила. Бројне публикације презентују различите методологије за развој поузданих компјутерских модела за предвиђање растворљивости на основу структуре једињења. Квалитет модела за предвиђање растворљивости битно зависи од тачности експерименталних вредности за растворљивост које су коришћене за тренирање модела. У овом раду проучаван је значај примене експерименталних података добијених под стандардизованим, униформним условима за тренирање модела за предвиђање растворљивости. Коришћена су три сета података – испитивани сет 1 који је добијен одабиром експерименталних вредности за растворљивост под одређеним критеријумима из различитих литературних извора ($n = 319$), затим испитивани сет 2 који је добијен заменом 28 вредности за растворљивост из испитиваног сета 1 вредностима за растворљивост добијеним стандардизованом експерименталном методом у једној лабораторији ($n = 319$) и испитивани сет 3 који је добијен додатком још 56 компоненета у испитивани сет 2, за које су вредности растворљивисти такође одређене под стандардизованим условима у истој лабораторији ($n = 375$). Затим је примењена хеуристичка метода за селекцију најзначајнијих дескриптора, коришћењем једнопараметарских и више-параметарских анализа. Постављене су корелације између најзначајнијих дескриптора и растворљивости коришћењем мултилинеарне регресионе анализе за сва три испитивана сета података. Уочена је значајна разлика између једначина које су добијене коришћењем различитих сетова података, што указује на то да је након увођења нових експерименталних података неопходно додатно оптимизовати постојеће моделе. Показано је да коришћење униформних експерименталних података условљава побољшање коефицијената корелације. Ови резултати говоре у прилог све заступљенијем ставу да је за побољшање поузданости предвиђања растворљивости потребно користити сетове података великог броја различитих једињења чија је растворљивост мерена под стандардизованим условима.

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