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Antonio Llinas, and Alex Avdeef

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Solubility Challenge revisited after 10 years, with multi-lab shake-flask data, using tight (SD ~0.17 log) and loose (SD ~0.62 log) test sets

**Dedicated to the memory of Anton J. Hopfinger and Oleg A. Raevsky*

Antonio Llinas,[1] Alex Avdeef [2,†]

[1] DMPK, Respiratory, Inflammation and Autoimmunity, IMED Biotech Unit, AstraZeneca, Gothenburg, SE-43183 Sweden.
[2] *in-ADME* Research, 1732 First Avenue, #102, New York, NY 10128, USA

Abstract

Ten years ago we issued, in conjunction with the Journal of Chemical Information and Modeling, an open prediction challenge to the cheminformatics community. Would they be able to predict the intrinsic solubilities of 32 druglike compounds using only a high-precision set of 100 compounds as a training set? The "Solubility Challenge" was a widely-recognized success and spurred many discussions about the prediction methods and quality of data. Regardless of the obvious limitations of the challenge, the conclusions were somewhat unexpected. Despite contestants employing the entire spectrum of approaches available then to predict aqueous solubility and disposing of an extremely tight data set it was not possible to identify the best methods at predicting aqueous solubility, a variety of methods and combinations all performed equally well (or badly). Several authors have suggested since then that it is not the poor quality of the solubility data which limits the accuracy of the predictions, but the deficient methods used. Now, ten years after the original Solubility Challenge, we revisit it and challenge the community to a new test with a much larger database with estimates of interlaboratory reproducibility.

INTRODUCTION

This paper revisits the Solubility Challenge competition introduced in 2008 by Llinas *et al.,*[1] and followed up in 2009 by Hopfinger *et al*.[2] It briefly examines the impact of the quality and breadth of measurements of aqueous solubility on the efficacy of empirical methods to predict solubility of druglike molecules. The present contribution is paired with another recently published paper[3] to address contemporary issues of solubility measurement, interpretation and prediction. The new contributions are intended to serve as prologue or accompaniment to an upcoming session on solubility at the IAPC-8 meeting in Split, Croatia, 9-11 September 2019. Since 2009, the International Association of Physical Chemists series of symposia maintained extensive coverage of the topic of solubility measurement, both from solid state and solution perspectives. At the 2015 IAPC-4 meeting, the "*Thermodynamic Solubility Measurement of Practically Insoluble Ionizable Drugs - Case Studies & Suggested Method Improvements*" special session resulted in a 'white paper' publication drawing on expert consensus thoughts of researchers from six countries (Hungary, Russia, Serbia, Spain, Sweden, and United States).[4]

SOLUBILITY PREDICTIONS

Many empirical methods for predicting solubility of druglike molecules have been described in the pharmaceutical literature, in an effort to anticipate solubility requirements and risks during structural design in the early stages of drug discovery. In this context, the prediction of solubility has been a subject of

considerable interest for at least sixty years. In 1968, Hansch and coworkers noted that the octanol-water partition coefficients, *log P*, are correlated linearly with aqueous solubility values, *log* S_w, for nonionizable liquid samples.[5] This observation influenced Yalkowsky and coworkers to develop the General Solubility Equation (GSE), to extend the prediction of solubility to solids in water.[6-12] The melting point (*mp*) and *log P* are the only variables, both experimental determined, in the equation used to predict solubility of substances in water (in molarity units): *log* S_w = 0.5 -*log P* -0.01(*mp*-25). In deriving the GSE, it was assumed that the test compounds were nonionizable and fully-miscible in octanol, and that that water and octanol phases were not appreciably mutually soluble. The implicit assumption about the constancy of the entropy of melting was most concordant with the relatively rigid aromatic solutes initially considered. Later, it was suggested that calculated *log P* could be used in place of experimental values. More recently, a version was proposed based on entirely calculated descriptors.[11] It is noteworthy that no training set of molecules is required in the GSE method.

From the outset, Yalkowsky and Banerjee [12] proposed an external test set of 21 molecules: nine sparingly-soluble pesticides (*log* S_w -3.4 to -7.9), eleven simple drugs (*log* S_w 0.5 to -4.1), and a laxative molecule (with somewhat inconsistently-determined solubility). Three of the pesticides of are liquids at room temperature.

Since the late 1990s, others have frequently used the Yalkowsky-Banerjee external test set to assess empirical solubility prediction methods.[13-17] Reported prediction root-mean square errors (RMSE) ranged 0.6-1.4 log, averaging at 0.9 log.[13, 14] Many of the training set molecules used in these prediction methods consisted of a few hundred simple organic molecules, including agrochemicals, many in liquid form at room temperature, but only relatively few druglike molecules. The training sets did not appear to cover the chemical space resembling today's pharmaceutical discovery compounds. As reviewed by Dearden[13] and Taskinen and Norinder,[14] many prediction methods had been tried, including multiple-linear regression (MLR), principal components regression (PCR), partial least-squares (PLS), artificial neural networks (ANN), k-nearest neighbors (kNN), support vector machines (SVM), and random forest regression (RFR), utilizing hundreds of calculated descriptors. Often, the most important descriptors included *log P* and molar refractivity, *MR* (which accounts for molecular size and polarizability).

It was widely believed that the typical error in measured aqueous solubility was above 0.6 log unit,[18] and that prediction methods were approaching that limit. However, the earlier training sets were under-represented in druglike molecules which were practically insoluble and highly lipophilic. At high and low solubility values, experimental *log P* values did not correlate with the experimental *log* S_w values strongly.[19] Also, the experimental 0.6 log error value may not have been adequately assessed.

SOLUBILITY CHALLENGE (2008-2009)

Training sets with higher proportions of druglike molecules were subsequently introduced,[20-25] measured with an average error *much better* than 0.6 log, as indicated by interlaboratory comparisons. A set of high-precision intrinsic solubility measurements was described by Llinas *et al.*[1] and Hopfinger *et al.,*[2] who proposed a competition to further test the limits of prediction methods, which became widely known as the 'Solubility

Challenge.' The authors used the CheqSol method[26] to measure the intrinsic solubility (*log* S_0) of 132 structurally diverse drugs and biologically significant molecules. (The method is not recommended for nonionizable molecules.) The *log* S_0 values of 100 molecules were offered as the training set for the prediction of an external test set of 32 molecules (not in the training set), whose values were not revealed before the completion of the competition. Ninety-nine valid entries from participant were received in the Solubility Challenge. The completed entries were analyzed, scored and described in the follow-up paper.[2]

Although the CheqSol method indicates very impressive random errors of about 0.04 log unit, based on repetitive measurements by the same investigator, using the same apparatus, and the same sample, it was less certain to what extent unknown systematic errors might affect the accuracy of results.[27, 28] For example, when 125 published CheqSol values were compared to those obtained by the shake-flask "gold-standard" method, it was noted that RMSE = 0.52 log unit and there was a slight bias of -0.13 log unit.[29] A more up-to-date comparison, drawing on 232 published CheqSol results, including a recent study, [30] hinted that the realistic *interlaboratory* reproducibility of the potentiometric method may be underestimated by about a factor of 4.[31] This is still much better experimental precision than the 0.6 log unit value often cited in many earlier studies.[18]

The 32-molecule test set in the Solubility Challenge contained solubility values of four polymorphs of diflunisal and two of trazadone, of which the lowest values (assumed to be that of the thermodynamically most stable polymorph) were used in scoring the predictions for these two compounds. Four out of the 32 test molecules could not be measured successfully, and one molecule had decomposed during the measurements, which was not immediately evident. [32]

The unique and valuable contribution of the Solubility Challenge study was that it avoided the usual problems arising out of uncritically combining data from many sources, obtained under varied experimental conditions, not always well documented in the original sources. The Solubility Challenge provided a state-of-the-art perspective on predictive capabilities. However, it was not definitively evident which prediction methods were the best, since they all perform about equally. Nevertheless, the study has spurred many discussions regarding the efficacy of solubility prediction methods and quality of solubility data.[3, 4, 19, 27-29, 33]

POST-CHALLENGE INVESTIGATIONS

On reviewing the Solubility Challenge competition, Palmer and Mitchell[27] hypothesized that experimental data quality might not be the limiting factor in predicting the aqueous solubility of druglike molecules. The investigators found solubility values from the literature for 85 of the 132 molecules in the Solubility Challenge CheqSol set. Values from multiple sources were averaged for 26 of the 85 molecules. Values from Rytting *et al*.[24] accounted for 24 of the 85 molecules. (The Rytting data are S_w type. It is not clear if corrections were made by Palmer and Mitchell to convert these to the S_0 scale.) Regardless of which training set was used to construct the model, the investigators found the prediction quality using the RFR model to be about the same, with test set RMSE ~0.9. It seemed perplexing that CheqSol with highly precise (~0.05 log) data should produce nearly the same quality of prediction, compared to "noisy" (assumed SD ~0.6 log) literature data. It

was not ruled out that the hidden systematic errors in the two sets mitigated the anticipated difference in metrics from data of disparate precision.

Nevertheless, the perplexing outcome was interpreted to mean that the limiting factor in accurately predicting aqueous solubility of druglike molecules was the deficiency of prediction methods (algorithms and/or descriptor sets), and not, as had been thought, the uncertainty in the experimental measurements.

Boobier *et al.*[28] explored the 'wisdom of the crowd' approach to prediction, by asking human experts to predict solubility. The 'DLS-100' set of published solubility values (40% CheqSol type) were split into a 75-molecule training set and a 25-molecule test set. Invitations were e-mailed to 229 participants. Training-set molecules and their corresponding solubility values were displayed in a random order to the participants. They were then shown each test-set molecule and were asked to predict its solubility. In parallel, the investigators used ten different machine learning algorithms to predict solubility. The machine-vs-human comparisons were then evaluated. The best machine algorithm turned out to be ANN "multi-layer perception": RMSE = 0.99 log and r^2 = 0.71. The best individual human predictor generated almost identical metrics: RMSE = 0.94 log and r^2 = 0.72. For either human or machine, combining individual predictions into a consensus predictor, by taking their *median*, generated promising results.

DATA QUALITY

Before the Solubility Challenge study, it was a widely-held view that the lack of reliable data had held back both the understanding of the equilibrium processes and the derivation of good prediction models.

Thermodynamic solubility measurements are not easy to do well.[3, 4, 29, 33] The conditions used for the experiments need to be precisely reported, as small changes in pH and temperature can substantially affect solubility. Crystal polymorphism and hydrate formation can also be important, but such details are often not reported alongside solubility measurement, as these require additional solid-state characterizations. Reaching equilibration can be especially slow when supersaturated solutions form. The solid in the suspension may be amorphous. Ambient levels of CO_2 can significantly affect measured S_w values of sparingly soluble bases. So can unanticipated buffer-drug interactions and aggregate/micelle formations.[34] Comparing "raw" water solubilities (S_w) determined in unbuffered solutions can be problematic. Kinetic solubilities could be mistaken for thermodynamic values. Using inaccurate values of pK_a to interpret the *log S*-pH data can lead to inaccurate intrinsic solubility values. For example, the calculated CheqSol log S_0 value depends on the pK_a provided; an error in the latter becomes an underlying systematic error in the former, notwithstanding the highly-precise *log* S_0 obtained. Merging lists of data from secondary sources, without checking primary publications can lead to mismatches of data types and decreased overall quality of the training set.

When an effort is made to critically factor in the possible sources of systematic error, the interlaboratory reproducibility turns out to be significantly better than widely appreciated. The 'white paper' mentioned earlier[4] suggested a number of concrete ways to improve the measurement of equilibrium solubility, to obtain high quality intrinsic solubility data. The study also made suggestions how legacy data could be better processed to ensure consistent intrinsic solubility values, by normalizing the values for (a) *pH* (to produce

intrinsic solubility, S_0, derived from, S_w, or multiple-pH measurements) and for (b) temperature (by computationally transforming solubility measured in the range 10-50 °C to the standardized value at 25 °C [33]).

A study of equilibrium solubility data quality based on the review of over 800 publications was recently reported.[29] The project is ongoing, and now there are 6355 S_0 entries in the *Wiki-pS_0* database (*in-ADME* Research), for 3014 different pharmaceutically-relevant molecules (solids at room temperature), drawing on the review of 1325 publications. Of all the entries, 2144 are singletons, most commonly reported as S_w, but transformed to S_0 (using the measured pK_a), and temperature-adjusted[33] (if necessary) to 25 °C. The indication of interlaboratory reproducibility comes from the 870 molecules for which consistent solubility was reported from two or more different sources (comprising 4209 individual S_0 values). This is tantamount to another kind of 'wisdom-of-the-crowd' approach. Some molecules have been studied in surprisingly large number of different laboratories. For example, 33 different reports of the solubility of diclofenac have been found to date. Seventeen of these studies include measurements at several different pH values.[3] The average interlaboratory reproducibility, based on the curated 870 replicated studies, has been determined[31] to be 0.17 log unit, significantly lower than that suggested in the past. [18]

However, there are a number of drug molecules in the *Wiki-pS_0* database whose solubility has not been measured consistently between different laboratories. For example, clofazimine has the interlaboratory standard deviation, *SDi* = 0.93 log unit, based on five reported values. Terfenadine intrinsic solubility has been reported in eleven studies: *SDi* = 0.71.

On the other hand, diclofenac is a drug with a consistently measured solubility across many laboratories. At 25 °C, its log S_0 = -5.34 ±0.18, n = 33. To obtain this value, critical processing of the reported *log S*-pH data was essential.[3] The *SDi* of diclofenac is almost identical to the overall estimated interlaboratory reproducibility of 0.17 mentioned above. Many of the possible challenges in the interpretation of data in the assessment of interlaboratory reproducibility are apparent in the case study of diclofenac, as described and illustrated elsewhere.[3]

The number of druglike molecules with *log S_0* values suitable for prediction training sets continues to increase.[20-25] The intrinsic data introduced in the Solubility Challenge is substantial.[1, 2] The DLS-100[28] is also a set of good data. The Bergström laboratory[21-23] has published intrinsic solubilities of experimentally very challenging drugs. One can expect that the fresh pool of available high-quality experimental data can be again tested – in a new 'Challenge.'

THE NEW CHALLENGE

It has been ten years since the results of the Solubility Challenge were described.[1, 2] The landmark study, and subsequent similar studies, used reasonably good data, albeit as small sets of 100-132 druglike molecules. We became motivated to revisit the Challenge, guided by a much larger database (6355 S_0 values), which has quantifiable estimates of interlaboratory reproducibility, as noted. Accordingly, we constructed two new test sets.

Set 1 consists of 100 druglike molecules, the *log* S_0 values of which had been reported by at least three laboratories, so that average values could be calculated, along with the *SDi*. Out of 870 molecules with solubilities multiply reported, we selected the set of 100 that has typical *SDi* values, ranging from 0.11 to 0.22 log, with average *SDi* = 0.17 log. Set 1 may be called the high-consensus "tight set."

Set 2 is referred to as the low-consensus "loose set." It comprises 32 molecules with the highest *SDi* of the 870-set, ranging from 0.50 to 0.93 log, with average *SDi* = 0.62 log.

The two sets of test compounds are listed in the Supporting Information, in the Microsoft Excel® file, along with SMILES notations for each molecule. Also included as a benchmark are the predictions using the Yalkowsky GSE.[6-12] The method, which requires no training, indicated RMSE = 1.1 and 1.2 for Sets 1 and 2, respectively.

We invite interested participants to use their *own* 25 °C *log* S_0 training sets and methods to predict the solubility values of the test set molecules. The possible limitation of not providing a common training set is that some participants may still use incompatible ensembles of solubility type measurements (e.g., *log* S_w mixed with *log* S_0), possibly not done at a common temperature. With the increased availability of quality experimental data and the discussions of how to pool data from different sources,[3, 4, 29, 33] it is our expectation that the majority of participants will have appropriate data in their training sets. Entrants are asked to fill in the designated spaces in the submission Excel file provided in the Supporting Information. The test set *log* S_0 values and the comparative scores in the competition will be presented in a follow-up publication, adopting the procedure of Hopfinger *et al.*[2] To encourage a broad spectrum of participants with different levels of experience, the identities of the entrants will not be revealed in the competition. Not 'whose' but 'which' approach works the best in predicting solubility of druglike molecules an important aim of the competition.

For those participants new to the field, who may not have an extensive set of molecules with which to develop a prediction model, the last section of the Excel file in the Supporting Information provides a number of references to reliable collections of solubility data. However, some of the tabulations contain S_w values, which may need to be converted to intrinsic values, as described in detail elsewhere.[35] The sources listing intrinsic solubility values of druglike molecules have been accordingly marked in the Excel file.

Nota bene: *a critical first step in the prediction calculations is for the participants to remove from their own training sets any molecules presented here in the provided test sets. See the Excel file for further elaboration.*

TIMELINE

The deadline for the submission of the solubility predictions is set to be four months after the announcement of the acceptance of this publication. On acceptance of this work, efforts will be made to announce the start of the competition through various media, including Twitter, chemrxiv (https://chemrxiv.org), LinkedIn, Research Gate, and other forums. Please fill in all the yellow fields in the submission form with the predicted intrinsic solubility values (*only* in log molar units) for each of the compounds in the two test sets, and provide brief descriptions of the prediction method (origin and nature of the training data and types of descriptors used), and e-mail the Excel file to alex@in-ADME.com by no later

than the above four-months window. The results will be assessed by the authors of the follow-up publication, and the contributor(s) making the best prediction will be invited to submit a manuscript to this journal describing their solubility prediction analysis.

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We are saddened to learn that two giants of computational chemistry, Profs. Anton J. Hopfinger and Oleg A. Raevsky, died 5 December 2018 and 5 March 2019, respectively. We dedicate this paper to their memory.

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ASSOCIATED CONTENT

Supporting Information Available: Microsoft Excel® file: fill-in form, comprising the molecules of the two test sets, the interlaboratory standard deviation for each molecule, the number of sources used to calculated the errors, and SMILES notation for each molecule. Also included are the predictions using the General Solubility Equation. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

†**E-mail: alex@in-ADME.com**

ORCHID

Antonio Llinas: 0000-000304620-9363

Alex Avdeef: 0000-0002-3139-5442

Notes

The authors declare no competing financial interest.

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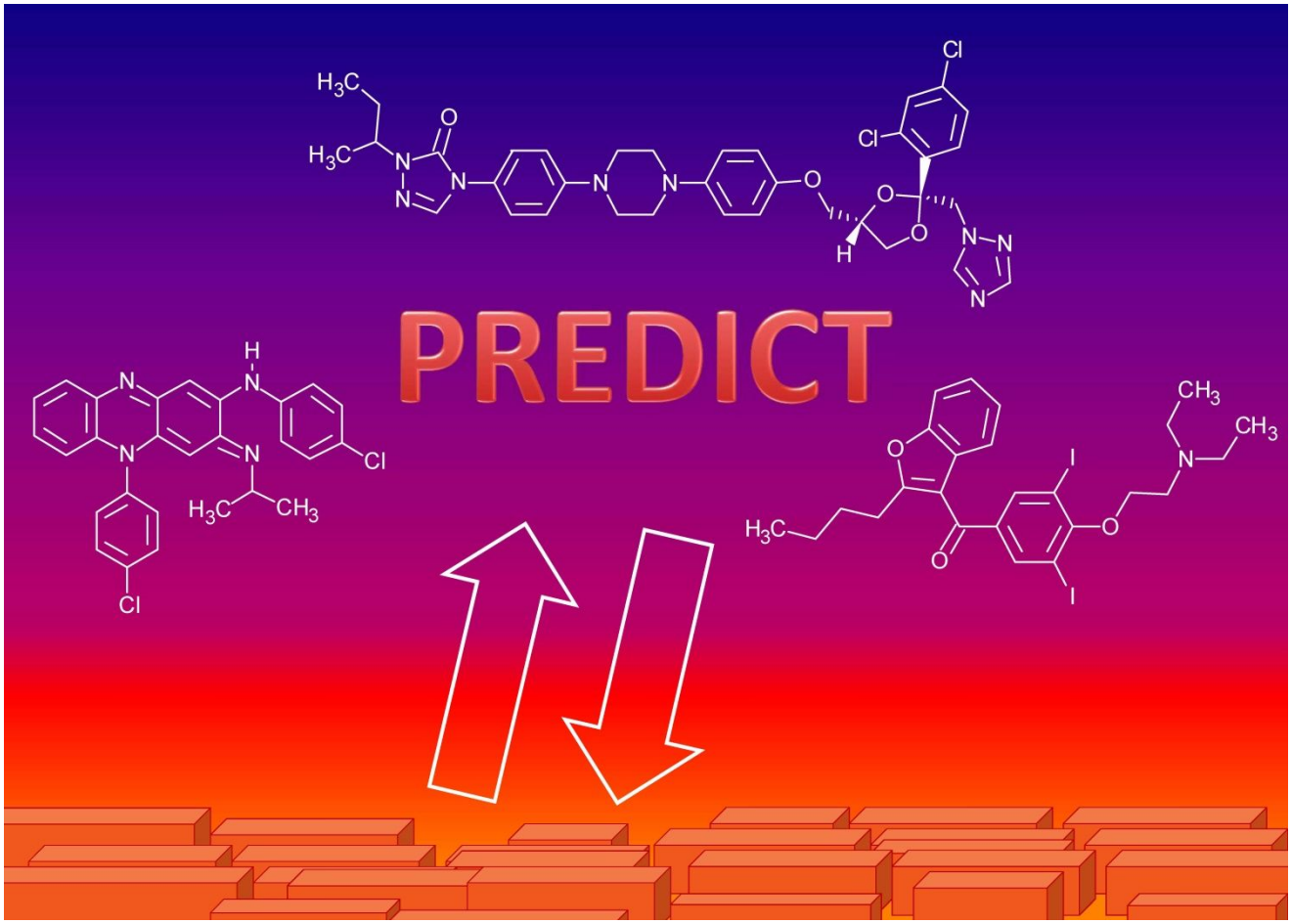
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