Scientific research article

Predicting drug solubility in cosolvent systems using artificial intelligence algorithms

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SUMMARY

Introduction: Solubility is one of the most important physicochemical properties in the pharmaceutical sciences and is involved in processes ranging from drug development to environmental biotoxicity assessment. Accurate prediction of solubility, especially aqueous solubility, has been a scientific challenge due to the complexity of the dissolution process, which involves lattice energies, solvation, solute ionization, and solute-solvent interactions. While various approaches have been used to predict solubility, such as semi-empirical models and group contribution methods, accurate prediction remains difficult. Statistical and machine learning approaches often use numerous descriptors, making rational interpretation and refinement of prediction models difficult. **Purpose:** This study proposes an approach based on autonomous learning, specifically using a neural network model. Experimental and theoretical descriptors are carefully selected according to their relevance to physicochemical aspects of the dissolution process. **Methodology:** A solubility data set of four structurally related sulfonamides (sulfadiazine, sulfamerazine, sulfamethazine, sulfamethazine, and sulfacetamide) in different solvents under different temperature conditions and cosolvent composition is used to develop an artificial neural network model using less than 37 descriptors. **Results:** The developed AI algorithm shows acceptable correlation with experimental data, suggesting its potential as an approximation tool for optimizing solubility-related processes in the pharmaceutical industry.

***Key words*:** solubility; drugs; pharmacy; artificial intelligence; neural network.

RESUMEN

Predicción de la solubilidad de fármacos en sistemas cosolventes mediante algoritmos de inteligencia artificial

Introducción: La solubilidad es una de las propiedades fisicoquímicas más importantes en las ciencias farmacéuticas, esta propiedad está involucrada en diversos procesos, desde el desarrollo de fármacos hasta la evaluación de la biotoxicidad en el campo ambiental. La predicción precisa de la solubilidad, particularmente la solubilidad acuosa, ha sido un desafío científico debido a la complejidad del proceso de disolución, que involucra energías de red, solvatación, ionización del soluto e interacciones soluto-solvente. Si bien se han utilizado diversos enfoques para predecir la solubilidad, como modelos semi-empíricos y métodos de contribución de grupos, la predicción precisa sigue siendo difícil. Los enfoques estadísticos y de aprendizaje automático a menudo emplean numerosos descriptores, lo que dificulta la interpretación racional y el perfeccionamiento de los modelos de predicción. **Objetivo:** Este estudio se propone un enfoque basado en el aprendizaje autónomo, específicamente mediante un modelo de red neuronal. Se seleccionan cuidadosamente descriptores experimentales y teóricos de acuerdo con su relevancia para los aspectos fisicoquímicos del proceso de disolución. **Metodología:** Se utiliza un conjunto de datos de solubilidad de cuatro sulfonamidas estructuralmente relacionadas (sulfadiazina, sulfamerazina, sulfametazina y sulfacetamida) en varios solventes bajo diferentes condiciones de temperatura y composición de cosolvente, desarrollando un modelo de redes neuronales artificiales utilizando bajo 37 descriptores. **Resultados:** El algoritmo de IA desarrollado muestra una correlación aceptable con los datos experimentales, lo que sugiere su potencial como herramienta de aproximación para optimizar los procesos relacionados con la solubilidad en la industria farmacéutica.

Palabras clave: Solubilidad; fármacos; farmacia; inteligencia artificial; red neuronal.

RESUMO

Predição da solubilidade de fármacos em sistemas cosolventes usando algoritmos de inteligência artificial

Introdução: Solubilidade é uma das propriedades físico-químicas mais importantes nas ciências farmacêuticas. Esta propriedade está envolvida em vários processos, desde o desenvolvimento de fármacos até a avaliação da biotoxicidade no campo ambiental. A previsão precisa da solubilidade, particularmente da solubilidade aquosa, tem sido um desafio científico devido à complexidade do processo de dissolução, que envolve energias de rede, solvatação, ionização do soluto e interações soluto-solvente. Embora várias abordagens tenham sido usadas para prever a solubilidade, como modelos semi-empíricos e métodos de contribuição de grupo, a previsão precisa continua difícil. Abordagens estatísticas e de aprendizado de máquina geralmente empregam vários descritores, dificultando a interpretação racional e o refinamento dos modelos de previsão. **Objetivo:** Este estudo propõe uma abordagem baseada na aprendizagem autônoma, especificamente utilizando um modelo de rede neural. Descritores experimentais e teóricos são cuidadosamente selecionados de acordo com sua relevância para os aspectos físico-químicos do processo de dissolução. **Metodologia:** Um conjunto de dados de solubilidade de quatro sulfonamidas estruturalmente relacionadas (sulfadiazina, sulfamerazina, sulfametazina e sulfacetamida) em vários solventes sob diferentes condições de temperatura e composição de cosolvente é usado, desenvolvendo um modelo de rede neural artificial usando menos de 37 descritores. **Conclusão:** O algoritmo de IA desenvolvido mostra correlação aceitável com dados experimentais, sugerindo seu potencial como uma ferramenta de aproximação para otimizar processos relacionados à solubilidade na indústria farmacêutica.

Palavras-chave: Solubilidade; drogas; farmácia; inteligência artificial; rede neural.

1. INTRODUCTION

Drug solubility is a critical property in many processes ranging from drug development (prediction of synthetic routes, extraction and crystallization [1], purification, recrystallization, quantification, preformulation, formulation, quality analysis among others (design of chemical processes), it is also a determining factor in the therapeutic performance of the drug (availability, distribution, metabolism, excretion and toxicity). In the environmental field, solubility also plays an important role in bioremediation processes and biotoxicity [2] assessment [3, 4].

In this context, the prediction of aqueous solubility has been the subject of intensive research [5], using various approaches such as semi-empirical models, such as the general solubility equation [6, 7], group contribution methods (UNIFAC, UNIQUAC.) [8, 9], van't Hoff [10], extended Hildebrand solubility approach [11-13], two-parameter Weibull function model [14, 15], Buchowski-Ksiazczak [16], van't Hoff-Yaws [17], Apelblat [18, 19], Wilson [20], NRTL [20], modified Wilson [21, 22]. More recent developments have focused on quantitative structure-activity relationship (QSAR/QSPR) [23, 24], through statistical analysis and autonomous learning techniques [25]. Despite these advances, accurate solubility prediction remains a major scientific challenge, as exemplified by the two solubility challenges presented to the research community in 2008 and 2019 [26, 27]. This is due to the complex nature of the dissolution process, which involves lattice/sublimation energy, solvation energy, solute ionization and phase interactions [28-30]. Each of these properties is difficult to predict and can be computationally expensive [31]. Statistical and automatic learning approaches often use many descriptors (>100) [32], which has led to difficulties in rational interpretation and improvement of prediction models [33]. Finally, prediction is hampered by the poor quality of experimental solubility data, which is affected by measurement techniques and the purity of the solute and solvents [34-36].

In this paper we report on an approach to predict drug solubility in cosolvent mixtures at different temperatures by means of autonomous learning, specifically by means of a neural network model, where experimental and theoretical descriptors have been selected according to their relevance to the physicochemical aspects of the dissolution process (Figure. 1).

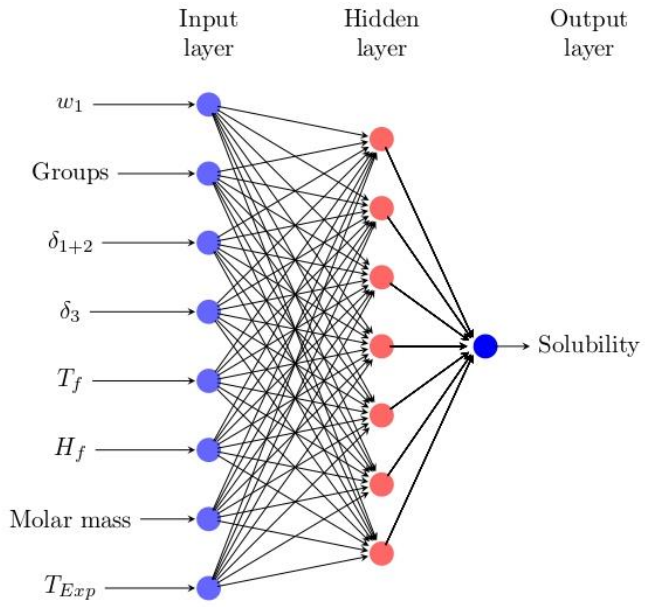

Figure 1. Artificial neural network schematic of the AI-Solubility algorithm.

2. METHODOLOGY

This work presents the development of an artificial neural network to predict drug solubility using 38 descriptors (Table 1).

The model development was carried out in the Google Colaboratory environment, using the NumPy (version 1.25.2), Pandas (version 2.0.3) and Matplotlib (version 3.7.1) libraries for data processing and plotting. The 4615 available data were split into 80% training data and 20% test data using the train_test_split function of the scikit-learn library with a random seed of random_state=0. The data were then normalized.

The data was then normalised using the StandardScaler method. A neural network was implemented with an input layer of 38 neurons, a hidden layer of 128 neurons and a ReLu activation function, and an output layer of one neuron and a ReLu activation function to predict solubility.

The neural network was trained using the Adam optimizer with a learning rate (learning_rate=0.001) of 35 epochs using the Keras library of TensorFlow. To avoid overfitting, Dropout, with a dropout rate of 20%, was used as a regularization technique by deactivating neurons during training to avoid overfitting. The different accuracy metrics were evaluated to analyze the model performance.

Table 1. Descriptors used in AI algorithm development.

N	Descriptors	Unit/symbol/name		N	Descriptors	Unit/symbol/name
1	Study temperature	K		20	Group 14	Phenyl (trisubstituted)
2	Molar mass	g/mol		21	Group 15	Phenyl (tetrasubstituted)
3	Melting temperature	K		22	Group 16	Ring closure, 5 or more atoms
4	Melting enthalpy	kJ/mol		23	Group 17	Ring closure, 3 or 4 atoms
5	Hildebrand solubility parameter of the drug (δ_3)	$MPa^{1/2}$		24	Group 18	Conjugation in ring, for each double bond
6	Group 1	$-CH_3$		25	Solvent 1	Water
7	Group 2	$-CH_2-$		26	Solvent 3	*N*-Methyl-2-pyrrolidone
8	Group 3	>CH-		27	Solvent 4	Carbitol
9	Group 4	>C<		28	Solvent 5	*tert*-butyl
10	Group 5	$-NH_2$		29	Solvent 5	*N,N*-dimetilformamida
11	Group 6	-NH-		30	Solvent 7	Dimethyl sulfoxide
12	Group 7	>N-		31	Solvent 8	Methanol
13	Group 7	-CO-		32	Solvent 9	Ethanol
14	Group 8	-COOH		33	Solvent 10	1-Propanol
15	Group 9	-SO2		34	Solvent 11	Acetonitrile
16	Group 10	-O-		35	Solvent 12	Ethylene glycol
17	Group 11	-F		36	Solvent 13	Propylene glycol
18	Group 12	Phenyl		37	Solvent 13	1,4-dioxane
19	Group 13	Phenyl (*o, m p*)		38	Hildebrand solubility parameter of solvents and cosolvent mixtures (δ_{1+2})	$MPa^{1/2}$

3. RESULTS AND DISCUSSION

For the development of the AI algorithm, solubility data reported in the literature were used for 4 structurally related drugs (sulfonamides), sulfadiazine (SD) [37-47], sulfamerazine (SMR) [3, 37, 42, 47-53], sulfamethazine (SMT) [37, 42, 46, 49, 54-59], sulfacetamide (SCT) [60] in the solvents listed in Table 1. Thus, 4615 solubility data were obtained under different temperature and cosolvent composition conditions.

The first one is the study temperature, the influence of this descriptor is described in most of the solubility studies, presenting a positive effect, since as the temperature increases the studies show that the solubility also increases, this is because higher temperatures provide more kinetic energy to the molecules helping them to break free from the crystal lattice and dissolve in solvent; in general, energy is required to break the bonds holding the molecules in the solid together; the second descriptor is the molar mass of the drug, Sverre describes how in most of the cases the solubility shows a relationship with the molar mass of the drug [61]. Theoretically, as the molar mass of the drug increases, so does its molar volume, so theoretically, as the molar mass of the drug increases, its solubility would decrease because it becomes more difficult for the solvent molecules to retain the solute particles [62]. However, the studies reported by Delgado *et al.* show an inverse relationship to those reported by Toll et al. and Johnsen *et al.* [38, 49, 63], showing that as the molar volume decreases, the solubility decreases; a clear example is the solubility of SD, SMR and SMT, as the molar volume decreases (SD (150.0 cm^3/mol)<SMR (164.5 cm^3/mol)<SMT (179.0 cm^3/mol)), so does the solubility (solubility in water at 298. 15 K SD (x_3=0.4809±0.0023·10^5) < SMR (0.1712±0.0027·10^4) < (0.2814±0.014·10^4). In addition to demonstrating the direct relationship between solubility and molar volume, the results of the work of Delgado et al. showed a clear relationship between solubility and the temperature and enthalpy of fusion of the drug, being more soluble the drugs with lower temperatures and enthalpies of fusion (SD (T_f=532. 65 K; $\Delta_f H$=44.3±0.4 kJ·mol^{-1}); SMR (T_f=508.15 K; $\Delta_f H$ =41.3±1.0 kJ·mol^{-1}); SMT (T_f=468.15 K; $\Delta_f H$ =39.2±0.7 kJ·mol^{-1})) (descriptors 3 and 4). In general, the relationship between descriptors 1, 3 and 4 is well described in the theory of regular solutions and ideal solubility [64-68]. The fifth descriptor is the solubility parameter of the drug, several studies have shown a relationship between the solubility and the solubility parameter of the drug, showing that the maximum solubility is obtained in solvents or cosolvent mixtures with solubility parameters similar to those of the drug [4, 69-72], however, other studies by Cardenas et al, Delgado et al and Ortiz el al. show an opposite behavior [3, 51, 59, 73].

Descriptors 6-24 focus on the Group Contribution Method, which decomposes each chemical compound into first-, second-, and third-order functional groups based on its molecular structure. The number of each different functional group present in a compound is used as a predictor in a multiple linear regression model without attempting to reduce the number of parameters in the model, as the method attempts to characterize the contributions of each different group. Thus, molecular properties are the result of aggregate contributions from individual atoms or groups [74-82]. The equilibrium solubility of a solute depends on the relative affinity between the solvent molecules and the solute molecules. Therefore, the forces of molecular interactions such as ionic, van der Waals, dispersion and hydrogen bonding interactions affect solubility. In this context, descriptors 25-37 correspond to the cosolvent composition expressed as the mass fraction (w_1) of each of the solvents [83-88]. Finally, parameter 38 is the solubility parameter of the solvent or cosolvent mixture; a large number of works have demonstrated the relationship between this descriptor and solubility [85, 89-92].

When evaluating the individual relationship of each of the descriptors with the solubility data, the coefficients of determination (r^2) do not exceed 0.2, showing F between 5- 424.6, which is extremely small for an N of 3615 data, demonstrating the low correlation between each of the descriptors and solubility.

The database can be queried or downloaded from the Mendeley repository [93], and all development code can also be downloaded from the Mendeley repository [94].

The function **train_test_split(X, y, ...)** first splits the data into a training set and a test set, then the parameter test_size specifies the percentage of the data to be used for the test set. In this case, the value is 0.2, which means that 20% of the data is used to test the model, and the remaining 80% is used to train the model. That is, 80% of the total data set was used to train the model, and the remaining 20% was used to evaluate the model's performance. To ensure that we were working with the same split each time we ran the code, we set the parameter and set a seed for randomization with **random_state=0.**

For the model to be meaningful, it is important that the data be scaled uniformly. Otherwise, some features with large values may dominate the model, while others with small values may be ignored. Therefore, an object of the **StandardScaler** class of the **sklearn.preprocessing** library is created to standardize or scale the data features.

Once the data partitioning and scaling parameters are set, the neural network model is defined and compiled in Keras for training, using **keras.Sequential()** to create a sequential model. In this type of model, the layers are stacked in a linear fashion, i.e. the output of one layer is the input of the next; then a dense layer is added with **layers.Dense(128, ...),** which is a fully connected layer. This layer will have 128 neurons. The size of the network input is specified, in this case the inputs have 66 features (which could refer to a dataset with 37 columns, for example).

A Dropout layer (regularization) is set using **Layers.Dropout(0.2),** so that at each training step, this layer randomly deactivates a percentage of the neurons in the previous layer, in this case 20% (0.2). Dropout is a technique to prevent overfitting, helping the model not to become too dependent on certain neurons, and therefore to generalize better to unseen data. Add another dense layer with 64 neurons **(model.add(layers.Dense(64, activation='relu')),** using ReLU as the activation function. This layer also follows the same structure as the previous ones, and its size and activation are chosen to learn more complex features, finally an output layer **(model.add(layers.Dense(1)))** of 1 neuron is generated.

The Keras model is set up for training with the Adam optimizer, using a learning rate of 0.001. In addition, the loss function is specified, which was the mean square error, and the predictions were evaluated using the mean absolute error, which is commonly used for regression problems. It measures the difference between the values predicted by the model and the actual values, penalizing larger errors due to squaring.

The code trains the model for 35 epochs (Figure 1), using the scaled training data **X_train_scaled** and its corresponding **y_train labels**. During training, the model also evaluated its performance on the validation data **X_test_scaled** and y_test to measure its generalization ability. The training history (such as loss and metrics) was stored in the history variable for further analysis (see archive in the Mendeley repository). To avoid overfitting, which occurs when a model learns the noise in the training data instead of the actual pattern, **dropout** was used. Thus, the summary of the model is shown in Table 2.

Table 2. Summary of the model structure.

Layer (type)	Output Shape	Param #
dense (Dense)	(None, 128)	8576
dense_1 (Dense)	(None, 128)	16512
dropout (Dropout)	(None, 128)	0
dense_2 (Dense)	(None, 64)	8256
dense_3 (Dense)	(None, 1)	65

Total params: 100,229 (391.52 KB), Trainable params: 33,409 (130.50 KB), Non-trainable params: 0 (0.00 B), Optimizer params: 66,820 (261.02 KB).

One of the most important parameters in evaluating an AI algorithm is the loss function, also called the error function because it quantifies the difference between the predicted results of an AI algorithm and the actual target values. Thus, in the regression problem of predicting solubility data from reported data, the loss function evaluates the prediction of the neural network from the training sample of the training data set. Thus, the loss function quantifies the difference or error between the network's predicted solubility and the reported solubility data. When evaluating the loss of the model using the code line **print(f'Loss: {results[0]}')** the value returned is very small $5.0740 \cdot 10^{-6}$. This indicates that the model has done a good job since the loss is close to zero, as for the mean absolute error, a value of 0.0013 was obtained, which is the average of the error in the model predictions, reflecting that the model makes a very small error in its predictions.

Figure 2 shows the correlation between the experimental data and those computed by the AI algorithm; the computed data shows an acceptable correlation (r^2=0.86), although the mean absolute error is very low; therefore, it is possible that compensation processes are occurring that lead to low absolute errors.

A disadvantage discussed by many authors is the inability to correlate the results with specific physicochemical properties, since the AI algorithms relate the variables to each other and use statistics to measure the correlation between the different characteristics of the data. Therefore, it doesn't allow to show clearly the energy relations that would allow to rationalize the results from a physicochemical point of view, as it is the case when using mathematical models such as van't Hoff, Yalkowsky-Roseman-van't Hoff, Apelblat, Buchowski-Ksiazczak λh, Yaws, NRTL, Wilson and modified Wilson [11, 95-100]. However, despite these drawbacks, the results show that the IA algorithm can be a good approximation tool for optimizing solubility-related processes in the pharmaceutical industry.

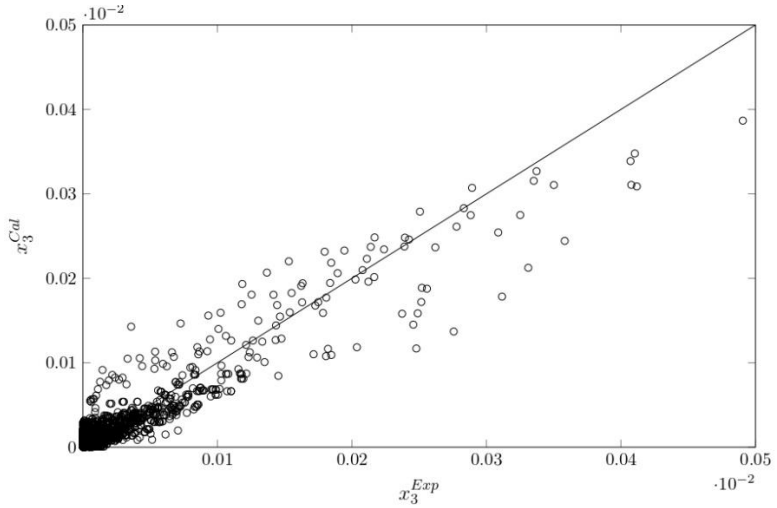

Figure 2. Experimental solubility data versus predicted solubility.

CONFLICTS OF INTEREST

Authors have no conflict of interest.

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