Multi-instance learning of graph neural networks for aqueous $pK_a$ prediction

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Abstract

Motivation: The acid dissociation constant ($pK_a$) is a critical parameter to reflect the ionization ability of chemical compounds and is widely applied in a variety of industries. However, the experimental determination of $pK_a$ is intricate and time-consuming, especially for the exact determination of micro-$pK_a$ information at the atomic level. Hence, a fast and accurate prediction of $pK_a$ values of chemical compounds is of broad interest.

Results: Here, we compiled a large-scale $pK_a$ dataset containing 16 595 compounds with 17 489 $pK_a$ values. Based on this dataset, a novel $pK_a$ prediction model, named Graph-$pK_a$, was established using graph neural networks. Graph-$pK_a$ performed well on the prediction of macro-$pK_a$ values, with a mean absolute error around 0.55 and a coefficient of determination around 0.92 on the test dataset. Furthermore, combining multi-instance learning, Graph-$pK_a$ was also able to automatically deconvolute the predicted macro-$pK_a$ into discrete micro-$pK_a$ values.

Availability and implementation: The Graph-$pK_a$ model is now freely accessible via a web-based interface (https://pka.simm.ac.cn/).

1 Introduction

The acid dissociation constant $pK_a$, an equilibrium constant defined as the negative logarithm of the ratio of the protonated and deprotonated form of a compound, is a key parameter to describe the ionization ability of substances. It has been reported that about two-thirds of marketed drugs are ionizable in the aqueous solution (Manallack, 2007). Hence, in the design of new drugs, $pK_a$ is a crucial physical property to be considered, which has profound effects on biological activities, ADMET (absorption, distribution, metabolism, excretion and toxicity) properties and other properties of drugs (Charifson and Walters, 2014; Manallack et al., 2013). Apart from the pharmaceutical industry, the $pK_a$ is also related to environmental ecotoxicology, agriculture and chemical industries. Hence, the fast and accurate prediction of $pK_a$ values of chemical compounds from their structures is of great interest.

Graph neural networks (GNN) are a type of neural network to process graph structure data (Defferrard et al., 2016; Niepert et al., 2016). Since first introduced into the prediction of molecular properties several years ago (Duvenaud et al., 2015), reports of different GNN architectures and their successful applications have been rapidly accumulating in this field (Sun et al., 2020; Zhang et al., 2021). However, so far, graph neural networks have rarely been applied in the prediction of $pK_a$, presumably because the $pK_a$ values are not only molecular-level ‘global’ properties but also atomic-level ‘local’ properties (Fig. 1). The molecular-level ‘global’ properties refer to the macro-$pK_a$, the acid dissociation constant related to the observable loss or gain of a proton from a molecule regardless of specific ionization site. The ‘local’ properties refer to micro-$pK_a$, the acid dissociation constant related to the loss or gain of a proton from a single titratable site (Işık et al., 2018). Apart from the macro-$pK_a$, a powerful $pK_a$ prediction model should also be capable of providing micro-$pK_a$ information at the atomic level. Such information can

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but rare in regression tasks. For instance, labels through MIL is that there should be a clear mathematical progression tasks such as medical image analysis, text classification, and video annotation (Carbonneau et al., 2019). To the best of our knowledge, this study was the only attempt to predict compound pK_a with graph neural networks. However, the training of their model relied on the pK_a dataset containing atomic level labels, which were mainly obtained from quantum chemical calculation or molecules with a single ionizable site. Hence, this method is difficult to extend to the pK_a prediction of heterogeneous chemical classes with multiple ionizable sites. Another alternative strategy to obtain micro-pK_a data is to assign the macro-pK_a value of a molecule to its major responsible ionization site and take it as an approximation of the micro-pK_a value. Recently, some pK_a prediction models have used this strategy (Hunt et al., 2020; Yang et al., 2020), but there are also two significant problems. As illustrated in Figure 1, (i) for molecules such as propane-1,2,3-triamine, there are multiple sites having similar ionization capacity, this approximate treatment may bring large errors; (ii) the selection of major responsible ionization site is a non-trivial process and requires substantial chemical domain knowledge, and in many cases, a macro-pK_a value could not be unambiguously assigned to one major ionizable group.

Multi-instance learning (MIL) is a kind of weakly supervised learning algorithm for data with only coarse-grained labels (Zhou, 2018). In classic MIL, the training set is composed of many ‘bags’, each of which contains a series of ‘instances’. A bag is labeled as positive if containing at least one positive instance; otherwise, it is labeled as negative. The goal of MIL is to train a classifier that can correctly label unseen bags. Due to the ability to provide instance-level interpretation, MIL has attracted extensive attention in many classification tasks such as medical image analysis, text classification and video annotation (Carbonneau et al., 2018; Wang et al., 2019; Zhou et al., 2017). However, so far, MIL has rarely been used in regression tasks. This is because a necessary prerequisite for obtaining instance labels through MIL is that there should be a clear mathematical relationship between instance labels and bag labels. This relationship is common in classification tasks (such as ‘or’ relationship) but rare in regression tasks. For pK_a, there is a relatively clear relationship between macro-pK_a and micro-pK_a. For example, Figure 1 shows the formula between macro-pK_a and micro-pK_a of basic compounds.

Here, combining multi-instance learning and graph neural networks, we designed a novel pK_a prediction model named Graph-pK_a. In Graph-pK_a, a molecule is regarded as a ‘bag’, and those ionizable atoms in this molecule are regarded as ‘instances’. It means that the macro-pK_a value of a molecule is designated as the label of a bag, which is available in the training set, and the unavailable information regarding to the micro-pK_a values of ionizable sites are considered as the labels of instances. Under this scheme, Graph-pK_a can follow the MIL framework to learn the labels of instances through training against the labels of bags (Fig. 2). Furthermore, it should be noted that those molecules containing multiple ionization sites may have multiple macro-pK_a values. In this work, we only consider the most acidic and basic pK_a values, which are key parameters that can unambiguously and concisely describe the ionization capabilities of compounds. Some chemical information websites, including ChEMBL (Gaulton et al., 2017) and DrugBank (Wishart et al., 2018) also describe the prediction for the pK_a of compounds in terms of the most acidic and basic pK_a values.

2 Materials and methods

2.1 S-pK_a dataset

A large pK_a dataset named S-pK_a was compiled, mainly from three main sources: (i) datasets used in several previous studies on pK_a; (ii) a free software named QSAR Toolbox; (iii) manual extraction from various literature. Those chemical structures from different sources were standardized and then merged. The structure standardization procedure includes removing all salts from molecules, neutralizing charged molecules, and standardizing SMILES strings. In addition, considering that the accuracy of publicly available experimentally determined pK_a values was often dubious (Rupp et al., 2011), each data would undergo manual inspection to ensure that it belongs to the most acidic or basic pK_a value of its corresponding molecule before adding to the S-pK_a dataset. The detailed processes of data collection and cleaning is given in Supplementary Material and Supplementary Figure S1. The S-pK_a dataset can be separated into an acidic subset and a basic subset, containing the most acidic pK_a values of 9043 chemical structures and the most basic pK_a values of 8436 chemical structures, respectively (Supplementary Fig. S2a).

The distribution of pK_a values in the acidic and basic subset is shown in Figure 3a. The most acidic pK_a values varied from -3.3 to 0, while the most basic pK_a values varied from 10.1 to 14. Since to learn micro-pK_a via MIL is a critical concept utilized in the establishment of the Graph-pK_a model, the acidic or basic ionizable sites of compounds in the S-pK_a dataset are all enumerated and displayed (Fig. 3b). In this study, the acidic ionizable sites are defined as non-carbon atoms connected with at least one hydrogen atom, and the basic ionizable sites are defined as nitrogen atoms with no positive formal charge. The distribution of the molecular weight of compounds across the S-pK_a dataset is also shown in Supplementary Figure S2b.

2.2 Graph-pK_a model

The architecture of Graph-pK_a is shown in Figure 2. It begins by describing each molecule as an undirected graph where nodes and edges correspond to atoms and chemical bonds, respectively. The molecular graph is then input into the graph neural layers where atoms receive the message of other atoms in the molecule and use the aggregated messages to update their own features. The graph neural layer in Graph-pK_a is the same as our previously developed Attentive FP (Xiong et al., 2020), a molecular representation learning scheme that uses a graph attention mechanism. Here, six graph neural layers are stacked in Graph-pK_a for the extraction of atom features.

The major difference between Graph-pK_a and other graph neural networks lies in the approach to deal with the features of nodes extracted by graph neural network layers. In molecular graph neural networks such as GCN (Duvenaud et al., 2015), MPNN (Gilmer et al.,...
However, in Graph-pK\textsubscript{a}, which are next used to fit and predict the molecular properties. These features are aggregated with various pooling operations such as average pooling and Set2Set to generate the features of the whole molecule, which are next used to fit and predict the molecular properties. In the acidic and basic pK\textsubscript{a} prediction model, the mask values are respectively positive infinity and negative infinity. Finally, the macro-pK\textsubscript{a} values of molecules are calculated according to the approximate mathematical relationships between them and the predicted pK\textsubscript{a} values of ionizable atoms. Since some atoms in molecules are not ionizable, their predicted pK\textsubscript{a} values will be masked.

In basic pK\textsubscript{a} prediction model:
\[
pK_{a\text{basic}}^i = FC(X_i) \tag{4}
\]
\[
pK_{a\text{basic}}^i = \begin{cases} pK_{a\text{basic}}^i, & A' \in Q \\ -\infty, & A' \notin Q \end{cases} \tag{5}
\]
\[
pK_{a\text{basic}} = \log \left( \sum_{i=1}^{N} 10^{-pK_{a\text{basic}}^i} \right) \tag{6}
\]

where FC is referred to a fully connected neural network layer, \( P \) is the acidic ionizable sites, \( Q \) is the basic ionizable sites, \( N \) is the number of heavy atoms in a molecule, \( -\infty \) is the positive infinity, \( pK_{a\text{basic}}^i \) and \( pK_{a\text{basic}} \) are the most acidic/basic pK\textsubscript{a} values of a molecule.

Obviously, formula 3 and 6 are the key formulas for MIL. Yang \textit{et al.} also had used formula 6 to calculate the macro-pK\textsubscript{a} values in their study (Yang \textit{et al.}, 2020). Here, we provided the derivation of formula 3 and 6 in Supplementary Material and Supplementary Figure S3.

2.3 Implement of Graph-pK\textsubscript{a} and other benchmark methods

In Graph-pK\textsubscript{a}, the conversion from a SMILES string to an undirected graph and initialization for it was implemented with the DGL-LifeSci package. The representations of the graph were initialized with eight kinds of atom features and four kinds of bond features (Supplementary Table S1). The Graph-pK\textsubscript{a} model was implemented using the PyTorch and DGL. The loss function used to train Graph-pK\textsubscript{a} was MSELoss. Attentive FP is a graph neural network with the same GNN layers as Graph-pK\textsubscript{a}, but without MIL, which was also implemented as a control for model performance evaluation. For baseline models except Attentive FP, the molecular fingerprints used to encode the molecular structures were a kind of combined molecular fingerprint that integrated eight types of common molecular fingerprints including CDK, Estate, CDK graph only, MACCS, PubChem, Substructure, Klekota-Roth and 2D atom pairs. Those molecular fingerprints had 9121 bits in total and were calculated using PaDEL (Yap, 2011).

2.4 Model training and evaluation

In the experiment of predicting macro-pK\textsubscript{a}, the S-pK\textsubscript{a} dataset was randomly split into training/validation/test set in a 70:15:15 ratio. Graph-pK\textsubscript{a} and other models were trained on the same training set. The best set of hyperparameters for each model were determined based on the result on the validation set. The search ranges and optimal values of these hyperparameters are provided in Supplementary Table S2. The final model performance was assessed on the test set and two external tests set through three independent runs. The metrics for evaluating model performance were mean absolute error (MAE), root mean squared error (RMSE) and coefficient of determination (\( R^2 \)). The structural similarity between the two molecules was calculated using the 1024-bit Morgan2 fingerprints and the Tanimoto coefficient.

In the experiment of predicting micro-pK\textsubscript{a}, about 500 molecules that possessed multiple different acidic/basic ionization sites and whose dominant ionization sites had been uniquely assigned by Hunt \textit{et al.} (2020) were extracted as test data. Those molecules were
then removed from the S-pK_a dataset. Graph-pK_a was retrained on the remaining dataset with the same set of hyperparameters previously used. The metrics for evaluating the model are consistency rate and difference values. Consistency rate is the probability that the dominant ionization sites of molecules selected by Graph-pK_a are the same as that of human experts. Different value is used to quantify the degree of divergence between Graph-pK_a and human experts. They are calculated as follows:

\[
cl = \begin{cases} 
1, & h_i \in G_i \\
0, & h_i \notin G_i
\end{cases}
\]  

\[
\text{consistency rate} = \frac{1}{n} \sum_{i=1}^{n} cl_i
\]  

\[
\text{difference value} = \text{Abs}(f(g_i) - f(h_i))
\]

where \( h_i \) is the most acidic/basic atom of molecule \( i \) selected by human experts, \( G_i \) is the most acidic/basic atoms of molecule \( i \) predicted by Graph-pK_a, \( g_i \) is an arbitrary element in \( G_i \), the reason why \( G_i \) is a collection is that some molecules have multiple dominant ionization sites with the same ionization ability, \( f \) is referred to a function of Graph-pK_a for atomic pK_a prediction.

3 Results and discussion

3.1 Comparison with benchmark methods

In order to evaluate the performance of Graph-pK_a, four conventional machine learning models were implemented and taken as benchmark methods. A kind of combined molecular fingerprints was used as the representation of molecules and the input of these machine learning models, due to its good performance on a previous study for pK_a prediction (Mansouri et al., 2019). The comparison between Graph-pK_a and other models was carried out on the S-pK_a dataset that was randomly divided into training, validation and test set. The performances of those models on the test set are shown in Figure 4. Among the four machine learning models, ANN and XGBoost performed comparatively well, which was consistent with some previous studies (Mansouri et al., 2019; Yang et al., 2020). However, the performances of these two models still obviously fell behind Graph-pK_a, which achieved a MAE around 0.53 and a \( R^2 \) around 0.92 on the test sets (Fig. 4a and b). As known, the performance of QSAR models is closely related to the similarity between predicted molecules and the molecules of the training set. To evaluate the generalization capability of different models, we also calculated the pairwise similarity of test set molecules to the training set molecules, and split the test set molecules into five individual subsets according to their maximum similarity to training set molecules (Supplementary Table S3). Then, the MAE of those models on each subset was compared. As shown in Figure 4c and d, the Graph-pK_a outperformed other machine learning models on nearly all similarity subsets, which demonstrated it possesses high robustness and generalization ability. For the molecules with max similarity higher than 0.5 to the training set, the MAE of the model was lower than 0.65. If using it as the threshold for acceptable errors, 81.1% of test molecules were within the applicability domain of the models. Furthermore, the performance of Attentive FP on macro-pK_a prediction was not better than that of Graph-pK_a, meaning that MIL could endow Graph-pK_a with the prediction ability of micro-pK_a without significant trade-off on its prediction ability of macro-pK_a.

3.2 Evaluation on external datasets

The performance of Graph-pK_a was further validated by testing against two external datasets that were obtained from two blind pK_a prediction challenges named SAMPL6 and SAMPL7. These two challenges were launched by the Drug Design Data Resource Community in 2018 and 2020, respectively. The SAMPL6 dataset comprises 24 kinase inhibitor-like molecules with 31 experimental pK_a values, and the SAMPL7 dataset comprises 22 molecules (most are sulfonamides) with 20 experimental pK_a values. There are two pK_a values not belonging to the most acidic or basic pK_a values in the SAMPL6 dataset and two molecules without corresponding experiment pK_a values in the SAMPL7 dataset, they were excluded from this testing. The performances of Graph-pK_a and some commonly used software and models on these two external datasets are shown in Table 1 and Supplementary Table S4. Graph-pK_a achieved a low MAE of 0.594 and 0.758 as well as a high \( R^2 \) of 0.918 and 0.819 on SAMPL6 and SAMPL7 datasets, respectively, comparable to the performance of those commercial software established based on large collections of proprietary data.

Although our Graph-pK_a model has achieved satisfactory prediction performance, there are potentially two limitations. Frist, Graph-pK_a is only trained to predict the most acidic and basic pK_a values and its capability to predict other types of pK_a values such as the 2nd strongest acidic and basic pK_a values has not been fully evaluated. This is mainly because of the difficulty in the collection, cleaning, and labeling of this kind of training data. Second, the tautomism of molecules has not been taken into account in Graph-pK_a, which means that the model will give different prediction results for different tautomers of the same molecule. We leave this issue to follow-up studies, such as averaging the predicted values of different tautomers.

3.3 Performance on micro-pK_a prediction

Macro-pK_a values can describe the ionization degree of the molecule in the solvent but can’t pinpoint the ionization state of each atom in this molecule. To acquire more comprehensive knowledge about the ionization of molecules, the prediction of micro-pK_a values is equally important. Thus, the performance of Graph-pK_a on predicting micro-pK_a was also evaluated here. Unfortunately, the experimental determination of micro-pK_a values is highly complicated, and there is currently no available micro-pK_a dataset. Given this situation, a Turing-like test was designed to determine if Graph-pK_a exhibited the intelligent behavior (i.e. to designate the most acidic/basic atoms...
in a molecule structure) that was indistinguishable from that of a human expert. The results of expert judgments were obtained from a recent work of Hunt et al. for pK_a prediction (Hunt et al., 2020), where each pK_a value in their collected dataset (Hunt’s dataset) and two external test sets (Jensen’s dataset and SAMPL6 dataset) was carefully inspected and assigned to a specific site by human experts. As shown in Figure 5a, the overall consistency rates between the most acidic/basic atoms predicted by Graph-pK_a and the most acidic/basic atoms selected by the human experts were over 90%. To further quantify the degree of divergence between Graph-pK_a and human experts on those controversial molecules, the difference values of the predicted pK_a between the most acidic/basic atoms predicted by Graph-pK_a and those selected by the human experts are shown in Figure 5b. It could be observed that the difference values of 80% these controversial molecules were within 1.2 pK_a units, which indicated that the divergences between Graph-pK_a and human expert mainly derived from those molecules whose several atoms had similar ionization capability.

Some examples of agreement and disagreement between Graph-pK_a and human experts are respectively shown in Figure 5c and d. In the assignment of the most acidic atoms, two controversial molecules of note were A1 and A2, and most of the others were hydroxamic acid derivatives. Hunt et al. attributed the acidities of hydroxamic acid derivatives all to their hydroxyls. In fact, the dissociation ability of hydroxyl hydrogen and amino hydrogen in hydroxamic acid derivatives all to their hydroxyls. In fact, the dissociation ability of hydroxyl hydrogen and amino hydrogen in hydroxamic acid was quite similar (Bartmess, 2010) (also see R1, R2 in Fig. 5e, http://ibond.nankai.edu.cn), and the prediction results of Graph-pK_a supported their equivalent protonation potential. In the assignment of the most basic atoms, the two most controversial molecules were B1 and B2. Our prediction for B1 was supported by a record from PubChem that the pK_a value of the amine in B1 was 7.75 (https://pubchem.ncbi.nlm.nih.gov/compound/135398737). In addition, the basicity of the 1,3,4-Oxadiazol ring in B2 should be very weak, given that the pK_a of 1,3,4-thiadiazole was only -4.9 (R3 in Fig. 5e, https://www.scripps.edu/baran/heterocycles/Essentials1-2009.pdf). According to Graph-pK_a prediction, the basicity of B2 was attributed to the pyridine ring, instead of the 1,3,4-Oxadiazol ring. This assignment was further confirmed by quantum chemical calculation. As shown in Supplementary Figure S4, the protonation energies of nitrogen atom in the pyridine ring were -5.25 kcal/mol, significantly lower than that of nitrogen atoms in the 1,3,4-Oxadiazol ring (4.74 and 5.39 kcal/mol). The methods of quantum chemistry calculation are described in Supplementary Material.

The bold entries in the “MAE”, “RMSE”, and “R2” columns represent the best results in corresponding datasets.

The results are cited from articles of Hunt et al. (2020) and Yang et al. (2020). The results of Epik predictions are from Schrödinger Suite 2017; the results of ChemAxon predictions are from ChemAxon Marvin Suite 20.15.0. The results of Yang’s XGB and Yang’s NN are from a webserver (http://pka.husqgroup.com/prediction).
explicit supervision in multi-instance learning. It can be expected that when there are more available training data in the future, the capability will be further improved.

3.4 Visualization of the atomic embeddings

In order to visualize the features of the atoms learned by the Graph-pK_a model, the embeddings in the last hidden layer of several types of acidic ionization sites in the training data were extracted and submitted to principal component analysis. As shown in Figure 6, after training, the atomic embeddings from phenol hydroxyl, carboxyl, and sulfonamide groups were respectively gathered together. However, the distributions of atomic embeddings from alcoholic hydroxyl and amide groups were still relatively dispersed. These patterns suggest that alcoholic hydroxyl or amide groups in different chemical environments exhibit relatively larger variances, posing challenges for accurate micro-pK_a prediction. We speculated that a possible reason was that, although alcoholic hydroxyl and amide groups widely existed in the training set, they have less contribution to the macro-pK_a of the whole molecule due to their weak acidity.
Therefore, they had lower weights and were less supervised during model training. Three molecules and their atomic embeddings visually display such a situation. After training, the atomic embeddings from carboxyl groups of the three similar molecules are close, whereas the atomic embeddings from amide groups of the three molecules are dispersed. Apparently, adding more samples whose dominant ionization groups are alcoholic hydroxyl groups or amide groups into training data may alleviate this problem.

3.5 Web server for the prediction of $pK_a$

For the convenience of the community, a free web server wrapping the Graph-pK$_a$ model has been developed (https://pka.simm.ac.cn/). This web server was built using the python language and could be simultaneously accessed by multiple users. The web server can take multiple types of inputs including drawing a molecule from the molecular editor or uploading a .txt/.mol/.sdf file. There are two main functions in this web server: pK$_a$ prediction and similarity search (Supplementary Fig. S5). In the pK$_a$ prediction module, the most acidic/basic pK$_a$ values and their corresponding micro-pK$_a$ values of the input molecule are predicted. The Monte Carlo dropout is used to evaluate the uncertainty of the prediction results and calculate the 95% confidence interval of the predicted value (Gal and Ghahramani, 2016). It is noteworthy that, due to our definition of possible ionization sites and the processing of input molecules, the web server does not support the pK$_a$ prediction for C-H bonds and ionized molecules. In the similarity search module, the most acidic/basic atoms of the molecules from the S-pK$_a$ dataset and the most acidic/basic atoms of the molecular input by the user are first predicted by Graph-pK$_a$. Then, the embeddings of those predicted most acidic/basic atoms in the last hidden layer are extracted. Finally, the Euclidean distances between the atomic embeddings of the input molecule and that of the molecules in the S-pK$_a$ dataset are calculated. If the Euclidean distance is close enough (the threshold is set as less than 0.05), molecules are considered to be similar, and for each input molecule, up to four similar molecules and their experimentally determined pK$_a$ values will be output for reference.

4 Conclusions

In this work, we have developed a novel in silico pK$_a$ prediction model named Graph-pK$_a$. Combining multi-instance learning into graph neural network, Graph-pK$_a$ not only outperforms those conventional machine learning models based on molecular fingerprints in predicting macro-pK$_a$s but more significantly, can learn the micro-pK$_a$ values of atoms through training against the macro-pK$_a$s values of molecules. A Turing-like test demonstrated that it gained chemical insights to locate the most acidic/basic sites of molecules, which compared favorably with that of human experts. Such micro-pK$_a$ inference ability greatly enhances the interpretability and practicability of this model. Furthermore, in Graph-pK$_a$, the fitting and prediction of macro-pK$_a$s are all dependent on the reasoning of micro-pK$_a$s, which can also avoid shortcut learning to some extent (Geirhos et al., 2020). In the end, a Web application based on Graph-pK$_a$ model has been made freely available at https://pka.simm.ac.cn.

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References

Bartmess, J.E. (2010) The Brønsted Acid/Base Character of Hydroxylamines, Oximes and Hydroxamic Acids. Patai’s Chemistry of Functional Groups. John Wiley & Sons, Ltd., Chichester, UK.

Carboneau, M.-A. et al. (2018) Multiple instance learning: a survey of problem characteristics and applications. Pattern Recognit., 77, 329–351.

Charron, P.S. and Walters, W.P. (2014) Acidic and basic drugs in medicinal chemistry: a perspective. J. Med. Chem., 57, 9701–9717.

Defferrard, M. et al. (2016) Convolutional neural networks on graphs with fast localized spectral filtering. In: Proceedings of the 30th International Conference on Neural Information Processing Systems. New York, USA, pp. 3844–3852.

Duvenaud, D. et al. (2015) Convolutional networks on graphs for learning molecular fingerprints. In: Proceedings of the 28th International Conference on Neural Information Processing Systems, Montreal, Canada, pp. 2224–2232.

Gal, Y. and Ghahramani, Z. (2016) Dropout as a Bayesian approximation: representing model uncertainty in deep learning. In: International Conference on Machine Learning. New York, USA, pp. 1050–1059.

Gaulton, A. et al. (2017) The ChEMBL database in 2017. Nucleic Acids Res., 45, D945–D954.

Geirhos, R. et al. (2020) Shortcut learning in deep neural networks. Nat. Mach. Intell., 2, 665–673.

Gilmer, J. et al. (2017) Neural message passing for quantum chemistry. In: International Conference on Machine Learning. Sydney, Australia, pp. 1263–1272.

Hunt, P.A. et al. (2020) Predicting pKa using a combination of semi-empirical quantum mechanics and radial basis function methods. J. Chem Inf. Model., 60, 2989–2997.

Ipek, M. et al. (2018) pKa measurements for the sample prediction challenge for a set of kinase inhibitor-like fragments. J. Comput. Aided Mol. Des., 32, 1117–1138.

Manallack, D.T. (2007) The pKa distribution of drugs: application to drug discovery. Perspect. Med. Chem., 1, 25–28.

Manallack, D.T. et al. (2013) The significance of acid/base properties in drug discovery. Chem. Soc. Rev., 42, 485–496.

Mansouri, K. et al. (2019) Open-source QSAR models for pKa prediction using multiple machine learning approaches. J. Cheminform., 11, 1–20.

Niepert, M. et al. (2016) Learning convolutional neural networks for graphs. In: International Conference on Machine Learning. New York, USA, pp. 2014–2023.

Roszak, R. et al. (2019) Rapid and accurate prediction of pK a values of C–H acids using graph convolutional neural networks. J. Am. Chem. Soc., 141, 17142–17149.

Rupp, M. et al. (2011) Predicting the pKa of small molecules. Comb. Chem. High Throughput Screen., 14, 307–327.

Sun, M. et al. (2020) Graph convolutional networks for computational drug development and discovery. Brief. Bioinform., 21, 919–935.

Wang, S. et al. (2019) RMDL: recalibrated multi-instance deep learning for whole slide gastric image classification. Med. Image Anal., 58, 101549.

Wishart, D.S. et al. (2018) DrugBank 5.0: a major update to the DrugBank database for 2018. Nucleic Acids Res., 46, D1074–D1082.

Xiong, Z. et al. (2020) Pushing the boundaries of molecular representation for drug discovery with the graph attention mechanism. J. Med. Chem., 63, 8749–8760.

Yang, Q. et al. (2020) Holistic prediction of pKa in diverse solvents based on machine-learning approach. Angew. Chem. Int. Ed., 59, 19282–19291.

Yap, C.W. (2011) PaDEL-descriptor: an open source software to calculate molecular descriptors and fingerprints. J. Comput. Chem., 32, 1466–1474.

Zhang, Z. et al. (2021) FraGAT: a fragment-oriented multi-scale graph attention model for molecular property prediction. Bioinformatics, 37, 2981–2987.

Zhou, Y. et al. (2017) Adaptive pooling in multi-instance learning for web video annotation. In: Proceedings of the IEEE International Conference on Computer Vision Workshops. Venice, Italy, pp. 318–327.

Zhou, Z.-H. (2018) A brief introduction to weakly supervised learning. Natl. Sci. Rev., 5, 44–53.