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Development of Multi-Task QSTR Models for Acute Toxicity Prediction Towards *Daphnia magna* Using Machine Learning in the OCHEM Platform

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Abstract: This research employed a multi-task modeling approach to assess the acute toxicity of various chemicals through quantitative structure-toxicity relationship (QSTR) models. An expert system was constructed using several machine-learning techniques and was developed with resources from the publicly available Online Chemical Database and Modeling Environment (OCHEM). The study details the underlying assumptions and methodologies for model selection, descriptor identification, and the strategic development that contributed to the research's successful outcomes. The dataset utilized for QSTR modeling comprised 2678 compounds, with acute toxicity evaluations conducted on *Daphnia magna* organisms. The predictive performance of the QSTR models was validated through both cross-validation and external test sets. The consensus regression model shows strong predictive accuracy, with a coefficient of determination (q^2) ranging from 0.74 to 0.77. The consensus prediction for the external evaluation set afforded high predictive power, achieving a q^2 value between 0.79 and 0.81. Furthermore, additional validation was achieved using experimental data from 20 compounds, showcasing robust predictive capabilities. Importantly, a considerable proportion of the toxicity values predicted by the models were in close agreement with results from *in vivo* studies, highlighting the reliability of the approach used.

Keywords: acute toxicity, *Daphnia magna*, multi-task learning, QSTR, OCHEM

1. Introduction

In recent years, there has been a significant increase in the production of synthetic organic compounds, which are extensively utilized across various industries. The constant rise in the number of new chemical substances being developed has become an issue of great concern for both the environment and human safety [1]. This is because releasing new chemicals into the environment can significantly impact the ecosystem and seriously threaten the health of humans and other living organisms. It is therefore essential to regulate the production, use, and disposal of these chemicals to ensure that they do not pose potential threats to the environment and human health [1].

The development of new biologically active compounds, particularly potential pharmaceuticals, significantly emphasizes safety considerations. Ensuring the safety of these compounds is crucial throughout the research and development process [2]. This includes assessing various types of toxicity and potential side effects. In the past years, there has been an increasing focus on using *in silico* methods to predict the toxicological effects of novel substances across various chemical categories [3]. These computational techniques enable researchers to evaluate the potential toxicity of new chemicals without relying heavily on extensive laboratory testing, thereby streamlining the evaluation process for new chemicals. Over the years, many *in silico* models have been developed to predict the toxicity of chemical compounds [4–6]. Such models have enormous potential in the pharmaceutical industry as they can facilitate screening new drug candidates and identify potential toxic effects early in drug development. Application of these models can significantly speed up the drug discovery process, reduce the need for animal testing, and ultimately lead to the development of safer and more effective drugs [7, 8].

Usually, the toxicity of chemical compounds is assessed using different types of biological assays that describe different toxic effects (acute toxicity, neurotoxicity, etc.,), model organisms (crustacean *Daphnia magna* [9], fish *Danio rerio* [4], marine bacteria *Vibrio fischeri* [10], etc.,), or the toxicity result (LC_{50}, EC_{50}, LD_{50}, etc.,). Frequently, only a small selection of substances undergo testing in numerous assays or for various species and endpoints. The absence of experimental data across all assays can impede the identification of their toxicity. Nevertheless, given that toxicity data sets are interconnected, it is reasonable to anticipate that these connections can help create models with greater predictive capability for each data point by concurrently modeling them (multi-task learning) [11]. Multi-task modeling is an approach that uses information from different related properties to develop models that can predict multiple QSTR endpoints. This can increase the efficiency and accuracy of

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model forecasts for specific tasks based on the design and development of such models. The multitasking approach can increase the productivity of several tasks, forecasting and classifying the paths of their comprehensive analysis and modeling [12]. In this regard, our study presents a series of quantitative structure-toxicity relationship (QSTR) models specifically targeted at assessing the acute toxicity of chemical compounds. These models employ multi-task learning methods, allowing them to learn from related tasks simultaneously improving their predictive capabilities. The development of these models is supported by the Online Chemical Database and Modeling Environment (OCHEM) server [13], which provides a robust platform for integrating chemical data and facilitating advanced modeling techniques. With this study, we aim to provide more accurate and efficient tools for assessing the toxicity potential of various compounds, ultimately contributing to safer chemical practices.

2. Materials and Methods

2.1. Data

The database of compounds that were tested in this study consisted of different classes of molecules with acute toxicity obtained from the OCHEM database [13]. The OCHEM database contains experimental data on acute toxicity, with information primarily sourced from the ECOTOX database (https://cfpub.epa.gov/ecotox/), VEGA (https://www.vegahub.eu/), and various scientific publications. The website offers public access to the chemical structures associated with the compounds in the training and test sets and a comprehensive list of publications (https://ochem.eu/).

The united dataset was formed from 2678 compounds. Subset 1 consisted of 1892 compounds, the acute toxicity of which toward *Daphnia manga* was measured by the value of EC_{50}, which varied from 0.14 nM to 312 mM. Subset 2 consisted of 786 compounds, the acute toxicity of which toward *Daphnia manga* was measured by the value of LC_{50}, which varied from 21.7 nM to 348.9 mM.

EC_{50} and LC_{50} are statistical measures used in toxicology to estimate the concentration of a toxic substance required to produce a specific effect in a population. EC_{50} refers to the toxicant concentration necessary to achieve the desired effect in 50% of a large population under certain conditions. On the other hand, LC_{50} is a special case of EC_{50} in which the recorded effect is death. The model-building process used the values of $\log(1/EC_{50})$ and $\log(1/LC_{50})$, respectively. To thoroughly evaluate the quality of the developed models, all data sets were randomly divided into a training set (80% of compounds) and an external test set (20% of molecules).

2.2. Machine-learning methods (MLMs)

When building the QSTR models, various methods and sets of descriptors available in OCHEM were tested. Several models were created by the Transformer Convolutional Neural Network (Trans-CNN) [14], Transformer Convolutional Neural Fingerprint (Trans-CNF) [15], Associative Neural Network (ASNN) [16], Text Convolutional Neural Network (Text-CNN) [17], and Least Squares Support Vector Machine (LS-SVM) [18]. The optimized parameter settings were used for each MLM offered by the OCHEM platform.

Transformer Convolutional Neural Network. Trans-CNN uses information about molecules based on their SMILES notation to build QSTR models [14]. The method predicts a target value by averaging individual predictions for a batch of nonstandard SMILES belonging to a single molecule. Within-batch variance can serve as a measure of the confidence interval of a forecast, and the ability to canonicalize SMILES can be used to determine the uncertainty of forecasts.

Transformer Convolutional Neural Fingerprint. Trans-CNF is similar to Trans-CNN, but instead of using a convolutional neural network, it employs a convolutional neural fingerprint to process the latent representation of the neural network [19]. The CNF model is built upon the convolutional graph framework introduced by Duvenaud et al. [15]. This model leverages hierarchical convolutional layers and a matrix multiplication that functions as a hash technique. It specifically operates on the SMILES representation of molecules, utilizing one-hot encoding for the SMILES to facilitate convolutional operations and subsequent matrix multiplications. This approach enables the model to capture relationships between neighboring atoms in a chemical structure, with the matrix multiplication serving as an embedding mechanism in a latent space. One notable advantage of the CNF model is that it maps a sparse matrix, the one-hot encoding of a SMILES, into a dense vector, the neural fingerprint. The CNF model has demonstrated high prediction accuracy, which can be explained by including the augmentation techniques originally developed for computer vision and recently adapted for QSAR studies [15].

Associative Neural Network. ASNN is a highly effective and efficient algorithm that combines the strength of an ensemble of feed-forward backpropagation neural networks with the k-nearest neighbors (kNN) method, providing exceptional accuracy and reliability for a wide range of applications. While neural networks create global models, kNN provides local correction of the global model set [16]. This combination helps to correct the bias of the neural network ensemble, thereby increasing its accuracy. The ensemble consisted of 100 neural networks developed using the default parameters provided by OCHEM.

Text Convolutional Neural Network. Text-CNN has been specifically designed for text recognition tasks [17]. It was trained on billions of words from Google News. Molecules can be encoded as textual sequences using the SMILES image of a molecule. Such representation of the molecule encodes the topological information based on general rules of chemical bonding. The method was adapted for working with SMILES by DeepChem developers (https://deepchem.io/).

Least Squares Support Vector Machine. LS-SVM represents a variation of traditional support vector machine (SVM), a widely used supervised learning technique for data analysis and pattern recognition, particularly in classification and regression tasks. Unlike classical SVM which relies on solving a convex quadratic programming problem, LS-SVM provides solutions through a set of linear equations. This approach was introduced by researchers Suykens and Vandewalle [18]. As a kernel-based learning method, LS-SVM leverages the power of kernel functions to transform data into higher-dimensional spaces, enhancing the model's capability to identify complex patterns.

2.3. Descriptors

OCHEM offers a variety of widely used software packages designed for calculating extensive sets of molecular descriptors, which play a crucial role in cheminformatics. In this study, the selected descriptors were used to construct the ASNN and VS-SVM predictive models.

One such tool is the ALogPS program [20], which specializes in computing the 1-octanol/water partition coefficient and predicting aqueous solubility. This program is essential for understanding the hydrophilic and hydrophobic properties of compounds, crucial for many applications in drug development and environmental chemistry.

Another important aspect of molecular analysis involves E-State indices [21]. These indices are derived from the principles of chemical graph theory and provide 2D descriptors that integrate both electronic and topological features of the analyzed compounds. This dual focus enhances the ability to assess molecular behavior and interactions.

Mold2 is another powerful software option that efficiently calculates a wide range of descriptors, capturing vital two-dimensional structural information essential for the characterization of chemical compounds [22]. This widely accessible software is developed by the Bioinformatics Center, under the leadership of Dr. Wade Tong at the National Center for Toxicology Research (https://www.fda.gov/science-research/bioinformatics-tools/mold2).

The Chemistry Development Kit version 2.3 [23] represents a comprehensive toolkit comprising Java libraries for processing various types of chemical information. This version is capable of calculating an impressive total of 256 molecular descriptors, which encompass geometrical, topological, constitutional, electronic, and hybrid aspects of molecular structure, thereby providing a robust framework for chemical analysis.

In this study, the alvaDesc package was also employed [24], which is renowned for its ability to compute over 5,600 descriptors independent of three-dimensional molecular information. These descriptors include constitutional, topological, and pharmacophore metrics, along with ETA and Atom-type E-state indices, functional group counts, and fragment analyses. Beyond these, alvaDesc offers a vast array of three-dimensional descriptors such as 3D-autocorrelation, Weighted Holistic Invariant Molecular descriptors, and GETAWAY, all of which provide critical insights into the spatial characteristics of molecules (https://www.alvascience.com/alvadesc-descriptors/). Furthermore, the alvaDesc program is adept at calculating various model-based physicochemical properties, which include molar refractivity, topological polar surface area, estimations of molecular volume, as well as LogP and LogS values for aqueous solubility coefficients, adding to its utility in predictive modeling and analysis.

2.4. Validation of models

The QSTR models were assessed through a fivefold cross-validation technique, supplemented by external validation sets [25]. To reduce the risk of overfitting during variable selection, OCHEM implemented multiple repetitions across all stages of model development within each validation fold. This rigorous approach enhances the reliability of the models, enabling them to make accurate predictions. Finally, the quality of the developed models was confirmed using the previously mentioned test sets.

The evaluation of regression models was conducted using several key metrics to assess their performance. The root mean square error (RMSE) was used to quantify the average deviation of predicted values from actual values and the mean absolute error provided insight into the average absolute deviations between these values [26]. Additionally, the squared correlation coefficient, R^2, served as an indicator of how well the model aligns with the data, and the coefficient of determination, q^2, assessed the model's predictive capability. These metrics are essential for understanding the accuracy and reliability of regression models and guiding potential improvements and adjustments.

OCHEM also provides insights into the applicability domain of its developed models (https://docs.ochem.eu/x/l4CZ.html) and the accuracy of their forecasts, which is crucial for ensuring the reliability and relevance of the models generated through the platform [13, 27]. In addition, the OCHEM guideline contains detailed information on the MLMs used, the descriptors selected, the statistical coefficients applied, and the rigorous validation procedures implemented (https://docs.ochem.eu/).

3. Results and Discussion

3.1. Analysis of the developed QSTR models

The initial dataset of 1892 compounds was split by chance into training (1514) and test (378) sets as described in Section 2.1. A series of QSTR models were systematically developed utilizing a range of learning methodologies and distinct sets of molecular descriptors, all implemented in the OCHEM platform. Following the development process, a comprehensive post hoc analysis was performed to evaluate the performance of these models. The results showed that the non-descriptor-based models consistently achieved the highest performance, outperforming the others in both the leaderboard and individual scores. The findings from the analysis are detailed in Table 1. This table exclusively presents the values of the RMSE, which is a critical metric for assessing the accuracy of our predictions. The RMSE values are the basis for calculating other related coefficients derived from this primary measure. Consequently, a comprehensive understanding of the RMSE is essential, as it directly influences the interpretation of the additional coefficients not displayed in this table.

The findings indicate that descriptor-free models achieved average RMSE values between 0.82 and 0.84 for training sets, and

Table 1. Comparison of performances of the developed QSTR models

No	Machine-learning method	Descriptors	Training set (RMSE)			Test set (RMSE)		
			EC_{50}	LC_{50}	Mean*	EC_{50}	LC_{50}	Mean
1	Trans-CNN	–	0.79	0.85	0.82	0.77	0.69	0.73
2	Trans-CNF	–	0.76	0.83	0.795	0.75	0.67	0.71
3	Text-CNN	–	0.82	0.86	0.84	0.87	0.90	0.885
4	ASNN	ALogPS, OEstate	0.95	1.00	0.975	0.88	0.92	0.90
5	ASNN	CDK23	0.91	0.95	0.93	0.81	0.87	0.84
6	ASNN	Mold2	0.94	0.94	0.94	0.93	1.00	0.965
7	ASNN	alvaDesc	0.94	1.00	0.97	0.91	0.92	0.915
8	LS-SVM	ALogPS, OEstate	1.00	1.00	1.00	0.99	1.00	0.995
9	LS-SVM	CDK23	0.9	0.88	0.89	0.91	0.95	0.93
10	LS-SVM	Mold2	0.94	0.96	0.95	1.00	0.99	0.995
11	LS-SVM	alvaDesc	1.0	1.00	1.00	1.00	1.10	1.05

Note: RMSE: root mean square error; *Average RMSE of toxicity predictions for both endpoints.

Table 2. Statistical coefficients of the regression models

No	Method	Endpoint	Training set			Test set		
			R^2	q^2	MAE	R^2	q^2	MAE
1	Trans-CNN	EC_{50}	0.75 ± 0.01	0.75 ± 0.01	0.59 ± 0.01	0.79 ± 0.02	0.79 ± 0.02	0.55 ± 0.03
		LC_{50}	0.71 ± 0.02	0.71 ± 0.02	0.65 ± 0.02	0.83 ± 0.03	0.83 ± 0.03	0.48 ± 0.04
2	Trans-CNF	EC_{50}	0.77 ± 0.01	0.77 ± 0.01	0.56 ± 0.01	0.80 ± 0.02	0.80 ± 0.02	0.55 ± 0.03
		LC_{50}	0.73 ± 0.02	0.73 ± 0.02	0.62 ± 0.02	0.83 ± 0.03	0.82 ± 0.03	0.50 ± 0.04
3	Text-CNN	EC_{50}	0.74 ± 0.01	0.74 ± 0.01	0.62 ± 0.01	0.74 ± 0.03	0.72 ± 0.03	0.64 ± 0.03
		LC_{50}	0.71 ± 0.02	0.71 ± 0.02	0.65 ± 0.02	0.72 ± 0.04	0.65 ± 0.05	0.70 ± 0.05
4	Consensus*	EC_{50}	0.77 ± 0.01	0.77 ± 0.01	0.56 ± 0.01	0.80 ± 0.02	0.79 ± 0.02	0.56 ± 0.03
		LC_{50}	0.74 ± 0.02	0.74 ± 0.02	0.61 ± 0.02	0.82 ± 0.03	0.81 ± 0.03	0.53 ± 0.04

Note: *The consensus model was a simple average of the three models. MAE is mean absolute error. R^2 and q^2 are the squared linear correlation and coefficient of determination, respectively.

for test datasets, RMSE values varied between 0.73 and 0.885. In contrast, descriptor-based models reported RMSE values ranging from 0.94 to 1.0 for training sets and from 0.84 to 1.05 for test datasets. These results demonstrate some advantages of using non-descriptor-based approaches within the context of QSTR modeling for this data. Therefore, these MLMs offer opportunities for improved predictive performance and may streamline the modeling process by minimizing the need for extensive feature engineering.

3.2. Design of the final model

In the previous studies focused on activity and toxicity prediction, the conception of consensus modeling emerged as an effective strategy for enhancing model performance. The study highlighted that combining MLMs that utilized descriptor-free models, specifically those with the three lowest RMSE scores—Trans-CNN, Trans-CNF, and Text-CNN—could lead to a more robust consensus model. This approach aimed to leverage the strengths of each method to improve overall predictive accuracy. Given that the performance of all methods was very similar, we used a simple average of model predictions. The results are shown in Table 2 and Supplementary Figure 1. A consensus model, an average of three models was also used to estimate the applicability domain of predictions [27].

3.3. Application of consensus QSTR model

We used a small data set from our previous works as an additional external validation set. These compounds have shown antibacterial properties, and their acute toxicity has only been assessed through experimental methods in the past.

The compounds under study belong to three different classes. Isoxazole-containing sulfonylamides (compounds **1–8**) are detailed in the study by Hodyna et al. [28], and imidazolidinone sulfonamides (compounds **9–14**) are detailed in the study by Hodyna et al. [29]. Trifluoromethylated pyrroles (compounds **15–20**) were previously discussed in the study by Hodyna et al. [30] (Supplementary Table 1).

The 18 compounds fell within the model's applicability domains, indicating reliable predictions generated by the consensus model (see Table 3). Notably, the proposed QSTR model demonstrated exceptional predictive reliability, with approximately 84% of the projections falling within 0.5 log units of the experimentally determined values. This strong correlation between predicted and experimental outcomes underscores the models' accuracy and effectiveness. Only 3 chemicals displayed residue values that ranged between 0.5 and 1 log unit. The results indicate that these models can serve as reliable tools for assessing chemical toxicity, potentially facilitating the development of safer chemical products and substances.

In Figure 1, the results shown in Table 3 are presented graphically, providing a clearer understanding of the data trends. The third column of Figure 1 added the predicted EC_{50} values for the compounds under study (Supplementary Table 2). When analyzing the predicted values for both LC_{50} (lethal concentration for 50% of the test organisms) and EC_{50} (effective concentration for 50% of the test organisms), it becomes apparent that there is only a slight discrepancy between them, typically within the range of 0.1 to 0.2 log units (see Figure 1). This close alignment suggests that, although the input data is represented as EC_{50} and LC_{50}, the predicted values effectively converge, indicating a strong correlation between the two measures. This similarity reinforces the idea that LC_{50} can be viewed as a specific instance

Table 3. Prediction of the toxicity of 20 compounds by the consensus QSTR model

No	LC_{50} (mg/L)		$Log(1/LC_{50})$			
	Exp.	Pred.	Exp.	Pred.	Difference	AD*
1	>100.0	95.95	3.49	3.51	0.02	TRUE
2	45.33 ± 13.40	116.5	3.85	3.44	0.41	TRUE
3	37.32 ± 10.59	116.8	3.96	3.46	0.50	TRUE
4	25.69 ± 6.08	16.08	4.18	4.38	0.20	TRUE
5	21.84 ± 5.12	15.88	4.27	4.4	0.13	TRUE
6	33.23 ± 10.04	15.44	4.10	4.43	0.33	TRUE
7	44.45 ± 14.36	33.64	3.91	4.03	0.12	TRUE
8	41.08 ± 13.97	36.68	3.96	4.01	0.05	TRUE
9	16.01 ± 2.59	10.97	4.36	4.52	0.16	TRUE
10	22.35 ± 3.79	11.01	4.22	4.53	0.31	TRUE
11	17.62 ± 3.87	6.05	4.27	4.73	0.46	TRUE
12	44.34 ± 6.89	11.8	3.94	4.51	0.57	TRUE
13	18.62 ± 4.89	2.84	4.23	5.04	0.81	TRUE
14	44.35 ± 6.89	1.66	4.01	5.43	1.42	FALSE
15	4.89 + 1.32	5.60	4.74	4.68	0.06	TRUE
16	6.99 + 1.13	4.14	4.61	4.84	0.23	TRUE
17	33.39 + 4.57	10.6	3.76	4.26	0.50	TRUE
18	9.10 + 2.87	15.35	4.50	4.27	0.23	TRUE
19	7.76 + 1.75	0.70	4.62	5.66	1.04	FALSE
20	1.21 + 0.26	7.68	5.35	4.55	0.80	TRUE

Note: *AD – applicability domain.

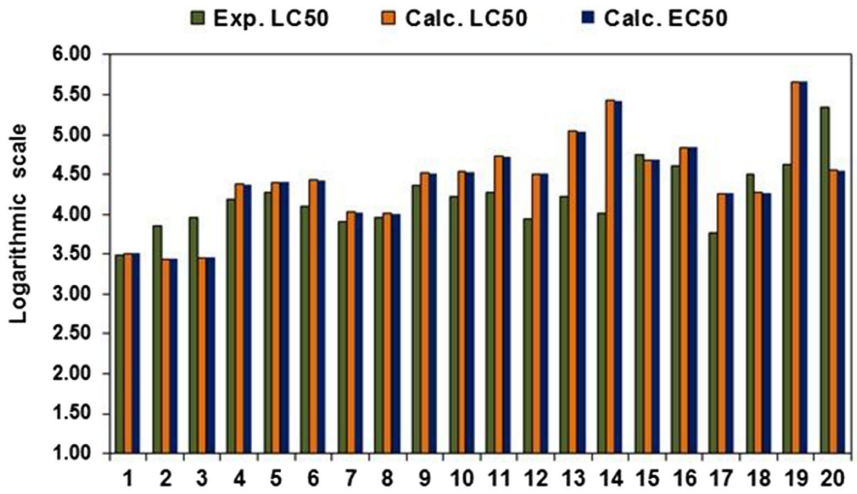

Figure 1. Experimental and predicted acute toxicity values of 20 compounds by the consensus QSTR model

of EC_{50}, where the measured effect pertains directly to mortality. Additionally, these results emphasize the value of using multi-task learning QSTR models. So, by analyzing predictions across various endpoints, it becomes possible to assess their reliability, especially in cases where there is significant variance among predictions for different endpoints. In summary, it can be concluded that models trained on large datasets covering different endpoints such as EC_{50} and LC_{50} demonstrate a higher ability to predict the potential acute toxicity of new compounds with greater accuracy.

4. Conclusion

Predictive models based on multi-task learning frameworks were developed using the OCHEM platform, focusing on various MLMs. These QSTR models exhibited impressive stability, robustness, and predictive accuracy, as determined through cross-validation and testing with randomized datasets. The strong predictive capabilities of novel QSTR models establish them as critical assets for assessing acute toxicity for potentially promising chemical compounds. The effectiveness of these models is further supported by favorable performance metrics derived from *in silico* calculations, which closely align with outcomes from *in vivo* studies. This congruence between computational predictions and actual biological results reinforces the reliability of the models, making them essential tools for toxicological evaluations in drug development and environmental safety assessments.

Ethical Statement

This study does not contain any studies with human or animal subjects performed by any of the authors.

Conflicts of Interest

The authors declare that they have no conflicts of interest to this work.

Data Availability Statement

The developed QSTR models are openly available in OCHEM at http://ochem.eu/article/164296. The data that support this work are available upon reasonable request to the corresponding author.

Author Contribution Statement

Vasyl Kovalishyn: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing. **Diana Hodyna:** Formal analysis, Investigation, Resources, Data curation, Writing – review & editing, Visualization. **Larysa Metelytsia:** Investigation, Resources, Writing – review & editing, Visualization, Supervision, Project administration.

Supplementary Information

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