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Chembench: A Publicly-Accessible, Integrated Cheminformatics Portal

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Abstract

The enormous increase in the amount of publicly available chemical genomics data and the growing emphasis on data sharing and open science mandates that cheminformaticians make their models publicly available for broad use by the scientific community. Chembench is one of the first publicly-accessible, integrated cheminformatics Web portals. It has been extensively used by researchers from different fields for curation, visualization, analysis, and modeling of chemogenomics data. Since its launch in 2008, Chembench has been accessed more than 1 million times by more than 5K users from a total of 98 countries. We report on the recent updates and improvements that increase the simplicity of use, computational efficiency, accuracy, and accessibility of a broad range of tools and services for computer-assisted drug design and computational toxicology available on Chembench. Chembench remains freely accessible at https://chembench.mml.unc.edu

Graphical Abstract

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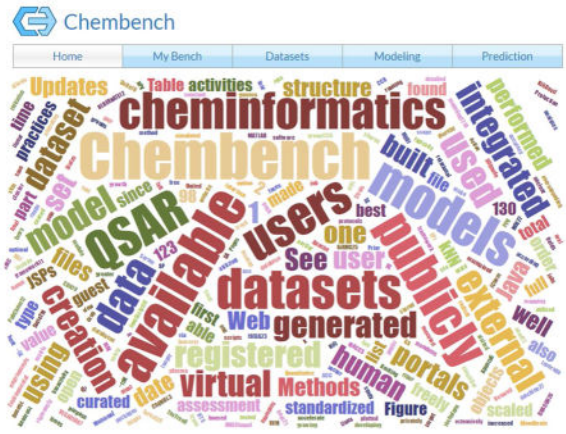
Competing financial interests

The authors declare no competing financial interests.

SUPPORTING INFORMATION

Details about publicly available datasets and predictors are provided in the Supporting Information. For the 86 publicly available datasets on Chembench, the name, size and type (categorical or classification) of the dataset are provided, as well as the descriptors available for modeling, the modelability index, and the date of creation (Table S1). For the 124 publicly available predictors, the name of the model and the underlying dataset, the statistical evaluation of the predictor, the machine learning technique and descriptors used, and the date of creation are all provided (Table S2). All publicly available datasets and predictors are available at https://chembench.mml.unc.edu/.



INTRODUCTION

The scientific community faces an unprecedented growth of chemical genomics data[1] caused by widespread proliferation of high-throughput screening (HTS) technologies in both academia and industry and ever-expanding, public databases of chemical structure and bioactivity, such as PubChem[2,3] and ChEMBL.[4] Quantitative Structure-Activity Relationship (QSAR) models can leverage these data to accelerate chemogenomics research and chemical safety assessment while simultaneously reducing the associated costs.[1,5,6] At the same time, there has been a community-wide push for increased openness in data and model sharing.[1,6] This trend is posed to promote greater cross-disciplinary collaborations and to advance the relevance and rigor of predictive modeling. This evolution in the culture of data science mandates cheminformatics groups to provide the scientific community with the free and open access to QSAR models.

Currently, freely-accessible QSAR models are typically shared through standalone software applications. Such examples include EPI Suite™ from the United States Environmental Protection Agency[7], VEGA-QSAR[8], and ToxTree.[9] While these standalone applications provide access to some QSAR models, new models cannot be developed by the user, thereby limiting the scope of available models. The optimal method for both developing and sharing QSAR models is the creation of freely-accessible, integrated cheminformatics Web portals.

Chembench[10] is one of the first publicly-accessible, integrated cheminformatics portals, along with OCHEM[11]. Chembench has been used for research in chemical genomics, drug discovery, computational toxicology, and other fields. Since its creation in 2008, Chembench has been extensively used for the development and distribution of QSAR models, as well as a teaching tool. To date, Chembench has been visited over one million times. Chembench has more than 550 active registered users from 38 different countries, with an additional ~5K individual non-registered users from a total of 98 countries (Figure 1). In order to keep Chembench as a state-of-the-art Web portal during this time of growing interest in open science and molecular modeling, constant updates and upgrades must be made. Here, we aim to report on the updates and improvements made in the recent years to increase the simplicity, speed, reliability, and openness of Chembench.

METHODS

Chembench is a Java-based system, utilizing Java Server Pages (JSPs) with JavaScript[12] at the front end of the website. The interface between data located on the JSPs and Java objects is maintained by the Apache Struts 2 framework.[13] HIBERNATE[14] provides the framework for mapping the Java objects to a relational database. Chembench is freely accessible at https://chembench.mml.unc.edu/.

Prior to QSAR modeling, the datasets are automatically curated following the protocols developed earlier in our group.[15–17] For structural standardization and compound visualization J Chem Suite[18] is used. Visualization scripts are executed using the R environment.

The models are built and rigorously validated according to best practices of QSAR modeling.[19,20] Chembench implements several chemical descriptor generation packages – CDK,[21] DRAGON,[22] MACCS keys,[23] MOE,[24] and ISIDA.[25] Molconn Z descriptors[26] are no longer supported; however, descriptors files for archived datasets are still available for download. In addition, users can also upload their datasets characterized by any descriptors precomputed outside of Chembench. The following machine learning algorithms are supported by Chembench for both continuous and classification model building: random forest,[27] support vector machine,[28] k-nearest neighbors (kNN) with genetic algorithm (GA) or simulated annealing (SA) descriptor selection.[29] Predictors are built using the scikit-learn package from Python.[30] Single compounds for prediction can be sketched using JSME, a free molecule editor written in JavaScript.[31] Calculations are performed on the KillDevil 800-node Beowulf Linux cluster housed at UNC-Chapel Hill.

CHEMBENCH ENVIRONMENT

Chembench facilitates cheminformatics analyses via four modules described below: My Bench; Datasets; Modeling; and Prediction. Each module can be utilized individually or integrated as part of an integrated study design.

My Bench

Every dataset, predictor (QSAR model), and prediction created by a register user on Chembench is privately stored and available for personal download. After receiving approval from the Chembench management team, registered users have the option to make all datasets, predictors, and predictions publicly available. Both registered and guest (non-registered) users are able to download all publicly available datasets and predictors. Curated datasets downloaded from Chembench contain, among other files, the standardized structure file and generated descriptor matrices. Predictors, when downloaded, contain the non-overlapping training and test sets used in each fold during cross-validation and the underlying Python scripts used for model building. Guest users are not able to download datasets and predictors associated with proprietary descriptors. Users can track the progress of all running jobs using the job queue feature.

Datasets

Chembench facilitates the creation of datasets for model building and validation. Modeling datasets can be used for either predictor generation or virtual screening, while prediction datasets are used exclusively for virtual screening. Users have the option to upload proprietary descriptors; otherwise, available descriptors (see Methods) are automatically generated from an uploaded structure file. The modelability index (MODI) of each dataset is calculated automatically.[32] Structures are standardized following our chemical data curation workflow,[16] and a chemical similarity heat maps, using either Tanimoto similarity[33] or Mahalanobis distance measure,[34] can be generated as an option. Rigorous external validation is an inherent part of model building. For this purpose, specific set of compounds can be selected for external validation or, as other options, random external set or n-fold external cross-validation can be used.[19] In order to promote best practices of QSAR modeling,[19] Chembench will automatically warn the user if the modeling dataset is too small (less than 40 compounds) for rigorous QSAR modeling. After the dataset has been created, the user can view chemical structures, examine the heatmap and a histogram of activities, as well as investigate each generated descriptor type and examine possible errors during calculation. Currently, there are 86 publicly available datasets on Chembench, including, for example, datasets of human skin sensitization,[35,36] P-glycoprotein substrates,[37] chemical toxicants tested against *Tetrahymena pyriformis,*[38] and blood–brain barrier permeability.[39] A full list of publicly available datasets on Chembench can be found in the Supporting Information.

Modeling

Chembench allows for the generation of statistically validated QSAR models of target endpoints for either personally uploaded or publicly available modeling datasets. Generated descriptors (See Methods) or externally uploaded descriptors, if applicable, are available for use in the predictor. Descriptors can be range scaled, auto scaled, or left unscaled. Users can manually set the maximum allowed descriptor cross-correlation. For each pair of descriptors, if the correlation coefficient is above the maximum, one of the two will be chosen randomly and removed; descriptors with zero variance across compounds will be automatically removed as well. It should be noted that if the descriptor type cannot be generated due to incompatible chemical structures (see Datasets), then this descriptor type will be unavailable for use in QSAR modeling. After the model has been built, the robustness of the predictor can be probed through a detailed assessment of external validation statistics. For models built with continuous data, the linear regression is plotted, and the Q^2, RMSE, and MAE are calculated. For models built with categorical data, a confusion matrix is generated from which specificity (SP), sensitivity (SE), correct classification rate (CCR), accuracy (ACC), negative predictive value (NPV), and positive predictive value (PPV) are calculated. All external validation results can be download as *.csv files. For all models, regardless of the machine learning algorithm, y-randomization[40] is performed with a corresponding statistical evaluation. For random forest, the individual trees can be investigated with the selected descriptors displayed. Additionally, feature selection is performed, and the most important descriptors are ranked. For SVM, a matrix search is used and the gamma parameter of each radical basis function (RBF) kernel can be identified. For kNN, the number of k nearest neighbors and descriptors used for each model

can be probed. All users can download publicly available models from Chembench, while only registered users can save, store, and download their personal models on Chembench. Currently, there are 124 publicly available predictors on Chembench that can either be downloaded or used for virtual screening (See Prediction), including, for example, predictors of the human intestinal transporter inhibition,[41] human oral bioavailability,[42] human plasma protein binding,[43] stress response and nuclear receptor signaling toxicity assays.[44] A full list of publicly available predictors can be found in the Supporting Information.

Prediction

Chembench possesses several prediction modalities for single compounds, batches of multiple compounds, and virtual chemical libraries. For instance, a single compound can be sketched using JSME[31] or its SMILES uploaded. Additionally, Chembench has integrated several publicly available chemical libraries, such as the DrugBank[45] and the ZINC lead-like library,[46] that can be used for virtual screening. A user can also upload a specific library of interest or a batch of compounds (See Datasets). Then, the specific activity or spectrum of activities of the compound(s) or the virtual library can be predicted by selecting the desired predictor(s). The user has the ability to predict one or more endpoints for one or more compounds. The applicability domain threshold,[19] if selected, can be manually set. Non-registered users, using publicly available predictors, have the ability to predict single compounds and publicly available chemical libraries. In order to encourage registration, non-registered users cannot perform batch predictions of multiple compounds. It should be noted that models built with user-uploaded, proprietary descriptors cannot be used in the “Predict a Single Compound” component of Chembench, as these descriptors cannot be automatically generated. Moreover, only random forest (RF) models are compatible with the “Predict a Single Compound” component in order to accelerate the speed of the prediction. For the prediction of a single compound using kNN or SVM models, the compound should be uploaded as a dataset, and the “Predict a Dataset” function should be used.

CONCLUSIONS

Chembench implements the best practices of QSAR modeling and validation,[19] and all publicly available models are fully compliant with OECD principles for the validation of (Q)SAR models.[47] Chembench provides a variety of cheminformatics and data science-related services including data curation, standardization, and visualization; descriptor generation; development, rigorous external validation, and interpretation of QSAR models; prediction of a single property or activity profile for compound(s) of interest or prepared virtual screening libraries; targeted design of novel compounds with desired activity profile; etc. While Chembench in its current form is useful for both expert and beginner modellers, it is constantly being updated to meet the needs of the scientific community. Updates in progress are fragment-based structural interpretation of QSAR models, implementation of SiRMS[48] descriptors, and additional datasets for download. Chembench was one of the first cheminformatics Web portals and, since its creation in 2008, continues to position itself as the gold-standard of publicly-accessible, integrated cheminformatics portals. Chembench, along with similar cheminformatics portals such as OCHEM,[11] promotes the principles of both open science and data and model sharing[49] in the era of Big Data.[1] The continuing

need for Chembench and the high quality of services it provides are supported by more than 1 million visits and more 550 registered and ~5K unregistered users from a total of 98 countries as of today. Chembench is freely accessible at https://chembench.mml.unc.edu/.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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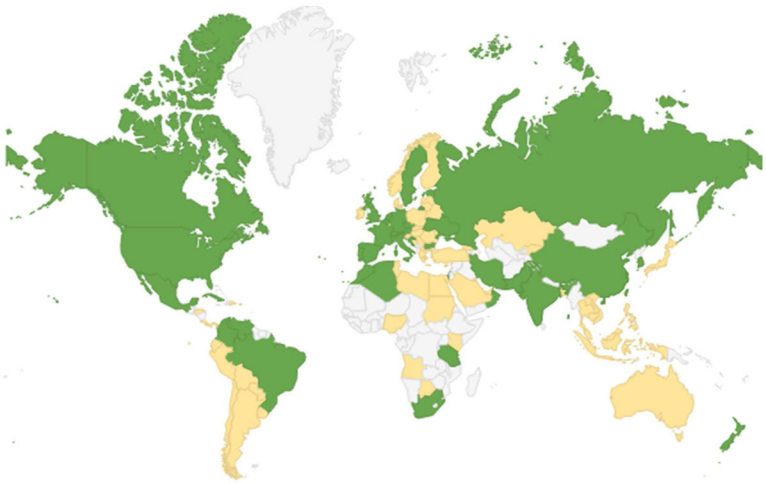

Figure 1.
World map of Chembench users. Countries with registered and guest users are shown in green and yellow, respectively.