Qptuna: an automated QSAR modelling platform for molecular property prediction in drug design

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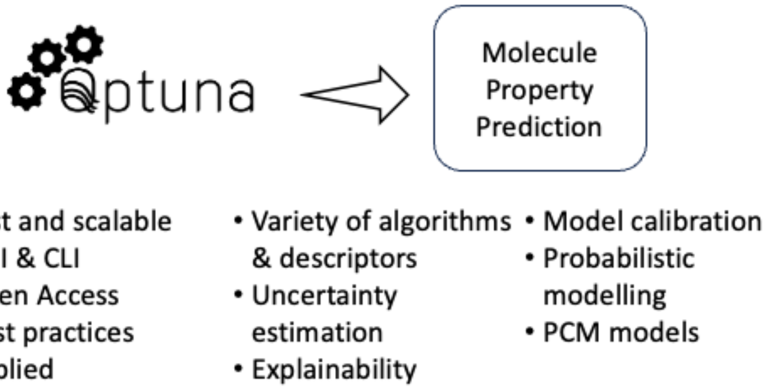

- Fast and scalable
- GUI & CLI
- Open Access
- Best practices applied

- Variety of algorithms & descriptors
- Uncertainty estimation
- Explainability

- Model calibration
- Probabilistic modelling
- PCM models

Abstract

Machine-learning (ML) and Deep-Learning (DL) approaches to predict the molecular properties of small molecules are increasingly deployed within the design-make-test-analyse (DMTA) drug design cycle to predict molecular properties of interest. Despite this uptake, there are only a few automated packages to aid their development and deployment that also support uncertainty estimation, model explainability and other key aspects of model usage. This represents a key unmet need within the field and the large number of molecular representations and algorithms (and associated parameters) means it is non-trivial to robustly optimise, evaluate, reproduce, and deploy models. Here we present Qptuna, a molecule property prediction modelling pipeline, written in Python and utilising the Optuna, Scikit-learn, RDKit and ChemProp packages, which enables the efficient and automated comparison between molecular representations and machine learning models. The platform was developed considering the increasingly important aspect of model uncertainty quantification and explainability by design. We provide details for our framework and provide illustrative examples to demonstrate the capability of the software when applied to simple molecular property, reaction/reactivity prediction and DNA encoded library enrichment analyses. We hope that the release of Qptuna will further spur innovation in automatic ML modelling and provide a platform for education of best practises in molecular property modelling. The code to the Qptuna framework is made freely available via GitHub.

Introduction

A typical drug design project consists of a design-make-test-analyse (DMTA) cycle aiming to optimise small molecules for activity against a desired protein target whilst at the same time maintaining a desirable absorption, distribution, excretion and toxicity (ADMET) profile, thereby improving chances for *in vivo* efficacy[1]. Since measuring such properties requires substance samples and is resource- and time-consuming, cycle times can be slow and compound prioritisation might be cumbersome[2, 3].

To address this, Machine learning (ML) and artificial intelligence (AI) approaches have been increasingly integrated into medicinal chemistry projects[4-6]. Here their routine use towards Quantitative Structure Activity Relationship prediction (QSAR) accelerates DMTA cycle times[7-9]. As shown in **Figure 1**, their application is designed to direct resources towards prospective screening experiments, and they have been used to screen extensive compound databases and to optimise efficacy[10-12]. *In silico* safety assessment can also minimize ethically concerned activities, such as animal or human experimentation[13, 14]. QSAR has also been combined with other fields such as molecular *de novo* design, where molecule property prediction is used to direct the objective function (capturing [un]-desired properties) of generative algorithms toward desirable chemical space[15-17], or coupled with active learning approaches to optimise free energy calculations[18]. Other applications include the prediction of chemical reaction yields, where reactants and yield are provided as training data[19].

The development of novel algorithms capable of rationalising complex relationships between chemical and biological information[20, 21], exponentially growing chemical and biological space added to molecule databases[22], falling cost of computational resources [23, 24], and MLOps systems for accessing production-level models[25] have spearheaded the development and use of QSAR models in practice[26-28]. Despite this, the assortment of workflows, algorithmic methods, and parameters means training and updating models is non-trivial and finding the relatively optimal modelling setup is a time-consuming task for data scientists. Consequently, there is a need to compare different models for specific properties reproducibly, efficiently, and robustly across different molecular representations and algorithms.

A platform offering this functionality should maintain and update QSAR models throughout their “life cycle” and needs to involve the standard steps critical for reliable model building in a temporal setting. The automatic evaluation of the ML stack (including the sequential steps of data ingestion, pre-processing and model training) is a distinct area identified as AutoML[29]. The application of AutoML toward the field of molecular property prediction has only partially addressed despite the early attempts to attract attention towards this unmet need[30]. There remains a lack of robust, modular and scalable platforms for QSAR modelling, though some automated tools have been presented (see **Table 1** for an overview). SL Dixon, J Duan, E Smith, CD Von Bargen, W Sherman and MP Repasky [31] developed a machine-learning application (AutoQSAR) for automated QSAR modelling. eTOXlab [32] and offers an alternative automated QSAR framework, but is no longer maintained and requires advanced Python programming skills. An online alternative OCHEM[33] is available, however the cloud-based infrastructure renders the software unsuitable for private or sensitive data. R Cox, DV Green, CN Luscombe, N Malcolm and SD Pickett [30] designed a Pipeline Pilot web application (QSAR Workbench) although this is restricted to Pipeline Pilot users. Automated Predictive Modeling[34] is also available but demands expert technical skills and significant resources for model development and maintenance. More recently, TranScreen provides a transfer-learning setup based on graph convolutional neural networks and focuses on small imbalanced data sets, though algorithmic choice is restricted to only deep-learning methods[35]. S Kausar and AO Falcao [36] also proposed an automated framework for QSAR model building, but this is based on KNIME and requires expert knowledge for their implementation with a complicated interface. AMPL[37] was also developed as a modelling pipeline as an open-source software suite, allowing users to build models for a wide array of molecular properties. It extends the open source DeepChem library, supports an array of ML and molecular featurization tools and offers uncertainty quantification. Despite this, only four sets of algorithms are available, a restricted number of four descriptors are available (the MOE descriptors also require a license), and no GUI is provided. PREdictive modeling FramEwoRk (PREFER) was recently proposed by J Lanini, G Santarossa, F Sirockin, R Lewis, N Fechner, H Misztela, S Lewis, K Maziarz, M Stanley, M Segler, et al. [38]. In this package, popular libraries are used for hyperparameter optimization, with the authors stating the most important factor being the ability to customise the framework. AutoSklearn is supported by an active community, but the package relies on notebooks and requires a detailed four step installation process. Uni-QSAR was recently published[39], though this software must combine 1D tokens, 2D topology graphs, and 3D conformers to generate learnt representations and does not offer the same level of functionality or ease of use compared to other packages. Other approaches towards automated QSAR procedures are also available but are tailored to specific settings such as blood-brain barrier penetration and aqueous solubility[40], Leishmania High-Throughput Screening Data[41] or Gaussian Processes[42], which limits applicability. Molflux[43] was also recently released as a foundational package for molecular predictive modelling, though this platform does not optimise for algorithm hyperparameters. A variety of data mining and automation tools could offer the ability to develop custom pipelines, such as Pipeline Pilot[44], KoNstanz Information MinEr (KNIME)[45], Orange[46], Taverna[47], Kepler[48] and the Loni Pipeline[49]. However, workflow managers require specific competency to design or run pre-existing configurations, and developing custom workflows requires time and effort. Ideally a platform should provide both a CLI and GUI, without the need for proprietary software or licenses, expert knowledge or complicated installation steps. Such a platform be developed with popular maintainable programming language with ability to use the state-of-the-art (well-maintained) open access packages for additional functionality. Uncertainty estimation and model explainability should also be considered during the design and development phase, given the increased focus placed onto these aspects of modelling[2, 4, 50], and since this will facilitate decision making when models are used in production.

In this vein, we have developed Qptuna; a platform which employs, to the best of our knowledge, all best practices from the field to deploy good QSAR models into production. The Qptuna platform deals with all user data inputs, molecule standardardisation, deduplication, splitting, hyperparameter optimization and model deployment in an easy to use, modular way. In this work, we will outline the platform structure, and provide easy to follow examples for how to use the model building tool. In the next section, we outline the overall workflow, it's implementation and the additional functions offered for QSAR modelling. The platform is released as open-source under a permissive license for educational purposes as well as facilitate further innovation in automatic QSAR modelling. It is intended to be a living project with continuous updates and new features. Here we consider the application of the tool toward three different types of applications reflecting the breath of modelling tasks a modern ML platform need to handle. The examples are aqueous solubility prediction, probabilistic reactivity prediction and calibrated DEL enrichment classification problems representing diverse examples which reflects the emerging landscape of popular QSAR tasks and demonstrates the versatility of the platform.

Implementation

An overview of the standardised protocol toward automated QSAR modelling is shown in **Figure 2**. The workflow is structured around three steps:

1. *(Bayesian) Hyperparameter Optimization:* Train many models with different parameters using Optuna. Only the training dataset is used here. Training is usually done with cross-validation.
2. *Build (Training):* Pick the best model from Optimization, and optionally evaluate its performance on the test dataset.
3. *"Producition build (Re-training):* Re-train the best-performing model on the merged training and test datasets. This step has a drawback that there is no data left to evaluate the resulting model, but it has a large benefit that this final model is trained on all available data.

As shown in the figure, the Qptuna workflow starts with data preparation which includes import of molecular structures and corresponding biological activity data for a specified molecule property prediction task. Several sanity checks are performed on the input data, including a check for valid response values and input molecules. Finally, an optimisation protocol is initiated, where internal validation can then be used to develop a QSAR model by following a rigorous internal and external validation process. Here, an initial split of data is performed to partition training instances into internal and external validation, to avoid data leakage. This is a critical step, where many different splitting strategies are available to afford a more realistic evaluation of model performance in practice. Hyper-parameter optimisation is performed using the Optuna package; a framework capable of performing Bayesian hyperparameter optimisation for a given set of descriptors and ML algorithms. Finally, a selected model can be created by initiating a "production build", which can comprise both internal and external training instances (model trained on all available data with the caveat of no performance assessment).

Hence, our open-source automated workflow embeds all the tools and steps necessary to perform all steps of the QSAR life cycle by following best practicing methods. The workflow is easily applied to build predictive QSAR models without having expertise in ML or programming. We illustrate how the model building workflow Qptuna integrates Bayesian hyperparameter optimisation and deploy this to example QSAR problems from a solubility prediction, a reactivity prediction problem and toward DNA encoded library enrichment classification, to illustrate capabilities.

Data Preparation

One of the most important steps in building QSAR models is the appropriate pre-processing of the data prior training[51-53]. This section describes how the steps implemented in Qptuna to ensure best practice in this regard.

Qptuna expects inputs to be in the form of a CSV or SDF file. The automated integration pipeline provides an opportunity for automation since queries can be polled for continuous updates from project teams. The proposed workflow is hence intended to cater for a variety of approaches.

Input data is retrieved and processed by retaining only the user's requested biological activity type records, and other relevant information related to chemical structures and assays (for example co-variates corresponding to time/date/protein) or side-information tasks for use in multi-task learning. Since the objective of QSAR is to quantify a ligand–molecular property values any response column value may be utilised and related to the algorithm for training. Qptuna validation also includes the identification of missing data and duplicates and dealing with several forms of the same molecule (including salt groups).

Next, deduplication of distinct compound replicates (based on the canonicalized SMILES of user inputs) is performed, where the current options are:

- Keep First and Keep Last: keep the first or last occurrence

- Keep Random (with a seed): keep a random observation
- Keep Minimum and Keep Maximum: keep min or max
- Keep Average: take the average
- Keep Median (default in Qptuna): take the median
- Keep All: all observations are retained

The default deduplication method in Qptuna is to Keep Median, which is recommended best practice due the ability to utilise all experimental data into one value (account for experimental variability across biological replicates), whilst being robust to outliers.

Response value transformations

Qptuna can be used to transform input labels so that log-scaled or irregularly distributed data can be transformed to a normal distribution as required for many Machine Learning inputs. The scaling or transformation of user response columns to normalise highly varying values in raw data is often performed for proper training of a predictive model, where often data is transformed with a logarithmic function. This transformation is deactivated and skipped by default, assuming that data is already normalised.

Data partitioning

To facilitate external assessment of the predictive performance of the developed QSAR model, user data is divided into the internal training set and external validation set through a variety of different approaches. By default, the platform applies a stratified (real-valued) shuffle split, where for classification the data is split ensuring the same distribution of classes. For regression, data is split according to a binning scheme of response values, ensuring that the (binned) distribution of regression values for modelling is kept consistent between test and training sets. This split is robust for both classification and regression settings and should provide a good approximation for most cases. A random split, predefined split and scaffold-based split (to emulate when models may be used for scaffold hopping) are also available. Hence there are a wide array of splitting strategies for most user applications. Next, the internal training set is further split using a K-fold cross validation process (either stratified or random) for internal hyperparameter optimisation, evaluation, and selection. The external split is never used for any feature selection or model training procedure, to avoid leakage. The full list of splitting strategies in Qptuna are as follows:

- Random
- Stratified (real-value) shuffle
- Temporal
- Scaffold-based
- Predefined (from a user column)

Descriptor calculation

The proposed workflow automatically calculates several molecular descriptors and structural characteristics for the retrieved molecules for each Optuna trial evaluated. Descriptors are also cached to reduce trial runtime. Users may submit own molecular descriptors using the precomputed descriptors option. Our workflow uses RDKit for most descriptor calculations, but the full complement includes:

- RDkit circular fingerprints (Morgan-like)
- RDkit circular fingerprints (Morgan-like) with counts
- RDKit physchem descriptors
- Avalon[54]
- MACCS[55]
- Jazzy[56]
- Composite descriptors (concatenate any combination of descriptors together)

- Predefined descriptors
- Scaled descriptors (ensures custom descriptors are scaled)

Model Selection

A variety of different algorithms for classification or regression are provided. We apply many popular ML approaches, such as neural networks (ChemProp[57]), support vector machines (SVMs), random forests (RF). We also provide an implementation of the Probabilistic Random Forest (PRF)[58] for use with the probabilistic data transform, which has been shown to improve uncertain bioactivity predictions[59]. Other algorithms are easily integrated given the modular nature of Qptuna.

Each Qptuna trial is evaluated via the primary performance metric (this is ROC-AUC or negated Mean Squared Error (MSE) by default) which can be altered by the user. Qptuna offers a many performance metrics offered by Sciki-learn in addition to BEDROC (implemented via RDKit)[60]. All are calculated and reported for review by the user, although one primary metric is normally used as an objective function in Optuna trials. The user may also (optionally) specify a multi-parameter optimisation for minimisation of the standard deviation of performance scores across the folds, thereby suggesting descriptor and algorithm pairs that are more generalisable across splits (and therefore in production). External validation is finally performed for the realised model on the external test set.

Functions offered by Qptuna compared to other platforms

Probabilistic modelling transformation

Since molecule properties derived from experiments have reproducibility limits due to experimental errors, any model based on this data have such unavoidable error influencing performance which should ideally be factored into modelling and output predictions. Consequently, a probabilistic transform of the activity scale is available in Qptuna, based on the approach performed here[59].

With this setting turned on, Qptuna treats compound response labels as probability distribution functions (rather than deterministic values) on a per-threshold basis based on the cumulative distribution function (CDF) of a normal distribution. Hence the activity values become represented in a framework in-between the classification and regression architecture, with philosophical differences from either approach. Compared to classification, this approach enables better representation of factors increasing/decreasing inactivity. Conversely, one can utilize all data (even delimited/operand/censored data far from a cut-off) at the same time as considering the granularity around the cut-off, compared to a conventional regression framework. Thereby, this Qptuna setting combines characteristics from both classification and regression settings.

Probability calibration

Probability calibration methods are also provided via the Calibrated Classifier with Cross Validation option (a procedure based on the inductive cross-validated approach available in Scikit-learn). The available functions are Sigmoid, Isotonic regression and VennABERS[61], and a review of those calibration methods for QSAR has been performed here[62]. Calibration should make predicted probabilities more accurate and thus more useful for making allocation decisions under uncertainty.

Uncertainty estimation

Qptuna also offers uncertainty via three different methods.

1. VennABERS calibration based on the “Uses for the Multipoint Probabilities from the VA Predictors” from [62]

2. Ensemble uncertainty (ChemProp models trained with random initialisations).
3. Dropout uncertainty at inference time (ChemProp models)
4. Model Agnostic Prediction Interval Estimator (MAPIE)[63] (uncertainty for regression)

Model Explainability

Model explainability is incorporated into Qptuna using two different approaches that focues on the input descriptors for molecules. Each depend on the algorithm chosen:

1. SHapley Additive exPlanations (SHAP)[64] (available for all models)
2. ChemProp interpret (available for ChemProp models and based on the interpret function in the original package)

Results and Discussion

This section demonstrates three diverse and relevant use cases for Qptuna:

1.) ESOL aqueous solubility regression[65]

2.) Probabilistic reactivity prediction (evaluated via regression metrics)[66]

3.) DNA encoded library (DEL) enrichment classification[67]

Each example use case is selected to exemplify platform capabilities and reflects the latest prediction task trends in the QSAR. The first solubility represents a typical regression task based on an assay readout important in early drug discovery. The second demonstrates how Qptuna can be deployed to different fields of cheminformatics, such as reactivity prediction, whilst the final third task highlights the scalability of Qptuna when applied to larger amounts of noisy data such as a classification DEL dataset.

Solubility modelling

As a first test case, we used Qptuna to generate models for a water solubility dataset and an overview of external performance is provided in **Table 2**. Our results show that there is a marked improvement during scaffold-based testing when using Qptuna over other approaches; with an improvement in Pearson correlation from 0.264 to 0.636 (margin of 0.372) between the simple RF & ECFP (No optimisation) baseline compared to a full Qptuna run (150 start-up trials, proper 300 trials) optimising for low standard deviation across hyper-parameter folds. Optimising for folds improved performance by a Pearson correlation margin of 0.130, which highlights that this approach can lead to better selection of hyperparameter in the analysis presented here. To our knowledge minimising for standard deviation across folds in an automated multi-parameter optimisation in this manner is not available in alternative open-source AutoML platforms. Results for the RF grid search also highlight the clear benefit for performing proper optimisation within Qptuna, since the grid optimised RF achieved a Pearson of only 0.297.

The stratified split also showed benefit in performing optimisation over a baseline, with improvements from 0.725 to 0.907 for the RF and ECFP model and obtained Qptuna models, respectively. Qptuna identified the same optimal (start-up) trial for this splitting evaluation approach, so there is no benefit to activating the multi-parameter optimisation approach for standard deviation for this analysis. The RF grid search present only modest performance gains over the baseline model, with a Pearson 0.763, further highlighting the importance of fully optimising both algorithm and descriptor spaces.

Taken together, these results highlight the benefit in performing hyper-parameter optimisation using the Qptuna package for a solubility dataset and present evidence for usefulness of the unique functionality offered by our package. Although some additional latency is introduced by the time taken for optimisation, we consider that this is mitigated by substantial performance gains as observed for the ESOL dataset.

Reactivity modelling

Qptuna was applied to a Buchwald-Hartwig reactivity prediction dataset[66] in order to demonstrate its usefulness when applied to this molecule property prediction endpoint. Probabilistic thresholding of the regression scale was implemented to outline the functionality offered within Qptuna, which to our knowledge is not offered by alternative software. In this procedure, reactivity response values were discretised in Qptuna using an activity threshold boundary of 5 and provided a standard deviation of 2, thereby accounting for experimental variability of reactivity assays within the modelling procedure and representing the reactivity prediction task in a probabilistic framework. In this setting, a yield of 5 is assigned a likelihood score of 50%, whereas scores of 2.5 or 7.5 would be assigned scores of 10.6% and 89.4%, respectively. Yields below or above the standard deviation range would also obtain the minimum and maximum values of 0% and 100%, respectively, thereby allowing the use of even delimited (qualified) values of “<” or “>”.

Results are shown in **Table 3** and demonstrate that Qptuna with probabilistic modelling combined with PRF performs with the most relatively optimal performance of any of the approaches evaluated; with an improvement in Pearson correlation from 0.880 and 0.967 (margin of 0.087) between the simple RF & ECFP (No optimisation or probabilistic modelling) baselines when compared to a full Qptuna run (15 start-up trials, proper 15 trials). This finding highlights the clear benefits for representing the reactivity scale in this manner and accounting for uncertainty near the decision boundary. To our knowledge, this approach is a unique option offered by Qptuna compared to other publicly available QSAR building platforms currently available.

DEL modelling

In this section we chose to evaluate Qptuna performance for a DEL enrichment dataset from KS Lim, AG Reidenbach, BK Hua, JW Mason, CJ Gerry, PA Clemons and CW Coley [67], since task type represents a more recently popularised prediction problem, comprising a highly imbalanced classification set with large numbers of enrichment response values. This provides an opportunity to not only benchmark the software on a larger, more noisy data set, but also to demonstrate the calibration methods available in Qptuna, to obtain better probability estimates representing the ground truth. This is an important aspect of model behaviour to consider since the outputs from poorly calibrated models can be misleading and not always actionable.

Results from our DEL classification analysis is presented in **Table 4**. The findings highlight the clear benefit for using Qptuna with the VennABERS calibration approach, since the VennABERS scaling has the most relatively optimal ROC AUC whilst also maintaining the highest negated Brier score loss (which indicates superior calibration performance), with 0.906 and -0.003, respectively. To our knowledge, this approach is a unique option offered by Qptuna compared to other publicly available QSAR building platforms currently available.

We next analysed how well calibrated the VennABERS (optimal Qptuna run) is compared to a (uncalibrated) Qptuna model obtained without the VennABERS functionality activated, for a stratified subset of 3,800 test set compounds. Results provided in **Figure 3** illustrate a reliability plot, which is a common method to evaluate model calibration by relating the ground truth likelihood of compounds obtaining a positive prediction as a function of different discretised probability bins. Our findings clearly demonstrate the superior calibration performance of the model obtained by the VennABERS predictor over the uncalibrated baseline, where a higher proportion of compounds are assigned estimates closer to the ideal as outlined by markers near to the diagonal (ideal) line. Again, this represents a key benefit for Qptuna over alternative software (when considering model calibration) which do not offer such techniques.

Discussion & Conclusion

In this work, we present a robust, modular, and extendable platform designed to be used as a QSAR modelling pipeline to obtain robust predictive models for molecule property prediction tasks. The pipeline can be utilized for fully automated QSAR modelling to assist all users including those not an expert in the ML field or those which have limited knowledge in data preparation and best practices for QSAR.

Since the training of a most relatively optimal model is reliant of many critical and time-consuming steps (including data collection and processing, data representation via descriptors, ML model fitting, validation, and hyper-optimisation), this QSAR modelling workflow completely automates these laborious and iterative processes. The following are the main advantages of Qptuna framework:

- Automatically deployable in the three-step framework, to generate production ready models
- Data ingestion (selecting only the property of interest) offering classification and regression
- Deduplication, removing invalid/missing data
- Descriptors calculation across a wide range of state-of-the-art options
- Data normalization, standardisation and transformation (including probabilistic transformation for probabilistic modelling)
- Best practice validation procedure using internal and external splits are followed
- State-of-the-art interpretation or explainability methods available
- Model calibration using inductive methods
- Uncertainty quantification options depending on the algorithm selected, which will aid the use of active learning in the DMTA cycle
- Support for model architectures utilising auxiliary domain information (e.g. Proteochemometric [PCM] modelling, dose, timepoint, etc.)

Due to the modular nature of the platform, the automated QSAR modelling framework is transparent in comparison to the more black-box solutions available from other QSAR modelling platforms. This extensible and highly customisable package will aid the development of robust predictive models and provide an ideal framework for a robust predictive model life cycle. Moreover, it ensures that the same protocol is used for updating models with new molecules as they become available, thereby improving reproducibility. By integrating the latest explainability and uncertainty quantification, we intend for the models generated by Qptuna to have more impactful and actionable predictions when used in production. Qptuna is made open source as an automated QSAR modelling framework to spur further innovation in the field. We hope to guarantee that the most important aspects of QSAR modelling are addressed and consistently applied when using Qptuna including for educational purposes.

Acknowledgements

None

Figures

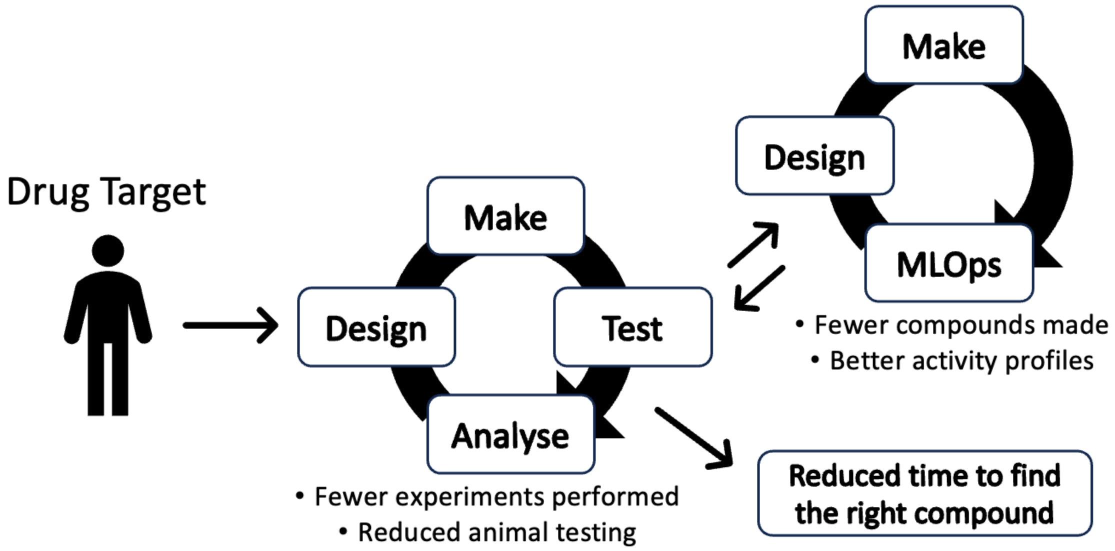
Drug Target
Make
Design
Test
Analyse
• Fewer experiments performed
• Reduced animal testing
Make
Design
MLOps
• Fewer compounds made
• Better activity profiles
Reduced time to find the right compound

Figure 1. Importance of integrating well-trained models into the drug design process. A well-established infrastructure of model hosting (MLOps) and re-training of models is required for effective model deployment. The principal way to impact the cycle via modelling approaches is to make the best up-to-date models available to all scientists at the point of Design.

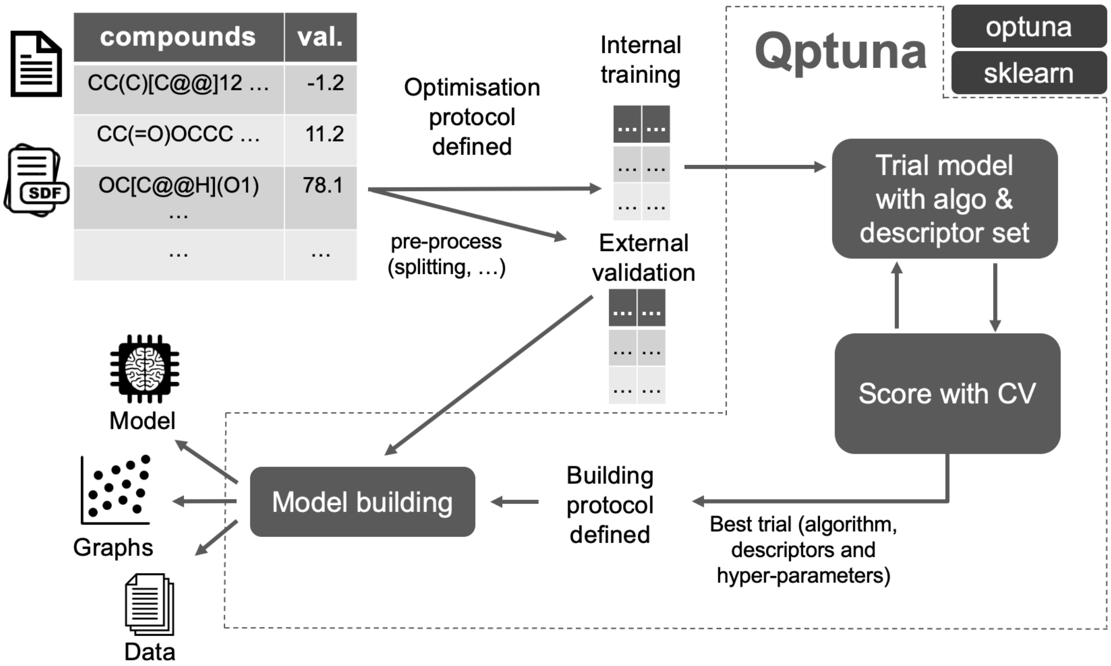
compounds
val.
CC(C)[C@@]12 …
-1.2
CC(=O)OCCC …
11.2
OC[C@@H](O1) …
78.1
…
…
SDF
Optimisation protocol defined
pre-process (splitting, …)
Internal training
External validation
Qptuna
optuna
sklearn
Trial model with algo & descriptor set
Score with CV
Best trial (algorithm, descriptors and hyper-parameters)
Building protocol defined
Model building
Model
Graphs
Data

Figure 2. Overview of the standardised Qptuna model building platform. Data quality validation, curation and descriptor calculation are considered by design in the Qptuna framework. A three-step optimisation, Cross Validation (CV) scoring and "production" build workflow is used. Recommended best practices for CV and rebuilding is followed.

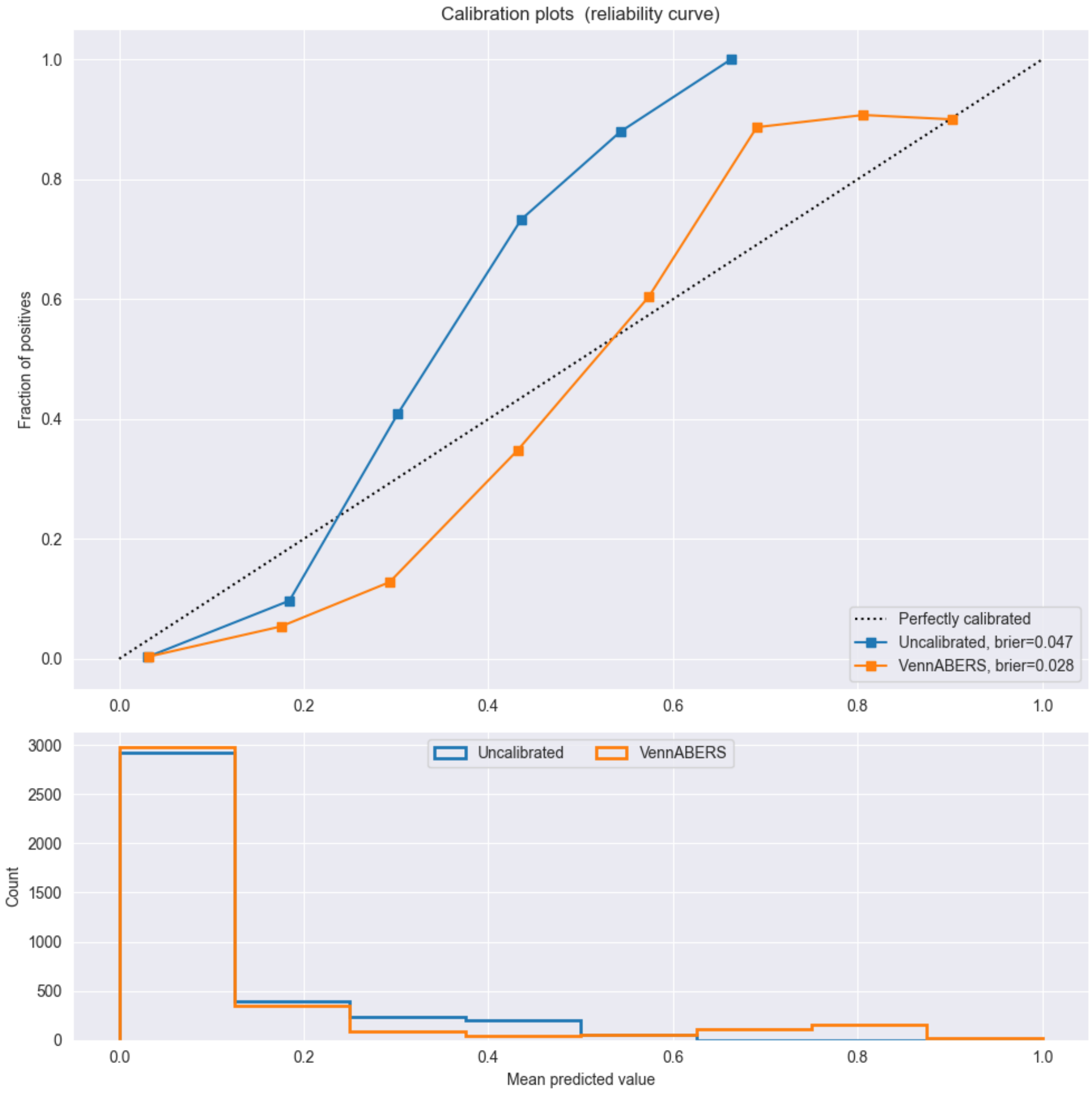

Figure 3. Most relatively best calibrated model are VennABERS scaled Qptuna models. A calibrated model using VennABERS generated predictions is closer to the ideal perfectly calibrated (dashed) diagonal line and with a superior (lower) Brier score loss of 0.028 versus 0.047 for an uncalibrated counterpart. On the bottom trellis, the change in the distribution of predictions is depicted via the histogram of mean predicted value versus discretised probability bins.

Tables

Table 1. Qptuna comparison with alternative open-source software for molecule property prediction.

Software	Dataset modellability/ pre-modelling analysis	Custom Splitting techniques	Number of descriptors	Composite descriptors	Custom descriptors?	Custom train/test splits?	Shallow models	Neural network-based algorithms	Inductive model calibration	Uncertainty estimation	Explainability	Multi-parameter optimisation?	Probabilistic transform
Qptuna	No	Yes	8	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
AMPL	No	No	4	No	No	No	Yes	Yes	No	Yes	No	No	No
PREFER	No	No	4	No	No	No	Yes	Yes	No	No	No	No	No
Uni-QSAR	No	No	5+	No	No	No	Yes	No	No	No	No	No	No

Table 2. ESOL prediction performance demonstrates the value of optimising parameters. Hyperparameter optimisation obtains better models regardless of split method considering all six performance metrics evaluated. Negated Mean Squared Error was used as the objective function for optimisation.

Modelling Approach	Split Methods		Time			External Performance					
	External	Internal (hyper-parameter)	Optimisation	Build	Total	Explained Variance	Max Error	Negated Mean Absolute Error	Negated Mean Squared Error*	Negated Median Absolute Error	Pearson correlation
RF & ECFP (No optimisation)	Scaffold	-	-	00:00:29	**00:00:29**	0.347	-4.13	-1.1	-2.274	-0.693	0.264
RF grid optimisation & ECFP		Stratified	**00:28:06**	**00:00:28**	00:28:34	0.362	-3.907	-1.095	-2.174	-0.764	0.297
Qptuna		Stratified	09:28:26	00:08:30	09:36:56	0.533	-3.601	-0.867	-1.527	-0.709	0.506
Qptuna Min Std.Dev		Stratified	02:44:56	00:01:11	02:46:07	**0.675**	**-3.496**	**-0.698**	**-1.124**	**-0.553**	**0.636**
RF & ECFP (No optimisation)	Stratified	-	-	00:00:27	**00:00:27**	0.727	-3.972	-0.819	-1.172	-0.631	0.725
RF & ECFP (grid optimisation)		Random	**00:18:25**	**00:00:22**	00:18:47	0.766	-3.964	-0.745	-1.009	-0.585	0.763
Qptuna		Random	04:14:41	00:01:29	04:16:10	**0.907**	**-3.587**	**-0.448**	**-0.398**	**-0.326**	**0.907**
Qptuna Min Std.Dev		Random	02:47:08	00:01:16	02:48:24	**0.907**	**-3.587**	**-0.448**	**-0.398**	**-0.326**	**0.907**

Table 3. Probabilistic modelling for reactivity prediction best considers experimental variability. Qptuna with probabilistic modelling provides the most optimal setup for modelling the probabilistic likelihood of a successful reaction (considering experimental variability), since the obtained performance is highest across all external performance across evaluated here.

Modelling Approach	Split Methods		Time			External Performance					
	External	Internal (hyper-parameter)	Optimisation	Build	Total	Explained Variance	Max Error	Negated Mean Absolute Error	Negated Mean Squared Error*	Negated Median Absolute Error	Pearson correlation
RF & ECFP (No optimisation & no probabilistic modelling)	Stratified	-	-	**00:01:40**	**00:01:40**	0.880	-0.710	-0.078	-0.017	-0.040	0.880
RF grid search & ECFP (No probabilistic modelling)		Random	**00:22:49**	00:01:59	00:24:48	0.905	-0.688	-0.064	-0.013	-0.025	0.905
Qptuna (No probabilistic modelling)		Random	01:56:09	00:05:27	02:01:36	0.953	-0.565	-0.042	-0.007	-0.010	0.953
Qptuna (Probabilistic modelling)		Random	01:25:41	00:26:34	01:52:15	**0.967**	**-0.480**	**-0.035**	**-0.005**	**-0.004**	**0.967**

Table 4. VennABERS calibration (scaling) for optimally calibrated DEL enrichment models. Qptuna with VennABERS scaling provides the most optimal setup during modelling, where the performance obtained shows the relatively best balance between ROC AUC (objective performance) whilst being well calibrated (indicated via negated Brier score loss, [an indicator for calibration performance]).

Modelling Approach	Split Methods		Time			External Performance							
	External	Internal (hyper-parameter)	Optimisation	Build	Total	AUC PR Calibrated	Average precision (AUC PR)	BEDROC	F1 (macro)	Negated brier score loss	Precision macro	Recall macro	ROC AUC
RF & ECFP (No optimisation or scaling	Stratified	Stratified	-	02:22:48	**02:22:48**	0.367	0.021	0.341	0.519	-0.08	0.514	0.647	0.801
RF & ECFP (No optimisation & VennABERS scaling)			**-**	02:31:33	02:31:33	0.331	0.017	0.295	0.499	**-0.003**	0.498	0.5	0.802
RF grid search & ECFP (No scaling)			1-03:10:26	02:24:55	1-05:35:21	**0.508**	0.051	0.424	0.499	-0.08	0.498	0.5	**0.906**
Qptuna (No scaling)			**1-02:22:20**	**00:11:19**	1-02:33:39	0.486	**0.226**	**0.467**	**0.553**	-0.122	**0.553**	**0.793**	0.874
Qptuna (VennABERS scaling)			3-21:56:44	02:24:55	1-00:21:39	0.499	0.033	0.437	0.499	**-0.003**	0.498	0.5	**0.906**

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