ADMET Predictor® release 9.5

By Simulations Plus, Inc. 4/12/2019

Dear ADMET Predictor User,

This new release of ADMET Predictor includes significant enhancements throughout the program, including to the ADMET Modeler™ and MedChem Designer™ modules. This document provides a brief overview of those changes. For detailed descriptions of all changes, please consult the relevant sections of the ADMET Predictor user manual.

Important Notes

A newer version of the Simulations Plus vendor daemon (simplus.exe) must be installed in order for ADMET Predictor 9.5 to communicate with the Flexera license server. The new daemon is included as part of the ADMET Predictor installation package, but it must be installed separately on the license server. Please contact your license administrator about performing this task before using ADMET Predictor 9.5 for the first time.

If you have previously installed a beta version of ADMET Predictor 9.5, you should uninstall it prior to installing this final release version. After following the normal Windows protocol for software uninstallation, you should completely remove the three installation folders. In most cases these folders are:

- C:\Program Files\Simulations Plus, Inc\ADMET_Predictor9.5
- C:\ProgramData\Simulations Plus, Inc\ADMET_Predictor9.5
- C:\Users\<user_name>\AppData\Local\Simulations Plus, Inc\ADMET_Predictor9.5
  where <user_name> is your specific username

Structure Sensitivity Analysis

The Structure Sensitivity Analysis (SSA) window is an interactive display that shows how the individual atoms of a chemical structure contribute to a predicted property. It therefore allows you to see which regions of a compound have the most influence on that property prediction. For example, you can see which fragments in your lead compound contribute the most to a predicted toxicity. This feature complements the existing Descriptor Sensitivity Analysis (DSA) feature, but provides localized atomic sensitivity information in a way that is chemically intuitive. There are currently 21 models that can be displayed in the window, and users can build their own models. The SSA window can be launched from both ADMET Predictor and MedChem Designer.

Regression Uncertainty

Many regression model predictions are now accompanied by uncertainty estimates that indicate the expected standard deviation of predictive error for each prediction. These estimates, provided both for built-in ADMET Predictor models and for user models created using ADMET Modeler, complement the confidence estimates that are already provided for classification models.

ADMET Modeler

Performance plots for regression models now have the option to display some or all error bars corresponding to the uncertainty estimates of the predictions. The Model Editor window provides new export and import options to facilitate the sharing of user models within your organization. The Model Performance Grid has a new metric, RMSU, which displays the root mean squared uncertainty for regression models. The Modeler and Performance Plot windows may now be resized to smaller dimensions.

New plot types have been added to facilitate the analysis of regression uncertainty models, paralleling Confidence Analysis plots for classification confidence models. These include cumulative distribution plots of the Squared Error and Ensemble Standard Deviation, Quantile-Quantile (Q-Q) plots of the same quantities, and Q-Q plots of the Normalized Error (observed model error divided by the uncertainty estimate).

Other significant changes include the following updates to the performance plot windows:

- The RMSU metric is also shown in the statistics at the bottom of the window.
- The window layout has been rearranged to provide better ergonomics upon resizing.

MedChem Designer

MedChem Designer now includes several prediction and display features from ADMET Predictor. These include the pKa Microstates and Atomic Properties windows, logD and solubility versus pH curves, and HPTK features such as %Fa/%Fb prediction and Cp-time curves.

Other significant changes include the following:

- The user interface has been modernized to be similar in look and feel to ADMET Predictor.
- Several common functional groups have been added as templates to facilitate structure drawing.

- Added options to select and move structures regardless of which tool is currently selected (i.e., the lasso tool is no longer required).
- Double clicking a selected structure now launches the dialog to modify the compound name.

ADMET Property Models

ADMET Predictor includes three new models for pharmacologically relevant transporters: breast cancer resistance protein (BCRP; substrate/nonsubstrate), organic cation transporter 2 (OCT2; inhibition) and bile salt export pump (BSEP; inhibition). There is a new Ames mutagenicity model built using data obtained from the Japanese National Institute of Health Sciences. Finally, there is an aldehyde oxidase (AOX) substrate classification model, and a model to predict likely atomic sites of AOX metabolism.

The following models have been improved through the addition of new data.

- Blood-brain barrier penetration (BBB_Filter)
- Human blood-to-plasma ratio (RBP)
- Rat plasma protein binding (rat_fup%)
- Rat liver microsome intrinsic clearance (CYP_RLM_CLint)

Metabolite Prediction

In addition to CYP enzymes, metabolite prediction now covers AOX, UGT and esterase enzymes, both in ADMET Predictor and MedChem Designer. Predictions take advantage of existing substrate and site models where available. UGT metabolite prediction, for example, incorporates the existing isoform-specific UGT substrate models, while AOX metabolite prediction incorporates the new AOX substrate and site models. Prediction also makes use of expert rules derived from literature examples of the relevant metabolic transformations. This helps ensure that predicted metabolites are restricted to those that would most likely be observed.

MedChem Studio Module

- The Classes tab has a feature to add new subclasses to an existing class by identifying compound subsets that simplify the existing R table. The feature uses the same algorithm as the existing R Group Subsets feature from the R Tables tab, but creates a new class for each identified compound subset. For each new class, a new R table is created automatically, and this R table will have fewer R groups than the original one,

increasing the structural similarity of the class members and making it easier to perform subsequent SAR analysis.

- The Frameworks method of class generation includes a new option called Consolidate Classes. Use of this option causes classes with larger scaffolds to be merged into classes with smaller ones, significantly reducing the total number of generated classes.
- Several features now take advantage of the recently added extended-connectivity fingerprint (ECFP) keys. These include calculating similarities between classes, generating classes using fingerprints and organizing classes by similar scaffold.
- The R Group Analyzer (RGA) can now be launched directly from the R Group Subsets dialog in the R Tables tab. After launch, the RGA will immediately display the “Rn x Rm” page to view the relevant substituent matrix.
- In the “Rn x Rm” and “Rn x Rn” pages of the R Group Analyzer, navigating through families now updates the scaffold in the upper left window. The scaffold now explicitly shows R groups shared by all compounds in the family.

Additional Changes

- The Pipeline Pilot and KNIME workflows have been simplified and modernized. These improvements, performed through collaboration with outside consultants, lays the groundwork for adding additional functionality in a future release.
- The installation includes two new files with structure alerts related to toxicity. ReactiveMetabolites.cqf contains alerts related to reactive metabolites, while ToxAlerts.cqf contains more general toxicity alerts. These files can be used to assign scores to compounds in the main ADMET Predictor spreadsheet or to visualize alerts on individual compounds in the new Structure Sensitivity window.
- There is a new feature to compute user-defined attributes automatically each time you predict ADMET properties. Typically these attributes would be equations based on built-in ADMET properties; examples could include lipophilic efficiency, the sum of CYP clearances, etc. Attribute definitions must be contained in a file called AutoADMETAttributes.cqf, which must be placed in the local application data folder. A new file called AttributeExamples.cqf provides some useful example attributes.
- The Atomic Properties window has new properties to display. "ALL_CYP_CLint of metabolism" shows the sum of predicted CYP clearance values for 1A2, 2C9, 2C19, 2D6 and 3A4 isoforms; "AOX_sites of metabolism" shows the predicted sites of AOX metabolism; and "pK50 values" shows pK50 values of ionizable atoms.
- Excel export from the ADMET Predictor spreadsheet now includes any heat-map column coloring.
- The feature to add the most basic and acidic pKa value to the spreadsheet has been expanded to include the second most basic and acidic pKa values. This feature also now

includes the option to consider the S+Mixed_pKa column when determining the extreme pKas.
- A new setting on the General tab lets you change what happens when you double click on a spreadsheet row. There is now an option to display the Compound Properties window rather than launch MedChem Designer.

Bug fixes

The most significant bug fixes are described below.

- Loading an equation from a file could sometimes result in truncation of the attribute name.
- The OSR feature in MedChem Designer could crash on some foreign language operating systems.
- Class boundaries could not be modified in the BCS/DCS Explorer window.
- The PK parameter-sensitivity analysis (PSA) feature could give incorrect results for rat species.
- Dialog text was not always displayed properly on some Asian operating systems.
- The dialog used to construct equations was unable to load CQF files containing comments.
- The SMARTS parser incorrectly required square brackets around the 'A' and 'a' atomic primitives.
- Copying and pasting a single query atom in MedChem Designer resulted in some query properties being lost.
- The Find Tautomer Duplicates feature could fail when the spreadsheet contained hidden rows; this could cause the main spreadsheet to contain empty rows.
- The R Group Analyzer feature could sometimes incorrectly label certain class scaffolds as being Markush.
- Modeler could crash when displaying DELTA models in a Performance Plot window while models were still being built.
- Modeler could crash when Reuse Kohohen map generated an error by picking the wrong Kohonen map file followed by selecting the option to generate a new Kohonen map.