



ADMET Predictor™ release 9.0

By Simulations Plus, Inc. 6/1/2018

Dear ADMET Predictor User,

This new release of ADMET Predictor includes significant enhancements to the recently introduced HTPK Simulation Module, as well as to the MedChem Studio™ module and ADMET Modeler™. Several new models have been added to predict the major clearance mechanism. The release also includes improvements to the user interface and numerous bug fixes.

HTPK Simulation Module

The HTPK (high-throughput pharmacokinetic) Simulation Module, introduced in ADMET Predictor 8.5, allows you to estimate fraction absorbed (%Fa) and relative bioavailability (%Fb) using the basic ACAT™ intestinal absorption simulation scheme used in GastroPlus™ linked to a single central compartment augmented with liver and kidney clearances. In version 9.0 we have added estimates of the pharmacokinetic parameters C_{max}, T_{max} and AUC, which are returned each time you estimate %Fa and/or %Fb.

There is a new feature to display plasma concentration as a function of time for a single compound. These curves are in close quantitative agreement with those generated from compartmental simulations using GastroPlus™.

There is also a new feature to evaluate the sensitivity of %Fa, %Fb, or other PK parameters to changes in compound solubility and permeability. As with the similar parameter sensitivity analysis (PSA) feature in GastroPlus™, this allows you to assess which of these two physicochemical properties needs to be improved in order to achieve optimal exposure.

Interface & Infrastructure Changes

The MedChem Studio™ module now includes functionality for generating and visualizing keys, a special class of substructure-based descriptors that includes the popular Extended-Connectivity Fingerprints (ECFPs) as one of the available methods. These and other types of keys have a

variety of uses within ADMET Predictor, including SAR elucidation and visualization of structure alerts for properties such as assay interference, reactive metabolites and acute toxicity. Users can easily identify keys that most correlate with a compound property, which can help to make SAR more visual and interpretable.

We have added a new graphical display to view both logD and solubility as a function of pH. This functionality has long been available in the GastroPlus™ software.

Other significant changes include the following:

- Confusion matrices now work for attributes with more than two categories.
- Class generation can now be performed using calculated fingerprints.
- Rules for standardizing tautomers have been improved.
- Generating classes from the Compounds tab now skips hidden compounds.
- There is a new right-click menu option to copy a compound attribute.

Classification Systems

We have implemented the Extended Clearance Classification System (ECCS) using our own molecular charge models and a new MDCK-LE (MDCK-limited efflux) permeability classification model based on data from Varma et al. Three binary classification models for clearance by metabolism, renal elimination and hepatic uptake have been added, along with a ternary ANNE model for predicting which of the three pathways is most likely to dominate clearance. A new chapter on Pharmacokinetic Properties has been added to the ADMET Properties section of the Manual that discusses the interplay between the different clearance models.

There is a new graphical display that shows how compounds are classified according to the popular Biopharmaceutics Classification System (BCS) and Developability Classification System (DCS). The highly configurable interface provides a convenient tool to interactively explore how compound dose, solubility and permeability are likely to play a role in successful compound development.

ADMET Modeler

Multiclass (greater than 2) classification models can now be built using Artificial Neural Network Ensembles (ANNs). Previously this could only be done using Support Vector Machine (SVM) models.

The workflow for building DELTA Models™ has been greatly simplified and streamlined through the introduction of an optional “Reference Variable” in Modeler’s Variable Selection page. Refer to the manual for further details.

Other significant changes include the following:

- Performance Plot displays for binary classification models can now be color coded by confidence value using one of two coloring schemes.
- The confidence value for the selected point is now shown along with its observed and predicted values in the Performance Plot window for binary ANNE classification models.
- Location of points in the Performance Plot window for classification models is no longer random but is organized along a semi-regular grid, reducing the likelihood of significant overlap between points.
- The trend line display in Performance Plots for regression models is now based on whatever points are currently displayed (train, test, or both).
- Training set statistics are now shown in Performance Plots (along with All and Test).
- The green circle indicator for the selected point in a Performance Plot has been replaced with a black crosshair.
- Use of class weights for binary ANNE models is now supported for the voting method as well as the averaging method.
- A prefix can now be added to a model’s Auxiliary Factor to specify addition of (“+”), subtraction of (“-”), and division by (“/”) that value instead of multiplication by (“*” or no prefix) or negation (“~”); this feature is used when DELTA Models are exported.

ADMET Property Models

- Most classification models have been rebuilt in order to improve their estimates of prediction confidence by allowing for split beta binomials. The AMES mutagenicity models, which were rebuilt in version 8.5, did not require a rebuild for this version.
- The models of human plasma protein binding (hum_fup%) and total HLM clearance (CYP_HLM_CLint) have been significantly improved through the addition of new data.

Bug Fixes

Some of the significant bug fixes are described below.

- Fixed problems in Modeler when the computer’s Region was set to one whose default decimal separator was comma, but was overridden by explicitly specifying period as the decimal separator.
- “dat” files written by Modeler now always use a period as the decimal separator regardless of the Region setting.
- Fixed point selection bug in Performance Plot windows when the plot was displayed in log

space.

- Removed extraneous “verify” heading in performance statistics sections of log files in cases where no verify statistic is reported.
- Adding a Risk model using the “Add new model” dialog window now places the model in the location specified by the “Insert model after” combo box.