ADMET Predictor® 10.4 (APX.4) Release Webinar

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Outline

- Introduction to ADMET Predictor
- New Features in Version 10.4
- Software Demonstration

ADMET Predictor Overview

Property Prediction

Physicochemical
Transporters
Metabolism
Toxicity
ADMET Risk

PBPK Simulations

%Fa, %Fb
Cmax, Tmax, AUC, CL, $T_{1/2}$
Cp-time curves
Optimal dose

Model Building

Molecular + atomic descriptors
Regression, classification
Uncertainty, confidence

Cheminformatics

Compound design (AIDD)
Scaffold clustering
R group analysis
Matched molecular pairs
Similarity / diversity

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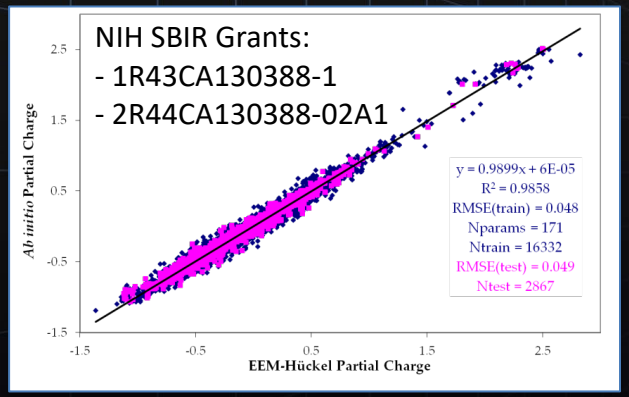
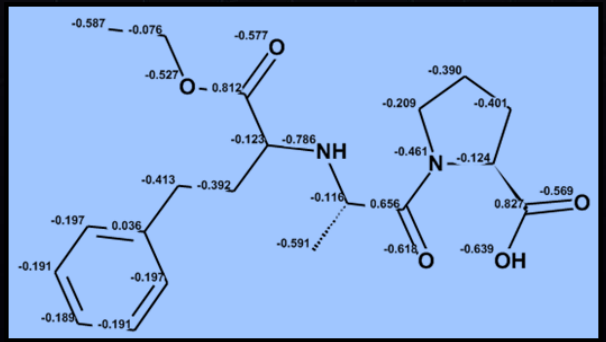
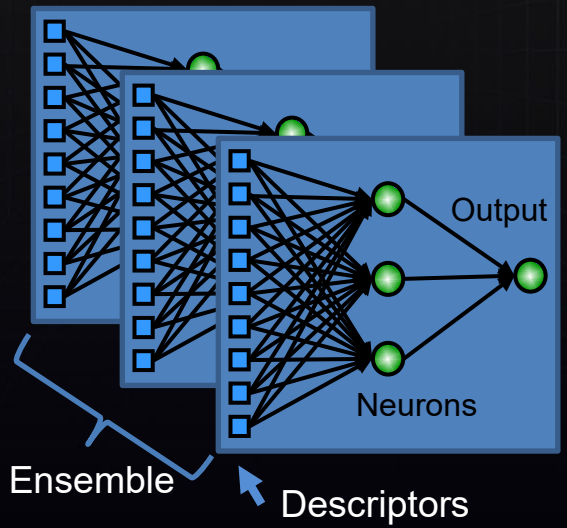
Property Prediction: Methodology

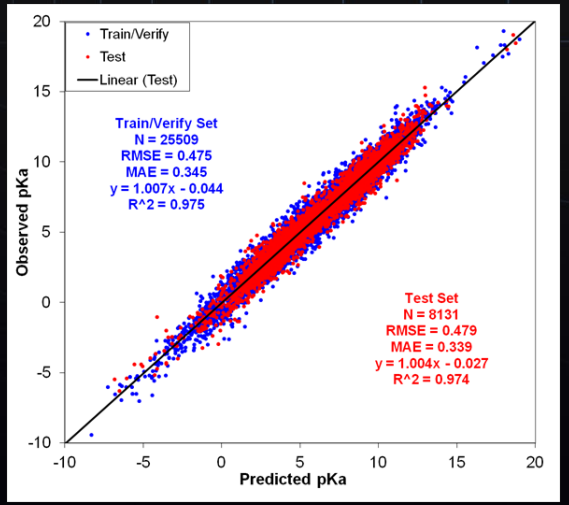




Neurons



pKa model



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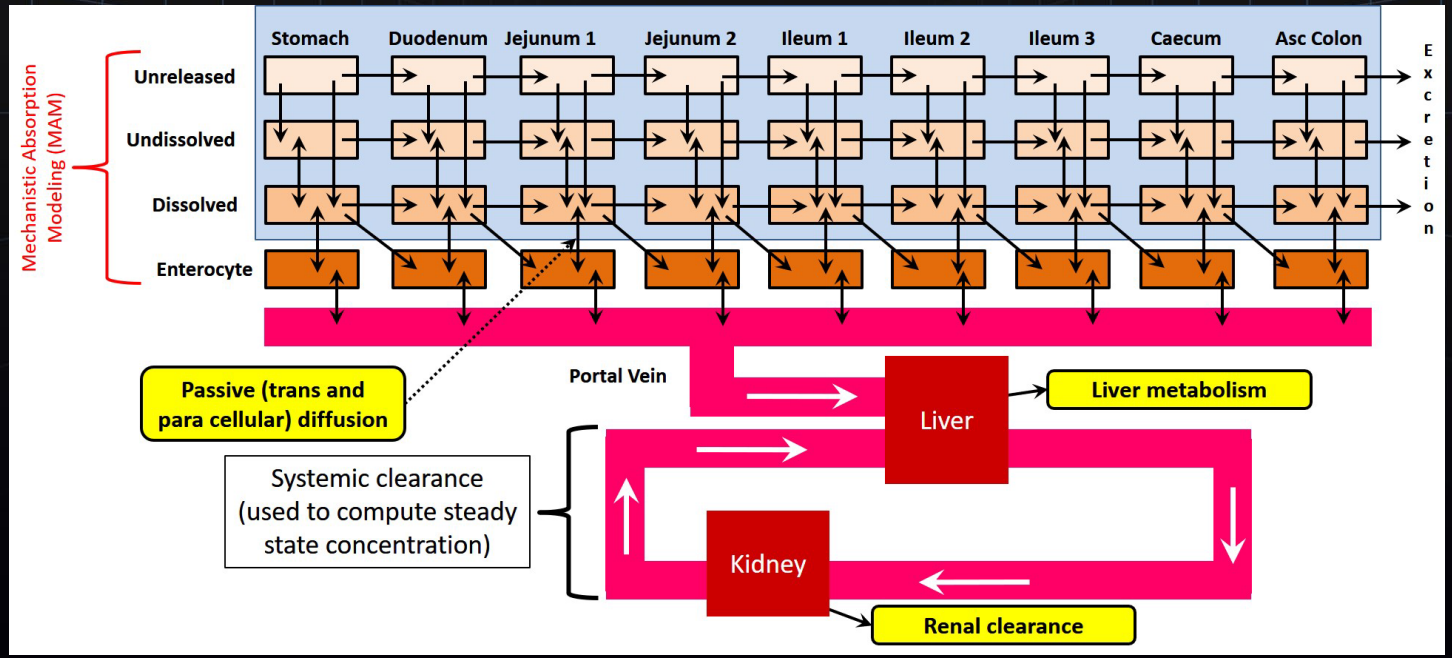
PBPK Simulation: Methodology

ACAT™ Model* + Compartmental Model



* Advanced Compartmental Absorption and Transit Model

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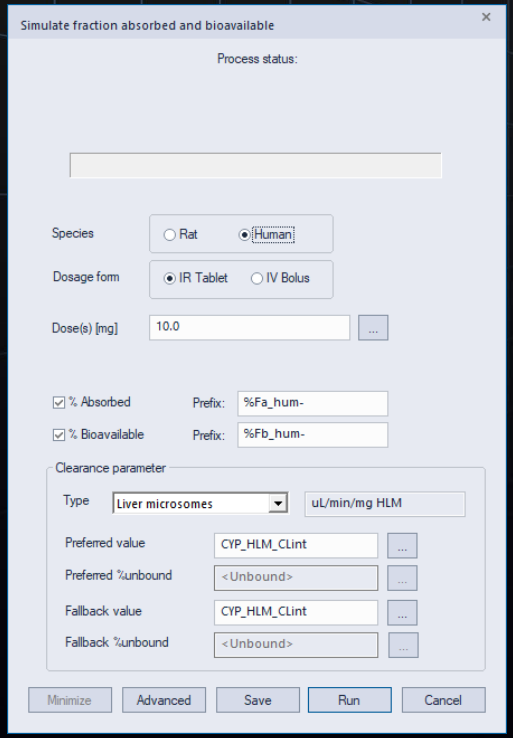
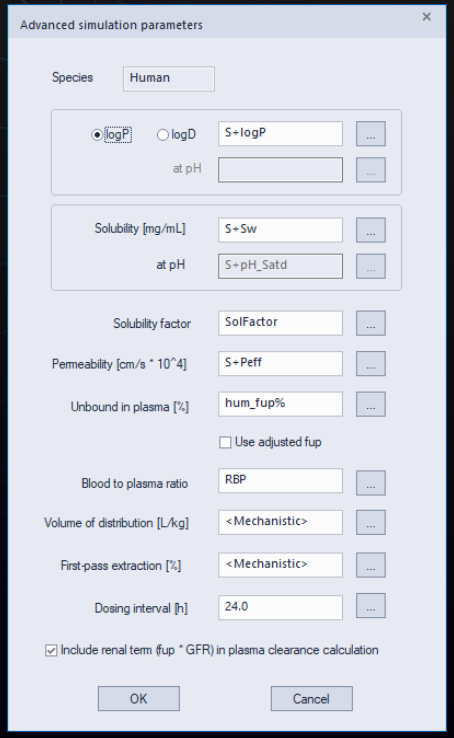
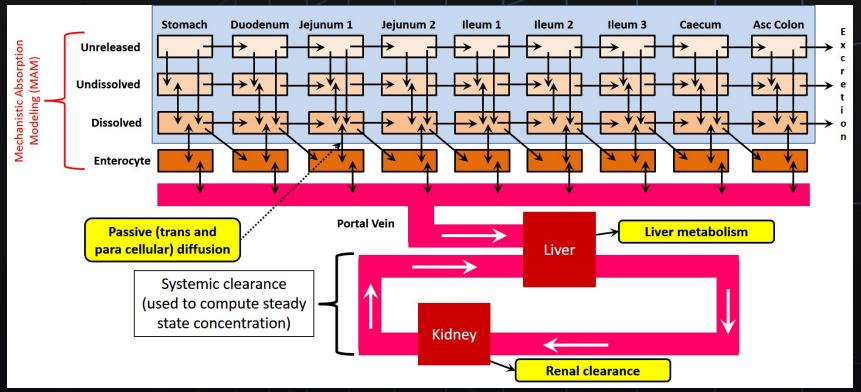
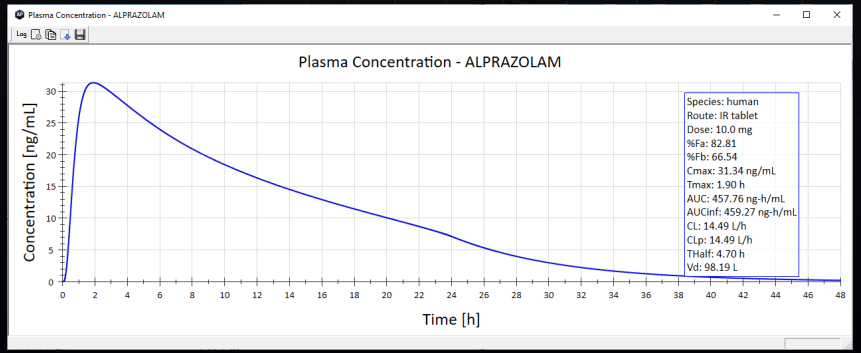
PBPK Simulation: Methodology









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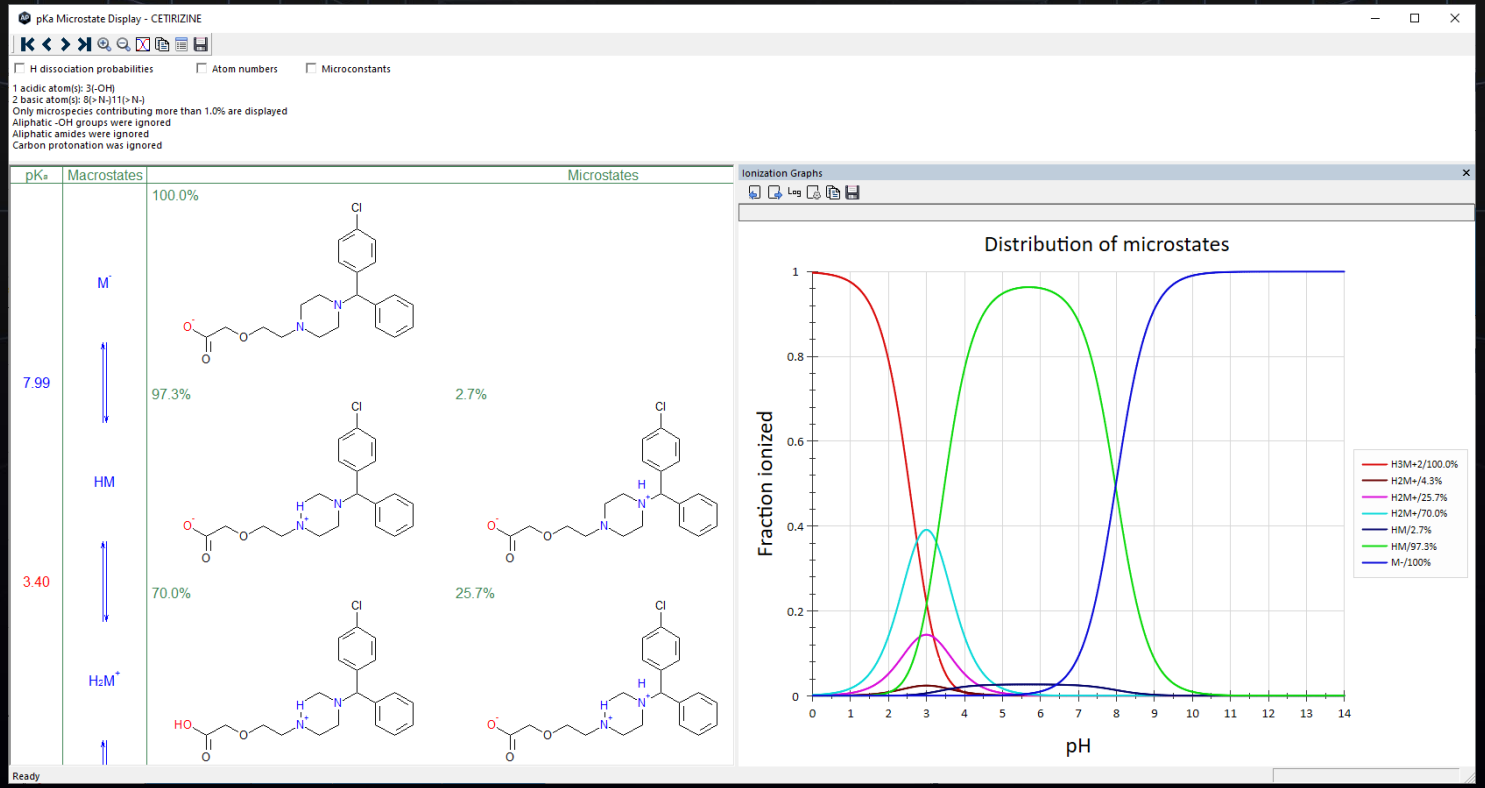
Additional Features



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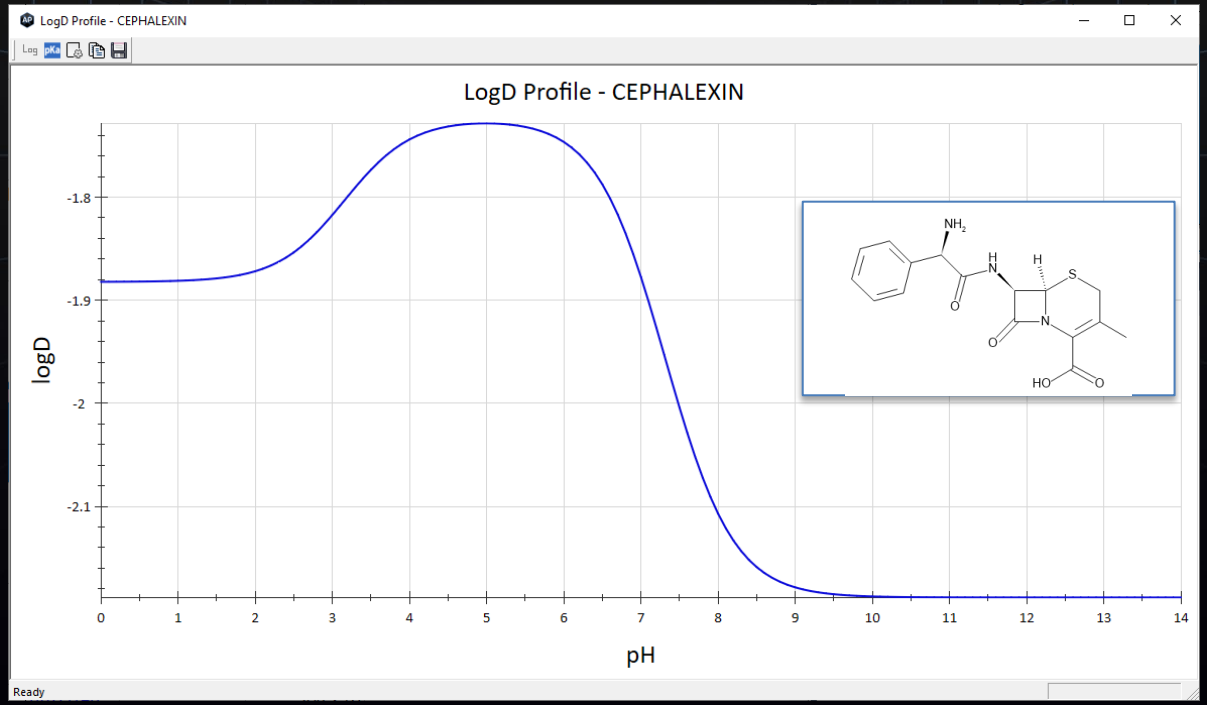
pKa Microstates

Additional Features



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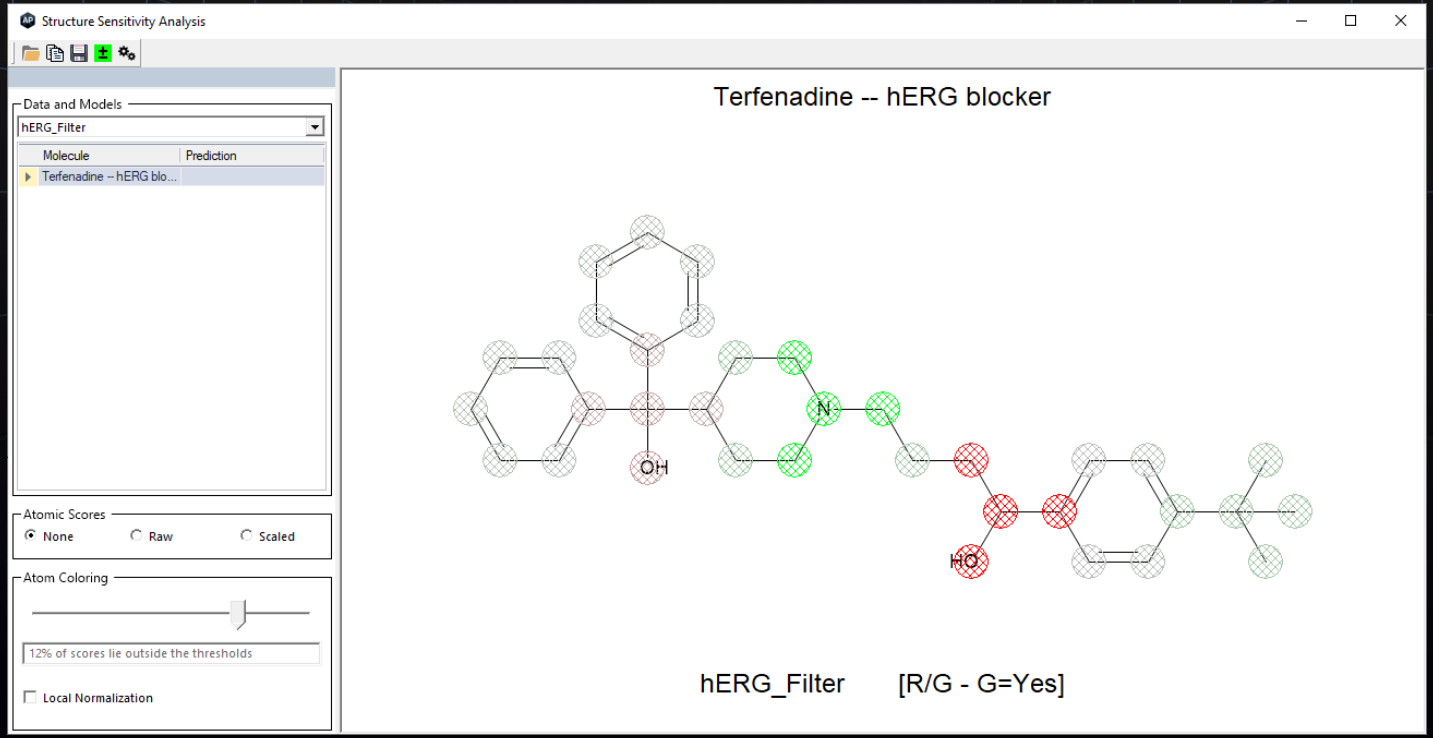
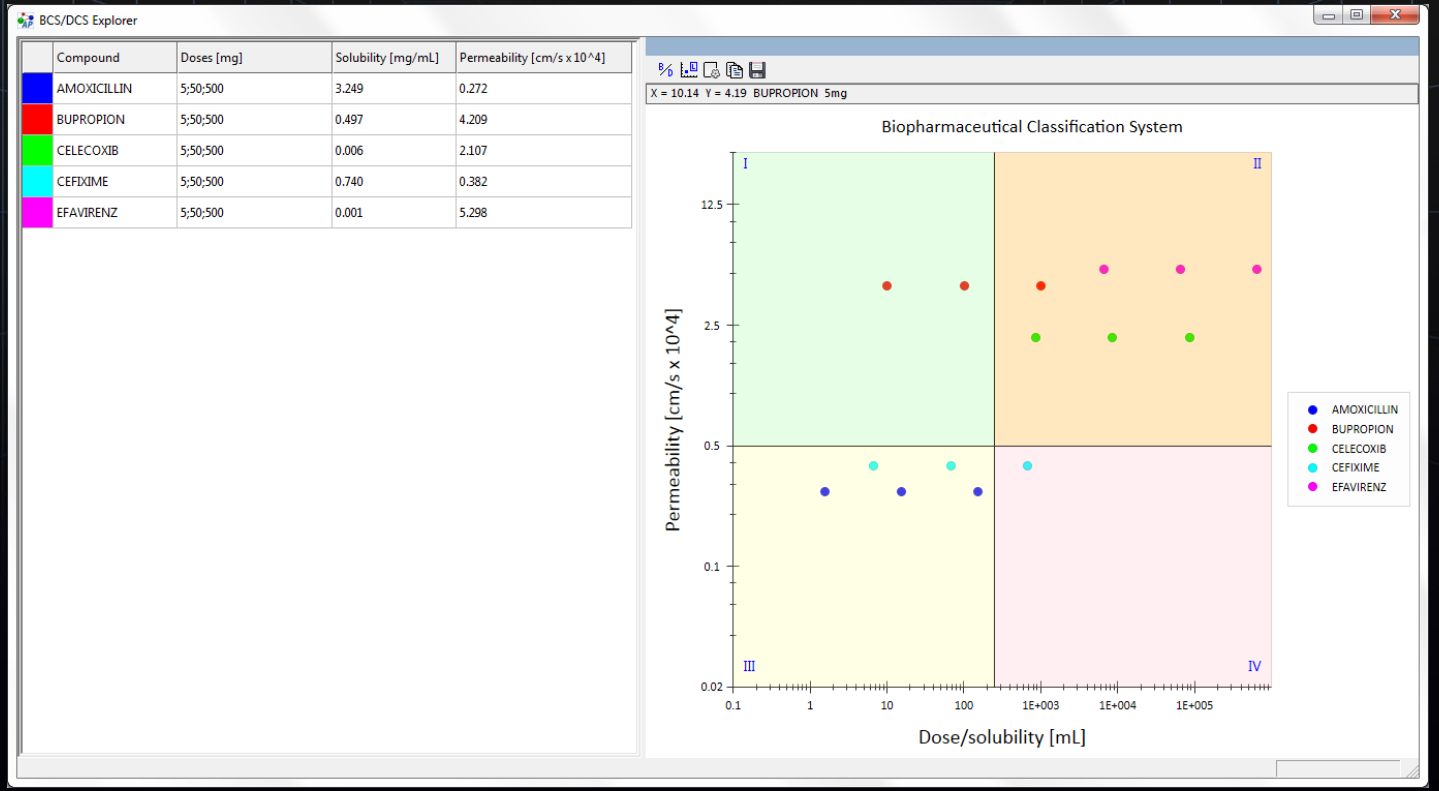
logD-vs-pH Profiles

Additional Features



Additional Features



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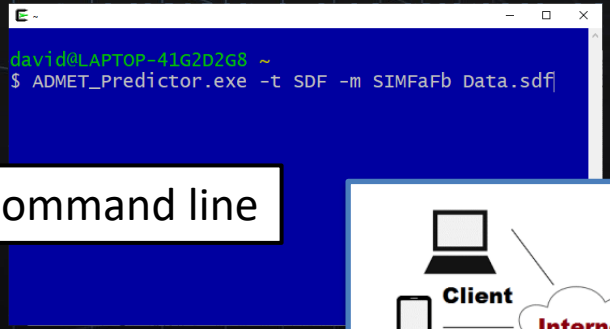
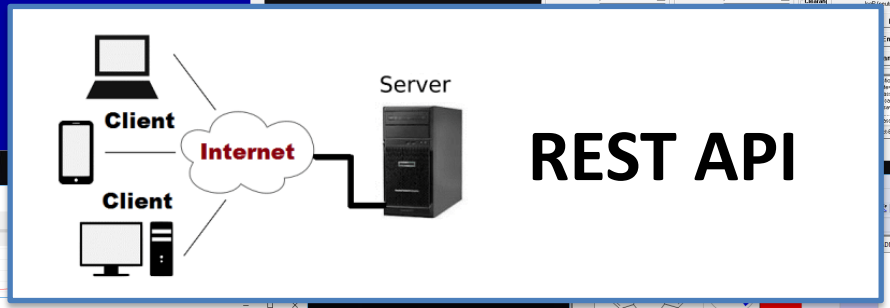
BCS/DCS Explorer

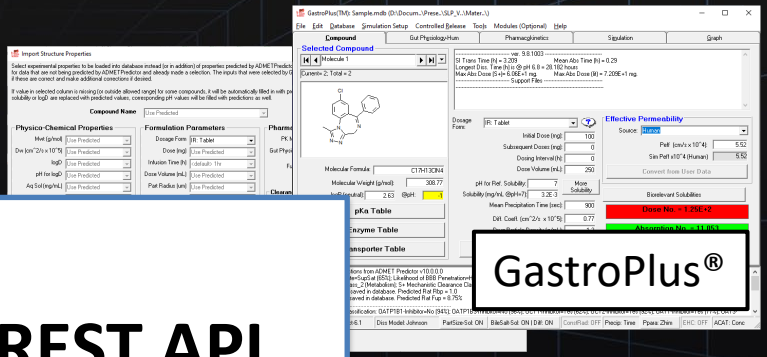
ADMET Predictor Deployment



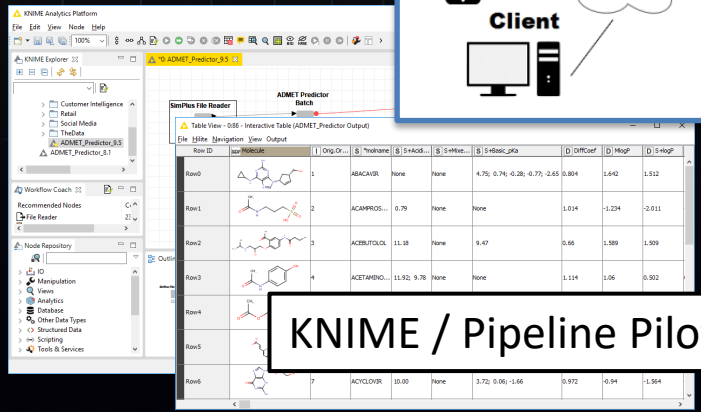
Command line



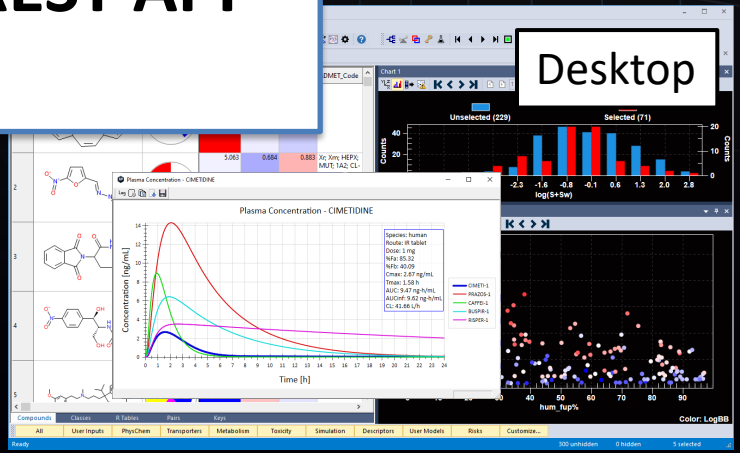
REST API



GastroPlus®



KNIME / Pipeline Pilot



Desktop

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Outline

- Introduction to ADMET Predictor
- New Features in Version 10.4
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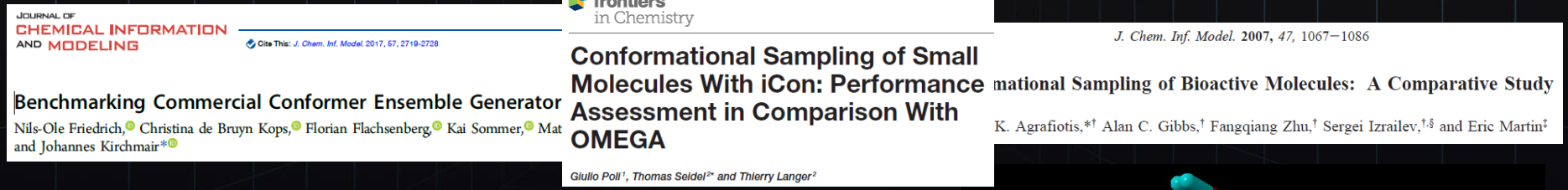
3D Conformer Generation

- Methodology described in ADMET Predictor user manual
  - MMFF94s* force field, macrocycles handled using distance geometry, no fragment library
- Configuration and deployment
  - Option for single or multiple conformers
  - Option for level of energy minimization
  - Option to incorporate user-defined 3D templates
  - Available from user interface and command line (Windows/Linux)
- Simplifies the use of our existing ADMET models built using our 3D molecular and atomic descriptors

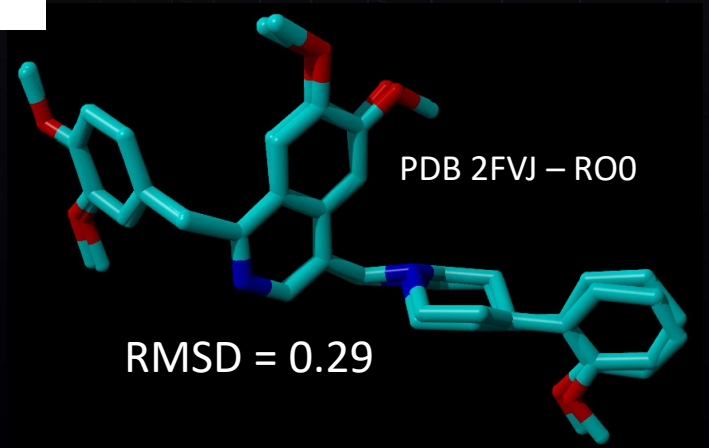
*Halgren TA. J Comp Chem 17 490 (1996)

3D Conformers: Performance

- Ability to reproduce PDB crystal structures was evaluated using the option to generate a diverse set of conformers



- ADMET Predictor is competitive with other commercial tools, with similar mean and median RMSD values when using equivalent software settings
- Requesting user evaluation/feedback: No additional license will be required for this functionality



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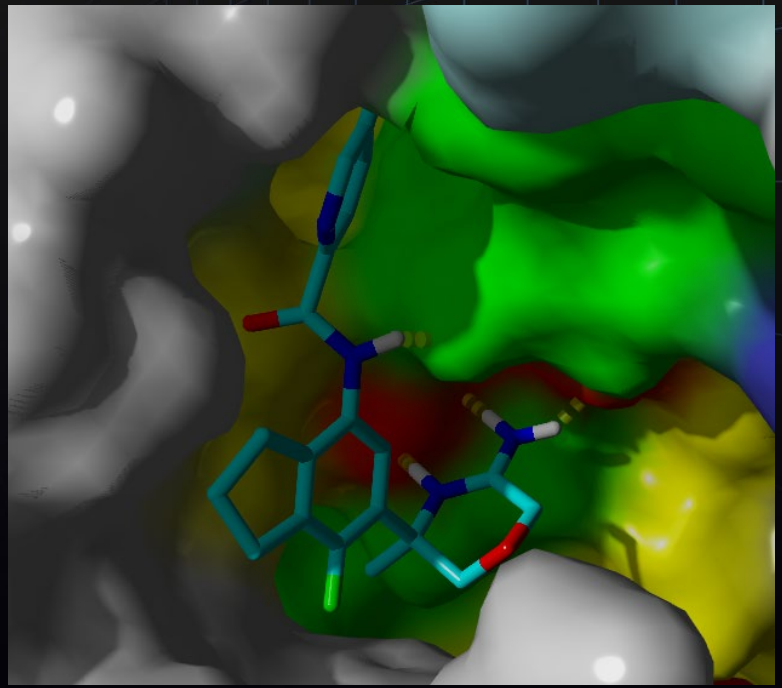
3D Conformers: AIDD Case Study

- AIDD is used to discover compounds simultaneously optimized across multiple target objectives defined by the user
- External applications – such as AutoDock Vina* – can be used to compute the objectives
- Using ADMET Predictor for 3D conformer generation, AIDD discovered several novel compounds with good predicted ADMET profiles and high docking scores against the BACE1 enzyme



https://www.simulations-plus.com/resource-center

*https://vina.scripps.edu

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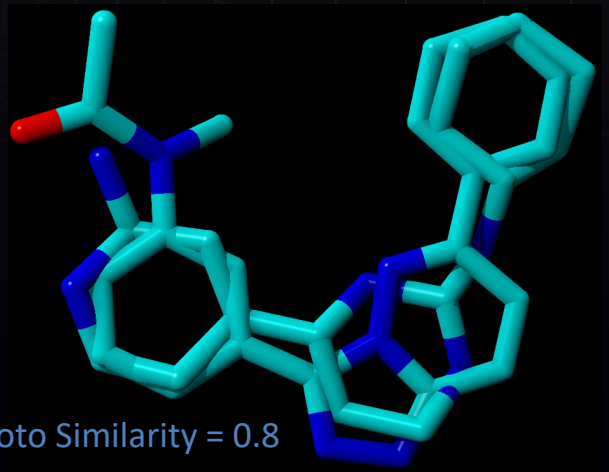
3D Conformers: Future Work

- Improvements to conformer generation algorithms
  - Option to use fragments, improved macrocycle conformer sampling
- Improvements to ADMET property prediction
  - New 3D descriptors and/or modeling techniques
- New functionality for 3D virtual screening
  - 3D shape + feature similarity
  - Prototype based only on volume overlap yields results similar to literature*



Tanimoto Similarity = 0.8

*Rush T et al. J Med Chem 48 1489 (2005)

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HTPK Enhancements

- Support for mouse physiology
  - New models for CLint (LM and hepatocytes), fup and RBP
- Cmin added as new result parameter
  - Steady-state Cmin in the dose-optimization workflow
- Command line option to save a file with values used for each HTPK input parameter, for each compound
- Command line supports a fallback value for the clearance source (e.g., microsomes versus hepatocytes)
- User interface allows a subset of result columns to be saved and displayed

HTPK: Validation

Evaluation of the Success of High-Throughput Physiologically Based Pharmacokinetic (HT-PBPK) Modeling Predictions to Inform Early Drug Discovery

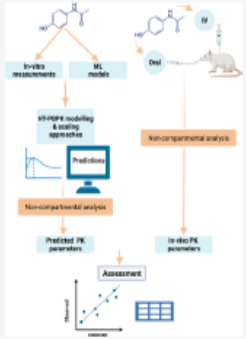
Doha Naga,[§] Neil Parrott, Gerhard F. Ecker, and Andrés Olivares-Morales*,[§]

Cite This: https://doi.org/10.1021/acs.molpharmaceut.2c00040

Read Online

- Roche Pharma Research and Early Development (pRED)
- Department of Pharmaceutical Sciences, University of Vienna
- HTPK provides useful estimates of PK parameters at discovery stage, and is viable alternative to full PBPK modeling

ABSTRACT: Minimizing in vitro and in vivo testing in early drug discovery with the use of physiologically based pharmacokinetic (PBPK) modeling and machine learning (ML) approaches has the potential to reduce discovery cycle times and animal experimentation. However, the prediction success of such an approach has not been shown for a larger and diverse set of compounds representative of a lead optimization pipeline. In this study, the prediction success of the oral (PO) and intravenous (IV) pharmacokinetics (PK) parameters in rats was assessed using a "bottom-up" approach, combining in vitro and ML inputs with a PBPK model. More than 240 compounds for which all of the necessary inputs and PK data were available were used for this assessment. Different clearance scaling approaches were assessed, using hepatocyte intrinsic clearance and protein binding as inputs. In addition, a novel high-throughput PBPK (HT-PBPK) approach was evaluated to assess the scalability of PBPK predictions for a larger number of compounds in drug discovery. The results showed that bottom-up PBPK modeling was able to predict the rat IV and PO PK parameters for the majority of compounds within a 2- to 3-fold error range, using both direct scaling and dilution methods for clearance predictions. The use of only ML-predicted inputs from the structure did not perform well when using in vitro inputs, likely due to clearance miss predictions. The HT-PBPK approach produced comparable results to the full PBPK modeling approach but reduced the simulation time from hours to seconds. In conclusion, a bottom-up PBPK and HT-PBPK approach can successfully predict the PK parameters and guide early discovery by informing compound prioritization, provided that good in vitro assays are in place for key parameters such as clearance.



Ames Model Improvements

- 11 Ames models rebuilt using new proprietary data obtained from the Ames/QSAR International Challenge Project from the Japanese National Institute of Health Sciences (NIHS)
- Data was examined and validated by Ames-test experts from NIHS and academia
- Expanded training sets have significantly enhanced the chemical coverage and reliability of the models, without loss of performance

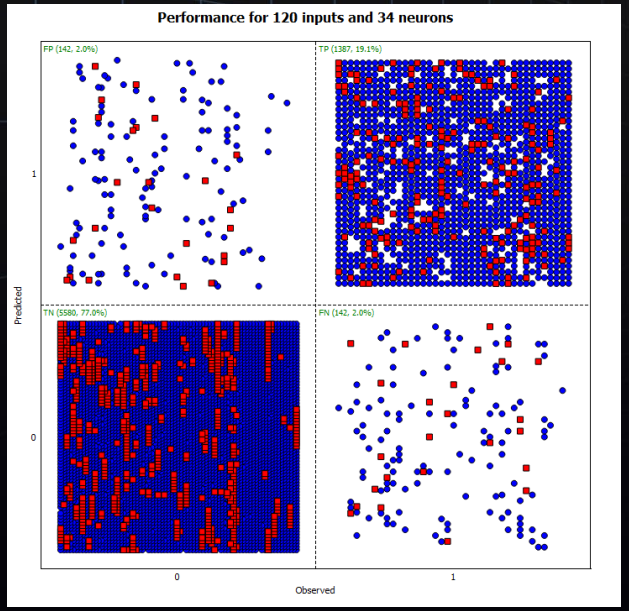
	100	102wp2	1535	97	98	m100	m102wp2	M1535	M97	M98	NIHS
APX.3	3815	945	2190	2364	3615	3445	803	2053	2210	3347	11736
APX.4	5076	2280	3501	3687	4926	4662	2123	3344	3538	4606	13141

REST API Enhancements

- New URI: /run_cmd
  - Simulates a command-line run on the server using the standard ADMET Predictor command-line argument syntax
  - No re-loading of ADMET models or possibility of license contention
  - Adds functionality missing in first release, such as predicting the predominant ionization microstate at a user-specified pH value
- Cp-time data can be collected during HTPK simulations
  - Time points can be sampled to reduce network bandwidth
- Service can run on Linux as well as Windows

AUC

Improved Tautomer Standardization Model



- Tautomer training set has been greatly extended using TautoBase* and other literature sources
- Presented at 2022 MIDD Conference
  - https://www.simulations-plus.com/resource-center
- No additional license is required

*Wahl O, Sander T. J Chem Inf Model 60 1085 (2020)

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More New Features in APX.4

- New command-line workflows
  - 3D : conformer generation, energy evaluation, minimization, rigid alignment
  - Select compounds from a file using a query
  - Add query-based attributes to compounds from a file
- Models can be built and deployed using pH-dependent ADMET properties and/or descriptors calculated at a user-specified pH value
- New command-line option for SD file input to preserve as much of the original SD records as possible in the SD output
  - For example, all explicit hydrogen atoms

More New Features in APX.4

- New modeling descriptors added
  - T_Lipole, N_AntiArom, N_PiSysAtoms, ddRepul, lpRepul
- Support for user-defined attributes based on equations with generic parameters mapped at runtime to constants or numeric attributes
- Support for user-defined transforms to modify spreadsheet columns
- Enhanced options for combining spreadsheet columns
  - Minimum, maximum, average, merge (replace missing values)
- The R Group Analyzer has improved handling of stereochemistry when defining unique R group substituents

Outline

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Thank You!

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