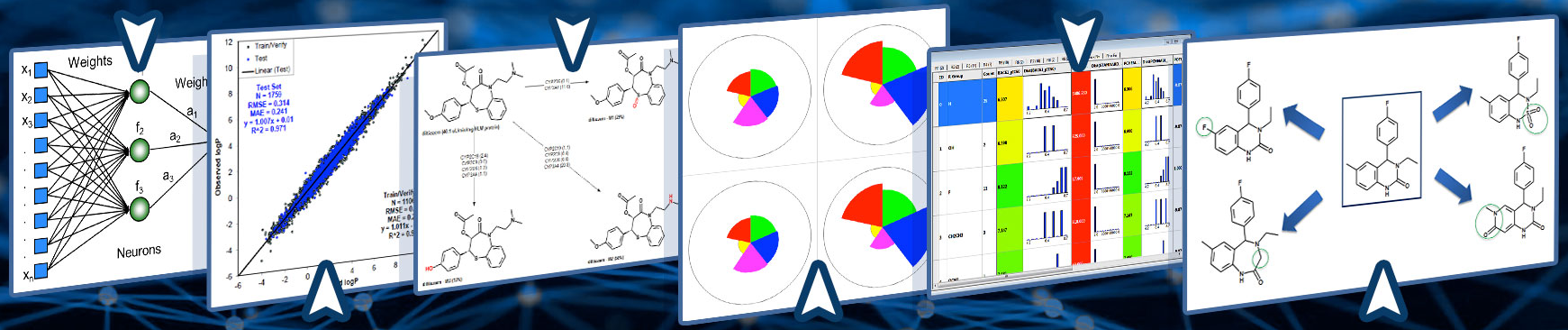
ADMET Predictor® 9.5

ADMET Property Estimation & Model Building

QSAR Model Building **CYP Metabolite Prediction** **R-Table Generation/Analysis**



>140 Predicted Properties **Data Visualization** ***De novo* Design**

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Recent Developments in ADMET Predictor® 9.5

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Outline

- Introduction to ADMET Predictor
- New Features in Version 9.5
- Software Demonstration

What is ADMET Predictor?

- **Property prediction software** (QSAR/QSPR)
  - Predicts over 140 ADMET properties from chemical structure
  - Identifies ADMET liabilities in the form of numeric risk scores.

- The **HTPK Simulation Module** lets you predict fraction absorbed and bioavailable, as well as other PK parameters, using a virtual human or rat simulation

- **ADMET Modeler Module** lets you build your own models using our advanced molecular and atomic descriptors
  - Also used by Simulations Plus for its commercial models

- **MedChem Studio Module** lets you prioritize lead series, discover SAR trends, and design novel compounds

Prediction Modules

PCB

pKa, Lipophilicity
Permeability, Solubility,
Pharmacokinetics,
Transporters,
Clearance Mechanism

Metabolism

CYP, UGT, AOX
Substrate/nonsubstrate,
Sites of Metabolism,
Kinetics, Inhibition,
Total HLM/RLM Clearance

Toxicity

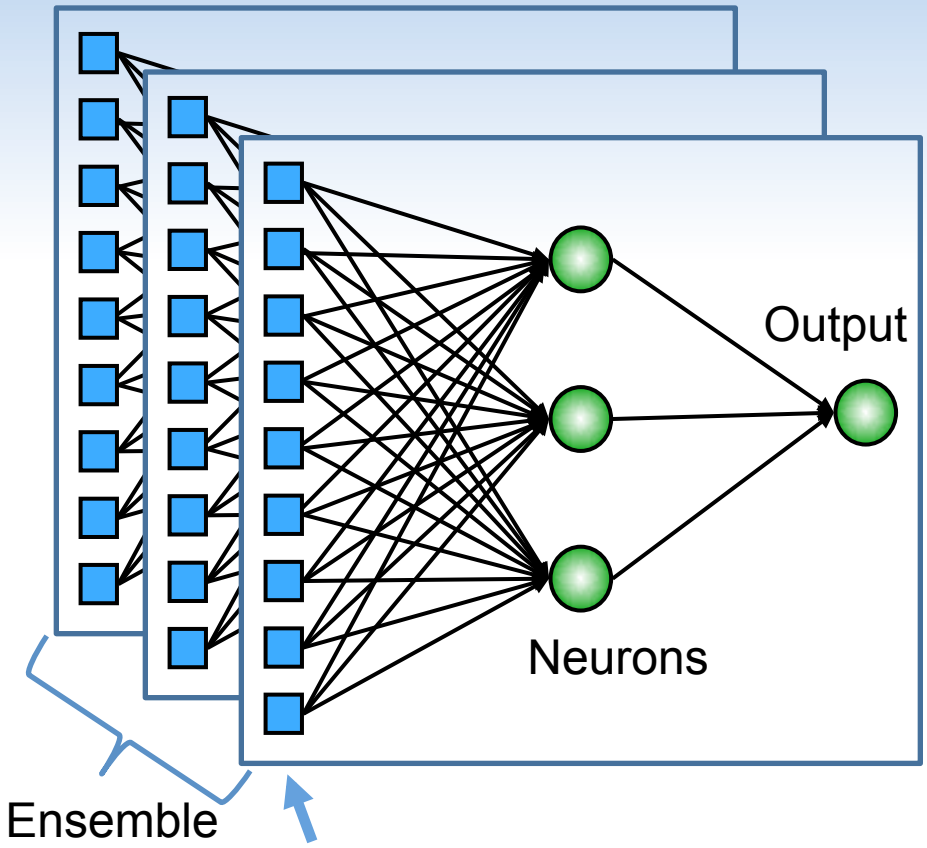
Cardiac, Liver, Acute,
Carcinogenicity,
Sensitization,
Environmental

HTPK

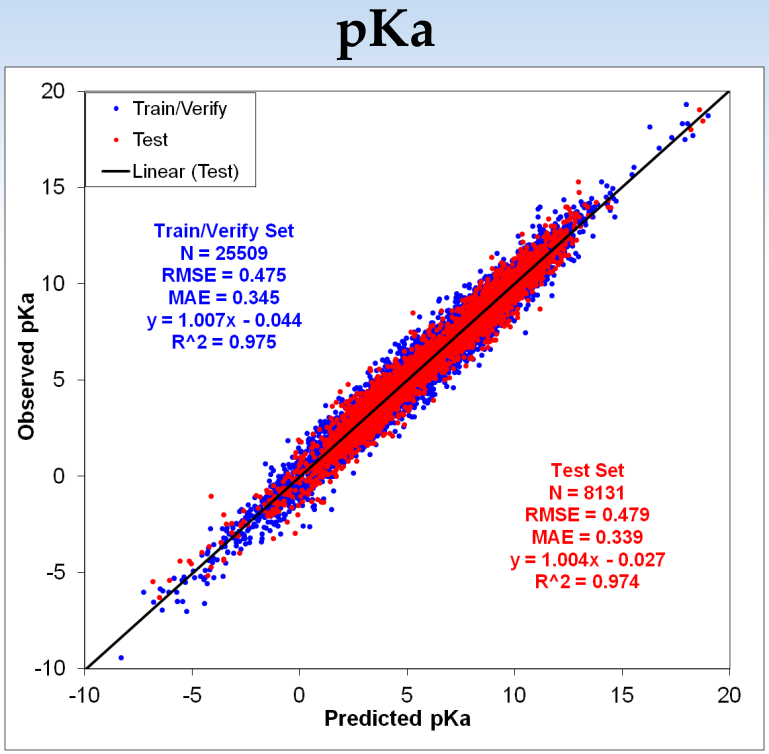
%Fa, %Fb,
Cmax, Tmax, AUC,
Optimal Dose

QSAR Models

Most ADMET Predictor predictions are from QSAR models



Proprietary molecular and atomic descriptors



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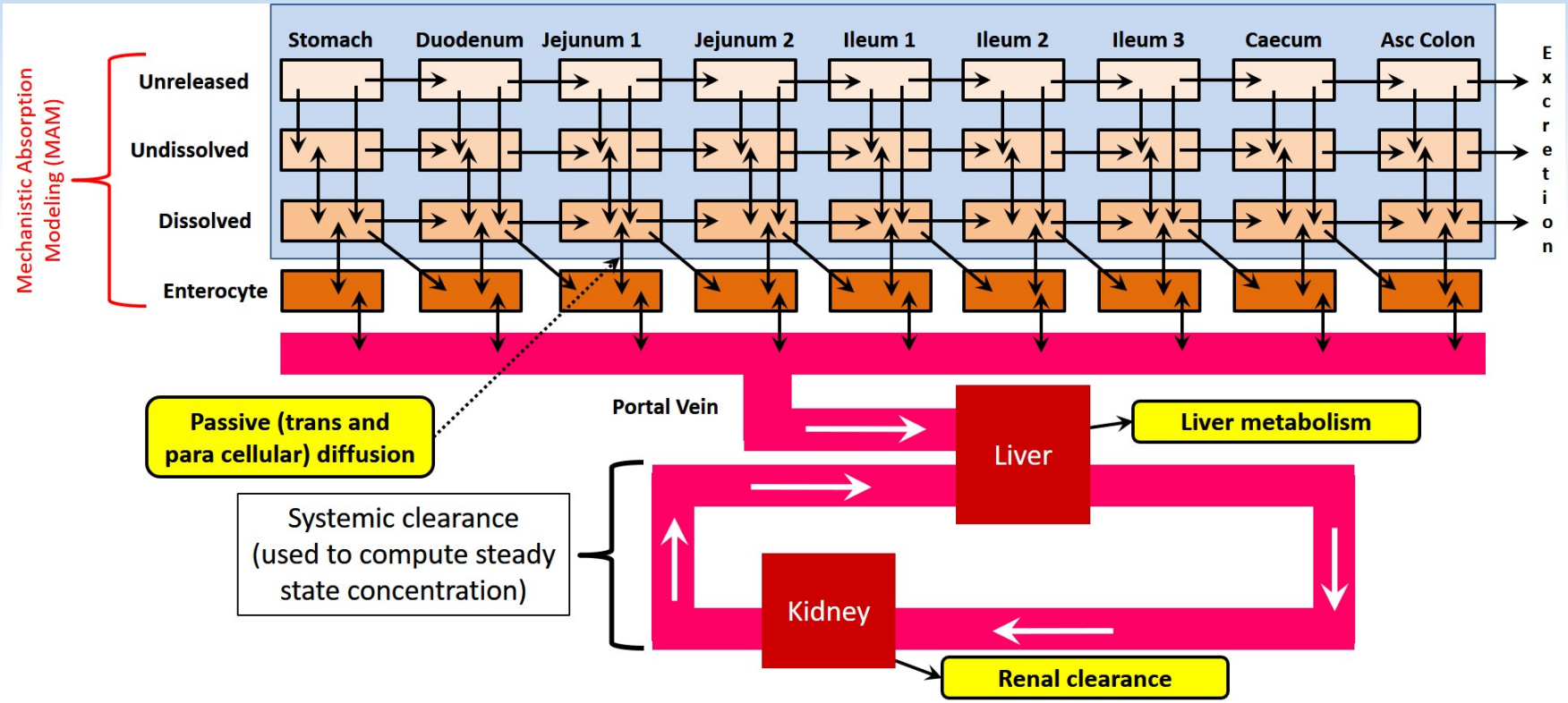
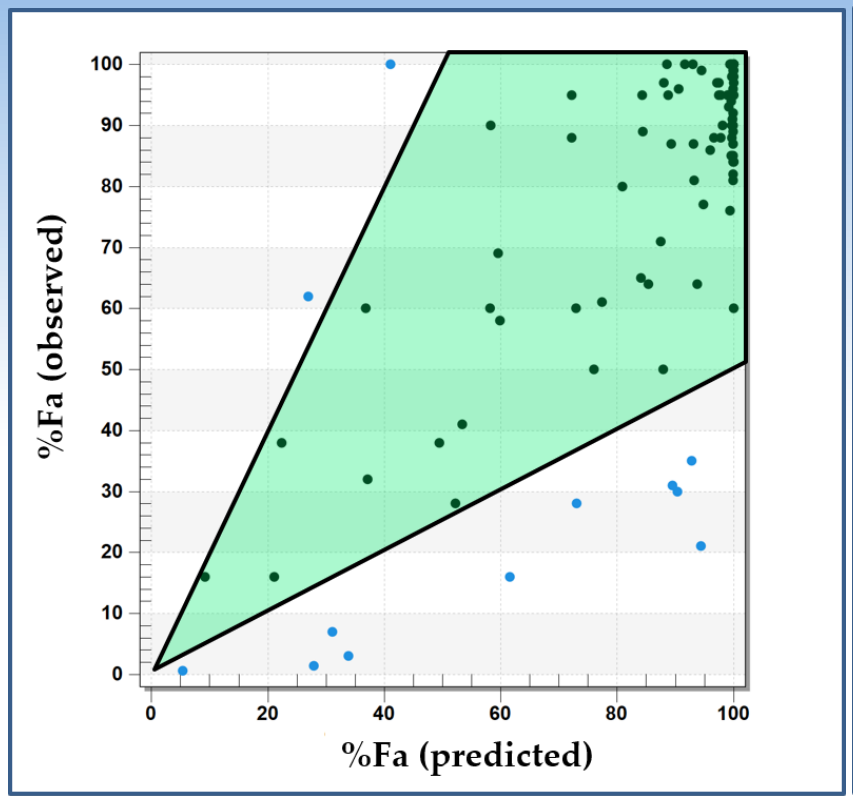
HTPK Simulation Module

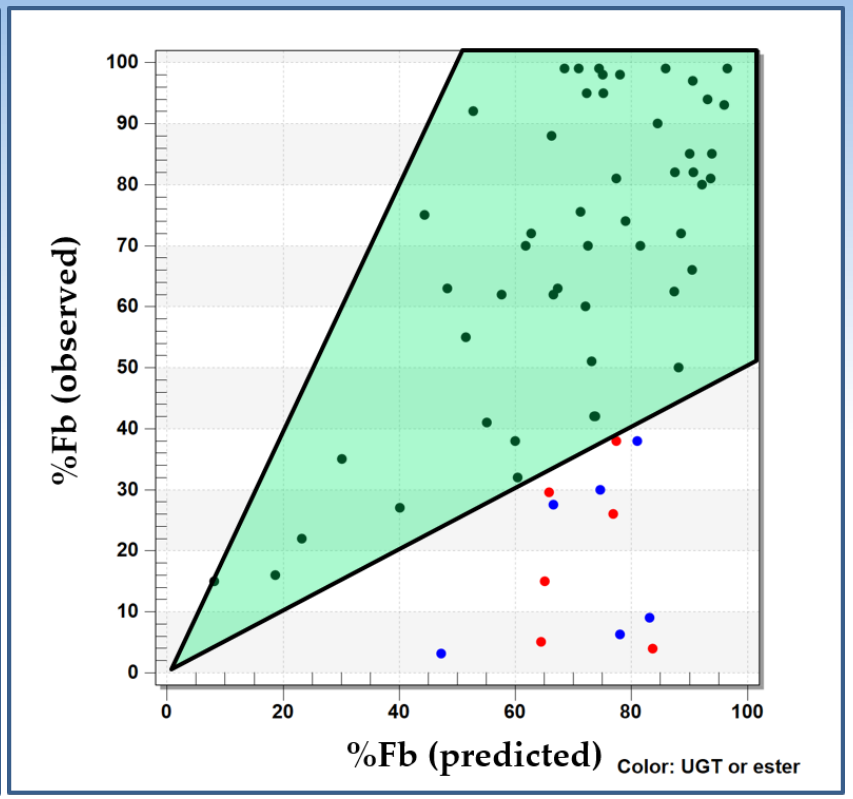
ACAT™ Model* with Compartmental Simulation



* Advanced Compartmental Absorption and Transit Model

HTPK Simulation Module





90% predicted within 2-fold of the observed value.

83% predicted within 1.5-fold

81% predicted within 2-fold of the observed value.

68% predicted within 1.5-fold

*Zhao et al. J. of Pharm. Sci, **2001**, 90, (6), 749.

*Toshimoto K et al. Drug Metab. Dispos, **2014**, 42, 1811.

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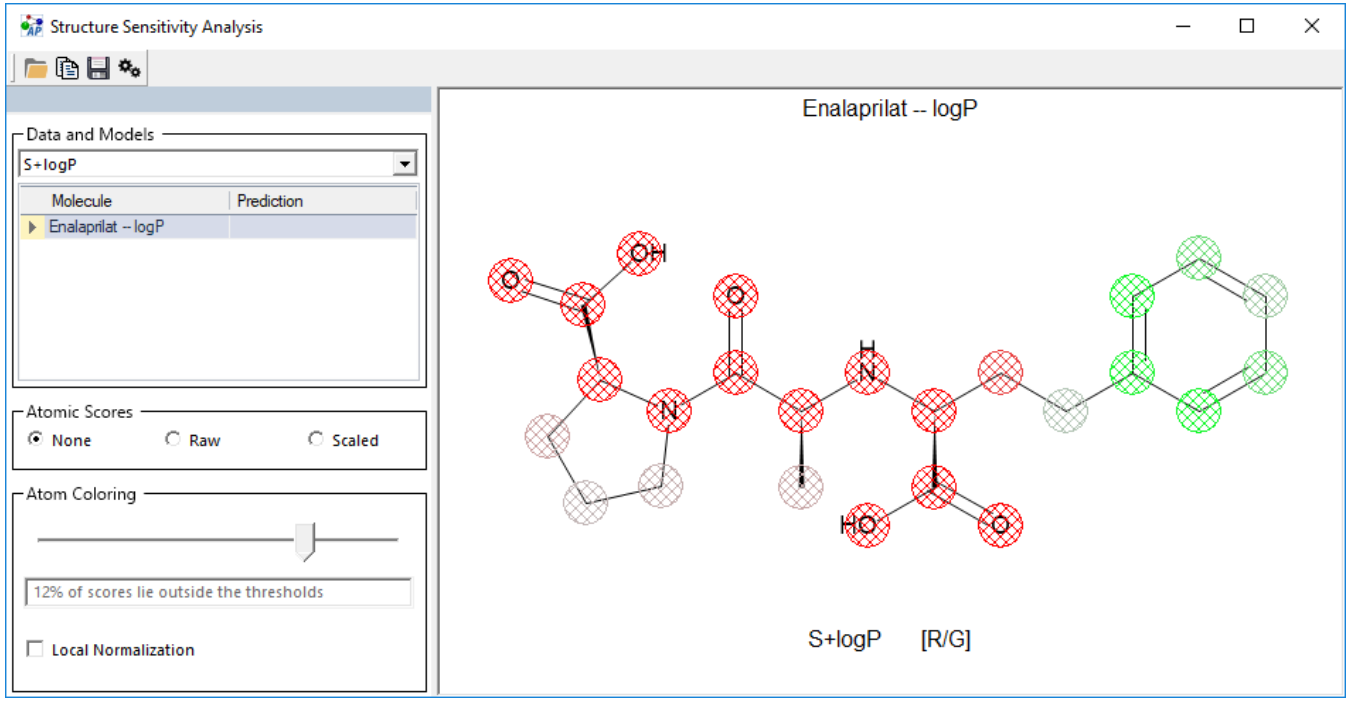
AP 9.5 New Features

- Structure Sensitivity Analysis
  - Interactive display that shows how the individual atoms of a chemical structure contribute to a predicted property
  - Allows you to see which regions of a compound are predicted to have the most influence on that property



Green atoms predicted to increase logP, and red atoms to decrease logP

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AP 9.5 New Features

- Structure Sensitivity Analysis (continued)
  - Compliments the **Descriptor Sensitivity Analysis** (DSA) feature, but is more chemically intuitive
  - Relies on separate models built on a large reference data set using partial least squares (PLS) regression with ECFP keys
  - A new compound is colored according to which ECFP keys it contains and the PLS coefficients of those keys
  - Models include physicochemical, metabolism and toxicity properties; 21 models in total
  - Users can also **build new models** using their own data

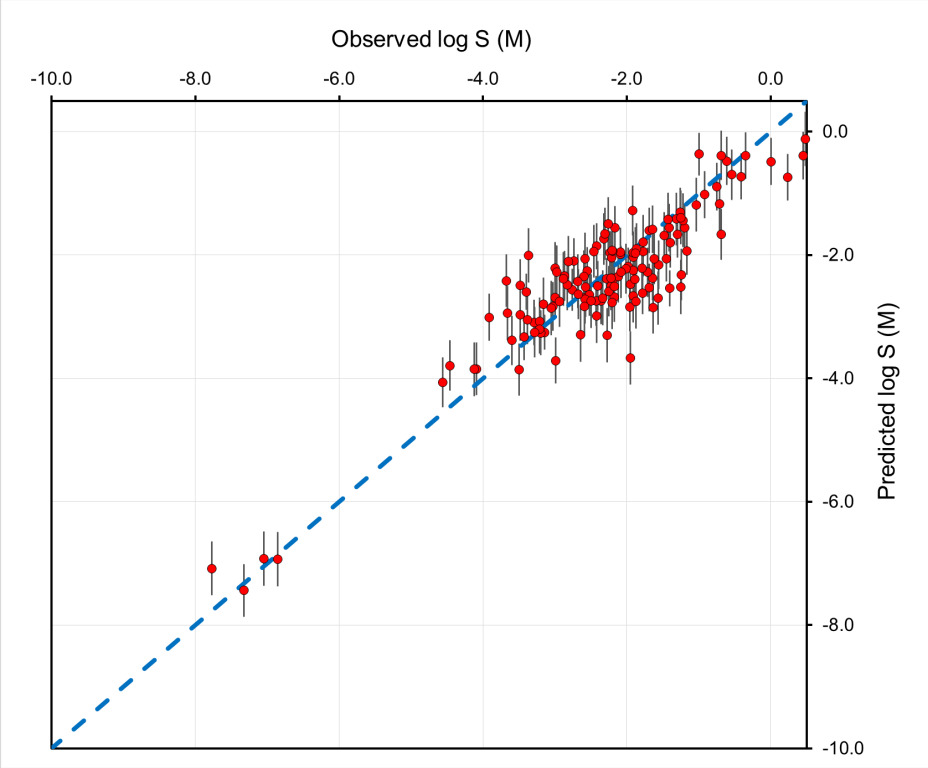
AP 9.5 New Features

- Regression Uncertainty Analysis
  - Regression-model predictions (built-in and user) now have accompanying uncertainty estimates
  - Compliment our existing classification confidence estimates
  - Uncertainty estimates are computed from the standard deviation of **predictions** from individual models that make up the ensemble (33 models by default)
    - Higher standard deviations lead to higher uncertainty estimates
    - Lower standard deviations lead to lower uncertainty estimates
  - Uncertainties are estimates of the standard deviation of **prediction errors**

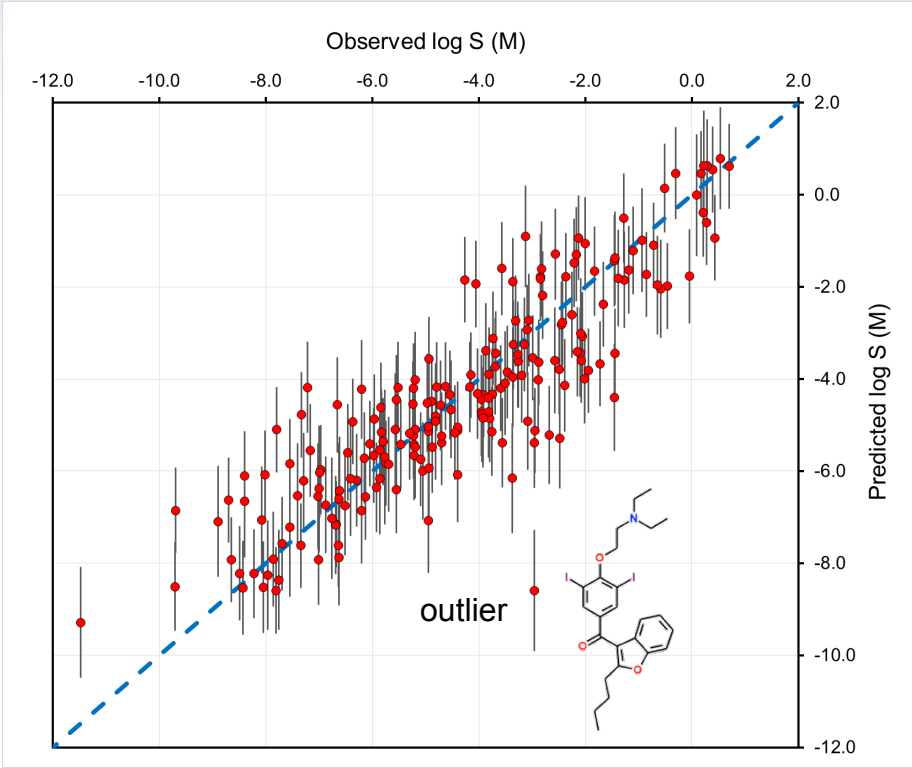
AP 9.5 New Features

Predicted vs observed solubility for compounds in the **test set**
Compounds with smaller uncertainties tend to have smaller errors

200 Smallest Predicted Uncertainties



200 Largest Predicted Uncertainties



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AP 9.5 New Features

- New Models
  - BCRP substrate/nonsubstrate
  - OCT2 inhibition
  - BSEP inhibition
  - Ames mutagenicity using data from Japanese NIHS
  - AOX substrate/nonsubstrate and sites of metabolism
- Improved Models with 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)

AP 9.5 New Features

- AOX / UGT / Esterase Metabolite Prediction
  - Incorporates relevant substrate and site models
  - Uses customizable rules derived from literature review
- ADMET Prediction Features in MedChem Designer
  - pKa Microstates display
  - Atomic Properties display (atomic descriptors + metabolism)
  - LogD and solubility versus pH profiles
  - AOX, UGT and esterase metabolite generation
  - HTPK features (%Fa, %Fb, Cp-time, etc.)
- Improved Pipeline Pilot and KNIME Workflows
  - Component modernization and simplification

Many more enhancements and convenience features

Acknowledgements

Simulations Plus

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- Bob Clark
- Michael Lawless
- Pankaj Daga
- Aleksandra Mikosz

Workflow Informatics

- Chris Lowden

NovaData Solutions

- Mike Mazanetz

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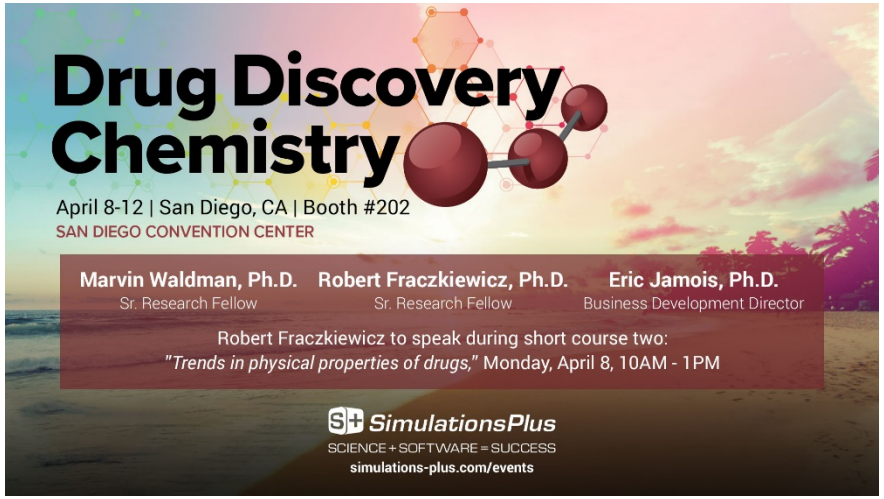
Upcoming conference attendance:



THANK YOU FOR ATTENDING

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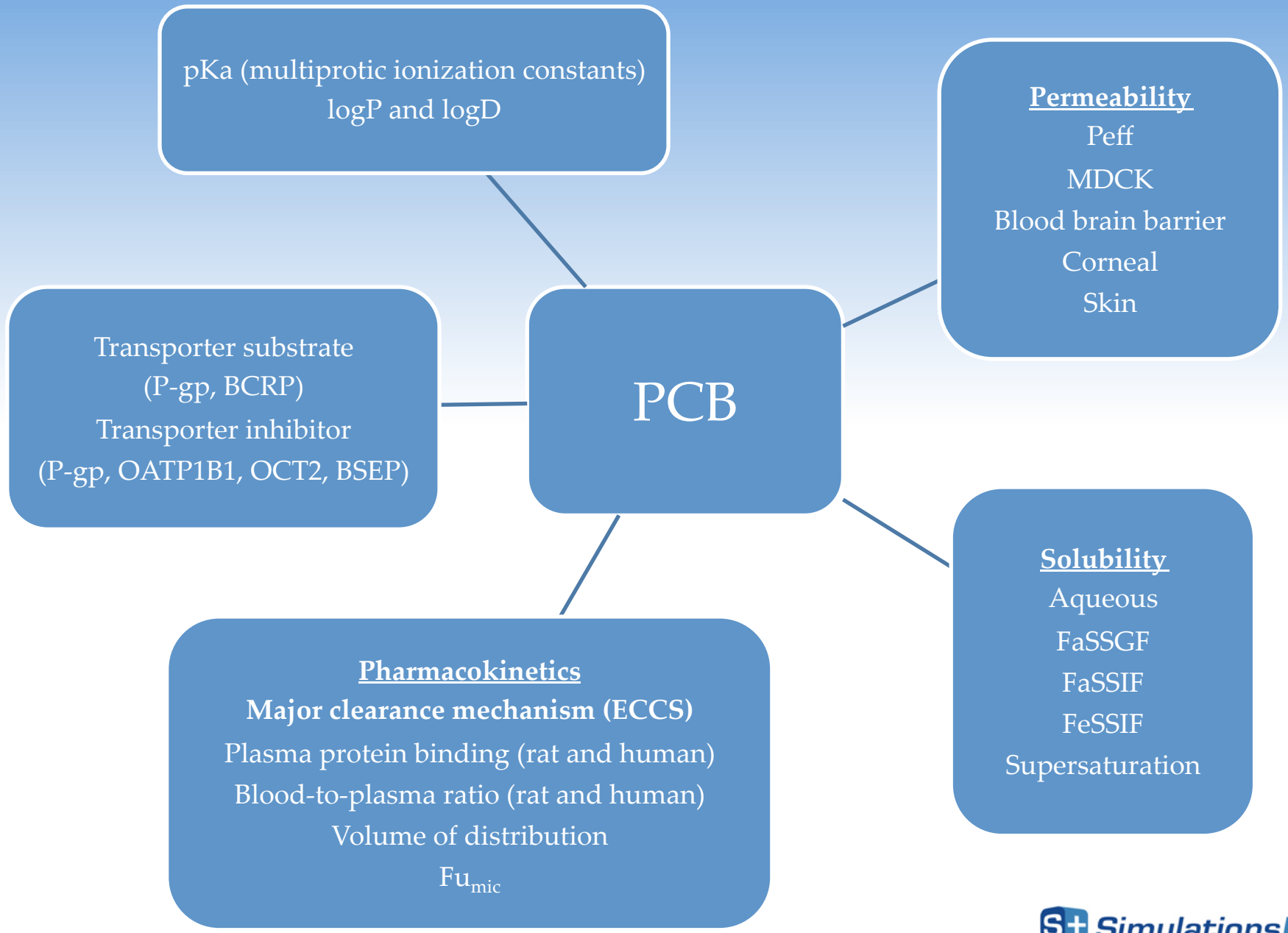
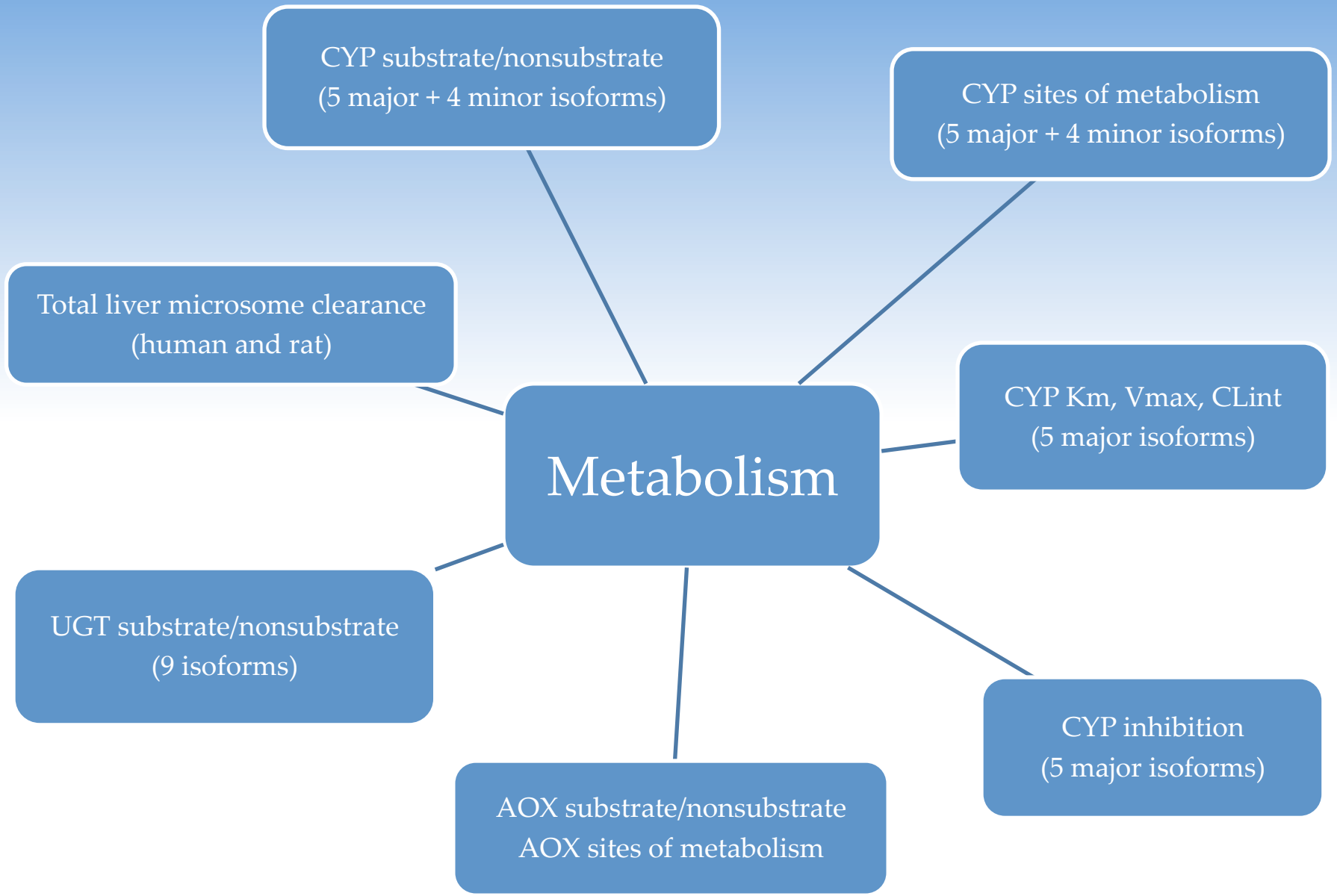
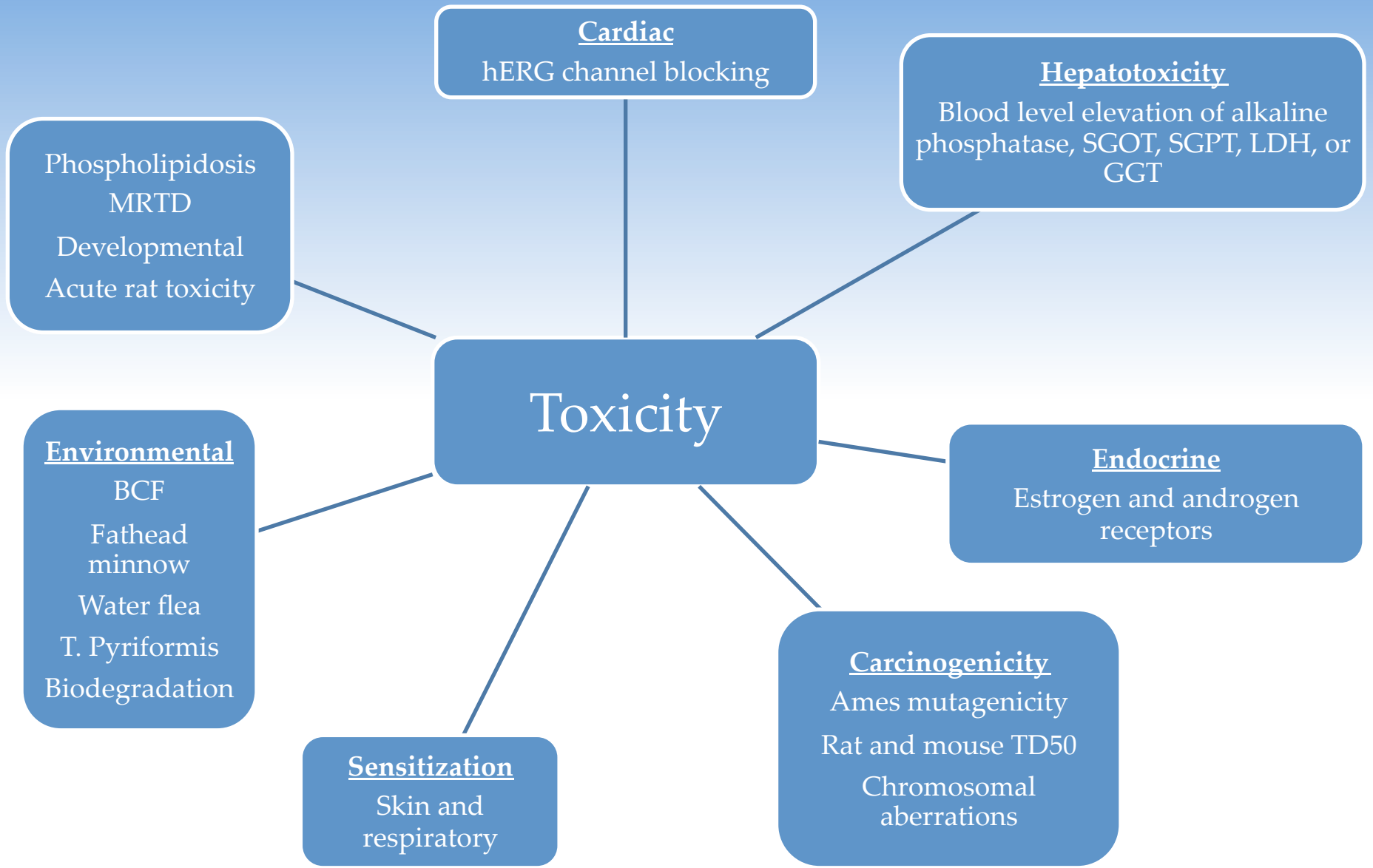
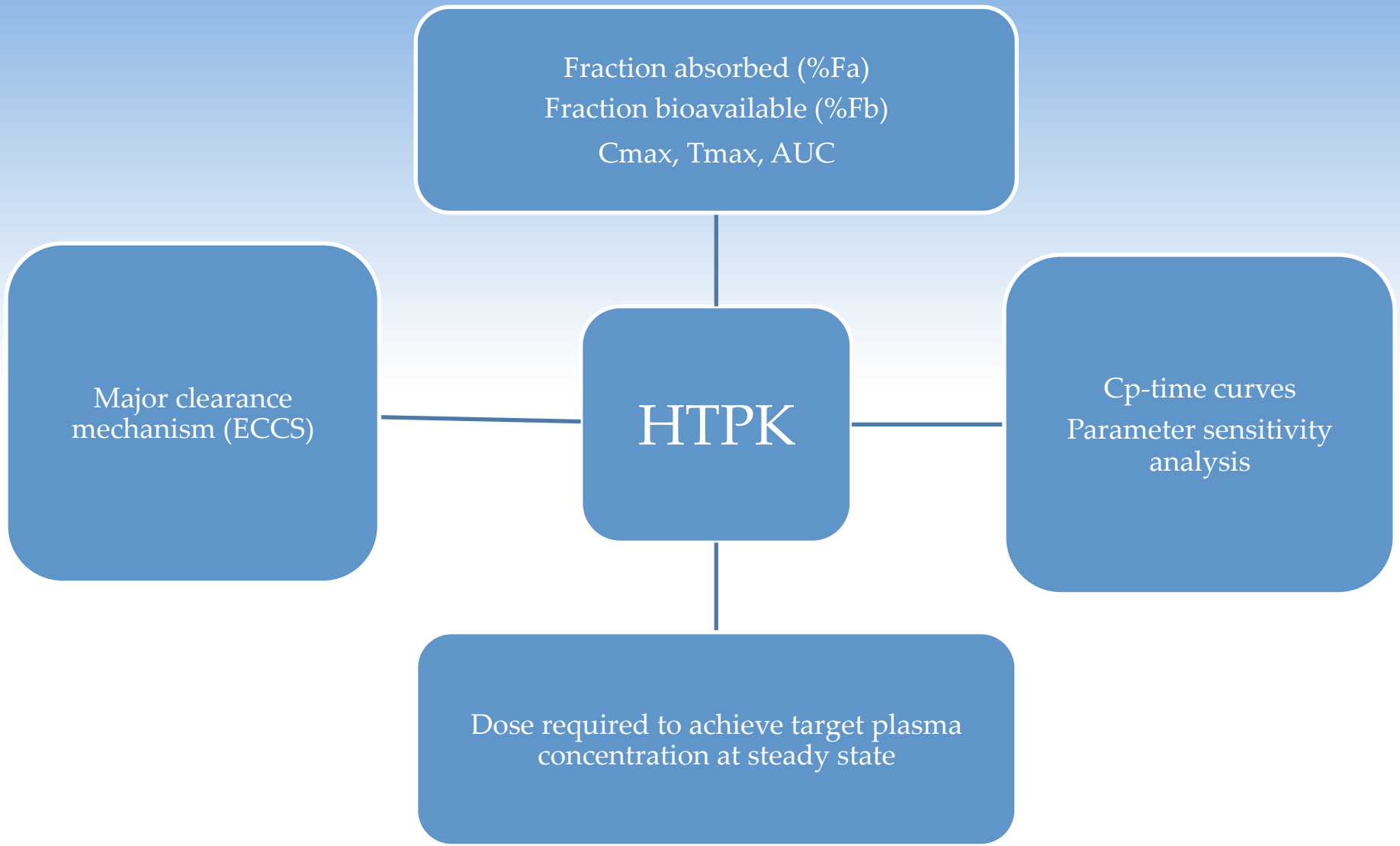
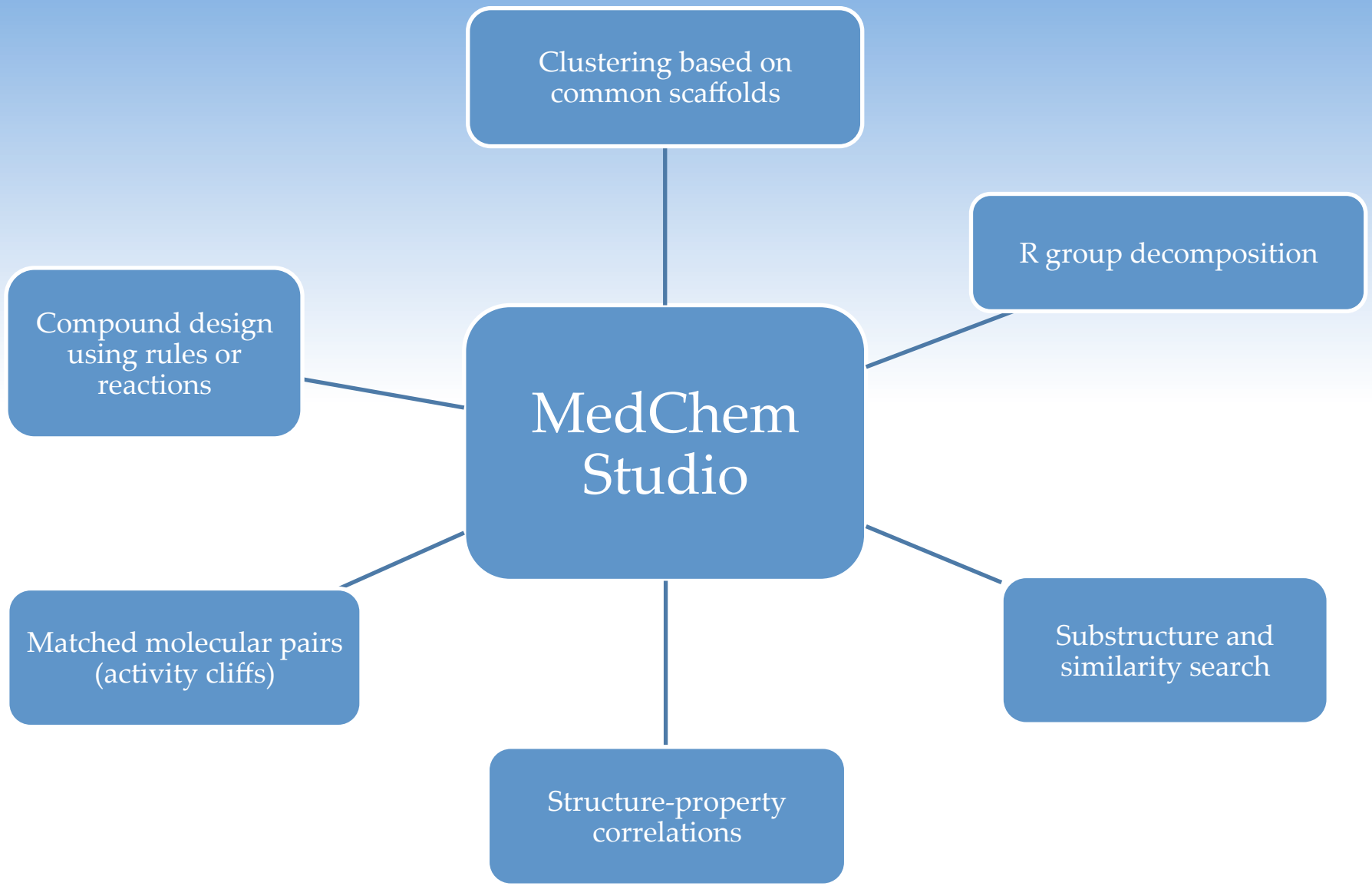
Additional Slides











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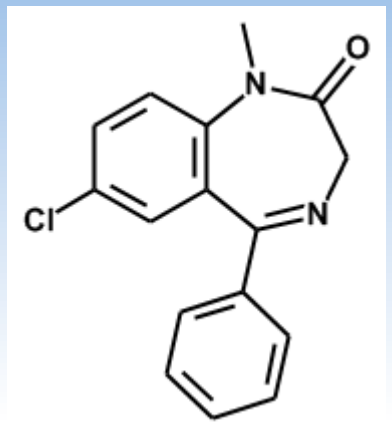
What is ADMET Risk™?

- A flexible scoring system that evaluates major risks
  - Absorption, metabolism, toxicity and pharmacokinetics
- A customizable set of rules (25 default rules)
  - based on predicted property values for the World Drug Index (WDI)
  - thresholds set to pass most commercial drugs
- Lets chemists evaluate many different risk factors simultaneously with one number
  - letter codes identify which properties exceed thresholds
- Rapidly identify lead molecules that exhibit the best tradeoff between multiple development objectives

Molecular and Atomic Descriptors

2D Structure



- Molecular descriptors
- Atomic descriptors

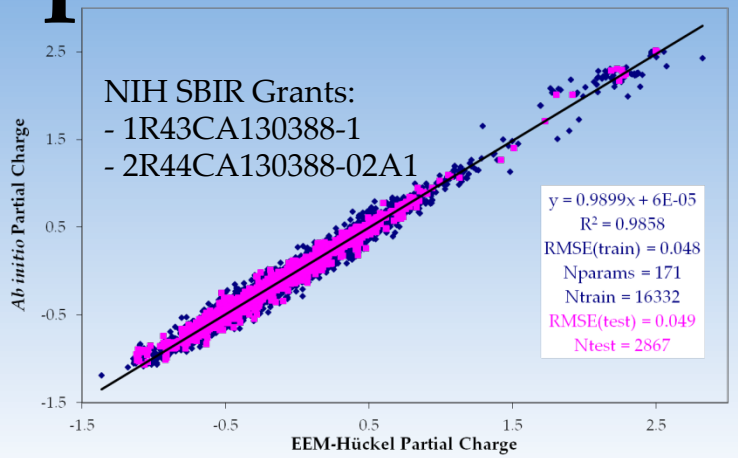
- *Molecular* descriptors are reasonable for modeling bulk properties (logP, solubility, etc.)
  - Interactions are relatively nonspecific

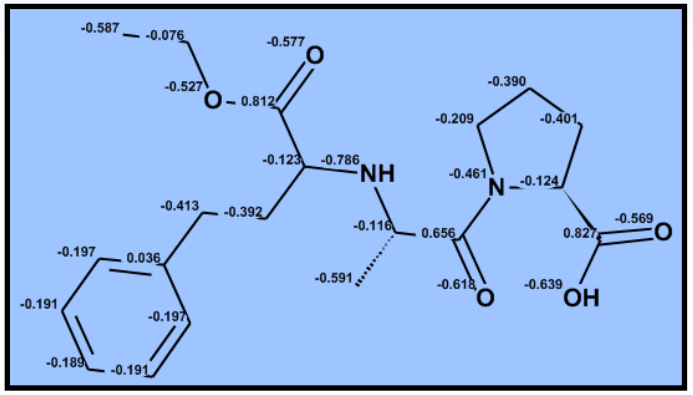
- *Atomic* descriptors are required for modeling specific interactions (pKa, metabolism, etc.)
  - Certain atoms are more important than others
  - The compound can change chemically

Atomic Descriptors

Partial atomic charges and reactivities

- EEM-Hückel charge model
  - parameterized from in-house *ab initio* database of partial atomic σ and π charges
  - EEM (Electronegativity Equalization Method) for σ charges
  - Hückel model for π charges
  - Reactivities
    - EEM σ atomic Fukui indices
    - Hückel π frontier orbital atomic densities
- E-State indices
- Local shape descriptors
  - Sheridan's SPAN
  - Atomic volumes
- Others
  - Polarizability, electronegativity, autocorrelation vectors
  - Special proprietary





- **148 localized descriptors <u>per atom</u>**
  - e.g., partial atomic charge
- **Excellent for predicting localized properties**
  - pK_a, sites of metabolism, specific binding, etc.

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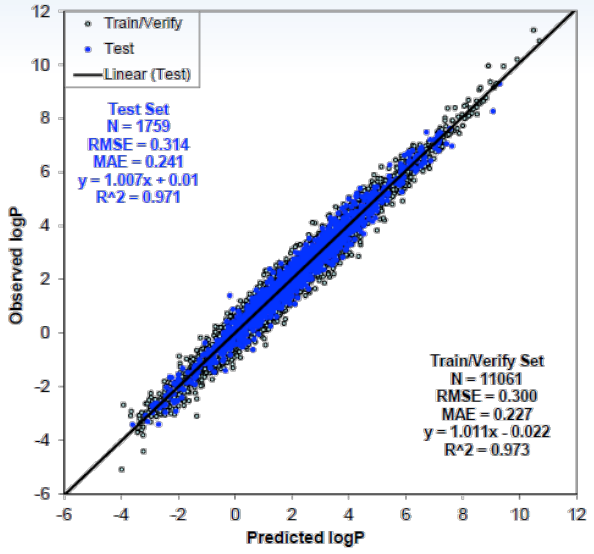
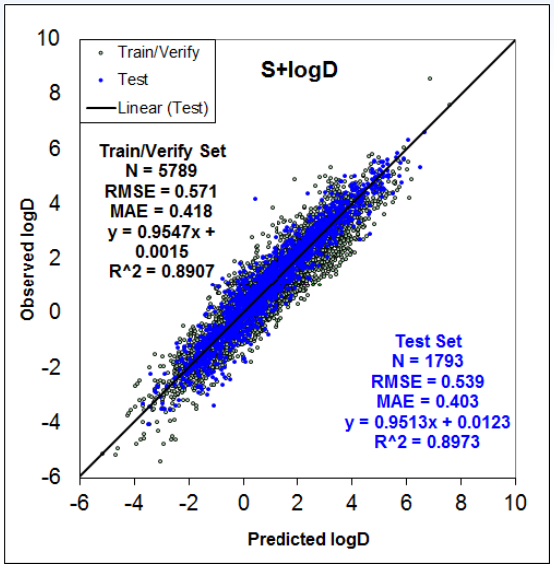
Model Performance

ADMET Predictor models are best-in-class
- verified by independent researchers

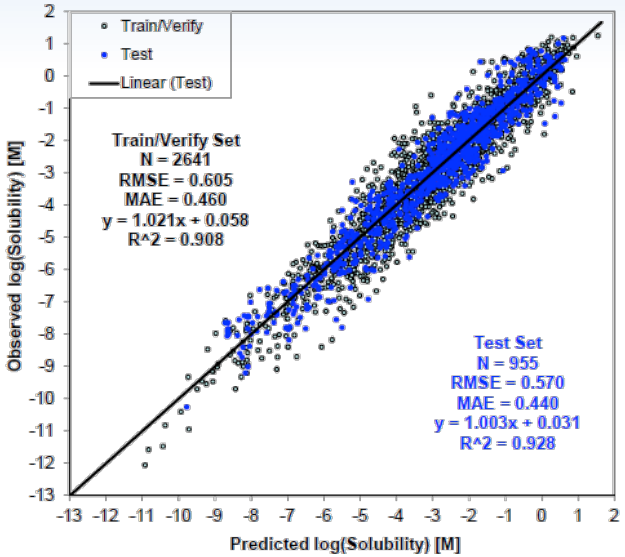
logP



logD



solubility



The user manual shows the performance of every model and describes the data used to build the model

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Third Party Validation

Independent comparison of aqueous solubility predictors

(Dearden JC. Exper. Opin. Drug Discovery 2006 1:31)

Table 4. Predictive abilities of some commercially available software for aqueous solubility prediction, based on 122-compound test-set of drugs.

Software	% Compounds predicted within ~~± 0.5 log unit~~	± 1.0 log unit	r^2	q^2	s	Ref.
SimulationsPlus	64.8	91.0	0.82	0.82	0.47	[203]
Admensa	72.1	86.9	0.76	0.74	0.65	[205]
Pharma Algorithms ADME Boxes	59.0	86.9	0.74	0.73	0.62	[206]
ChemSilico	59.8	86.0	0.67	0.65	0.73	[202]
ACDLabs	59.0	85.2	0.73	0.72	0.66	[204]
AlogS	51.6	81.1	0.67	0.66	0.73	[207]
PredictionBase	46.7	81.1	0.48	0.46	1.07	[208]
ESOL	54.9	78.7	0.60	0.59	0.84	[209]
MOLPRO	62.3	77.9	0.44	0.42	1.22	[210]
Absolv 2	44.3	74.6	0.53	0.51	0.95	[206]
QikProp	47.6	73.8	0.57	0.57	0.97	[201]
SPARC*	42.9	73.1	0.73	0.72	0.96	[211]
Cerius²ADME	37.7	72.9	0.61	0.60	1.02	[212]
WSKOWWIN	41.0	67.2	0.51	0.49	1.17	[213]
ADMEWORKS Predictor	34.4	66.4	0.42	0.39	1.24	[214]
AlogP98	38.5	62.3	0.42	0.40	0.77	[85,212]
CHEMICALC‡	23.3	45.7	0.35	0.34	1.96	[215]

*Based on 119 compounds; SPARC could not calculate solubilities of 3 compounds.
‡Based on 116 compounds, using log P method with calculated melting point, which was not available for 6 compounds; kindly calculated by Prof. G. Schüürmann.

SAMPL6 pKa Challenge

(https://en.wikipedia.org/wiki/SAMPL_Challenge)

ID	name	RMSE
xvxzd	Full quantum chemical calculation of free ener...	0.680 [0.546, 0.811]
gyuhx	S+pKa	0.730 [0.552, 0.916]
xmyhm	ACD/pKa Classic	0.774 [0.492, 1.034]
yqkga	ReSCoSS conformations // COSMOtherm pKa	0.903 [0.685, 1.117]
nb007	Epik-sequential	0.968 [0.764, 1.175]
8xt50	ReSCoSS conformations // DSD-BLYP-D3 reranking...	1.071 [0.780, 1.356]
p0jba	macroscopic pKa prediction from microscopic pK...	1.315 [0.687, 1.718]
37xm8	ACD/pKa GALAS	1.358 [0.844, 1.811]
hytjn	OE Gaussian Process	1.434 [0.976, 1.832]
q3pfp	OE Gaussian Process Resampled	1.484 [1.049, 1.865]
mkhqa	EC-RISM/MP2/cc-pVTZ-P2-phi-all-2par	1.596 [1.150, 2.037]
2ii2g	EC-RISM/MP2/cc-pVTZ-P2-q-noThiols-2par	1.683 [1.205, 2.131]
nb001	EC-RISM/MP2/6-311+G(d,p)-P2-phi-all-2par	1.702 [1.063, 2.391]
35bdm	macroscopic pKa prediction from microscopic pK...	1.719 [0.665, 2.338]
nb002	EC-RISM/MP2/6-311+G(d,p)-P2-phi-noThiols-2par	1.720 [1.080, 2.405]
ryzue	Adiabatic scheme with single point correction ...	1.745 [1.370, 2.101]

Table 2. Performance of algorithms

	Star (234)		Nostar (50)		Zwitterions (18)		Other (266)
Method	*MAE*	Rank	*MAE*	Rank	*MAE*	*AE*	*MAE*
A_S+logP	0.33	I	0.7	I	0.4	-0.01	0.4
ALOGPS[3]	0.39	I	0.7	I	0.64	-0.51	0.44
VLOGP[4]	0.50(0.41)	II	0.95(0.84)	I,III	0.87(0.69)	-0.8(-0.62)	0.56(0.47)
SLIPPER	0.58	II	0.91	I,III	1.2	-1.14	0.6
QikProp	0.58	II	1.01	III	0.83	-0.48	0.64
CSlogP	0.61	II	0.95	I,III	0.54	-0.06	0.68
TLOGP[5]	0.64	II	1.01	III	1.26	-0.97	0.69
Absolv	0.65	II	0.94	I,III	1.98	-1.97	0.61
QuantlogP[3]	0.7	II	1.03	III	1.91	-1.9	0.68
QLOGP	0.72	II	1.19	III	0.9	-0.24	0.79
VEGA[6]	0.8	III	1.07	III	1.53	0.95	0.8
AAM	1.37	IV	1.87	IV	2.96		1.36

Independent comparison of logP predictors

(Tetko & Poda, 2007)

Predicted by	Trained with	MAE	RMSE	R^2
ACD/Percepta v. 12	15932 lit pK_a	0.77	1.05	0.84
ADMET Predictor v. 6.1	14147 lit pK_a	0.73	0.95	0.86
ADMET Predictor v. 7.0	**14149 lit pK_a + 19467 Bayer pK_a**	**0.51**	**0.67**	**0.93**

The Simulations Plus-Bayer HealthCare pKa Collaboration

(Fraczkiewicz et al., J. Chem. Inf. Model. 2014)

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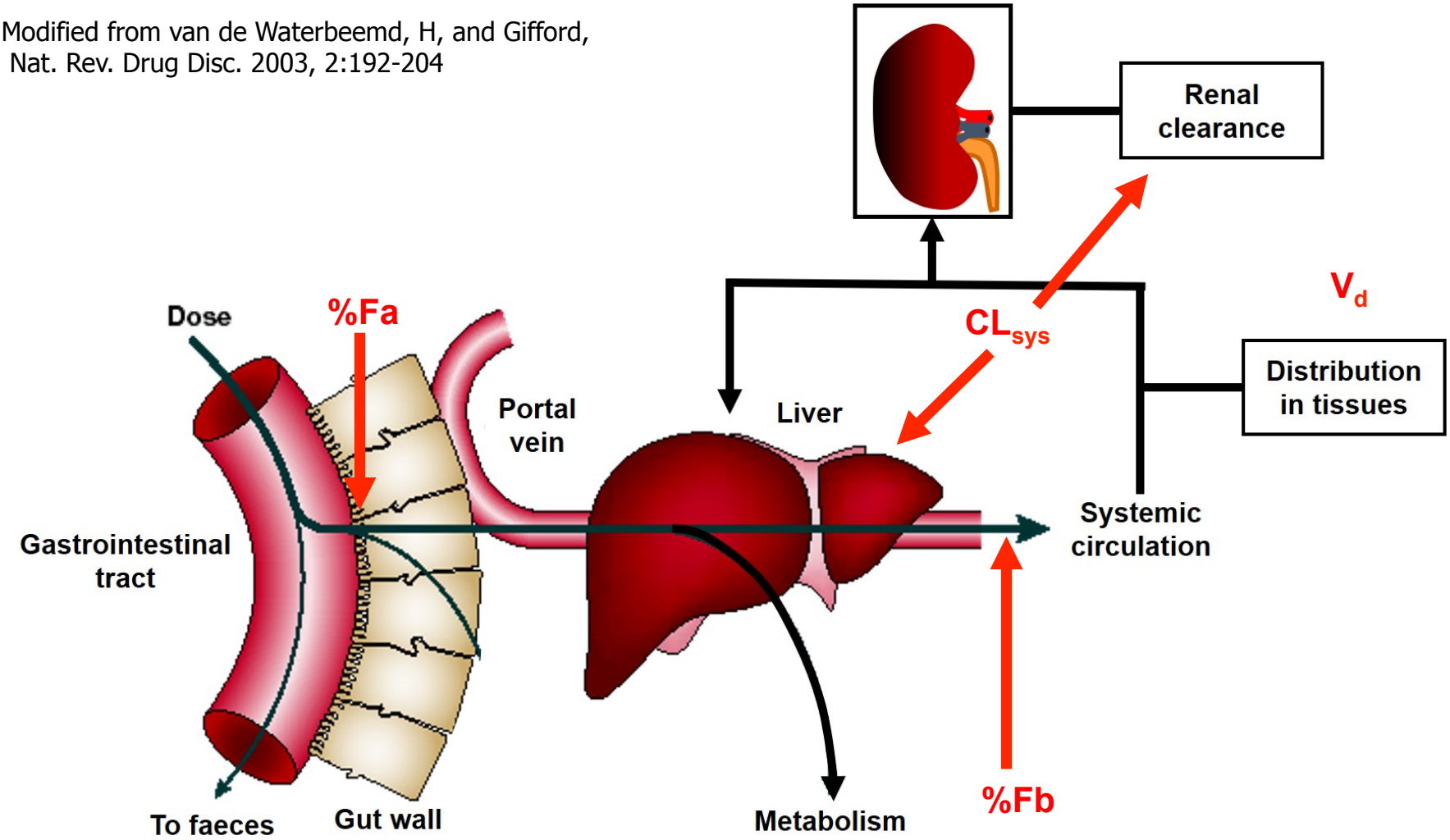
HTPK Simulation Module

- High-Throughput Pharmacokinetics
- Based on GastroPlus™ ACAT™ absorption model followed by single-compartment PK model
- Predicts fractions absorbed and bioavailable, and other PK parameters, for a given dose
- Predicts the dose required to achieve a target plasma concentration at steady state
- Human and rat species are supported
- Can use predicted or experimental physiological parameters as inputs

HTPK Simulation Module

* Modified from van de Waterbeemd, H, and Gifford, E. Nat. Rev. Drug Disc. 2003, 2:192-204



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