Early Assessment of PK Properties with the ADMET Predictor® HTPK Simulation Module

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High-Throughput PK - Vision

- Develop a simplified tool for non DMPK experts
- Provide reasonable estimates of important PK parameters at the discovery stage
- Avoid the need to input experimental values
- Identify potential development issues as early as possible, even before compounds are synthesized

ADMET Predictor® Modules

PCB

pKa, Lipophilicity
Permeability, Solubility,
Transporters

Metabolism

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

HTPK

Mechanistic
pharmacokinetics
simulations in
Human or Rat

Toxicity

Cardiac, Liver, Acute,
Carcinogenicity,
Sensitization,
Environmental

MedChem

Clustering, R Tables, Design, SAR

Modeler

QSPR Model Building

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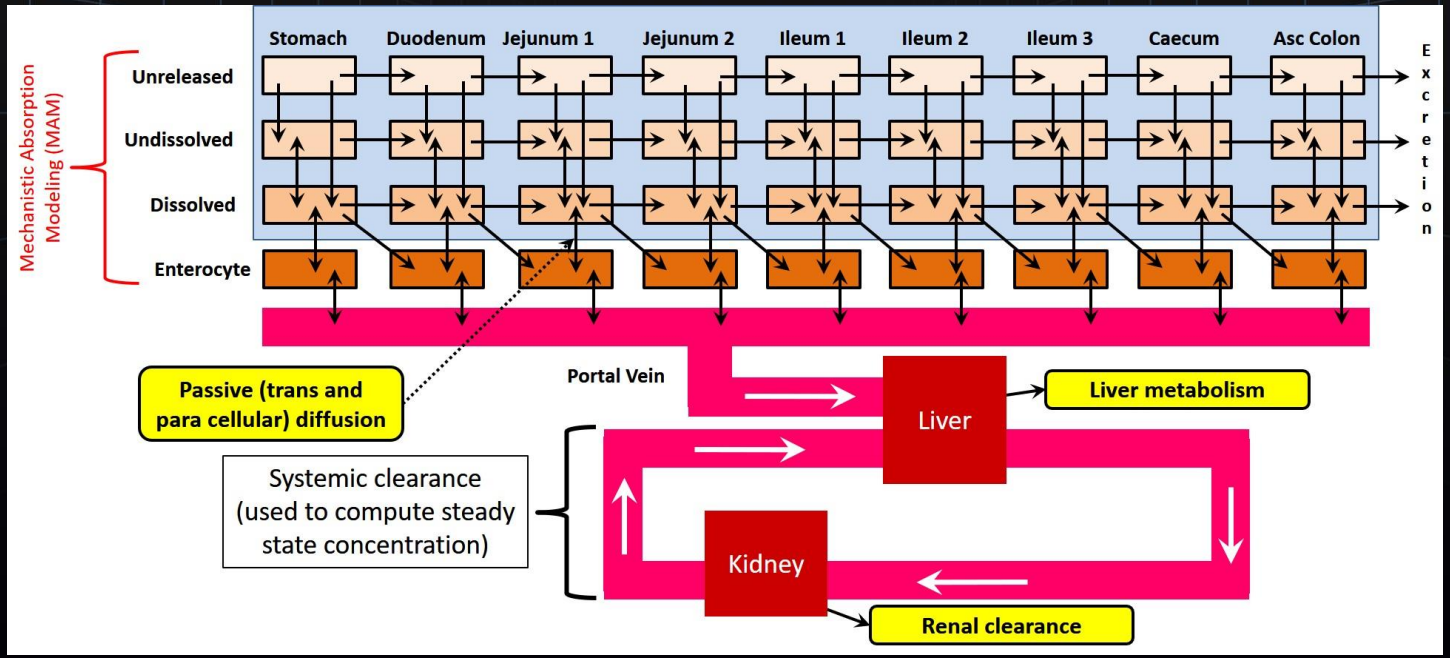
HTPK Simulation Model

ACAT™ Model* + Compartmental Model



* Advanced Compartmental Absorption and Transit Model

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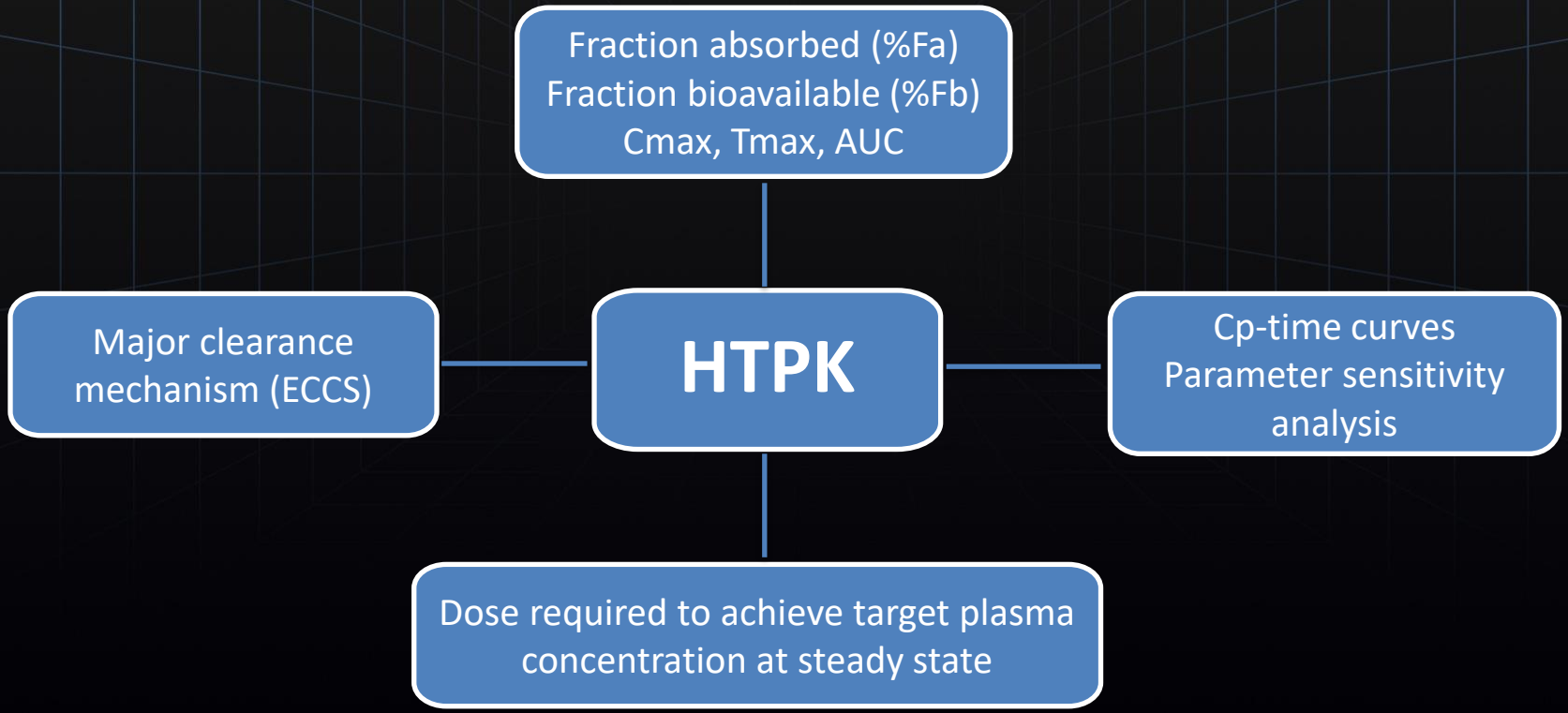
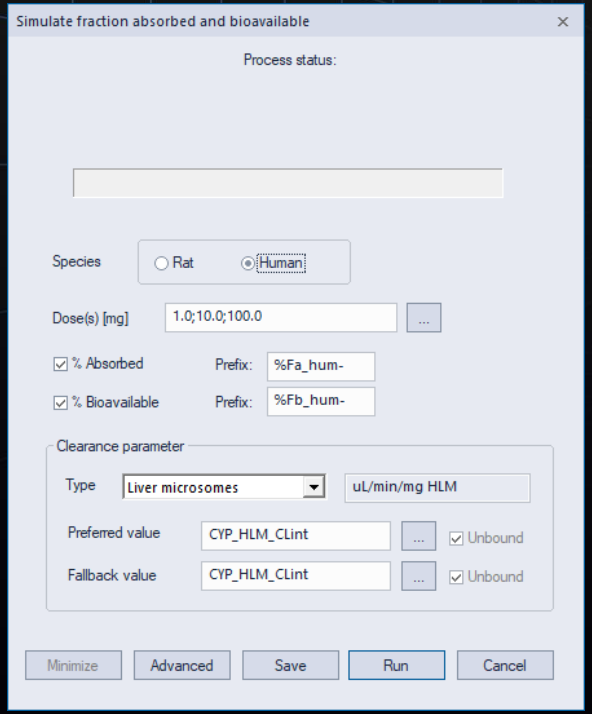
HTPK Predictions (AP 9.5)

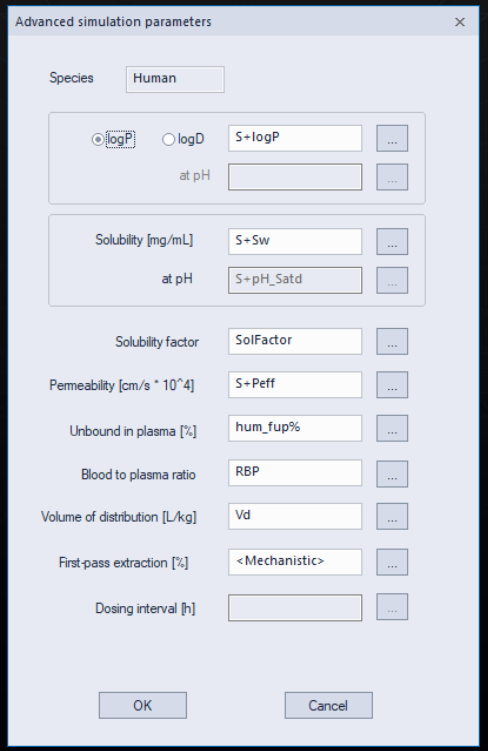


HTPK Simplifications

- Gut clearance is not considered
- Passive absorption kinetics only (paracellular included)
- Clearance is assumed to follow linear kinetics
- Enterohepatic circulation and biliary excretion not considered
- First-order precipitation kinetics assumed
- Dosage form is IR tablet
- Physiology limited to fasted adult human or rat

HTPK Input Parameters





Inputs can be experimental values or predictions

Predicted inputs can be from ADMET Predictor or your own models

Configuration files contain additional parameters (e.g., particle size)

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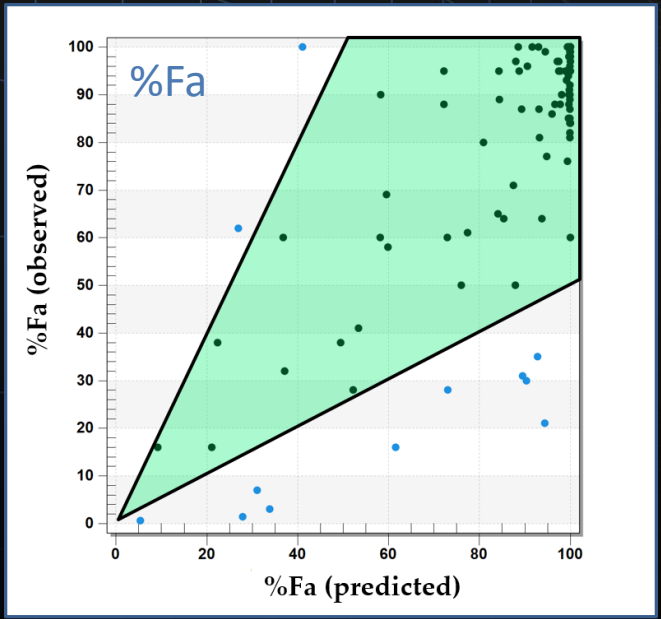
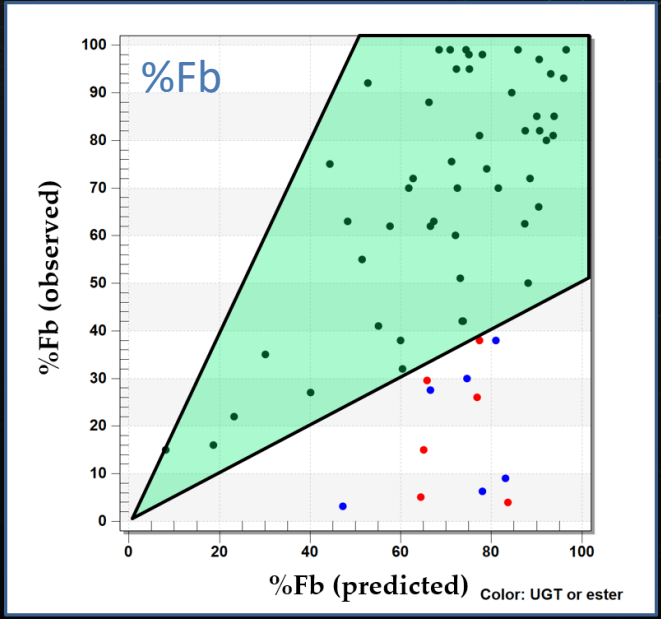
HTPK Validation



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

Only predicted properties used as inputs

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

%Fb data:
Toshimoto K et al. Drug Metab. Dispos, **2014**, 42, 1811.

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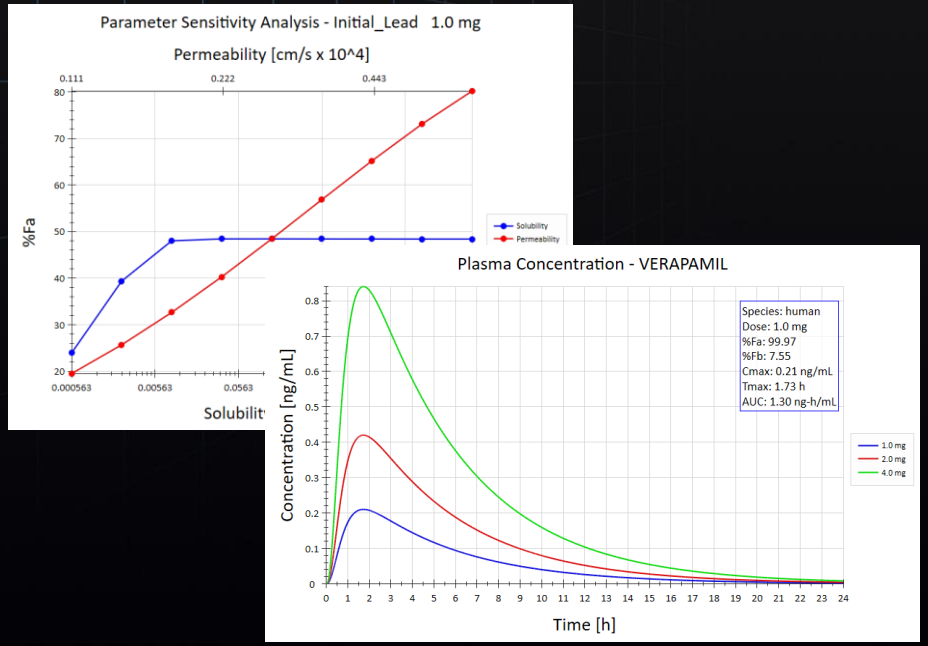
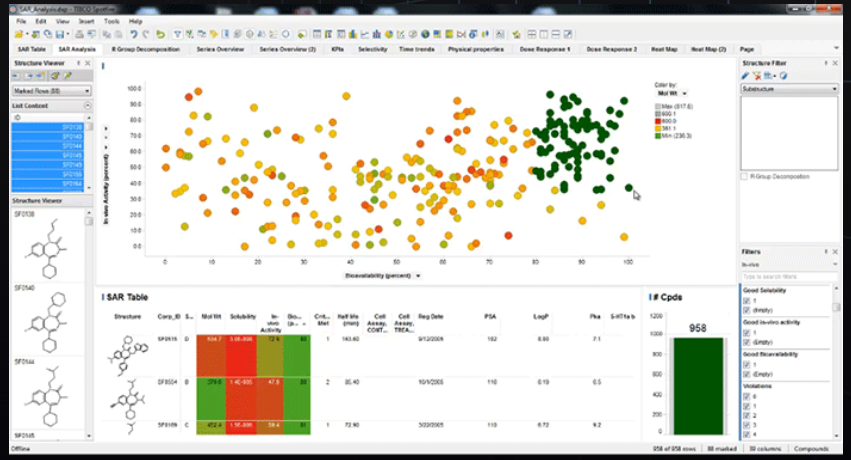
HTPK Visualization

Native ADMET Predictor®



Alternate Front End



- Command-line access (Windows + Linux)
- Workflow platforms
  - Pipeline Pilot
  - KNIME

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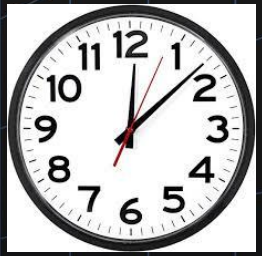
HTPK Performance



- Calculation of %Fa and %Fb in human after 24h at three different dose levels: 1 mg, 10 mg, and 100 mg.

- **10,560 diverse compounds from Enamine Diversity Set**
  - AP 9.5: 8min. 10 sec (22 cmpds/sec)
  - AP X with multithreading: 1min 44 sec (102 cmpds/sec)

HP ZBook 15v G5, Intel® Core™ i7-8750H CPU 2.2 GHz, 6 physical cores, 32 GB RAM, Windows 10 64-bit

HTPK Recent Citations

Vol 140, June 2020

Liver toxicity of anthraquinones: A combined *in vitro* cytotoxicity and *in silico* reverse dosimetry evaluation

Yitong Liu, Mapa S.T. Mapa, Robert L. Sprando

Division of Toxicology, Office of Applied Research and Safety Assessment, Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration

ADMET Predictor® X

Summer, 2020

General Features

- Parallelized predictions for multi-core CPUs
- Evolutionary multi-objective compound optimization
- Transporters module

HTPK Enhancements

- Driven by collaboration with large pharmaceutical company
- Support for multiple doses
- More PK parameters ($T_{1/2}$, CL, Cl_{plasma})
- Expanded command-line options
- Further enhancements coming in 2020

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Thank You

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