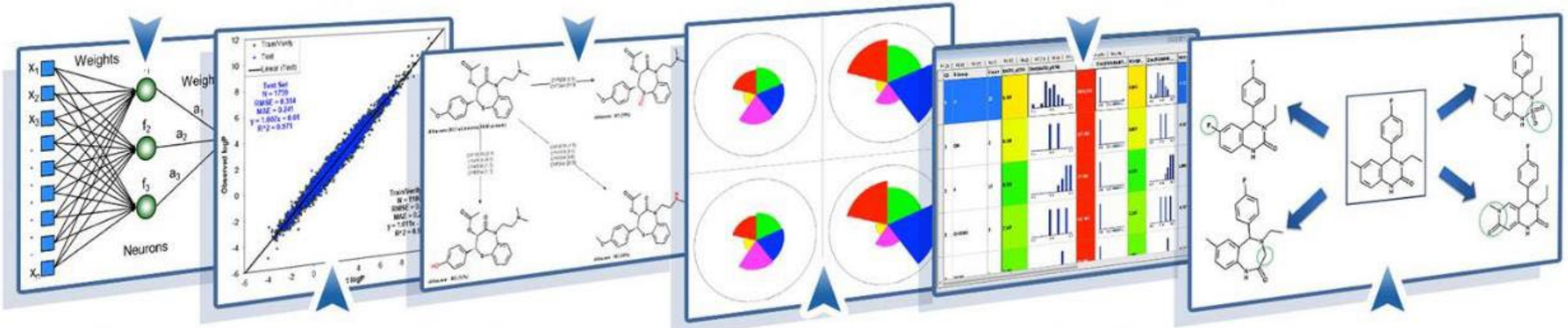
API Enabled HTPK

Deployment of Early PK Assessments for Drug Discovery

ADMET Predictor™

ADMET Property Estimation and Model Building

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



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

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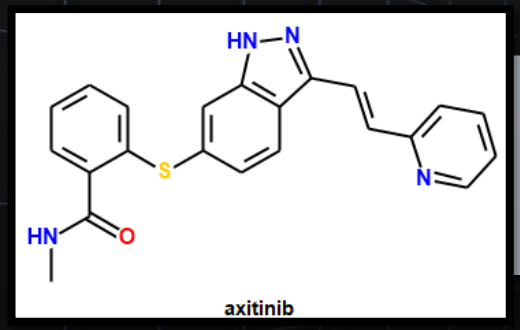
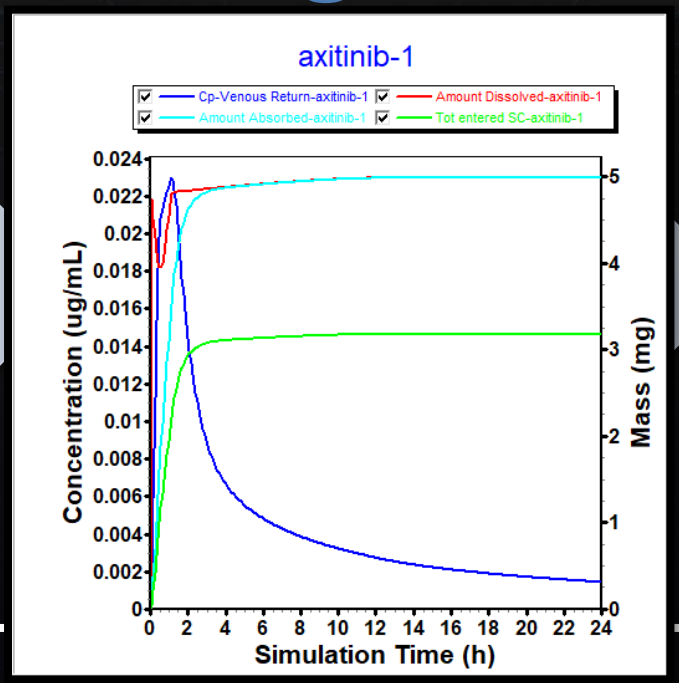
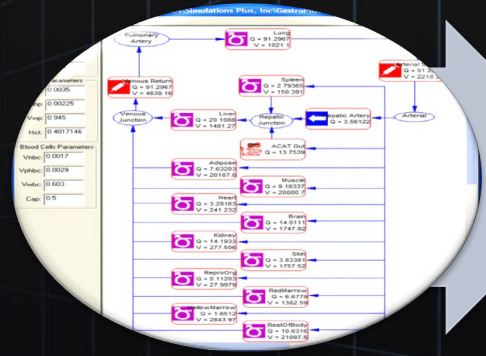
Machine Learning + PBPK Marriage







Machine Learning Models

Physiologically-Based Pharmacokinetics (PBPK)

Goal: rapidly simulate absorption and systemic exposure based on 2D chemical structures

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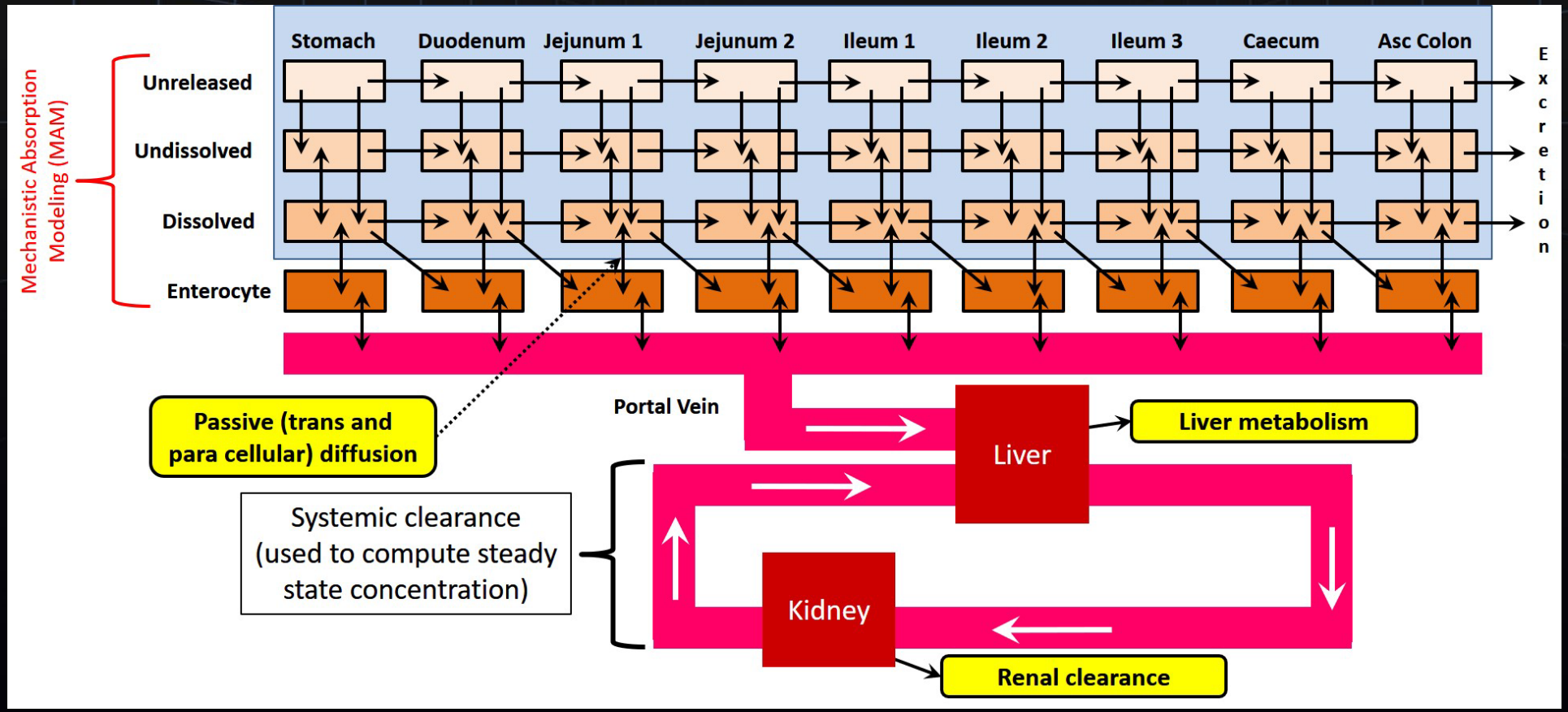
Mechanistic HTPK Simulation

GastroPlus® ACAT™ Model* + Compartmental (Minimal PBPK) Model



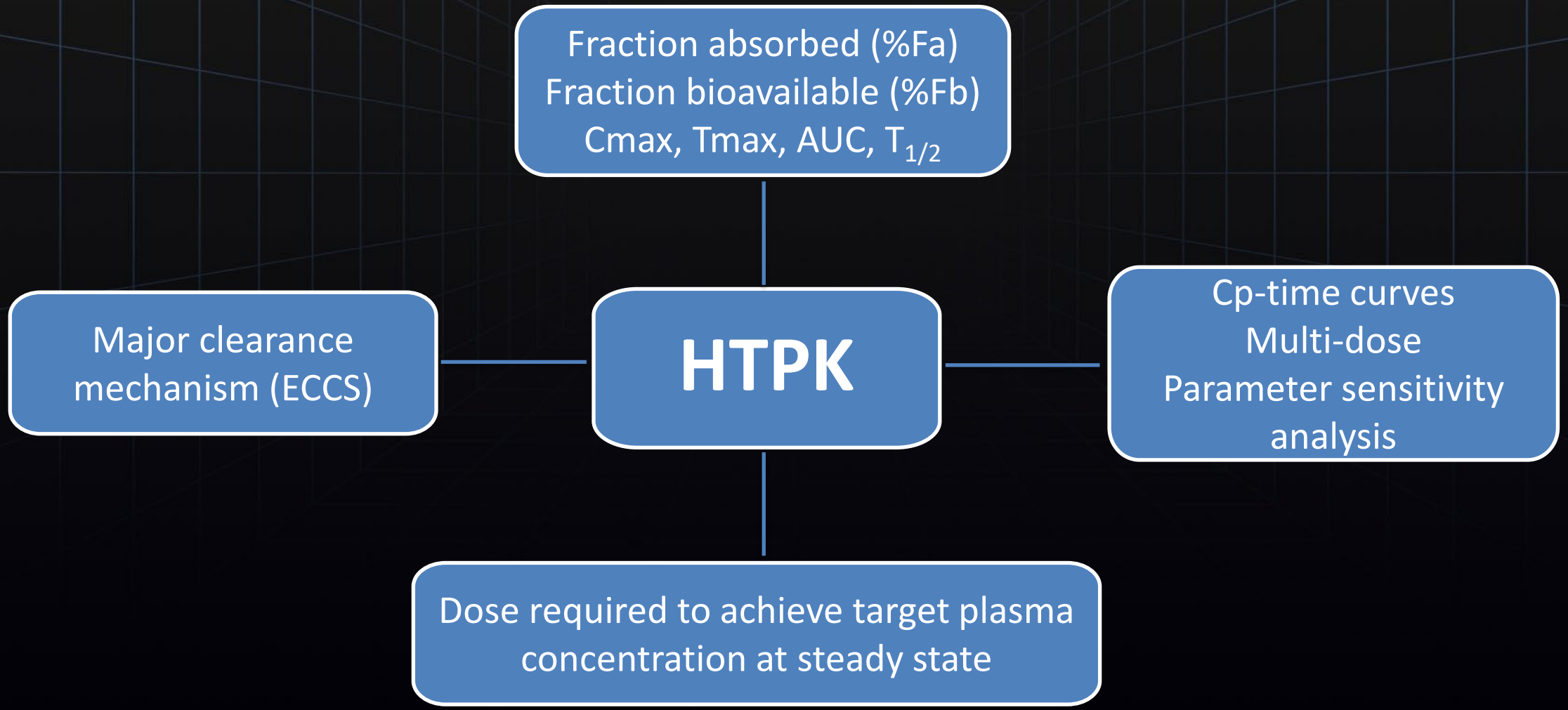
*

Advanced Compartmental Absorption and Transit Model

High-Throughput PK - Vision

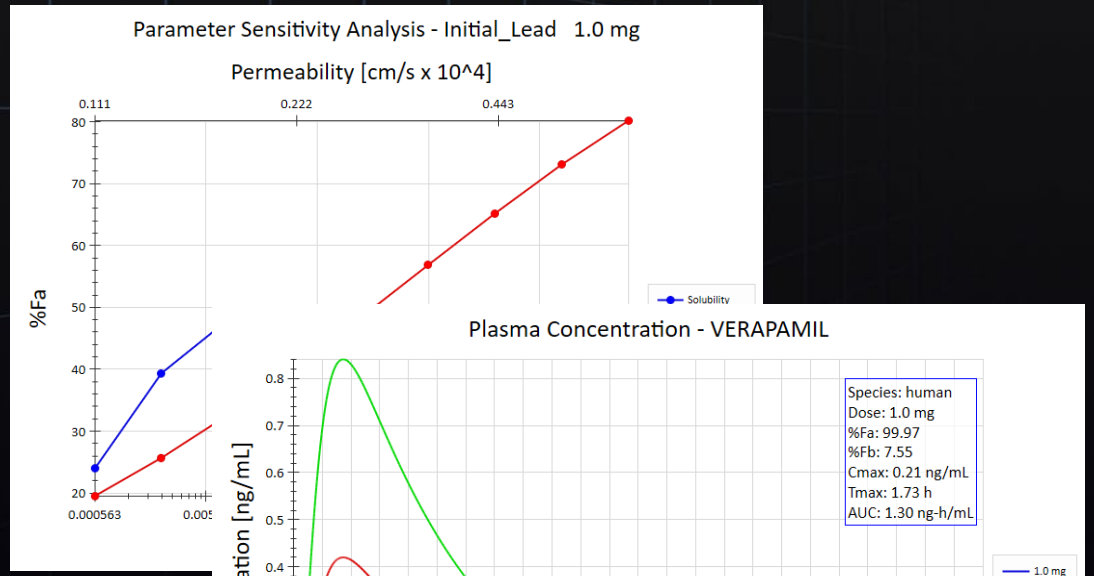
- Develop a simplified early PK assessment tool for non DMPK experts
- Identify potential development issues as early as possible, even before compounds are synthesized
- Fast-enough to incorporate mechanistic PK in AI-Driven compound optimization loops
- Provide dose and time-dependent modeling capabilities
- Avoid the need to input experimental values but allow their use if available.

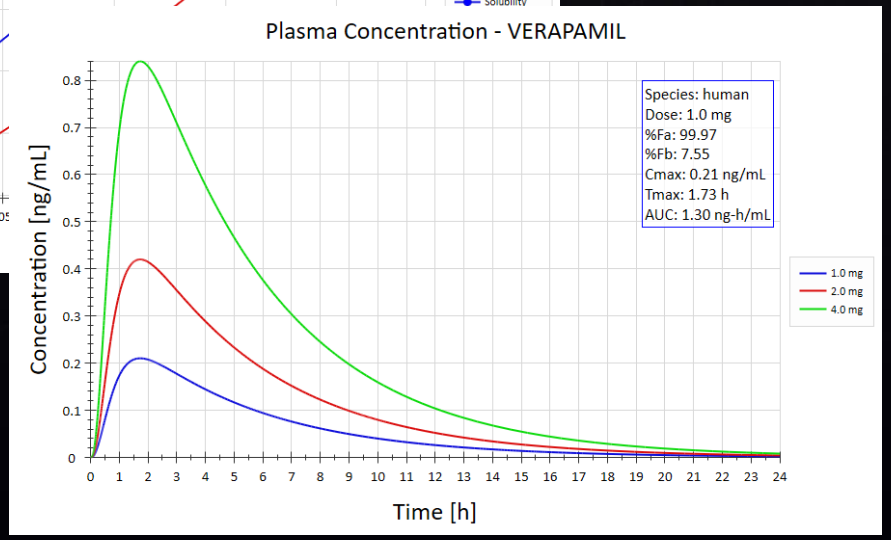
HTPK Predictions



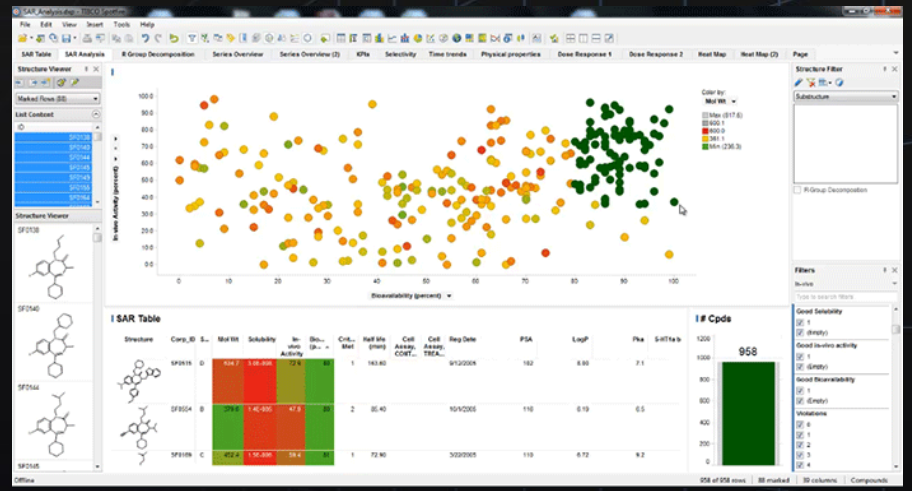
HTPK Deployment

Native ADMET Predictor®





Alternate Front End - Spotfire



Property Server Options

- Command-line access (Windows + Linux)
- Workflow platforms
  - ➢ Pipeline Pilot
  - ➢ KNIME
- New REST API

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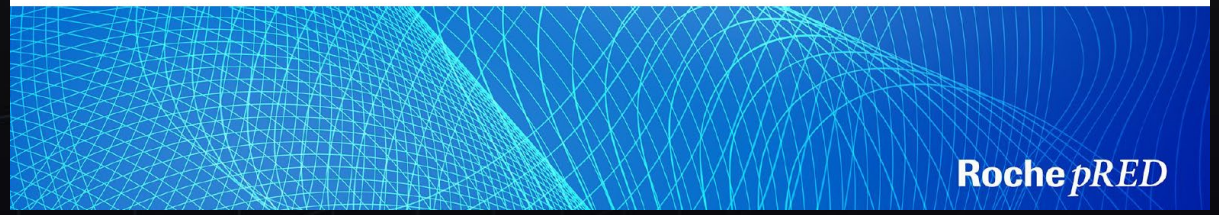
Deployment at Roche

Early assessment of PK properties using ADMET predictor HTPK Simulation Technology: Deployment of a high-throughput mechanistic PBPK approach at Roche

Dr. Andrés Olivares-Morales
Roche Pharma Research and Early Development (pRED), Roche Innovation Center, Basel, Switzerland.
21.04.2021



[Webinar Link]

[Publication Link]

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: *Mol. Pharmaceutics* 2022, XXXX, XXX, XXX-XXX
Publication Date: April 27, 2022
https://doi.org/10.1021/acs.molpharmaceut.2c00040
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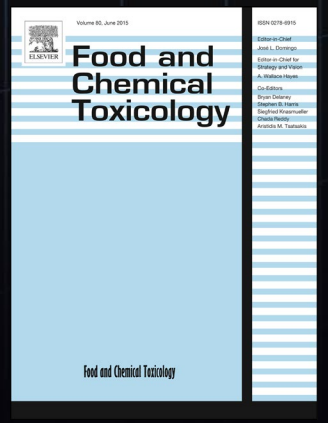
Other HTPK Citations

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



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

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

Vol 140, June 2020

Publication Link

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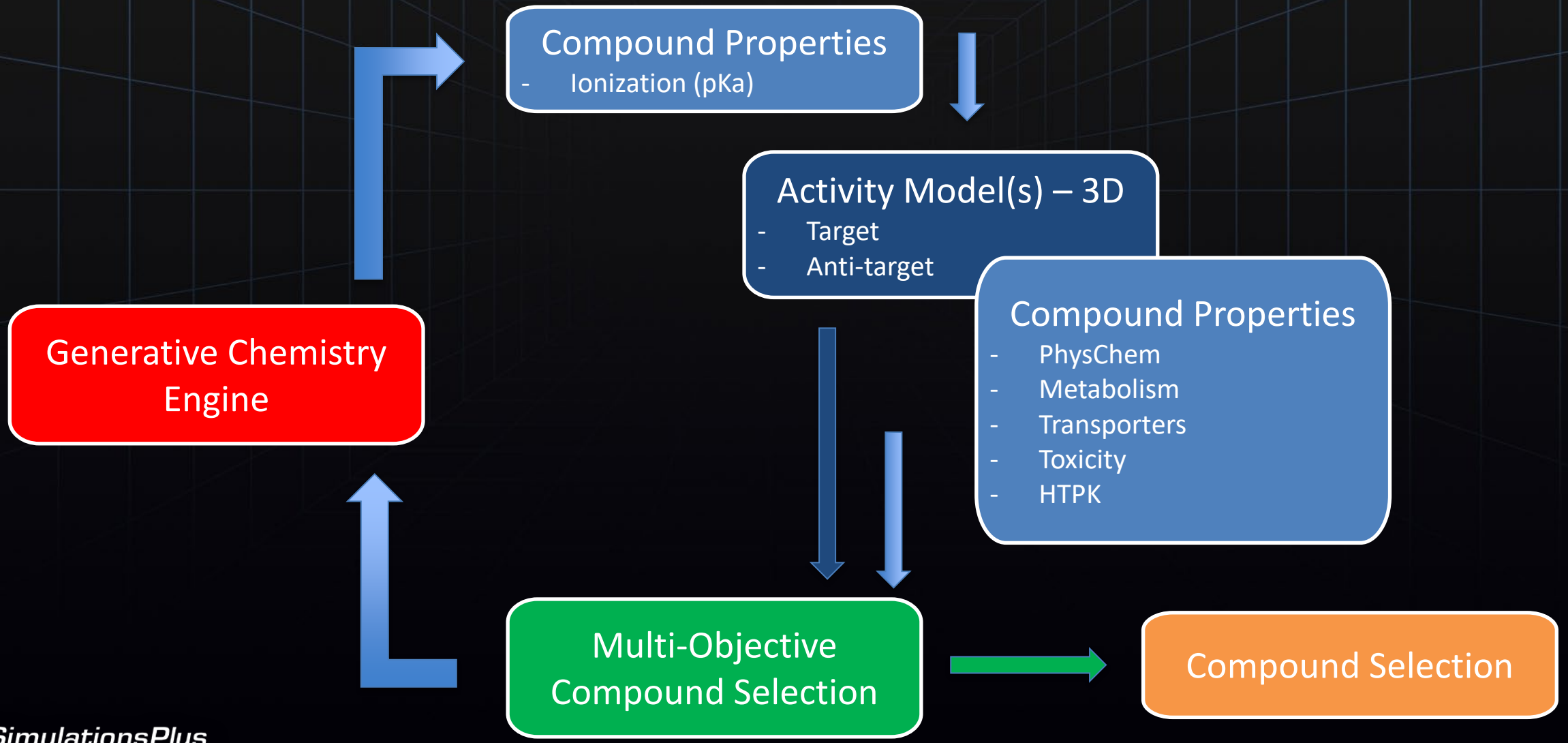
REST API - Vision

- Performance & Scope
  - Already running & available as a service
  - No start time vs command line
  - Jobs queued automatically
  - Access all model properties already in ADMET Predictor, including HTPK
  - Uses multi-threaded mode already available in ADMET Predictor
- Ease and Cost of Integration
  - Easier to integrate than command line wrappers
  - Maintain compatibility w/ command line syntax
- Licensing
  - Licenses checked out upfront
  - Avoid errors due to licenses not available in command line

Integration in AI Platform



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Performance Benchmark

Typical generation of 500 compounds per optimization cycle

- Ionization model: S+pKa models: 2.7 sec
- Solubility (S+Sw): 2.3 sec.
- %Fa from mechanistic HTPK at 10mg dose: 3 sec.

Calculation: Dell Vostro 5471 – i7-8550U 1.80 GHz
4 cores / 8 threads
16Gb RAM – 64bits – Windows 10

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Conclusions

- Mechanistic High-Throughput PK
- Truly high-throughput and multi-threaded
- Rooted in industry-leading GastroPlus® technology
- Complete flexibility to define parameter inputs
- Multiple deployment options, including API

- In-house and collaborated validation
- Use and deployment examples already available (Roche and FDA)