271

SYSTEMATIC EVALUATION OF UNDERLYING MODELS THAT IMPROVE PURELY IN-SILICO HIGH-THROUGHPUT MECHANISTIC PBPK PREDICTIONS ACROSS SPECIES

Jeremy Jones, Rafal Bachorz, David Miller, Michael Lawless, Vladimir Chupakhin, Robert Fraczkiewicz, Simulations Plus

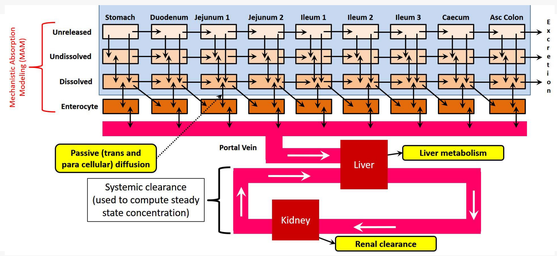
Jeremy.jones@simulations-plus.com

MAIN POINTS

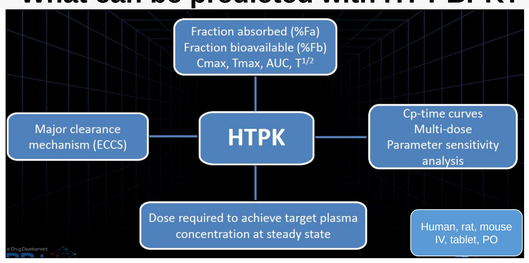
The ability to quickly and accurately predict key PK properties based solely on chemical structure can aid in several tasks:

- Prioritizing HTS hits
- Accelerating drug design/optimization
- Triaging environmental chemicals

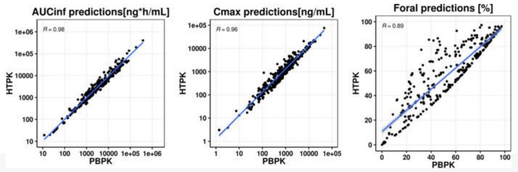
The high-throughput Physiologically Based Pharmacokinetic (HTPK Simulation) module in ADMET Predictor® (AP) achieves this task by integrating a simplified version of the GastroPlus® Advanced Compartmental Absorption and Transit (ACAT) model.



What can be predicted with HT-PBPK?



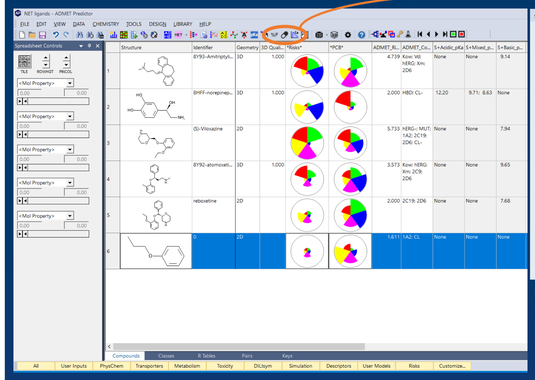
HT-PK produced comparable results to full PBPK modeling but reduced the simulation time from hours to seconds – Roche analysis

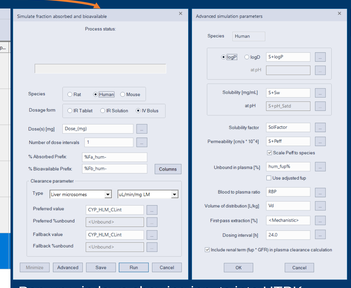


Scatter plots comparing AUC_{inf}, C_{max}, and F_{oral} predictions of the back-calculated clearance scaling method using the PBPK module (*x*-axis) vs the HTPK module (*y*-axis).
Pure *in silico* simulation, no experimental properties required!

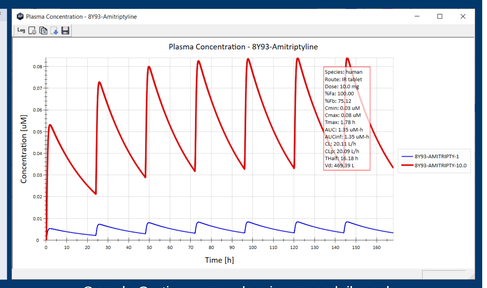
Mol Pharm. 2022 Jul 4; 19(7): 2203–2216

"This will *change the way we discover medicines* by bringing **PBPK simulations** to early drug design and optimization"





Pop-up windows showing inputs into HTPK
Clearance: liver microsomes or hepatocytes
Measured values can replace model predictions



Sample Cp-time curve showing once daily oral dosing of Amitriptyline over 7 days at 1 or 10 mg

New and improved models in AP12

Liver microsome clearance (human, rat, mouse)
Hepatocyte clearance (human, rat, mouse)
NEW: Fraction unbound to hepatocytes
- Previous Austin correction still available

Fraction unbound in plasma (human, rat, mouse)
Ratio of blood to plasma (human, rat, mouse)
Fraction unbound to microsomes
Biorelevant solubilities (FaSSIF, FeSSIF)

New route of administration (IR solution)
Predict 14 tissue partition coefficients
Adipose, brain, gut, heart, kidney, liver, etc.
Lipid-adjusted fup returned as output
Cp-time curves displayed as total or free conc.

Model improvements AP11 → AP12

Model	Train/test set size	RMSE (test)	r^2 (test)
Fup_h	1986/407→2451/649	1.333→1.098	0.508→0.606
Fup_r	1264/317→1410/353	1.311→0.920	0.511→0.518
Fup_m	1112/292→1128/316	1.287→1.008	0.650→0.663
LMCl_h	1569/277→3797/774	0.434→0.405	0.645→0.686
LMCl_r	1431/358→3707/682	0.418→0.412	0.579→0.583
LMCl_m	1075/269→1138/393	0.448→0.391	0.613→0.591
HepCl_h	1193/297→1492/383	0.518→0.393	0.458→0.497
HepCl_r	1074/269→1138/393	0.433→0.392	0.483→0.424
HepCl_m	218/55→214/71*	0.428→0.429	0.717→0.590
Fu_mic	100/14→407/75	0.160→0.131	0.878→0.863
FaSSIF	141/16→214/71	0.527→0.587	0.724→0.722
FeSSIF	139/18→161/41	0.471→0.502	0.748→0.790
RBP_h	163/41→453/114	0.095→0.084	0.446→0.551
RBP_r	372/124→558/140	0.116→0.122	0.410→0.340
RBP_m	86/22→73/16*	0.113→0.162	0.451→0.501

* Previous version had scaled non-mouse data; new version contains only mouse data

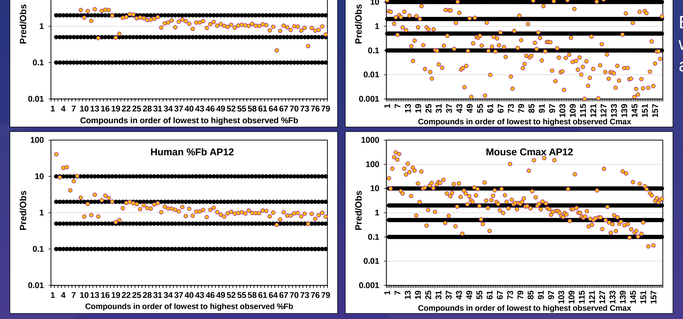
Effect of new models on in vivo PK predictions

Created a highly curated "Ground truth" PK dataset
PK endpoints: AUCt, AUCinf, Total CL, Cmax, Fb, T1/2, Vd
Only use data with a single, specified dose
Divide by species (h/r/m) and route of administration

Compare AP11 to AP12
Swap in one new model at a time or all at once and evaluate metrics

PK dataset: # measured values

	Fb	AUCinf	AUCt	Cmax	T1/2	CL	Vdss
Human oral	78	42	27	61	39		
Mouse po	92	59	79	161	116	37	
Rat po	232	197	57	295	63	88	
Human iv						154	156
Mouse iv						81	
Rat iv				47	103	98	



Predicted/Observed plots
Boundaries for predictions within 2-fold and 10-fold are displayed as black lines

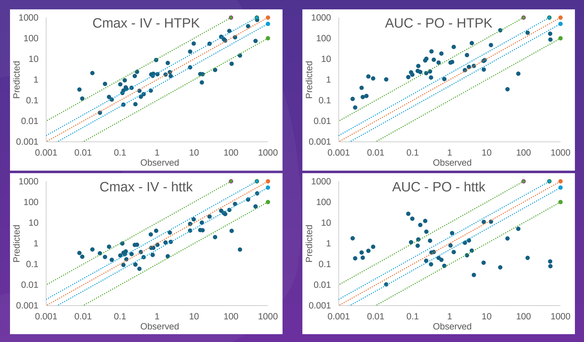
Conclusions:

Effects of individual new models were nearly all minor and somewhat unpredictable: some better, some worse
Full combination of new models led to overall modest improvements in PK predictions
-- IR solution route improved predictions for oral gavage delivery in rodents
-- Although only modest improvements, the chemical space covered by the models increased significantly
Future Directions: improve solubility/permeability models, optimize equations, increase size of PK dataset

Subset analysis: environmental chemicals

- Performed HTPK analysis on 45 mostly environmental chemicals (Wambaugh 2018) with known rat Cmax and AUC values
- Created predicted vs observed plots to ascertain the accuracy of predictions using **purely in silico predictions**
- Compared to httk results, which used **measured** fup and CLint values
  - The high throughput toxicokinetics (httk) platform is provided as a freely available R package from the US EPA

Toxicol Sci. 2018 May; 163(1): 152–169



	% within 2-fold		RMSE	
	httk	HTPK	httk	HTPK
PO-AUCt	23.2%	16.3%	349.4	290.3
PO-Cmax	11.1%	20.0%	42.5	55.8
IV-AUCt	21.3%	36.2%	74.6	50.4
IV-Cmax	38.8%	32.7%	77.8	77.1

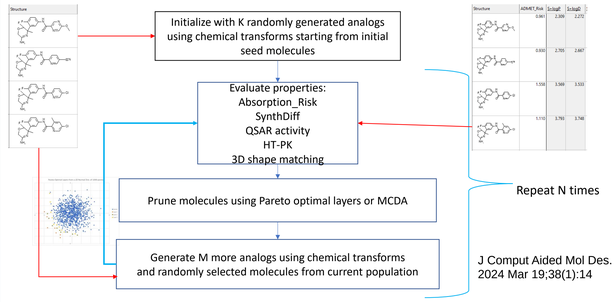
Conclusions:

- HTPK performs well against this small subset of environmental chemicals, but not as well as against the larger set of pharmaceutical compounds
- Outperforms httk in most metrics despite using in silico predictions vs measured values
- Compared to other platforms, HTPK has:
  - More thorough mechanistic input
  - Better underlying models
  - Faster calculations
  - More comprehensive output and analysis

CASE STUDY: Using HTPK in Early Drug Discovery for Novel RORγT inverse agonists

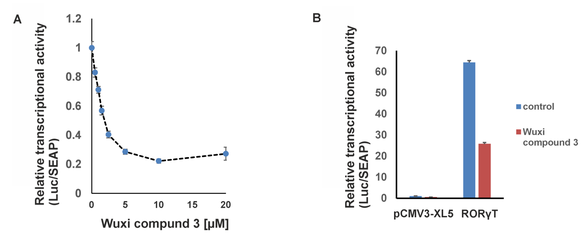
SLP scientists collaborated with the Polish Academy of Sciences (PAS) to design novel RORγT inverse agonists. RORγT inhibitors have been proposed to treat autoimmune diseases, but current scaffolds have toxicity-limiting utility.
The AI-driven Drug Design (AIDD) module was used to create novel inverse agonists for testing at PAS.

Automating the de novo drug design process: AIDD



J Comput Aided Mol Des. 2024 Mar 19;38(1):14

- A QSAR model was built using RORγT inverse agonist data from the literature.
- AIDD optimization parameters used are shown above.
- A multi-criteria decision analysis (MCDA) algorithm was used to rank compounds.
- The most similar commercially-available compounds were purchased from the Enamine REAL and WuXi GalaXi collections.
- These "AIDD-adjacent" molecules were evaluated in cell-based RORγ luciferase reporter assays.



Luciferase reporter assay in HepG2 (A) and Jurkat (B) cells

RESULTS AND CONCLUSIONS

- Despite limiting the universe of compounds to those from synthesis-on-demand collections, we found that 21/27 (**78%**) of the selected compounds inhibited RORγT activity in a cell-based assay by at least 25% at 10uM.
- These compounds have great predicted ADMET and PK properties, as these parameters were included in the design and optimization process.
- The most potent compound had a measured IC_{50} of 1.29uM (predicted IC_{50} was 1.28uM) and demonstrated activity in human T cells.
- This compound has an indolazine scaffold that has not yet been reported in the context of RORγT and represents an advanced pre-clinical lead from the very first round of the DMTA cycle.

SimulationsPlus

www.simulations-plus.com