HTPK: Conducting PK modeling and simulations at high speed

November 5, 2018

Robert Fraczkiewicz, David Miller, Marvin Waldman, Robert D. Clark

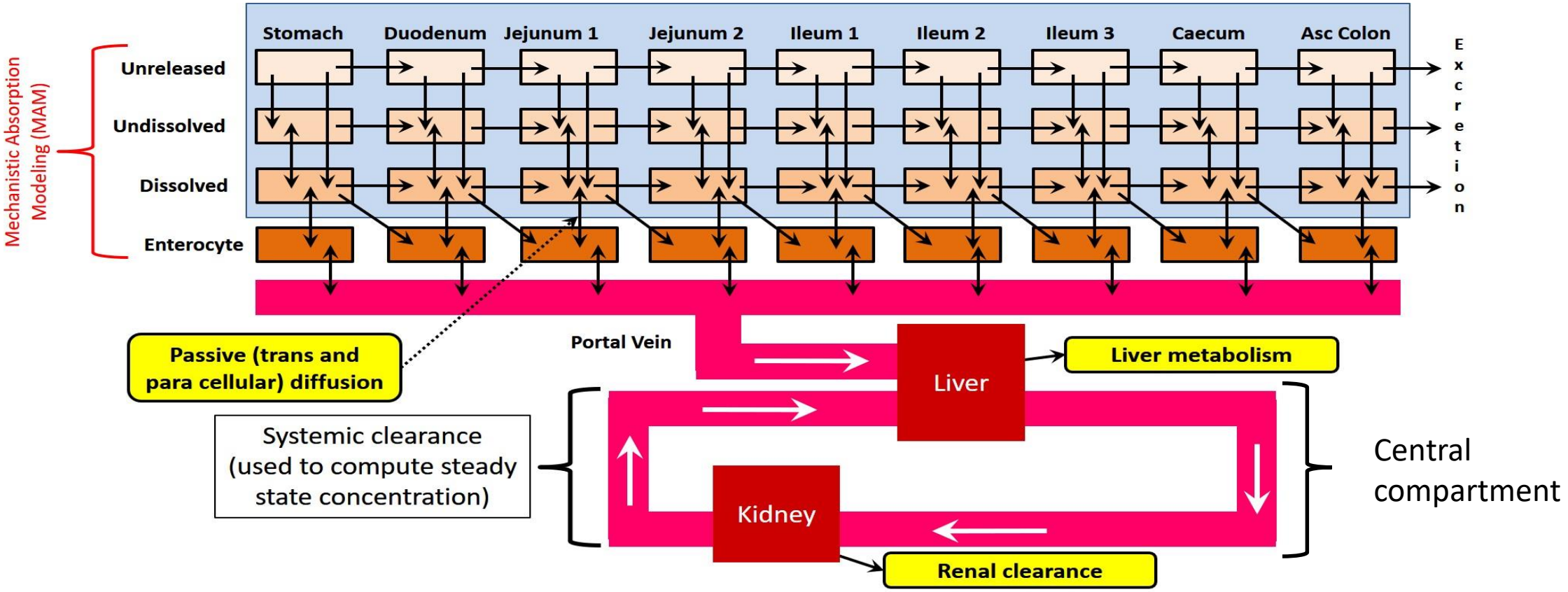
Session Description and Objectives

- HTPK lightens the burden of collecting and preparing input variables for full blown PK simulations by using structure-based predictions. In addition, batch processing and computational performance enable very fast screening and make it a viable tool in drug discovery.
- Objective: To compare predicted percent absorbed and percent bioavailable between the high throughput PK (HTPK) simulation module of ADMET Predictor™ and the ACAT™ / compartmental PK predictions from GastroPlus™ and tests its performance.

Biography and Contact Information

- Research Fellow at Simulations Plus, Inc.
- 20 years of experience in predictive molecular modeling and related software development.
- Author of the HTPK module.
- Robert@simulations-plus.com

Advanced Compartmental Absorption and Transit (ACAT™) model used by HTPK



- A system of 28 nonlinear ordinary differential equations

HTPK inputs

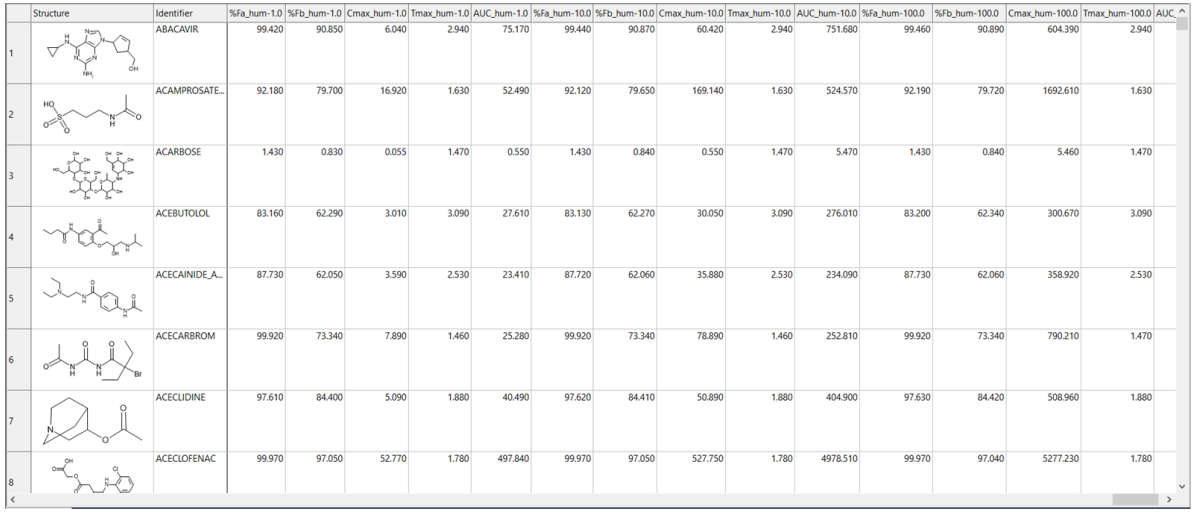
Input required for %Fa and %Fb	Corresponding ADMET Predictor model
Diffusivity in water	DiffCoef
Solubility in water	S+Sw
Salt solubility factor	SolFactor
Solubility in fasted intestinal fluid	S+FaSSIF
Solubility in fed intestinal fluid	S+FeSSIF
pKa	S+pKa
Human jejunal permeability	S+Peff
log P	S+logP
Volume of distribution	Vd
Percent unbound in plasma	hum_fup%
Microsomal fraction unbound	S+fumic
Metabolic clearance	CYP_HLM_CLint
Blood to plasma ratio	RBP
Precipitation time	<user input>
Dose	<user input>
Dose volume	<user input>
Particle radius	<user input>
Body weight	<user input>

- Any of the predicted inputs can be replaced by experimental values, if available.

HTPK outputs

Outputs generated by the %Fa/%Fb model
Fraction absorbed
Fraction bioavailable
Cp(t) = plasma concentration vs. time profile
C_max = maximum plasma concentration
t_max = time of peak plasma concentration
AUC = area under the Cp(t) curve
Sensitivity to permeability and solubility
Mechanistic estimation of the volume of distribution

Outputs generated by the OptDose model
Optimal dose to reach desired plasma concentration at steady state



	Structure	Identifier	%Fa_hum-1.0	%Fb_hum-1.0	Cmax_hum-1.0	Tmax_hum-1.0	AUC_hum-1.0	%Fa_hum-10.0	%Fb_hum-10.0	Cmax_hum-10.0	Tmax_hum-10.0	AUC_hum-10.0	%Fa_hum-100.0	%Fb_hum-100.0	Cmax_hum-100.0	Tmax_hum-100.0	AUC_
1		ABACAVIR	99.420	90.850	6.040	2.940	75.170	99.440	90.870	60.420	2.940	751.680	99.460	90.890	604.390	2.940	
2		ACAMPROSATE...	92.180	79.700	16.920	1.630	52.490	92.120	79.650	169.140	1.630	524.570	92.190	79.720	1692.610	1.630	
3		ACARBOSE	1.430	0.830	0.055	1.470	0.550	1.430	0.840	0.550	1.470	5.470	1.430	0.840	5.460	1.470	
4		ACEBUTOLOL	83.160	62.290	3.010	3.090	27.610	83.130	62.270	30.050	3.090	276.010	83.200	62.340	300.670	3.090	
5		ACECAINIDE_A...	87.730	62.050	3.590	2.530	23.410	87.720	62.060	35.880	2.530	234.090	87.730	62.060	358.920	2.530	
6		ACECARBROM	99.920	73.340	7.890	1.460	25.280	99.920	73.340	78.890	1.460	252.810	99.920	73.340	790.210	1.470	
7		ACECLIDINE	97.610	84.400	5.090	1.880	40.490	97.620	84.410	50.890	1.880	404.900	97.630	84.420	508.960	1.880	
8		ACECLOFENAC	99.970	97.050	52.770	1.780	497.840	99.970	97.050	527.750	1.780	4978.510	99.970	97.040	5277.230	1.780	

HTPK caveats

- The dose is fixed as an immediate release tablet.
- Any precipitate is presumed to have the same particle size as the original dosage form. The particle size is 25 μm by default but can be adjusted. Precipitation process is described by simpler equations in HTPK.
- Liver metabolism relies on QSAR models for predicting oxidation mediated by rat and human microsomal cytochrome P450s (CYPs). Glucuronidation is not accounted for quantitatively, nor are plasma or esterase activities.
- No provision is made for enterohepatic circulation (EHC) or biliary excretion.
- No active transport.
- Only fasted adult male rat and human physiologies are currently supported.

HTPK performance

- Calculation of fraction absorbed and fraction bioavailable in human after 24 h at **three** different IR doses: 1 mg, 10 mg, and 100 mg.
- 2284 diverse drugs extracted from World Drug Index.

Platform (*)	Processing time for 2284 drugs
Laptop A	3.9 min (~0.1 s/drug)
Laptop B	2.5 min (~0.06 s/drug)

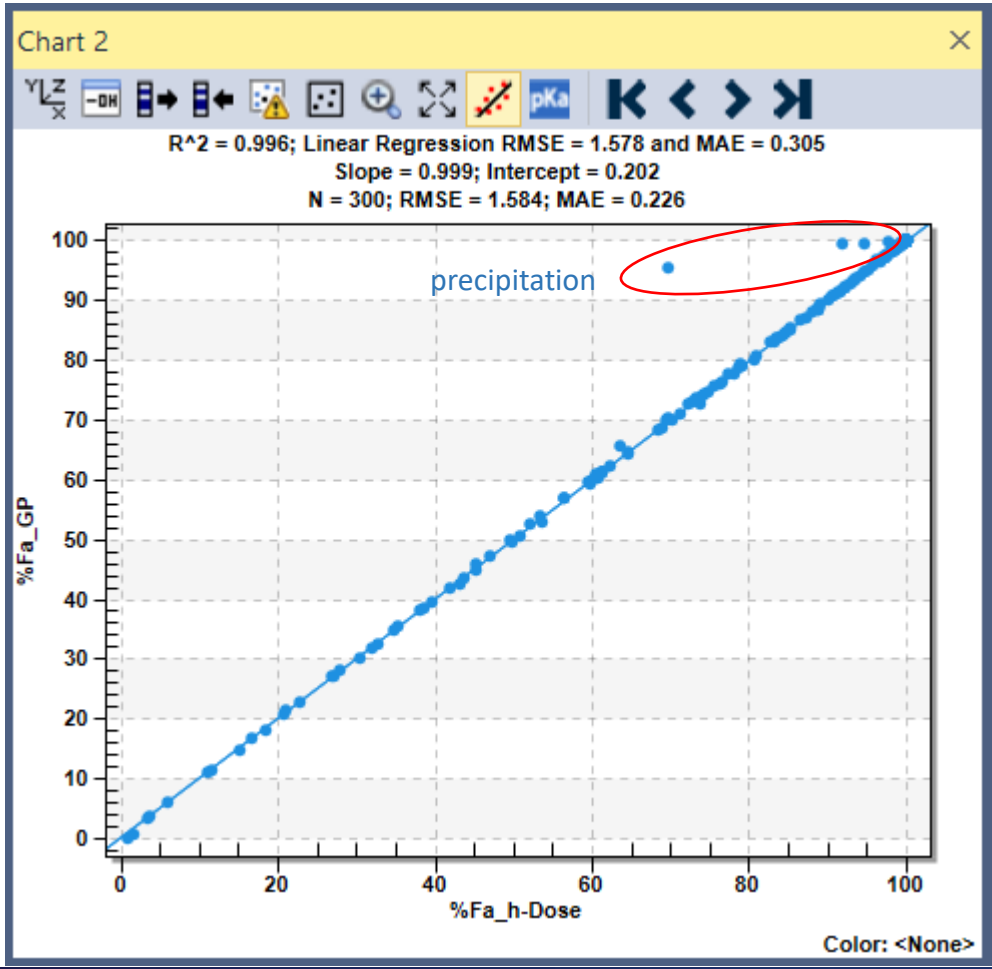
(*)

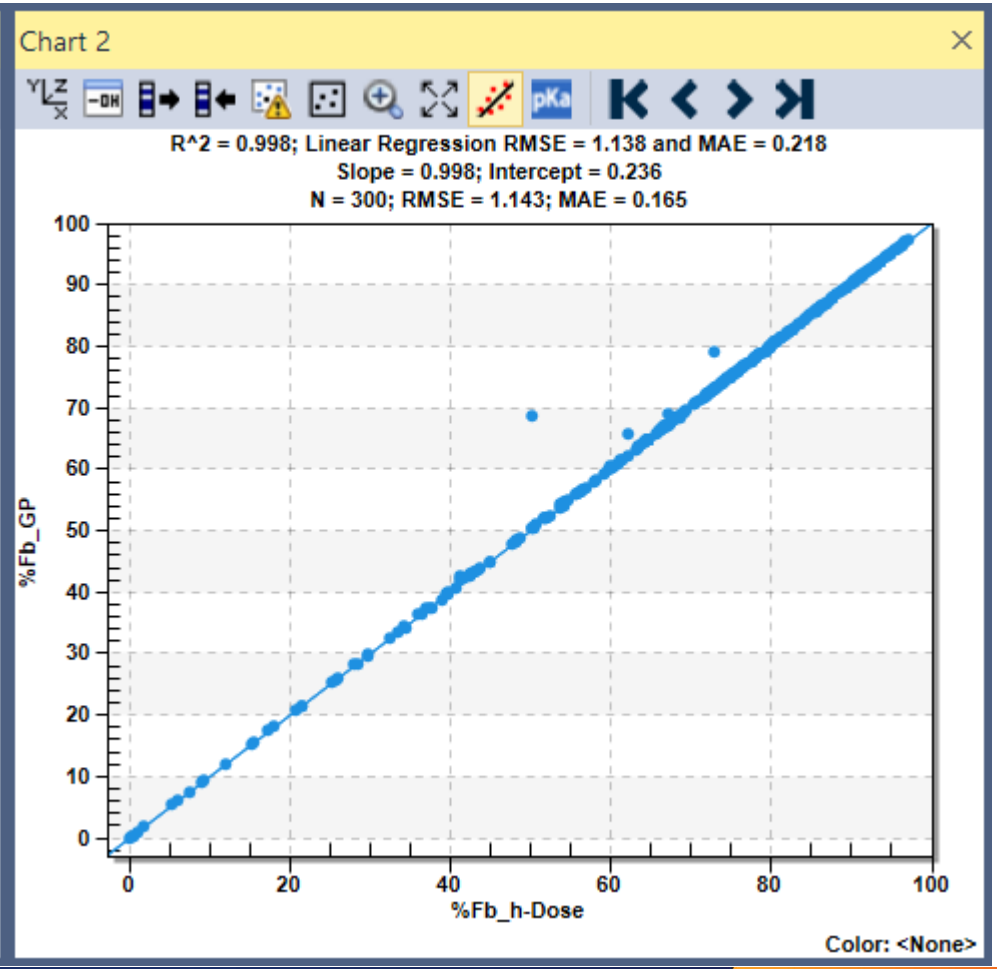
- *A = DELL XPS with Intel® Core™ i7-3537U CPU 2.5 GHz, 8 GB RAM, 64-bit, running Windows 7.*
- *B = ASUS R.O.G. with Intel® Core™ i7-7700HQ CPU 2.8 GHz, 16 GB RAM, 64-bit, running Windows 10.*

HTPK validation

%Fa and %Fb at 10 mg dose HTPK results compared against compartmental PK results obtained in GastroPlus™ v9.6 for a subset of 300 drugs extracted from the World Drug Index.

%Fa

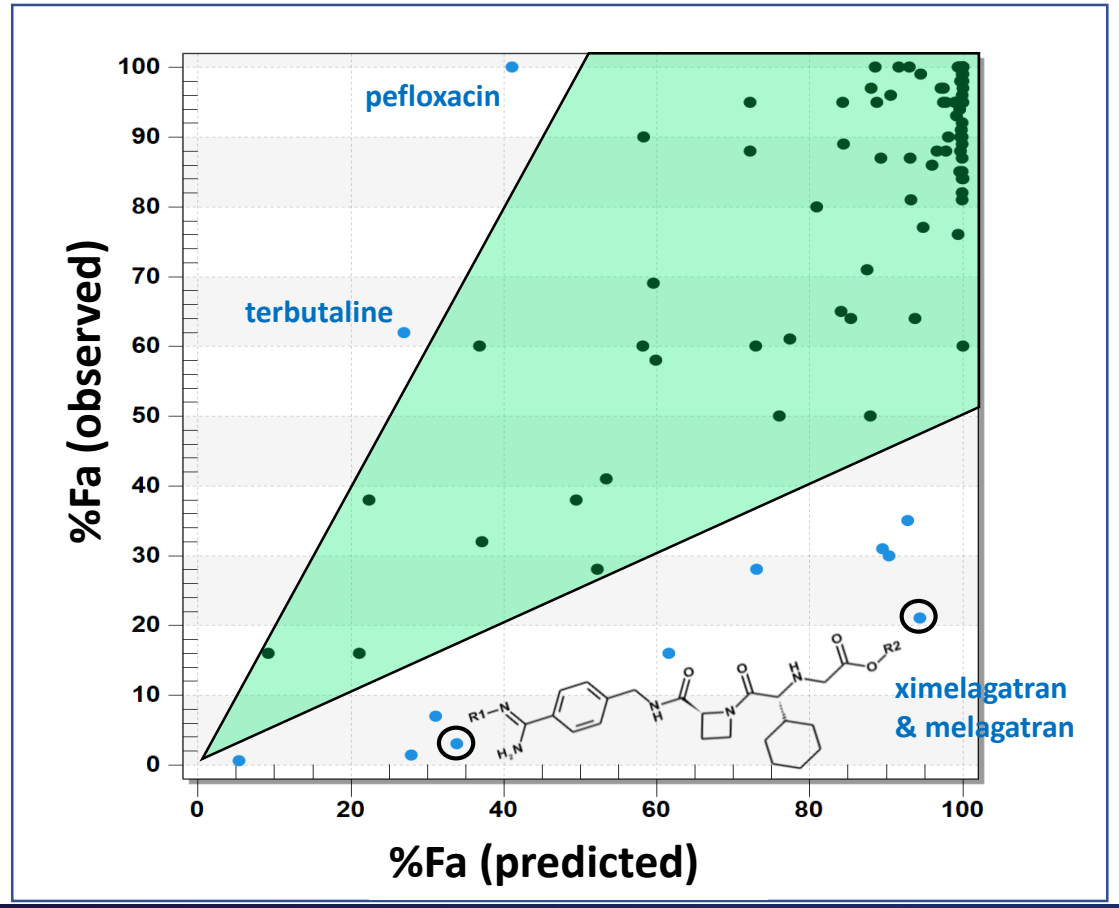




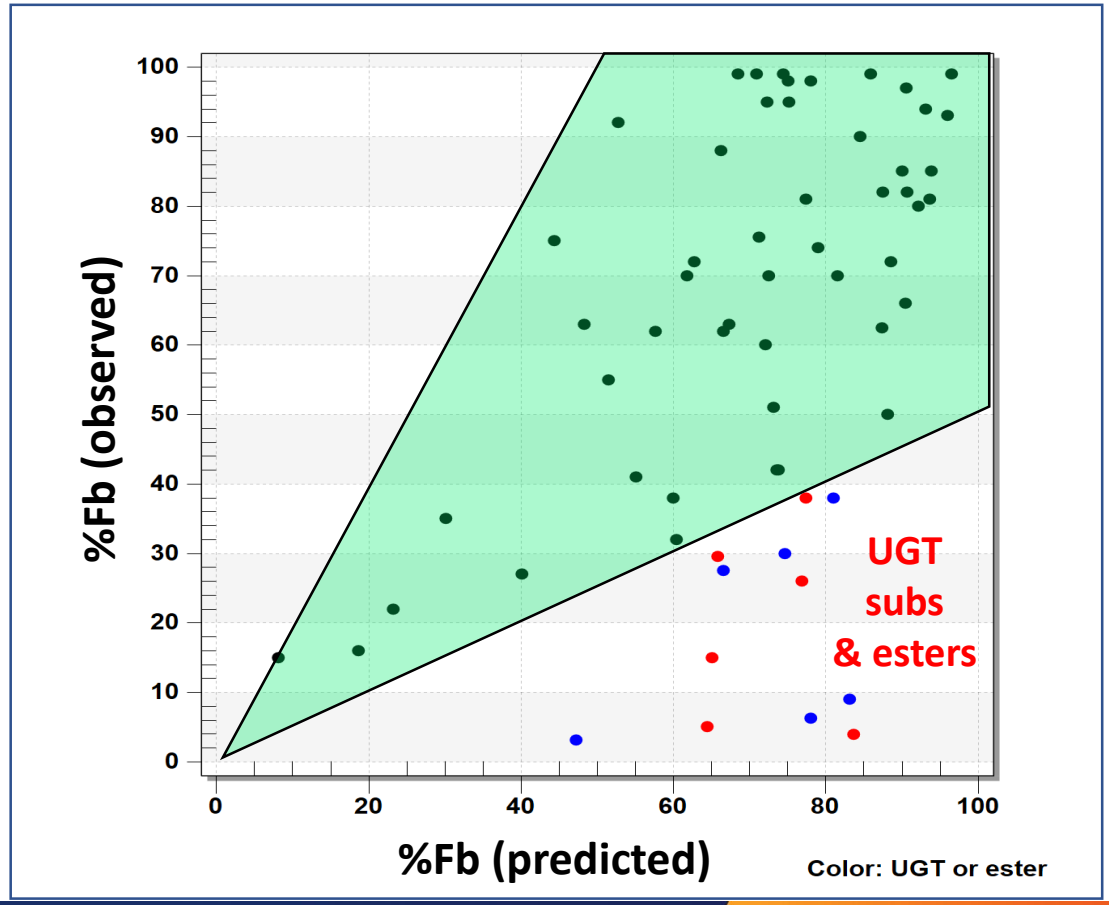
%Fb

HTPK validation

Predicted and observed human %Fa for 115 passively-absorbed compounds published in [Zhao et al. J. Pharm. Sci., **2001**, 90: 749.] 90% predicted were within 2-fold of the reported value, while 83% predicted were within 1.5-fold. There is some indirect evidence that pefloxacin and terbutaline are influx transporter substrates. Ximelagatran and melagatran are subjects to efflux.



Predicted and observed human %Fb for 62 compounds metabolized primarily by hepatic CYPs [Toshimoto et al. Drug Metab. Dispos. **2014**, 42:1811.] 81% predicted were within 2-fold of the reported value, while 68% predicted were within 1.5-fold. Some outliers are determined to be P-gp and/or UGT substrates.



Questions