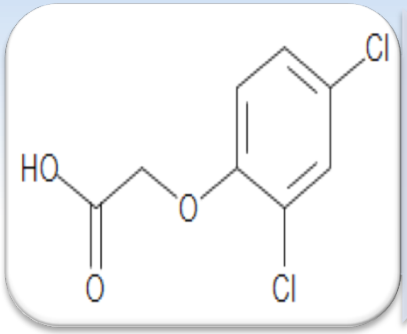
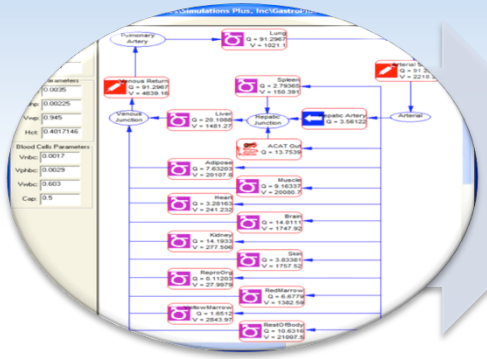
Saying “I do” to the QSAR/PBPK marriage…

Goal: **reliably** and **efficiently** utilize PBPK modeling
to reduce animal/human testing



Permeability, solubility vs. pH, pKa(s), logD vs. pH, Fup, blood:plasma ratio, tissue Kps, CLint, CLfilt



Quantitative Structure Activity Relationships (QSAR)

Physiologically-Based Pharmacokinetics (PBPK)

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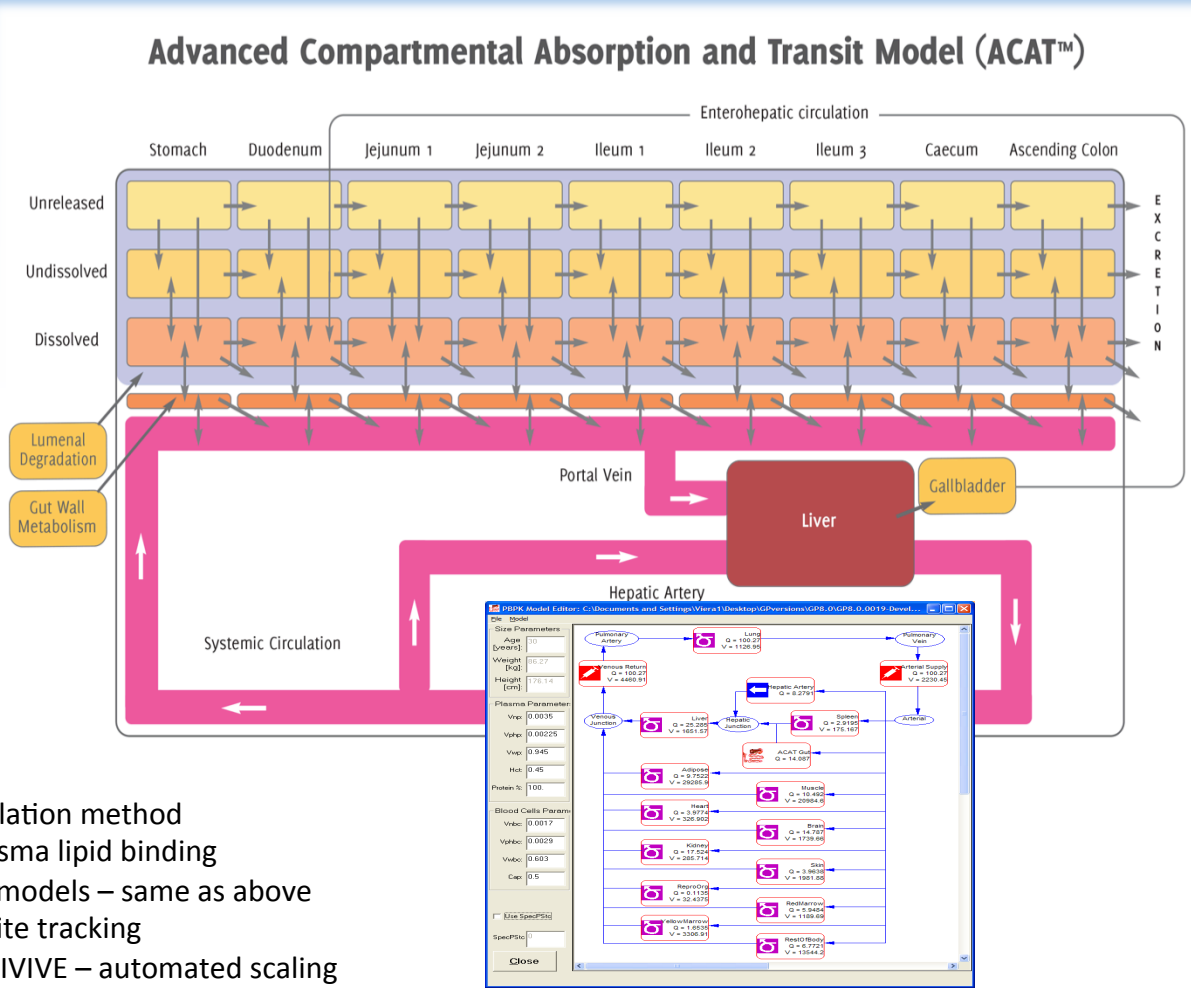
Why is GastroPlus unique?

Absorption & Dissolution:

- #1-ranked commercial QSAR models integrated
- #1-ranked commercial model for absorption rate calculations
- Several dissolution models – including the popular Z-factor approach
- Mechanistic nucleation/growth precipitation model
- Paracellular permeability
- Animal physiology models – dog, rat, mouse, cyno & rhesus monkeys, minipig, rabbit
- It's not just gut!



PBPK Modeling:

- #1-ranked Kp calculation method
- Adjustments of plasma lipid binding
- Animal physiology models – same as above
- Unlimited metabolite tracking
- Transporter-based IVIVE – automated scaling of tissue PStc
- Customization of model without equation writing

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That's not all!

ANYTHING you can do with other tools can be done with GastroPlus:

- Population PBPK models (since 2005)
- PBPK/PD modeling (since 2005)
- DDI predictions (since 2008)
- Mechanistic IVIVCs (since 2001)
- Nonlinear metabolism or transport kinetics in any tissue (since 2005)
- … and more!

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How do our model results compare?

Independent comparison of aqueous solubility predictors

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

Comparison of first-in-human (FIH) PBPK prediction accuracy in a 2-year study of 21 compounds
(Cole et al., ISSX 2008)

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	88.5	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.

Summary of IV profile prediction accuracy

APPROACH	PROFILE	Vss		CL	
	Weighted sum of squares (RANK)	AFE	% within 2-fold error (3-fold error)	AFE	% within 2-fold error (3-fold error)
GastroPlus	-11.7 (1)	1.4	90 (100)	1.6	80 (85)
PKSim	-6.4 (2)	1.7	70 (90)	1.6	80 (85)
Current Pfizer Approach	-3.8 (3)	1.6	75 (85)	1.6	80 (85)
SimCYP – hlm	5.6 (4)*	1.5	80 (95)	2.5	58 (74)
SimCYP – rhCYP	7.8 (5)*	1.5	80 (95)	2.4	55 (65)
ChloePK	8.5 (6)*	-	-	1.7	70 (80)

Summary of Oral profile prediction accuracy

AFE➔ Average Fold Error

APPROACH	PROFILE	AUC		Cmax	
	Weighted sum of squares (RANK)	AFE	% within 2-fold error (3-fold error)	AFE	% within 2-fold error (3-fold error)
GastroPlus	-9.8 (1)	2.7	50 (72)	2.0	67 (72)
Current Pfizer Approach	-5.3 (2)	3.9	33 (56)	2.5	44 (61)
SimCYP - rhCYP	-3.7 (3)	3.0	56 (67)	2.2	61 (72)
SimCYP - hlm	5.7 (4)*	3.6	41 (53)	2.7	53 (59)
PKSim	6.1 (5)*	4.7	22 (39)	5.0	17 (33)
ChloePK	7.0 (6)*	2.8	39 (50)	2.4	50 (61)

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
CLIP[7]	0.82	III	1.27	III	1.3	-0.95	0.87
LSER	0.87	III	1.26	III	2.32	-2.31	0.84
MLOGP	0.93	III	1.12	III	1.64	-1.51	0.92
SPARC[8,9]	0.93	III	1.17	III	0.72	0.06	0.99
COSMOFrag[3]	1.13	III	1.38	IV	2.48	-2.47	1.09
LSER UFZ[8]	1.19	IV	2.15	IV	2.32	-1.75	1.29
GBLOGP[7]	1.25	IV	1.76	IV	2.51	2.46	1.26
HINT	1.38	IV	2.14	IV	3.25	-3.24	1.39
AAM	1.37	IV	1.87	IV	2.96		1.36

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**

Independent comparison of pKa predictors

(Fraczkiewicz, Lobell, et al., PCMDDD 2013)

Independent comparison of logP predictors

(Tetko & Poda, 2007)

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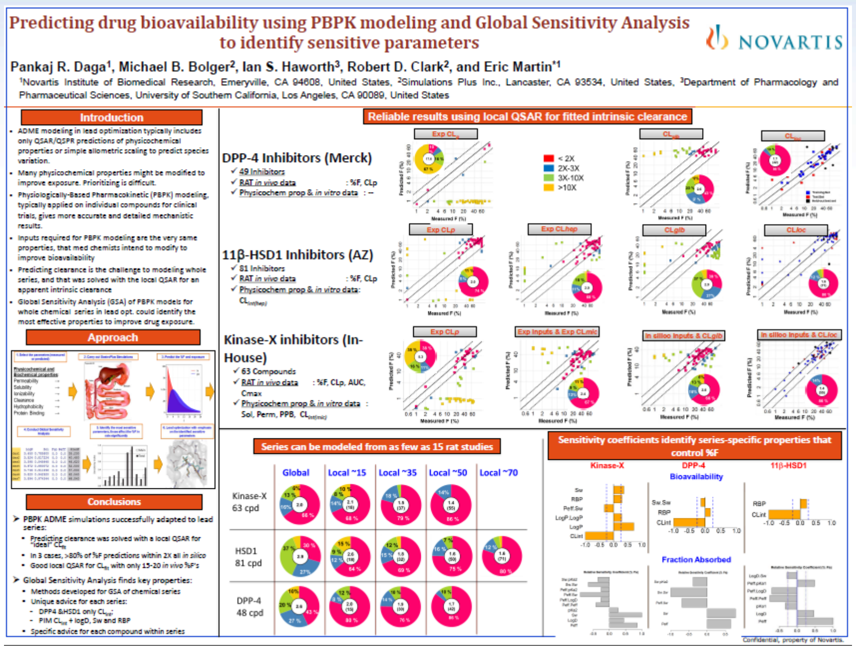
Recent validation: The QSAR/PBPK marriage

Daga et al. (2015) Gordon Research Conf.

Building QSAR models for clearance using 15-30 in vivo rat CL measurements:

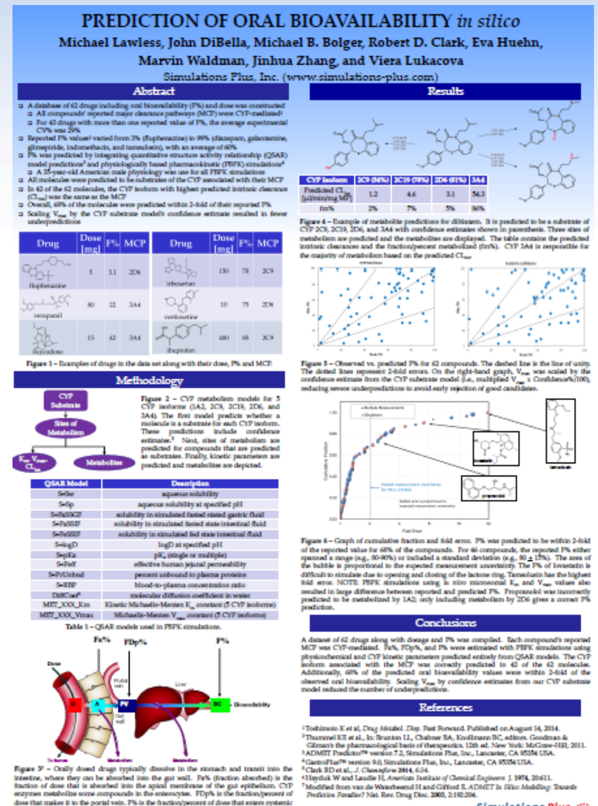
>75% of compounds predicted within 2-fold



Lawless et al. (2015) ISSX Annual Meeting

Using QSAR & PBPK to predict human F%:

70% of compounds predicted within 2-fold



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How does GastroPlus address your challenges?

Do I have the time & expertise to write code and manage updates?	No equation writing AND customization options available
How do I define all of the parameters required for a PBPK model?	#1-rated QSAR models integrated for complete *in silico* solutions
What about other species or different populations?	Complete database of animal and human (American & Asian – pediatrics and adults) physiology models included
What if my chemical is exposed through several dosing routes?	Mechanistic models for oral, pulmonary, dermal, and ocular delivery
How am I going to predict both local and systemic concentrations?	Track all variables and easily capture output in Excel
Where do I start with all of the chemicals I have?	Batch mode, automated sensitivity analysis and optimization available
How possible is it to predict metabolite exposure?	Unlimited metabolite tracking options
I am guessing the commercial tools must be expensive?	Flexible licensing options and expert consulting support
Will my commercial provider be around for the long haul?	Publicly traded for >18 years & counting

Regulatory scientists trained on GastroPlus PBPK modeling

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- In 2013, scientists from 17 companies in North America and Europe formed the GastroPlus User Group
- To date, >930 members on the LinkedIn group page – membership is free!

Mission Statement

Discuss best practices, Q&A and FAQs

Present and advance M&S science via social media, webinars and face-to-face meetings

Establish pre-competitive areas of research and collaboration across industry and academia

Understand and influence regulatory expectations for M&S submissions