Discovery PBPK: How to estimate the expected accuracy of ISIVB and IVIVB for new chemical entities

Michael B. Bolger, Ph.D.

Chief Scientist

Simulations Plus, Inc.

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Simulations Plus (NASDAQ: SLP)

>80 employees across 3 divisions

- **Simulations Plus, Inc.**
  - Incorporated in 1996
  - Focused on software development, PBPK modeling & simulation, and QSAR modeling
- **Cognigen Corporation, a Simulations Plus company**
  - Incorporated in 1992
  - Focused on software development, pharmacometric services, and population PK/PD data analyses
- **DILIsym Services, a Simulations Plus company**
  - Incorporated in 2015
  - Focused on systems toxicology modeling
- **PharmoGo.com (Distributor in China)**

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Michael Lawless, Ph.D. (Cheminformatics)

Walter S. Woltosz, M.S., M.A.S. (CEO)

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Discovery PBPK Agenda

- QSAR/PBPK for *in silico* / *in vivo* bioavailability (ISIVB)
  - Expected accuracy for percent absorbed (Fa%) and bioavailable (Fb%) and PBPK AUC:
  - ADMET Predictor method for minimal PBPK/High Throughput PK (HTPK)
  - Use of ECCS to filter new compounds for expected accuracy.
- PBPK in Lead Optimization
  - Novel Discovery PBPK method of local clearance modeling

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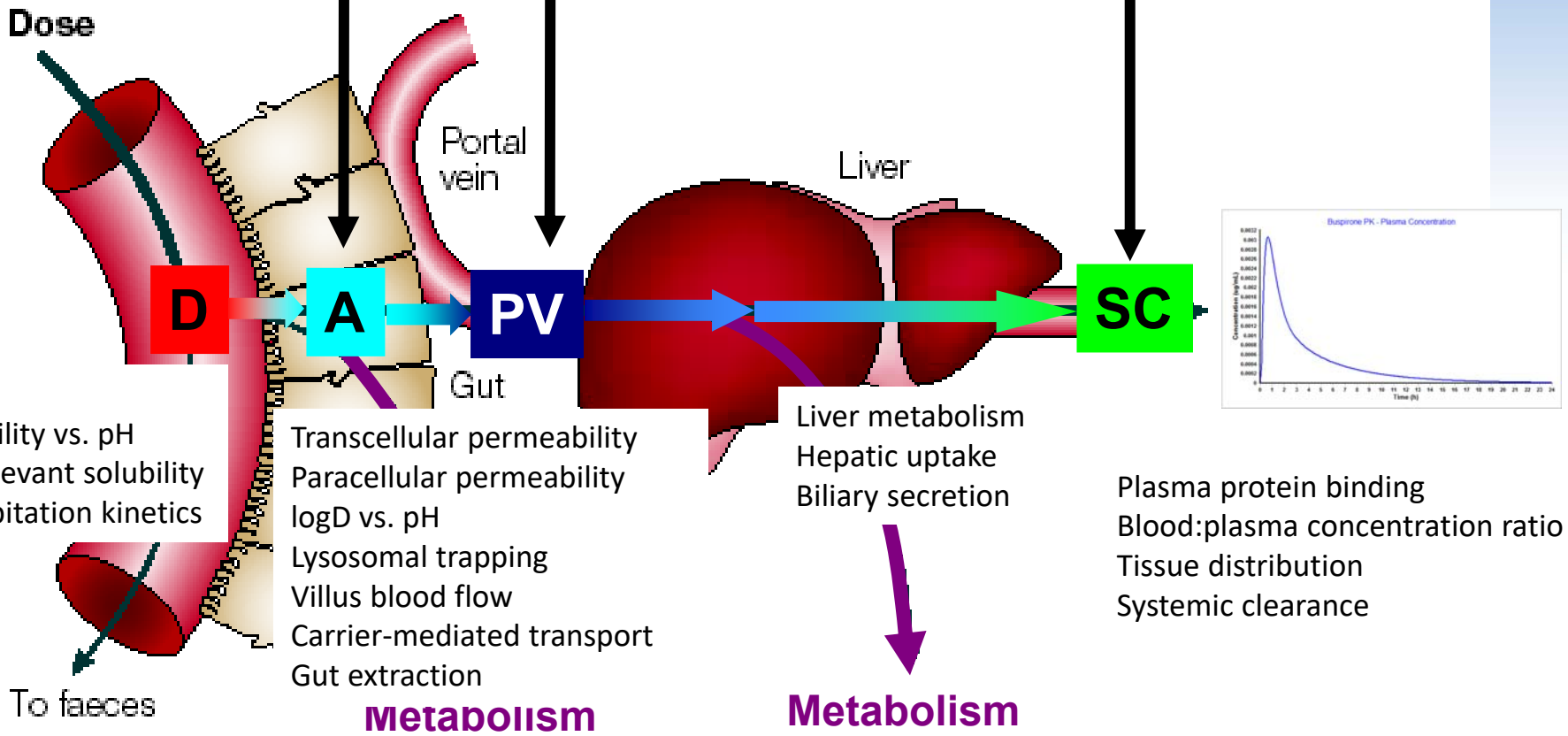
What's happening *in vivo*?

Fa%
Percent Absorbed

FDp%
Percent dose to portal vein

F%
Bioavailability



pK_a
Solubility vs. pH
Biorelevant solubility
Precipitation kinetics

Transcellular permeability
Paracellular permeability
logD vs. pH
Lysosomal trapping
Villus blood flow
Carrier-mediated transport
Gut extraction

Metabolism

Liver metabolism
Hepatic uptake
Biliary secretion

Metabolism

Plasma protein binding
Blood:plasma concentration ratio
Tissue distribution
Systemic clearance

* Modified from van de Waterbeemd, H, and Gifford, E. *ADMET In Silico Modelling: Towards Prediction Paradise?* Nat. Rev. Drug Disc. 2003, 2:192-204

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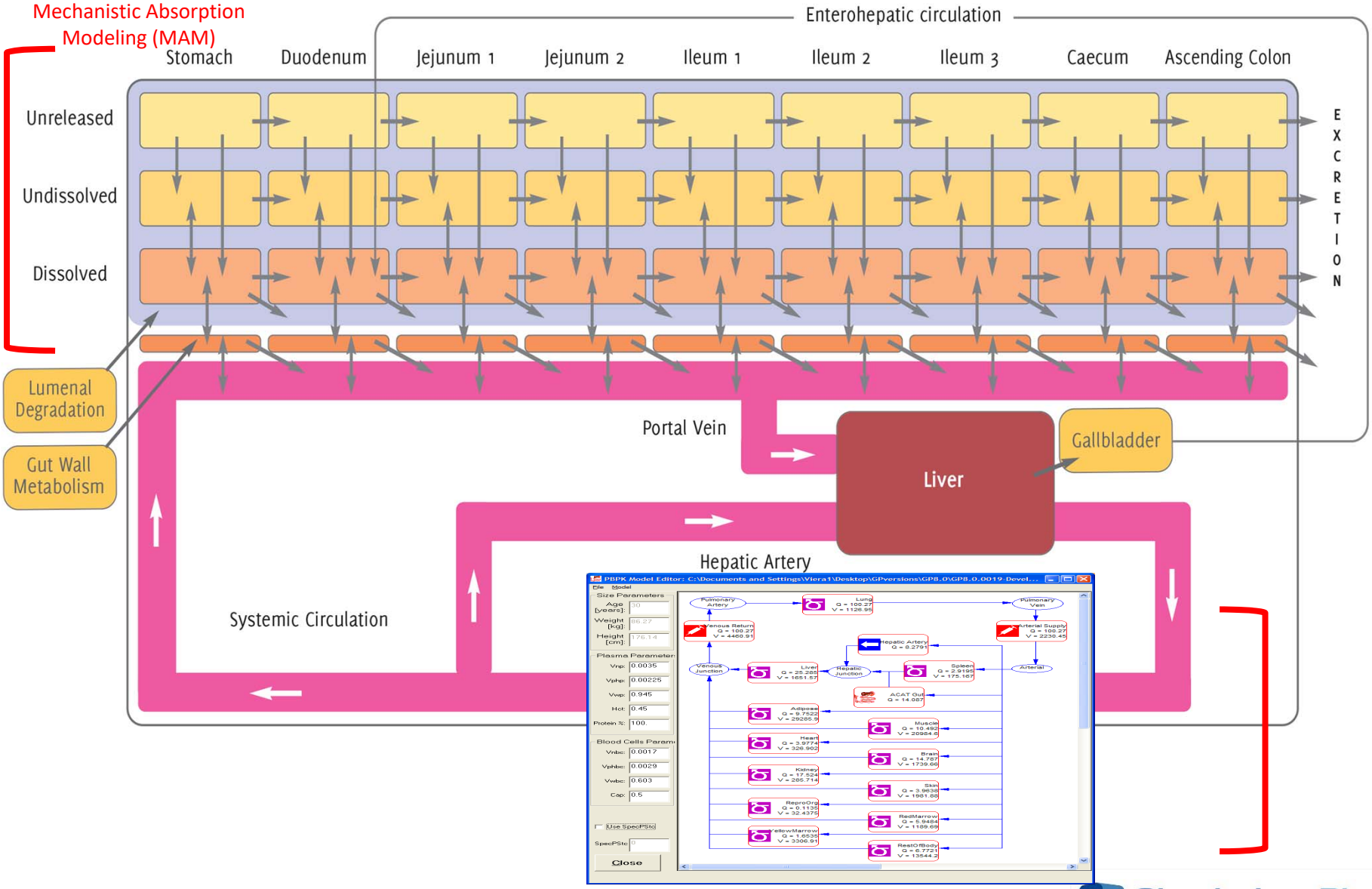
Advanced Compartmental Absorption and Transit Model (ACAT™)

Mechanistic Absorption Modeling (MAM)



Physiologically based Pharmacokinetics (PBPK)

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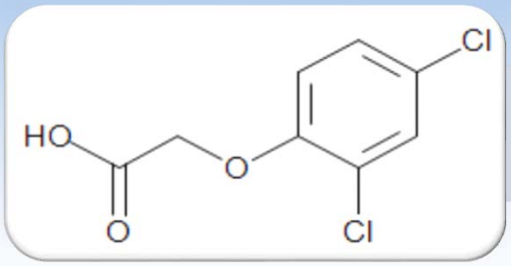
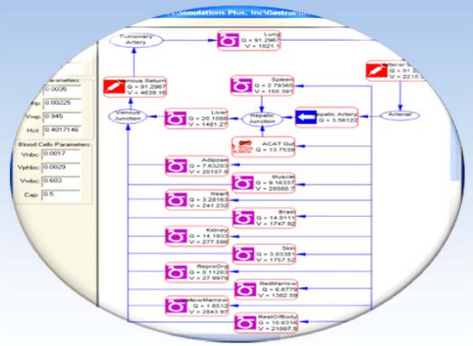
Biopharm. Property Estimation and PBPK



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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Literature Studies using GastroPlus™

Reference	Type of Study	Metric of Accuracy	% within 2-Fold
Parrott N, et al. J. Pharm. Sci., 94(12):2327 (2005)	PBPK in early discovery.	Oral AUC/Dose	48%: Average over six projects.
De Buck SS, et al., DMD 35(10):1766 (2007)	PBPK in clinical testing	Oral AUC and Cmax	74% AUC 65% Cmax
Poulin P. et al., J. Pharm. Sci. 100(10):4127 (2011)	PBPK prediction of Cp vs. time.	IV and Oral AUC	69% IV AUC 21% PO AUC
Jones HM et al., Clin. Pharmacokinet. 50(5):331 (2011)	PBPK prediction of Cp vs. time.	IV Vdss and CL and Oral AUC and Cmax	90% IV Vdss 80% IV CL 50% PO AUC 67% PO Cmax
Margolskee A, et al.,	PBPK prediction of Cp vs. time	Oral AUC and Bioavailability	35% PO AUC 65% Bioavailability

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ADMET Predictor: HTPK Simulation Module

- High-Throughput Pharmacokinetics
- Based on GastroPlus ACAT absorption model
- Predicts percent absorbed and percent bioavailable for a given dose
- Predicts the dose required to achieve a target plasma concentration at steady state
- Human and rat species are supported
- Can use predicted or experimental physiological parameters

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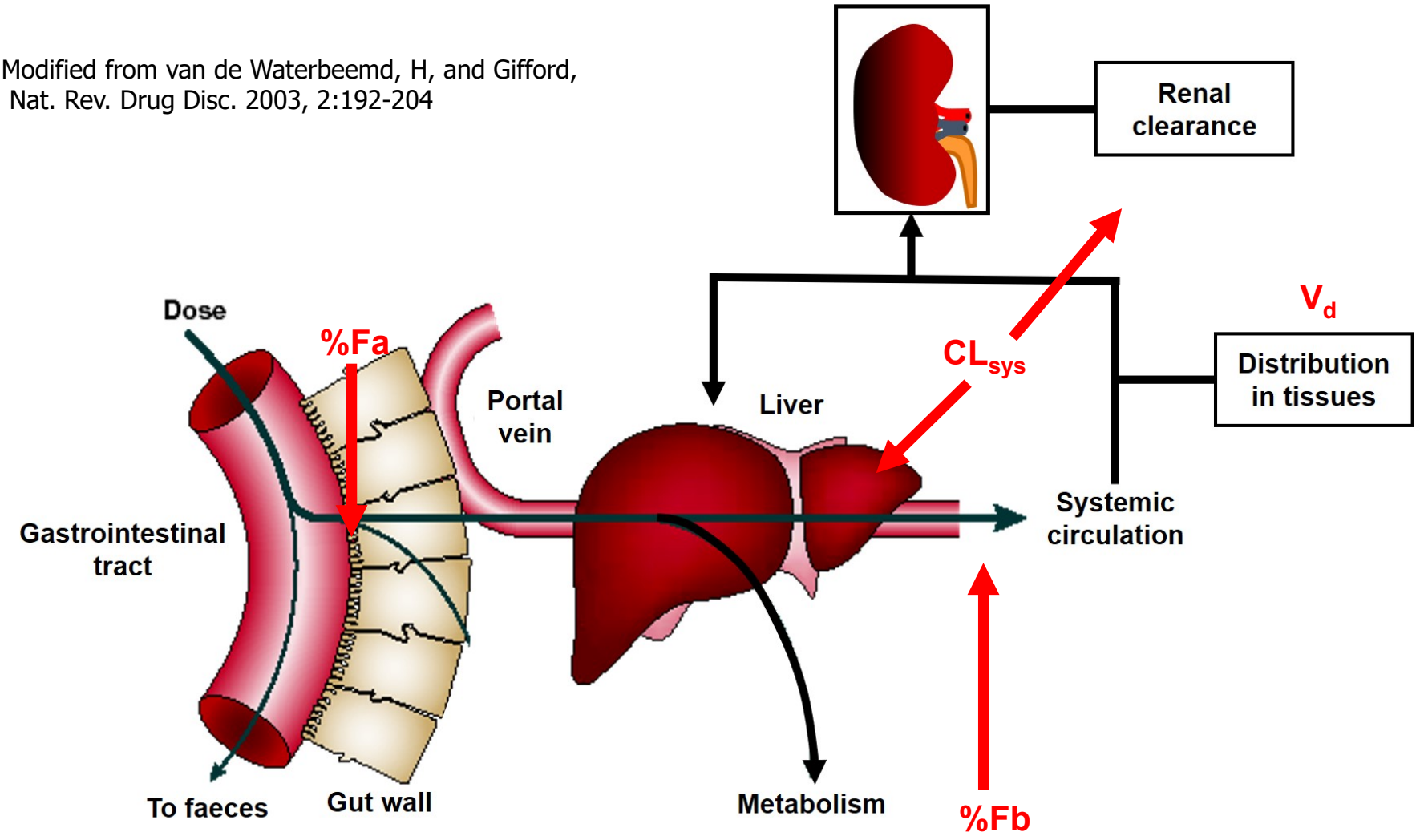
HTPK Simulation Module

* Modified from van de Waterbeemd, H, and Gifford, E. Nat. Rev. Drug Disc. 2003, 2:192-204



Gut clearance and active transport are not considered

Renal clearance based on fup*GFR

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Predicting Oral Bioavailability from Structure

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Oral Bioavailability Data Set

- 62 drugs with CYP metabolism as major clearance pathway[1]
  - 10 anions and 28 cations
- Oral bioavailability from Goodman & Gilman's "The Pharmacological Basis of Therapeutics" Table A-II-1 Pharmacokinetic data
- Dose information from obtained from either the drug data sheet or www.drugs.com

[1]M. Lawless, 2016 American Society for Cellular and Computational Toxicology (ASCCT)

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Method

- Predict of *in silico* physicochemical and biopharmaceutical properties of each molecule
- Predict CYP kinetic parameters, K_m and V_{max}
- Use above predictions in 35 year old, American male, PBPK model to predict oral bioavailability (F%)

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Examples of Variability in reported F%

Name	Fb_GP	F% (Goodman-Gilman)	SE
venlafaxine	27.5	10 - 45	18
montelukast	62	62	
indomethacin	99	~100	
meloxicam	97	97	
zolpidem	72	72 +/- 7	7
warfarin	93	93 +/- 8	8
itraconazole	55	55	
carbamazepine	70	>70	
tolbutamide	85	80 - 90	5
phenytoin	90	90 +/- 3	3
ibuprofen	85	>80	
methylprednisolone	82	82 +/- 13	13
clonazepam	98	98 +/- 31	31
prednisolone	82	82 +/- 13	13

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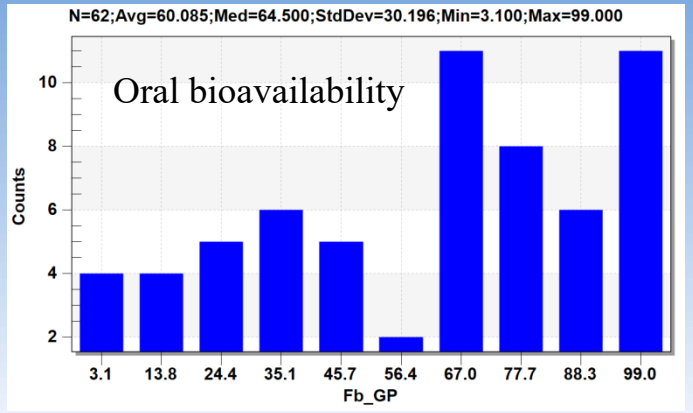
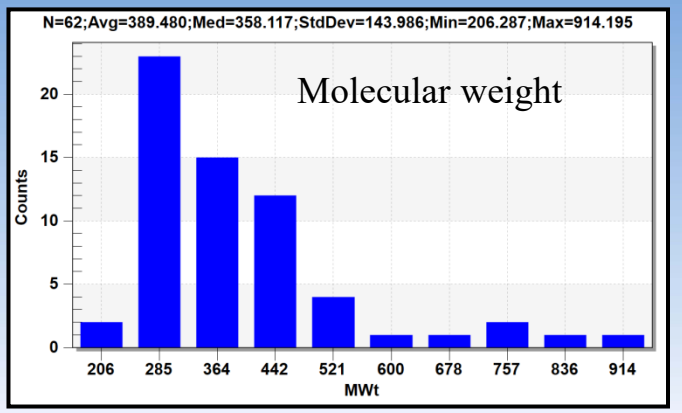
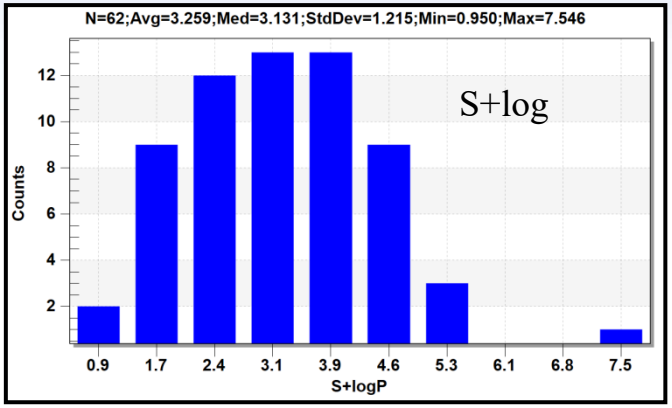
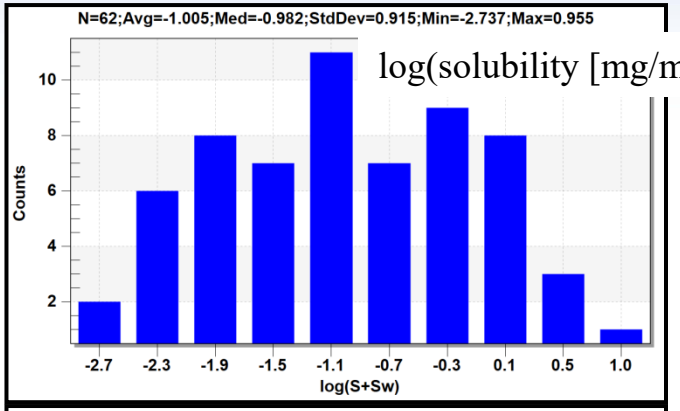
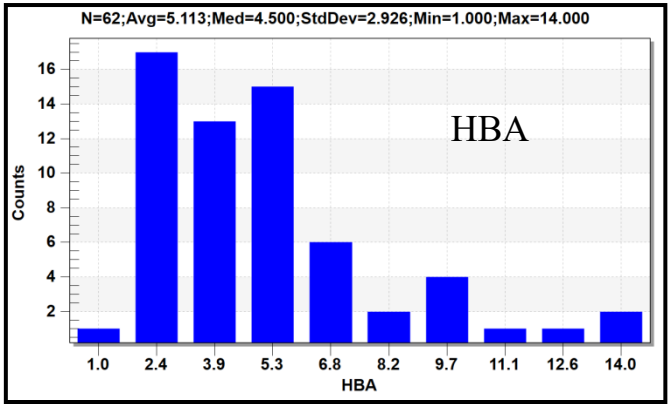
Data Set Property Distributions

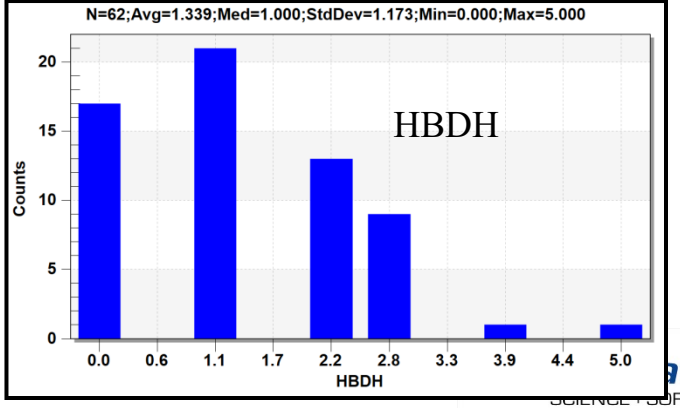












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Effective Permeability (Peff): Measurements in Human (2006)

Kim and Amidon et al. Mol. Pharm. (2006) 3(6):686

Table 2. The Human and Rat Permeabilities of the Test Compounds

compounds (permeability class)	dose (mg)	human permeability[a] (10^{-4} cm/s)	FA[a] %	rat permeability (10^{-4} cm/s)	rat P_{eff} ratio test/IS
piroxicam (H)	20	10.4 ± 5.9	100	2.62 ± 0.37	28.1
ketoprofen (H)	75	8.4 ± 3.3	100	1.55 ± 0.34	7.9
carbamazepine (H)	200	4.3 ± 2.7	100	1.79 ± 0.11	7.1
naproxen (H)	500	8.3 ± 4.8	100	1.19 ± 0.12	10.1
caffeine (H)	200	nd[d]	100	1.19 ± 0.23	5.5
antipyrine (H)	188	5.6 ± 1.6	100	0.96 ± 0.13	4.5
theophylline (H)	300	nd	96	0.68 ± 0.19	3.8
verapamil[b] (H)	120	6.7 ± 2.9	100	0.65 ± 0.05	3.9
propranolol (H)	80	2.8 ± 1.3	100	0.49 ± 0.07	3.2
pindolol (H)	10	nd	89	0.293 ± 0.11	1.2
metoprolol (H)	100	1.5 ± 0.9	96	0.20 ± 0.04	1.0
furosemide (L)	80	0.3 ± 0.3	61	0.117 ± 0.08	0.69
amoxicillin[c] (L)	875	0.3	45–75	0.120 ± 0.11	0.50
cimetidine (L)	800	0.3 ± 0.05	60	0.105 ± 0.06	0.44
enalaprilat (L)	20	0.1 ± 0.3	8	0.057 ± 0.06	0.42
mannitol (L)		nd	16	0.121 ± 0.05	0.39
ranitidine[b] L)	10	0.2 ± 0.06	50	0.073 ± 0.06	0.30
atenolol (L)	100	0.2 ± 0.2	50	0.060 ± 0.06	0.06
methyldopa (L)	500	0.1	45	0.016 ± 0.004	0.10
hydrochlorothiazide (L)	50	0.04 ± 0.05	67	0.001 ± 0.001	0.002

[a] Human permeability and FA data were taken from refs 19–26. [b] Verapamil[27] and ranitidine[28] are potential efflux pump substrates. [c] Amoxicillin shows nonlinear absorption kinetics. The high dose (3000 mg) of drug shows a FA of 45% while the low dose (500 mg) shows a FA of 75%.[29] [d] Not determined.

PepT1 substrate

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Effective Permeability (Peff): Measurements in Human (2013)

Table 1. BCS Classification of 30 Drugs Based on Human Effective Permeability (P_{eff}) and Dose Number[a]

drug	human *in vivo* permeability[b] ($\cdot 10^{-4}$ cm/s)	dose number[c]	BCS Class	fa (%)
α-methyldopa	0.10	0.1	III	55–65
amiloride	1.6	0.4–0.8	I	80–90
amoxicillin	0.30	0.9	III	45–75[e]
antipyrine	5.60	0.20	I	100
atenolol	0.20	0.02	III	50–60
carbamazepine	4.30	80	II	>90
cephalexin	1.56	2	II	>90
cimetidine	0.26	3	III	75
cyclosporine	1.61	350	II	>90
desipramine HCl	4.50	<0.03	I	100
enalapril maleate	1.57	0.003	(I)[d]	65
enalaprilat	0.20	0.003	III	8
fexofenadine	0.07	0.32	III	5–10
fluvastatin sodium	2.40	<0.9	I	95
furosemide	0.05	30	IV	40–60
hydrochlorothiazide	0.04	0.2	III	55
isotretinoin	0.99	>20	II	90
inogatran	0.03	<0.001	III	5–10
ketoprofen	8.70	0.2	I	100
L-dopa	3.40	1.0	(I)[d]	100
lisinopril	0.33	0.002	III	35
losartan	1.15	0.004	III	100
metoprolol	1.34	0.0004	I	95
naproxen	8.50	0.06	I	100
piroxicam	6.65	2.5	II	100
propanolol	2.91	0.01	I	100
ranitidine	0.27	0.01	III	50–60
terbutaline	0.30	0.01	III	40–50
valacyclovir	1.66	0.02	I[d]	>80
R-verapamil	6.80	0.004	I	100
S-verapamil	6.80	0.004	I	100

[a]Each P_{eff}-value was determined *in vivo* in the proximal jejunum in humans with a single-pass approach at pH 6.5 (phosphate buffer) and under isotonic conditions. [b]Human P_{eff} was determined at a concentration that was based on the most common clinical dose dissolved in 250 mL. For low solubility concentration, the highest possible drug concentrations were applied. [c]Dose number = dose/V_0/Cs_{min} (highest dose strength/initial gastric volume (250 mL))/minimum solubility. [d]High permeability due to carrier mediated absorption, currently not included in BCS class I. [e]75% at 500 mg; 45% at 3000 mg.

Lennernas H, Molec. Pharmaceut. 11(1):12 (2013)

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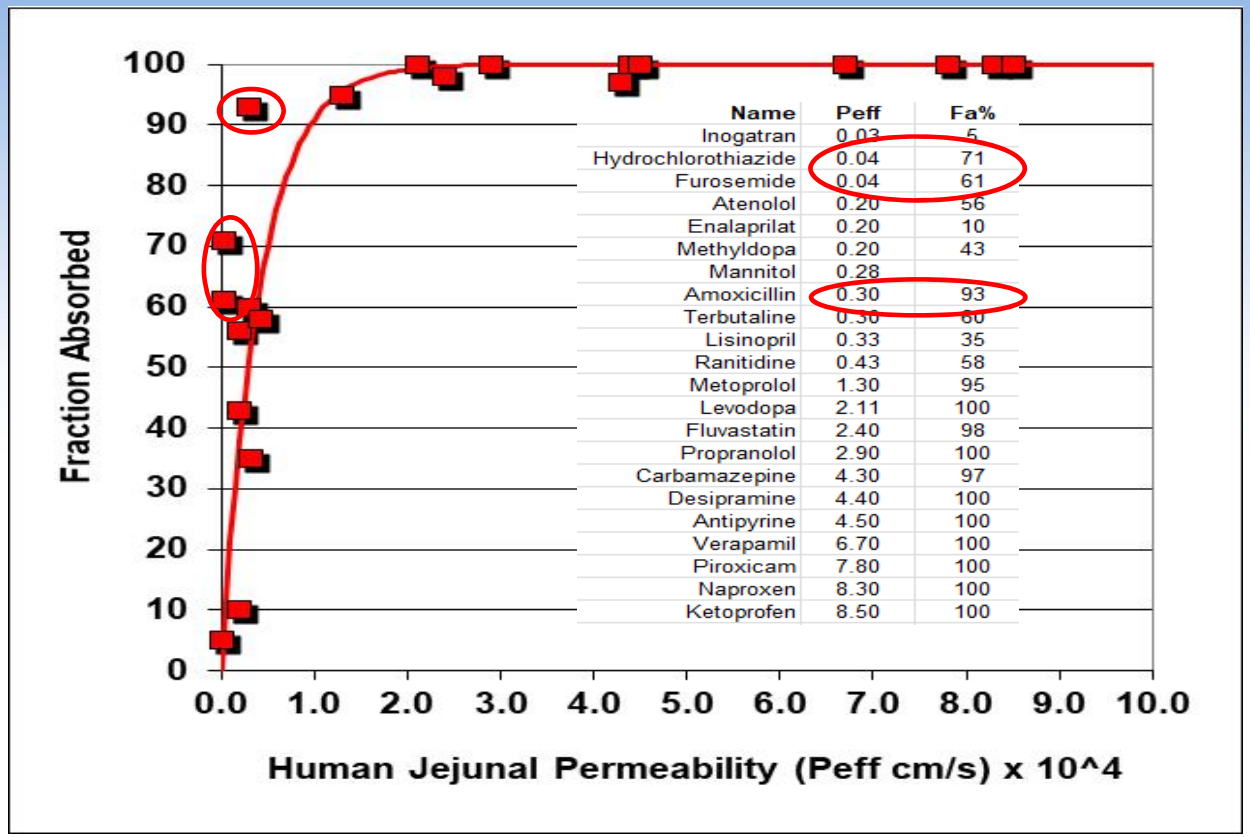
Percent Dose Absorbed vs. Human Permeability

$Peff_{1/2} = 0.29 \times 10^{-4}$ cm/s



Name	Peff	Fa%
Inogatran	0.03	5
Hydrochlorothiazide	0.04	71
Furosemide	0.04	61
Atenolol	0.20	56
Enalaprilat	0.20	10
Methyldopa	0.20	43
Mannitol	0.28	
Amoxicillin	0.30	93
Terbutaline	0.30	60
Lisinopril	0.33	35
Ranitidine	0.43	58
Metoprolol	1.30	95
Levodopa	2.11	100
Fluvastatin	2.40	98
Propranolol	2.90	100
Carbamazepine	4.30	97
Desipramine	4.40	100
Antipyrine	4.50	100
Verapamil	6.70	100
Piroxicam	7.80	100
Naproxen	8.30	100
Ketoprofen	8.50	100

- Very low concentration
  - no saturation effects

- Already in solution
  - no dissolution effects

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Parameter Sensitivity Analysis

- Fraction absorbed depends on many parameters, including permeability, solubility and dose
- Bioavailability additionally depends on intrinsic CL
- Virtual simulations let you see how these parameters affect %Fa and %Fb for individual compounds
- Subsequent slides show simulations on a set of 1000 commercial drugs

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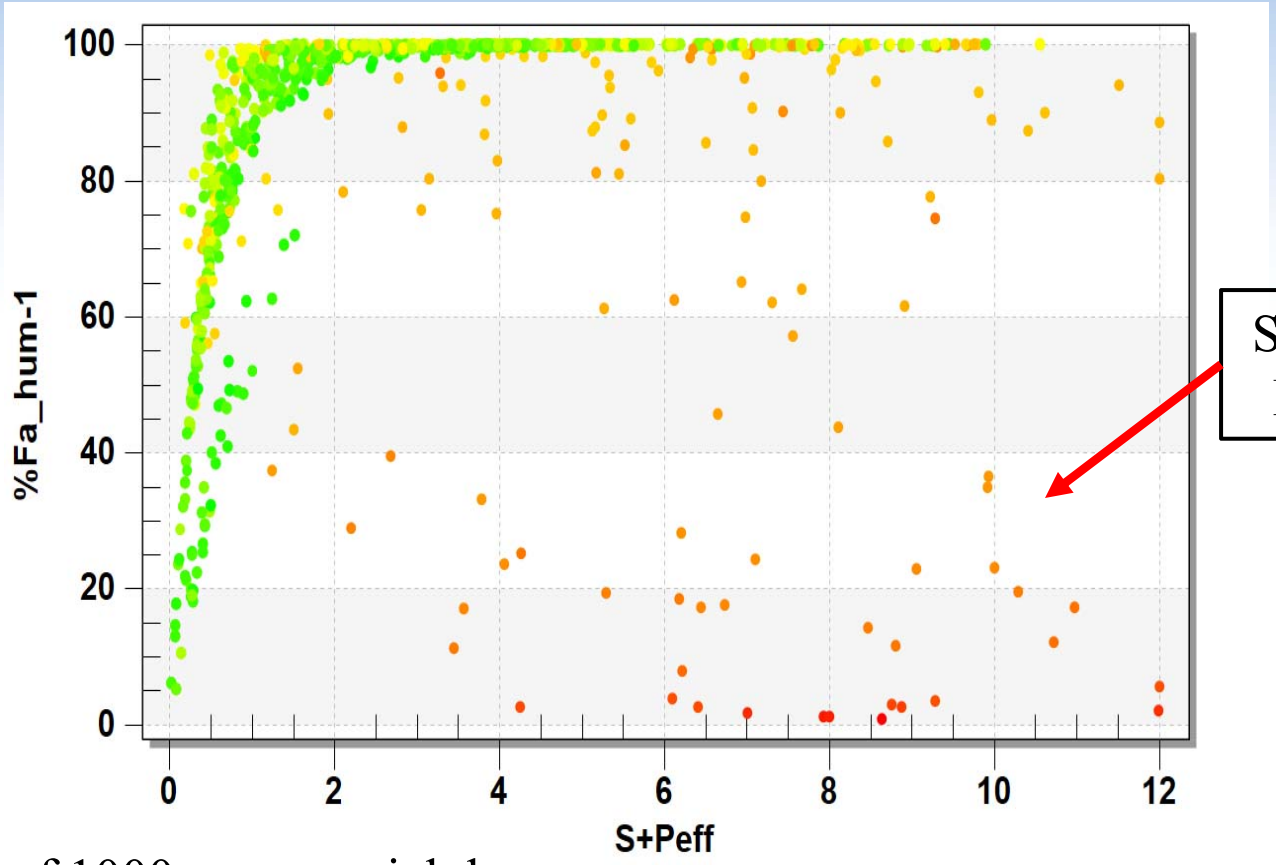
%Fa, Peff And Solubility

Predicted %Fa versus Peff shows a similar exponential relationship for higher-solubility* compounds (colored green)



Sample of 1000 commercial drugs

*Solubility predicted at pH 6.5

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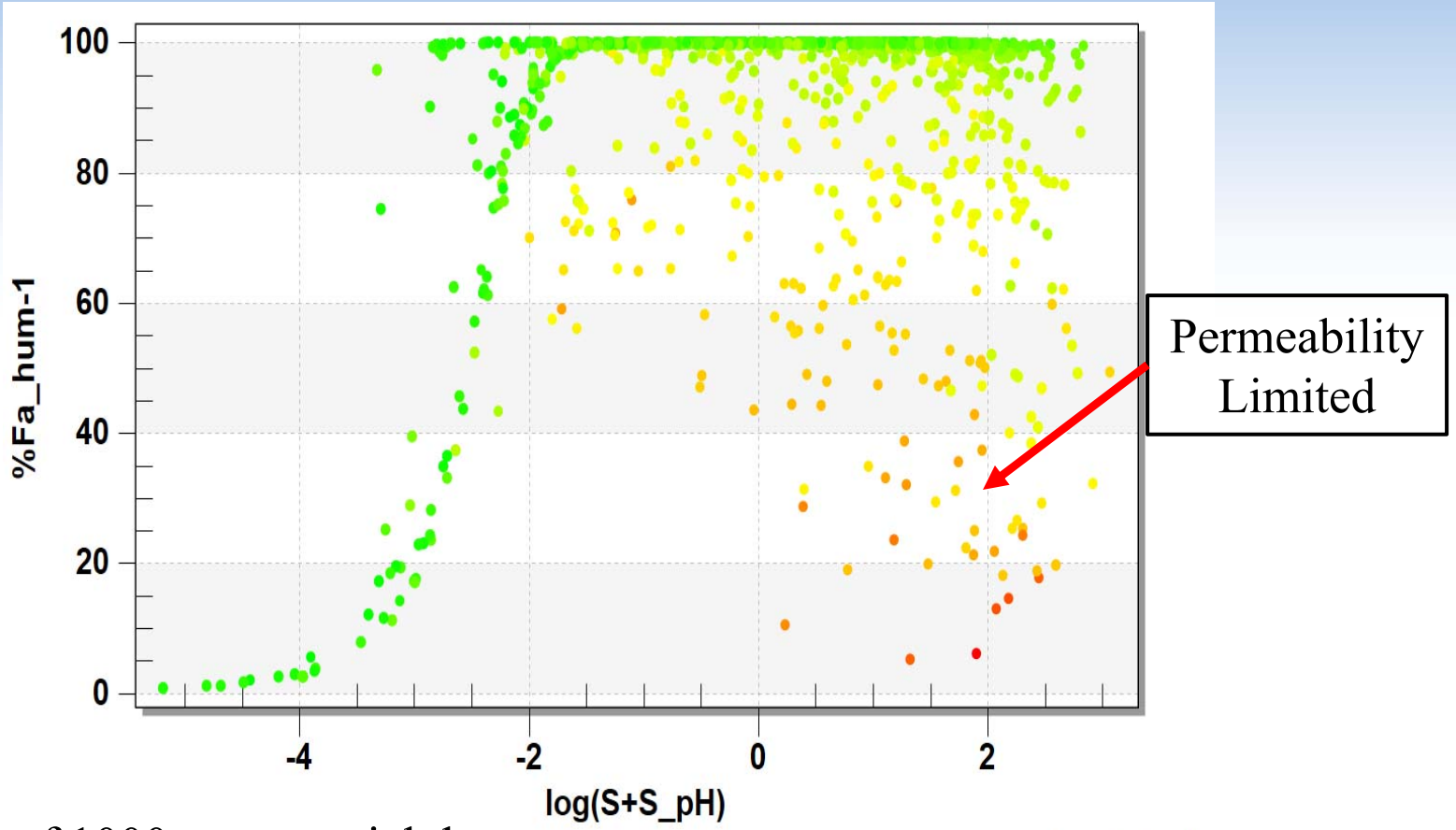
%Fa, Peff And Solubility

Predicted %Fa versus solubility* is sigmoidal for higher-permeability compounds (colored green)



Sample of 1000 commercial drugs

*Solubility predicted at pH 6.5

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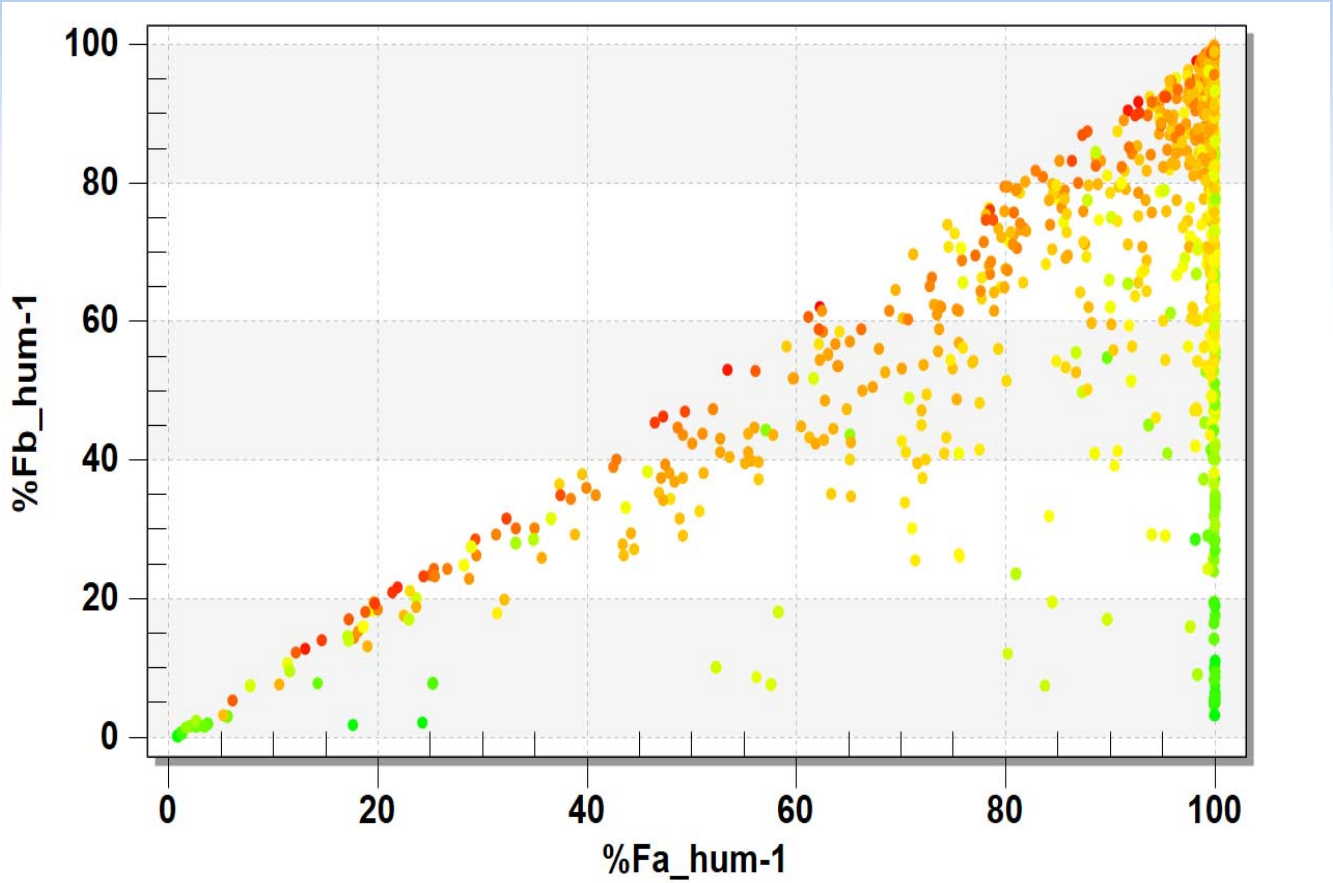
%Fa, %Fb And Clearance

Predicted bioavailability is smallest relative to absorption for compounds with high clearance (colored green)



Sample of 1000 commercial drugs

Color: CYP_HLM_CLint

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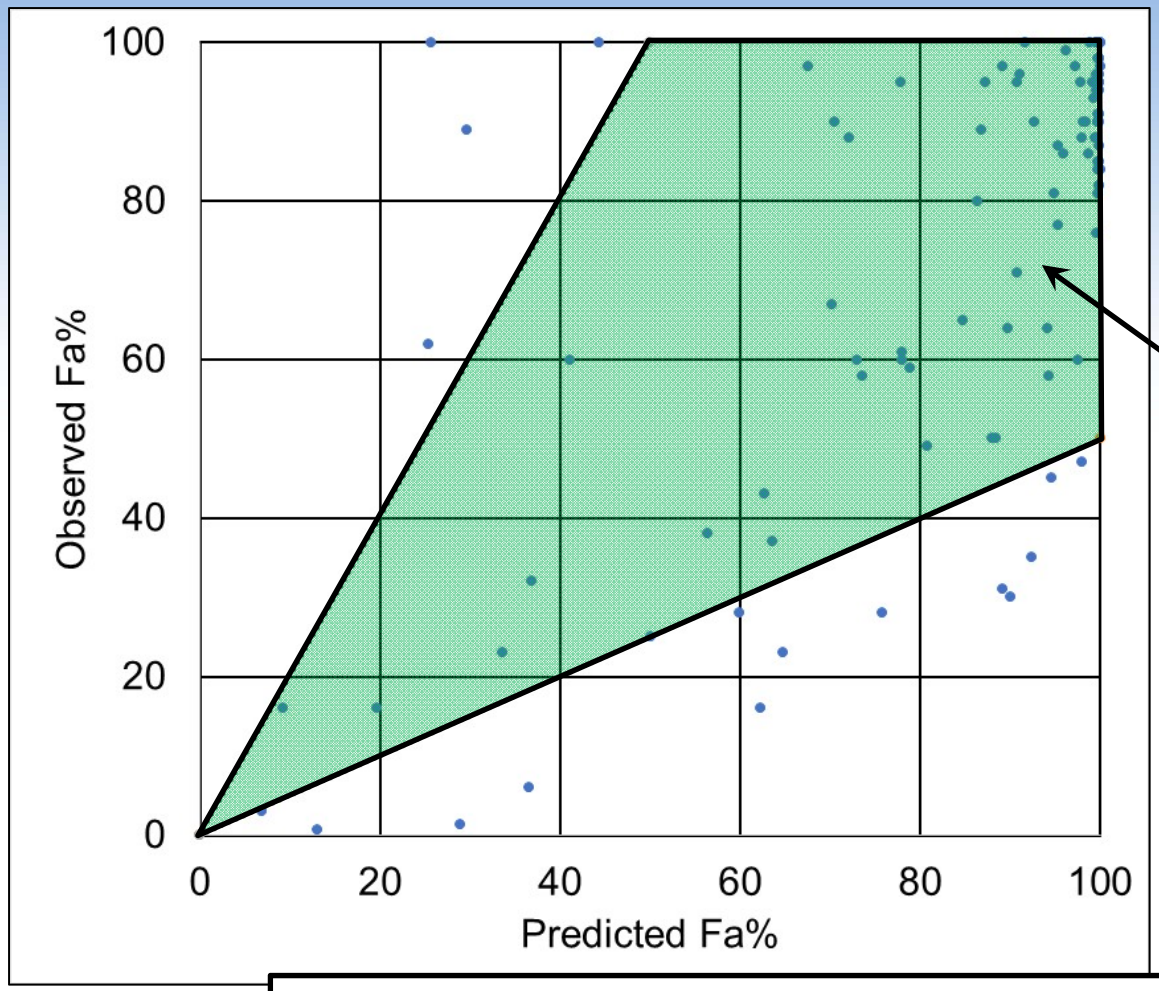
Zhao Data set
125 compounds with %Fa values*

Zhao et al. J. Pharm. Sci, **2001**, 90, (6), 749.



86% (107 molecules) were predicted within 2-fold of the observed value.

80% (100 molecules) were predicted within 1.5-fold

*Removed compounds that might not have passive absorption

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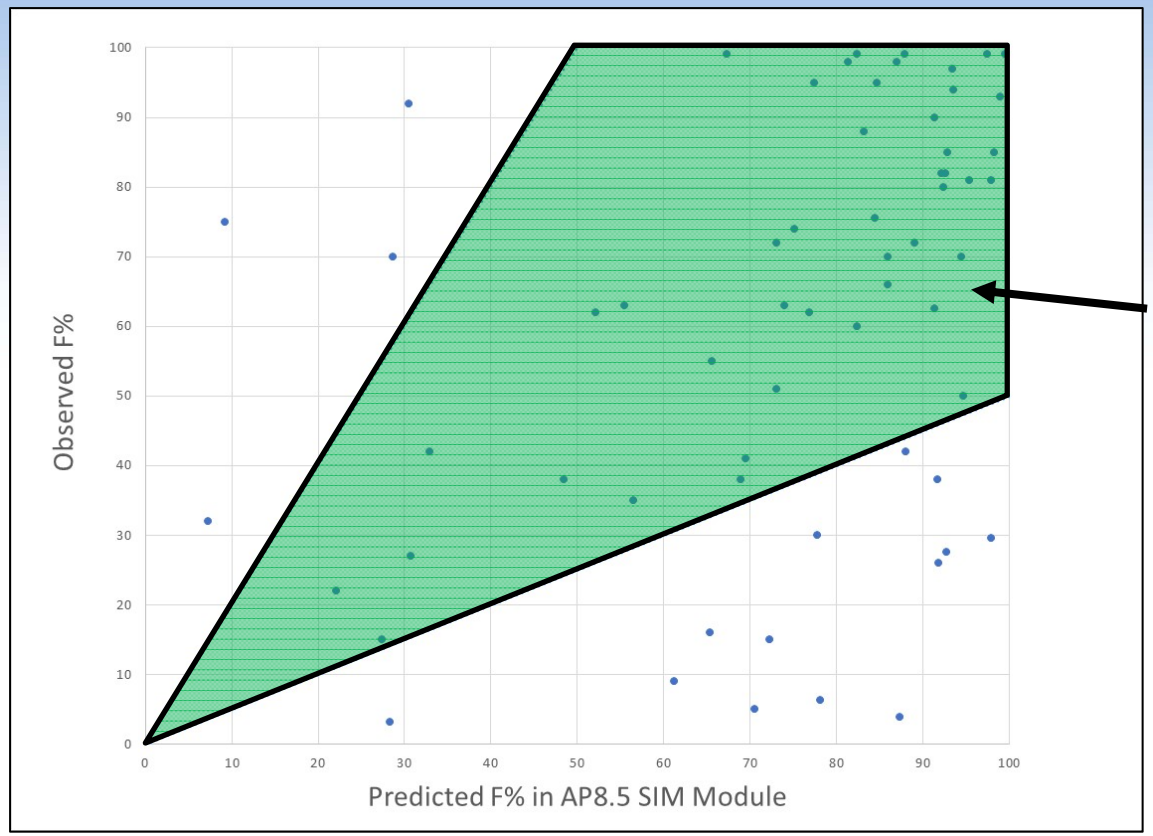
Oral Bioavailability

- A database of 62 drugs including oral bioavailability (%Fb) and dose was constructed
- All compounds' reported major clearance pathways (MCP) were CYP-mediated*



73% (45 molecules) were predicted within 2-fold of the observed value.

65% (40 molecules) were predicted within 1.5-fold

*Toshimoto K et al, *Drug Metab. Dispos.* 42:1811-1819, November 2014.

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Extended Clearance Classification System (ECCS)

Varma, et. al. Pharm. Res. **2015,** 32, 3785.

- Predicts rate-determining, predominant clearance mechanism
  - Metabolism, hepatic uptake, or renal
  - Limited to small molecules, MW ≤ 700 Da
- Based on physicochemical properties and passive permeability
  - Low or high MW (cutoff is 400 Da)
  - Ionization: acids/zwits or bases/neutrals
    - Used MoKa to predict pKa (at pH = 7.0)
  - Low or high MDCK permeability (>= $5x10^{-6}$ cm/s is high)
    - Used either experimental data or predictions
- Six classes (shown on next slide), 1A, 1B, 2, 3A, 3B, and 4.
- Scheme was applied to 307 compounds
  - Compounds had single clearance mechanism that accounted for >70% of systemic clearance
- Correctly predicted ~92% of the compounds
  - Class 3B is “hep. uptake OR renal”. The above statistic counts these as correct if the observed value is hep. uptake or renal

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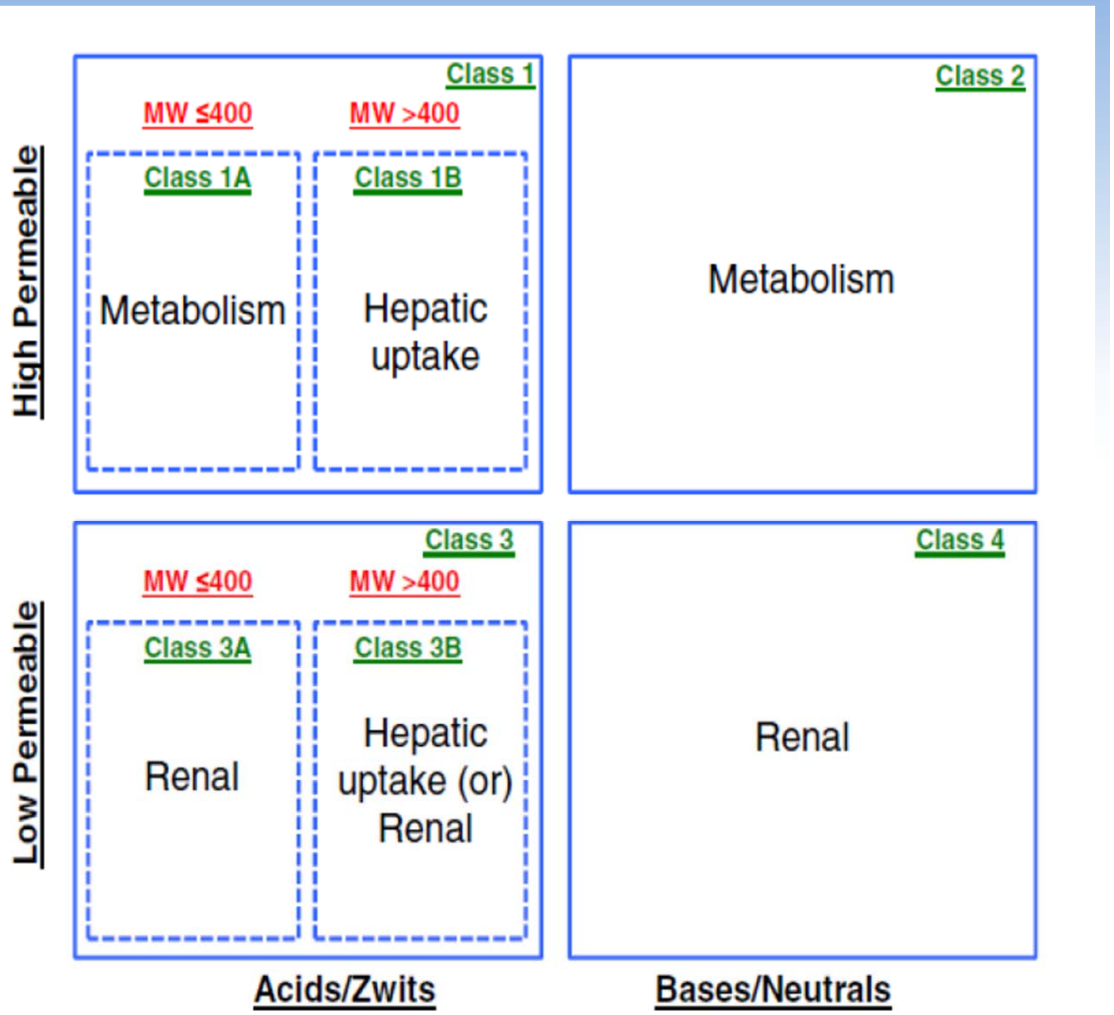
ECCS

Compound are assigned to one of six classes based on:

1) High or low permeability
2) High or low MW
3) Ionization class: acids/Zwitter ions versus bases/neutrals

Class 1A and 2 are metabolism
Classes 3A and 4 are renal
Class 1B is hepatic uptake
Class 3B is hepatic uptake or renal



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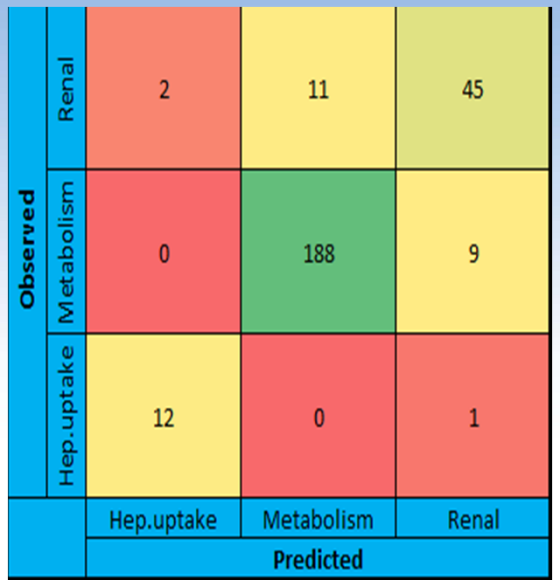
Varma and ADMET Predictor ECCS models

Varma ECCS



S+Hum CL Mech.

Statistic	ECCS	Hum CL Mech Bin
Concordance	91%	96%
Youden	0.78	0.94
Coverage	88%	92%

Varma M., et. al. Pharm. Res. 2015, 32, 3785.

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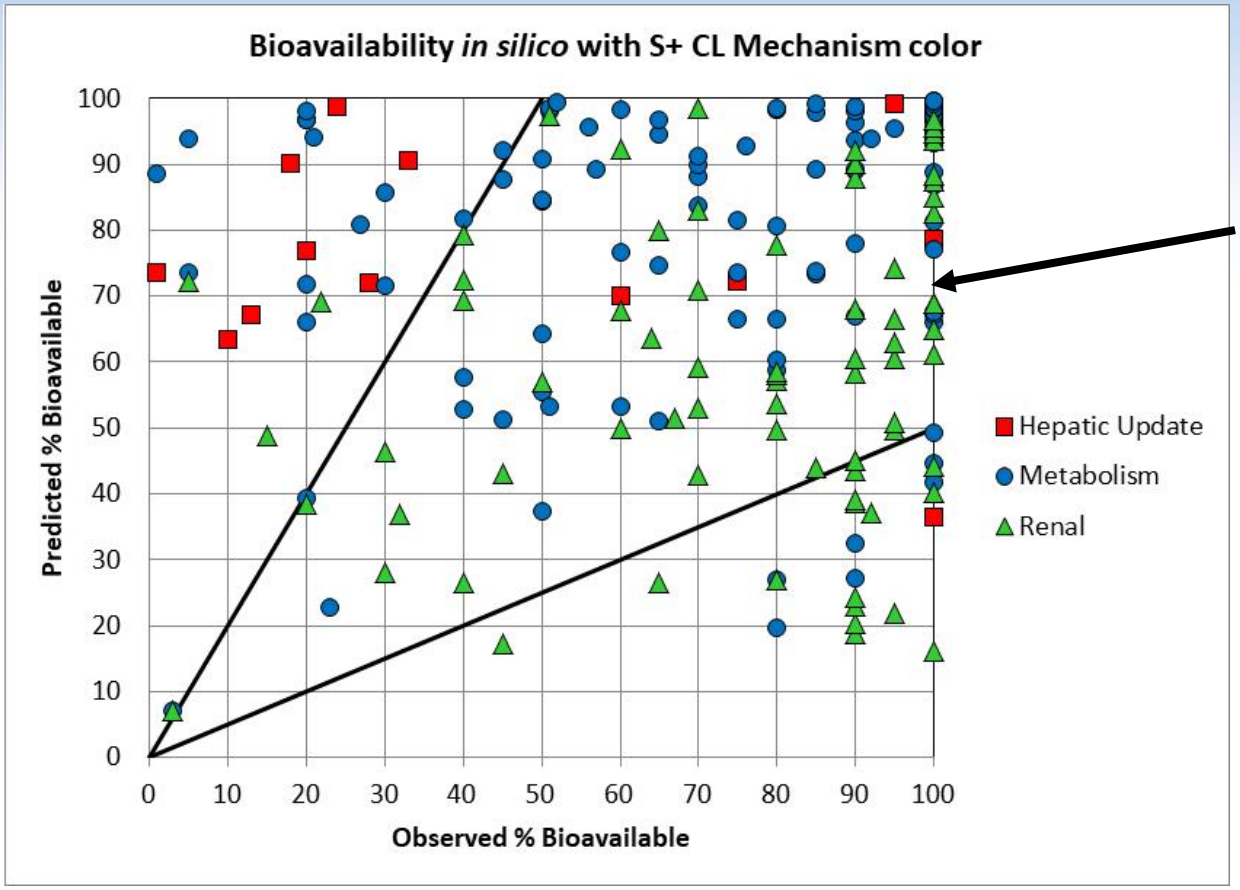
Oral Bioavailability *in silico*

- A database* of 187 drugs with oral bioavailability (%Fb) and dose was constructed.
- Structures were imported to ADMET Predictor / HTPK
- CL_{hep} and FPE estimated from S+ CYP_HLM_CL_{int}
- Points were colored according to S+ CL Mechanism



74% (138 molecules) were predicted within 2-fold of the observed value.

57% (107 molecules) were predicted within 1.5-fold

GastroPlus batch = 761 s
AP HTPK = 14 s

*Ritschel W.A., Handbook of Basic Pharmacokinetics (4th Ed. 1992)

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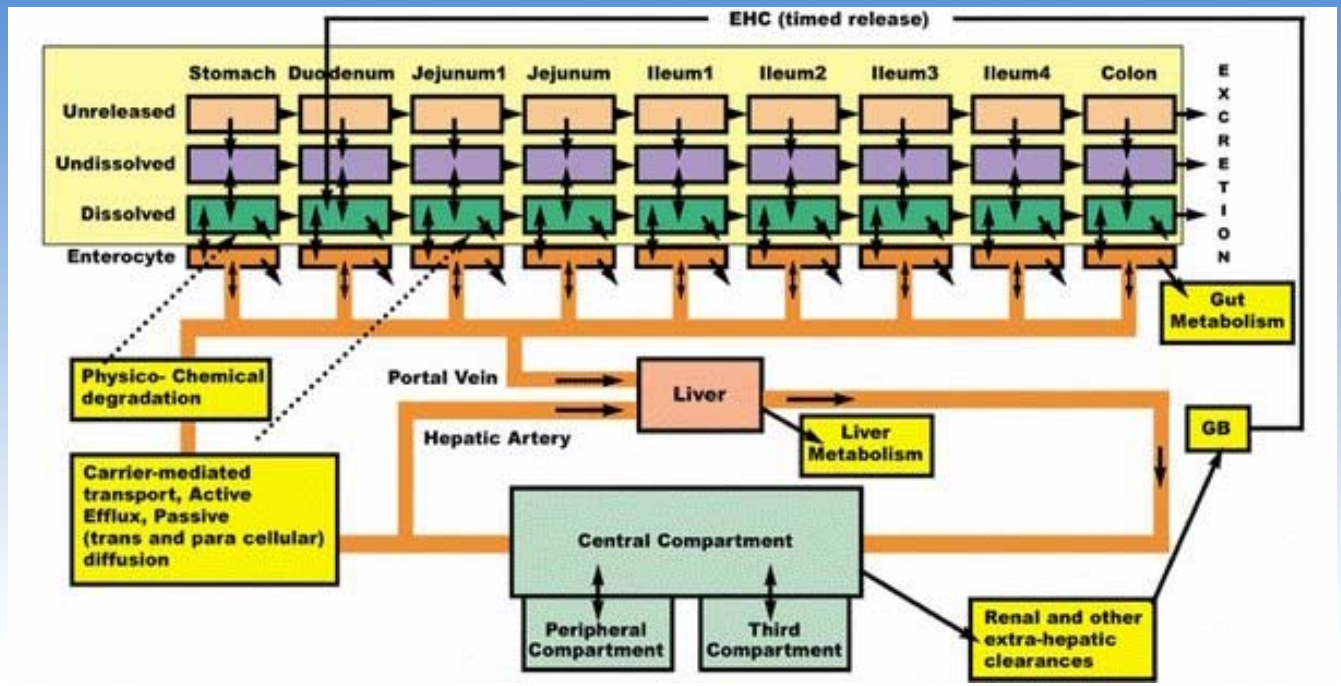

Predicting drug bioavailability using PBPK modeling and Global Sensitivity Analysis to identify sensitive parameters

Physiologically Based Pharmacokinetic Modeling in Lead Optimization. 1. Evaluation and Adaptation of GastroPlus To Predict Bioavailability of Medchem Series.
Daga PR, Bolger MB, Haworth IS, Clark RD, Martin EJ. **Mol Pharm. 2018 Mar 5;15(3):821-830**

Physiologically Based Pharmacokinetic Modeling in Lead Optimization. 2. Rational Bioavailability Design by Global Sensitivity Analysis To Identify Properties Affecting Bioavailability.
Daga PR, Bolger MB, Haworth IS, Clark RD, Martin EJ. **Mol Pharm. 2018 Mar 5;15(3):831-839**.

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Advanced Compartmental Absorption and Transit Model (ACAT™)

Mechanistic Absorption Modeling (MAM)

Enterohepatic circulation

Stomach | Duodenum | Jejunum 1 | Jejunum 2 | Ileum 1 | Ileum 2 | Ileum 3 | Caecum | Ascending Colon

Unreleased

Undissolved

Dissolved

EXCRETION

Lumenal Degradation

Gut Wall Metabolism

Portal Vein

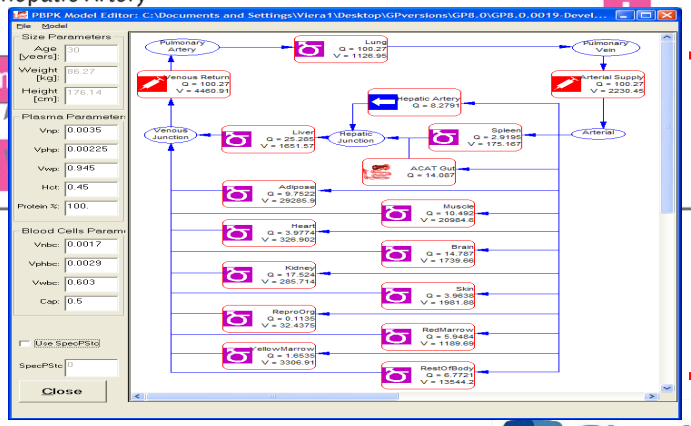
Gallbladder

Liver

Hepatic Artery

Systemic Circulation

2nd Com



The PBPK mechanistic equations used to estimate Vdss.
Systemic clearance is the hardest to estimate accurately.

Physiologically based Pharmacokinetics (PBPK)

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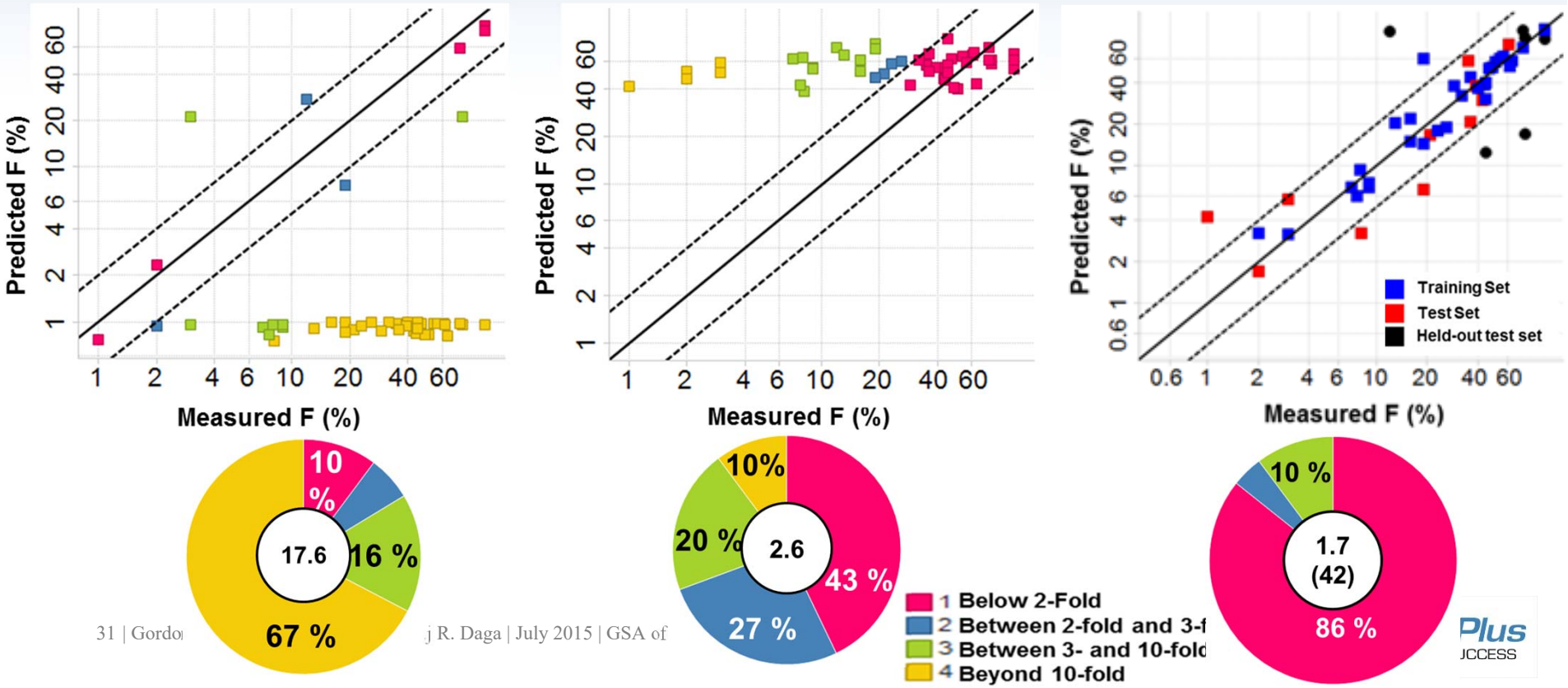
Trouble with Clearance can be overcome by fitted CL

Case Study #1: Dipeptidyl Peptidase-4 Inhibitors

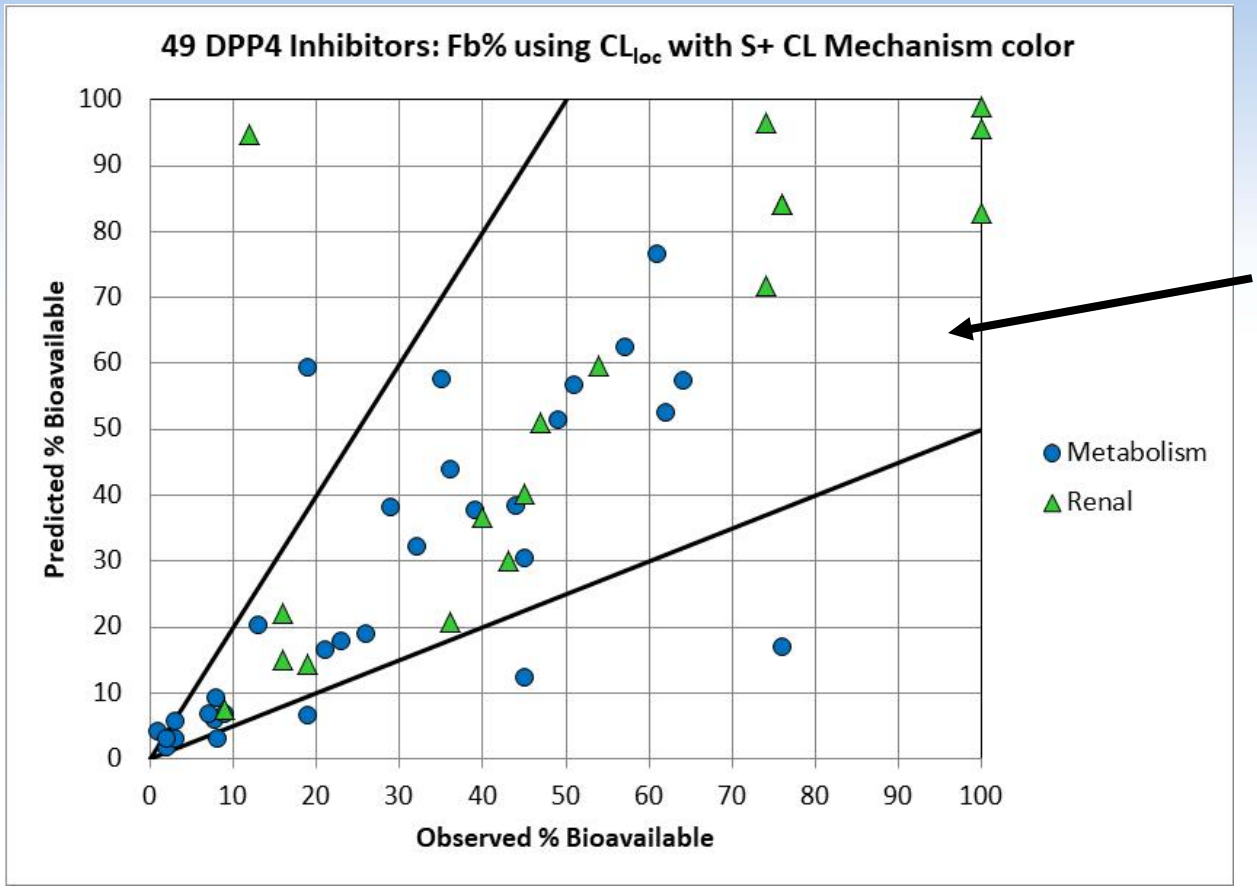
- 49 Compounds: Single Med Chem series reported by Merck in 9 papers.
  - RAT *in vivo* data : %F, CLp
  - Physicochemical prop & *in vitro* data : Not available

Exp CL_p | CL_{glb} | CL_{loc}



Oral Bioavailability in Discovery

- A database* of 49 DPP4 Inhibitors with oral bioavailability (%Fb) was constructed.
- Liver CL_{int} and FPE was estimated using a novel local clearance model (CL_{loc})
- Points were colored according to S+ CL Mechanism



86% (42 molecules) were predicted within 2-fold of the observed value.

76% (37 molecules) were predicted within 1.5-fold

*Daga P et al., Molec. Pharm. 15(3):831 (2018)

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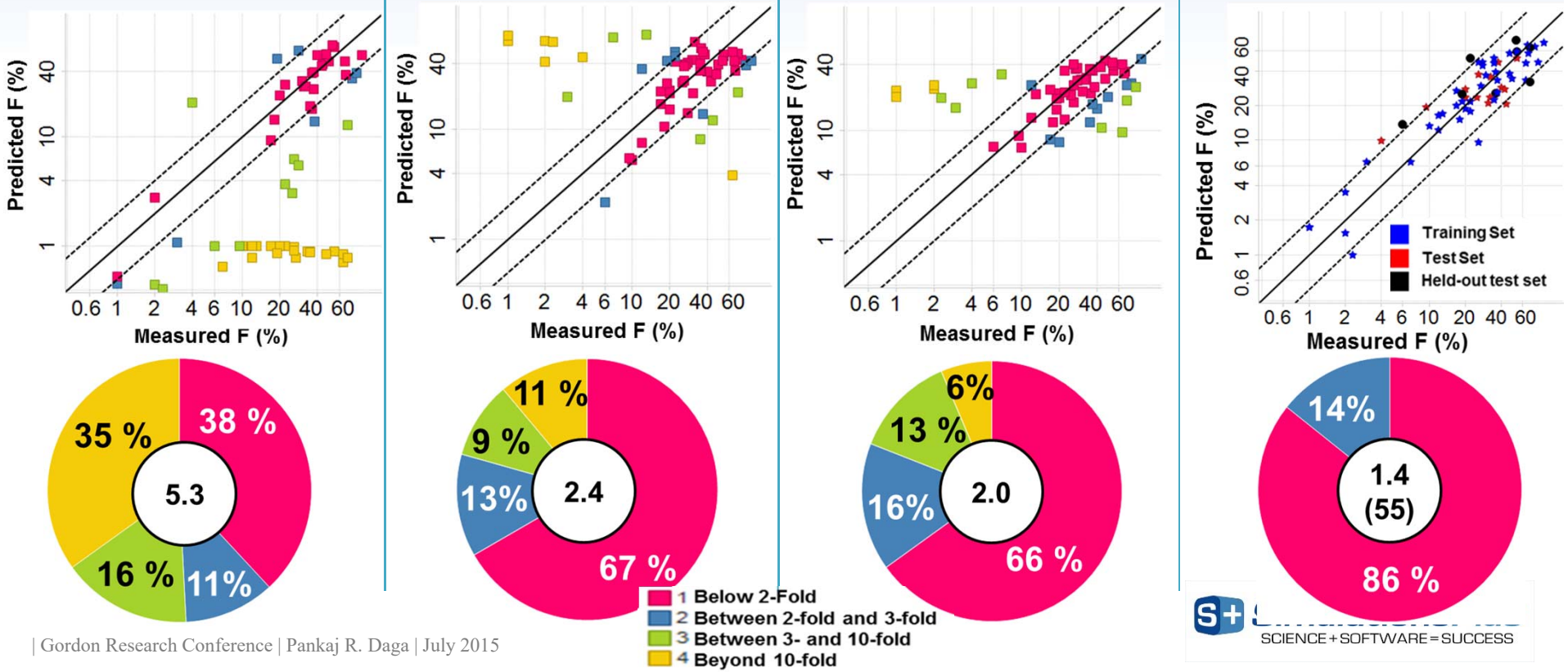
PBPK *in silico* inputs are adequate

Case Study #2: Internal PIM kinase Inhibitor series

- 63 compounds : Single med-chem series with experimental data
  - *In vitro* (Solubility, Caco2 permeability, Plasma Protein binding, CL_{int})
  - RAT PK data (%F, AUC, C_{max}, T_{max}, CL_{plasma}, V_{ss})

Exp CL_p	Exp input properties & CL_{int}	in silico input prop & CL_{glb}	In silico input prop & CL_{loc}



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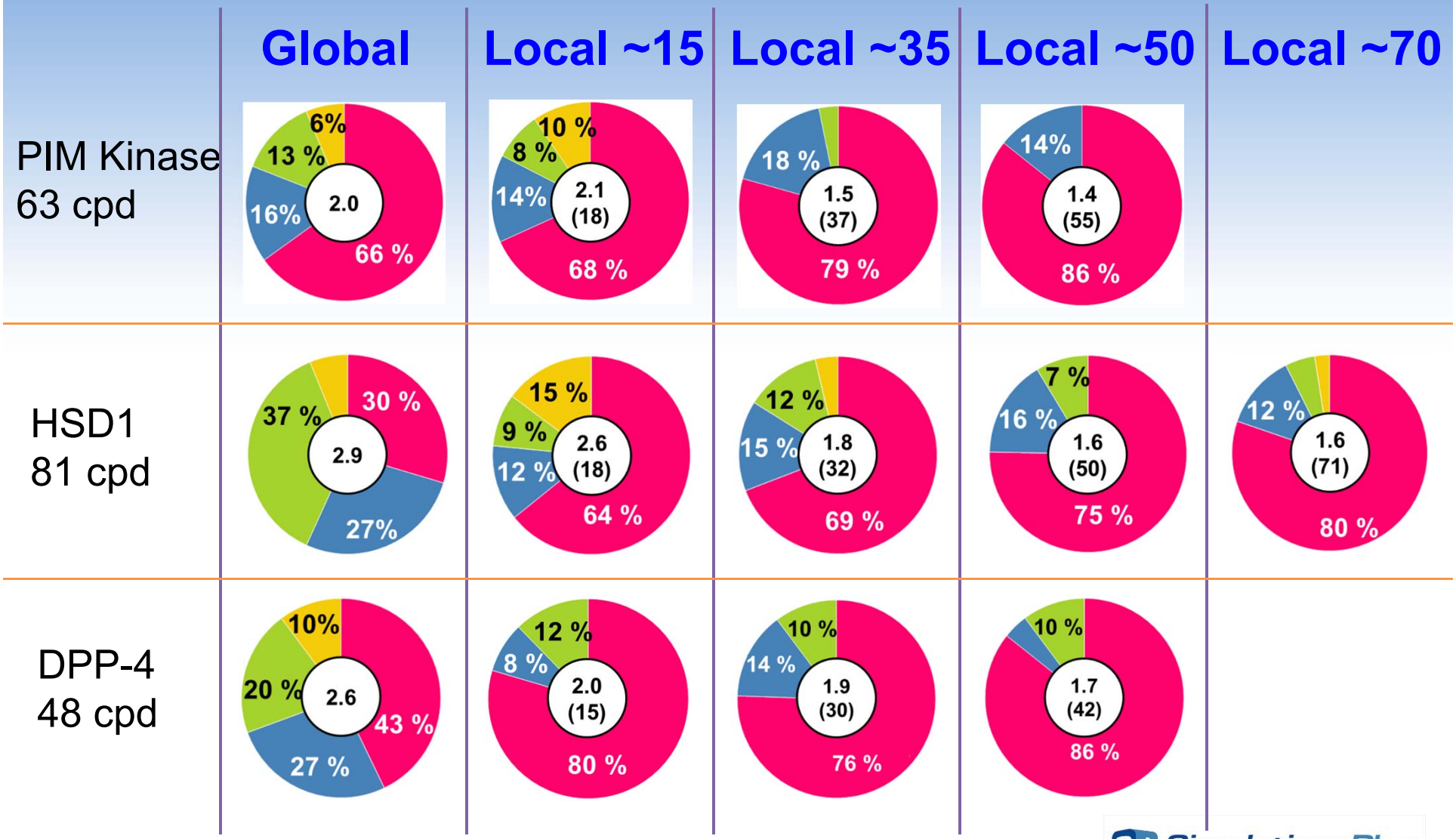
Local models OK w/ only 15 Rat %Fs

Increasing training data size, improved performance



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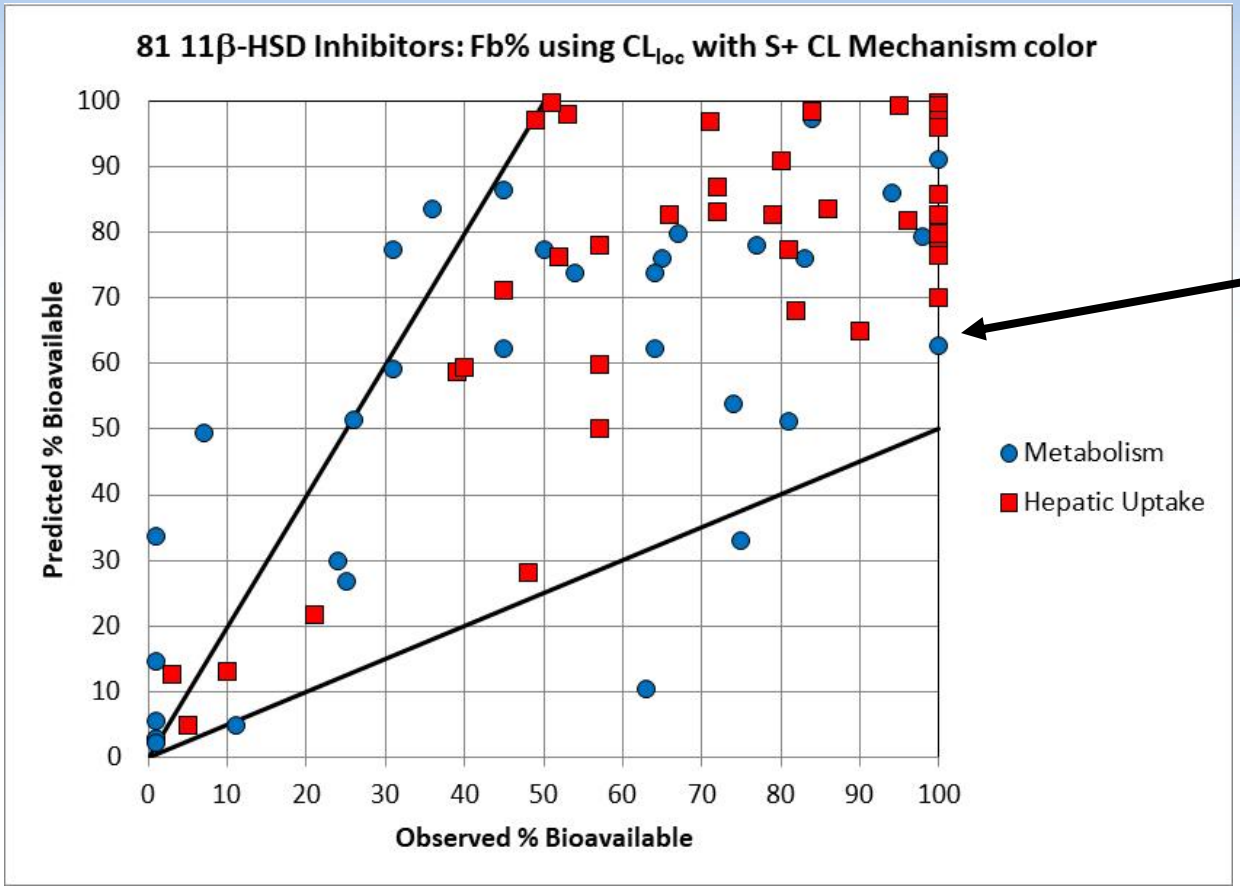
Oral Bioavailability in Discovery

- A database* of 81 11β-HSD Inhibitors with oral bioavailability (%Fb) was constructed.
- Liver CL_{int} and FPE was estimated using a novel local clearance model (CL_{loc})
- Points were colored according to S+ CL Mechanism



80% (65 molecules) were predicted within 2-fold of the observed value.

65% (53 molecules) were predicted within 1.5-fold

*Daga P et al., Molec. Pharm. 15(3):831 (2018)

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Conclusions

- PBPK modeling and simulation can be successfully used in the lead optimization phase of drug discovery.
- Using CL_{loc}, accurate bioavailability can be predicted for new compounds in a chemical series
- Physicochemical property estimates *in silico* can be successfully used in the absence of measured input properties for new molecules
- The approach can be used in early stage of lead optimization
  - Even with 15-18 molecules with Rat PK data
- ECCS models help to identify compounds with greater (primarily metabolized) or lesser (primarily renal or hepatic uptake) chance for accuracy in ISIVE and IVIVE.
- Purely *in silico* estimates of absorption and first pass extraction by CYP clearance can be used to estimate bioavailability for compounds that are primarily metabolized.

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Extra Slides

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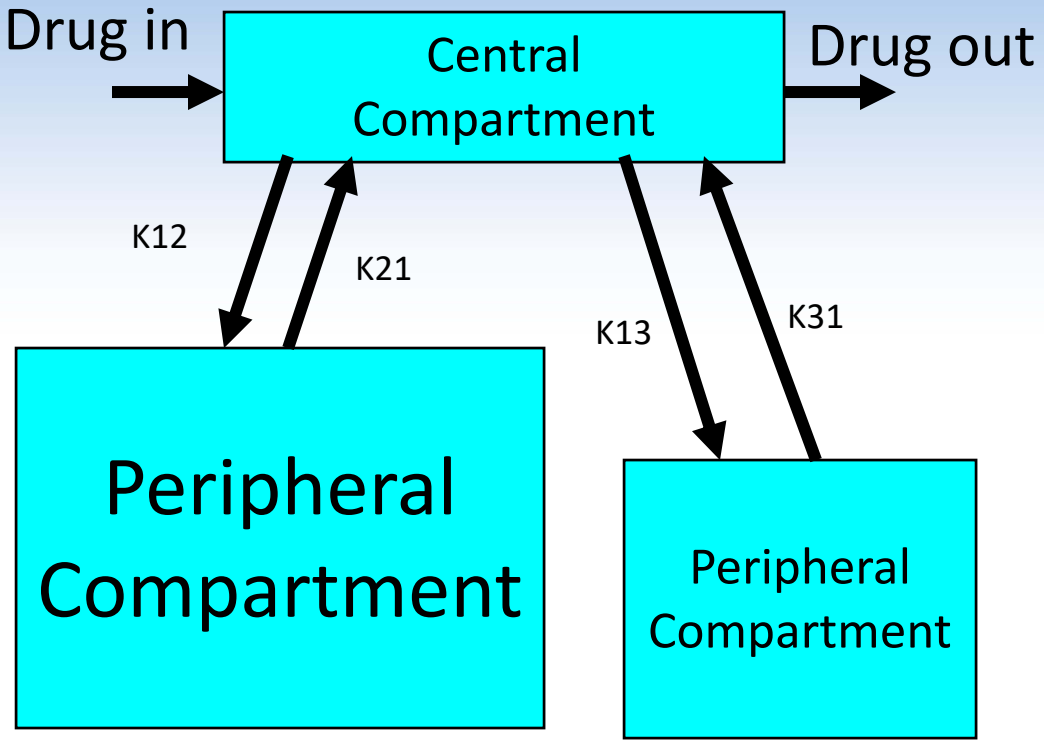
Traditional (Top-down) Compartmental PK

Traditional compartmental PK employs empirical models for one or more mathematical compartments.

Peripheral compartments serve as reservoirs with different volumes and different rates of exchange of drug with the central compartment.

The data defines the model – the model is not defined from physiology.

The model is used to describe and interpolate the data rather than to predict or conduct what-if simulations.



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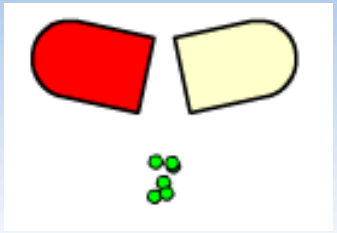
“Top Down” Volume of Distribution



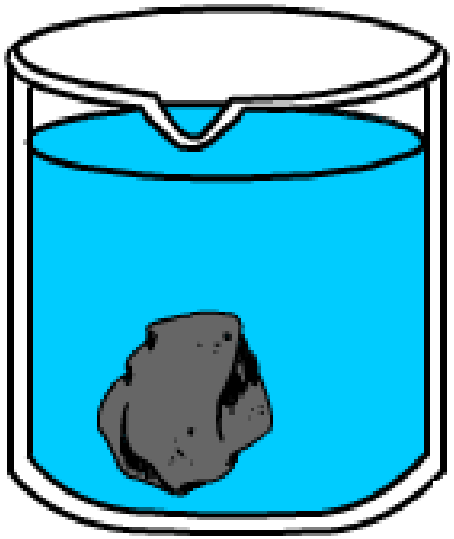
- What is the volume of fluid and rock in the beaker?
- Add 10 mg of Drug

  Measure Concn. = 12 mg/L

  V_d = Dose / C_0

  V_d = 10 mg/ 12 mg/L = 0.83 L

  V_{rock} = 1 - 0.83 = 170 mL



1 L Beaker

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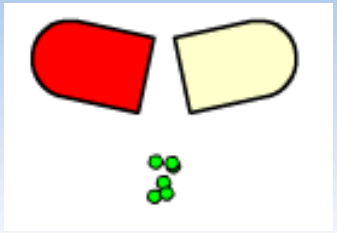
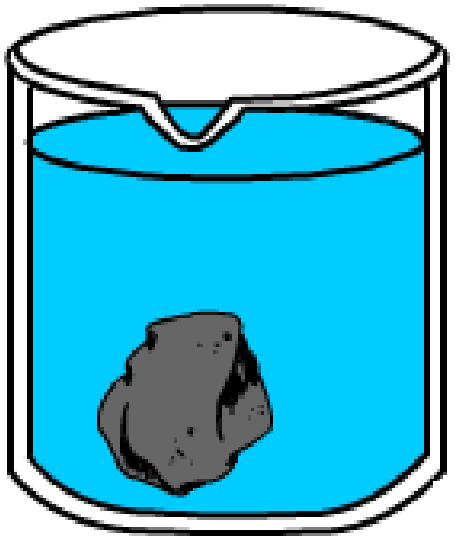
Top Down Volume of Distribution





- What is the volume of fluid and **lump of charcoal** in the beaker?
- Add 10 mg of Drug
- Measure Concn. = 0.12 mg/L

V_d = Dose / C_0

V_d = 10 mg/ 0.12 mg/L = 83 L

V_{rock} = 1 - 83 = -82 L

Thus, the calculated V_d is not a real volume but rather an apparent Vol.

1 L Beaker

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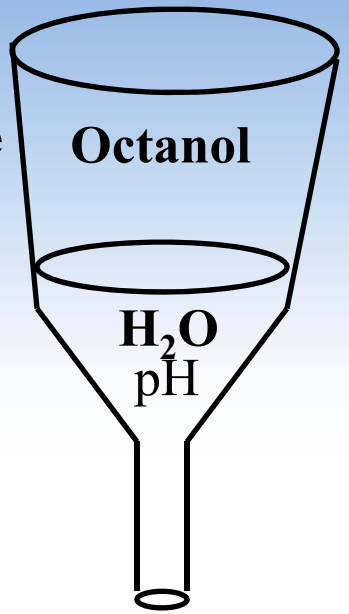
Distribution vs. Partition Coefficient

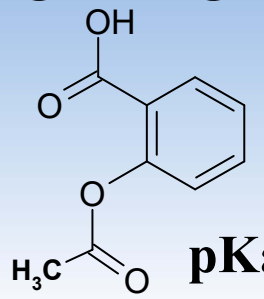
Hydrophobic phase

Hydrophilic phase

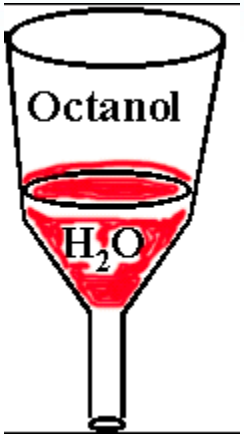


pH = 2

log D ~ log P = 2

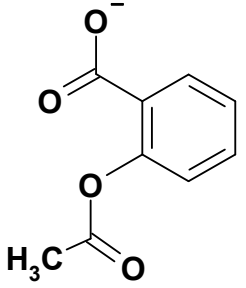


pKa = 3.5



pH = 8

Log D = -1.5



$$LogD_{oct/water} = \log \frac{C_{oct}^{aspirin}}{C_{water}^{aspirin}} = \log \frac{[HA]_{oct} + [A^-]_{oct}}{[HA]_{water} + [A^-]_{water}}$$

$$LogP_{oct/water} = \log \frac{[HA]_{oct}}{[HA]_{water}}$$

Log P is defined for the unionized species **only**

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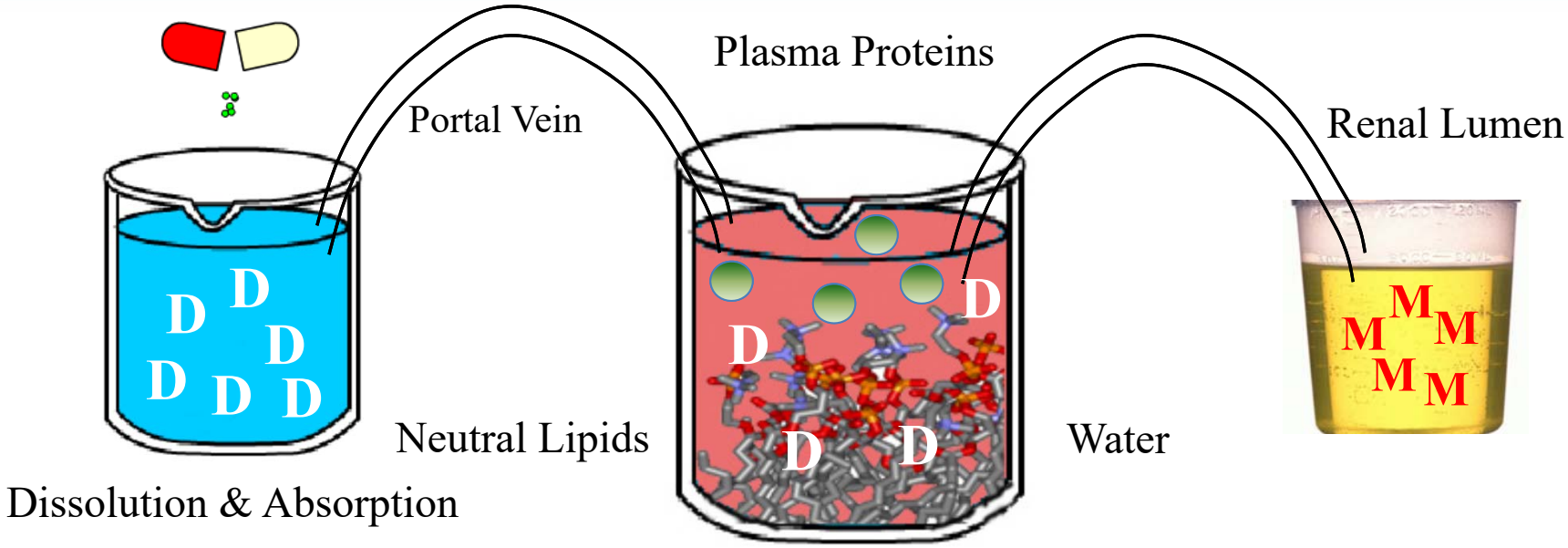
“Bottom-up” Volume of Distribution

- Tissue/Plasma partition coefficient (K_p) depends on drug physicochemical properties and biochemical protein binding properties (Poulin & Krishnan, 1995); (Poulin & Theil, 2000); (Berezhkovskiy, 2004).

$$Kp = \frac{K \cdot \left(V_{nlt} + 0.3V_{pht}\right) + V_{wt} \,/\, fu_t + 0.7V_{pht}}{K \cdot \left(V_{nlp} + 0.3V_{php}\right) + V_{wp} \,/\, fu_p + 0.7V_{php}}$$



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