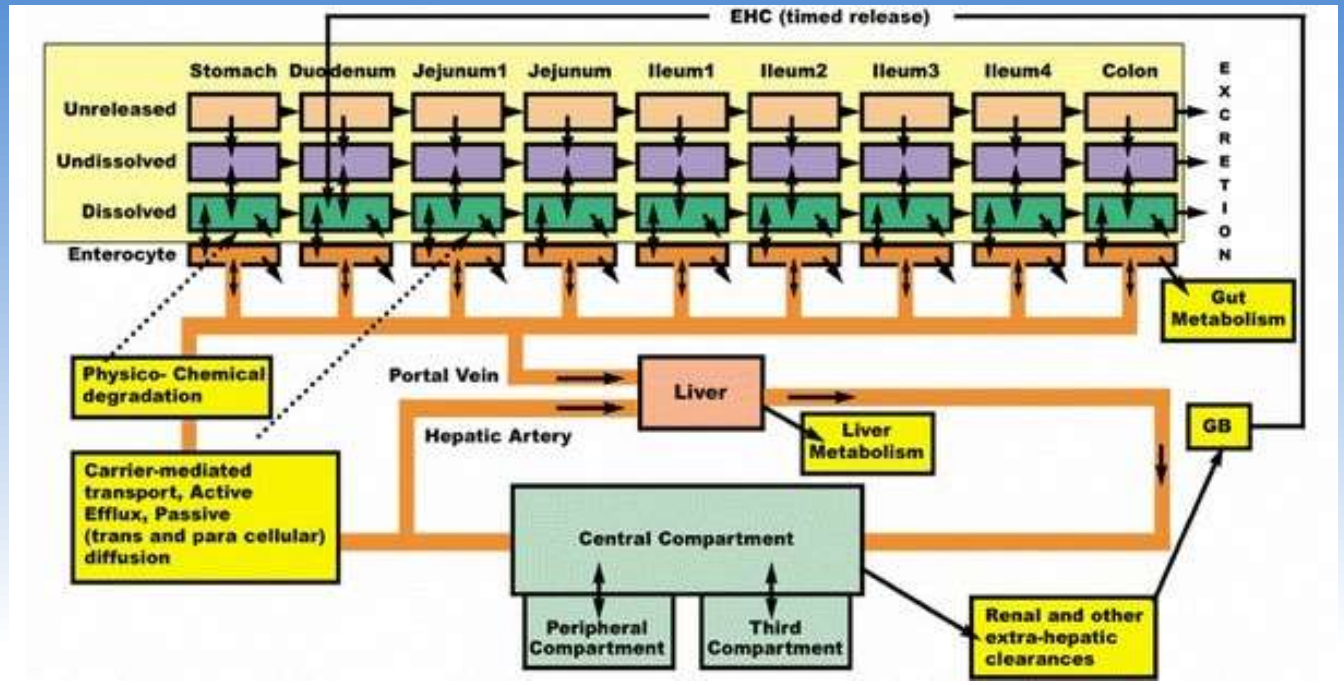

Rational Bioavailability Design

Optimizing Bioavailability during Lead Optimization with Global Sensitivity Analysis of Physiologically-Based Pharmacokinetic Simulations

Pankaj R. Daga, Michael B. Bolger, Robert D. Clark, Eric Martin*

Simulations Plus Inc, Lancaster CA

* Novartis Institute of Biomedical Research, Emeryville, CA

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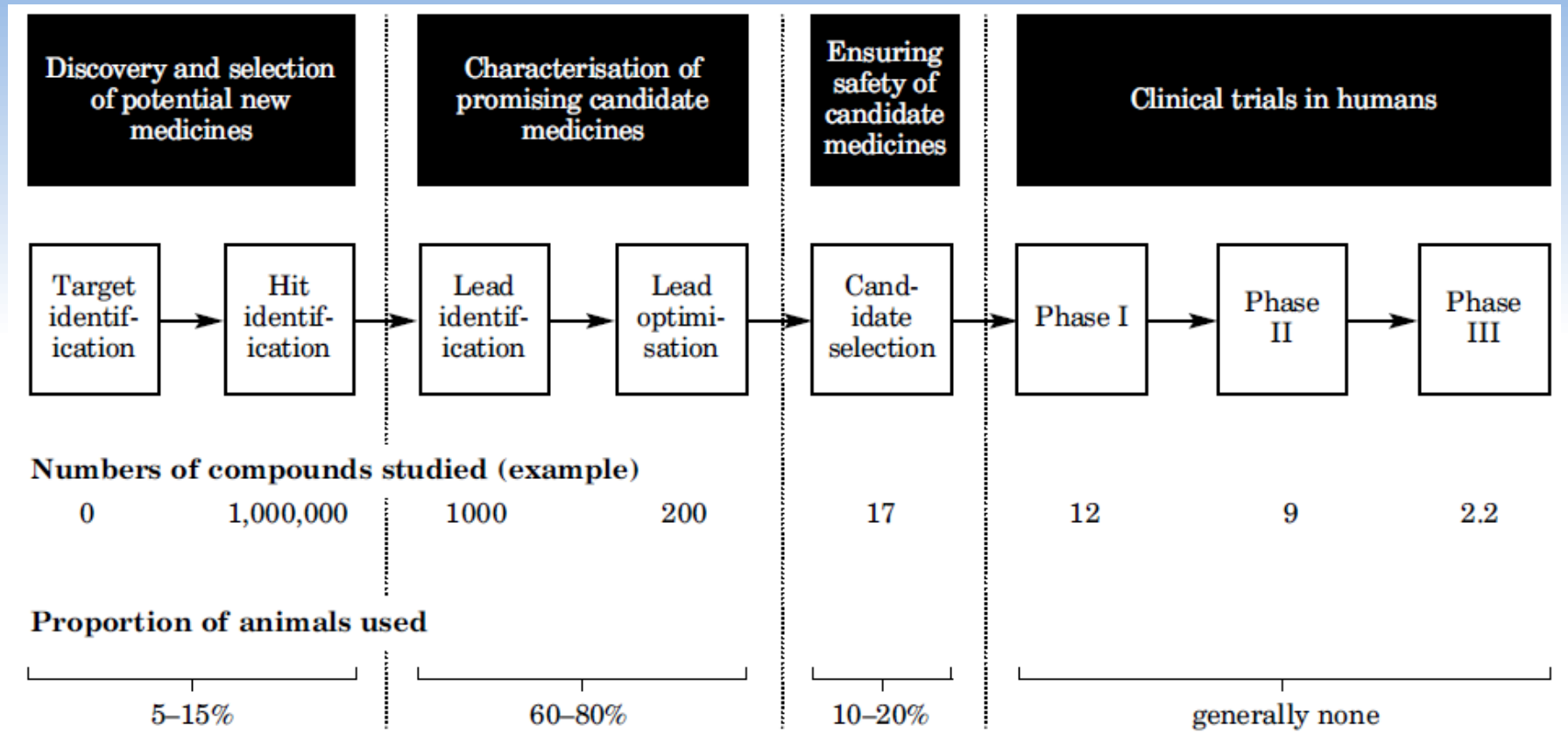
Drug Discovery & Development

About 60-80% of animal studies conducted during Lead Opt



Lead ID and Lead Opt together contribute ~32-35% towards the total cost

Thomas et al, *ATLA* **2010**, *38*, Supplement 1, 81–85

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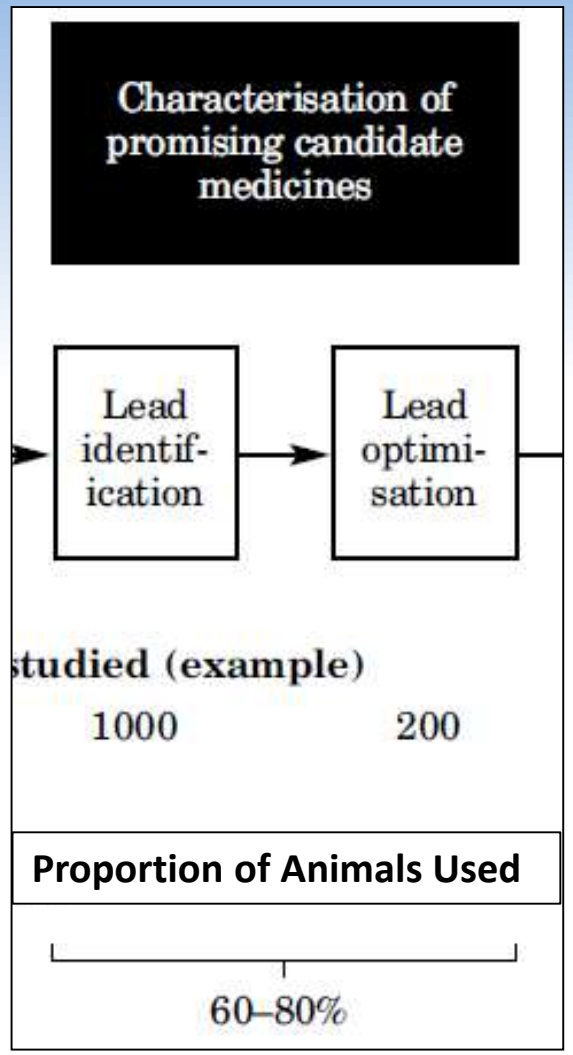
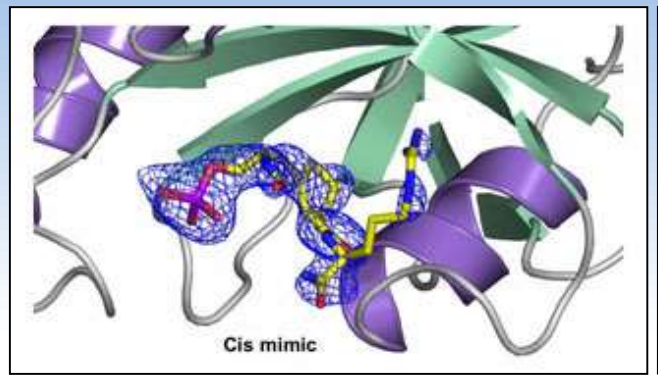
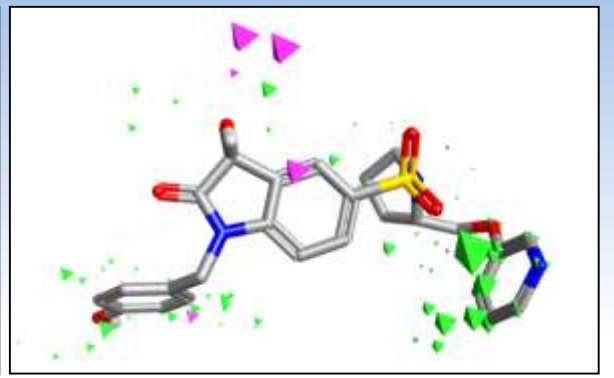
Lead Optimization

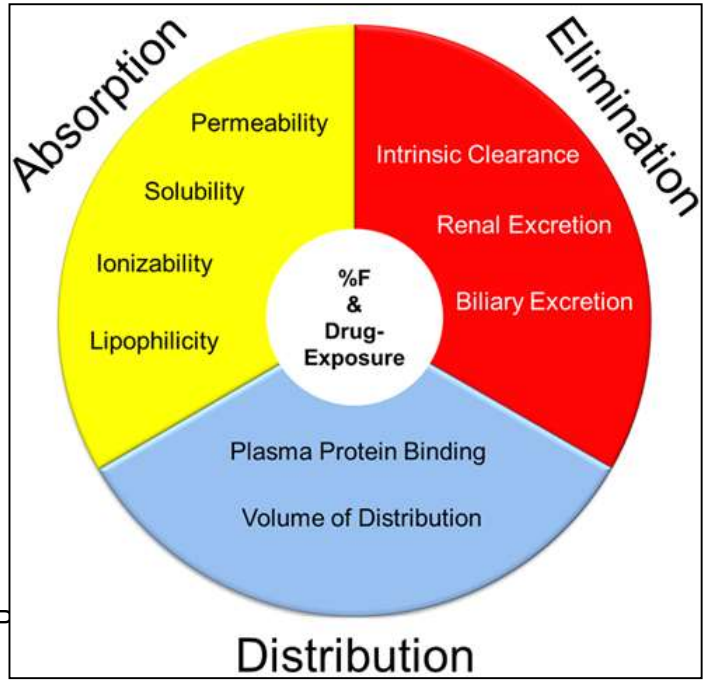
Chemists manipulate various properties to improve Drugability



Improving Binding Affinity and Potency







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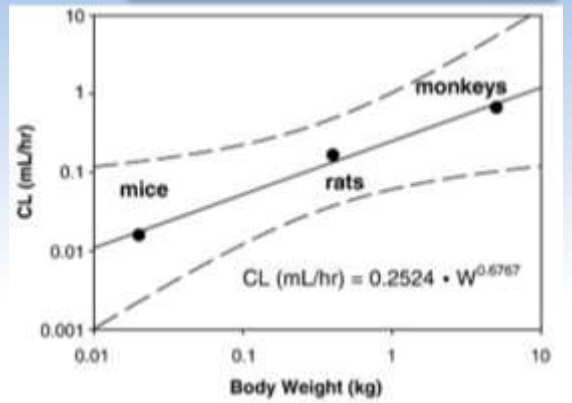
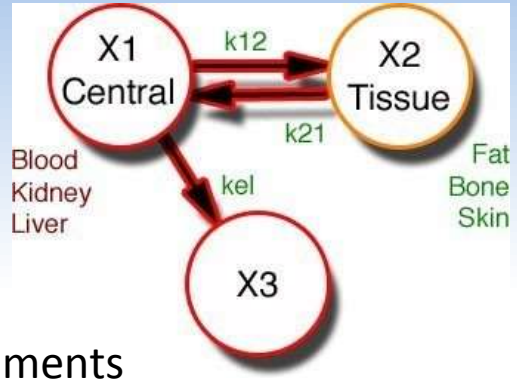
PBPK Models may Prove to be most Informative to Optimization

Model inputs are the properties med chemists can optimize

Allometric Scaling



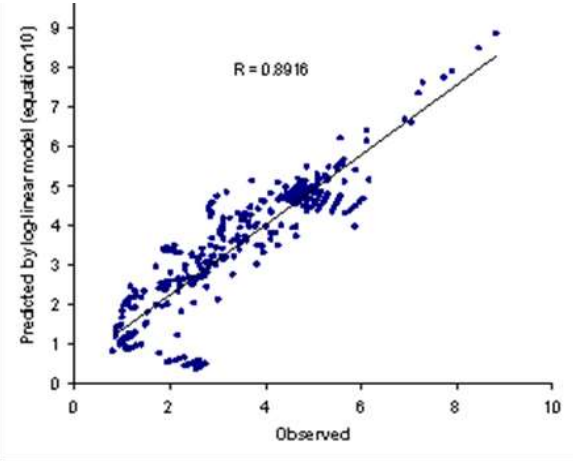
Traditional Pharmacokinetic Model



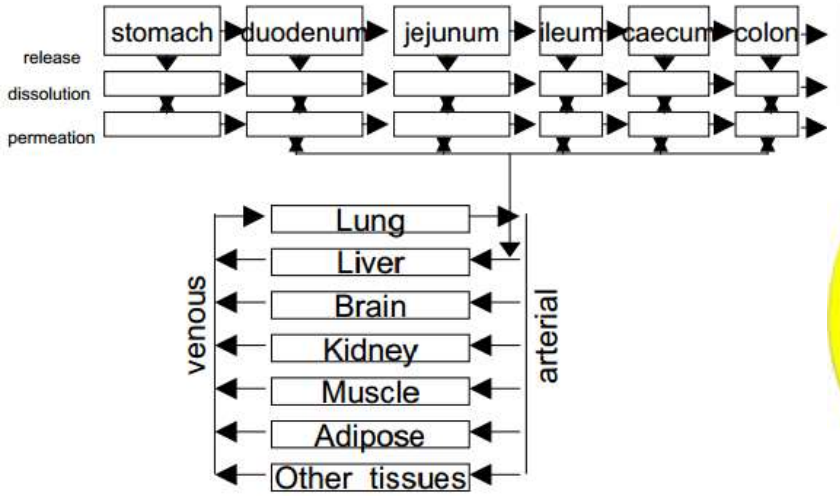
Compartmental and non-compartmental PK analysis, *in vivo* data modeled *a posteriori*

After animal experiments

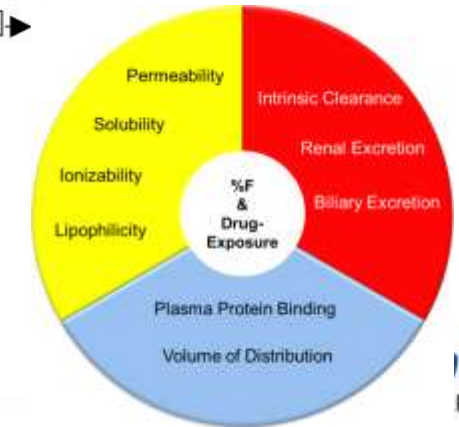
QSAR/QSPR



Physiologically-Based Pharmacokinetic Model



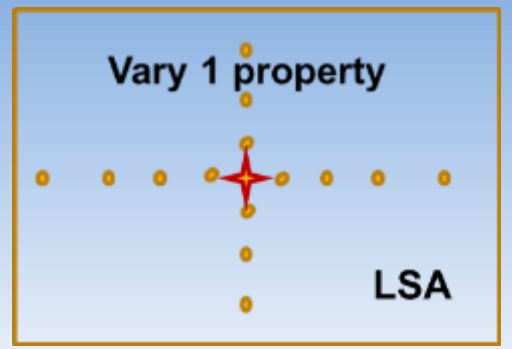
Integrate *in silico* and *in vitro*

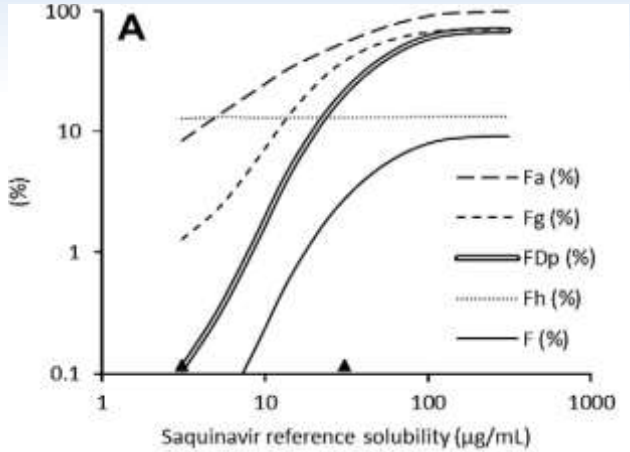


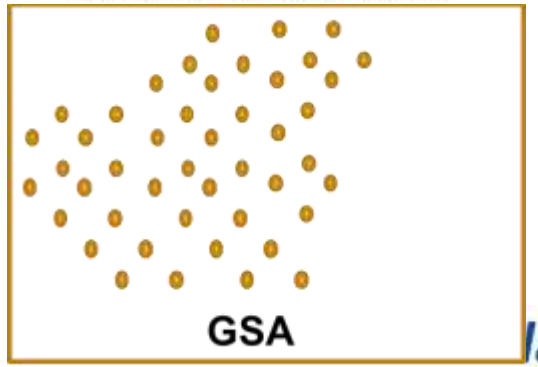
PBPK Modeling Typically Tuned for Individual Advanced Compounds

For Lead Optimization, we must optimize for entire med Chem series

- Typically applied to a few advanced compounds
  - Prioritize expensive animal studies or predict human dose
  - Usually based mainly on experimental inputs
  - Broader studies require global QSAR models
  - Sometimes includes *local* sensitivity analysis
- Lead optimization requires tuning for entire series
  - Requires *global* sensitivity analysis (GSA)
  - All inputs calculated from structure
  - These can be local QSAR models







Heikkinen *et al*, **2012**, *47*, 375–386

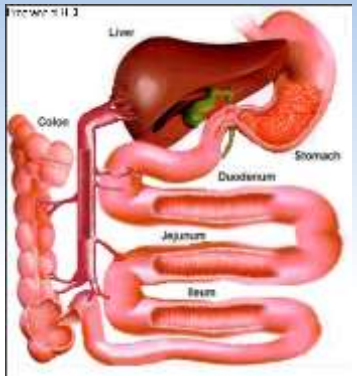
Our Approach Applies GSA to PBPK Modeling

First step is to show reliable results for a congeneric series

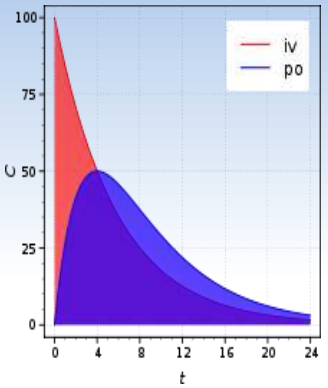
1. Select the parameters (measured or predicted)

Physicochemical and Biochemical properties:
Permeability →
Solubility →
Ionizability →
Clearance →
Hydrophobicity →
Protein Binding →

2. GastroPlus simulations for active med-Chem series

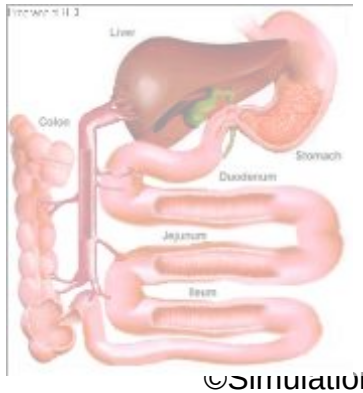


3. Predict the %F and exposure



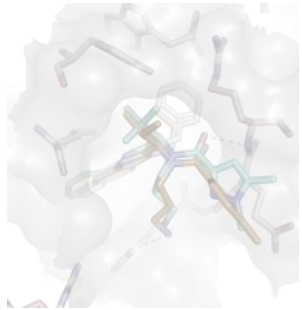
4. Sample the active property space

5. GastroPlus simulations for sampled points



6. Identify the most sensitive parameters, those affect the %F

7. Lead optimization with emphasis on the identified sensitive parameters



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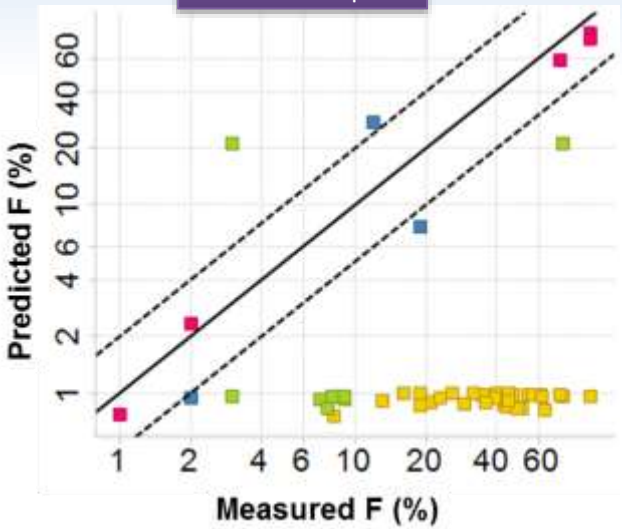
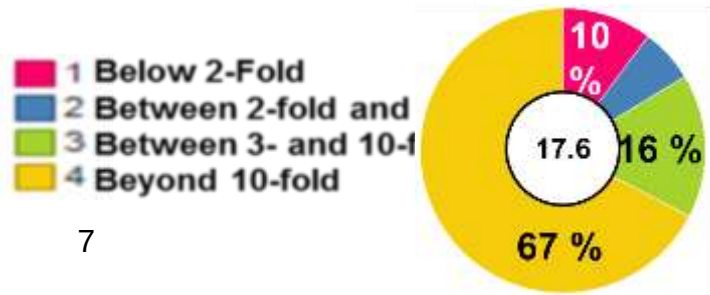
Case Study #1: Dipeptidyl Peptidase-4 Inhibitors

Trouble with Clearance can be overcome by fitted CL

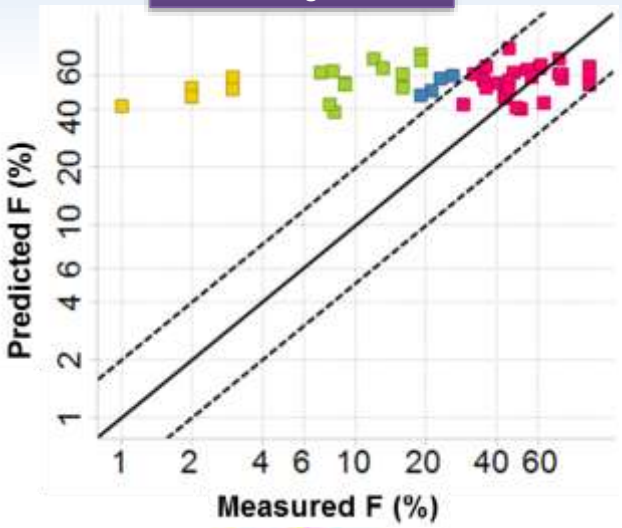
- 49 Compounds: Single congeneric series reported by Merck in various papers
  - RAT *in vivo* data : %F, CLp
  - Physicochemical prop & *in vitro* data : --

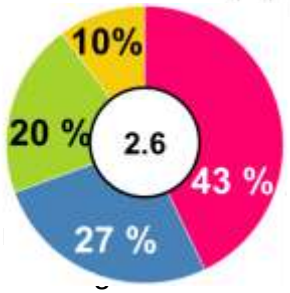
Exp CL_p



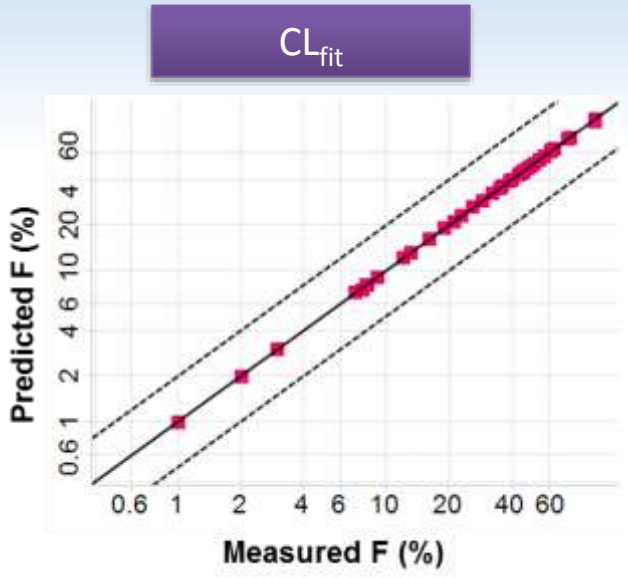


CL_{glb}





CL_{fit}



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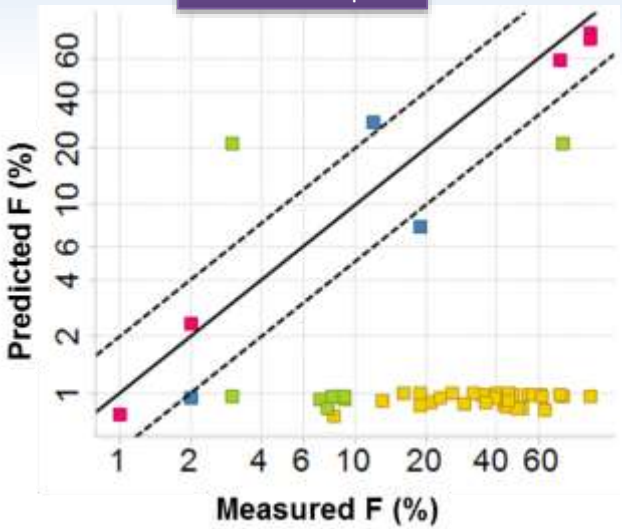
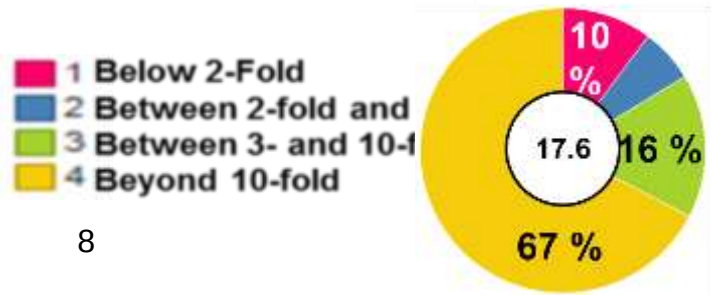
Case Study #1: Dipeptidyl Peptidase-4 Inhibitors

Trouble with Clearance can be overcome by fitted CL

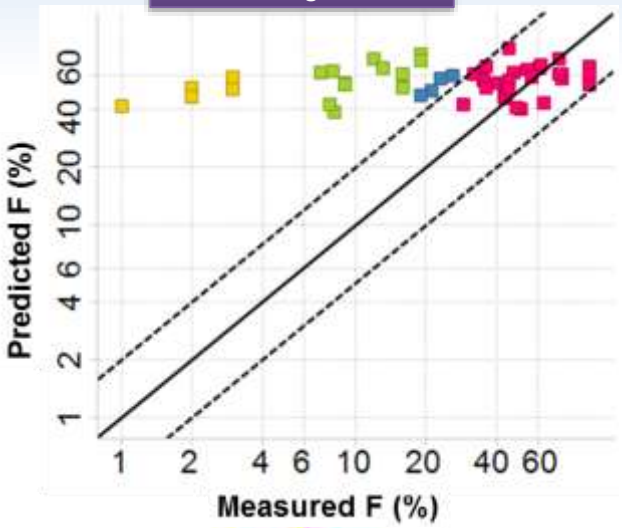
- 49 Compounds: Single congeneric series reported by Merck in various papers
  - RAT *in vivo* data : %F, CLp
  - Physicochemical prop & *in vitro* data : --

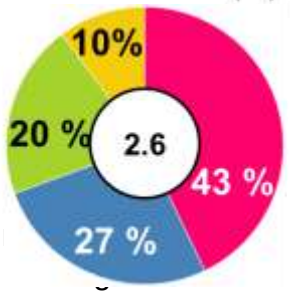
Exp CL_p



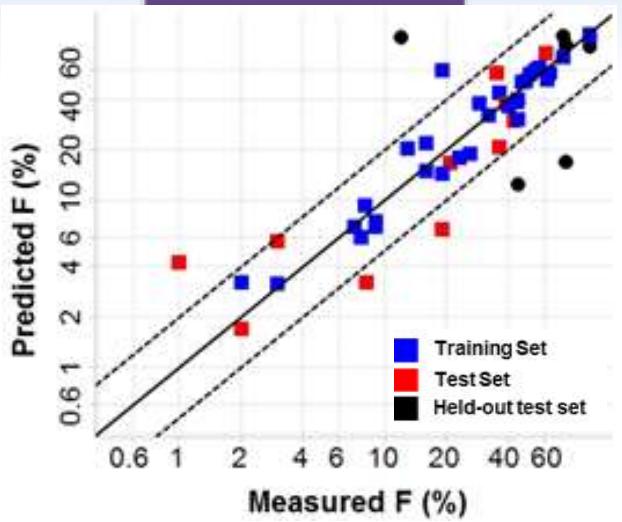


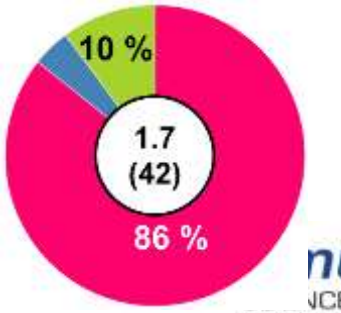
CL_{glb}





CL_{loc}

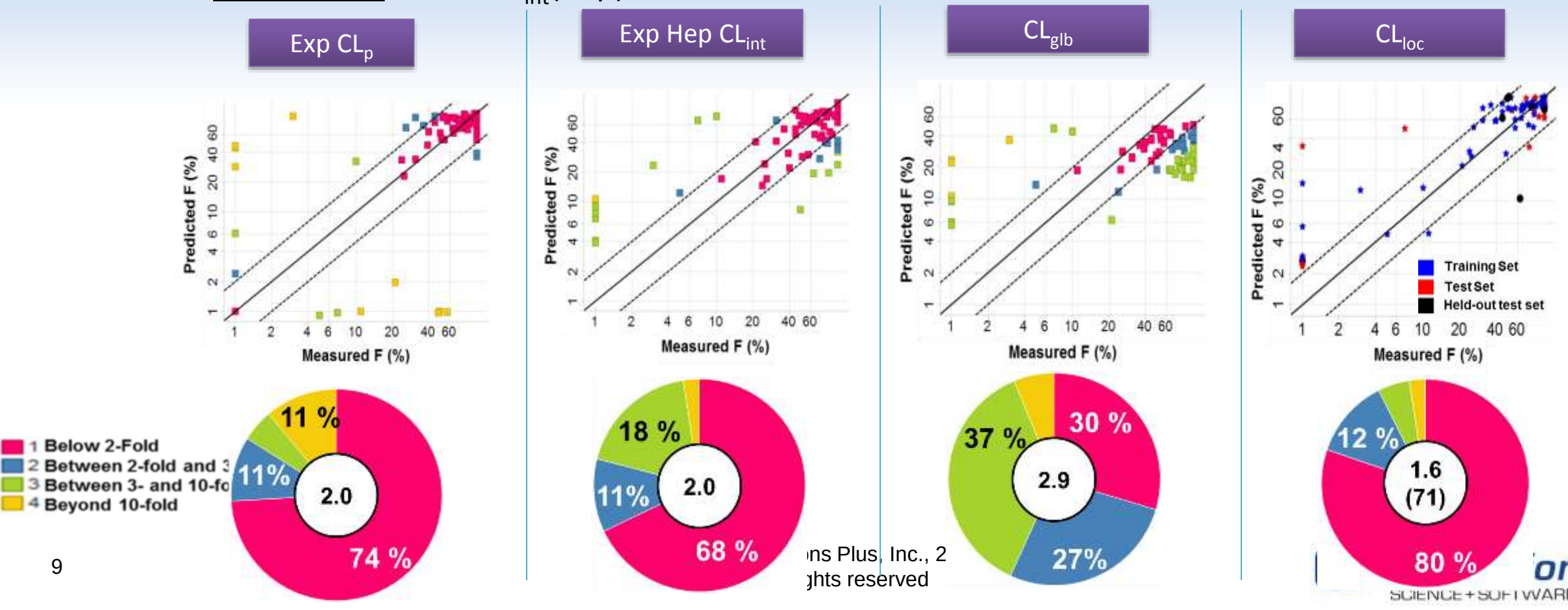




Case Study #2: 11β-HSD1 Inhibitors

Hepatocyte CL provides accurate estimate of CL and hence %F

- 81 Compounds: Single congeneric series reported by AstraZeneca in 4 papers
  - RAT *in vivo* data: %F, CLp
  - *in vitro* data: CL_{int}(hep)

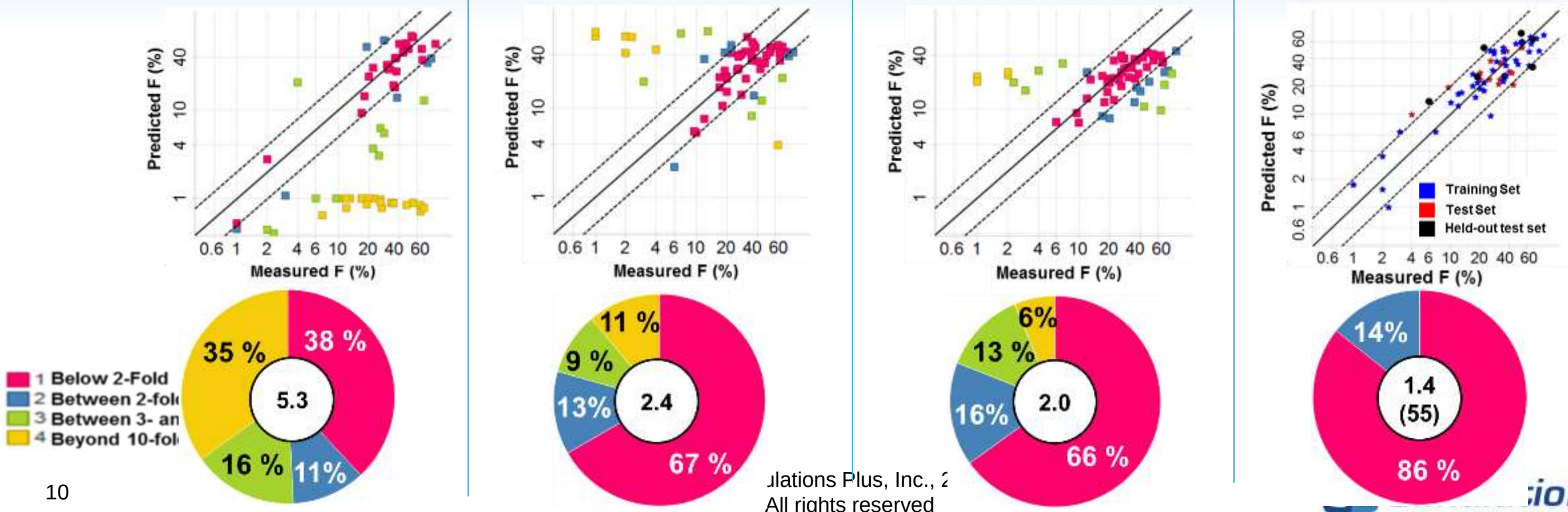


Case Study #3: Internal Kinase-"X" Inhibitor series

In silico inputs are adequate for GSA

- 61 compounds : Single congeneric series with experimental data
  - Physicochemical prop & *in vitro* data: (Solubility, Caco2 permeability, Plasma Protein binding, CL_{int})
  - RAT PK data (%F, AUC, C_{max}, T_{max}, CL_{plasma}, V_{ss})

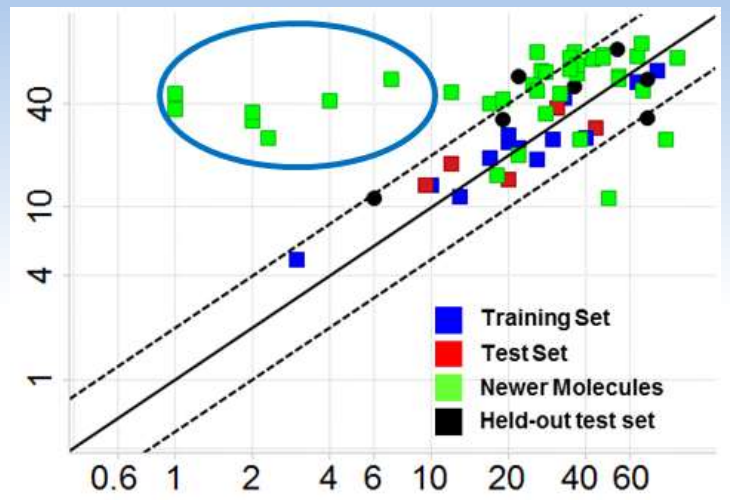
Exp CL_p	Exp input prop & CL_{int}	*in silico* prop & CL_{glb}	*in silico* prop & CL_{loc}

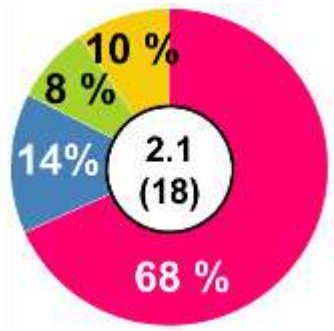


Our Approach can be used Early in Lead Optimization

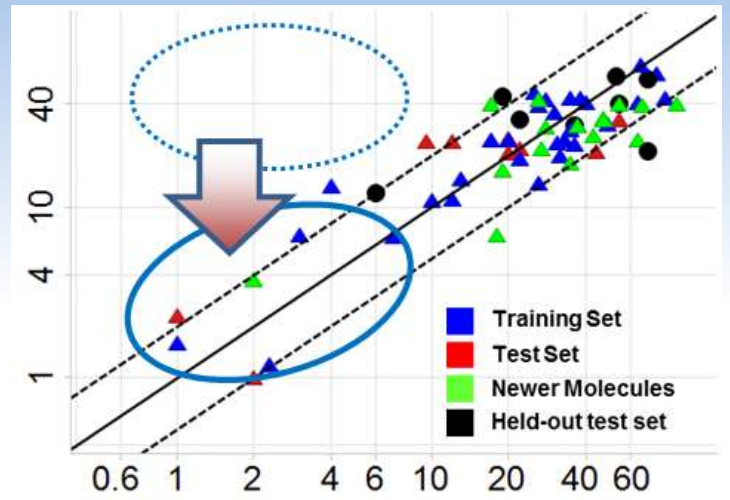
Kinase Dataset: Chronological Predictions

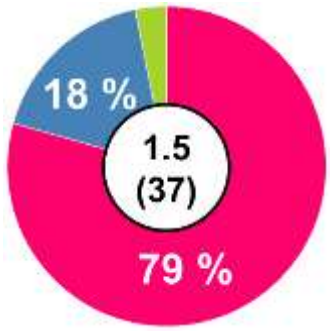
Model With 18 molecules



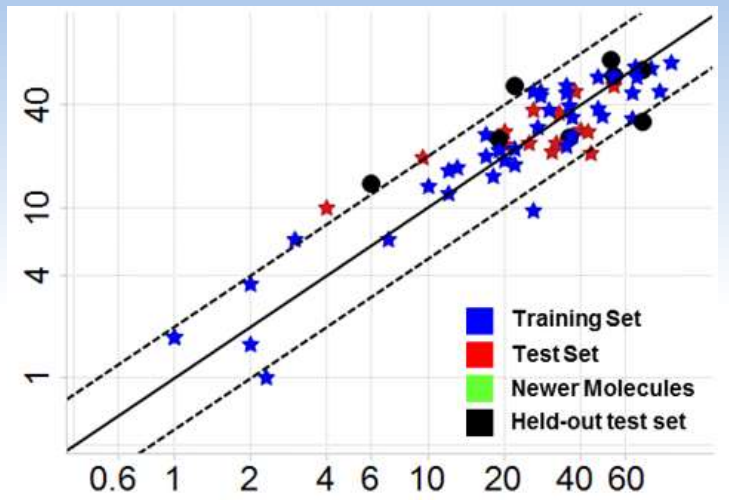


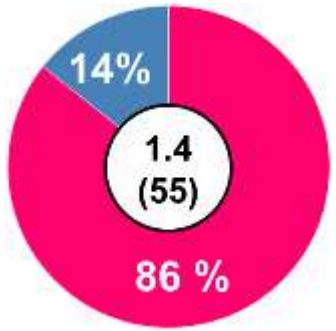
Model With 37 molecules





Model With 55 molecules





Number of compounds used to build QSAR model is shown in parenthesis within the inner circle

1 Below 2-Fold
2 Between 2-fold and 3-fold
3 Between 3- and 10-fold
4 Beyond 10-fold

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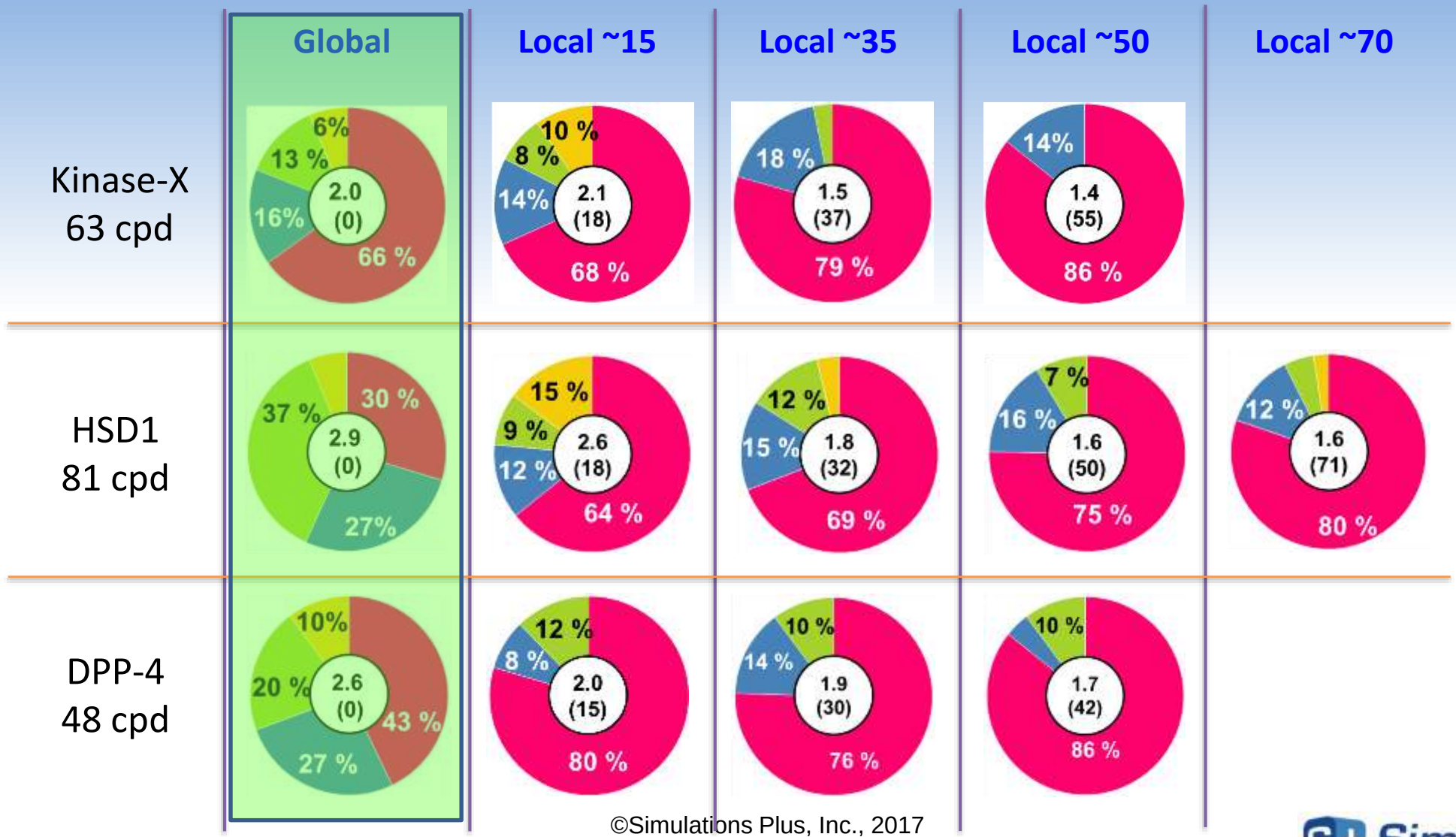
Local Models OK w/ only ~15 Rat Data Points

Increasing training data size, improved performance



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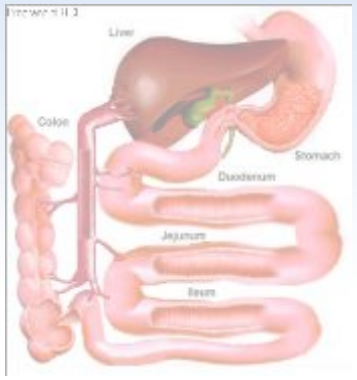
GastroPlus Adapted to %F Prediction for Congeneric Series

Second step: Global Sensitivity Analysis finds key properties

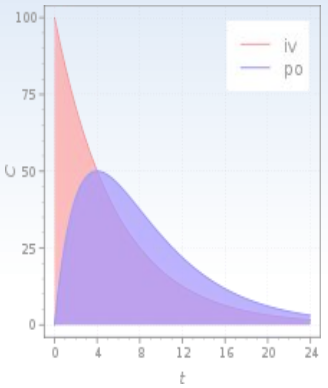
1. Select the parameters (measured or predicted)

Physicochemical and Biochemical properties:
- Permeability →
- Solubility →
- Ionizability →
- Clearance →
- Hydrophobicity →
- Protein Binding →

2. GastroPlus simulations for active med-Chem series

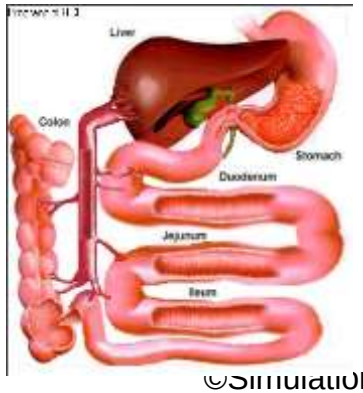


3. Predict the %F and exposure

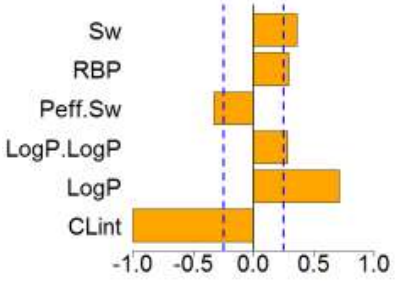


4. Sample the active property space

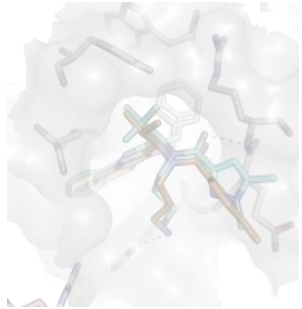
5. GastroPlus simulations for sampled points



6. Identify the most sensitive parameters, those affect the %F



7. Lead optimization with emphasis on the identified sensitive parameters



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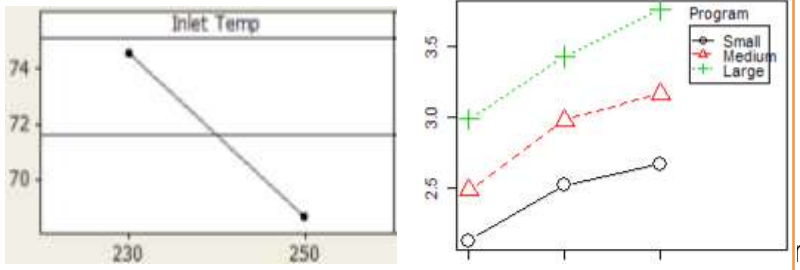
GSA is Similar to "Design of Experiments"

Instead of 2/3 levels of parameters, we use continuous data

Design of Expt

	Temp	Volume	Catalyst	Yield
Run1	0	10	0.1	Y1 %
Run2	100	10	0.1	Y2 %
Run3	0	50	0.1	Y3 %
Run4	0	10	1	Y4 %
Run5	100	50	0.1	Y5 %
Run6	0	50	10	Y6 %
Run7	100	10	10	Y7 %
Run8	100	50	10	Y8 %

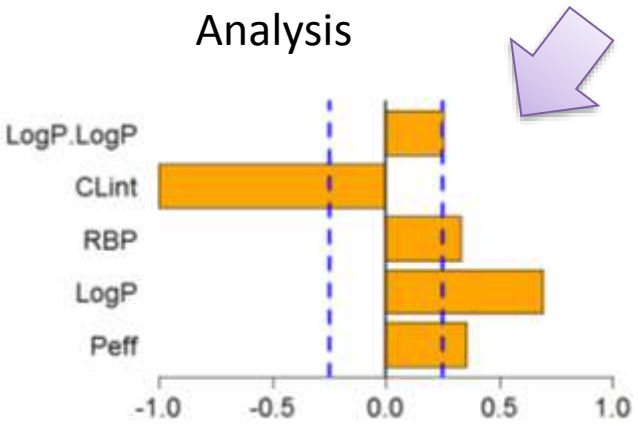
Analysis

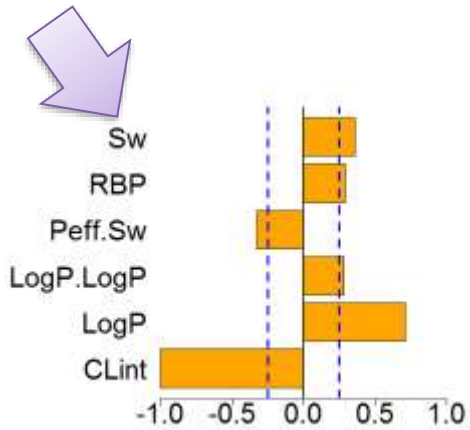


Global Sensitivity Analysis

Name	Peff	LogP	Sw	Fup	CLint	pKa1	pKa2	PredF
ZINC00002107	0.60	1.24	0.15	16.36	18.08	7.93	2.80	39.44
ZINC00007778	3.80	3.31	0.89	1.50	112.04	8.66	2.59	15.55
ZINC00011305	1.34	1.10	0.81	12.90	210.76	7.90	3.73	9.94
ZINC00029717	6.49	2.64	0.28	14.68	225.55	11.07	1.34	12.10
ZINC00032335	3.65	2.33	0.83	9.79	25.47	4.81	2.09	53.89
ZINC00032861	3.64	2.80	0.34	3.79	17.85	3.36	1.86	56.28
ZINC00049150	0.63	2.13	0.12	3.81	8.12	4.75	0.51	59.55
ZINC00054843	5.24	1.27	0.73	14.22	118.91	7.28	0.49	22.43
ZINC00055175	6.29	1.87	0.83	15.73	161.99	11.61	5.31	14.81
ZINC00056374	6.59	2.10	0.41	9.65	41.82	7.59	1.13	39.70
ZINC00066137	2.17	1.92	0.42	4.95	30.18	3.94	0.13	53.96
ZINC00072822	3.62	2.94	0.10	1.69	152.34	6.92	3.24	18.30
ZINC00073671	1.75	4.05	0.30	0.70	38.04	7.67	3.04	37.99
ZINC00083088	3.03	2.13	0.22	4.29	52.27	4.11	2.22	30.08
ZINC00091239	2.71	3.09	0.14	12.97	104.59	10.74	8.33	19.65

Analysis





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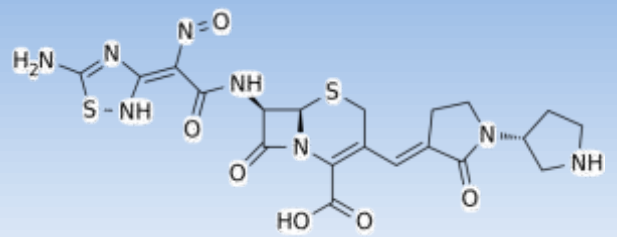
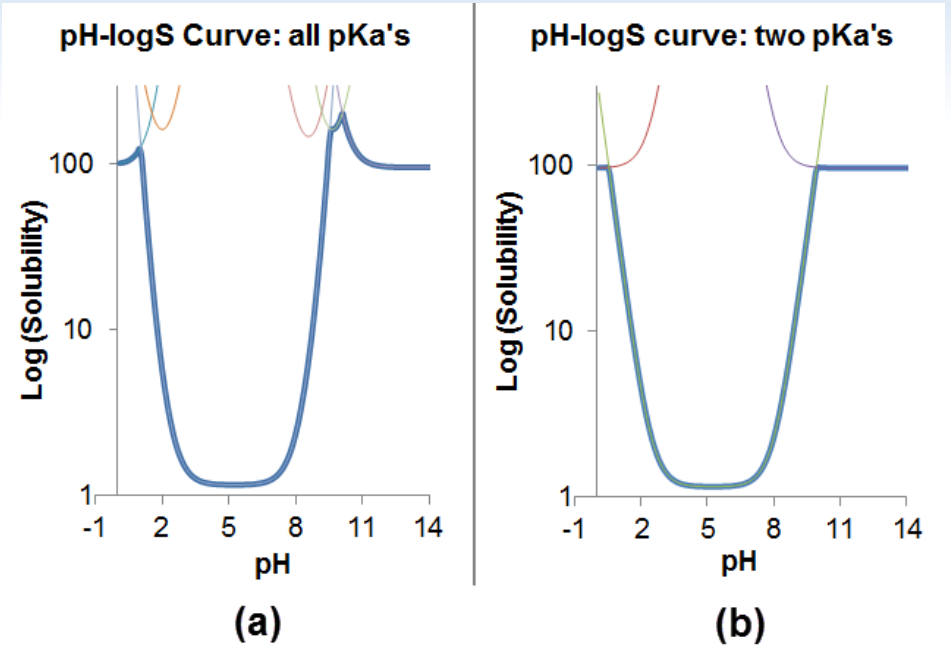
Difficulties Encountered: Applying GSA to PBPK

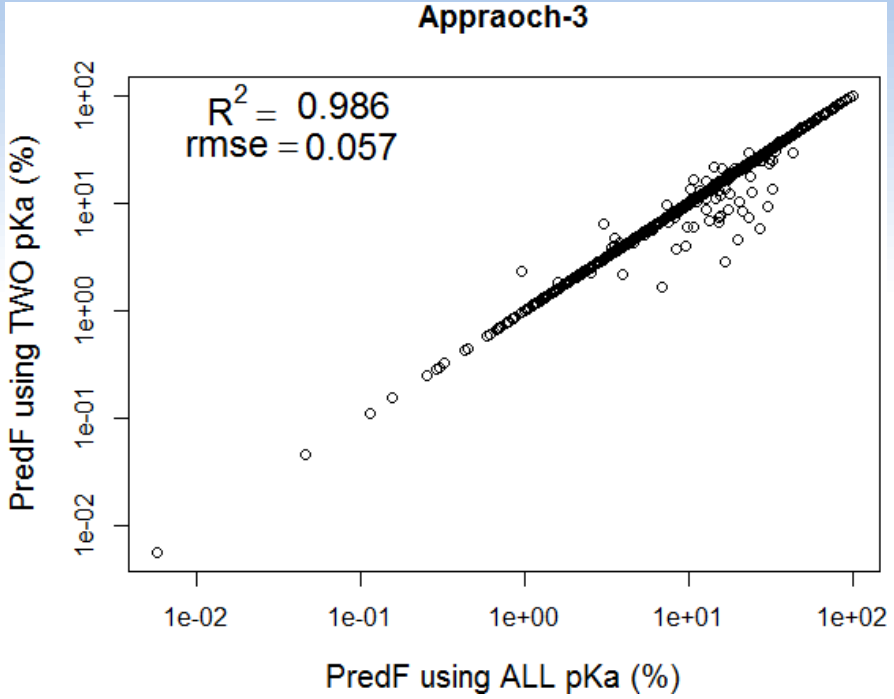
1. Two pKa's are adequate to predict accurate pH-Solubility profile



Ceftobiprole



Two pKa values sandwiching the Isoelectric pH



Comparison for ~2000 drugs & drug-like cmpds

Allows alignment of pKa's in GSA and simplifies message to med chemists

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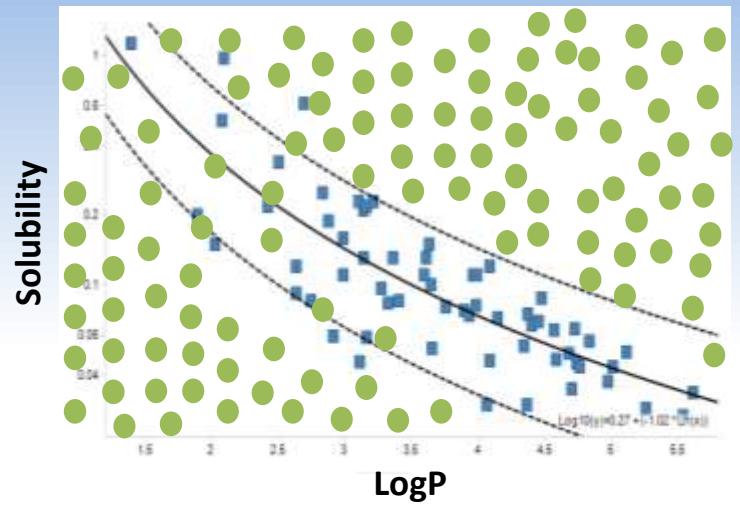
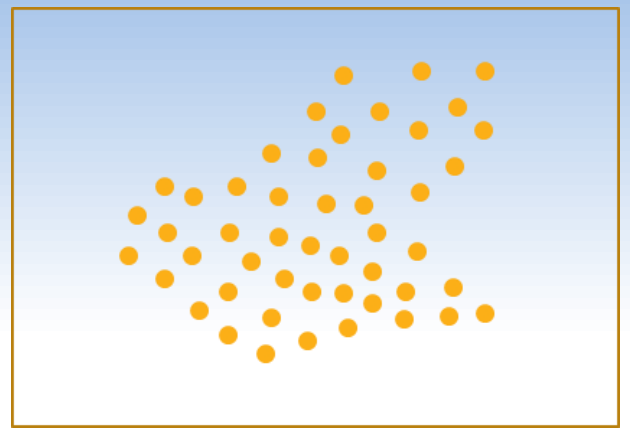
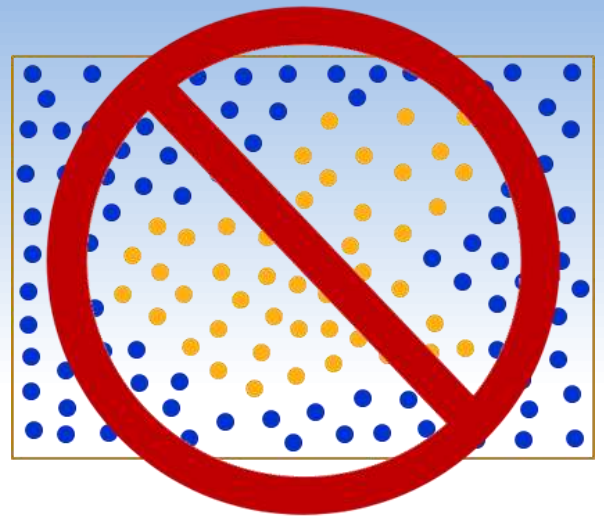
Difficulties Encountered: Applying GSA to PBPK (cntd..)

2. Don't sample impossible property combinations







- Can't use Fourier Amplitude Sensitivity Testing (FAST) or other standard algorithms
- Property sampling points can result in inaccessible combinations by selected series of compounds

Workflow for Sampling Valid Property-Space

Properties from "Drug-like" molecule DB avoids impossible combinations

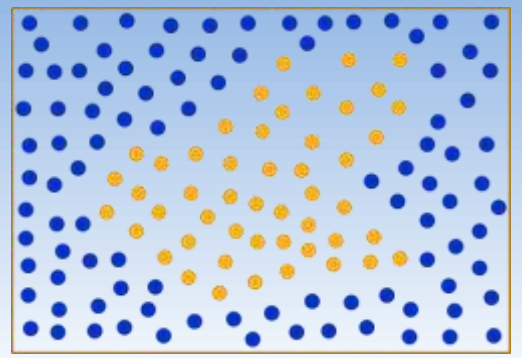
ZINC

Active compounds from Med Chem Series

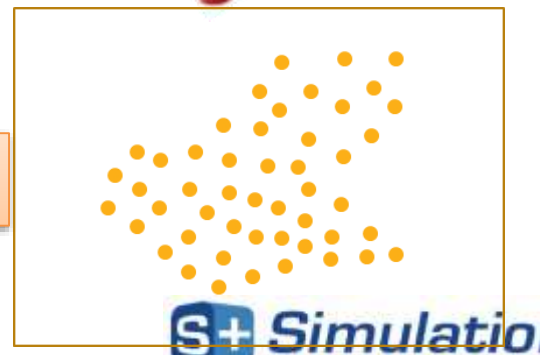
ADMET Predictor™

ADMET Property Estimation and Model Building

~16.5M



~3 M



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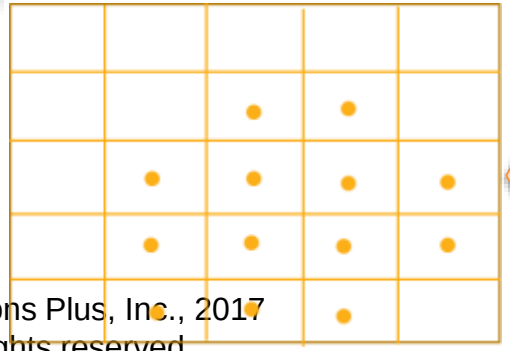

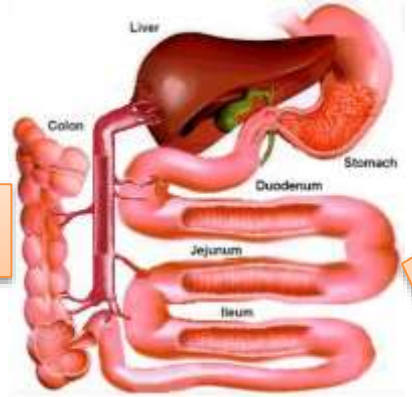

Simulation using only physicochemical properties, no structural information provided

PLS Regression

Name	Peff	LogP	Sw	Fup	CLint	pKa1	pKa2	PredF
ZINC00002107	0.60	1.24	0.15	16.36	18.08	7.93	2.80	39.44
ZINC00007778	3.80	3.31	0.89	1.50	112.04	8.66	2.59	15.55
ZINC00011305	1.34	1.10	0.8	12.90	210.76	7.90	3.73	9.94
ZINC00029717	6.49	2.64	1.28	14.68	225.55	11.07	1.34	12.10
ZINC00032335	3.65	2.33	0.5	9.79	8.12	4.81	2.09	53.89
ZINC00032861	3.64	2.80	0.34	3.79	8.12	3.36	1.86	56.28
ZINC00049150	0.63	2.13	0.12	1.5	8.12	4.75	0.51	59.55
ZINC00054843	5.24	1.27	0.73	1.5	118.91	7.28	0.49	22.4
ZINC00055175	6.29	1.87	0.8	3.73	161.99	11.61	5.31	14
ZINC00056374	6.59	2.10	0.7	9.65	41.82	7.59	1.13	39
ZINC00066137	2.17	1.9	0.2	4.95	30.18	3.94	0.13	53.1
ZINC00072822	3.62	2.3	0.10	1.69	152.34	6.92	3.24	18.30
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ZINC00083088	3.03	2.13	0.22	4.29	52.27	4.11	2.22	30.08
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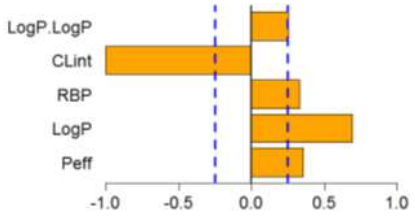

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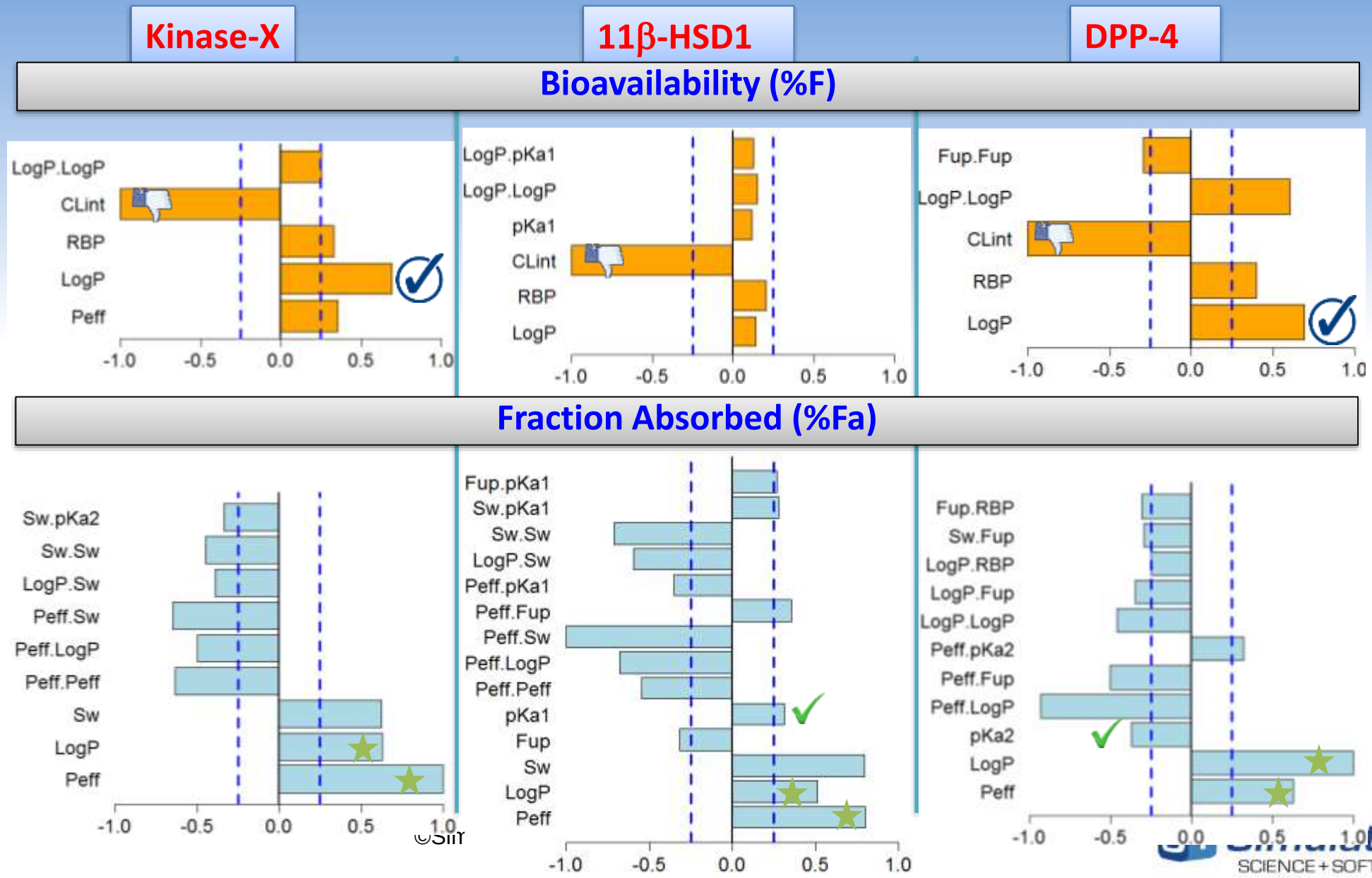
What can we Achieve with GSA-PLS Models?

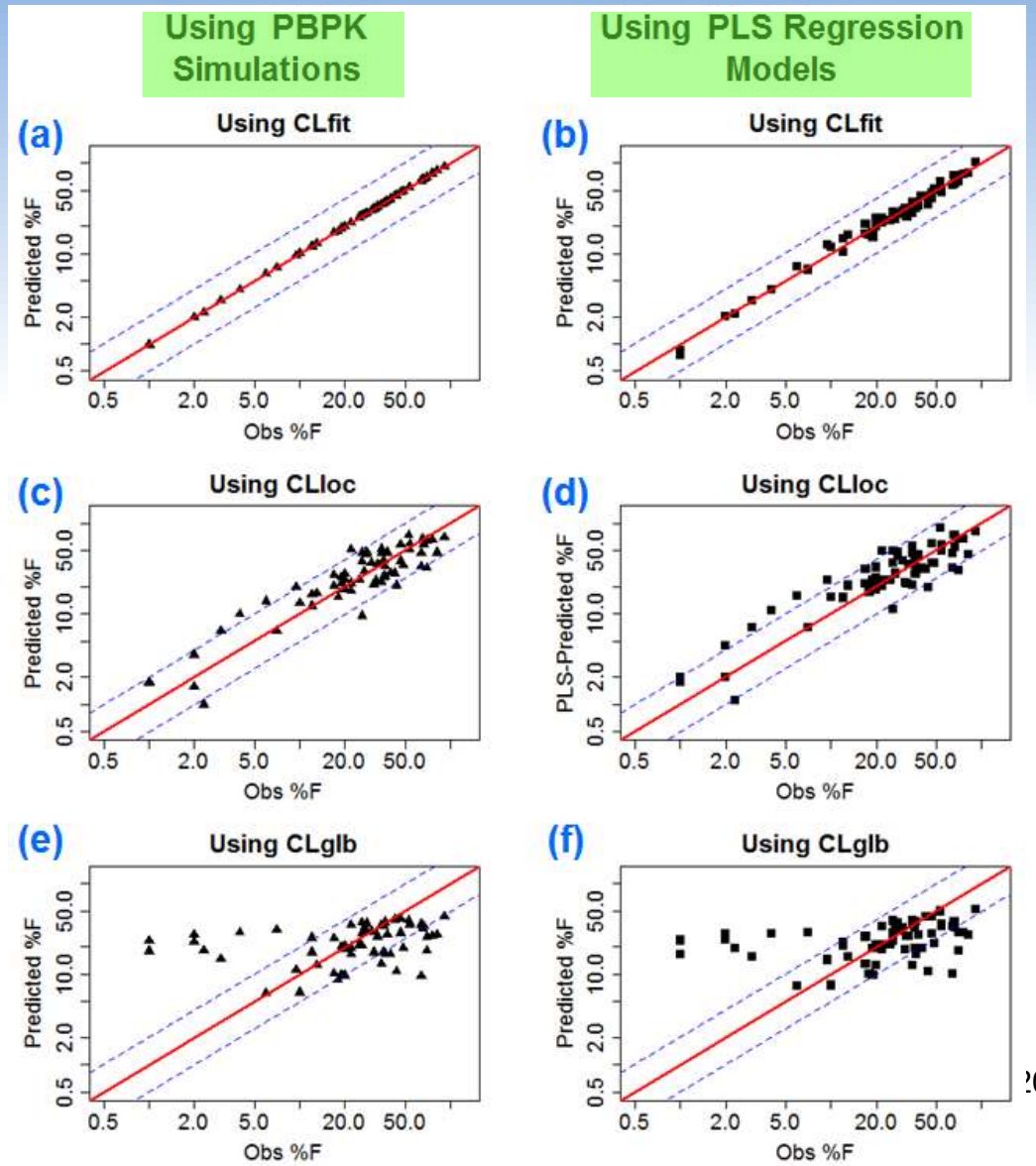
1. To find sensitive properties and their contribution
2. Faster prediction of %F of new compounds (virtual libraries of large number of cmpds)
3. Bioavailability landscape around specific compounds

Results are Unique for Each Series



High-Throughput Prediction of %F

%F predicted by PLS models is comparable to G+ prediction (Kinase-X)

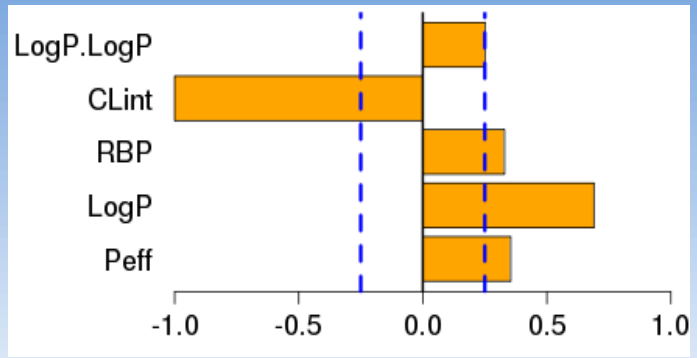


The deviation from the line of unity can be attributed to the error in the PLS model

The series-specific PLS model built using only 8 PC properties

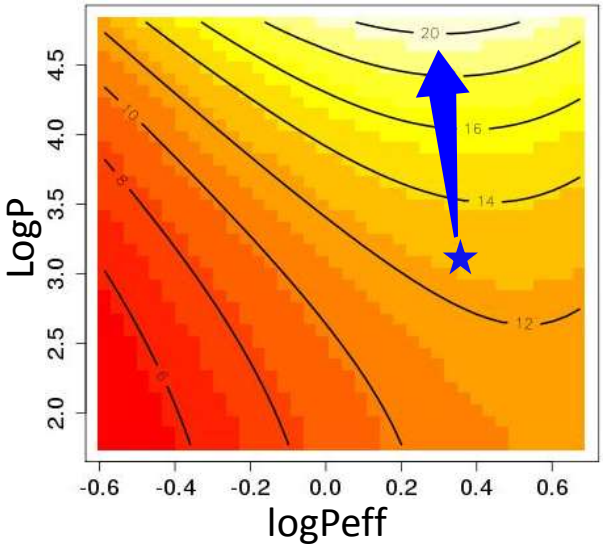
1. Sol
2. Human Peff
3. A-pKa
4. B-pKa
5. RBP
6. CL_{loc}
7. Fup
8. LogP

Specific Recommendations for Individual Compound



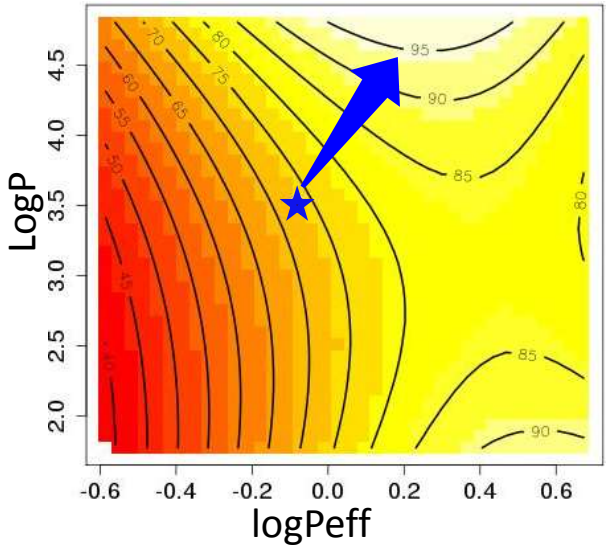
Only LogP

NVP-XXX000



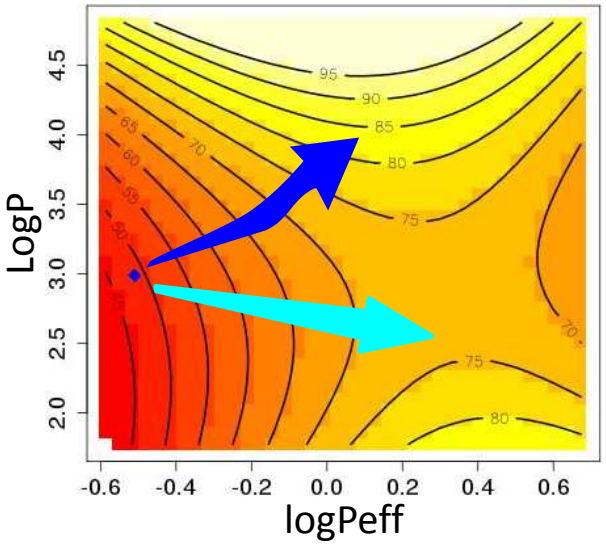
Only Peff

NVP-XXX001



LogP & Peff Both

NVP-XXX002



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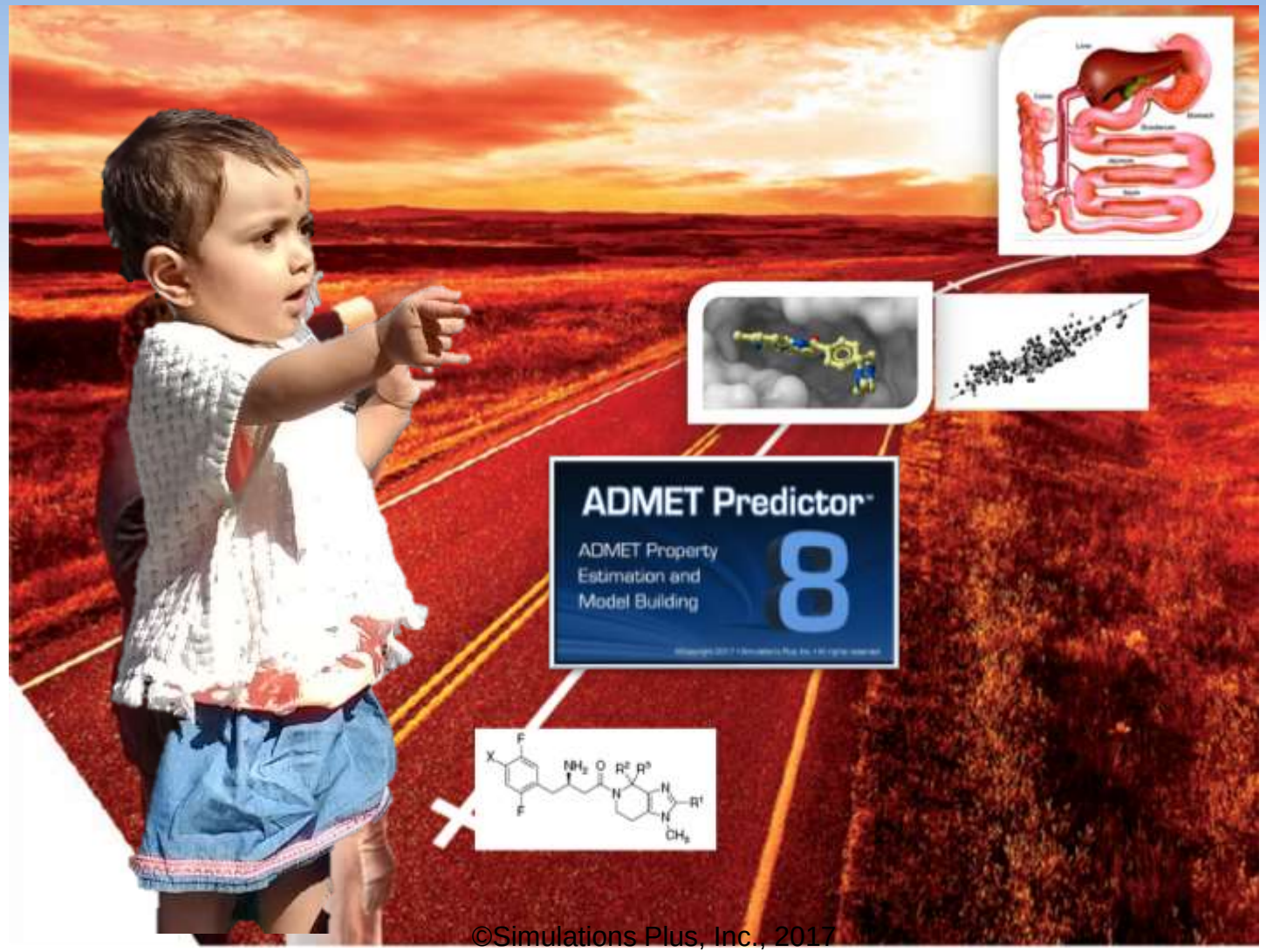
Application in Lead Optimization and Design of New Cmpds

Apply evolutionary algorithm & multi-parameter optimization (activity & prop's)



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Sampling/Library Generation & %F Prediction

Entire workflow can be run within ADMET Predictor 8.5

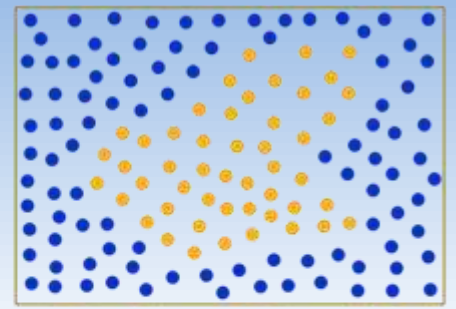
ADMET Predictor 8.5
- ❑ R Group Explosion
- ❑ R List explosion
- ❑ Combinatorial Library

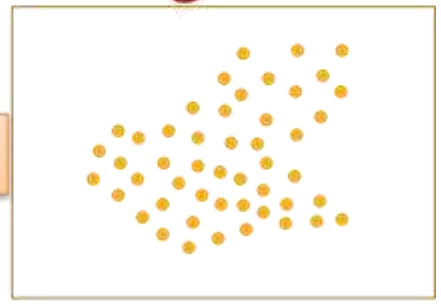
ZINC

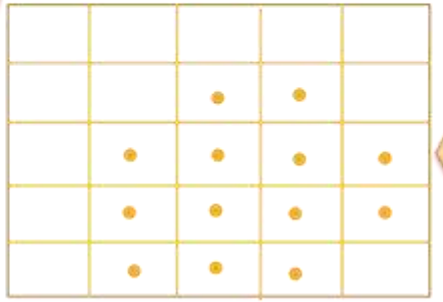
Active compounds from Med Chem Series

ADMET Predictor™

ADMET Property Estimation and Model Building







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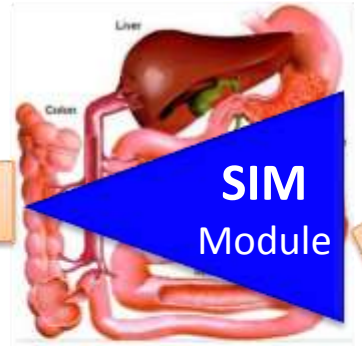

Simulation using only physicochemical properties, no structural information provided

PLS Regression

SimulationsPlus
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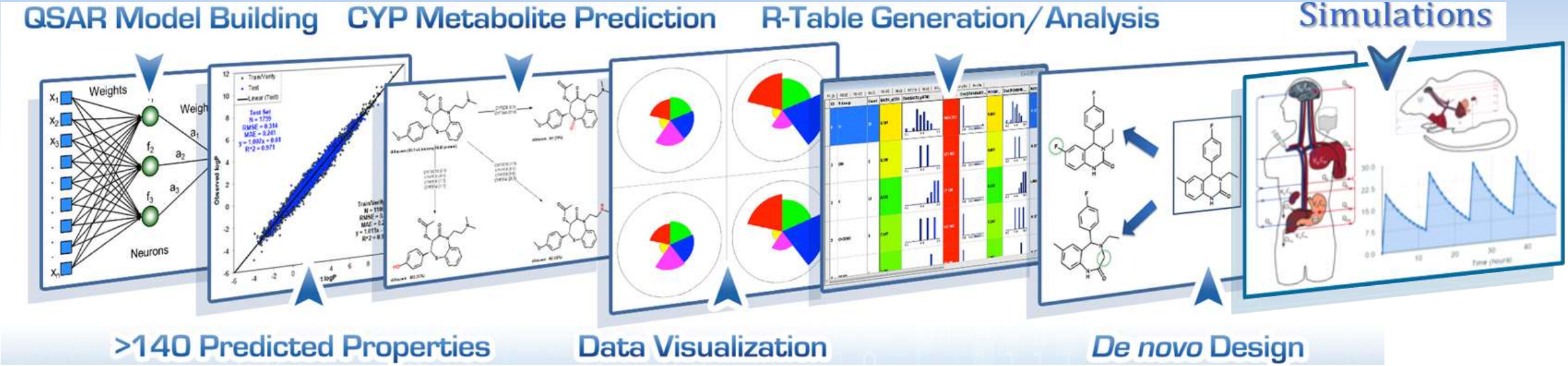
ADMET Predictor™ 8

ADMET Property Estimation and Model Building



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Conclusions

- PBPK modeling can be successfully used in lead optimization phase
- Use of Intrinsic Clearance, but not plasma clearance results in accurate estimate of %F
  - Using CL_{loc}, accurate bioavailability can be predicted for new compounds in a chemical series
- *in silico* predictions can be successfully used in absence of measured input properties (new molecules)
- GSA identifies sensitive properties (medchem series specific)
- The approach can be used in early stage of lead optimization
  - Even with 15-18 molecules with Rat PK data
- Sensitive properties can guide molecular design

Acknowledgements

NIBR

- CADD group, EMV
- MAP group, EMV
- Chemists and Biologists

SLP

- Marvin Waldman
- Robert Fraczkiewicz
- David Miller
- Ola Mikosz
- Michael Lawless
- John DiBella
- Walter S. Woltosz

Thousands of “Rats” who sacrificed their lives for betterment of human health

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