Structures, Molecular Descriptors, Model Development and Biopharmaceutical Property Estimation

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Outline

- Biopharmaceutical Properties (What's important?)
  - Human Jejunal Effective Permeability (Peff), Cell Culture Permeability (Papp)
  - pKa, log P, Native Solubility, Salt Solubility
  - BBB penetration, Plasma Protein Binding, Volume of Distribution
  - Estrogen receptor binding, carcinogenicity, mutagenicity, hERG IC_{50}
- Structures and Molecular Descriptor Generation
- Selected Biopharmaceutical Property Models
  - logP
  - Permeability
  - Solubility (and pKa and pH dependence)

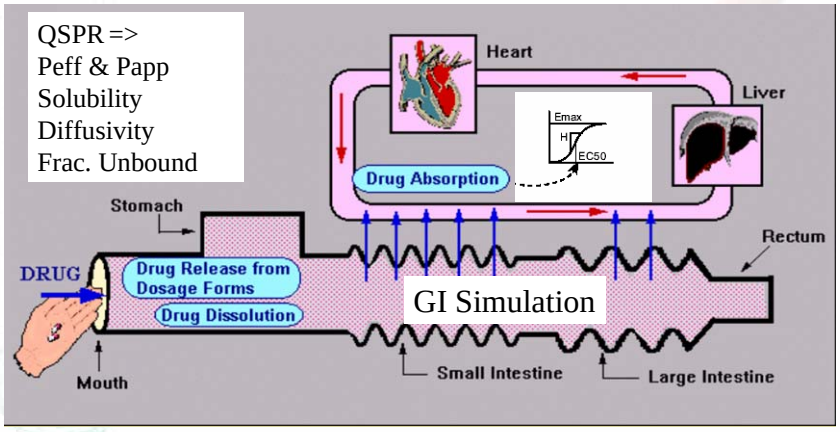
Outline

Steps in Model Building

- Descriptor Pruning
- Selection of Training, Verification, and Test datasets.
- Model Architecture
- Descriptor Sensitivity
- Model Training

- Applicability Domain / Optimum Prediction Space
- Computational Alerts
  - Rule of 5
  - ADMET Risk

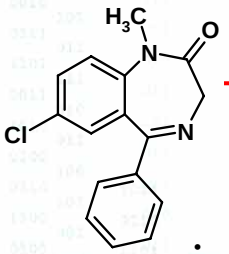
Quantitative Structure-Property Relationships and GI Simulation Models



Reproduced by permission of Gordon Amidon & Sally Choe

GOAL: Virtual ADME Screening

INPUT



→ 2D or 3D STRUCTURE → Predictor: molecular descriptors

- **1D (molecular formula is sufficient)**
  - 16 (MWt, N_Atoms, N_Halogen, M_NO, ...)
- **2D (connectivity table required)**
  - 206 (N_FrRotB, PriAmine, HBD, X0...)
- **3D (Cartesian atom coordinates required)**
  - 24 (RgGrav, PolASA, SolvE, Dipole, ...)

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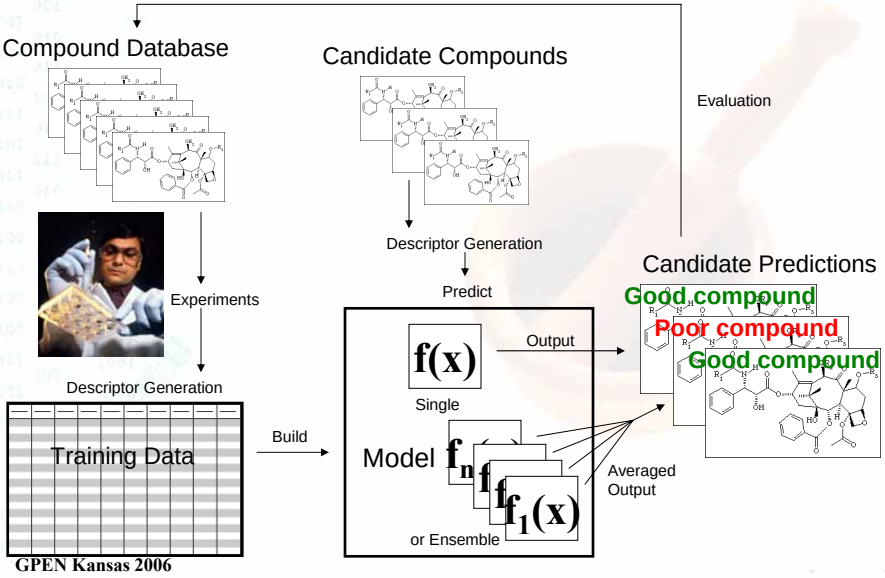
Predictive Modeling: A Continuous Cycle



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Key Biopharmaceutical Properties

- Partition Coefficient (oil / water)
- Solubility (how much can dissolve)
- Dissolution (how fast it dissolves)
  - *f*(Conc., Solub., Diffusion., Density, Particle size)
- Permeability (how fast it gets absorbed)
  - Human Peff (rate cm/s)
  - Cell Culture - [Caco-2, MDCK] Papp (cm/s)
    - Transcellular, Paracellular, Aqueous Boundary
- Fraction Absorbed to Portal Vein
  - *f* (Dissolution, Permeability, Solubility, Formulation)

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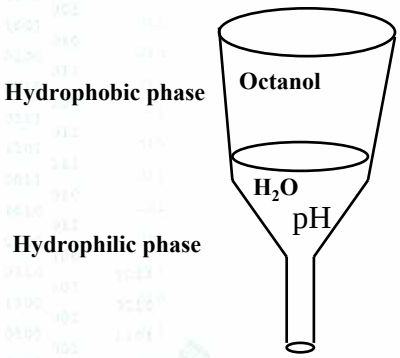
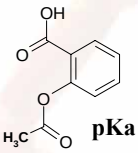
Distribution vs. Partition Coefficient



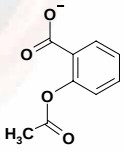
$$LogD_{oct/water} = \log \frac{C_{oct}^{aspirin}}{C_{water}^{aspirin}}$$

pH = 2
log D ~ log P = 2



pKa = 3.5

pH = 8
Log D = -1.5



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

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

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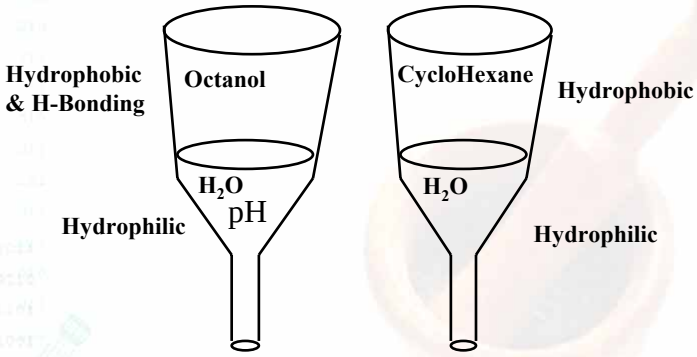
Distribution Coefficient



Log D_{oct} = log [Oct]/[H_2O] Log D_{CHex} = log [CHex]/[H_2O]

Log P is ion corrected for the unionized species

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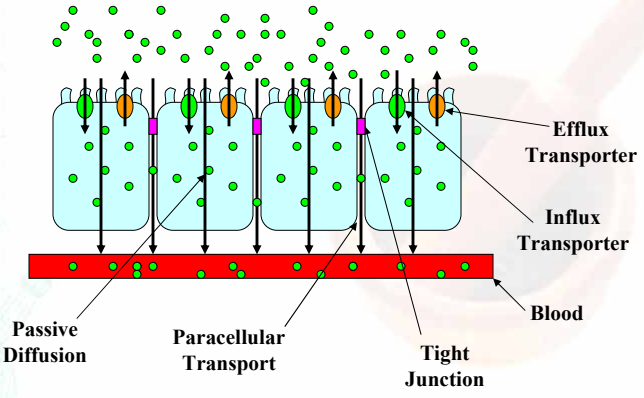
Permeability



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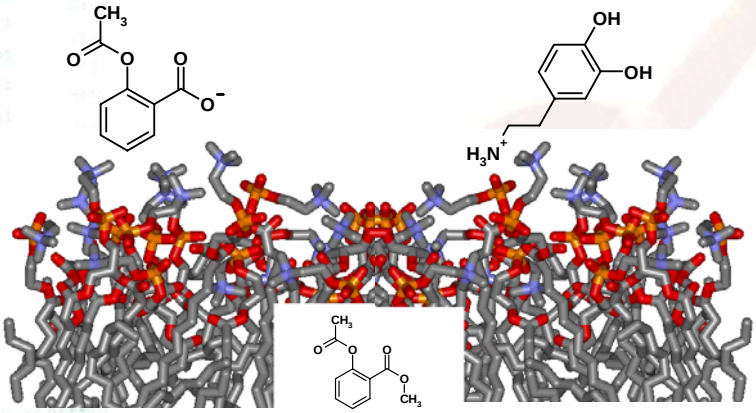
Passive Permeability

Transcellular and Paracellular



f (Hydrophobicity, H-Bonding, Ionization)

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Passive Transcellular Permeability

- Proportional to lipophilicity
  - log P
  - Non-polar solvent accessible surface area
- Inversely proportional to H-bonding
  - Count of total number of N and O
  - H-bond donors and acceptors
  - Sum of partial charges on H-bonding groups.

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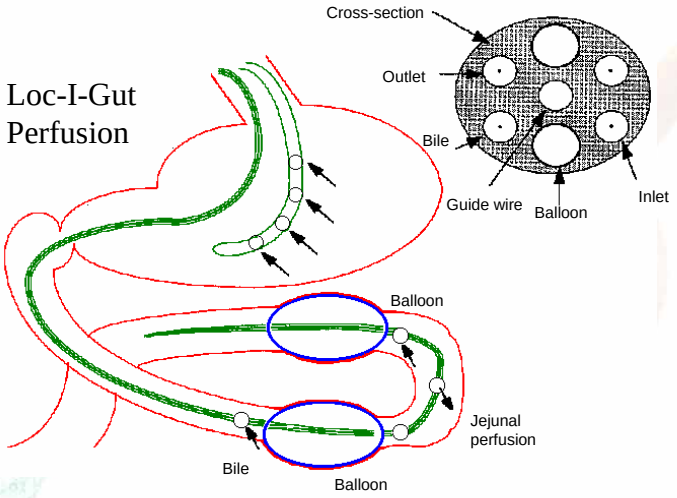
Human Effective Permeability

Loc-I-Gut Perfusion



Lennernas, H, et al. Pharm. Res. 9:1243-1251 (1992)

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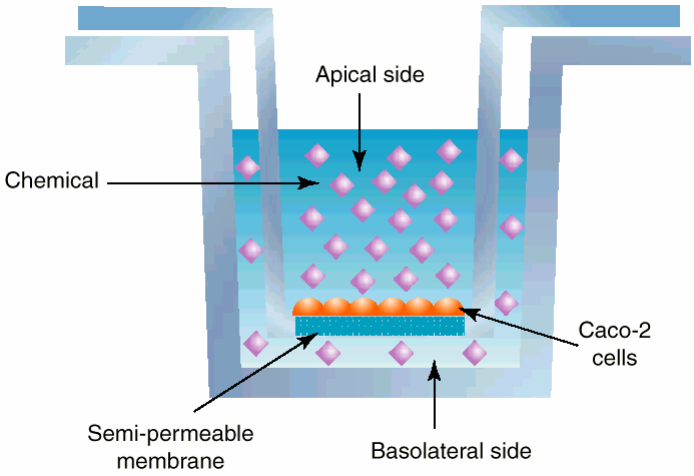
Epithelial Cell Permeability Assay



Li, A.P., DDT, 6(7):339-348

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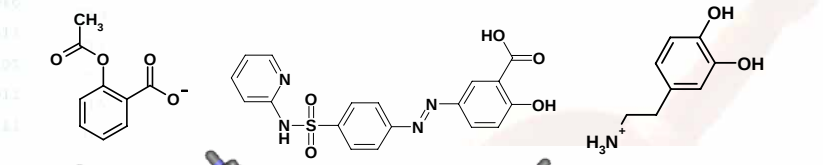
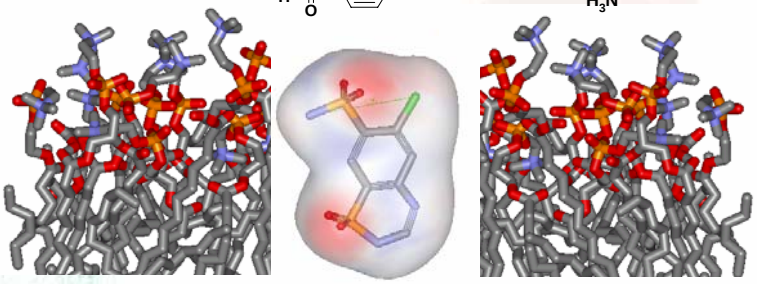
Paracellular Permeability

f (Size, Shape, Ionization)





Pore size = 2.3 - 11.6 Å (Colon < Caco-2 < MDCK < Jejunum)

Billich, (1969) J Clin Invest 48(7): 1336-47

Calculation of Paracellular Perm.

$$\frac{1}{P_e} = \frac{1}{P_{abl}} + \frac{1}{P_f} + \frac{1}{P_m}$$

Ref. A. Adson et al., J. Pharm. Sci., 83(11):1529 (1994)

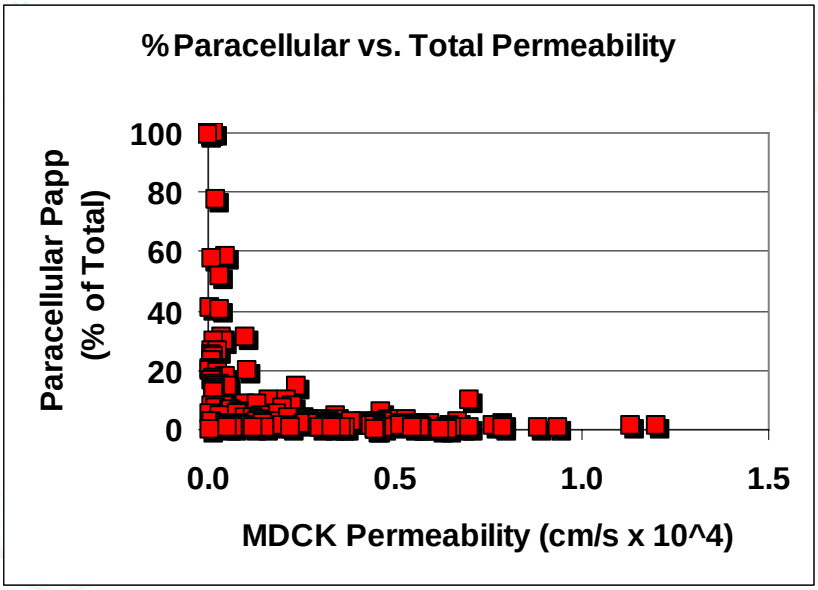
$$P_m = f_u (P^o_{trans} + P^o_{para}) + (1 - f_u) P^{\pm}_{para}$$

$$P^o_{para} = \frac{\varepsilon D f_r \left(\frac{r}{R}\right)}{\delta}$$

$$P^+_{para} = \frac{\varepsilon D f_r \left(\frac{r}{R}\right)}{\delta} \left(\frac{\kappa}{1 - e^{-\kappa}}\right)$$

$$P^-_{para} = \frac{\varepsilon D f_r \left(\frac{r}{R}\right)}{\delta} \left(\frac{\kappa}{e^{\kappa} - 1}\right)$$

P_e=Effective Perm.
P_{abl}=Aqueous Boundary
P_f= Filter
P_m = Membrane
P_{trans}= Transcellular
P_{para} = Paracellular
ε/δ =Porosity / Pore Length = 1.22
D = Diffusion Coefficient
$f_r(r/R)$ = Renkin equation
κ = Electrochem. E. (0.6)
Cation = 1.33
Anion = 0.73



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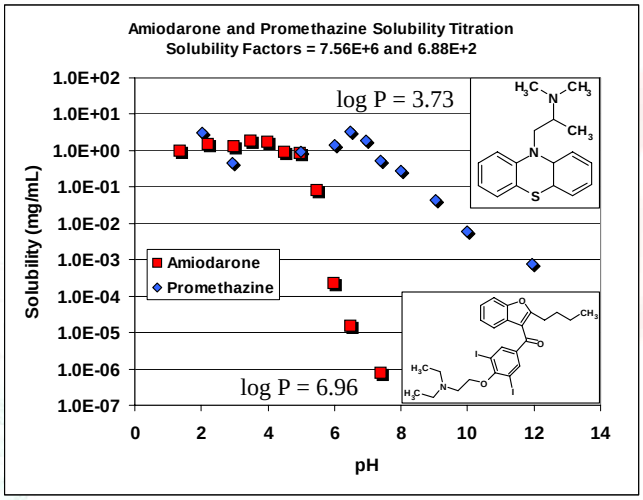
Methods for Solubility Measurement

- Native Solubility (Best for modeling)
  - Equilibrium Thermodynamic solubility in pure water. pH adjusts depending on saturated concentration and pKa of Acids or Bases.
- Solubility in Buffers (Best for salts)
  - Equilibrium Thermodynamic solubility at a known pH. Molecule could be ionized 0% - 100%.
- HTS-turbidity: (Rank order of solubility only)
  - Precipitation of molecule from solution in organic solvent by adding pH 7 buffer.

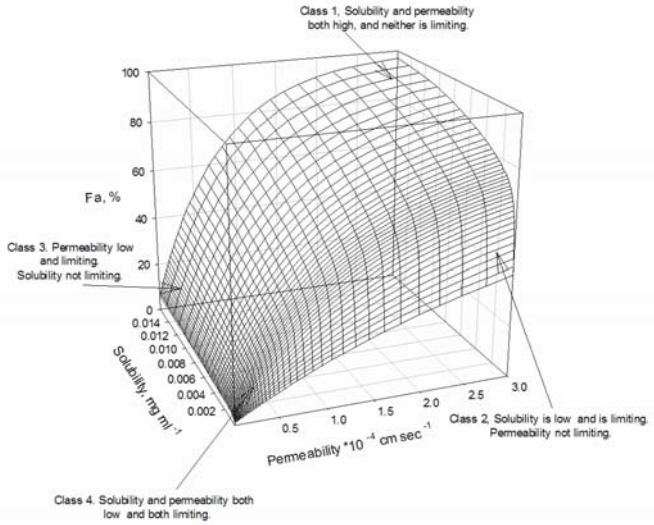
Hendriksen BA, Sanchez MF, and Bolger MB: (2003) The Composite Solubility Versus pH Profile and its Role in Intestinal Absorption Prediction. AAPS Pharm. Sci. 5(1):Article 4, 2003.

Fallacy of trying to model solubility from data collected at fixed pH (eg. 2 or 7.4)



Data: Courtesy of Christel Bergstrom and Per Artursson

Biopharmaceutical Classification (BCS)
F_a = *f*(Permeability and Solubility)



Hendriksen BA, Sanchez MF, and Bolger MB: (2003). AAPS Pharm. Sci. 5(1):Article 4, 2003

Estimating Biopharmaceutical and Pharmacokinetic Properties

Definition of molecular descriptor

The molecular descriptor is the final result of a logic and mathematical procedure which transforms chemical information encoded within a symbolic representation of a molecule into a useful number or the result of some standardized experiment.

Roberto Todeschini

ADMET Predictor™Descriptors Classified by Chemistry

- **Simple Constitutional Descriptors**
  - 27 (MWt, N_Atoms, N_Bonds, N_Rings,...)
- **Heteroatomic Functional Groups**
  - 79 (AlHdrxl, Sulfonmd, ArCbxyl, Barbitur, ...)
- **Topological Indices**
  - 3 (X0, X1, Wiener)
- **Atom-type Electrotopological State Indices[1]**
  - 68 (SsCH3, SdsN, SsOH, SddssS, SHsNH2, ...)
- **Ionization in Water**
  - 10 (N_IoAcAt, FAnion, FCation, FZwitter, ...)
- **Molecular Pattern Flags**
  - 5 (AlphaAA, AlphaAE, Steroid, ...)
- **Electronic Properties**
  - 8 (ABSQ, MaxQ, Dipole, PolarizG, ...)

1. Kier, L.B.; Hall, L.H.; "Molecular Structure Description"; Academic Press; 1999.

ADMET Predictor™ Descriptors Classified by Chemistry

- **Hydrogen Bonding**
  - 14 (HBA, HBD, HBAch, IHB, ...)
- **Molecular Size and Shape (3D)**
  - 14 (RgGrav, DStokes, TotASA, MIRxx, ...)
- **Solvation Effects (3D)**
  - 8 (PolASA, SolvE, SolvEMt, HBAwsa, ...)
- **Protein Recognition[1]**
  - 5 (PEoED, PEoEDIa, PEoEDIb, ...)
- **Moriguchi Descriptors for MlogP[2]**
  - 13 (M_CX, M_NO, M_PRX, M_UB, ...)
- **Meylan Flags for MH Sw Models[3]**
  - 15 (H_AlAlco, H_AlPyri, H_Falkan, ...)

1. Seelig, A., R. Gottschlich, and R.M. Devant; *Proc. Natl. Acad. Sci. USA*, 1994. **91**: p. 68-72.
2. Moriguchi, I., *et al.*, *Chem. Pharm. Bull.*, 1992. **40**: p. 127-130.
3. Meylan, W.M., P.H. Howard, and R.S. Boethling; *Env. Tox. Chem.*, 1996. **15**: p. 100-106.

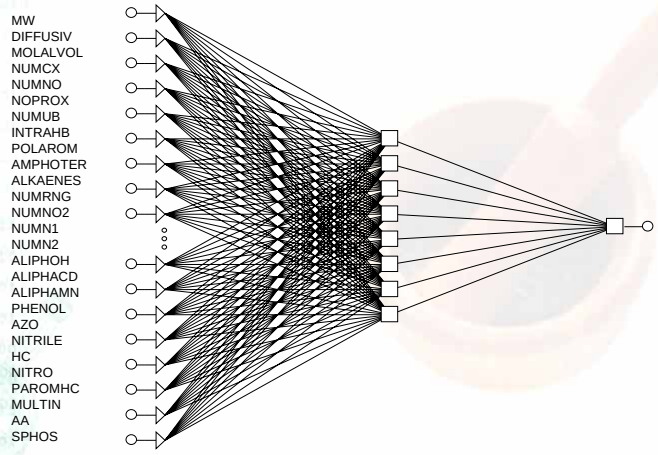
Descriptor Generation & Academic Prices

- Dragon (http://www.talete.mi.it/dragon_net.htm)
  - ~$450
- MolConn-Z (http://www.edusoft-lc.com/molconn/)
  - ~$550
- MOE (CCG) (http://www.chemcomp.com/)
- ADMET Predictor / Modeler (http://www.simulations-plus.com)
  - $3500
- PreADMET (http://preadmet.bmdrc.org/preadmet/index.php)
  - Free, one molecule at a time.
- Virtual Computational Chemistry Laboratory (http://www.vcclab.org/)
  - Free, plus it includes web-based model building software.

Methods for Modeling

- Multiple Linear Regression (MLR - Classical QSAR)
  - Simple, fast calculation
  - Results have quantitative meaning to chemists
  - Lack of interactions between independent variables
- Genetic Algorithm – Partial Least Squares (GA-PLS)
  - Good for small datasets when many descriptors are needed
  - Not as robust as ANNE or SVM
- Artificial Neural Network Ensembles (ANNE)
  - Highly accurate within the chemical space of training set
- Support Vector Machines (SVM)
  - Excellent for classification problems
  - Sometimes outperform ANNEs

Artificial Neural Networks (ANN)



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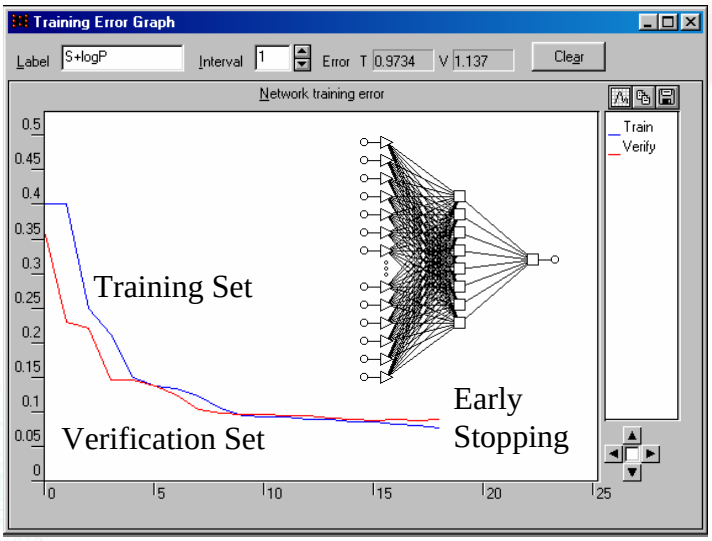
How to avoid over-training.



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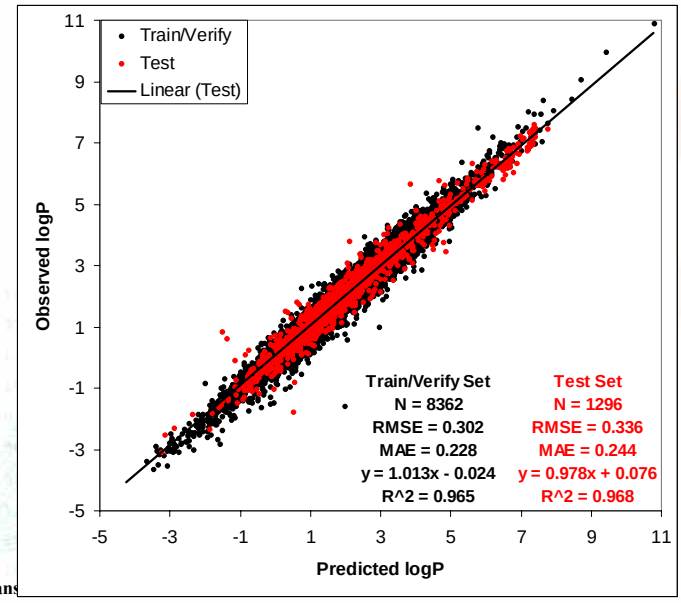
Partition Coefficient Estimation

3D S+log P Model (N=9658)



Independent Comparison of log P models

A COMPARISON OF COMMERCIALLY AVAILABLE SOFTWARE FOR THE PREDICTION OF PARTITION COEFFICIENT

J.C. Dearden, T.I. Netzeva and R. Bibby

School of Pharmacy and Chemistry, Liverpool John Moores University, Byrom Street, Liverpool L3 3AF, UK
E-mail: j.c.dearden@livjm.ac.uk

JMU
Liverpool John Moores University

Table 1. Predictive abilities of software packages for calculation of log P

Package	% of compounds with log P (calc.) within error ranges			Correlation of measured and calculated log P	
	≤ 0.5	> 0.5, ≤ 1.0	> 1.0	r^2	s
QMPRPlus	94.2	5.1	0.7	0.965	0.272
ACD	93.5	5.8	0.7	0.965	0.271
IA	93.5	5.1	1.4	0.958	0.297
ProPred	89.9	9.4	0.7	0.945	0.342
KOWWIN	89.1	7.3	3.6	0.947	0.335
SPARC	88.5	9.0	2.5	0.941	0.330
ClogP	88.4	10.9	0.7	0.961	0.287
AP-Algorithms	87.0	10.1	2.9	0.937	0.364
KlogP	81.9	15.9	2.2	0.929	0.388
ProLogP	81.2	15.2	3.6	0.912	0.431
SLIPPER	81.1	10.9	8.0	0.847	0.568
Cerius²	67.4	18.1	14.5	0.869	0.529
ABSOLV	67.4	17.4	15.2	0.797	0.654
QikProp	50.0	34.1	15.9	0.871	0.521

Note: in Table 1, r = correlation coefficient; s = standard error

Permeability Estimation

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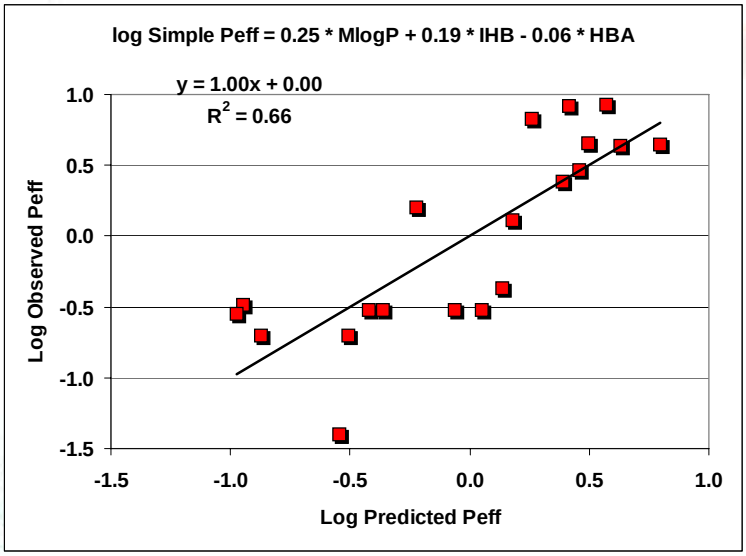
Example of Simple MLR model for Human Peff



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Pause to build Peff Model using Excel

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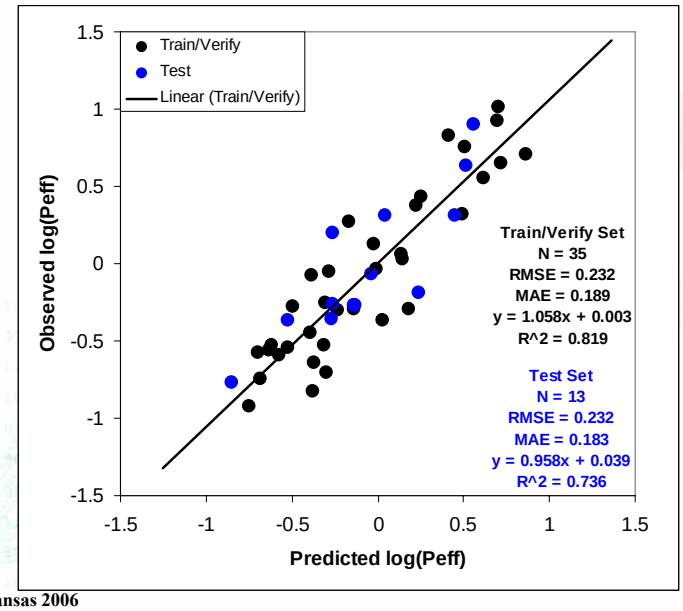
2D Model of Human Jejunal Permeability



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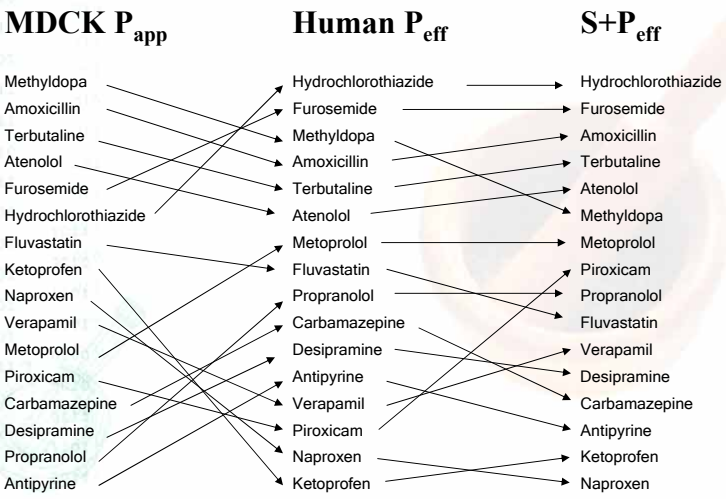
How well do S+Peff *in silico* results compare with in vitro measurements of permeability?



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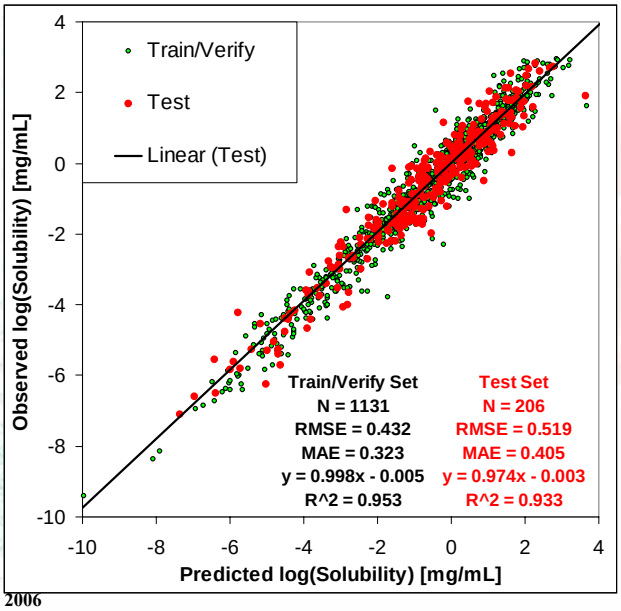
3D Native Solubility Model without Melting Point



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Deardon J., Expert Opinion Drug Discov. -1(1):31 (2006)

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		r^2	q^2	s	Ref.
	± 0.5 log unit	± 1.0 log unit				
SimulationsPlus	64.8	91.0	0.82	0.82	0.47	[203]
Admensa	72.1	86.9	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.

In Proof

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pKa and pH Dependence of Solubility Predicting Salt Solubility

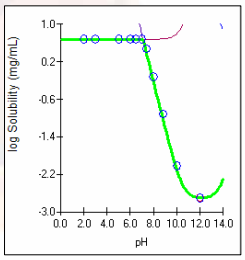
Composite Solubility vs. pH Profile

- Base Solubility

$$S_{WB} = S_{OB}\left(1+10^{\,pKa-pH}\right)$$

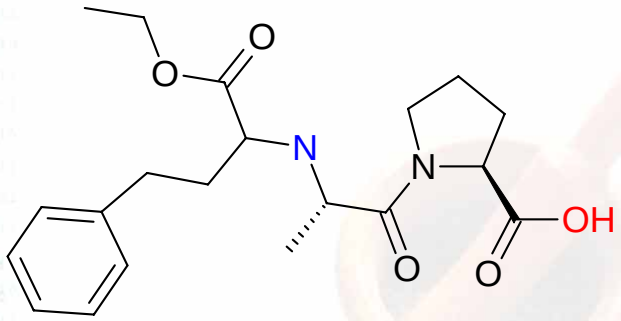
- pH of intersection between ionized and unionized when titrating from low to high pH

$$pH = pKa - \log\left[S_{ConjA} / S_{OB}\right]$$



Hendriksen BA, Sanchez MF, and Bolger MB: (2003). AAPS Pharm. Sci. 5(1):Article 4, 2003.

Atomic Descriptors



- **54 Special descriptors localized on a specified atom**
  - Partial charge, E-state, Access, ...
- **Excellent for predicting localized properties (pK_a, specific binding, etc.)**

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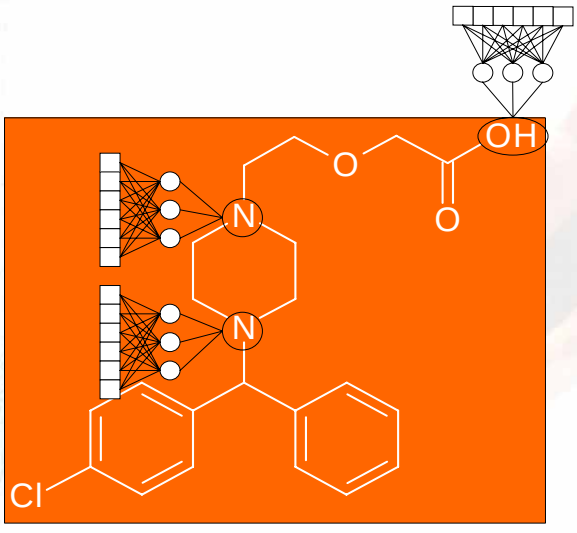
Prediction of multiprotic pK_a with artificial neural networks



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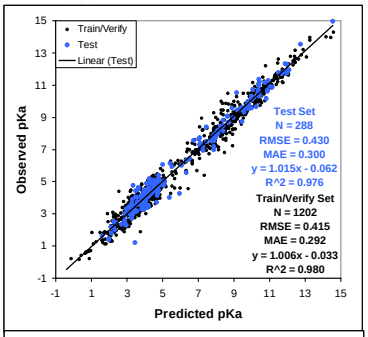
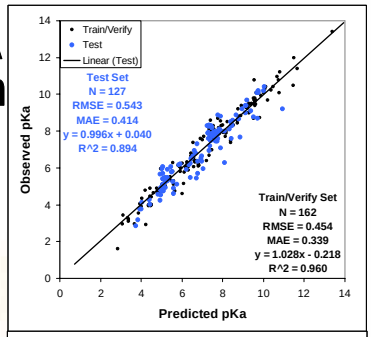
QMPRPlus ANN Models of Single pK_a

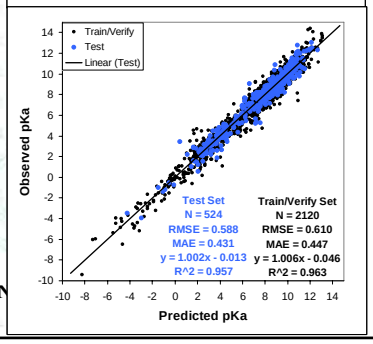
Hydroxyacids



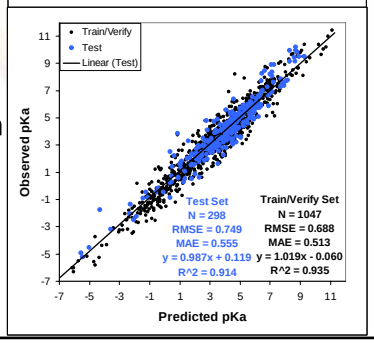
Amides



Amines



Aromatic N



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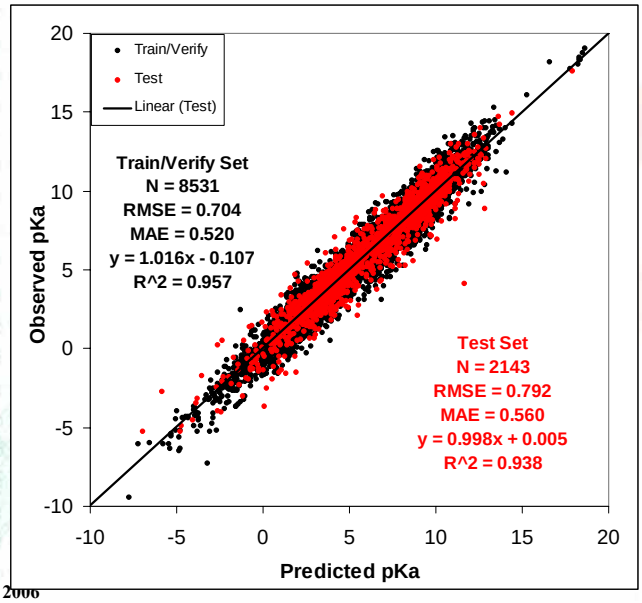
2D Model of pKa (N=10674 multiprotic pKa)



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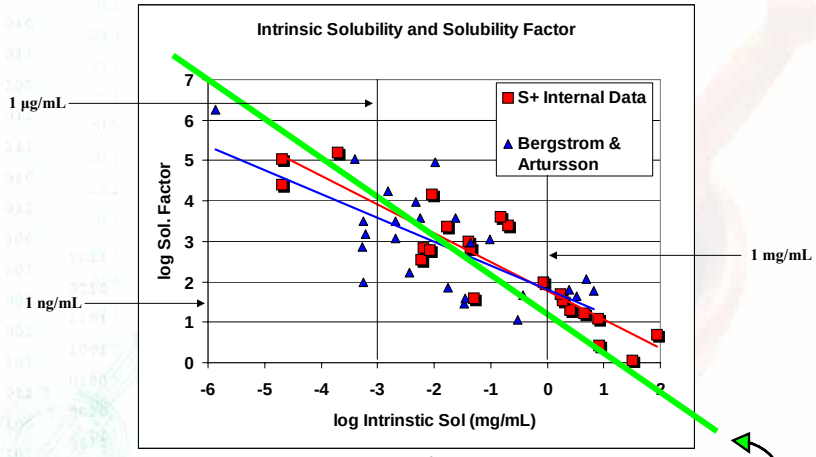
Solubility Factor



Data: Courtesy of Christel Bergstrom and Per Artursson

SF ~ 20/Intrinsic Solubility in mg/mL

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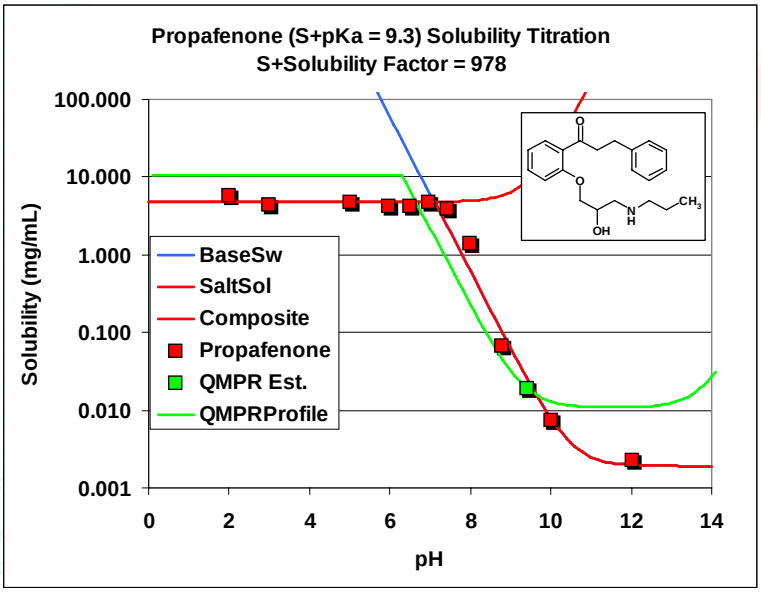
Data: Courtesy of Christel Bergstrom and Per Artursson



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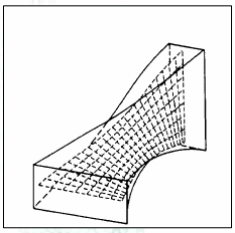
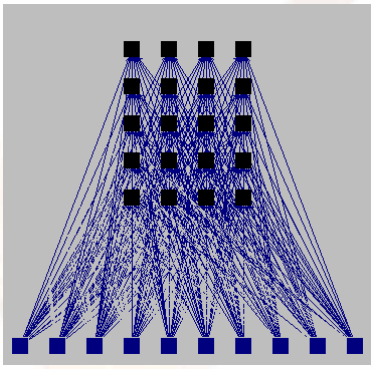
Steps in Model Building

- **Analyze data set**
  - Identical or Low Variance Descriptors
  - Under Representation
  - High Correlation Overlap
  - Cluster data in descriptor space by Kohonen self-organizing map
  - Divide into training pool and test set
- **Sensitivity analysis to identify *most* influential descriptors for a particular network architecture**
  - Changing number of nodes will change most sensitive descriptors
- **Partition of training pool into different training and verification sets for every network in an ensemble**
  - Efficient partitioning algorithm (Tetko & Villa)
- **Train matrix of artificial neural network ensembles**
- **Select best architecture as final model**

Kohonen Self-Organizing Feature Map For Selection of Training, Verification, and Test

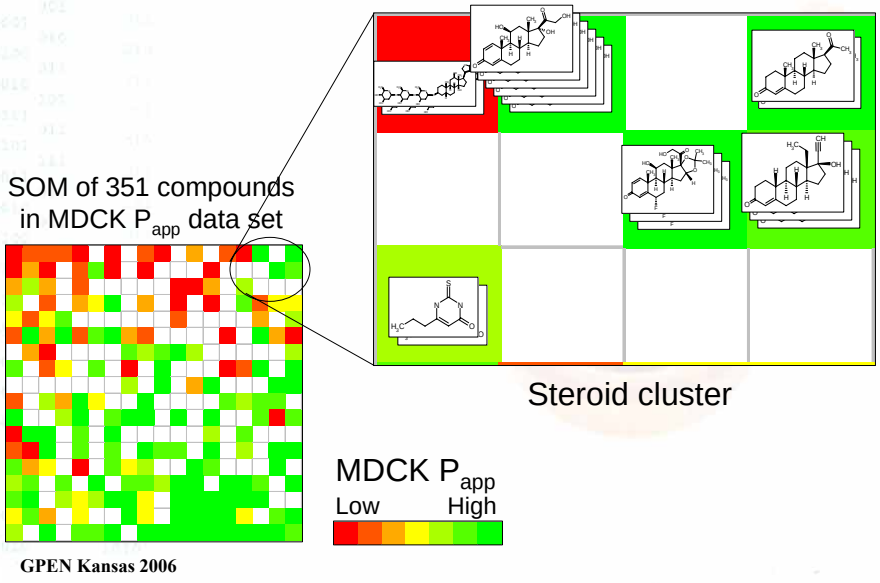
The Kohonen self-organizing feature map (SOFM) maps multidimensional data onto a 2-dimensional plane





From Kohonen, T. (1984). *Self-organization and associative memory*. Springer Verlag.

Kohonen SOM clusters like compounds



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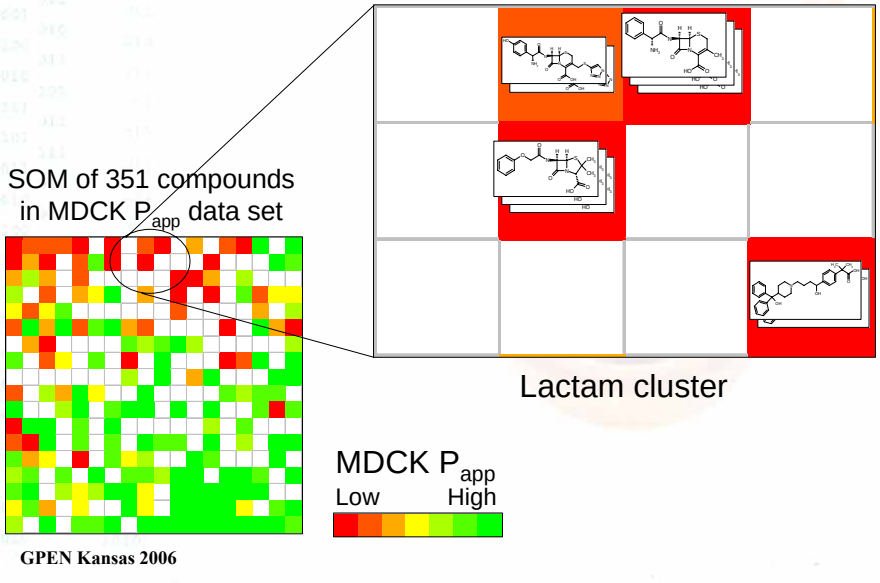
Kohonen SOM clusters like compounds



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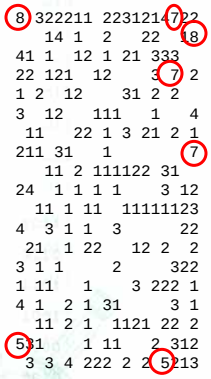
Kohonen SOM clusters like compounds



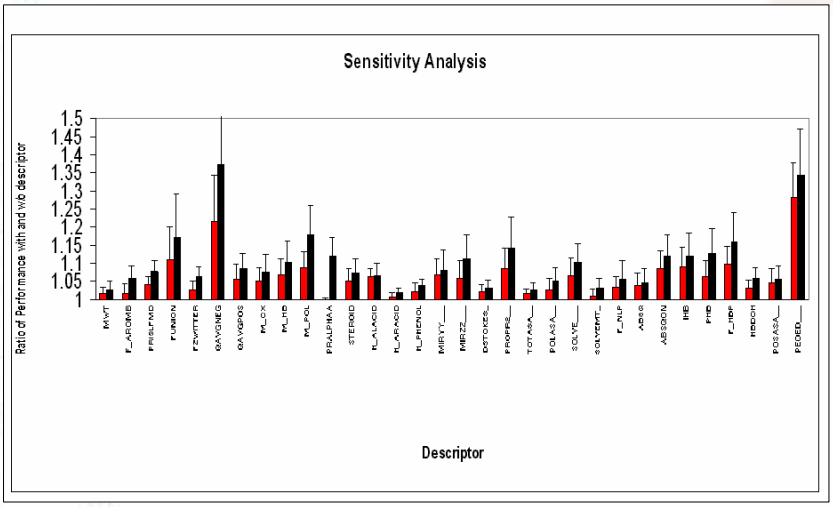
19x19 Kohonen map for log MDCK Papp data selects 74 compounds for test set, 187 for training pool
CPU Time = 3 minutes

Number of neurons containing compounds = 185
Number of training cases for genetic algorithm step = 185
Number of verify cases for genetic algorithm step = 102
Number of test cases sequestered = 74

Selecting Descriptors: Sensitivity Analysis

- Some descriptors have more influence on the predicted property than others.
- Train the model with a given architecture
  - ANN: Sequentially remove each descriptor and calculate the increase in error for predictions.
- Rank descriptors in order of sensitivity

MDCK P_{app} Sensitivity Analysis



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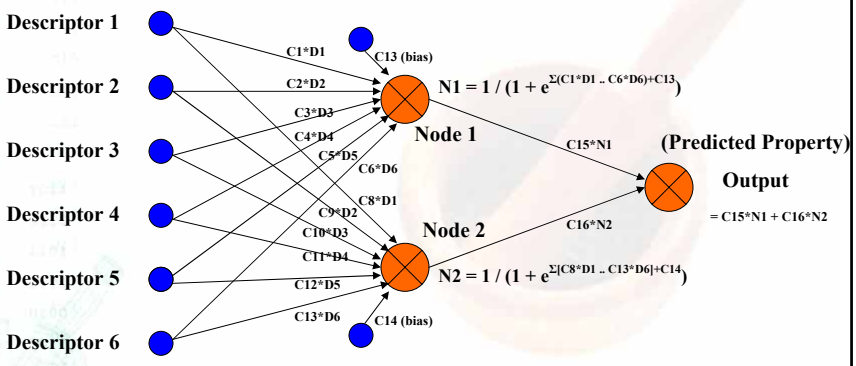
Training an Artificial Neural Network



Training = Adjust C1-C16 until Σ(Predicted-Observed)^2 is minimized

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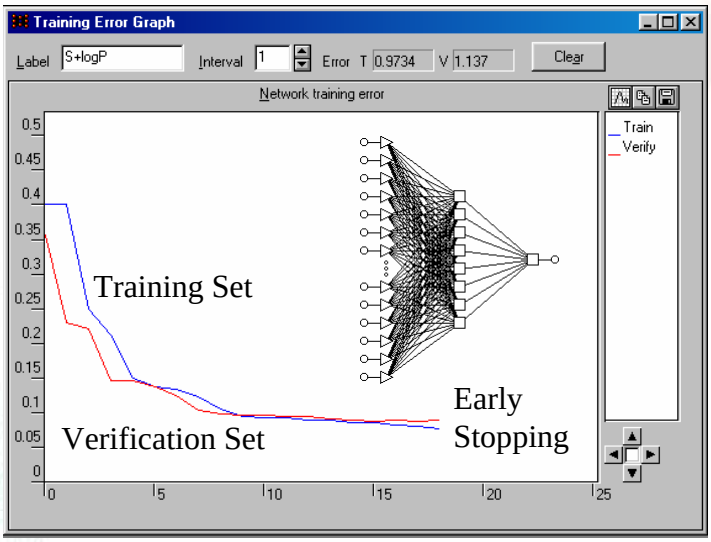
How to avoid over-training.



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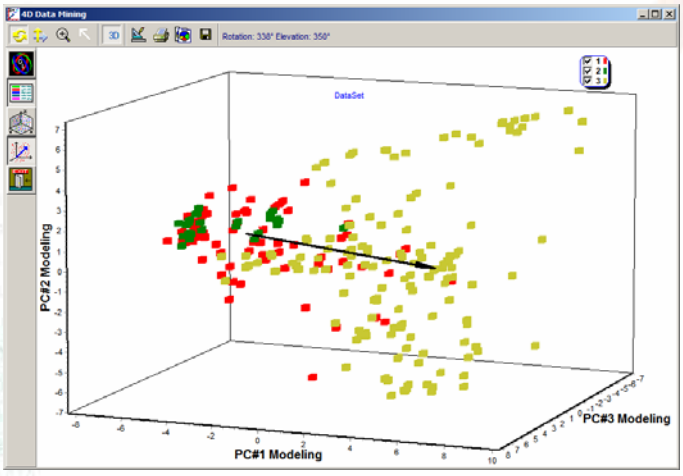
Applicability Domain / Optimum Prediction Space

Shen M., et al., J. Med. Chem. 45:2811 (2002)
Gombar V.K., et al., J. Chem. Inf. Comput. Sci. 36:1127 (1996)



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Computational Alerts

Lipinski's Rule of Five (RO5)

Poor absorption is more likely when:

Hb: HBD > 5

Mw: MWt > 500

LP: MlogP > 4.15

NO: M_NO > 10

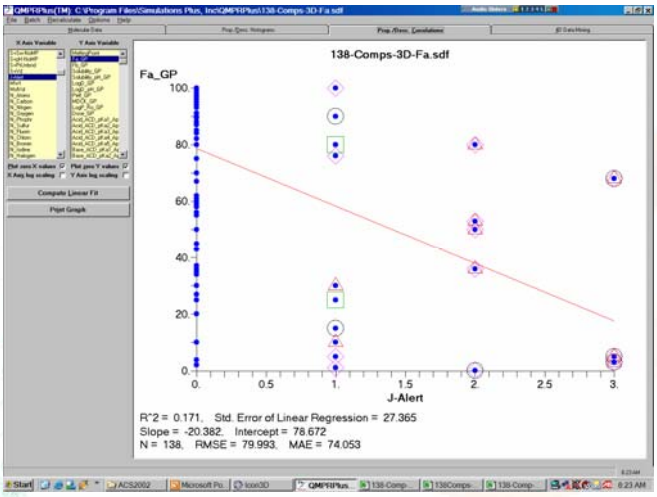
where:

HBD = number of hydrogen bond donors

MWt = molecular weight (in Daltons)

MlogP = log P calculated by Moriguchi's method (Moriguchi; 1992)

M_NO = sum of nitrogen and oxygen atoms



Rule of Five correlates poorly (at R^2=0.171) with experimentally determined fraction absorbed.

Data obtained from Zhao, Y. H.; Le, J.; et al.; *J. Pharm. Sci.* 2001; **90**(6):749-784.

Default ADMET Risk™

Poor absorption is more likely when:

LP:	MlogP < -0.59
Pr:	S+Peff < 0.864
Ha:	HBAoch < -2.406
PC(+2):	MolQ > 0

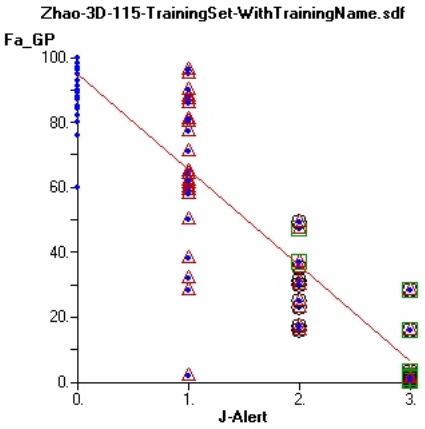
where:

MlogP = log P calculated by Moriguchi's method (Moriguchi; 1992)

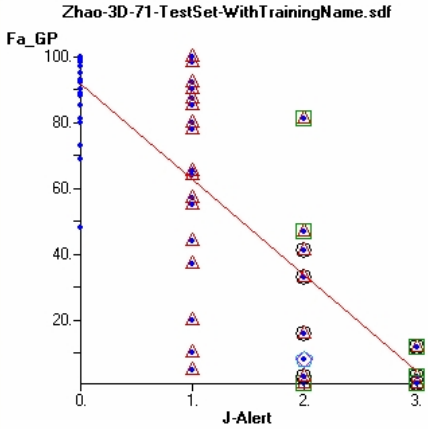
S+Peff = human jejunal permeability (Simulations Plus model; µm/s)

HBAoch = partial atomic charge on H-bond accepting oxygens

MolQ = number of functional groups bearing permanent charge, e.g., quaternary amine, sulfonium, diazo, etc.



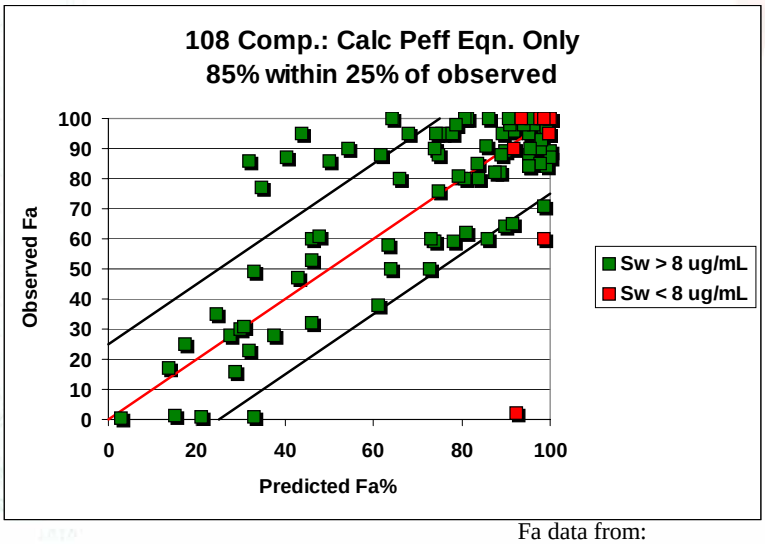
Performance of ADMET Risk in the training set
N = 115, R^2 = 0.799



Performance of ADMET Risk in the external test set
N = 71, R^2 = 0.623

GPEN Kansas 2006 Data obtained from Zhao, Y. H.; Le, J.; et al.; *J. Pharm. Sci.* 2001; **90**(6):749-784.

$$Fa = 1 - e^{-1.47*CalcPeff}$$



Fa data from:
Zhao et al., J. Pharm. Sci. 90:(6), 749 (2001)

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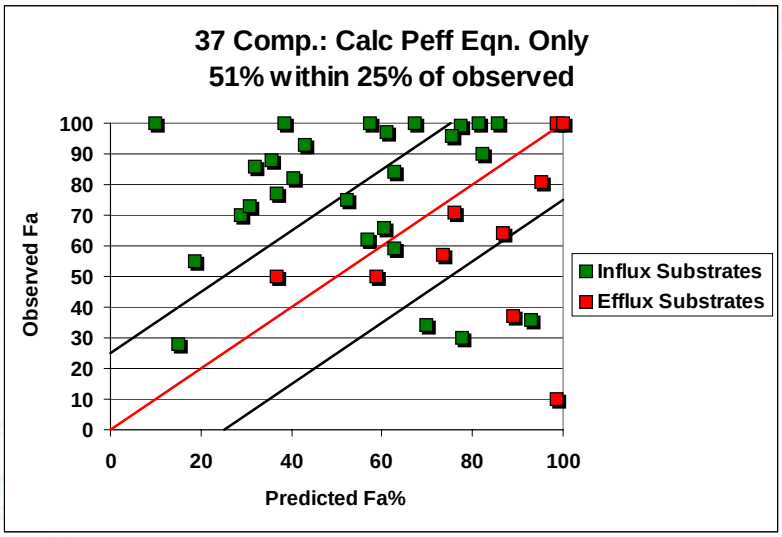
$$Fa = 1 - e^{-1.47 * CalcPeff}$$



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Transported Compounds

Effluxed Pgp
amiloride -tr –ef
etoposide -tr –ef
nadolol -tr –ef
norfloxacin -tr -ef
progesterone -tr -ef
quinidine -tr -ef
ranitidine -tr -ef
trovofloxicin -tr -ef
verapamil -tr –ef
lovastatin –tr -ef

Influxed PepT1
amoxicillin -tr -if
ampicillin -tr -if
benzylpenicillin -tr -if
captopril -tr -if
carfecillin -tr -if
cefadroxil -tr -if
cefatrizine -tr -if
cephalexin -tr –if
enalapril -tr -if
fosinopril -tr –if
lisinopril -tr –if
phenoxymethylpenicillin -tr -if

Influxed Amino Acid
α-difluoromethylornithine -tr –if
glycine -tr -if
levodopa -tr -if
cycloserine -tr –if

Influxed Other Transporters
bumetanide -tr -if
loracarbef -tr -if
mercaptoethanesulfonic acid -tr -if
methotrexate -tr -if
nicotinic acid -tr -if
nizatidine -tr -if
pravastatin -tr -if
sorivudine -tr -if
theophylline -tr -if
trimethoprim -tr -if
zidovudine -tr -if

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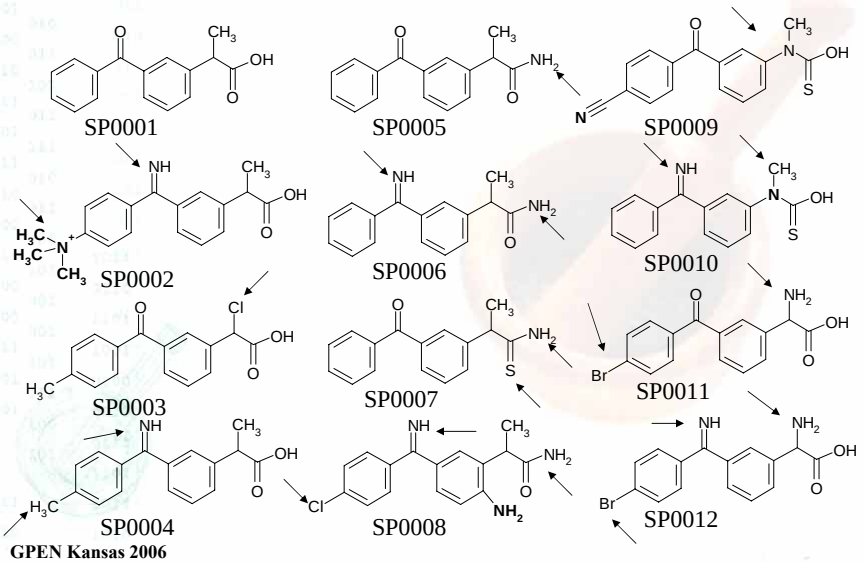
Other Pharmacokinetic and Toxicology Models

Modeling Software for Early Discovery: Structure-Property Modeling

- Which compounds in a library are obviously high risk?
  - Very low solubility
  - Very low permeability
  - Ionization effects
  - Saturable absorption at higher doses in human and laboratory animals
  - Very high volume of distribution
  - Very high protein binding
  - High/low blood-brain barrier penetration
  - Various types of toxicity
  - Combinations of the above

Which Ketoprofen Analogs Can Be Eliminated?



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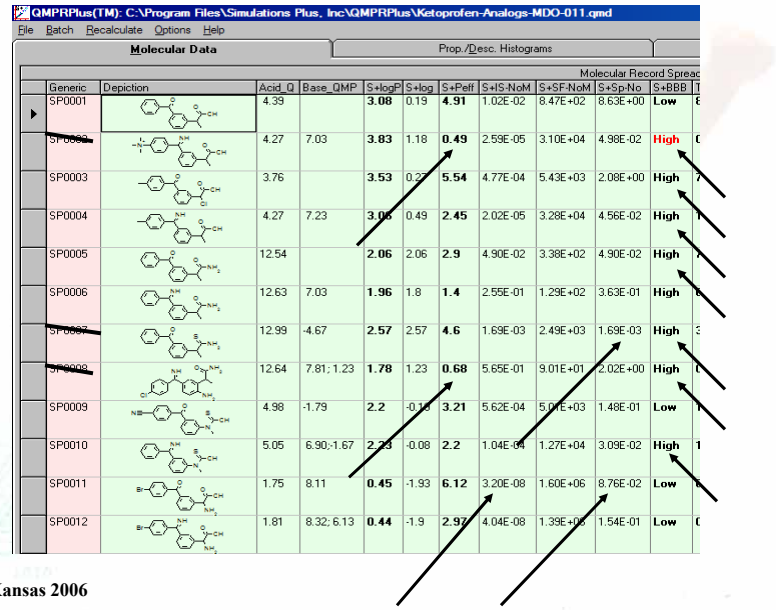
Which Ones Can Be Eliminated?



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Which Ones Can Be Eliminated?

MRTD < 2, Tox_ER > 0.002, Tox_FHM < 5, Tox_BRM < 50

Molecular Record Spreadsheet

Generic	Depiction	TOX_MRTD	TOX_ER	TOX_FHM	TOX_BRM_Rat	TOX_BRM_Sal	S+PrUnbnd	S+Vd	SimHIA_10	SimHIA_1000
SP0001		8.06	0.0001	13.83	166.53	Negative	1.77	0.23	97.4	95.09
SP0002		0.58	0.1171	1.49	1.93	Negative	15.43	0.55	85.22	16.06
SP0003		7.34	0.0001	3.87	131.83	Negative	1.51	0.23	97.36	96.1
SP0004		1.76	0.018	3.2	50.41	Negative	3.08	0.35	95.41	37.43
SP0005		7.64	0.0001	6.98	9.09	Negative	17.83	1.2	97.88	80.72
SP0006		0.95	0.0089	3.49	12.39	Negative	15.47	2.08	96.24	93.86
SP0007		3.99	0.0026	0.76	22.66	Negative	15.1	1.36	95.26	12.21
SP0008		0.79	0.0452	2.05	7.88	Undecided	25.53	3.11	87.32	86.59
SP0009		1.59	0.0004	9.47	205.91	Negative	1.68	0.35	93.45	51.87
SP0010		1.89	0.0072	2.27	183.69	Negative	4.06	0.88	91.04	16.69
SP0011		6.37	0.0006	9.19	2.13	Positive	8.2	0.48	88.86	43.42
SP0012		0.96	0.0493	4.17	2.54	Positive	8.01	0.94	81.04	52.73

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Customized ADMET Risk for Rank Ordering

QMPRPlus(TM): C:\Program Files\Simulations Plus, Inc\QMPRPlus\Ketoprofen-Analo

File Batch Recalculate Options Help

Molecular Data Prop./Desc. Hi

Generic	Depiction	J-Alert	J-Code
SP0001		0	
SP0009		1	T1_
SP0003		2	Bb_T3_
SP0011		2	T4_T5_
SP0005		2	Bb_T4_
SP0010		4	Bb_T1_T2_T3_
SP0004		4	Bb_T1_T2_T3_
SP0006		5	Bb_T1_T2_T3_T4_
SP0012		5	T1_T2_T3_T4_T5_
SP0007		5	Sw_Bb_T2_T3_T4_
SP0008		6	Pr_Bb_T1_T2_T3_T4_
SP0002		8	Pr_C1_C2_Bb_T1_T2_T3_T4_

LP	MlogP < -0.590
Pr	S+Peff < 0.864
Ha	HBAoch < -2.406
C1	QuaAmine_>[N+]<
Sw	S+Sp-NoMP < 8e-3
Bb	S+BBB = High
T1	TOX_MRTD < 2
T2	TOX_ER > 0.002
T3	TOX_FHM < 5
T4	TOX_BRM_Rat < 50
T5	TOX_BRM_Sal = Positive
Pb	S+PrUnbnd < 1
Vd	S+Vd > 15

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Viera Lukacova, Ph.D. (GastroPlus PBPK)

John DiBella, M.S. (DDDPlus)

Anand Prabhakaran, M.S. (DDDPlus)

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