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Computational Tools in Prediction of Drug Absorption and Distribution

Christel Bergström, PhD
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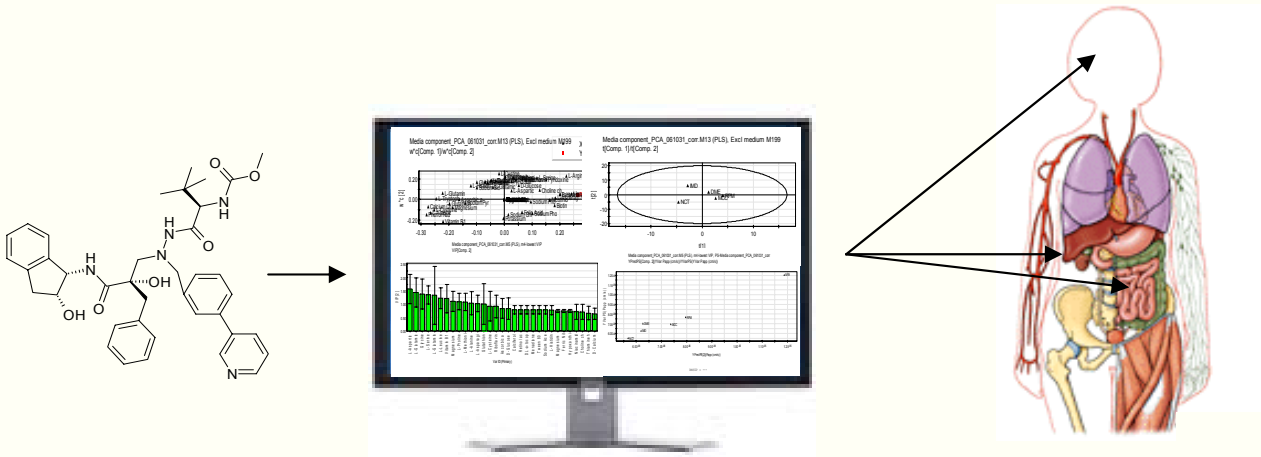

PhysChem Forum 3, June 13

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Outline

- Background; ADMET(absorption, distribution, metabolism, elimination/excretion, toxicity) modeling
- Computational tools used
  - Descriptor generation
  - Statistical methods
- Quality of experimental data
- Case studies:
  - Aqueous solubility
  - Membrane permeability
  - Active transport mechanisms
  - Absorption
- Conclusion

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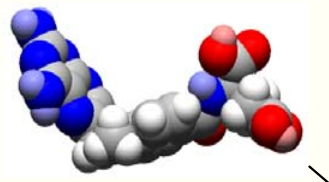
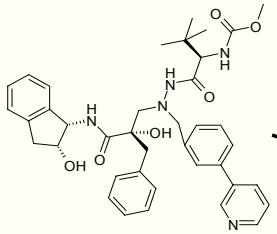
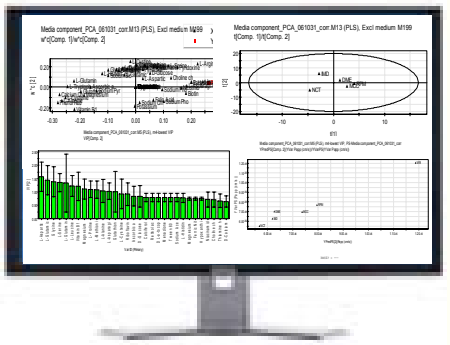
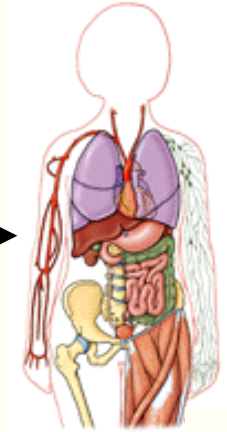
ADMET modeling









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Typical ADMET properties assessed in early process of drug discovery

- Dissolution/solubility
- Passive membrane permeation (permeability)
- Transport mechanisms
- CYP metabolism
- Specific toxicity

BCS

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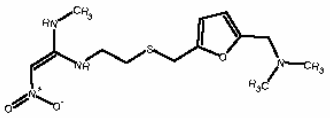
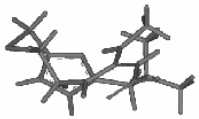
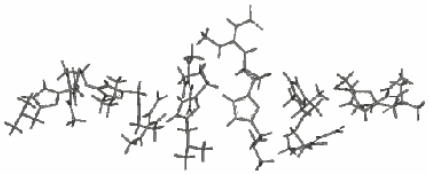
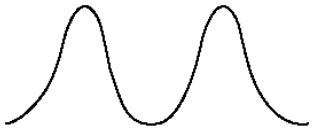
Computational tools: Descriptors

Representation	Descriptors
 2-D structure	Atom counts, fragment counts, topological indices
 3-D structure	Molecular surface properties, molecular volume, drug-probe interactions (GRID/VolSurf), CoMFA, etc
 Conformational space	Dynamic molecular surface properties and molecular volume
 Wave function	Molecular valence properties

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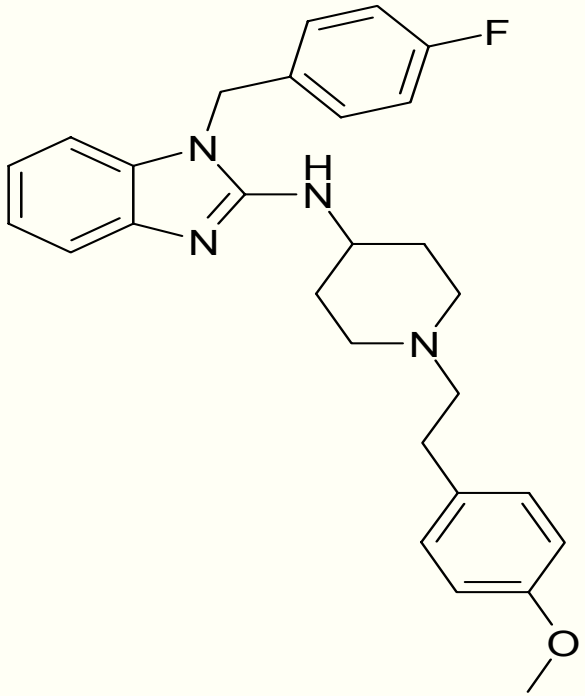
Molecular descriptors – 2D

- Size
- Ring structure
- Flexibility
- H-bonds
- Polarity
- Electronic environment
- Charge
- Lipophilicity (ClogP)



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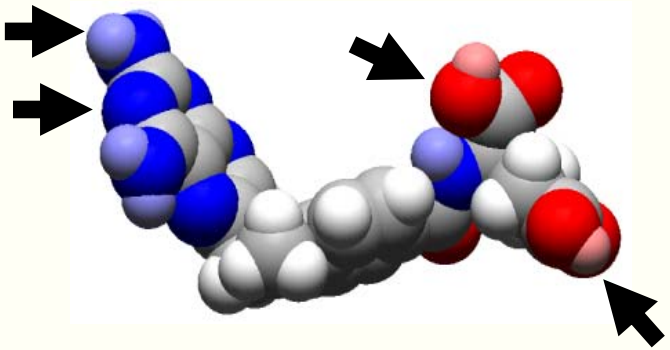
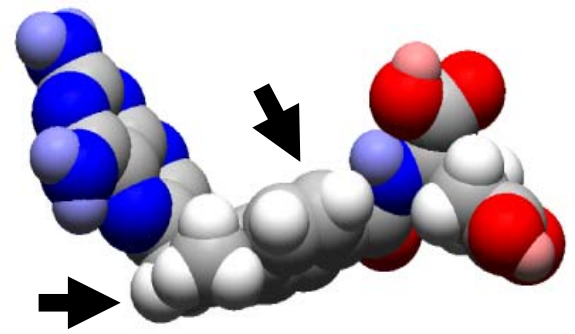
Molecular descriptors – 3D

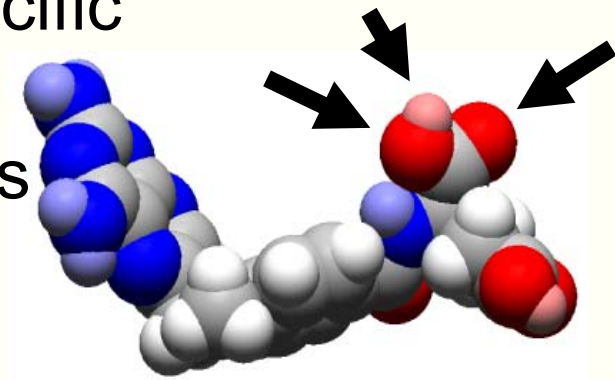
Polar surface area (PSA):
O, N and H bound to these heteroatoms



Non-polar surface area (NPSA):
Total surface area – PSA
Non-polar atoms (C, halides etc)



Partitioned Total Surface Area (PTSA): Surface area of a specific atom/functional group (eg. –COOH)
sp^3-O (-OH) and sp^2-O (=O) plus H's



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Computational tools: statistics

- Rule-based system/ decision tree
- Correlations: linear/ sigmoidal
- Multivariate problems – linear:
  - Multlilinear regression (MLR)
  - Principal component analysis (PCA)
  - Partial least squares projection to latent structures (PLS)
- Multivariate problem – non-linear:
  - Non-linear PLS
  - Neural network (NN)

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Multivariate data analysis: PCA & PLS

- PCA: Multivariate data analysis of characteristics of the observations:
  - Groups/outliers/trends
  - Correlationa obs./descr. och descr./descr.
- PLS; relates two matrices, X and Y, to eachother by linear mathematics
- Instead of all variables that are included in the matrix, super variables with condensed information are extracted and used for prediction.
- PLS-DA (discriminant analysis) uses the supervariables to separate between two groups

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Quality of data; typical ”literature” data

- Mixed sources and methods; introduces large noise

- Understanding the applicability domain: usage of training set and the transparency of the models

Training set n = 797 $r^2 = 0.92$ Test set n = 1587 $r^2 = 0.67$

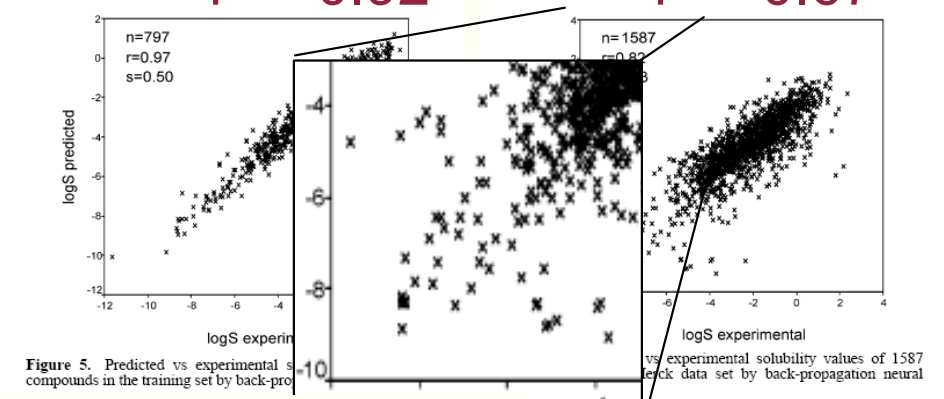

Figure 5. Predicted vs experimental s... compounds in the training set by back-pro... vs experimental solubility values of 1587 ...erck data set by back-propagation neural

Huuskonen data set MERCK data set

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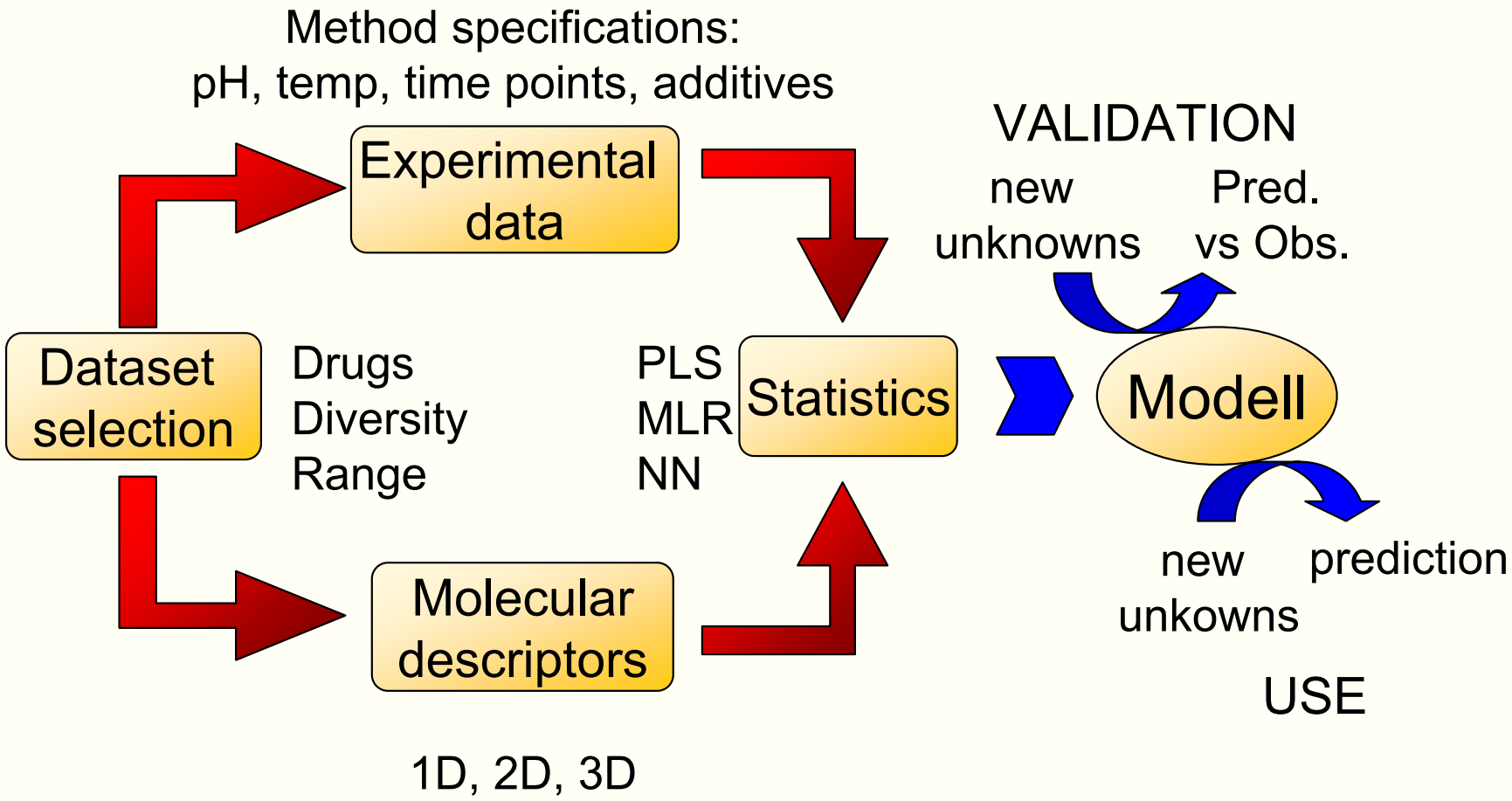
ADMET modeling: the flow

Use training set/test set



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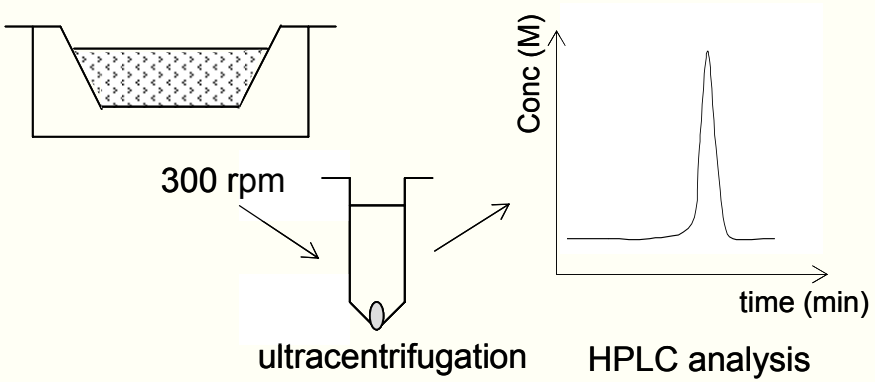
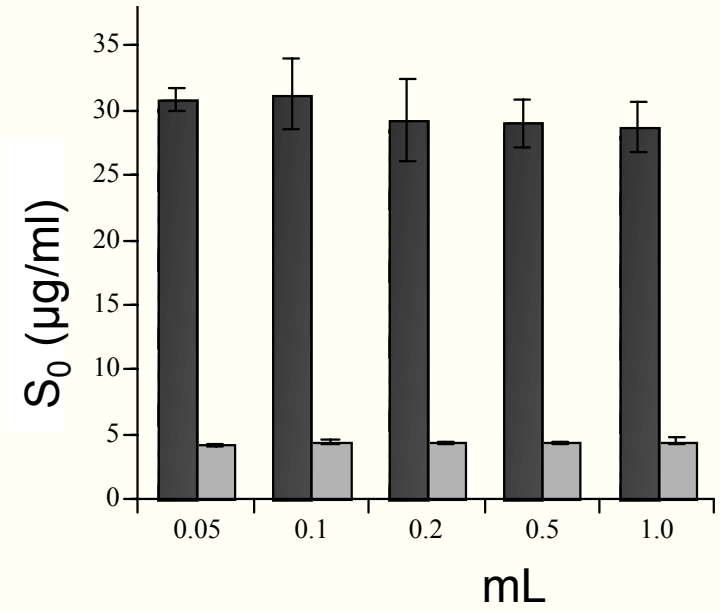
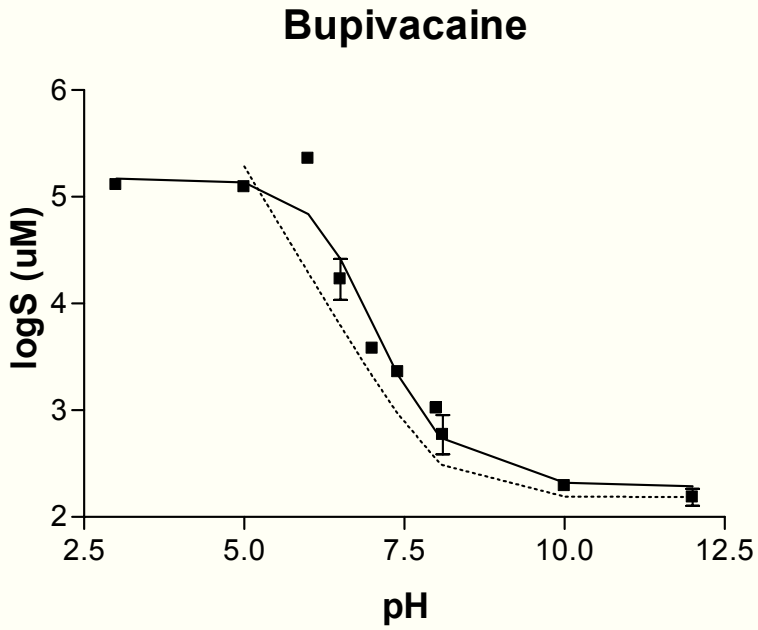
Case I: Models of aqueous drug solubility



Solubility range determined;
tamoxifen intrinsic 2.9 nM
verapamil pH-dep 2 M





Bergström et al., Pharm Res 2002

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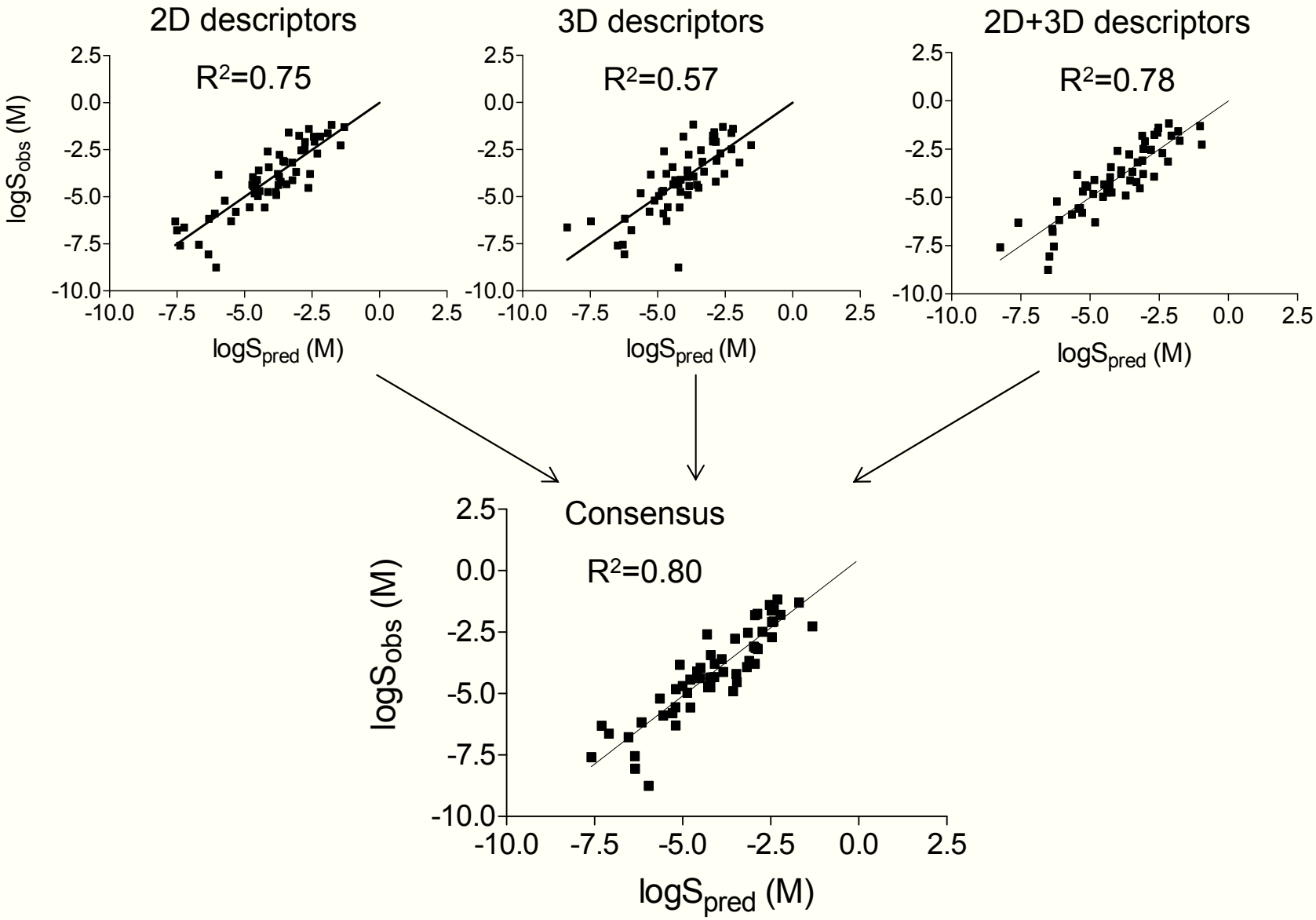
Global Models for Larger Datasets



Bergström et al., JCICS 2004

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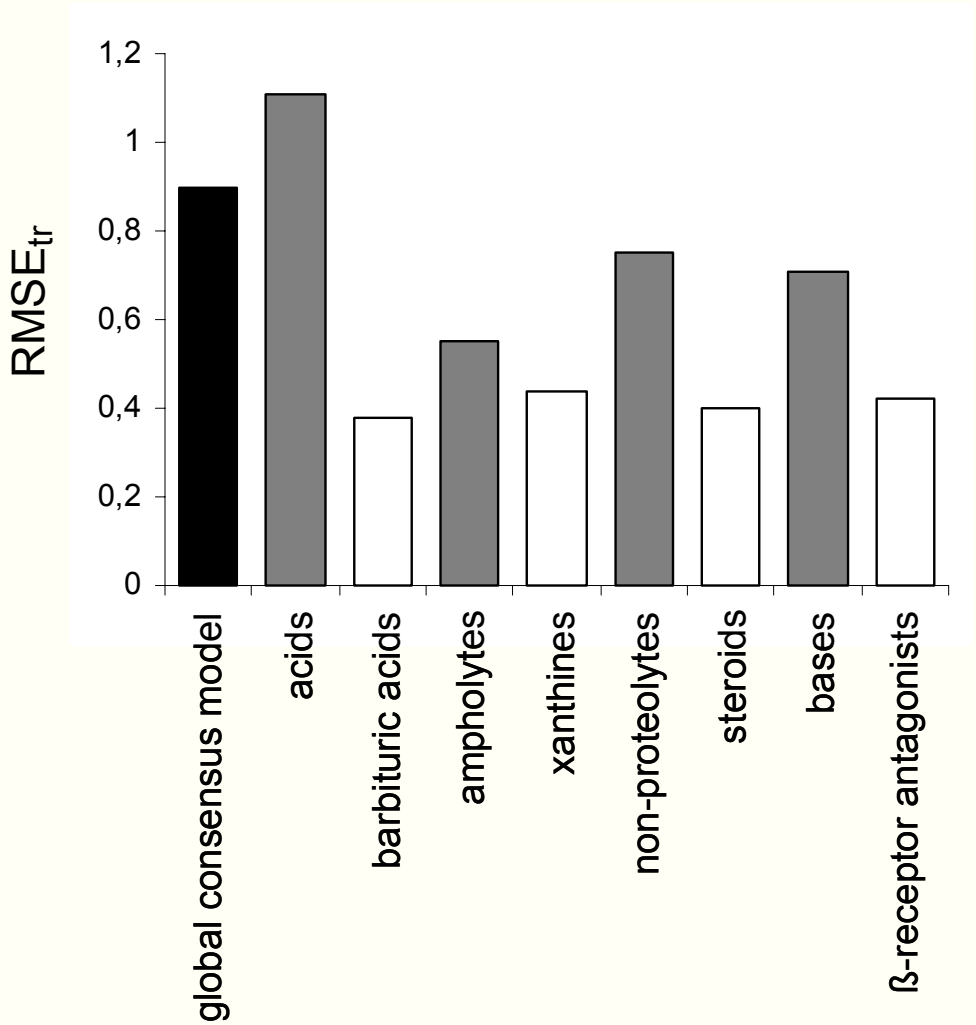
Local Models Result in Higher Accuracy



Bergström et al., JCICS 2004

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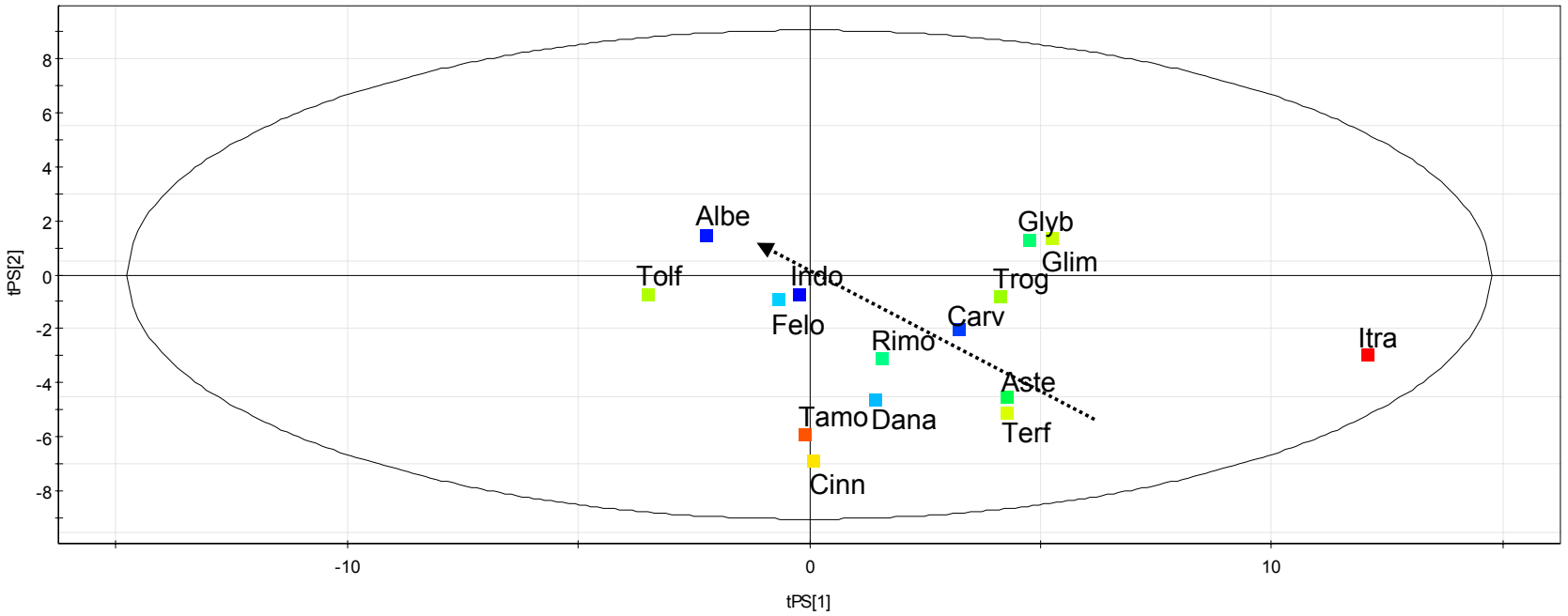
Identifying poorly soluble compounds



Bergström et al., submitted

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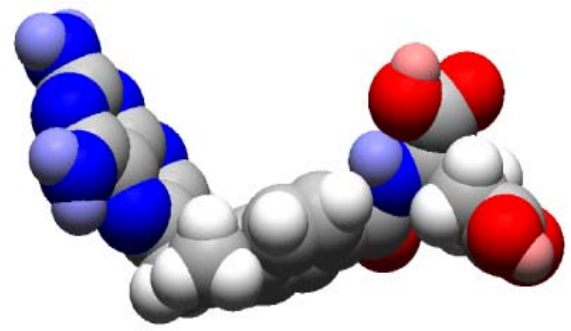
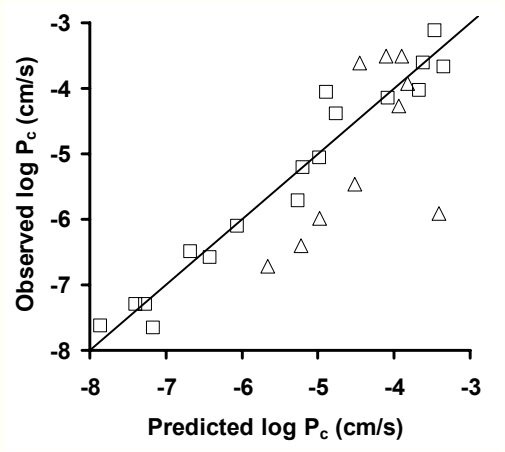
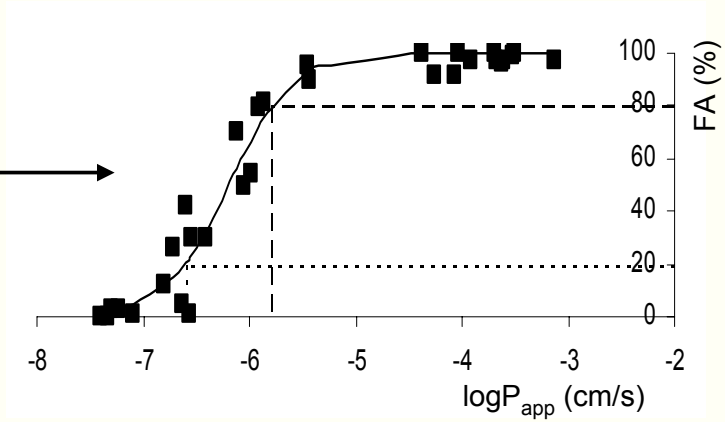
Case II: Models of membrane permeability (passive)







Bergström et al., JMC 2003

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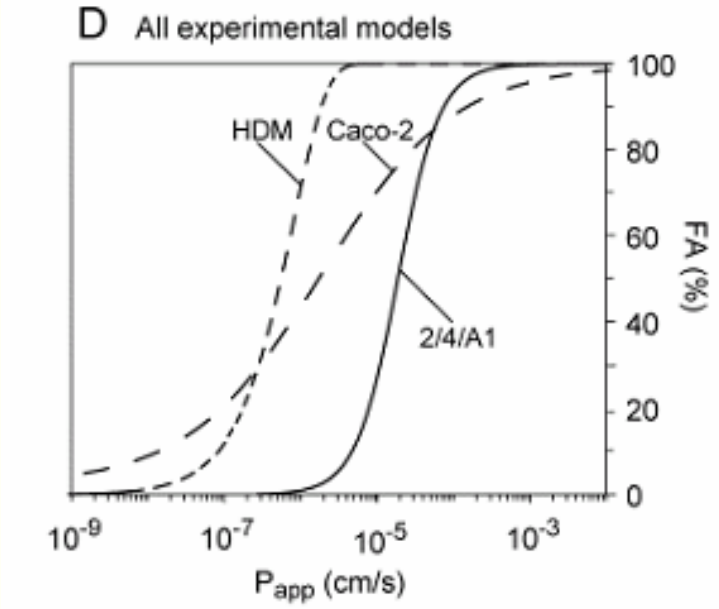
In vitro systems for prediction of fraction absorbed

Membrane model	TEER[a]	Paracellular pathway
HDM	5000 Ω × cm2	Non-paracellular
Caco-2	230 Ω × cm2	Tight-paracellular
2/4/A1	50 Ω × cm2	Leaky-paracellular

Passive transcellular transport Passive paracellular transport



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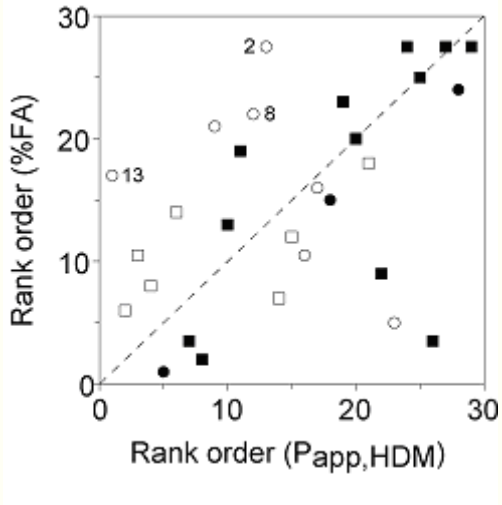
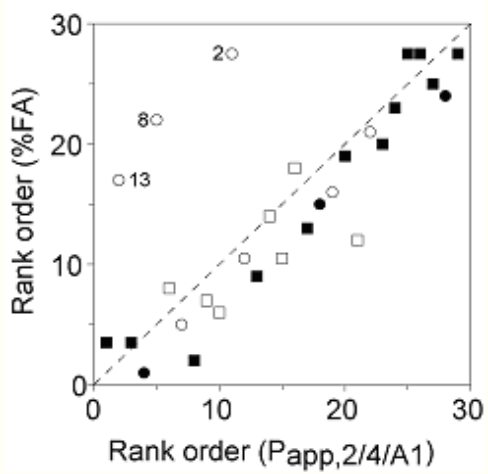
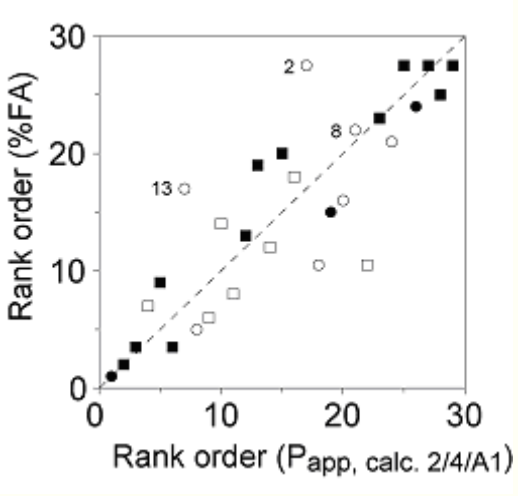
In silico prediction of permeability



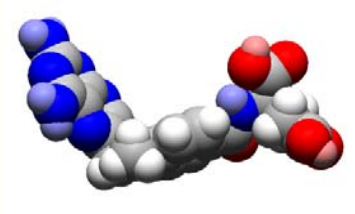
In vitro



In vitro



In silico



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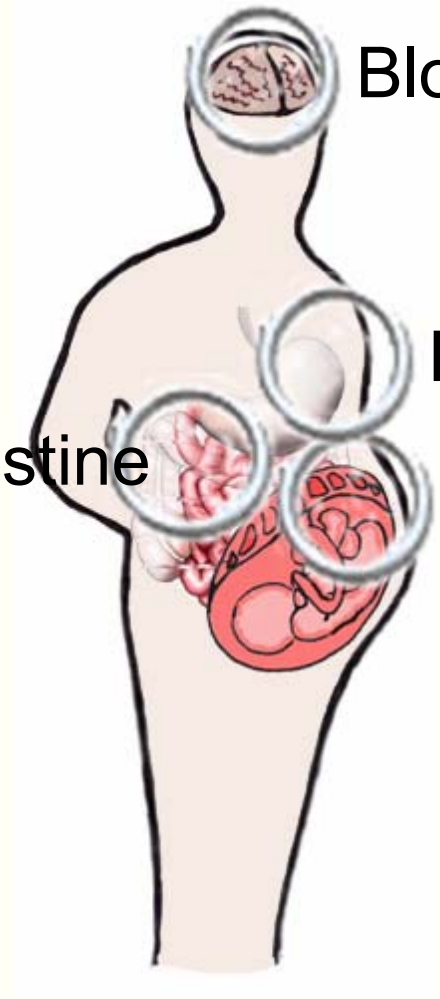
Case III: Active transport .
Breast Cancer Resistance Protein (BCRP)



Blood-brain barrier

Mammary gland

Small intestine

Blood-placenta barrier

- Liver
- Kidney
- Stem cells

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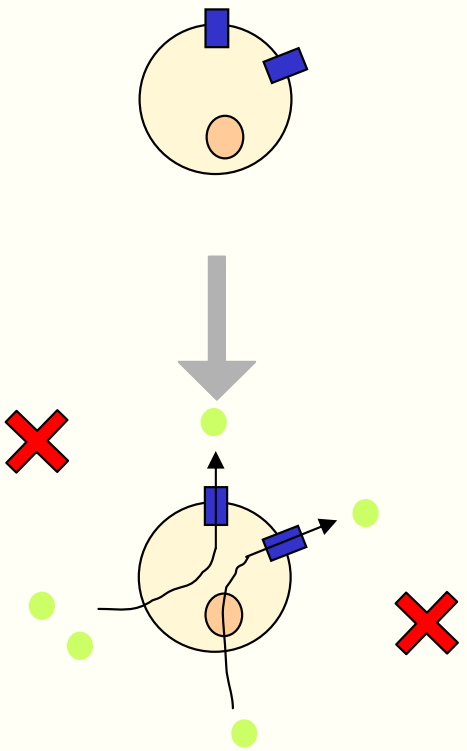
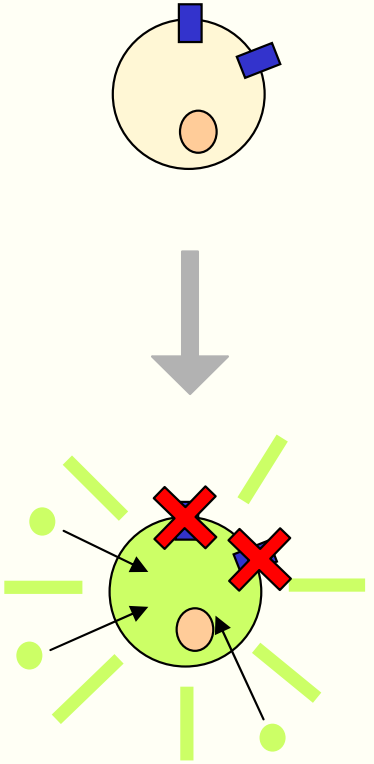
Experimental assay: Efflux inhibition



No inhibitory effect:
mitoxantrone is effluxed
➔ low intracellular fluorescence



Inhibition:
mitoxantrone is retained in the cells
➔ high intracellular fluorescence

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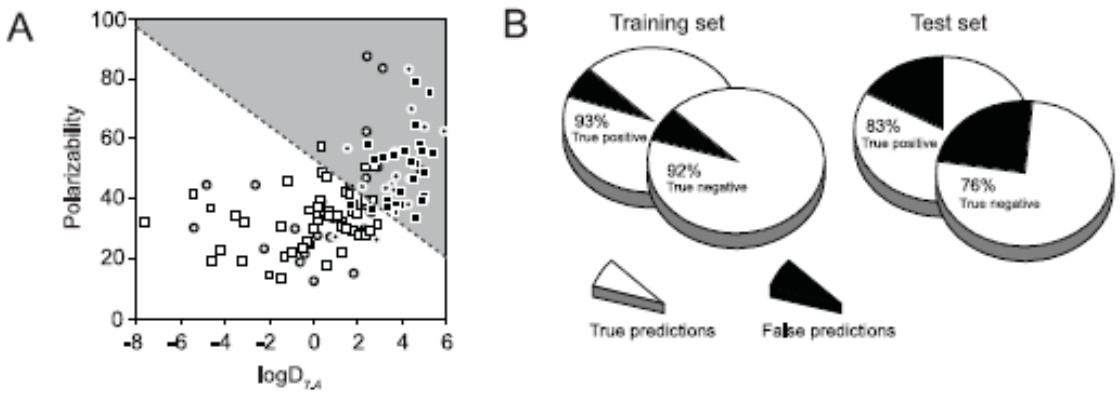
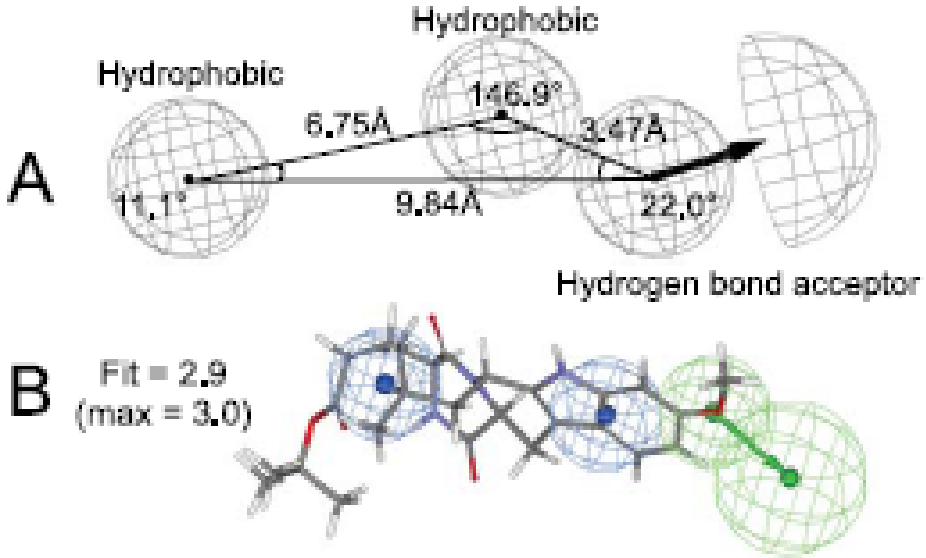
Computational modeling



PLS-DA



Common features pharmacophore modeling

Matsson et al., submitted

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Case IV: BCS prediction

- To investigate accuracy of absorption prediction when both solubility and permeability are incorporated.
- Used the WHO list of essential drugs
- 15 compounds used for developing the two models, validated with 21 compounds.

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A BCS extended for the drug discovery process

- High solubility: maximum dose given orally is soluble in 250 ml, pH 1-7.5
- High permeability: >80% absorbed
- Low permeability: <20% absorbed
- Intermediate permeability: 20-80%

Summary: six classes instead of ”normal” four.

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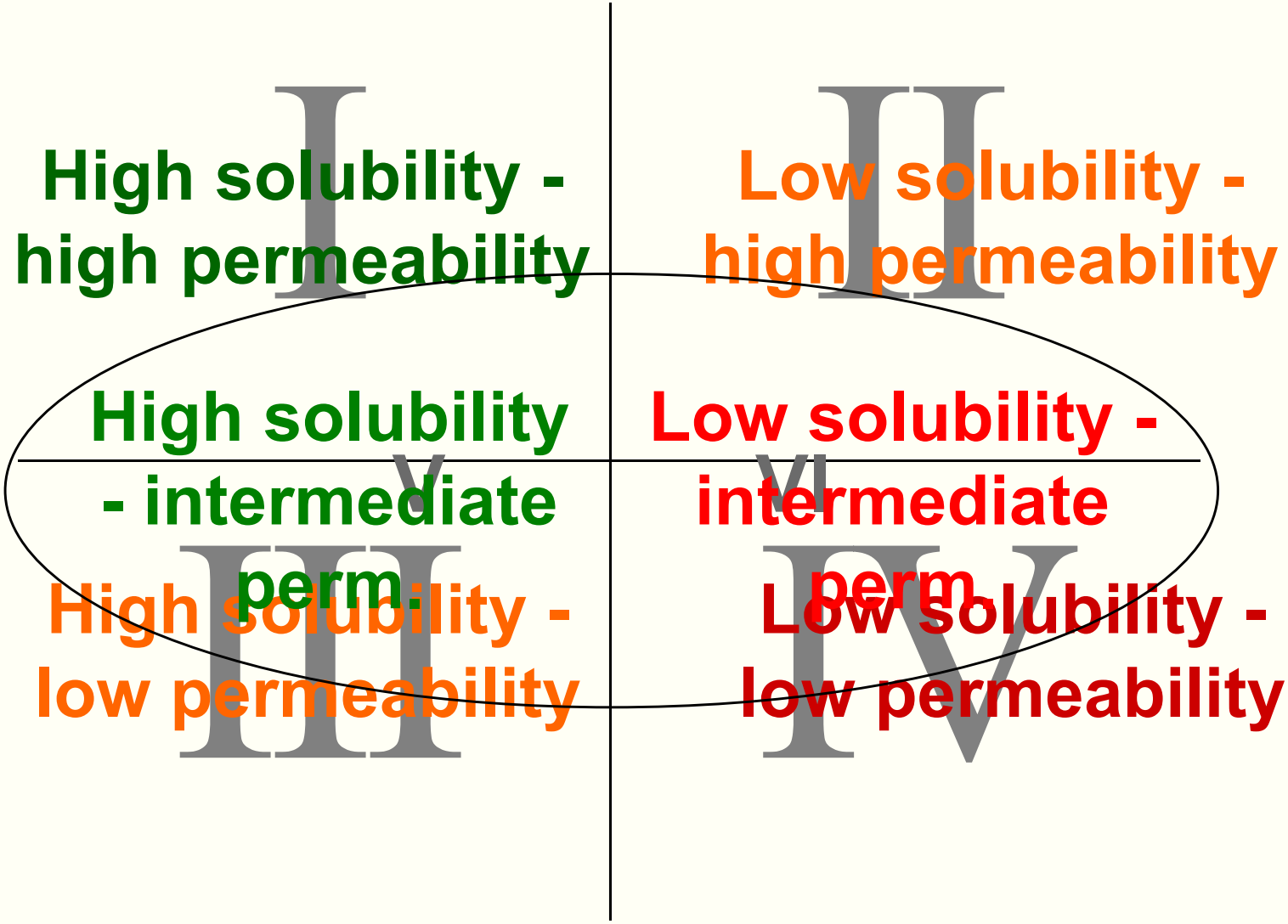
BCS Classes



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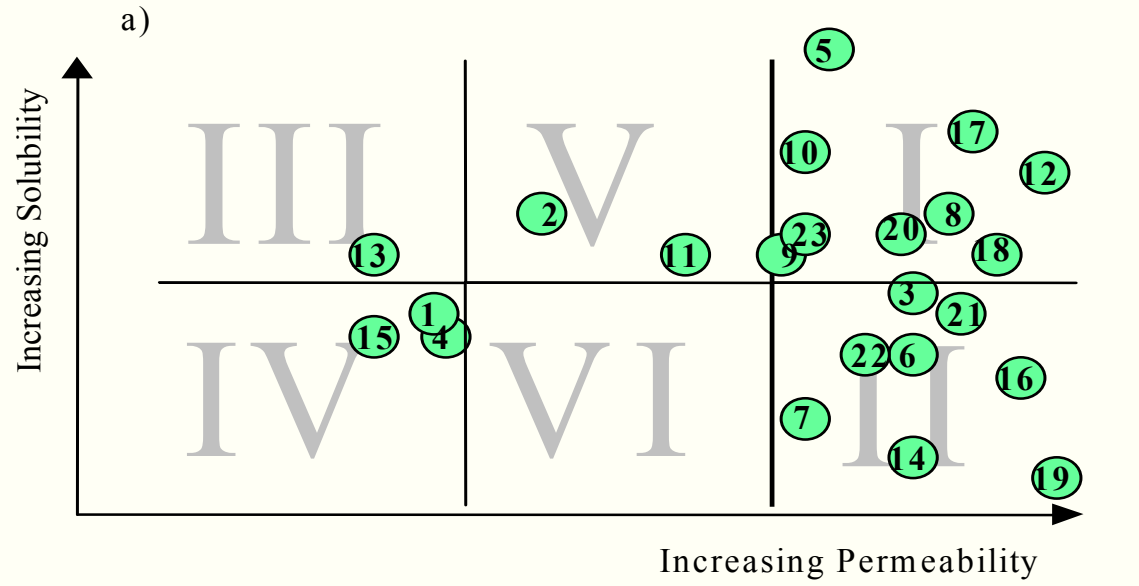
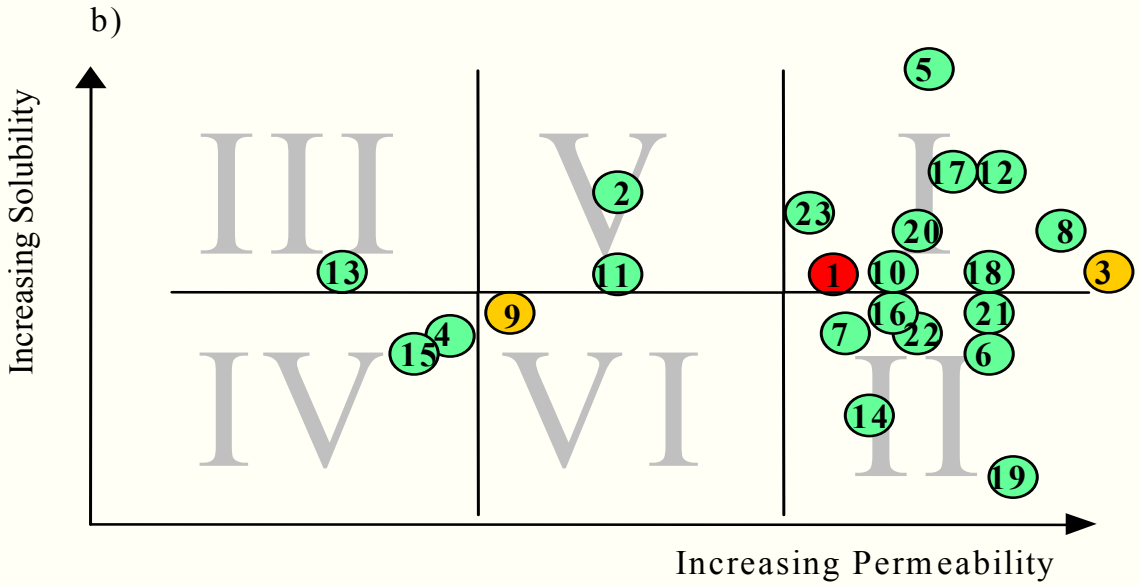
Theoretical BCS





Bergström *et al.*, *J.Med.Chem.* 2003

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Conclusions

- Need to use different computational tools when developing models for underlying mechanisms/ processes involved in drug absorption, distribution and elimination
- Important to base the models on high quality experimental data
- Very important to use a training set which covers the ”chemical” space under investigation
- Always make a proper validation of your model

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Conclusions

- It is an advantage if the model developer understands the experiments and/or the responses which are to be predicted.

- Several ADMET properties have been modeled and predictive models are available. Now remains
  - to simultaneously model the properties to investigate how mechanisms interact
  - to evaluate the relevance of the combination of in silico+in vitro models for prediction of the in vivo situation.

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- Dr Carola Wassvik
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- Jenny Olofsson

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