In silico ADME

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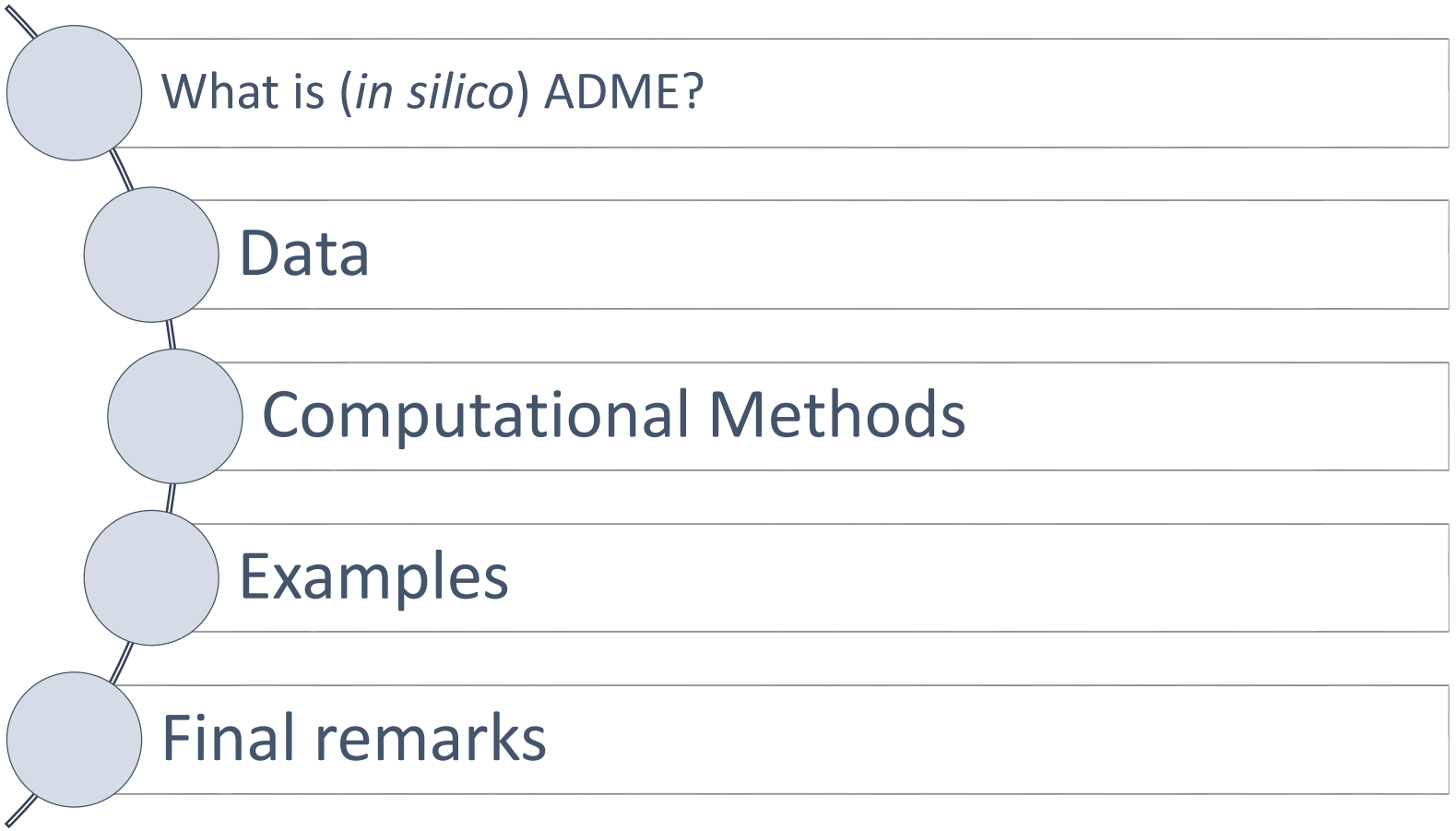
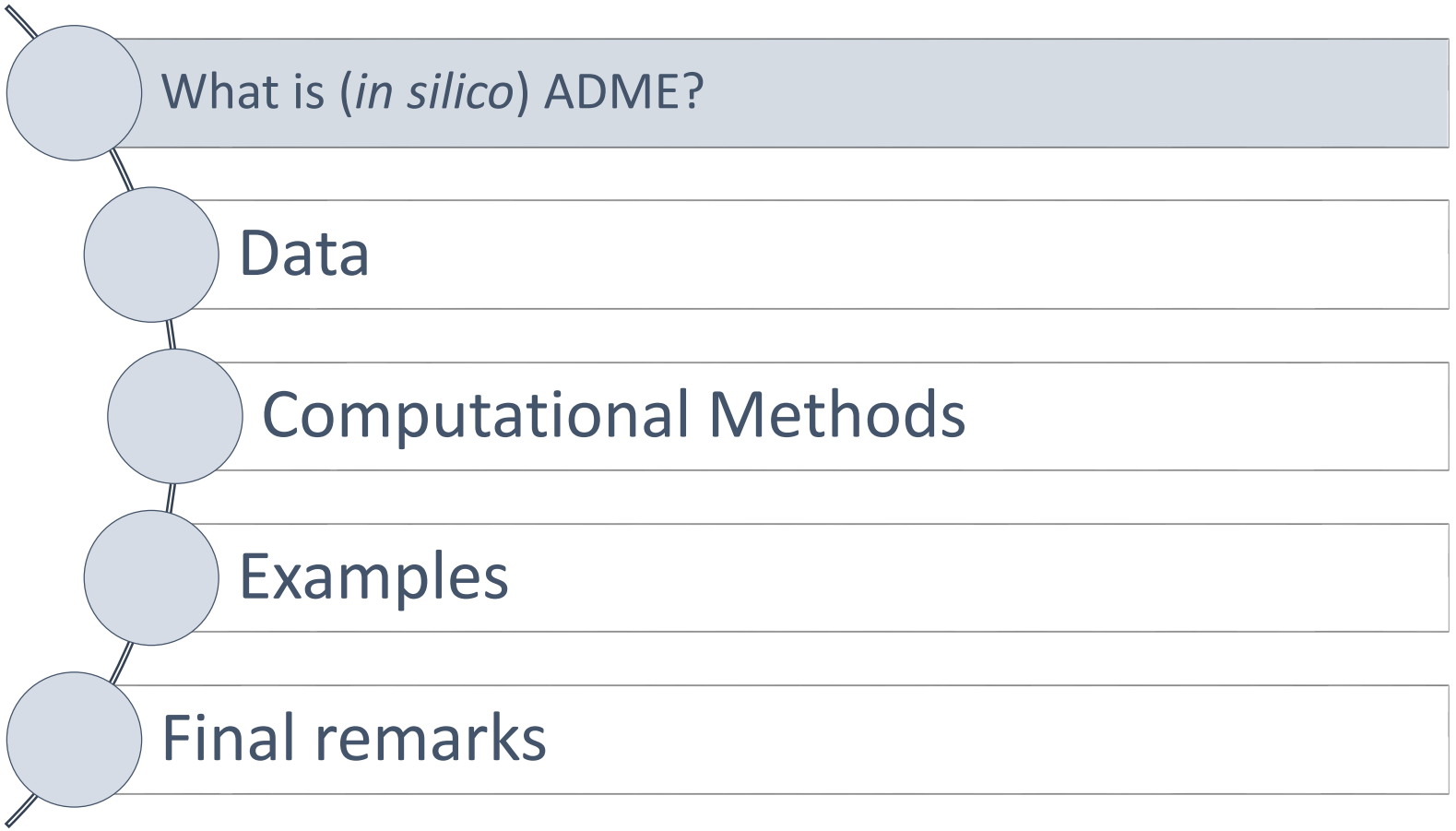
AstraZeneca, Gothenburg, Sweden

Outline


What is (*in silico*) ADME?
Data
Computational Methods
Examples
Final remarks

Outline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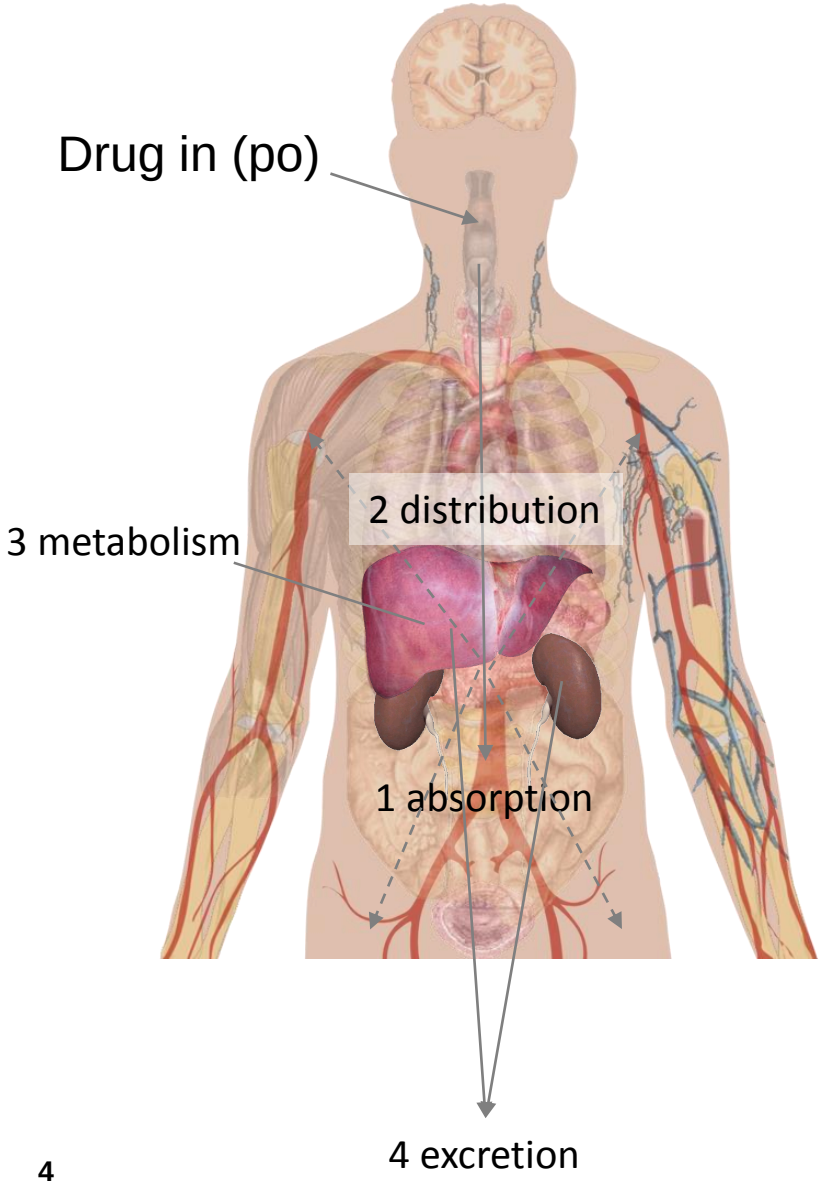
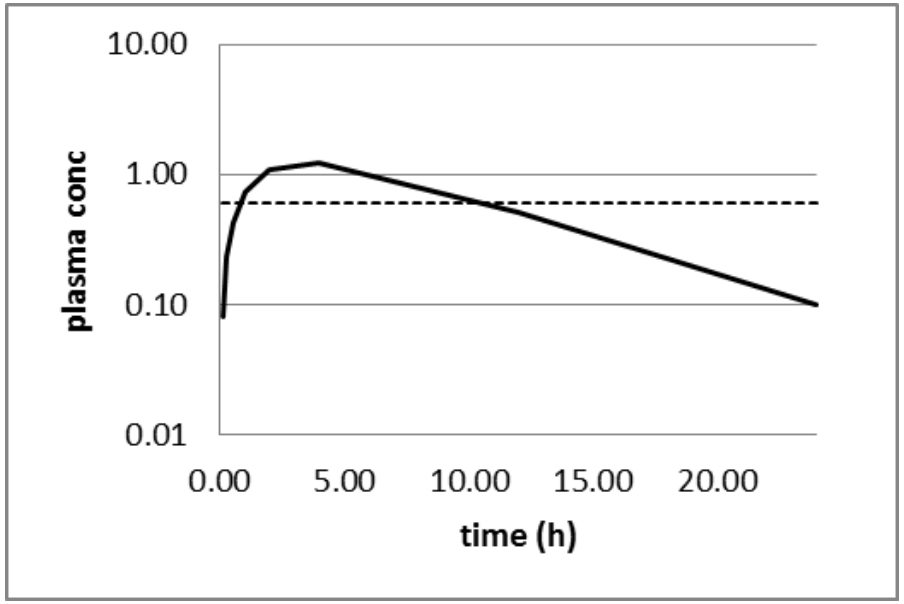
Absorption-Distribution-Metabolism-Excretion (ADME)





ADME properties define **pharmacokinetics** of a compound

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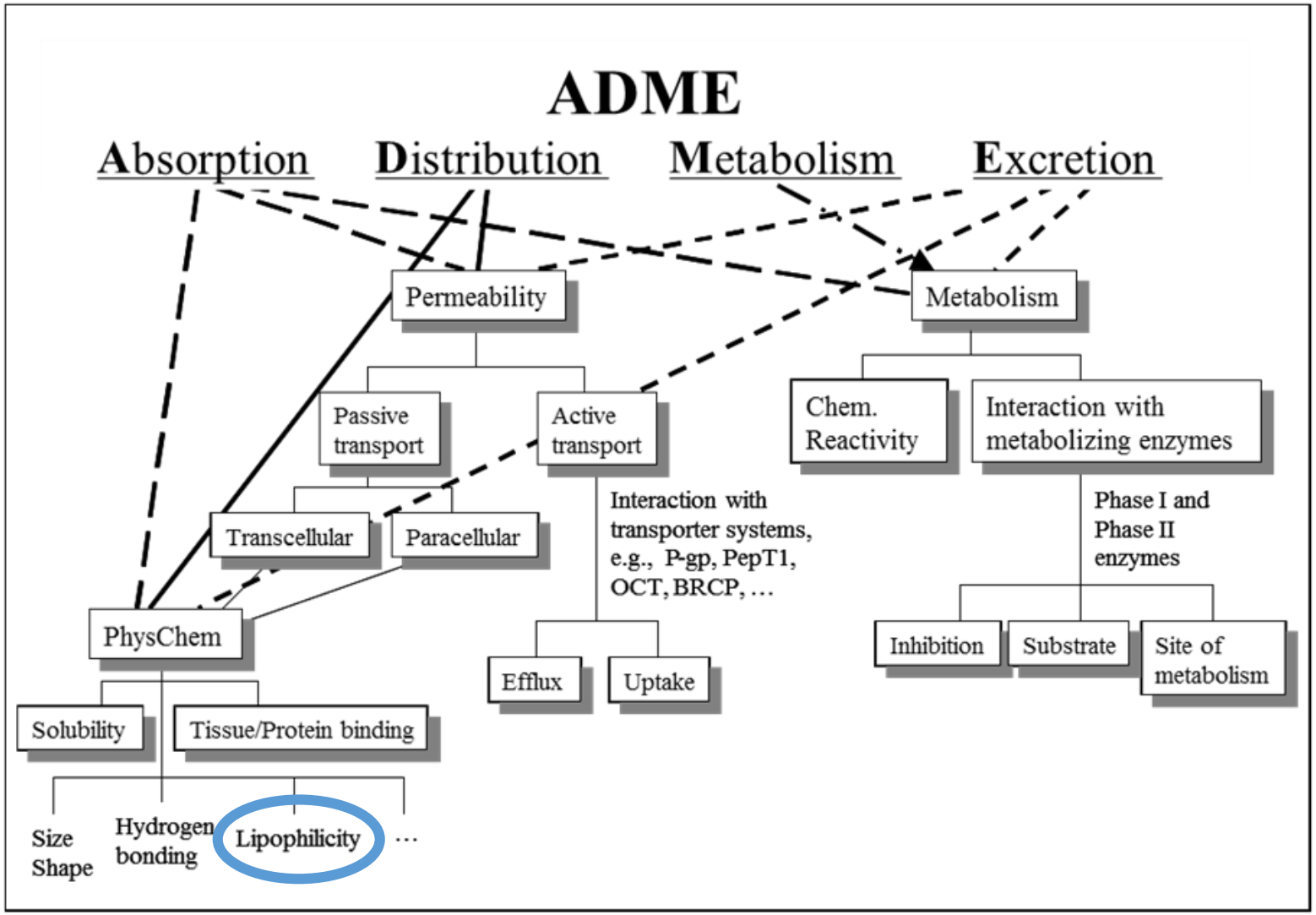
Absorption-Distribution-Metabolism-Excretion (ADME)

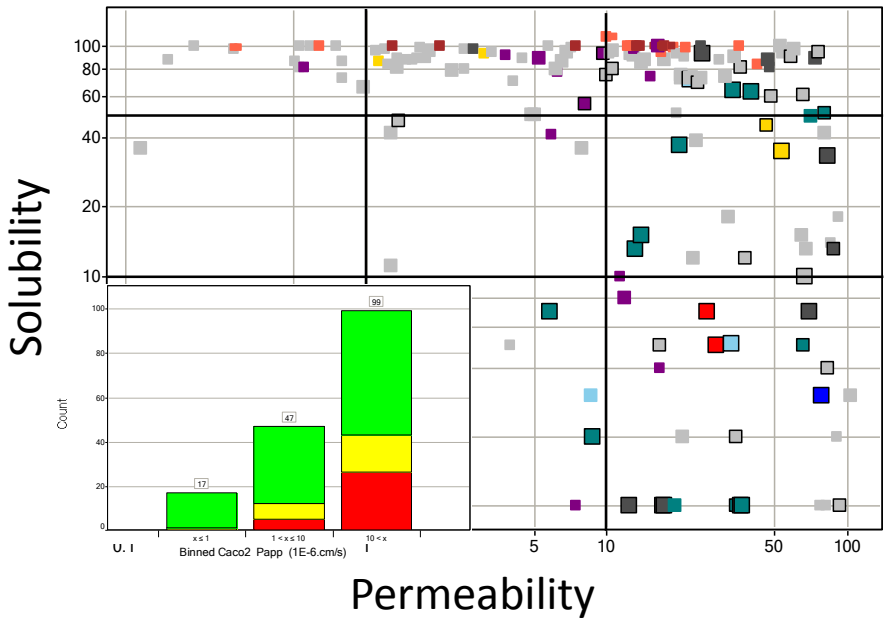


see S.Winiwarter et al. *Use of Molecular Descriptors for ADME Predictions.* Compr. Med. Chem. II, D.J.Triggle & J.B.Taylor, Eds., Vol. 5, Elsevier, 531-554 (2007)

Intercorrelations of ADME parameters

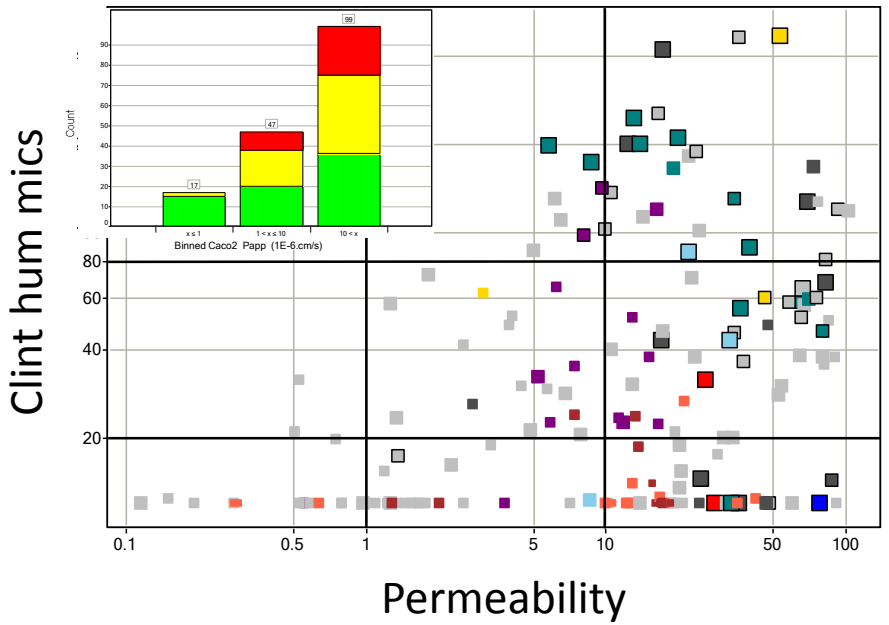
(in house screen results)

Permeability vs. Solubility



→ High permeability increases risk for low solubility

Permeability vs. Metabolic stability



→ High permeability increases risk for high Clint

NOTE: high permeability is **not** the cause for low solubility or high Clint
but all three properties are correlated to lipophilicity

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in silico ADME

… is the use of **computer modeling** to understand structure-property relationships and to **predict DMPK** (drug metabolism and pharmacokinetics) properties **from compound structure**

in silico ADME

Special issue in Mol. Pharm. 2013:

Predictive DMPK: In Silico ADME Predictions in Drug Discovery
Jane R. Kenny, *Molecular Pharmaceutics* **2013** *10* (4), 1151-1152

Physicochemical and DMPK In Silico Models: Facilitating Their Use by Medicinal Chemists
Daniel F. Ortwine and Ignacio Aliagas, *Molecular Pharmaceutics* **2013** *10* (4), 1153-1161

Evolution of ADME Science: Where Else Can Modeling and Simulation Contribute?
Dennis A. Smith, *Molecular Pharmaceutics* **2013** *10* (4), 1162-1170

Role of Electrostatic Potential in the in Silico Prediction of Molecular Bioactivation and Mutagenesis
13 *10* (4), 1171-1182

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Models for Cytochromes P450
sen, *Molecular Pharmaceutics*

13 *10* (4), 1224-1235

P) Inhibitors by Virtual
Pharmaceutics **2013** *10* (4),

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Raub, *Molecular*

Metabolized by Aldehyde
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ELSEVIER

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Nature Reviews D

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Han van de Waterbe

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Focus on success: using a

358 *Current Topics in Medicinal Chemistry,* 2011, *11,* 358-38

***In-Silico* ADI**
Discovery Ap

M. Paul Gleeson[1,*]

[1]*Department of Chemi*
Thailand; [2]*European I*
United Kingdom; [3]*Ce*
10900, Thailand

Abstract: AI
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Keywords: ADME, *in*

Advanced Drug Delivery Reviews 86 (2015) 83–100

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

ELSEVIER

Recent progresses in the e
in-silico ADME prediction

L. Tao [a,b], P. Zhang [b], C. Qin [b], S.Y.

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China
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2017; DOI: 10.1021/acs.jmedchem.7b00487

Perspective

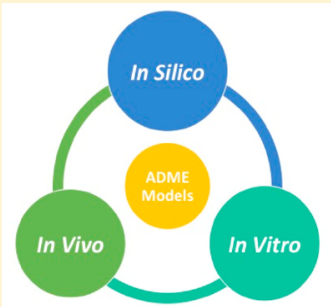
pubs.acs.org/jmc

In Silico Absorption, Distribution, Metabolism, Excretion, and Pharmacokinetics (ADME-PK): Utility and Best Practices. An Industry Perspective from the International Consortium for Innovation through Quality in Pharmaceutical Development

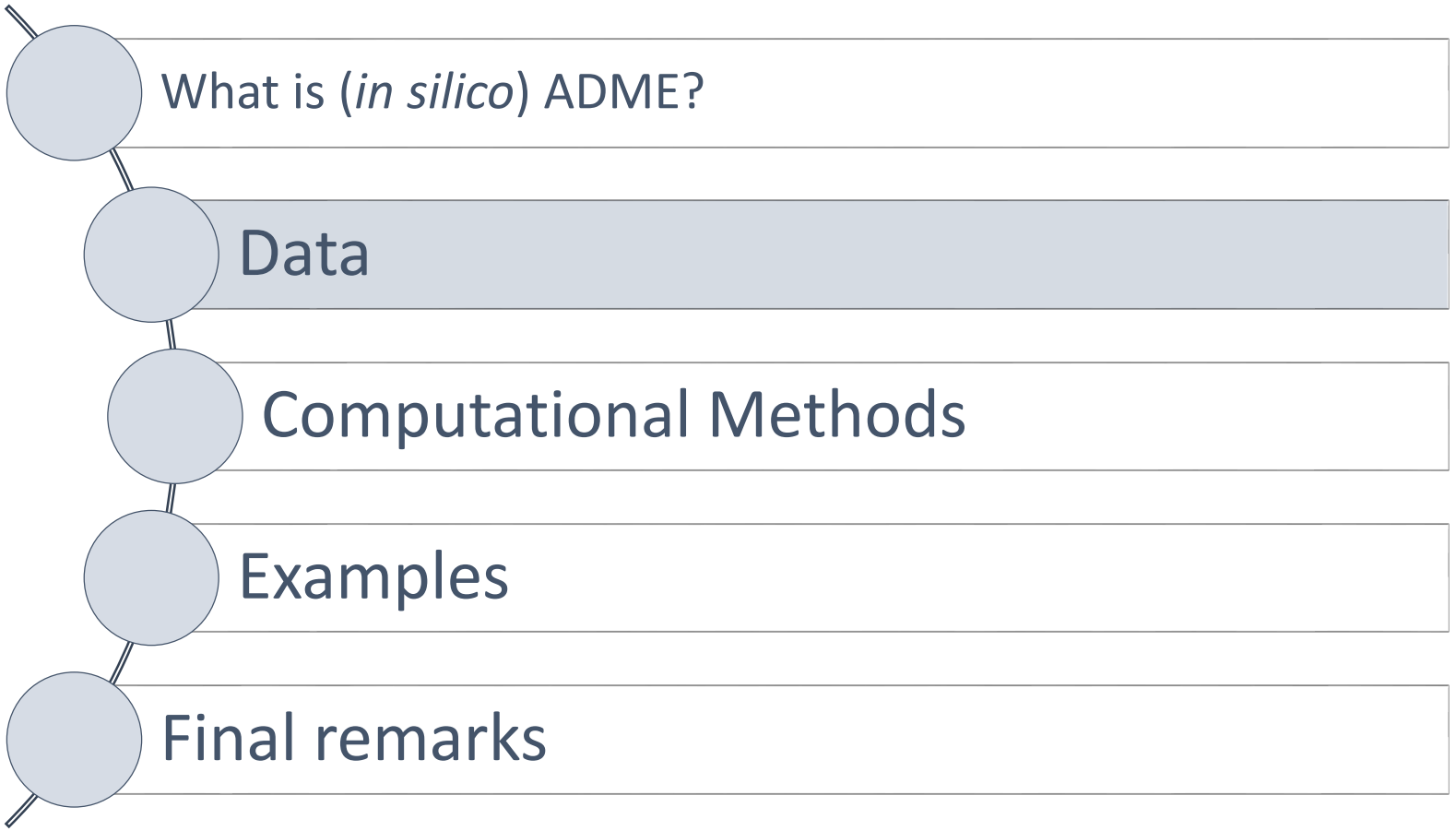
Miniperspective

Franco Lombardo,[†] Prashant V. Desai,[‡] Rieko Arimoto,[§] Kelly E. Desino,[∥] Holger Fischer,[⊥] Christopher E. Keefer,[#] Carl Petersson,[▽] Susanne Winiwarter,[○] and Fabio Broccatelli*[,◆]

ABSTRACT: *In silico* tools to investigate absorption, distribution, metabolism, excretion, and pharmacokinetics (ADME-PK) properties of new chemical entities are an integral part of the current industrial drug discovery paradigm. While many companies are active in the field, scientists engaged in this area do not necessarily share the same background and have limited resources when seeking guidance on how to initiate and maintain an *in silico* ADME-PK infrastructure in an industrial setting. This work summarizes the views of a group of industrial *in silico* and experimental ADME scientists, participating in the *In Silico* ADME Working Group, a subgroup of the International Consortium for Innovation through Quality in Pharmaceutical Development (IQ) Drug Metabolism Leadership Group. This overview on the benefits, caveats, and impact of *in silico* ADME-PK should serve as a resource for medicinal chemists, computational chemists, and DMPK scientists working in drug design to increase their knowledge in the area.



Outline


What is (*in silico*) ADME?
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Important ADME parameters considered in drug discovery

In vitro

Absorption:
solubility, permeability in cell layer, efflux, transporter inhibition

Distribution:
(protein) binding, blood-plasma ratio

Metabolism:
metabolic stability, metabolite ID, reactive metabolite screen, enzyme inhibition

Excretion:
permeability and efflux

In vivo

Absorption:
fraction absorbed, bioavailability

Distribution:
volume of distribution, tissue-distribution, blood-plasma ratio

Metabolism:
in vivo clearance, *in vivo* metabolite ID

Excretion:
in vivo clearance (renal/biliary/hepatic)

DDI – drug-drug interactions

PhysChem: lipophilicity, solubility, pKa, binding properties

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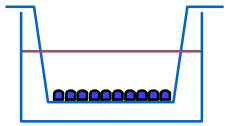
ADME Data

In vitro

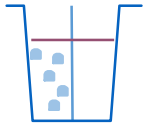
specific systems*

- apparent permeability
- intrinsic clearance
- fraction unbound in plasma/tissue
- enzyme or transporter inhibition

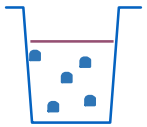
* eg cell lines (CaCo2, MDCK, HepRG, hepatocytes) or cellular fractions (mirosomes), plasma, tissue, medium, …

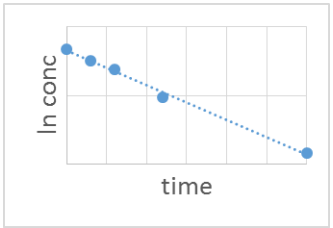


$P_{app} = (dQ/dt)/(AC_d)$



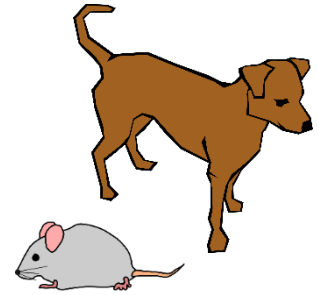
fu % = (C_{buffer}/C_{plasma}) *100



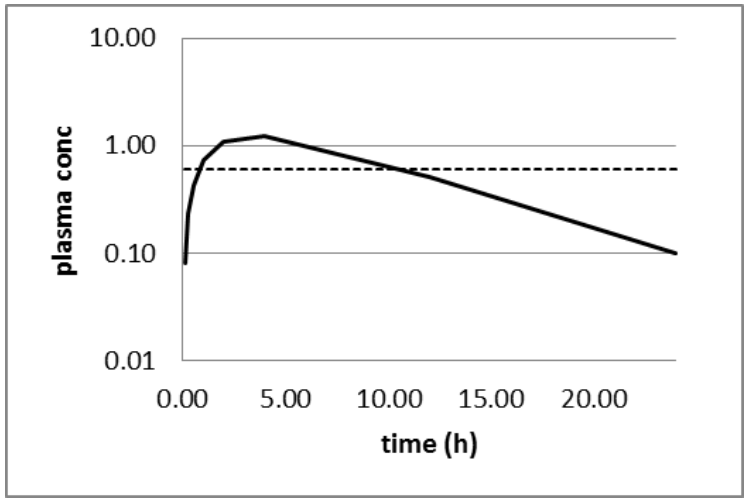


CLint = -slope/cell(protein)conc

In vivo



C_{min}, C_{max}, AUC
bioavailability
volume of distribution
clearance
drug drug interactions



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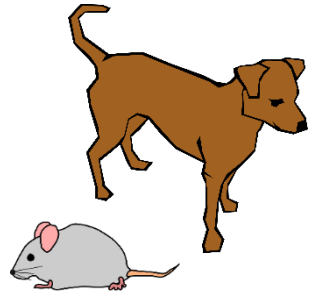
ADME Data

In vitro

different species
reduced cost
less variable
high throughput possible
many datapoints available



In vivo

different species
expensive
variable
low throughput
less data available for modeling

ADME data in drug discovery **required to** estimate **human *in vivo* properties**

***in silico* ADME models** mostly based on *in vitro* data
can be used to:
predict ADME properties for virtual compounds
define which compounds need testing

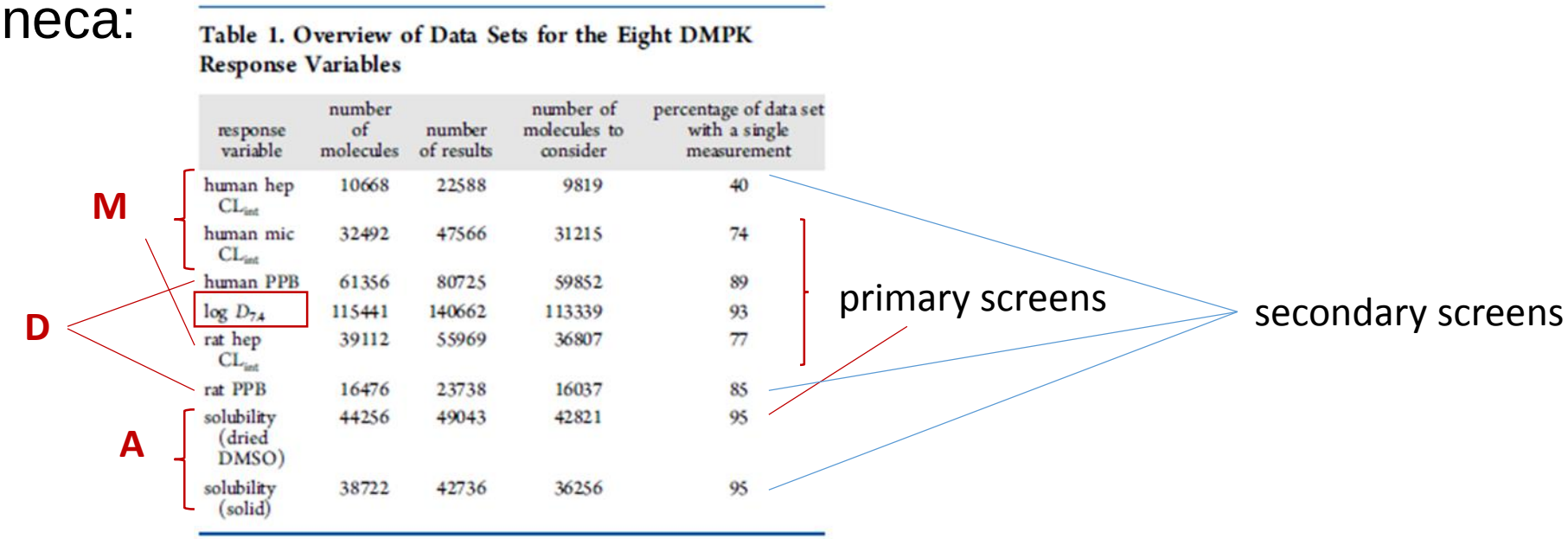
Amount of data available

Public (literature) data sets - ~several 100 to 1000 datapoints
in vitro or in vivo, often from different sources

Industrial (in vitro) datasets can be much bigger
eg, within AstraZeneca:

Table 1. Overview of Data Sets for the Eight DMPK Response Variables

response variable	number of molecules	number of results	number of molecules to consider	percentage of data set with a single measurement
human hep CL_{int}	10668	22588	9819	40
human mic CL_{int}	32492	47566	31215	74
human PPB	61356	80725	59852	89
log $D_{7.4}$	115441	140662	113339	93
rat hep CL_{int}	39112	55969	36807	77
rat PPB	16476	23738	16037	85
solubility (dried DMSO)	44256	49043	42821	95
solubility (solid)	38722	42736	36256	95



Wenlock & Carlsson, J. Chem. Inf. Model. 2015, 55, 125−134

Need to ascertain data compatibility!

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Data variability

Inherent assay variability – biological systems

Variability logD < PPB < CLint

2- to 3-fold variability to be expected

response variable	number of molecules with three or more repeat measurements	range in observed stdev	typical stdev
human hep CL_{int}	540	0.01–0.61	0.11
human mic CL_{int}	830	0.01–0.67	0.12
human PPB	1696	0.01–1.56	0.16
log $D_{7.4}$	1445	0.01–2.12	0.19
rat hep CL_{int}	919	0.01–0.92	0.16
rat PPB	668	0.01–1.25	0.16
solubility (dried DMSO)	363	0.01–1.78	0.25
solubility (solid)	466	0.01–1.60	0.28

Wenlock & Carlsson, J. Chem. Inf. Model. 2015, 55, 125−134 (all <2-fold)

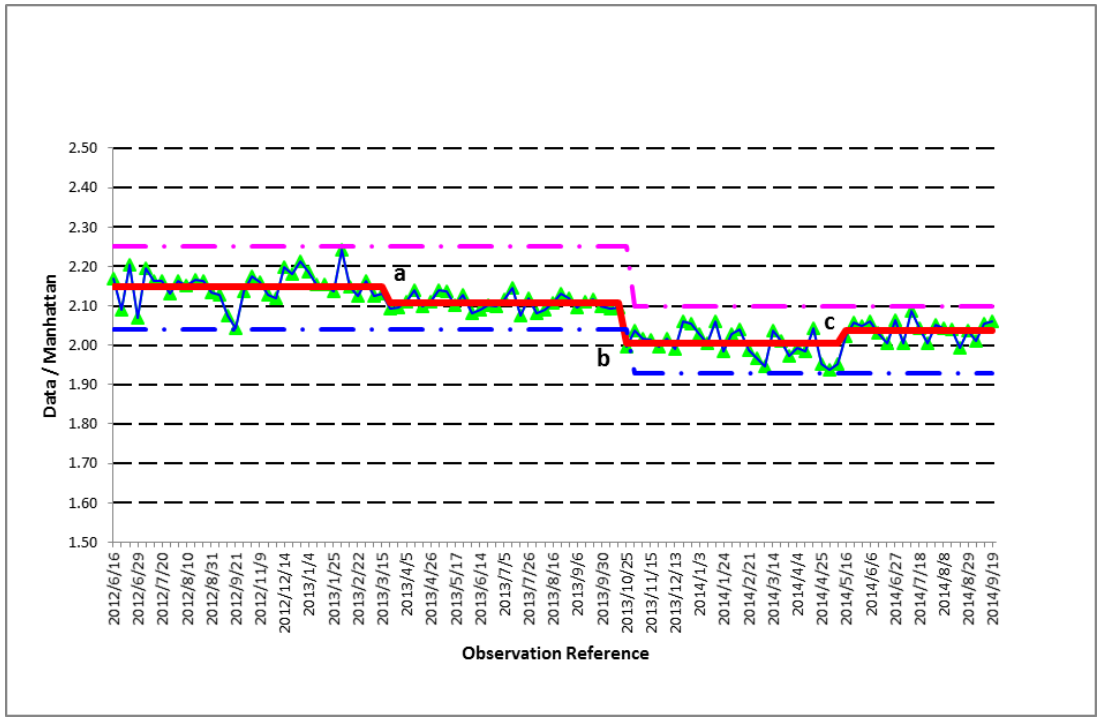
Variability impacts on model results:

RMSEP ~= sqrt (error propagation of population variance in x and y variables)
= sqrt(var-x+var-y) = sqrt ($0.2^2+0.2^2$)=0.28

→ RMSEP=0.3 is indicating a very good model!

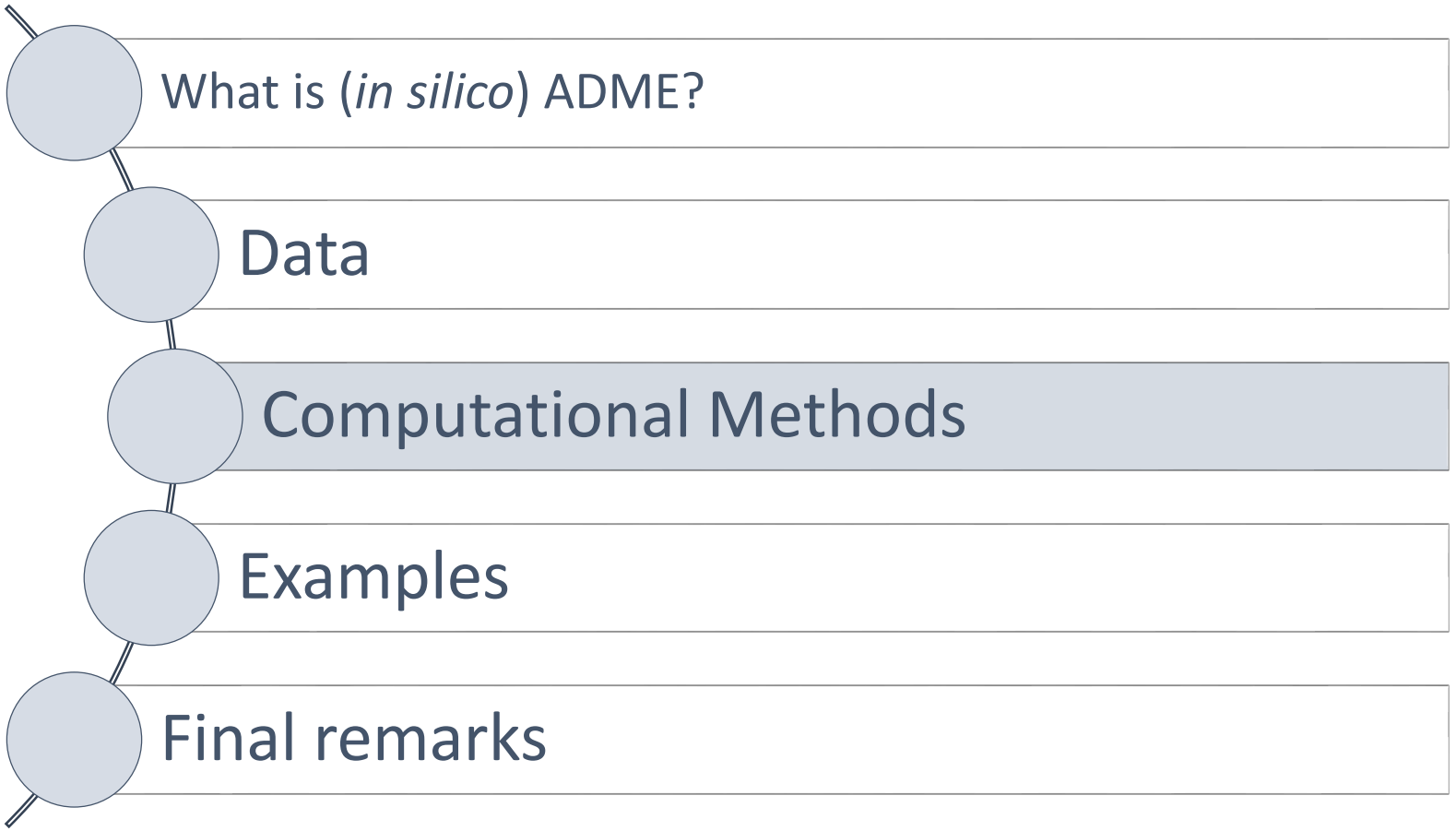
Data variability

Assay variability over time
– usually monitored (marker cmpds)



Winiwarter et al, J. Comput. Aided Mol. Des. 2015, 29, 795–807

Outline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Computational methods

Machine learning approaches (QSPR type)

multivariate analysis, PLS, RF, SVM, NN, …

to consider: amount of data, data variability, data skewness, molecular descriptors to use, prediction confidence

Molecular modeling approaches

pharmacophore analysis

molecular docking

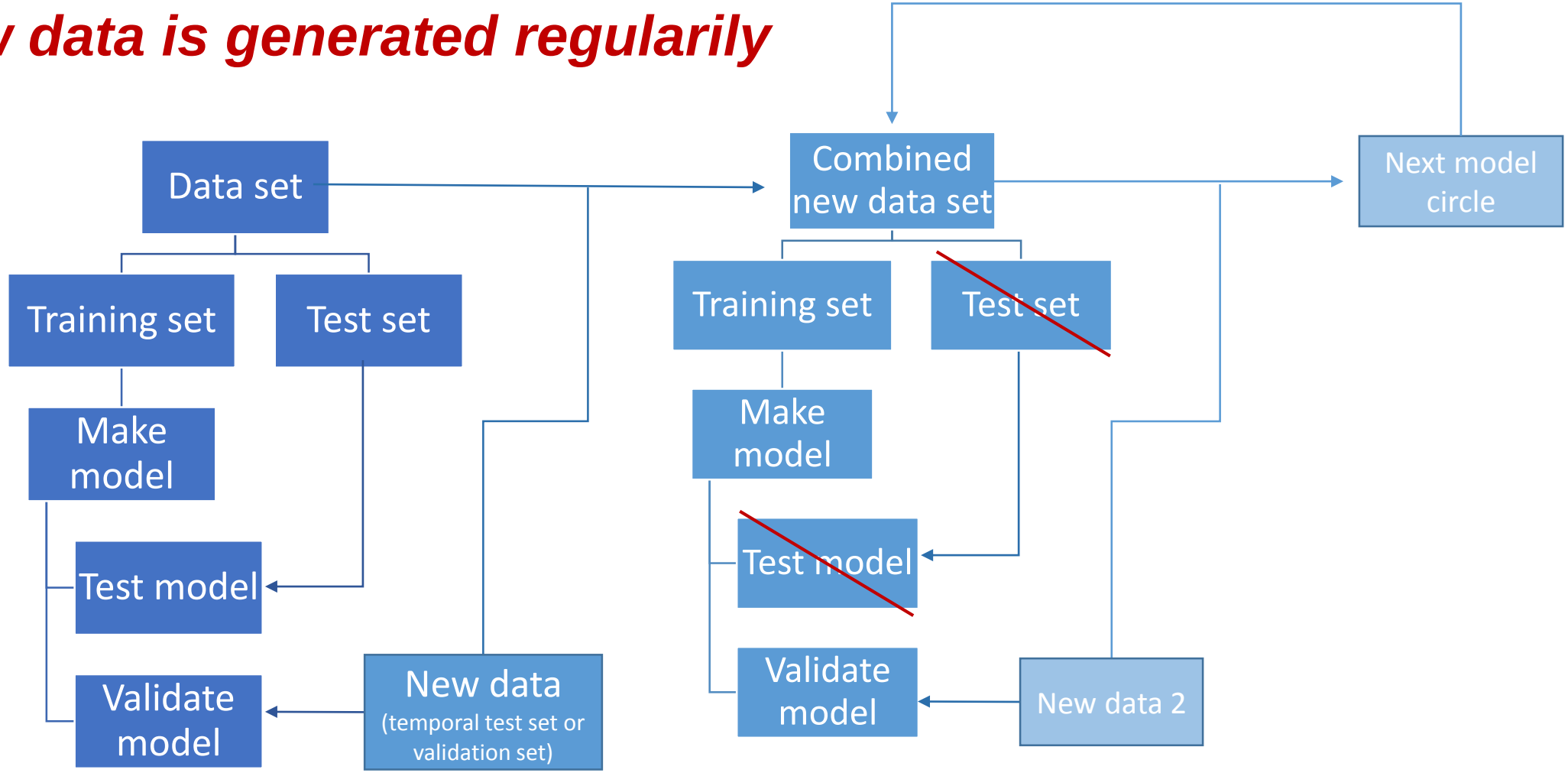
quantum mechanics

Specific ADME software

eg site of metabolism predictions

Modelling process

… if new data is generated regularily



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Validation and confidence

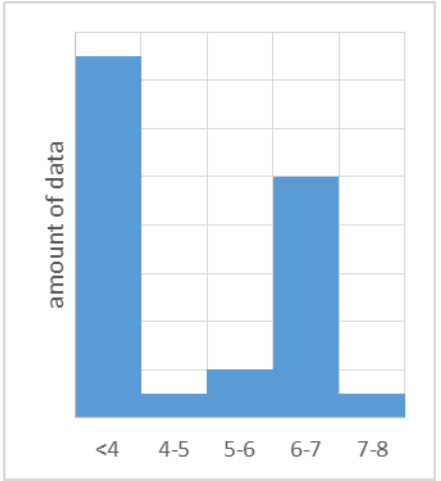
Overall measures based on test/validation sets

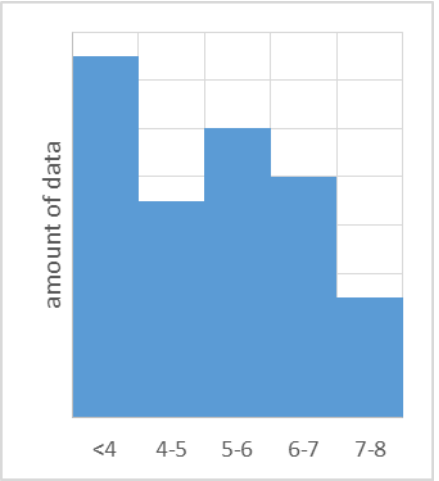
- (eg RMSE, R^2, ranking ability, …)

Individual measures for each predicted value:

- Distance to training set
  - Based on descriptors used in model
  - Based on other descriptors
- Distance to model (eg PLS)
- Conformal prediction framework – confidence

Classification or regression models





- Depends on
  - data (range, skewness)
  - data quality/variability
  - assay interpretation
  - expected model usage
- Regression mostly preferred (user perspective)
- Regression models can also be used for classification

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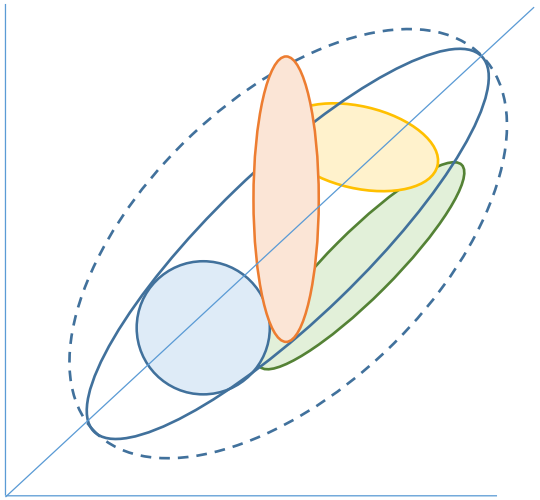
Global or local models

Global models

Overall view

May be less suited for specific compound series

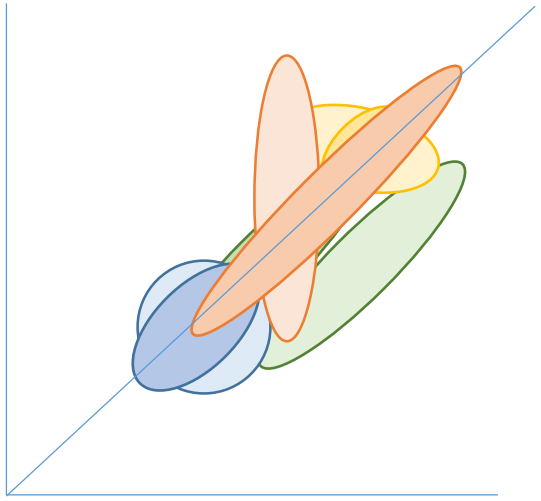


Local models

May give better local predictions

Only for specific chemical space

Data may not be sufficient



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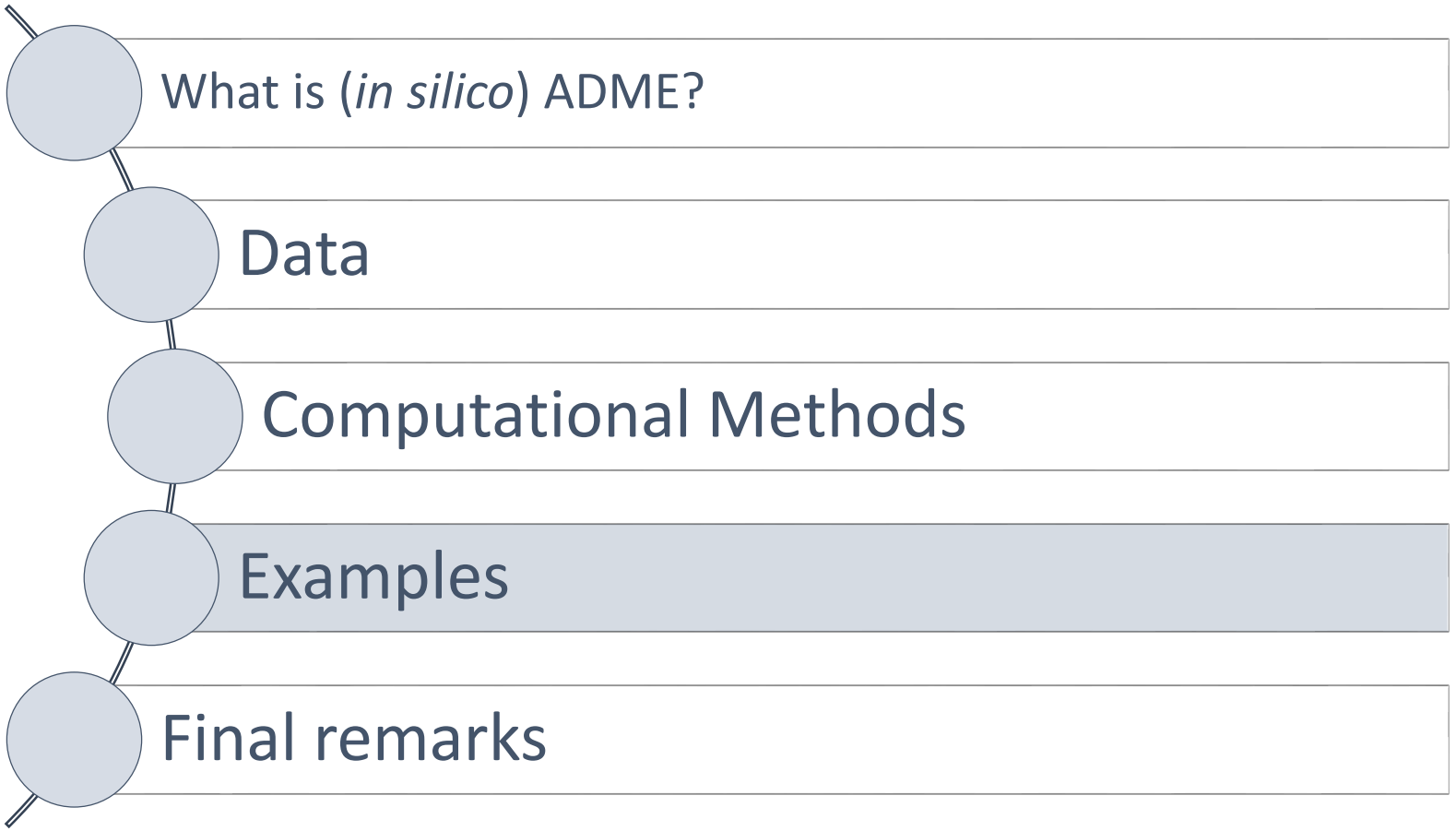
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In silico ADME examples – Absorption

Lipinski's Rule of 5

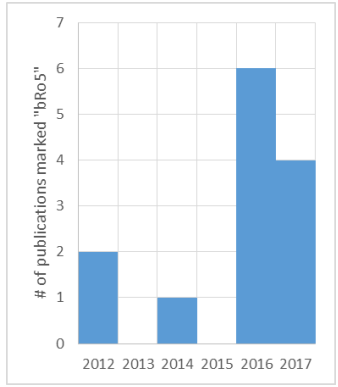
Risk for poor absorption if two or more of the below rules are violated

- # of hydrogen bond donors < 5
- # of hydrogen bond acceptors < 10
- clogP < 5
- MW < 500

(Adv.Drug.Del.Rev. **23** (1997) 3; Based on analysis of >2000 oral drugs that reached at least phase II)

Big influence on drug design since then

Today increasing interest in 'beyond rule of 5' space (bRo5)



eg, DeGoey et al, Journal of Medicinal Chemistry (2017)
Matsson et al. Advanced Drug Delivery Reviews (2016)

In silico ADME examples – Absorption

Many QSAR models for human intestinal absorption (HIA) in literature, eg:

Palm et al Pharm Res 1997 (20 cmpds), showed importance of polar surface area (PSA)

Clark et al J.Pharm.Sci.1999 (PSA<140Å^2; 3 literature datasets, 74 cmpds)

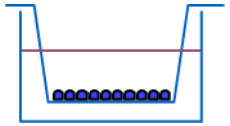
Zhao et al, J.Pharm.Sci. 2001 (training set 38 cmpds, test set 131 cmpds, used Abraham's general solvation equation; RMSEP=14)

Moda et al, Bioorg.&Med.Chem.Lett. 2012 (training set 510 cmpds, test set 128 cmpds, 'HologramQSAR', R^2_{pred} = 0.8)

…

In silico ADME examples – Permeability

in vitro data - P_{app}



Using specific cell lines (eg Caco 2) or artificial membranes (eg PAMPA)
Many QSAR models in literature (often on smaller datasets)
Important descriptors: lipophilicity, hydrogen bonding, size (PSA, HB, MW, logD, …)

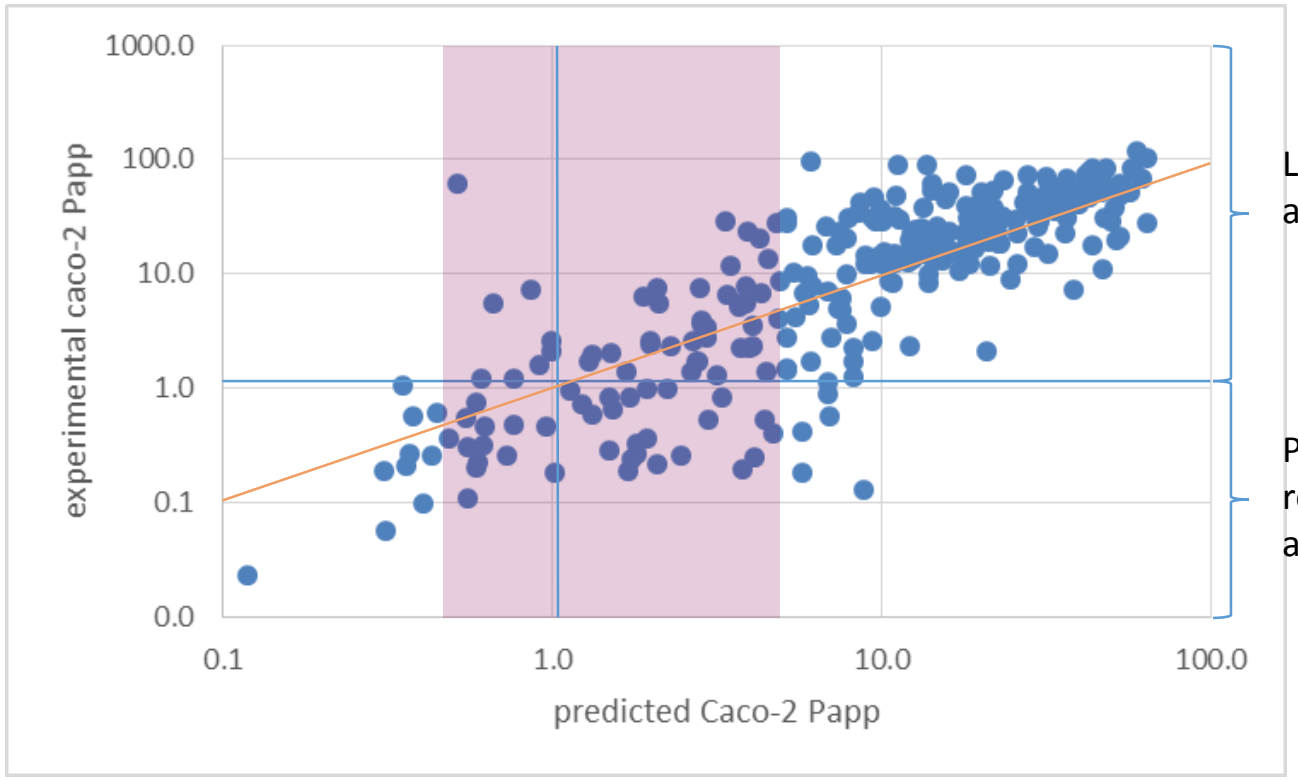
Many ways to correlate logD, MW (and HB), see eg:

- Camenisch et al, Eur.J.Pharm.Sci. 1998
  - log Perm = a*log D – a*log(1+β*D)+ b, MW to be considered additionally
  - based on 30 cmpds
- Farrel, DMD 2012
  - permeability correlated to logD and MW, using a quadratic function
- Waring, Bioorg.Med.Chem.Lett. 2009
  - analysed >9500 internal cmpds with regard to clogD, HBD and MW
  - combinations define whether good permeability can be expected

In silico ADME examples – Permeability

Intrinsic Caco-2 permeability

Routinely used at AstraZeneca, data set increasing by about 100 datapoints per month

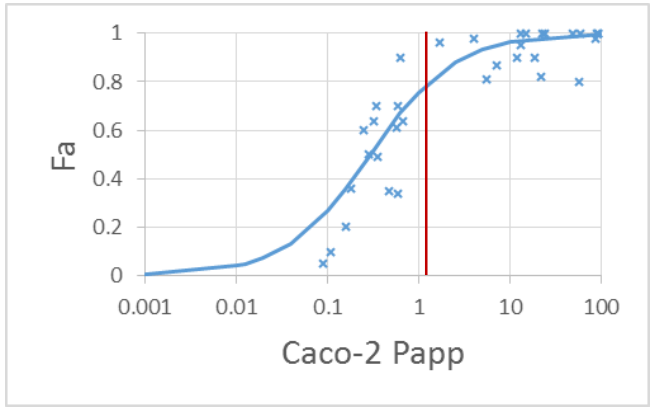


Likely good absorption

Potentially restricted absorption

Training set: n>2500
Test set: n=280

R^2=0.68
RMSE=0.45



In Vitro Intrinsic Permeability: A Transporter-Independent Measure of Caco-2 Cell Permeability in Drug Design and Development, Fredlund et al. Mol. Pharmaceutics 2017, 14, 1601−1609

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In silico ADME examples – BBB-distribution

BBB-distribution
brain-plasma ratio (K_p; log K_p = logBB)

lipophilicity important

simple rules: PSA<60-70 enables brain penetration (Kelder et al. Pharm.Res. 1999, 16, 1514)

N+O<5 → drug has good chance to enter brain
logP-(N+O) positive → logBB positive (Norinder et al. Adv.Drug Del.Rev., 2002, 54, 291)

BUT: free concentration in brain determines whether a compound can be active in brain

→ free brain-plasma ratio ($K_{p,uu,brain}$)

lipophilicity not important, transporter interactions determine (hydrogen bonding)

In silico ADME examples – BBB-distribution

Free brain plasma ratio models – $K_{p,uu,brain}$

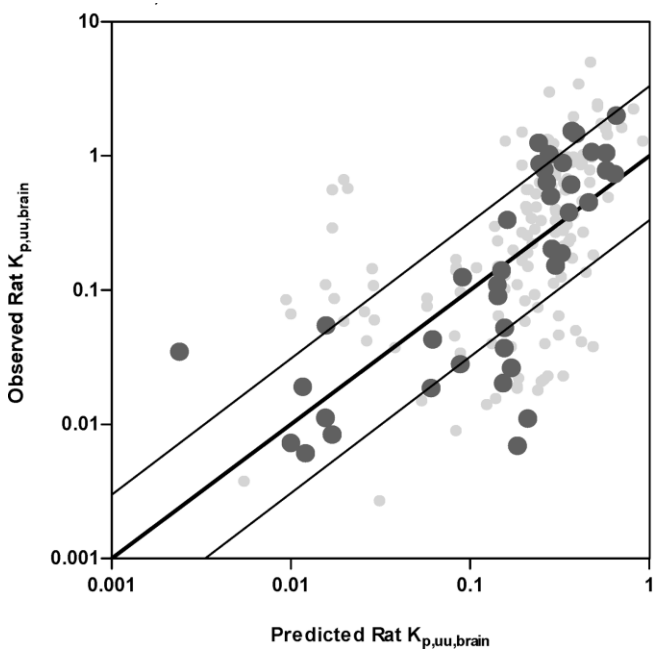
Experimental info: 3 measurements required: in vivo brain-plasma ratio (here from an infusion study in rats); in vitro plasma protein binding; in vitro brain tissue binding (here brain slice technique)

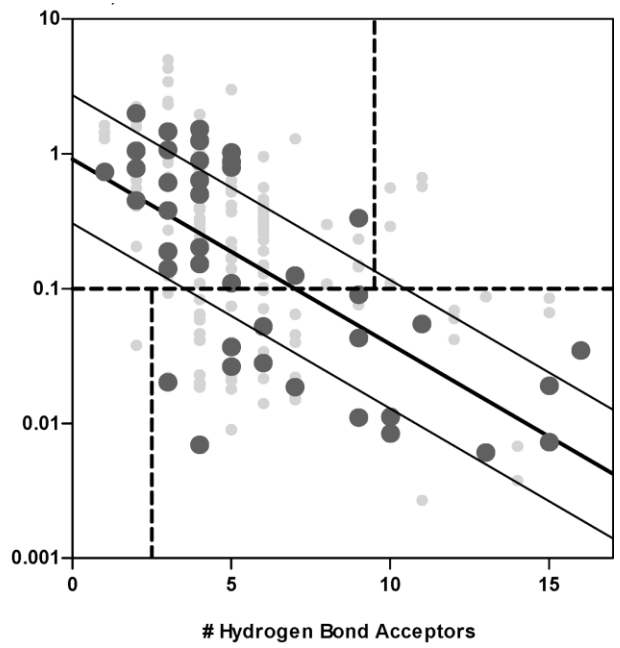
First $K_{p,uu,brain}$ model: Fridén et al J. Med. Chem. 2009, 52, 6233

41 cmpds, RMSE(x-fold): 3.48;
PSA and HBA important;

external test set (~70 literature cmpds)
RMSE(x-fold):3.99;

HBA useful as simple rule of thumb

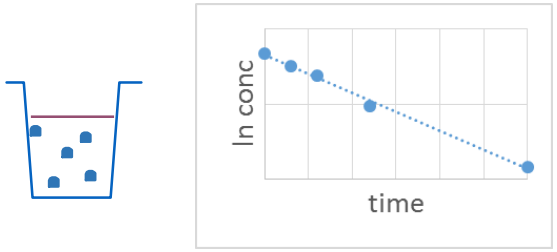




S.Winiwarter, in silico ADME (Sept 2017)

In silico ADME examples – Metabolism

Metabolic stability



CLint = -slope/cell(protein)conc

In vitro measurements:

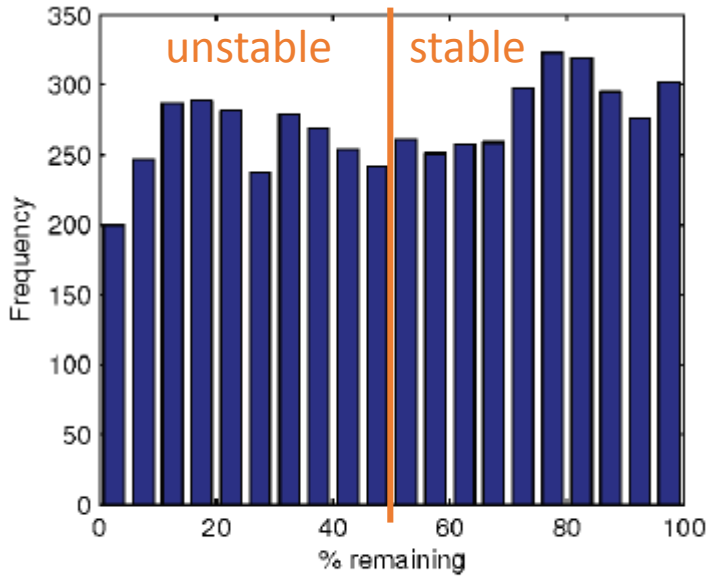
liver microsome or hepatocytes incubations

Various metabolising enzymes contribute depending on compound structure (CYP family, UGT family, …)

Lipophilicity important, but structural features to be considered

In silico ADME examples – metabolic stability

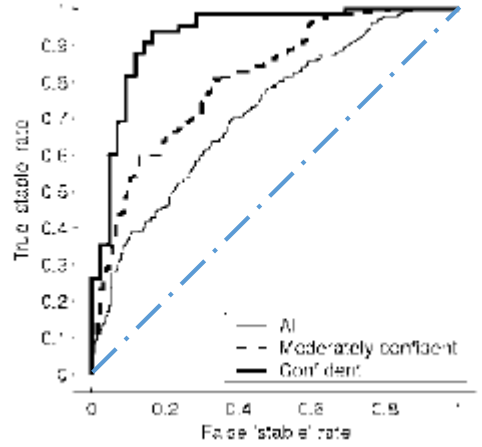
A Probabilistic Approach to Classifying Metabolic Stability
Schwaighofer et al. J. Chem. Inf. Model. **48** (2008) 785



(a) Histogram of experimental values for training data

Data possibly ok for regression, but classification deemed more appropriate for intended usage

Probabilistic approach gives 'probability of being stable'



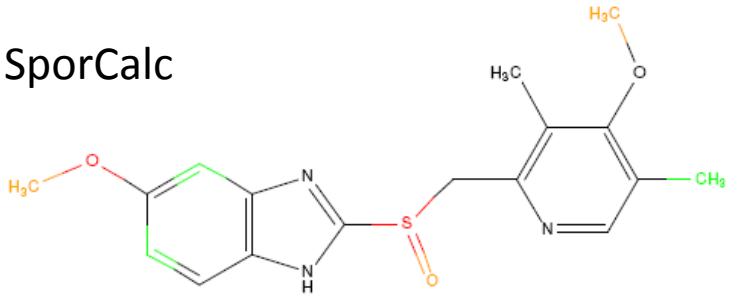
Test data	all data	moderately confident		confident		
assay	AUC	% of data	AUC	% of data	AUC	n
human	71.8	50.7%	80.7	17.0%	92.8	631
mouse female	69.0	59.5%	80.6	18.7%	95.0	326
mouse male	83.5	55.2%	93.7	21.3%	100.0	183
rat male	76.4	37.5%	93.8	15.9%	92.7	264

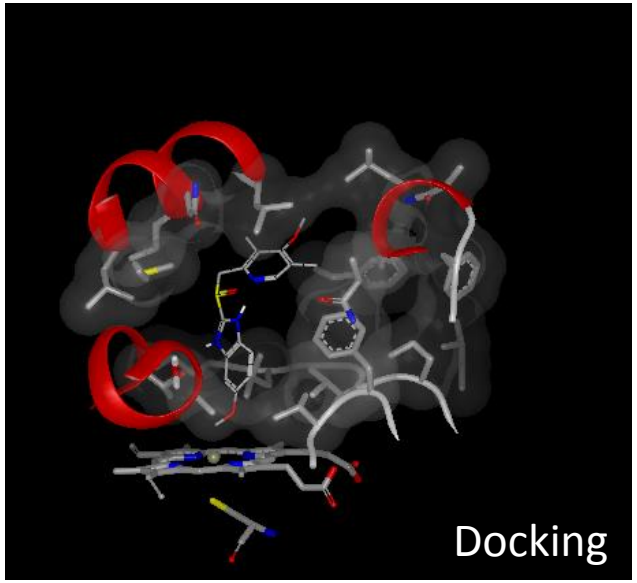
moderately confident: predicted to be stable with probability <35% (unstable) or > 65% (stable)
confident: predicted to be stable with probability <20% (unstable) or > 80% (stable)

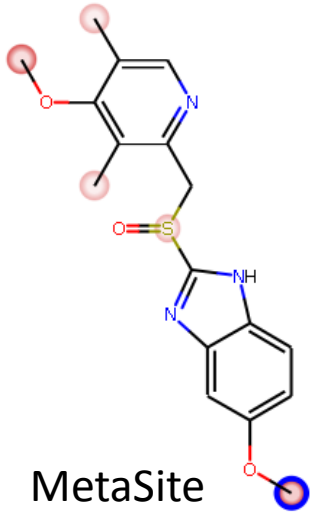
In silico ADME examples – Site of Metabolism (SOM)

Example omeprazole

SporCalc

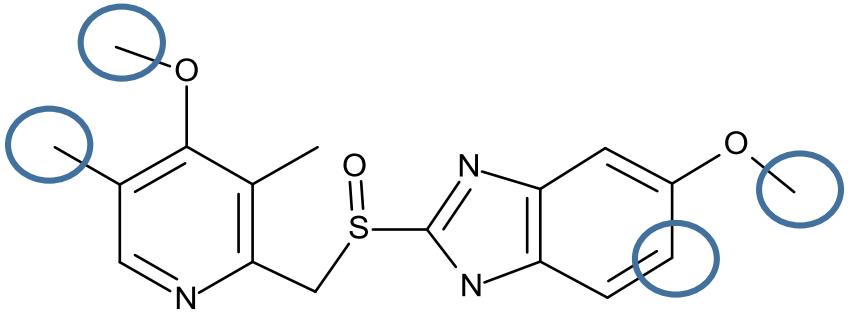






MetaSite

Experimental sites of metabolism:



Hoffmann, K.-J.; Drug Metab Dispos, 1986, 14, 341.

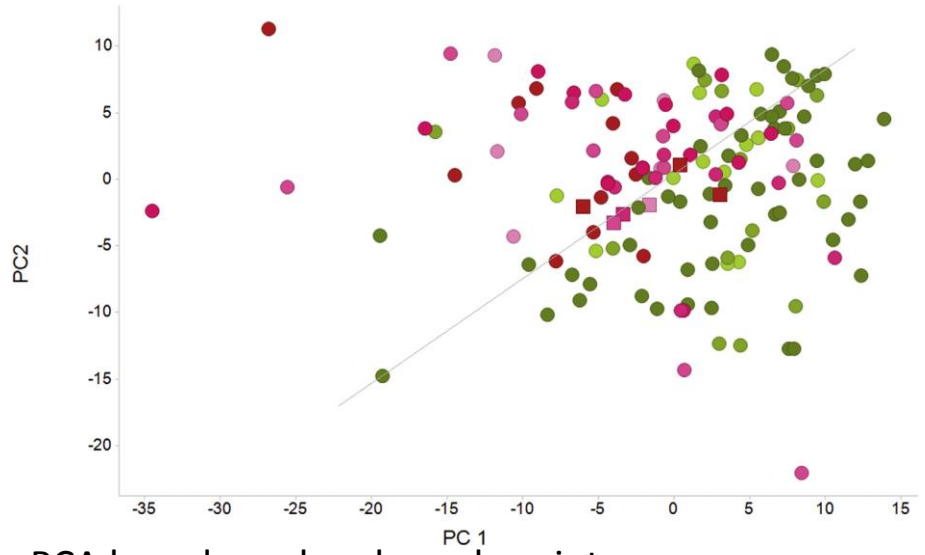
Review on SOM prediction tools: Afzelius et al, DMD, 2007, 39, 61.

In silico ADME examples – OATP1B1 inhibition

Combination model approach

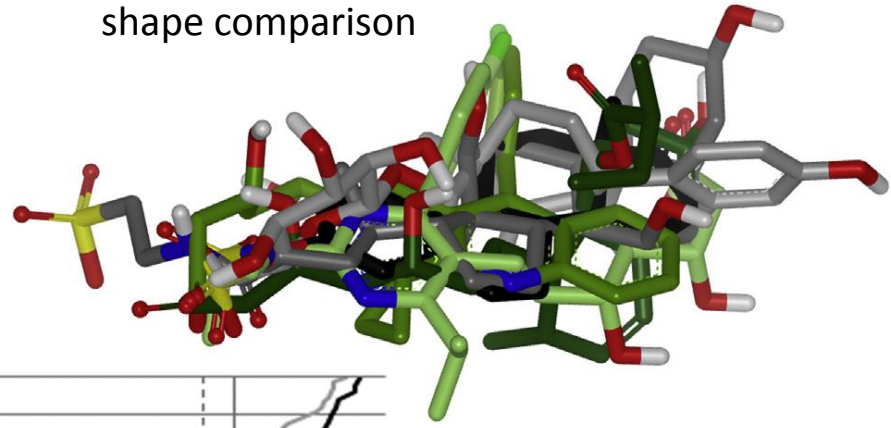
Modeling Organic Anion-Transporting Polypeptide 1B1 Inhibition to Elucidate Interaction Risks in Early Drug Design

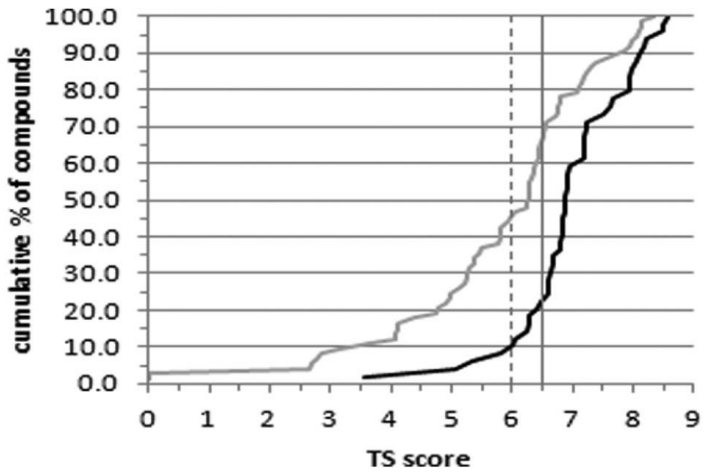
Zamora & Winiwarter, J. Pharm. Sci. **105** (2016) 3214



PCA based on physchem descriptors
separation between active (red) and inactive (green) seen
(exp data from Karlgren et al Pharm Res. 2012;29:411-426)

Superposition of 6 known OATP1B1 inhibitors used for shape comparison





Transportophor similarity score

In silico ADME examples – Aqueous Solubility

Highly correlated with lipophilicity, but solid phase properties important (and less easy to predict)

Solubility Challenge: Can You Predict Solubilities of 32 Compounds Using a Database of 100 Measurements?
Llinas et al. JCIM **48** (2008) 1289

Findings of the Challenge to Predict Aqueous Solubility
Hopfinger et al. JCIM **49** (2009) 1

99 full entries scored,
some compounds well predicted by most methods, others not

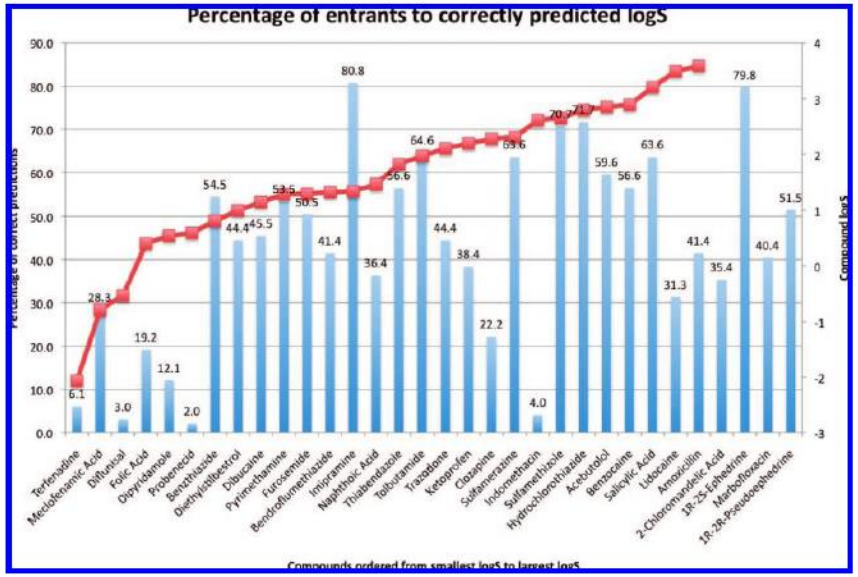
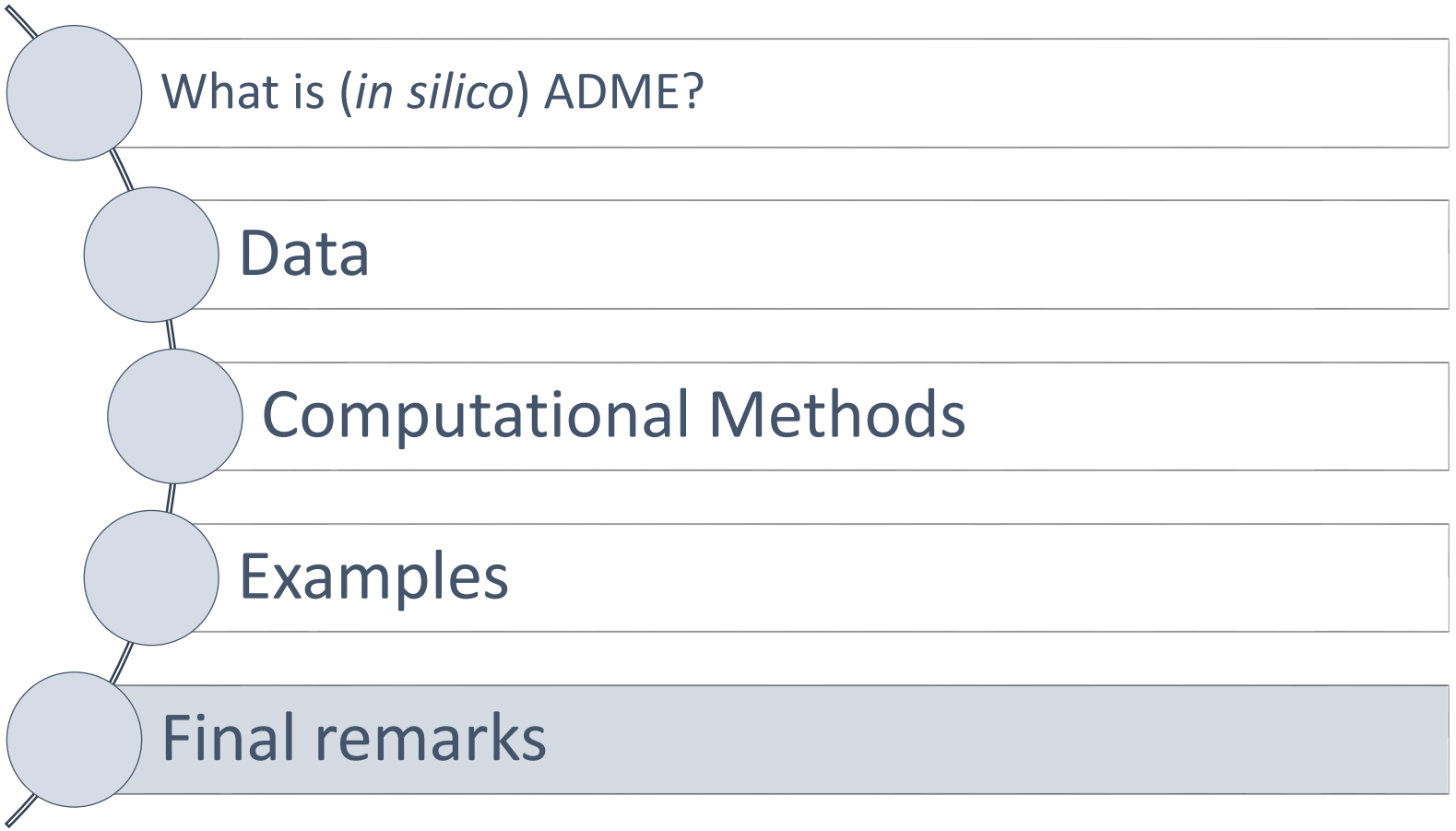


Figure 2. The histogram plot of the prediction set compounds ranked with respect to their measured solubilities, given by the red curve, versus the percent of correct predictions, where correct is defined as being less than ±0.5logS from the measured value. LogS values are not given for the final four compounds on the right as they are too soluble to measure. The definition for a correct prediction of a too soluble to measure compound is given in the text.

Outline


What is (*in silico*) ADME?
Data
Computational Methods
Examples
Final remarks

In silico ADME – utility and caution

In silico ADME is an established tool in drug discovery

Many ways to predict ADME parameters have been published and are being used

Quality and usefulness differs due to

- Quality of data
  - (biological data may have inherent variability)
- Relevance of data
  - (eg, brain-plasma ratio should be based on free conc)

→ Make sure you understand the data before you start to model

Literature

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Zamora & Winiwarter, J. Pharm. Sci. **105** (2016) 3214

Llinas et al. JCIM **48** (2008) 1289; Hopfinger et al. JCIM **49** (2009) 1