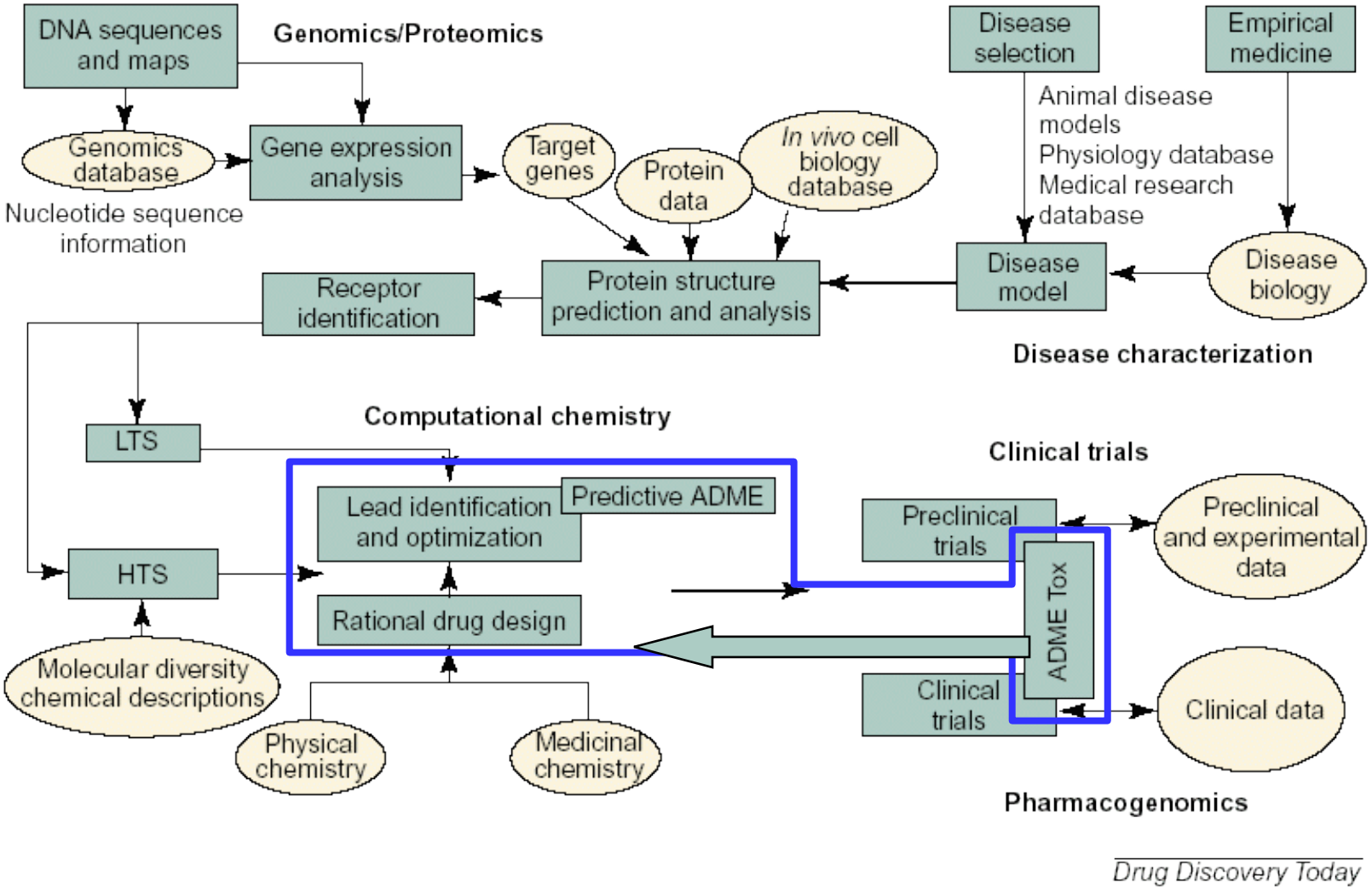
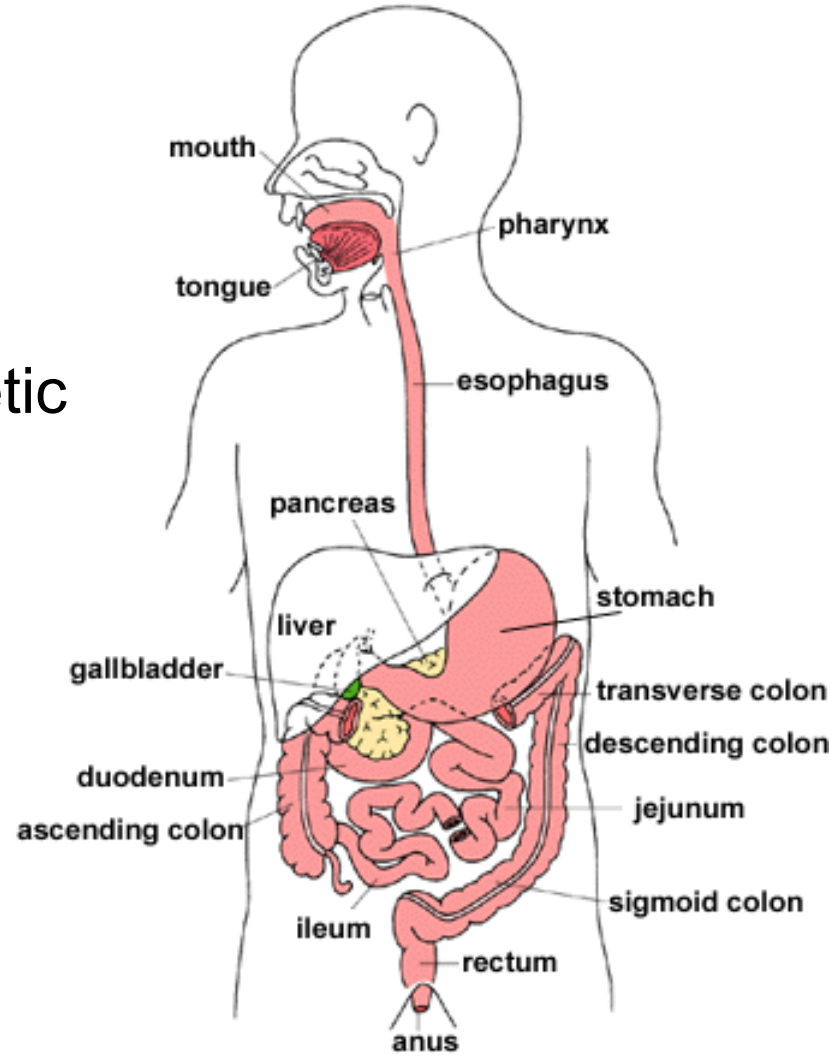
ADME models in the *drug discovery pipeline*



eADMET prediction

early
Absorption
Distribution
Metabolism
Elimination
Toxicology

} Pharmacokinetic
Bioavailability



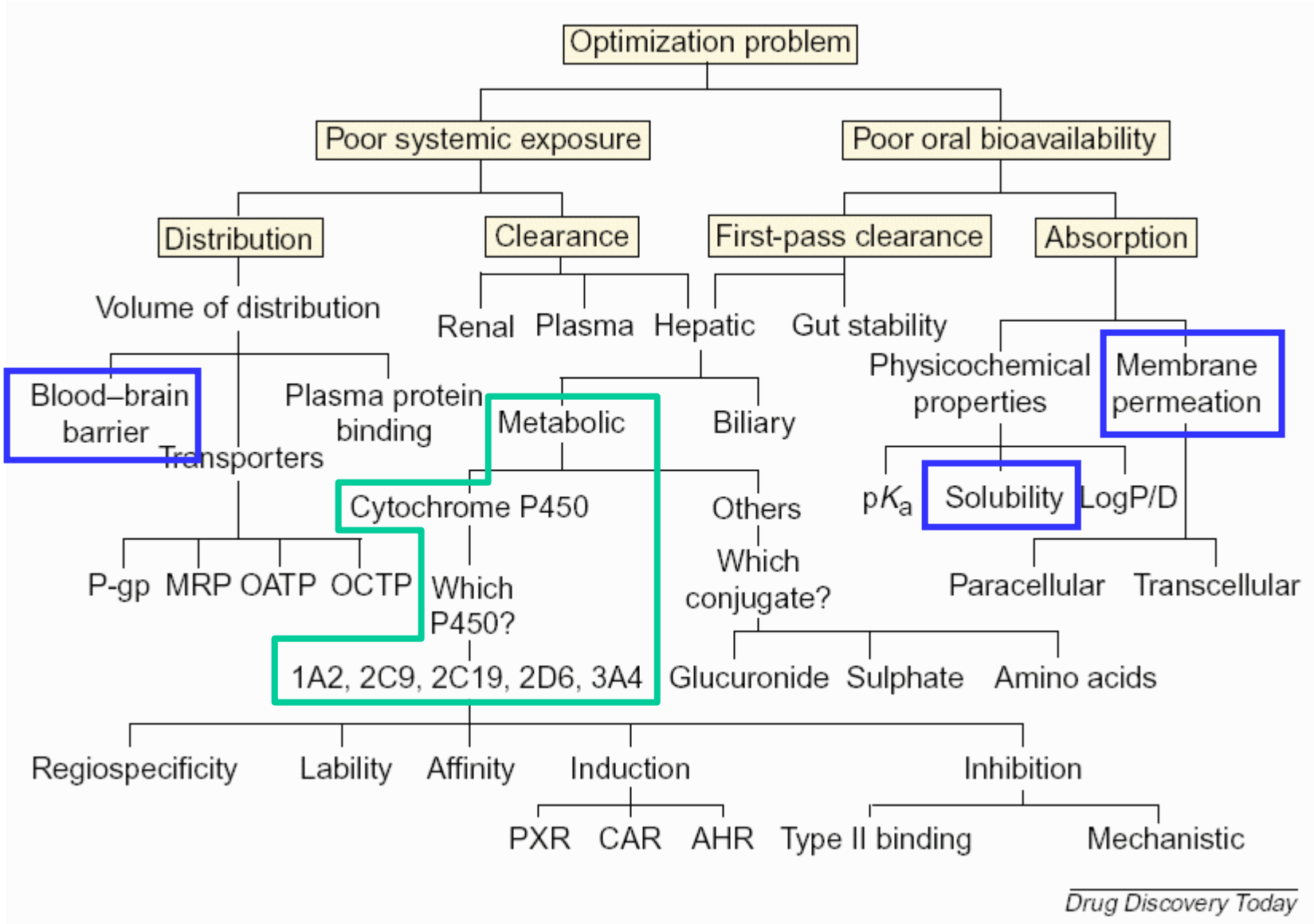
ADME models (I)

Following models are useful for *in silico* design:

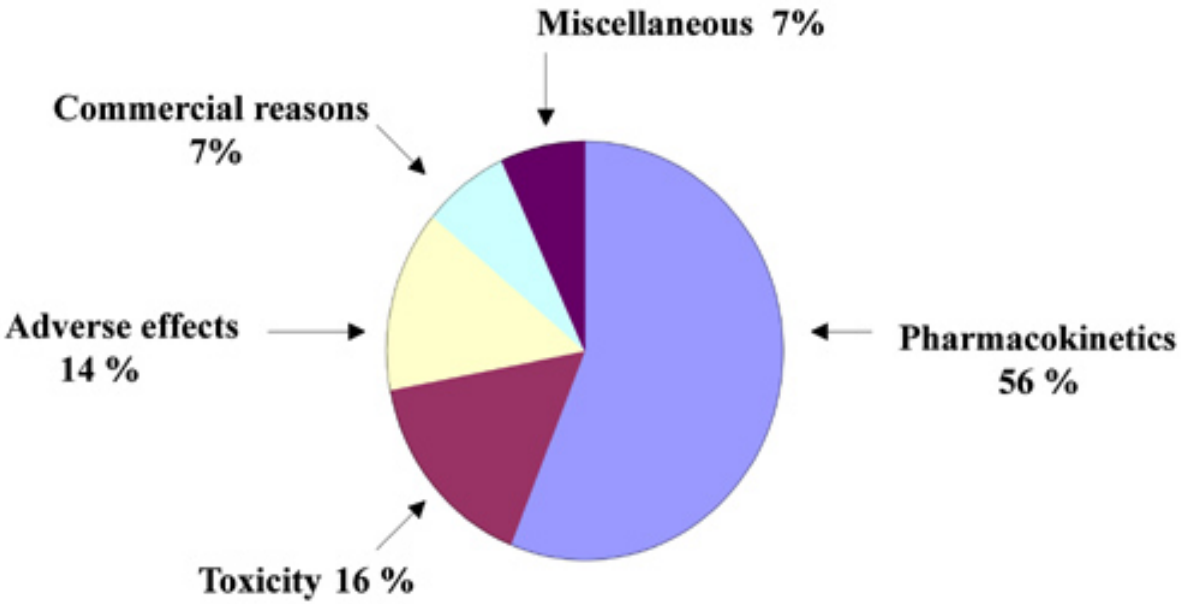
primary models	secondary models
solubility	transport (uptake and efflux)
intestinal absorption	common toxicity
bioavailability	hepatotoxicity (PXR, CAR)
metabolic stability	nephrotoxicity
blood-brain-barrier permeation	immunotoxicity
mutagenicity	neurotoxicity (receptor binding)
cardial toxicity (*h*ERG-channel)	drug-drug interactions (Cytochrome P450)
plasma protein binding	

Covered in this lecture and the upcomming lectures

ADME models (II)



Why is ADME prediction that important ?



Reasons that lead to failure or withdrawl of a potential drug around 1995 – 2000

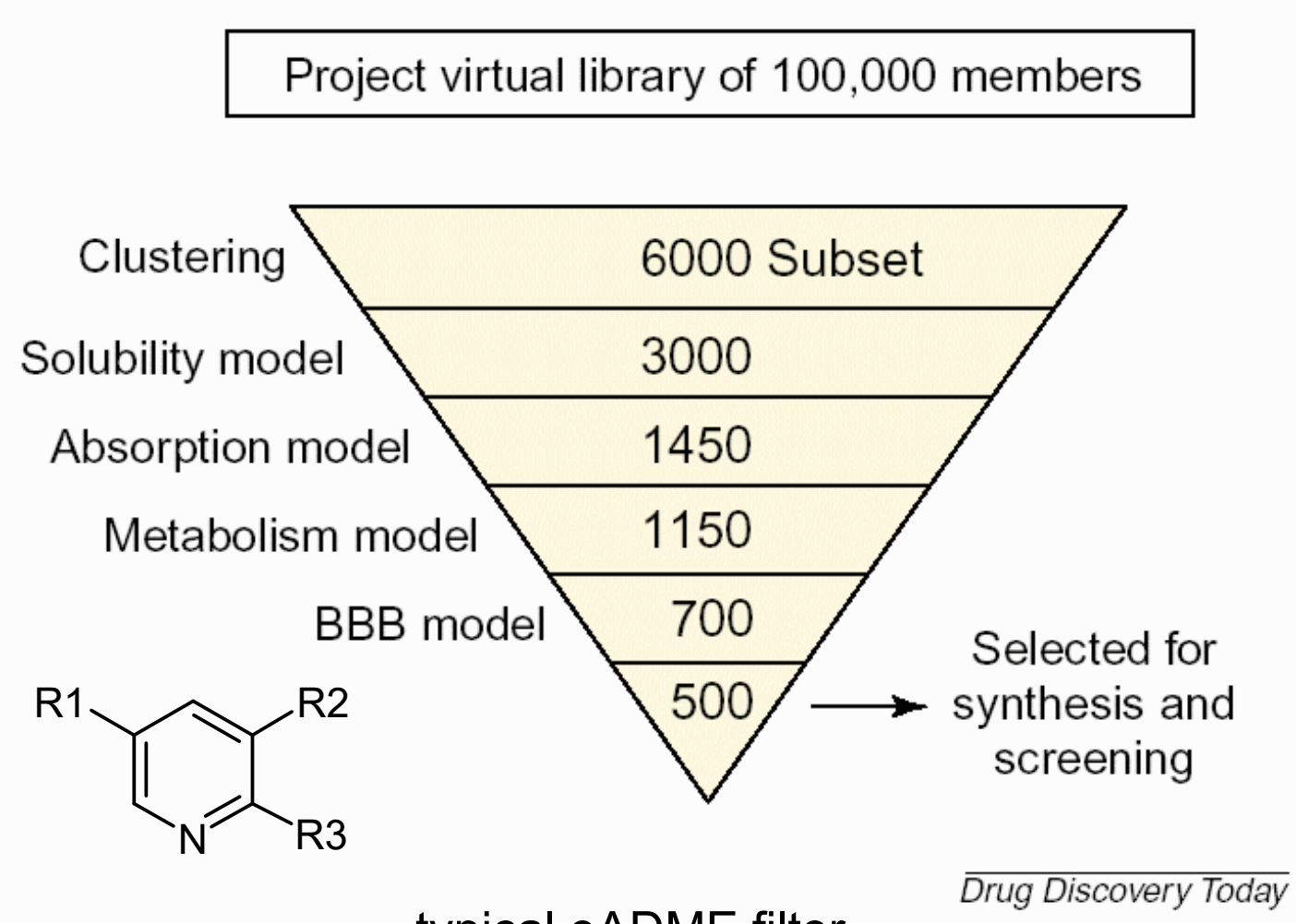
Why is ADME prediction that important ? (II)

Our aim is to reckognize unsuitable compounds as soon as possible:

- saving resources
- avoiding unnecessary clinical trials
- The later a drug has to be withdrawn, the more expensive it gets.

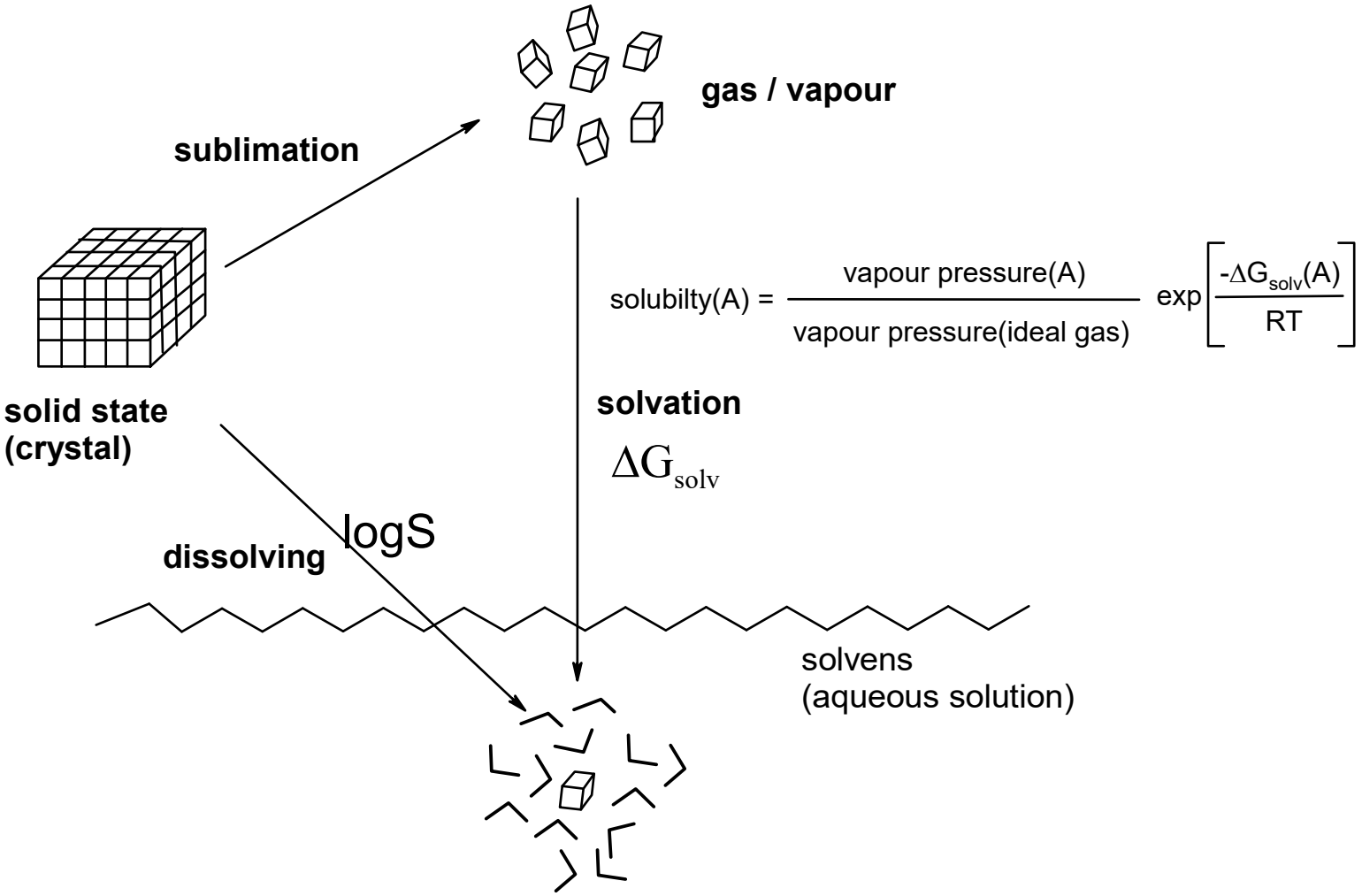
„Fail early, fail fast, fail cheap“

Compound selection for the High Throughput Screening (HTS)



typical eADME filter

solvation versus solubility



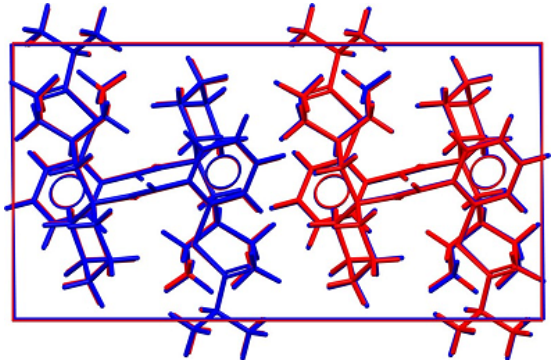
Solubility models (I)

Direct computation of the solubility from a thermodynamic cycle (lattice energy, heat of solvation) is possible, but

1. The prediction of the lattice energy by computational methods requires knowing the space group of the crystal
2. Computation of the heat of solvation is errorprone itself

Thus, mainly QSAR approaches are applied.

However, automated workflows that derive specifically tailored force fields for the molecule at hand exist, although these are computationally very demanding.

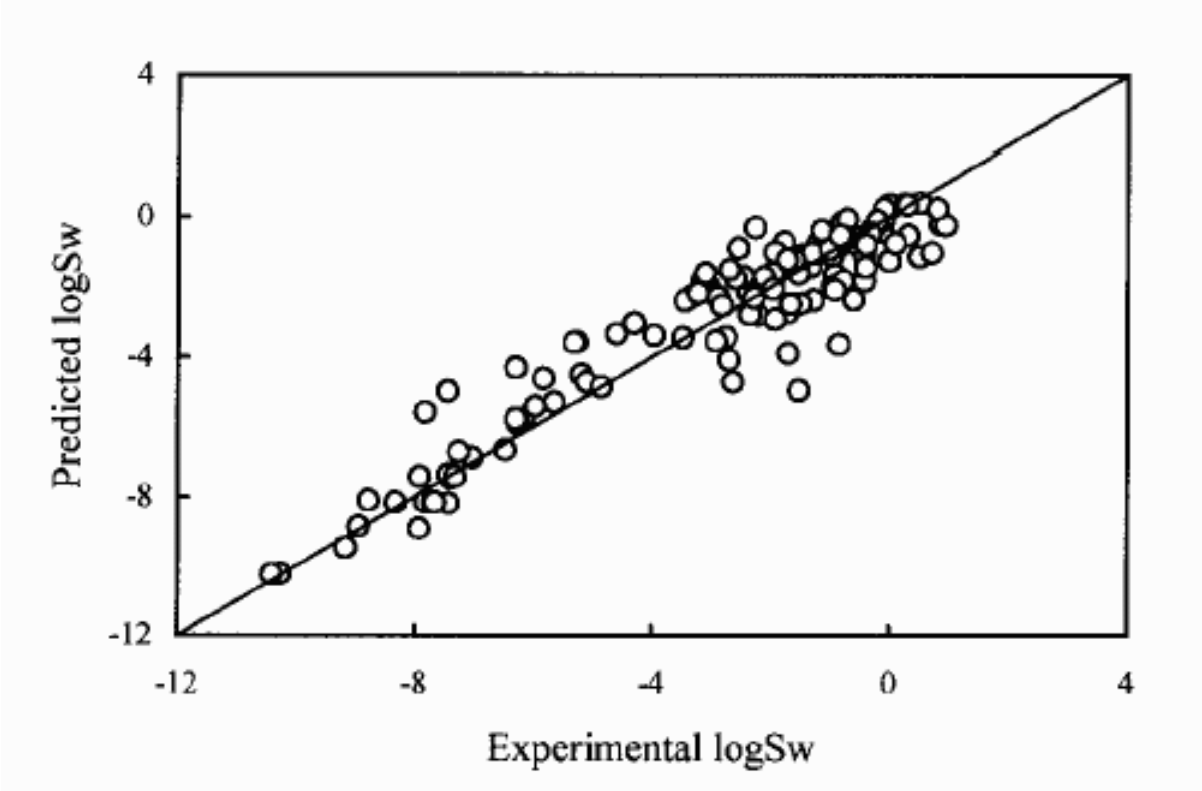


Lit: Neumann MA et al. *Nat. Commun* **6** (2015) 7793.

Reilly et al. *Acta Cryst. B* **72** Pt4 (2016) 439-459.

Solubility models (II)

descriptors: connectivity indices



r^2=0.89, q^2= 0.84, se = 0.98, n=120, F=297.80

Lit. C. Zhong et al. *J.Pharm.Sci.* **92** (2003) 2284

Solubility models (III)

Further approaches show that the applied descriptors must account for lipophilic and H-bond properties, as well as the flexibility of the compounds

Lit: A. Cheng et al. *J.Med.Chem.* **46** (2003) 3572

D. Butina et al. *J.Chem.Inf.Comput.Sci.* **43** (2003) 837

Besides common QSAR equations, also machine learning approaches are used:

Lit: A. Yan et al. *J.Chem.Inf.Comput.Sci.* **43** (2003) 429

J.K. Wegener et al. *Ibid* **43** (2003) 1077

Z. Ye, D. Ouyang *J.Cheminf.* **13** (2021) 98

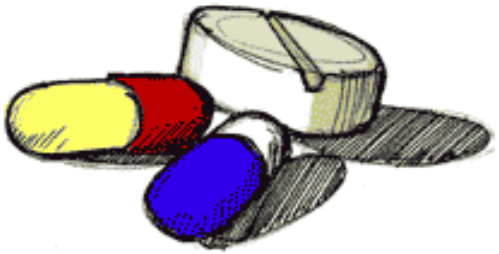
S. Lee et al. *ACS Omega* **7** (2022) 12268

Predicting the solubility of a compound in various solvents and solvent mixtures is likewise an issue for chemical synthesis.

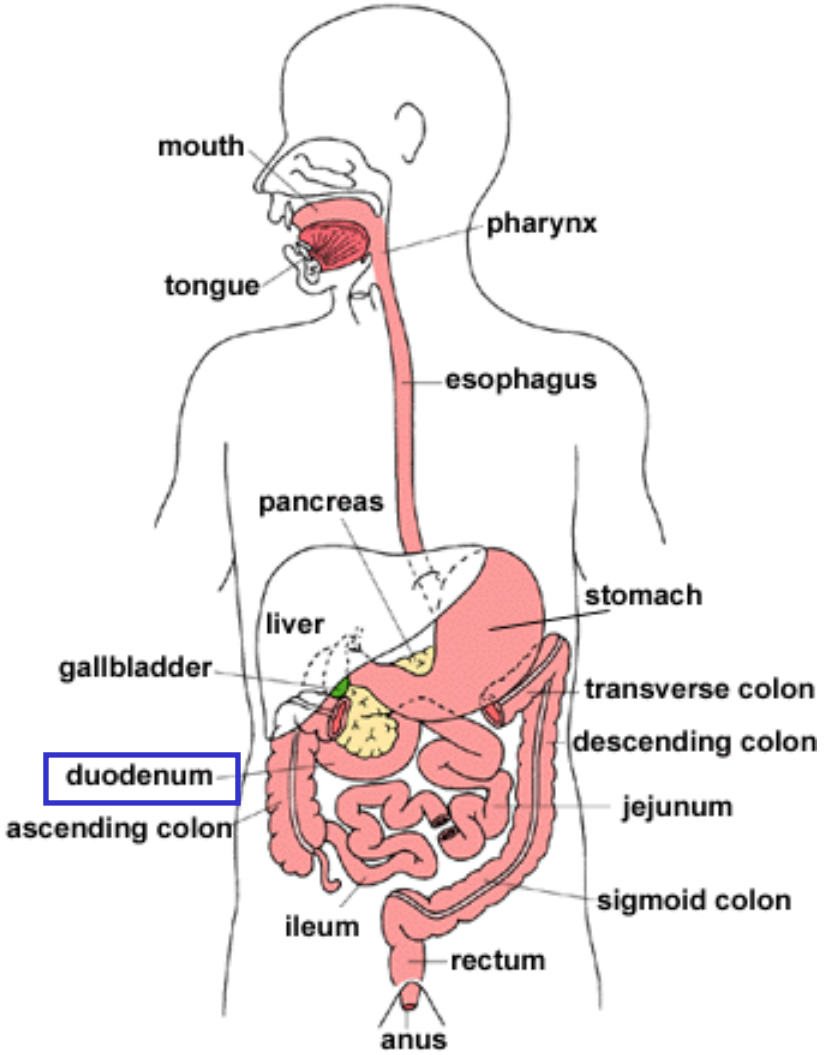
Absorption

How much and how fast is a substance absorbed?

Drugs should be orally applicable for convenience

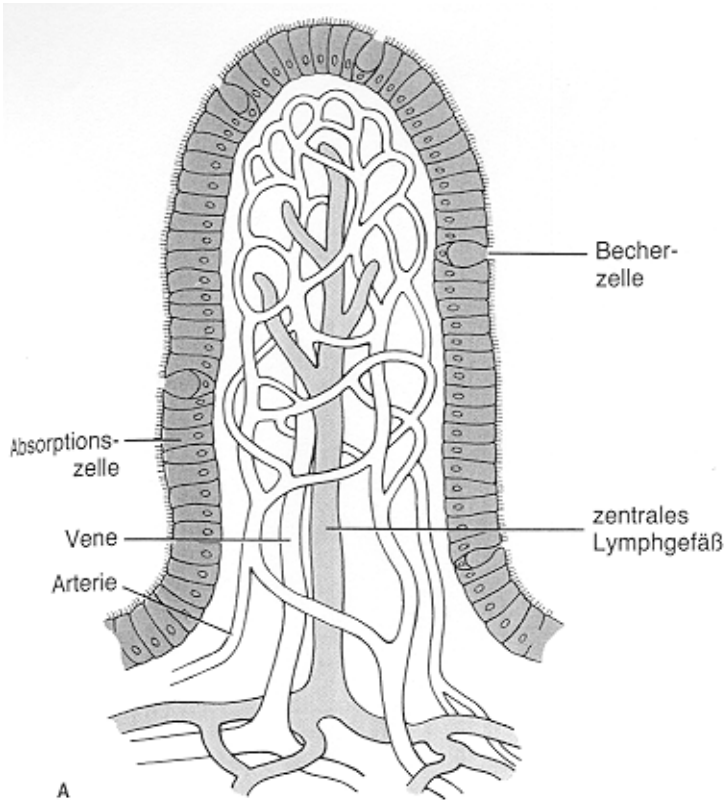


After passing the stomach, they are resorbed from the colon/intestine into the blood. Transport via the portal vein into the liver.

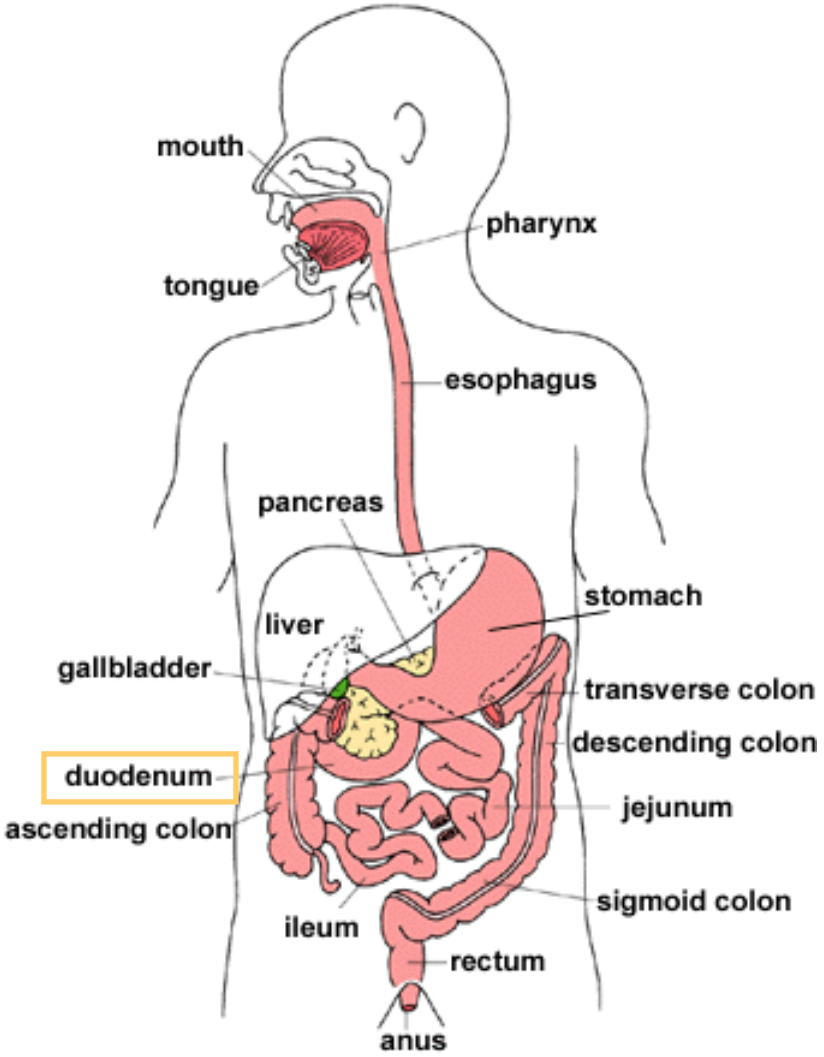


Absorption in the duodenum (I)

Uptake of a substance into the systemic circulation

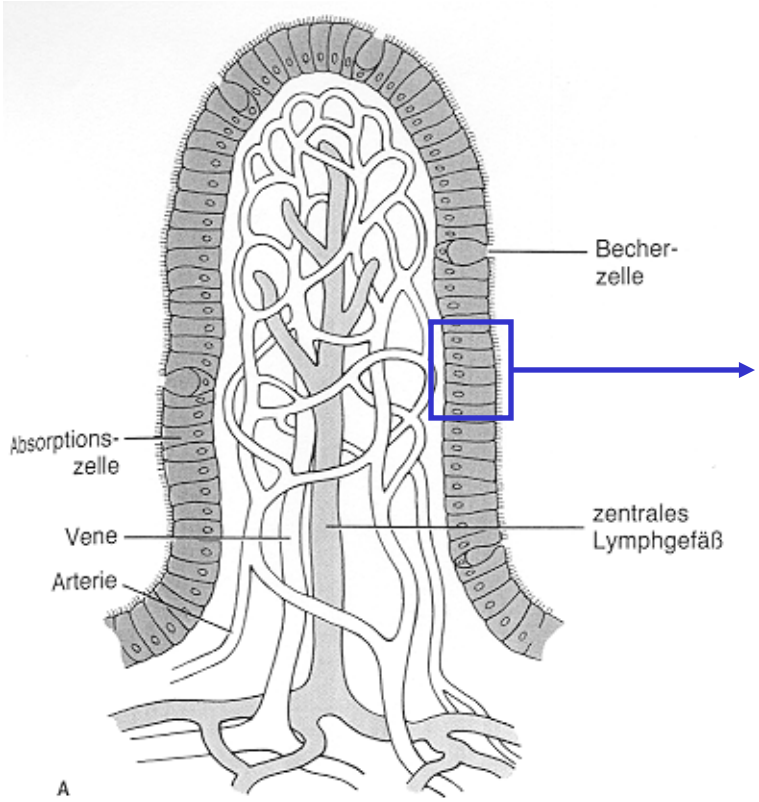


Cross-section from the colon wall

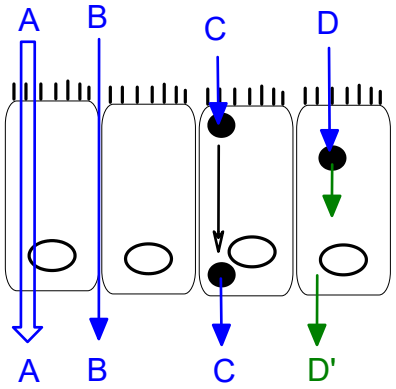


Absorption in the duodenum (II)

Uptake of a substance into the systemic circulation



Cross-section from the colon wall



A transcellular (passive diffusion)

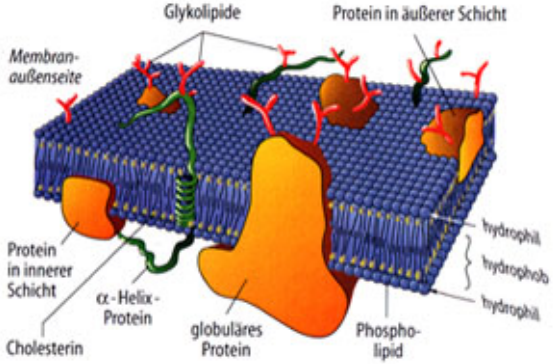
B paracellular

C active transport

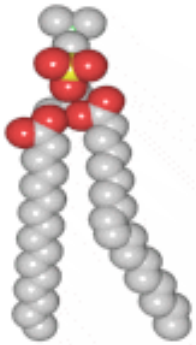
D transcytosis

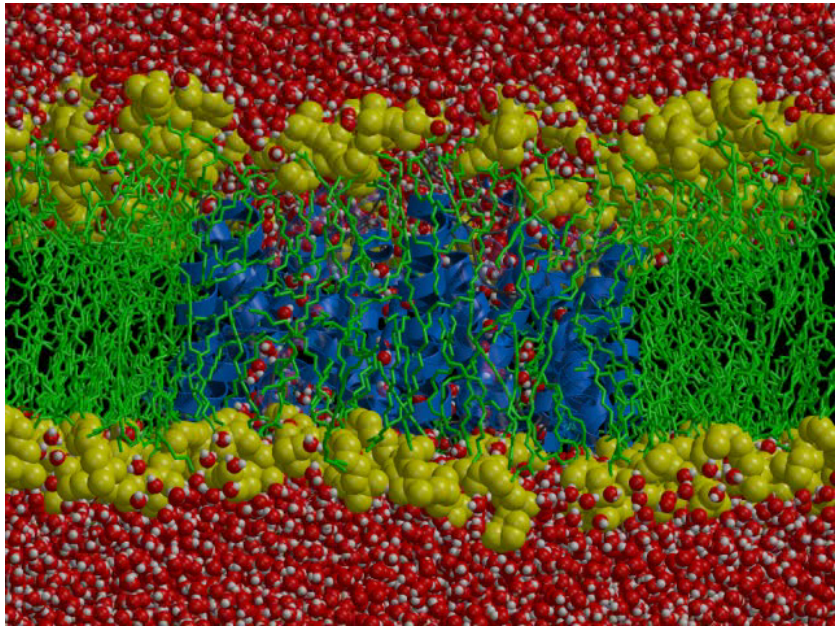
Absorption in the duodenum (III)

model of the cellular membrane



phospholipid



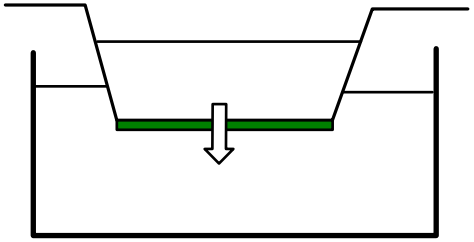


De Groot et al. *Science* **294** (2001) 2353

Caco-2 cell monolayer

Experimental approach for the prediction of intestinal absorption

monolayer of a culture of cells that are derived from a colon cancer



Advantage: reproducable results, in good agreement with *in vivo* studies

Disadvantage: these cells exhibit somewhat different metabolic properties than cells for the duodenum (MDR1 transporter = P-glycoprotein is over expressed, which leads to increased efflux of many substances)

Besides Caco-2 cells, also synthetic membranes are used for screening

What factors determine the passive diffusion through lipidbilayers ?

Small molecules should pass through faster than large

descriptor: molecular weight (MW) and molecular shape

phospholipid bilayers are lipophilic on the inside

Thus, lipophilic molecules should pass through the interior faster

descriptor: logP (water/*n*-octanol partition coefficient)

phospholipid bilayers have a hydrophilic surface

descriptors: number of H-bond donors and acceptors

observation: the permeability is related to the heat of solvation

Descriptors derived from molecules to predict ADME properties

Frequently occuring in QSAR equations and machine learning algorithms are:

logP water/*n*-octanol partition coefficient

number of violations of Lipinski‘s rule of five

topological indices (e.g. from fingerprints)

polar surface area

count of polar atoms (can form hydrogen-bonds)

count of titratable groups (acids, bases; will be charged at neutral pH)

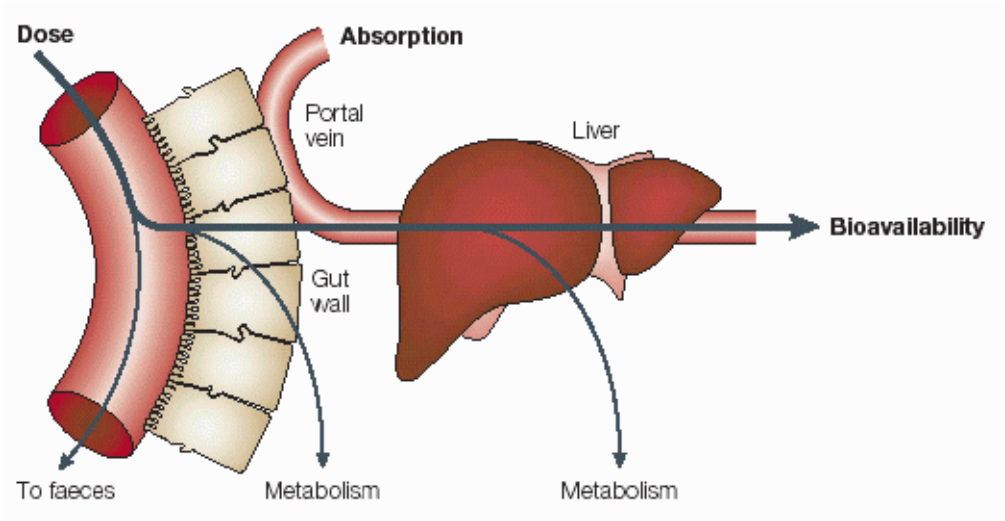
count of halogen atoms (lipophilic)

Lit: S. Lee et al. *ACS Omega* **7** (2022) 12268

Lipinski´s Rule of 5

Combination of descriptors to estimate intestinal absorption.
Insufficient uptake of compounds, if

Molecular weight > 500	slow diffusion
logP > 5.0	too lipophilic
> 5 H-bond donors (OH and NH)	too many H-bonds with the
>10 H-bond acceptors (N and O atoms)	head groups of the membrane

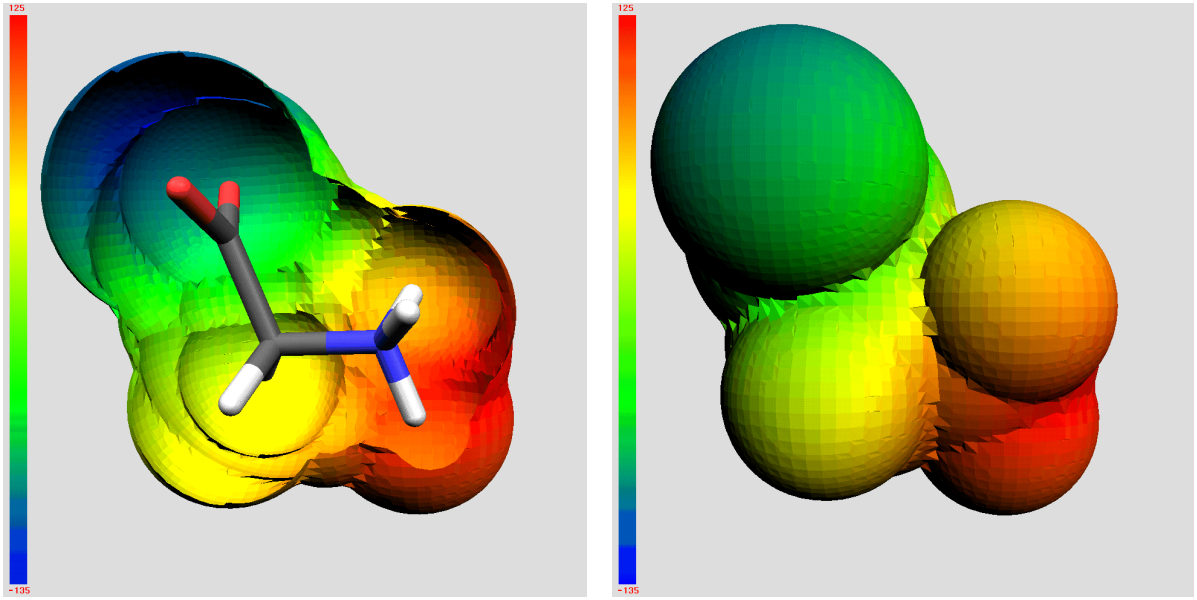


C.A. Lipinski et al. *Adv. Drug. Delivery Reviews* **23** (1997) 3.

Polar Surface Area (PSA)

The PSA is defined as the part of the molecular surface of a compound that stems from the nitrogen and oxygen atoms, as well as the polar hydrogens bonded to them.

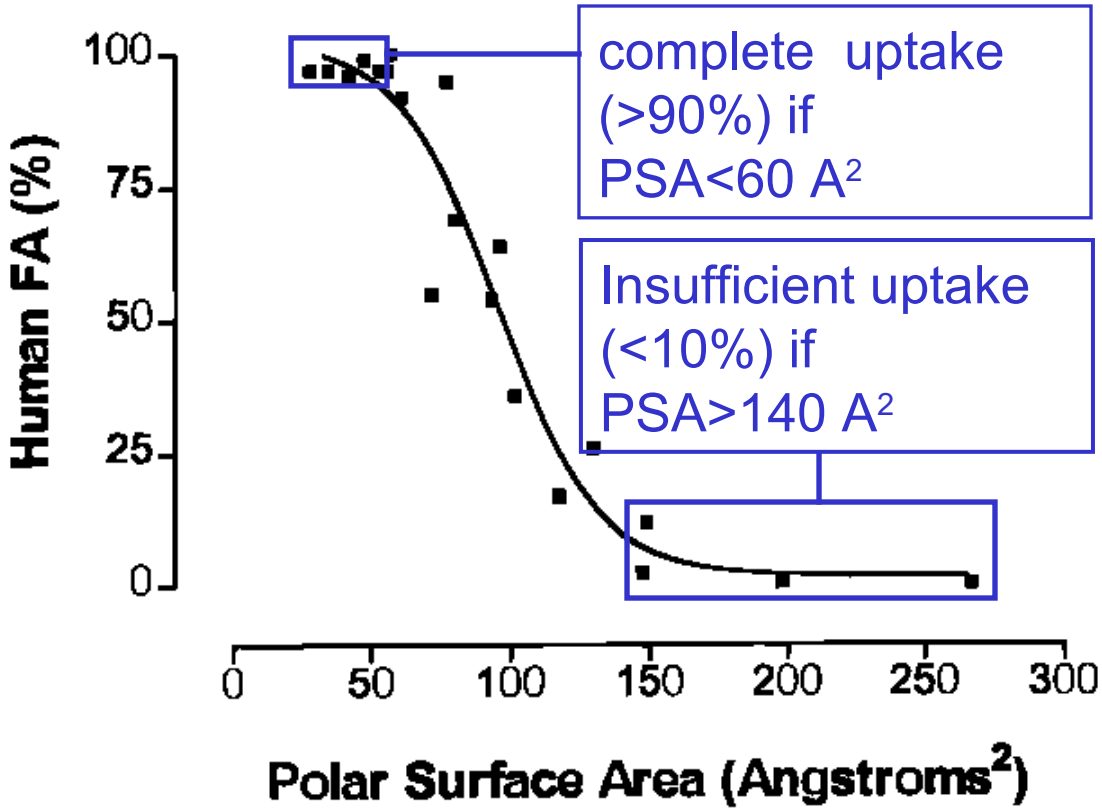
= a quantitative measure for the ability to form H-bonds



Like all other 3D descriptors the PSA is in general dependent from the conformation.

Models for absorption

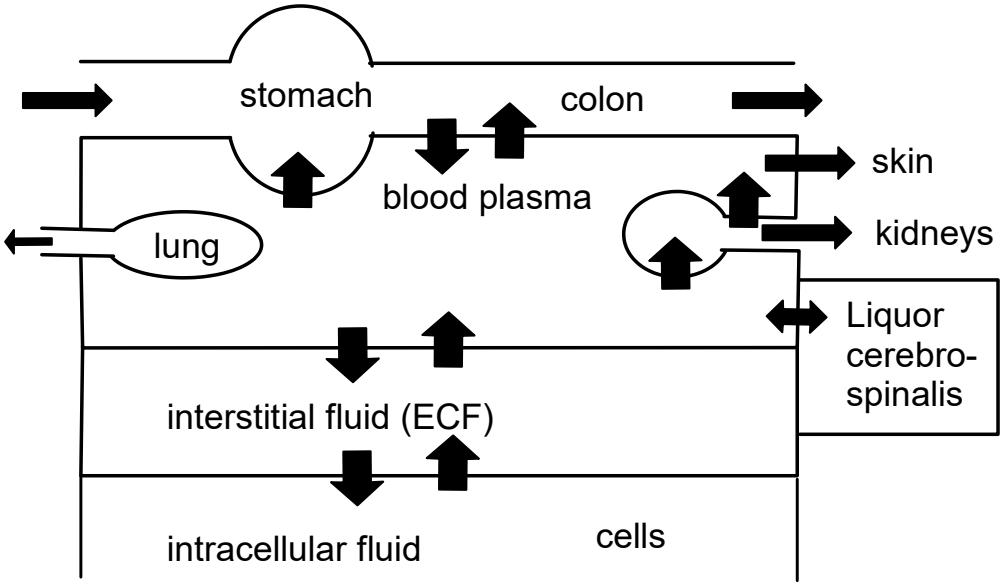
New studies show, however, that there is a sound correlation between Caco-2 absorption and uptake (fractional absorption) in human (%FA) regardless of possible conformers.



Lit: D.E. Clark, *J.Pharm.Sci.* **8** (1999) 807; *Drug Discovery Today* **5** (2000) 49; K. Palm et al. *J.Med.Chem.* **41** (1998) 5382

Pharmacokinetic and Bioavailability

The body/organism is regarded as an open system that tries to restore the equilibrium after each disturbance/dosage



The body is partitioned into a series of compartments. Between these compartments there is a constant flow / exchange.

distribution / invasion

The total path of a substance can be separated into

1) diffusion in the solvent
2) diffusion through tissue and membranes
3) transport by the blood
4) a) diffusion to the receptors
   b) diffusion into other compartments
   c) diffusion into elimination organs
5) irreversible elimination

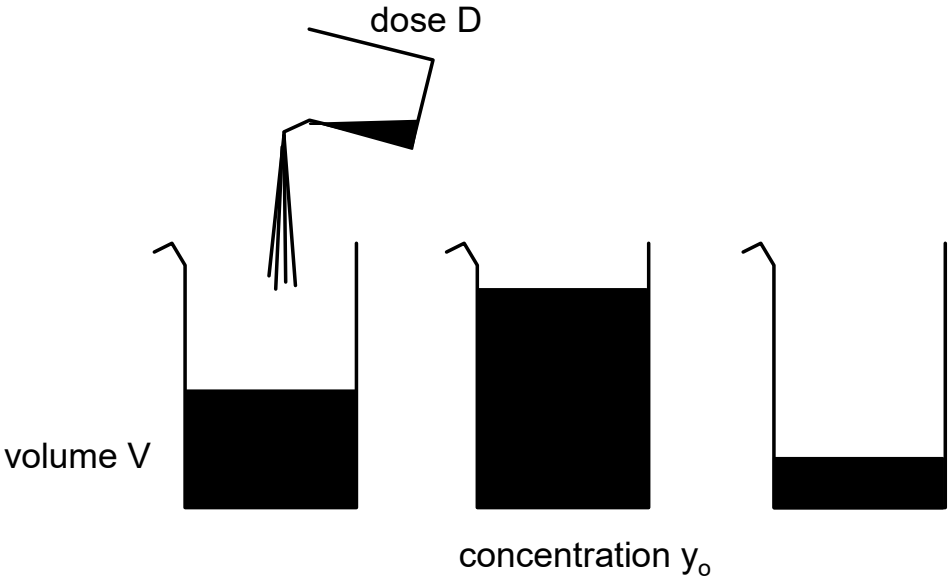
absorption

invasion (according to Dost) ≈ distribution

High constant of elimination: short period anesthetics

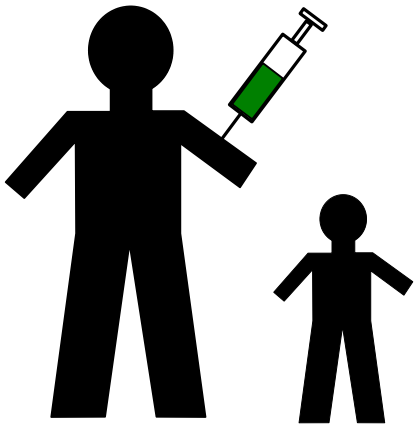
Low constant of elimination: antibiotics

Volume of distribution and dosage



$$y_0 = \frac{D}{V}$$

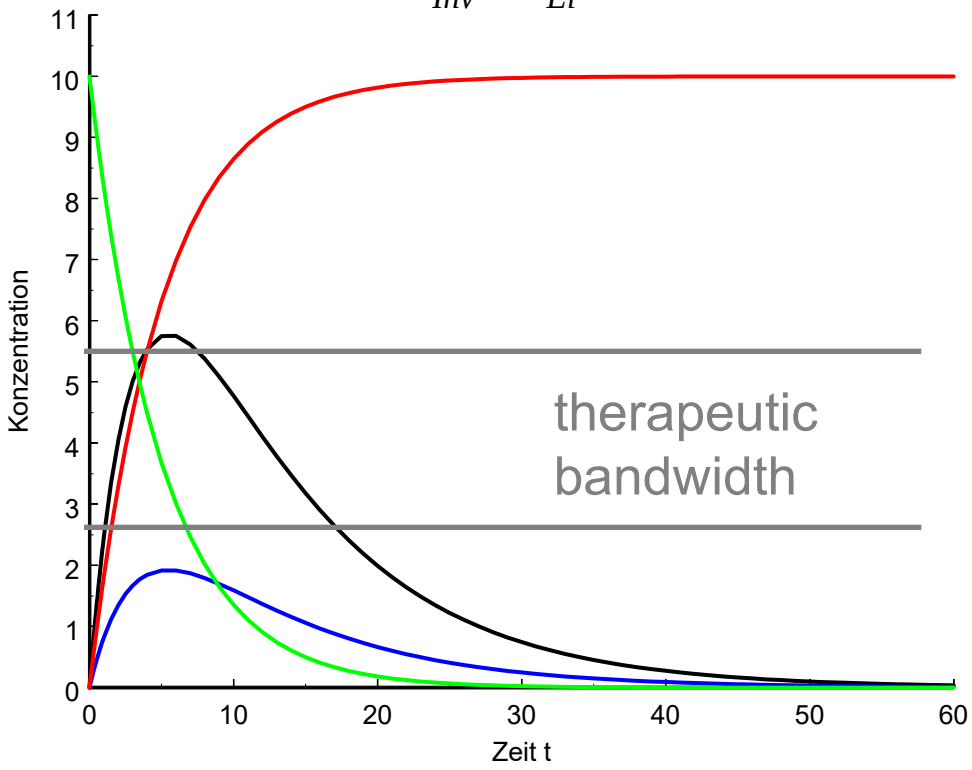
The dosage depends on the volume of distribution



Invasion / systemic exposure

The full concentration can only be achieved by intravenous application. Otherwise invasion and elimination interact. This correspond physico-chemically to subsequent reaction.

$$[A]_t = [A]_0 \frac{k_{Inv}}{k_{Inv} - k_{El}} \left(e^{-k_{El} t} - e^{-k_{Inv} t} \right)$$ Bateman function



only invasion

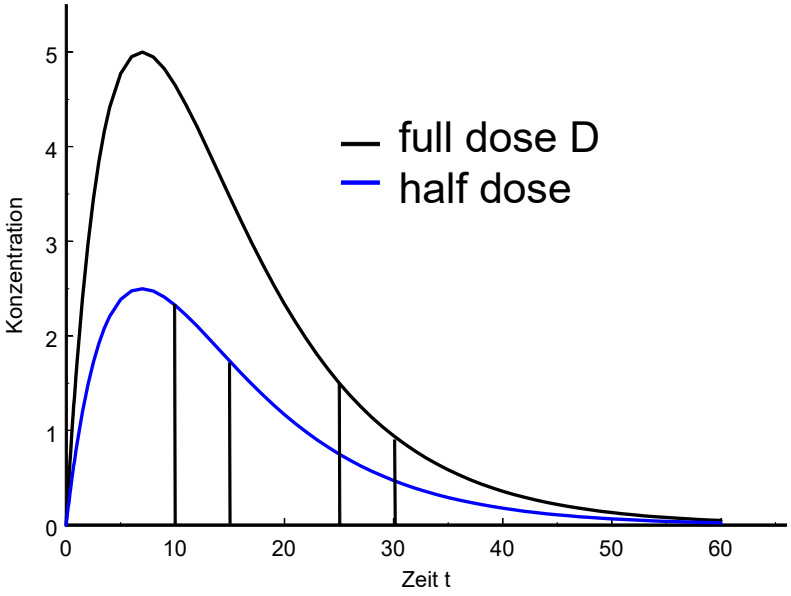
only elimination

fast invasion

slow elimination

The principle of Dost (I)

Dependence of the concentration profile for different dosage



Between two sample points, the area S (transit) below the curve can be obtained by integration of the Bateman function as:

$$S = \frac{D}{Cl_{tot}}$$

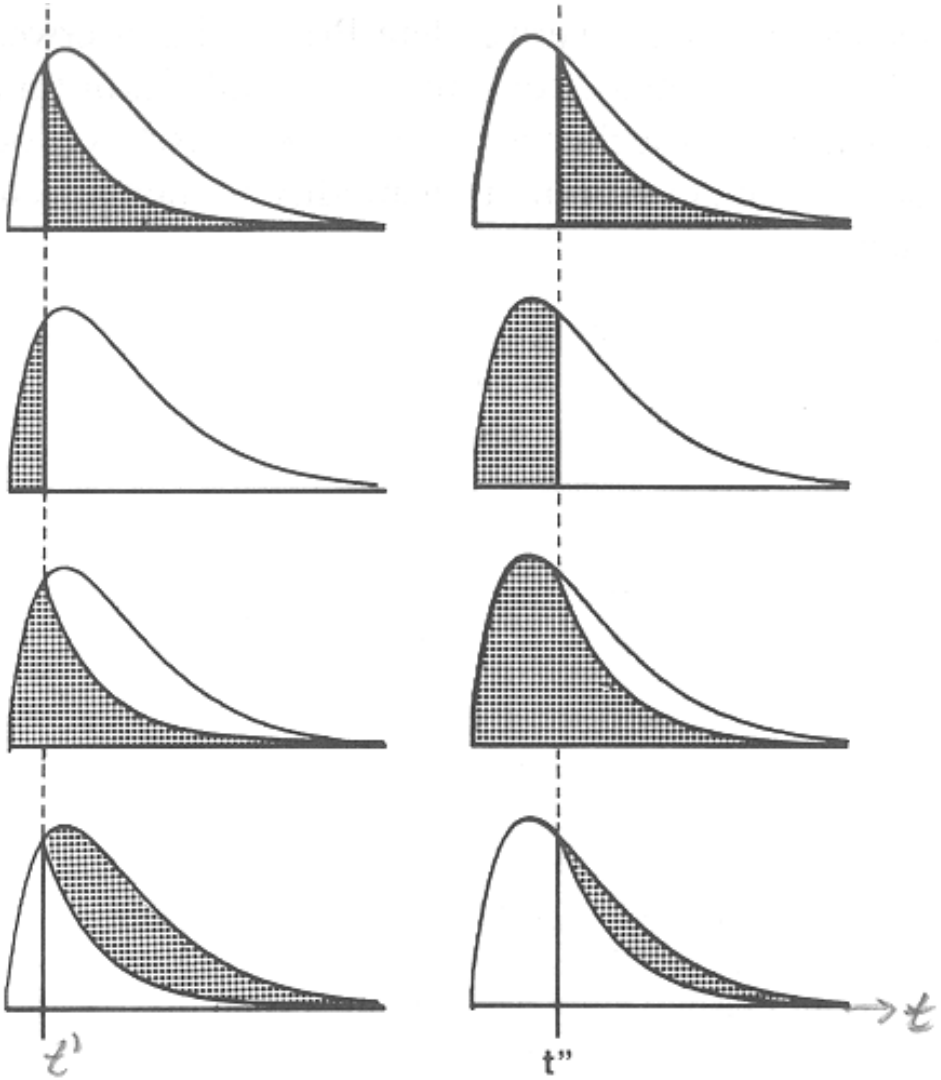
Total clearance: volume that is cleared per unit of time

$$Cl_{tot} = \frac{\ln 2}{t_0} V \left[\text{volume/time} \right]$$

Corresponding areas correspond to the ratio of the doses

The principle of Dost (II)

The reference curve is obtained by intravenous application of the dose



occupancy

= measurable concentration

transit

= already irreversible eliminated amount

transfer

= cccupancy + transit
= absorbed amount

availments

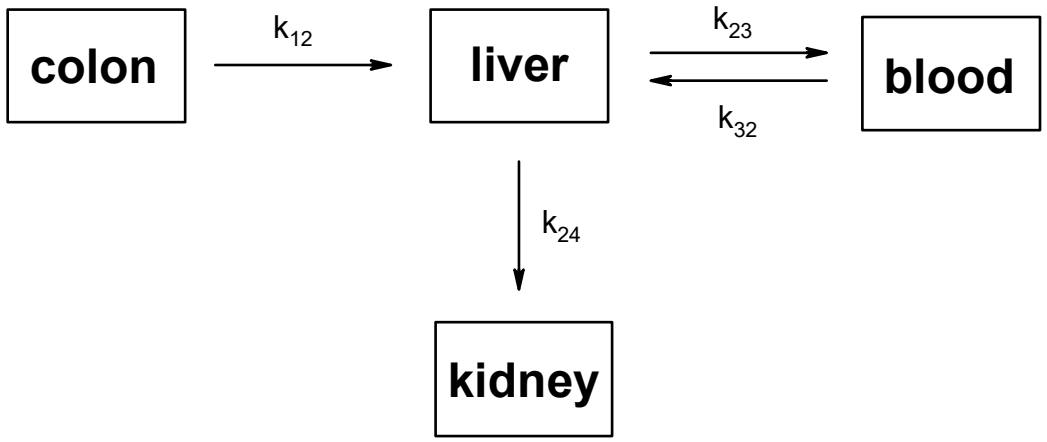
= amount that is still available for invasion

Experimental data for pharmacokinetic models

chemical data	**biological data**
partition coefficients	anatomic dimensions
metabolic turnover rates	flow of blood through the organs
V_{max}, K_m, K_i	volume of organs
solubility	
vapour pressure	respiration
diffusion constant	body mass
protein binding constants	
	age, gender
	extent of physical activity

Pharmacokinetic models (I)

Compartment models
assumption:
no metabolic conversion inside the compartments

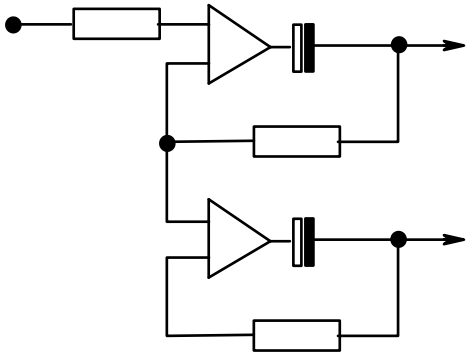


The concentration profile with time can be calculated by using linear differential equations

Lit: J.E.W.Beneken, J.H.van Oostrom „Modeling in Anethesia“, *Journal of Clinical Monitoring and Computing* **14** (1998) 57-67.

Pharmacokinetic models (II)

Systemic blood circulation as electric network (1930)



Simulation via analog computers (patch cords between the modules, resistors, capacitors)

And by simulation as electronic integrated network (SPICE)

Applicability: inhalative anesthetics (low metabolic conversion, lipophilic, are exhaled), intracellular transport.

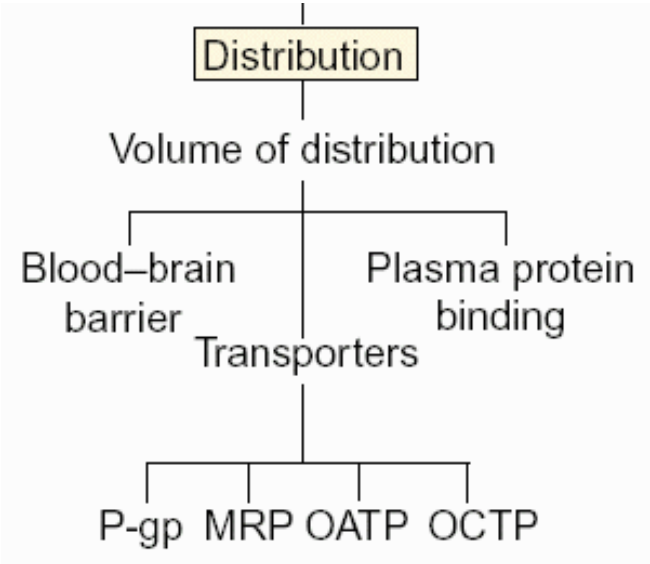
Lit: G.Fleischli, E.N.Cohen, *Anesthesiology* **27** (1966) issue 1, 64-69.

G.Vasilescu, L.Chen, *Asian J. Control* **13** (2011) issue 5, 738-748.

Distribution

From within the plasma the drug has to reach other compartments, depending on its target.

Substances that act on the central nervous system (CNS) have to cross the blood-brain barrier. Conversely, other drugs should not pass this barrier.



Besides passive diffusion, active transport has to be considered. Charged and polar substance require active transport.

Plasma protein binding / Distribution

The available concentration of drugs can be reduced due to binding to other proteins. This occurs in the plasma, the extra-cellular and interstitial fluid.

$$A + B \rightarrow \mathrm{AB} \text{ with } v_{bind} = k_{bind}[A][B]$$

$$\mathrm{AB} \rightarrow \mathrm{A} + \mathrm{B} \text{ with } v_{diss} = k_{diss}[\mathrm{AB}]$$

In the equilibrium state no change is measurable, thus

$$k_{bind}[A][B] = k_{diss}[\mathrm{AB}]$$

$$K = \frac{[\mathrm{AB}]}{[A][B]} = \frac{k_{bind}}{k_{diss}}$$

Binding proceeds according to the Langmuir‘s absorption isotherm (the heat of absorption is independend from the degree of coverage) and therefore fulfills the law of mass action [Massenwirkungsgesetz])

Besides proteins also mucopolysaccharides (binding- and supporting tissue (stroma)) can absorb substances.

Metabolism (I)

(bio-)chemical reactions of xenobiotics in the body

First pass effect:

Extensive metabolization of mainly lipophilic molecules, such with MW>500, or those that have a specific affinity to certain transporters, during the first passage through the liver

Phase I:

Oxidation, reduction and hydrolysis
esp. Cytochrome P450 enzymes

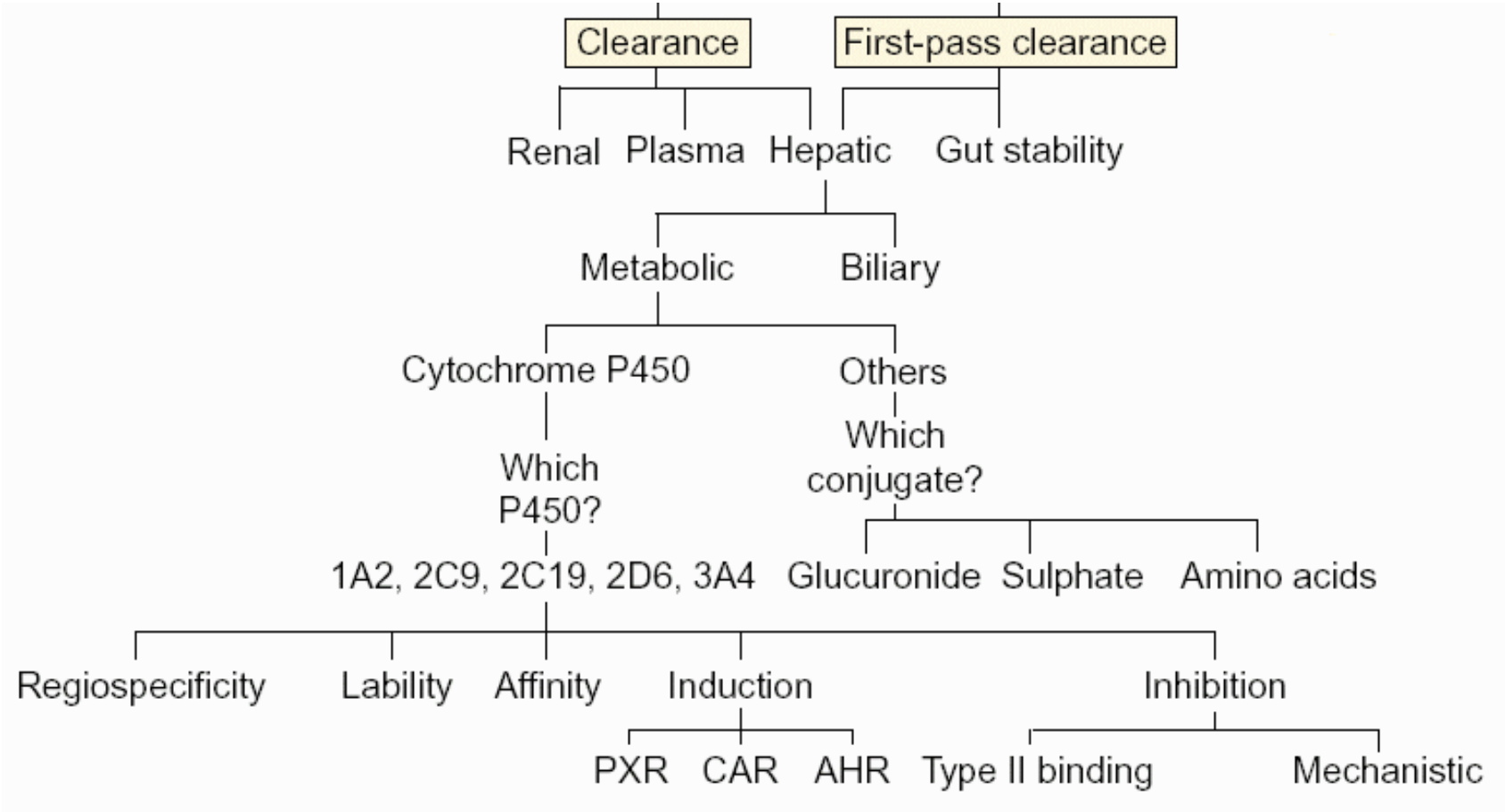
Phase II:

Conjugation with small molecules (e.g. glutamine)

Phase III:

elimination by transporters

Metabolism (II)



experimental (*in vitro*) methods:
human liver microsomes, hepatocytes and recombinant P450 enzymes (expressed in *E. coli, or yeast cells*)

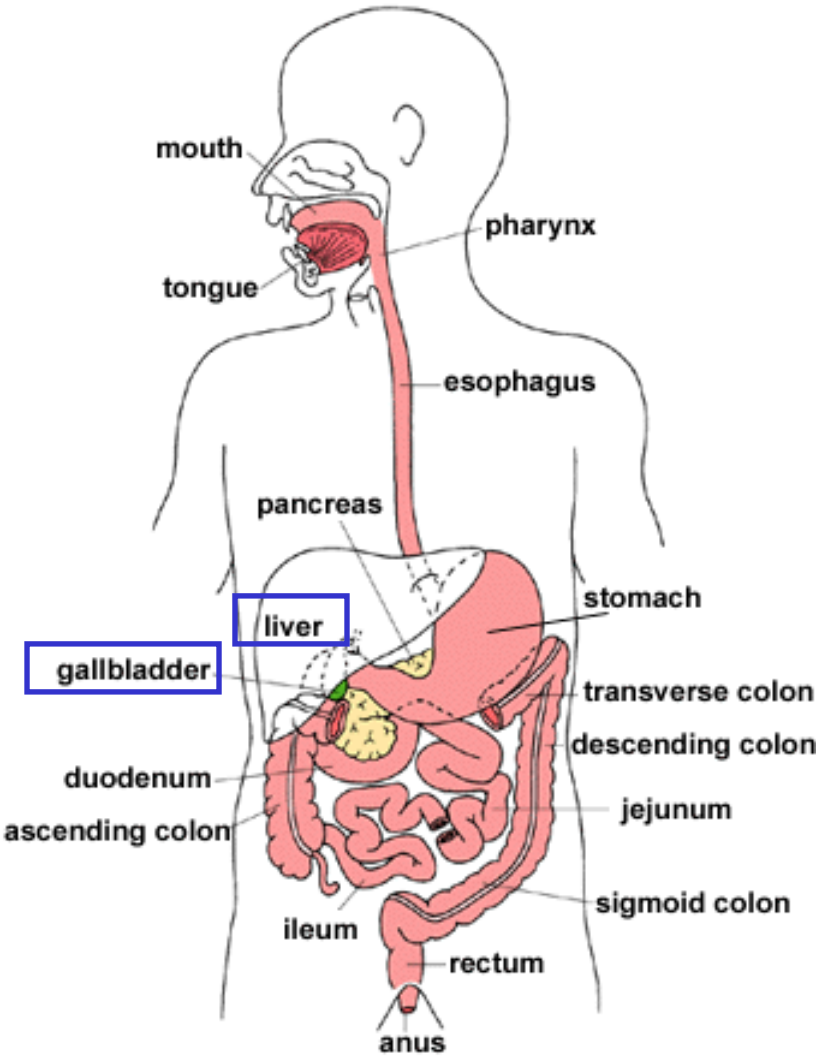
Elimination / Excretion

Elimination comprises all processes that lead to removing of a substance from a compartment. These can also be of metabolic nature.

Lipophilic substances can be excreted using bile [Gallensaft], hydrophilic compounds via urine.

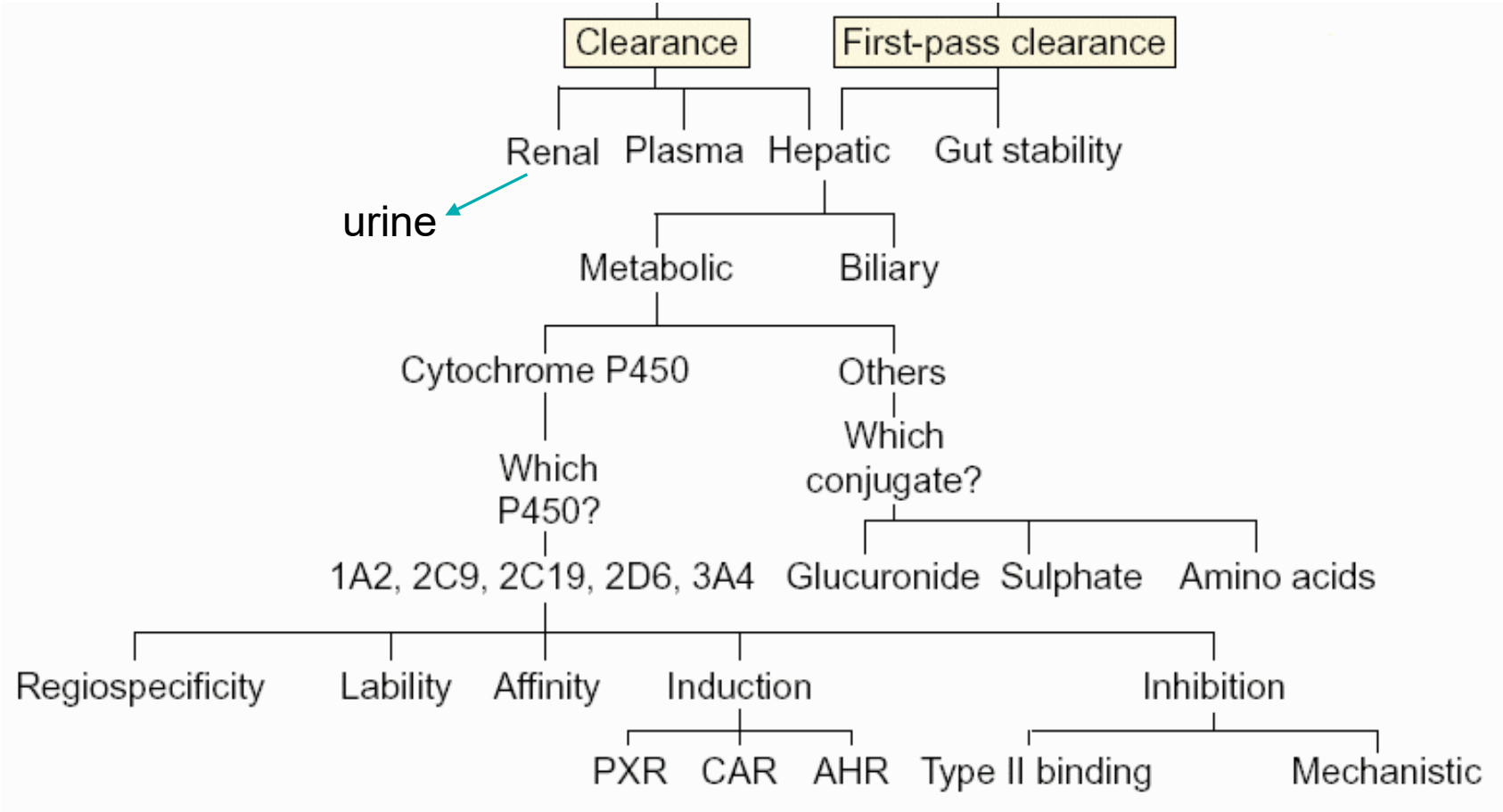
In general:

MW <300	300-500	>500
bile	bile & urine	urine



Elimination / Clearance

Metabolic paths (overview)



Elimination / Clearance (III)

From the physico-chemical point of view, elimination of a substance is a 1st order decay process (depending on the present concentration of the compound)

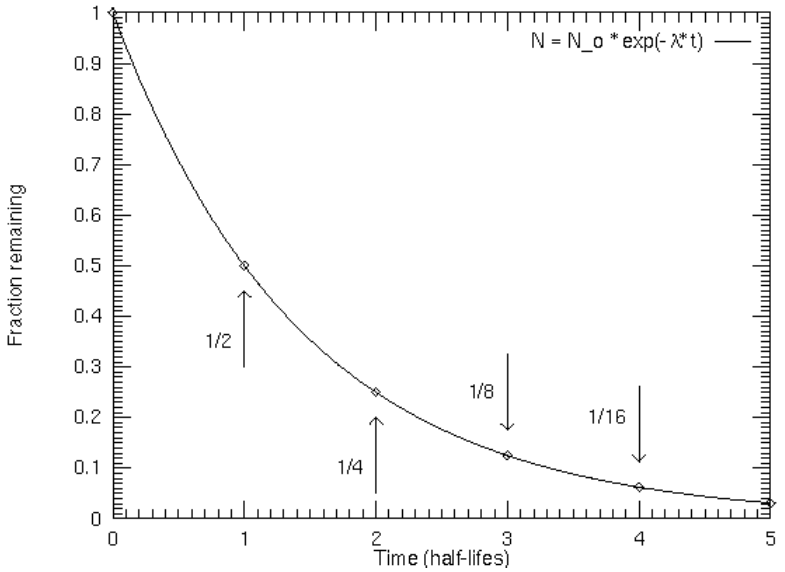
$A \rightarrow B$ with $v = k[A]$ k rate constant of elimination

$$\frac{-d[A]}{dt} = k[A] \quad |\cdot \frac{dt}{[A]}$$ and integration leads to

$$-\int_{[A]_o}^{[A]_t} \frac{d[A]}{[A]} = \int_0^t k\,dt \quad \text{or} \quad \ln \frac{[A]_t}{[A]_0} = -kt \quad \text{or}$$

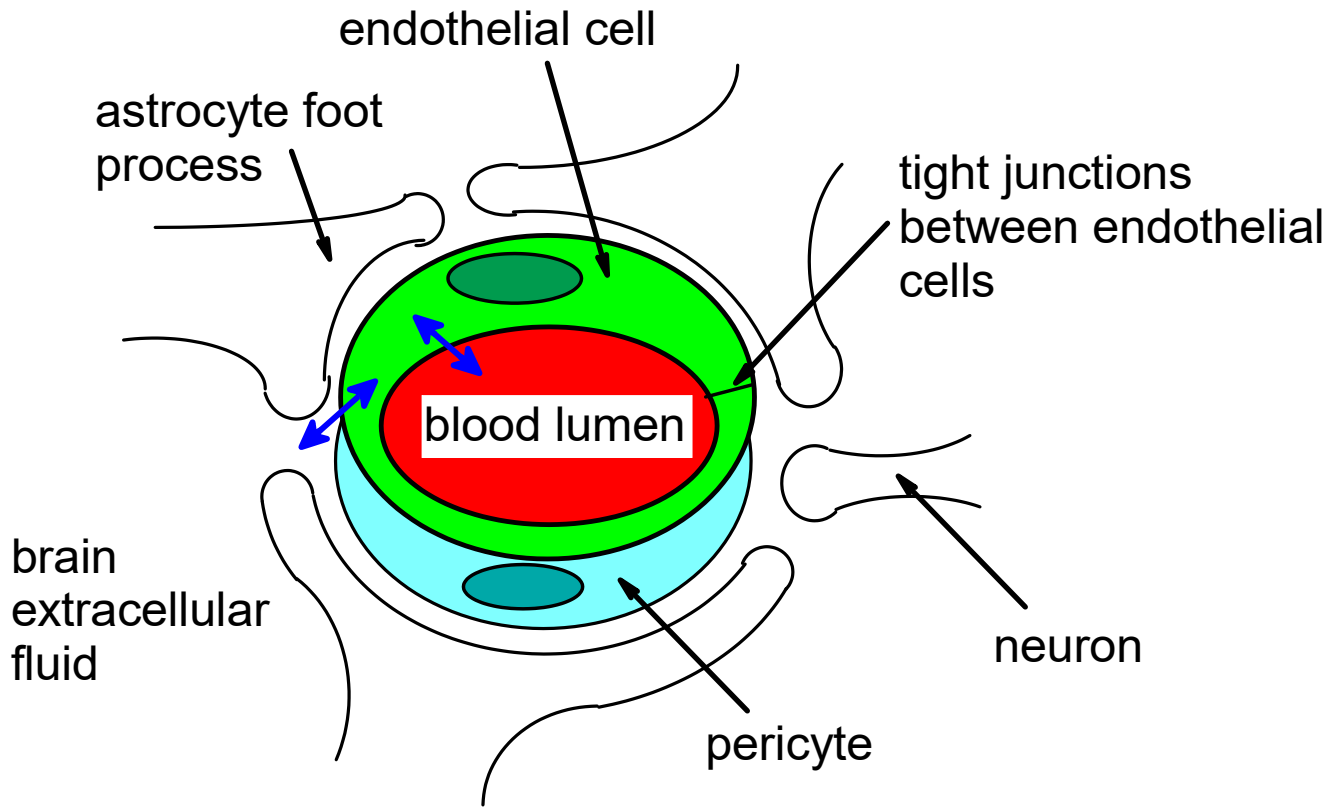
$$[A]_t = [A]_0\, e^{-kt}$$

with the half life $t_{1/2} = \frac{\ln 2}{k}$



The blood-brain barrier (BBB)

Cross section through a cappilary vessel



According to: J.-M. Scheerman in *Pharmacogenomics*, J.Licinio & Ma-Li Wong (Eds.) Wiley-VCH (2002) pp. 311-335.

Function of the blood-brain barrier

in silico prediction of the blood-brain barrier permeability in the course of pre-clinical development is particularly important, since

- only substances that shall act on the central nervous system (CNS), should pass the blood-brain barrier effectively.
- BBB-screening is particular „expensive“ (testing on animals not avoidable: microdialysis, isotope labeling)
- models using artificial membranes (endothelial cells) are still in development.

Blood-Brain Barrier (II)

As a measure for the permeability of the blood-brain barrier, the logarithmic ratio of the concentrations is used

logBB = log([brain]/[blood]) range: –2.00 to +1.00

Mainly in the blood –1.0 < logBB < 0.3 mainly in the brain

It can be assumed that the logBB has been determined for about 300 drugs, only. However, for much more compounds a qualitative assignment (CNS+ or CNS–) is known.

Lit. D. E. Clark, *J. Pharm. Sci.* **8** (1999) 815

Blood-Brain Barrier (III)

In contrast to the absorption from the duodenum, the polarity of the compounds that cannot be described by the PSA comes into account. Example:

	PSA	logBB	ClogP	polarizablity (AM1)	
benzene	0	–0.69	2.1	1	3.8
3-methylpentane	0	2.01	3.7	14.8	

An according QSPR equation was derived

logBB = a PSA + b ClogP + c with r = 0.887

Lit. D. E. Clark, *J.Pharm.Sci.* **8** (1999) 815

F. Lombardo et al. *J.Med.Chem.* **39** (1996) 4750

Formerly used descriptors

Each of these terms is correlated to logBB by itself:

- logP — fragment based (MlogP, ClogP,...)
- Polar surface area — contributions from N, O and H atoms
- hydrogen-bond donors and acceptors — numerical count
- size and shape — molecular volume and globularity

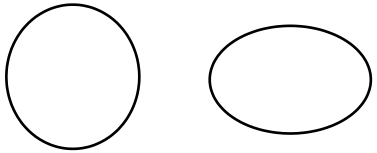
Descriptors for size and shape

Connected to the shape of the molecule are:

Molecular volume, globularity, number of rotatable bonds

globularity:

Ratio of the surface (assuming the molecule would be a perfect sphere) to the actual surface. Always < 1



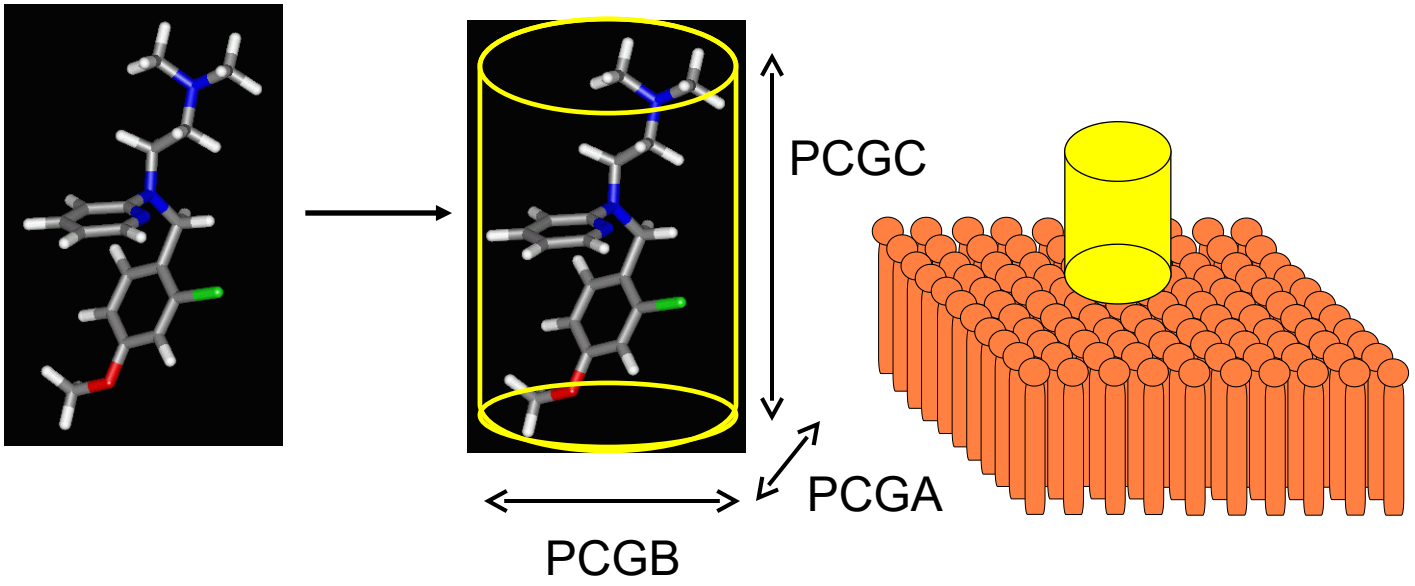
Principle components of the molecular geometry:

3D extension of the molecule in space

New descriptors for size and shape

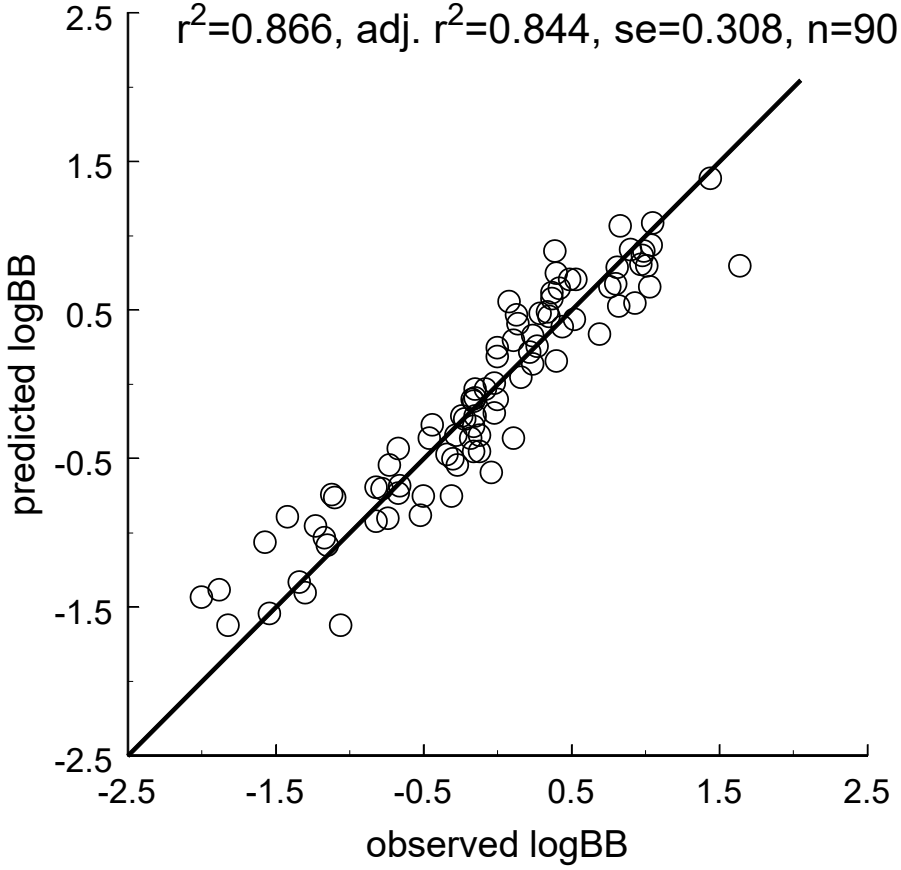
- Descriptors such as the globularity are correlated to the molecular weight and the number of hydrogen atoms

+ Replaced by three terms derived from the molecular geometry



BBB-model with 12 descriptors

Descriptors mainly from QM calculations: electrostatic surface, principal components of the geometry, H-bond properties



Lit: M. Hutter *J.Comput.-Aided.Mol.Des.* **17** (2003) 415.

ADME – historical development

1960 Corwin Hansch QSAR for small data sets
logP for toxicity

1980 *in vitro* studies replace *in vivo* studies

1990 first *in silico* ADME (computer) models,
docking into protein structures,
homology modeling of proteins (CYP P450)

1997 Lipinski‘s rule of five for (passive) absorption

2003 X-ray structure of human CYP2C9 (1OG2.pdb)

2004 X-ray structure of human CYP3A4 (1TQN.pdb)

2005 X-ray structure of human CYP2D6 (2F9Q.pdb)

2015 Routine use of machine learning for ADME property prediction

Web-based online tools

A number of institutes and companies have put up servers for the prediction of ADME related properties.

Usually these apply Java-applets that allow drawing molecules, allow input either as SMILES string or one of the may 3D coordinate files.

A summary including hyperlinks is offered by the *Virtual Laboratory*

https://vcclab.org
https://ochem.eu contains a collection of experimentally determines properties (e.g. logBB, Caco2, plasma protein binding)

Lit. I.V. Tetko, *Mini Rev.Med.Chem.* **8** (2003) 809.
I.V. Tetko et al., *J.Comput.-Aided Mol.Des.* **19** (2005) 453.