Model-based QSAR and Disposition Function

1. Basic Steps of Drug Action
2. Biological Characteristics
3. Construction of MB-QS(T)AR
4. Disposition function in MB-QS(T)AR
   --- Empirical forms
   --- Simulation-based forms
   --- Time-hierarchy based form
5. Comparison with Empirical QSAR

Theory of Model-based QS(T)AR

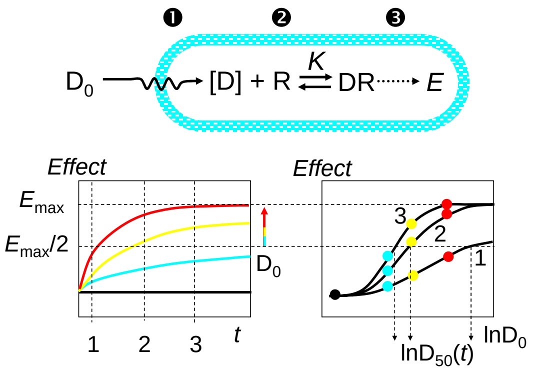
Drug action consists of three steps:

❶ drug disposition in the receptor surroundings
--- a description of the kinetics of drug concentration in receptor surroundings needed

❷ drug-receptor interaction – the interaction energy must be expressed in terms of drug structure/properties

❸ transformation of the receptor modification into biological response(s)

Drug Action: Basic Principles

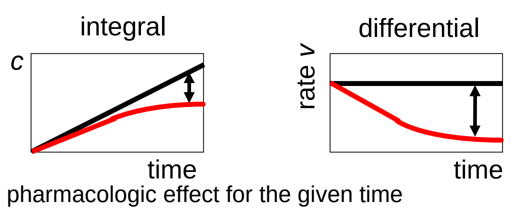


Biological Characteristics and Pharmacological Response

- biological characteristics can be classified according to the time course as
  --- differential (rate *v*) - constant or oscillating in time (blood pressure, heart rate, respiration rate, rate of enzymatic reaction)
  --- integral (concentration *c*) - increasing in time (concentration of microorganisms, concentration of blood sugar or of product of enzymatic reaction)
- pharmacological response (effect *E*) - change in biological characteristics after drug administration

Biological Characteristics and Pharmacological Response II

- enzymatic reaction under steady state conditions
-



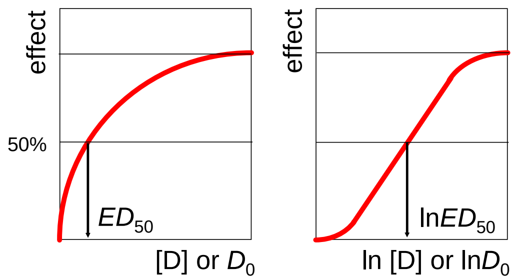
- pharmacologic effect for the given time

$$E = c - c_D;\ \frac{E}{E_{max}} = \frac{c - c_D}{c} \qquad E = v - v_D;\ \frac{E}{E_{max}} = \frac{v - v_D}{v}$$

Biological Characteristics and Pharmacological Response III

- depending upon the used biological characteristics, the effects are
  --- differential
  --- integral
- integral effects are more difficult to describe by MB-QS(T)AR because the response is ‘integrated’ by the biosystem
- differential effects are used to construct MB-QS(T)AR wherever feasible (time courses of integral effects are numerically differentiated)

Isoeffective Concentrations



[D] - drug concentration in the receptor surroundings, proportional at any moment to the dose D_0

Receptor

- the part of the biosystem that, after interaction with the drug molecule(s), initiates a sequence of molecular events leading to pharmacologic response
- typically proteins
  --- only receptoric function (trigger a cascade of messengers, effect may not be proportional to the fraction of occupied receptors)
  --- enzymes (effect proportional to the receptor modification)
- but also nucleic acids, polysaccharides (*e.g.* cell walls of G^- bacteria), and lipids (membranes)

Simplifications for QS(T)AR Models

Drug action consists of three steps:

❶ drug disposition described by the disposition function $A(d_i, t)$

❷ drug-receptor interaction – characterized by the association constant *K*, if the interaction is has 1:1 stoichiometry, and is fast and reversible

❸ biological response(s) is an immediate consequence of receptor modification, effect is proportional to the fraction of modified receptors

Construction of QS(T)AR Models

Basic steps and assumptions

- describe the drug-receptor interaction
- express the kinetics of receptor modification
- relate the effect to the receptor modification
- describe the time course of drug concentration in the surroundings of the receptor [D] using the disposition function $A(d_i,t)$ $[D] = D_0 \times A(d_i, t)$
- substitute the dose D_0 by the isoeffective concentration

Step 1: Interaction Scheme

- <u>scheme of the drug-receptor interaction</u>
- most common fast (=non-covalent) 1:1 interaction, characterized by the association constant *K*

$$D + R \xleftrightarrow{K} DR \qquad (1)$$

- can be more complicated, e.g.

$$D + R \xleftrightarrow{K} DR \xrightarrow{k} DR^*$$

the second step can be covalent interaction or a coordination bond formation or...

Step 2: Kinetics of Receptor Modification

- the simplest scheme $D + R \overset{K}{\leftrightarrow} DR$
- the association constant *K*

$$K = \frac{[DR]}{[D] \times [R]} = \frac{[DR]}{[D] \times ([R]_0 - [DR])}$$

- the concentration of modified receptors

$$[DR] = [R]_0 \times \frac{K \times [D]}{K \times [D] + 1}$$

Step 3: Effect vs. Receptor Modification

- the relation depends on the type of biological characteristics
- for differential response– the rate is proportional to the concentration of free enzyme molecules: v ~ $[R]_0$ and v_D~[R]; [DR]=$[R]_0$-[R]

$$\frac{E}{E_{max}} = \frac{v - v_D}{v} = \frac{[DR]}{[R]_0}$$

- the fraction of modified receptors is

$$\boxed{\frac{E}{E_{max}} = \frac{K \times [D]}{K \times [D]+1}}$$

Step 4: Use of Disposition Function

- use the disposition function to express the drug concentration in the receptor surroundings because the drug loss due to the interaction with the receptors is negligible:

$$[D] = [D]_0 \times A(d_i, t)$$

- the kinetics of the effect is then

$$\frac{E}{E_{max}} = \frac{K \times D_0 \times A(d_i,t)}{K \times D_0 \times A(d_i,t)+1}$$

Step 5: Incorporate Isoeffective Dose

- isoeffective dose (ED_{50}) elicits half of E_{max}

$$0.5 = \frac{K \times ED_{50}(t) \times A(d_i,t)}{K \times ED_{50}(t) \times A(d_i,t)+1}$$

- after rearrangement, a QSTAR equation is obtained

$$\boxed{\frac{1}{ED_{50}(t)} = K \times A(d_i,t)}$$

Basic Equation for Model-based QS(T)AR

- valid for most frequent circumstances
  --- fast and reversible 1:1 interaction
  --- differential response

$$\log \frac{1}{ED_{50}(t)} = \log A(d_i,t) + \log K$$

- the drug-receptor association constant K
  --- expressed by structure-specific methods
  as a function of structure or properties
- the disposition function is expressed for the given situation (a multitude of descriptions)

Other Model-based QS(T)AR Equations

- other mechanisms of the drug-receptor interactions, e.g. non-covalent interaction stabilized by a covalent interaction (a coordination bond…) $D + R \leftrightarrow DR \rightarrow DR^*$ will lead to different forms of equations
- other factor – the form of the disposition function depends on the size of biosystem…
- in general, model-based QS(T)AR are represented by many nonlinear equations of even (differential) equations that cannot be solved explicitly

Advantages of Model-based Equations

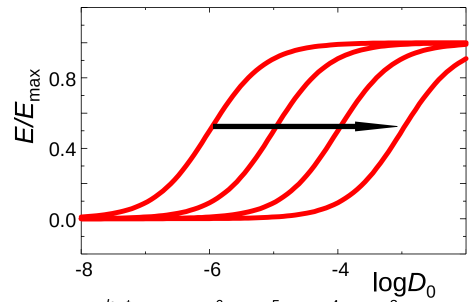
- building the knowledge base
- usage of previous information
  --- known drug-receptor interaction mechanisms
  --- known forms of the disposition function
- integration with other experimental data, e.g. with the dose-response curves, with kinetics of effects for individual drugs (see next slides)
- analysis of drug effects at different levels and integration of the results, e.g. measurement of distribution and of the effect separately
- better predictions, especially outside the descriptor space (see later)

Integration with Experimental Data

- Step 4: $$\frac{E}{E_{max}} = \frac{K \times D_0 \times A(d_i,t)}{K \times D_0 \times A(d_i,t)+1}$$
- for one-compartment models $$A(d_i,t) = (1/V_{df}) \times e^{-k_e \times t}$$
- equation describing the dose-response curve and the kinetics of effect

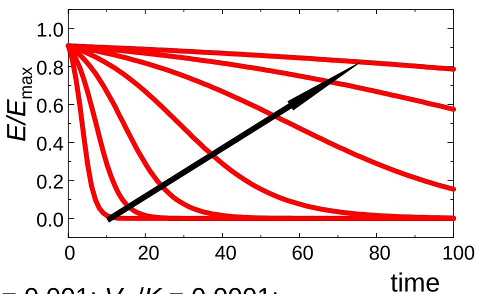
$$\frac{E}{E_{max}} = \frac{K \times D_0}{K \times D_0 + V_{df} \times e^{k_e \times t}}$$

Dose-Response Curve



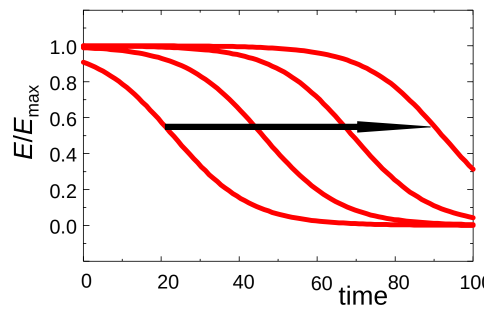
$V_{df} \times e^{k_e \times t}/K = 10^{-6},\ 10^{-5},\ 10^{-4},\ 10^{-3}$

Effect vs. Time - Influence of k_e



D_0 = 0.001; V_{df}/K = 0.0001;
k_e = 0.64, 0.32, 0.16, 0.08, 0.04, 0.02, 0.01

Effect vs. Time - Influence of Dose



V_{df}/K = 0.0001, k_e = 0.1, D_0 = 0.001, 0.01, 0.1, 1

Disposition Function

- drug disposition in the receptor surroundings
  --- described by the disposition function *A* with variables
  - dose D_0
  - descriptors *d*
  - the exposure time *t*

$$[D] = D_0 \times A(d_i,t)$$

- the form of description as the product of the dose and a function is generally valid for linear systems
- linear systems – consist of linear processes only
- linear process – the rate or the extent is proportional to the free drug concentration

ADME/Tox Processes

	Specific	Nonspecific
Absorption (intestinal)	transporters for sugars, oligopeptides, nucleosides	trans-bilayer transport
Distribution	in some cell types: P-gp, MRP	trans-bilayer transport
Metabolism	reactions catalyzed by Cyt P450's and others	spontaneous reactions with -SH, OH, NH_2
Excretion	organic cation/anion transporter peptides	filtration, passive reabsorption
Toxicity	many	narcosis, uncoupling, alkylation

Models of Subcellular Pharmacokinetics

Available forms of the disposition function:

- Explicit descriptions for reduced scenarios
  - --- transport through single membrane
  - --- uni-directional transport in a series of membranes as combined with protein binding and metabolism
  - --- time-hierarchy based model for the elimination phase
- Numerical descriptions for full scenarios
  - --- transport in a series of membranes as combined with protein binding and metabolism

Drug Disposition I

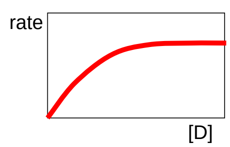
Drug disposition mostly consists of linear processes:

- slow processes – the rate is proportional to the free drug concentration
  - --- passive trans-bilayer transport
  - --- hydrolysis
  - --- non-enzymatic reactions with low-molecular-weight cell constituents
- fast processes – the extent is proportional to the free drug concentration
  - --- protein binding

Drug Disposition II

- drug disposition includes some processes that are, in principle, nonlinear:
  - --- enzymatic metabolism
  - --- transport via protein carriers
- these processes are nonlinear for higher drug concentrations and linear for therapeutic drug concentrations

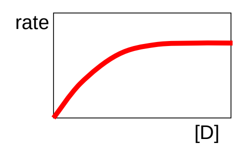
$$v = \frac{e_m \times v_m \times [D]}{K_m + [D]}$$



Drug Disposition III

- drug disposition includes some processes that are, in principle, nonlinear:
  - --- enzymatic metabolism
  - --- transport via protein carriers
- these processes are nonlinear for higher drug concentrations and linear for therapeutic drug concentrations

$$v = \frac{e_m \times v_m \times [D]}{K_m + \cancel{[D]}}$$



Basic Equation for Model-based QS(T)AR

- valid for most frequently occurring circumstances
  - --- fast and reversible 1:1 interaction
  - --- differential response

$$\log \frac{1}{ED_{50}(t)} = \log A(d_i, t) + \log K$$

- the drug-receptor association constant K
  - --- expressed by structure-specific methods as a function of structure or properties
- the disposition function is expressed for the given situation

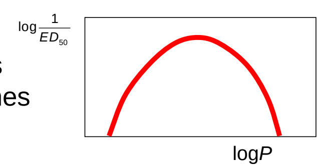
Hansch Equation I

- the first multi-descriptor QSAR equation

$$\log \frac{1}{ED_{50}} = \log A(d_i, t) \quad + \quad \log K$$

$$\log \frac{1}{ED_{50}} = \underbrace{a \times (\log P)^2 + b \times \log P}_{\log A(d_i,t)} + \underbrace{c \times \sigma + d \times E_S}_{\log K} + e$$

- "random walk" of drug molecules through membranes



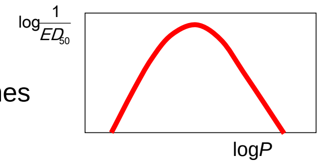
Kubinyi Equation I

- improved transport description

$$\log\frac{1}{ED_{50}} = \log A(d_i, t) \qquad + \qquad \log K$$

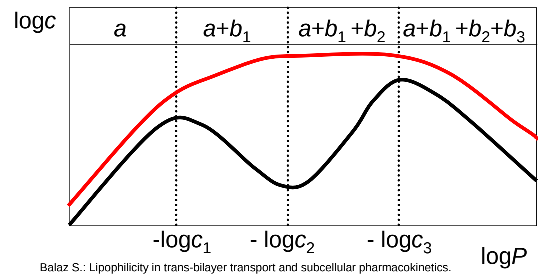
$$\log\frac{1}{ED_{50}} = a\times\log P - b\times\log(\beta\times P+1) + c\times\sigma + d\times E_S + e$$

- partial simulation of drug transport through membranes



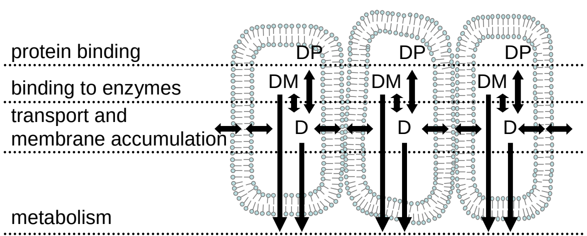
Simulation-Based Disposition Functions

$$\log\frac{1}{ED_{50}} = a\times\log P^{\beta} + \sum_{i=1}^{3} b\times\log(c_i\times P^{\beta}+1) + \log K + d$$



Balaz S.: Lipophilicity in trans-bilayer transport and subcellular pharmacokinetics. *Perspectives in Drug Discovery and Design* **19** (2000) 157-177

Time-hierarchy Based Disposition Function I



Drug distribution (transport) is much faster than elimination and is considered instantaneous. Then the concentration of the free drug molecules (c_A) in all aqueous body phases (including plasma) is identical.

Time-hierarchy Based Disposition Function II

$$c = \frac{c_0}{AP^{\beta}+B}\, e^{-\frac{CP^{\beta}+D}{AP^{\beta}+B}t}$$

- P is the reference partition coefficient, *t* is time
- the terms describe individual processes:
  - A - membrane accumulation and protein binding
  - B - distribution in aqueous phases
  - C - lipophilicity-dependent metabolism
  - D - other elimination processes
- for ionizable compounds, A - D (Y) can become

$$\mathbf{Y = Y_0 + \sum_{i=1}^{m} Y_i\, 10^{\,sgn \sum_{j=1}^{i} pK_{aj}}}$$

Time-hierarchy Based Disposition Function III

$$c = \frac{c_0}{AP^{\beta}+B}\, e^{-\frac{CP^{\beta}+D}{AP^{\beta}+B}t}$$

k_e

V_{df}

- P is the reference partition coefficient, *t* is time
- the terms describe individual processes:
  - A - membrane accumulation and protein binding
  - B - distribution in aqueous phases
  - C - lipophilicity-dependent metabolism
  - D - other elimination processes
- for ionizable compounds, A - D (Y) can become

$$\mathbf{Y = Y_0 + \sum_{i=1}^{m} Y_i\, 10^{\,sgn \sum_{j=1}^{i} pK_{aj}}}$$

Cross-Validation

- a statistical technique assessing predictivity of models
  --- a group of compounds is omitted from the data set
  --- the model is re-optimized
  --- the activities of omitted compounds are predicted
- predictivity is characterized by
  --- Predictive Sum of Squares (PRESS)
  --- predictive correlation coefficient (q^2)