Bio- & Pharmacokinetics

Hyperboost Training Course Model-based Data Analysis for Clinical Applications

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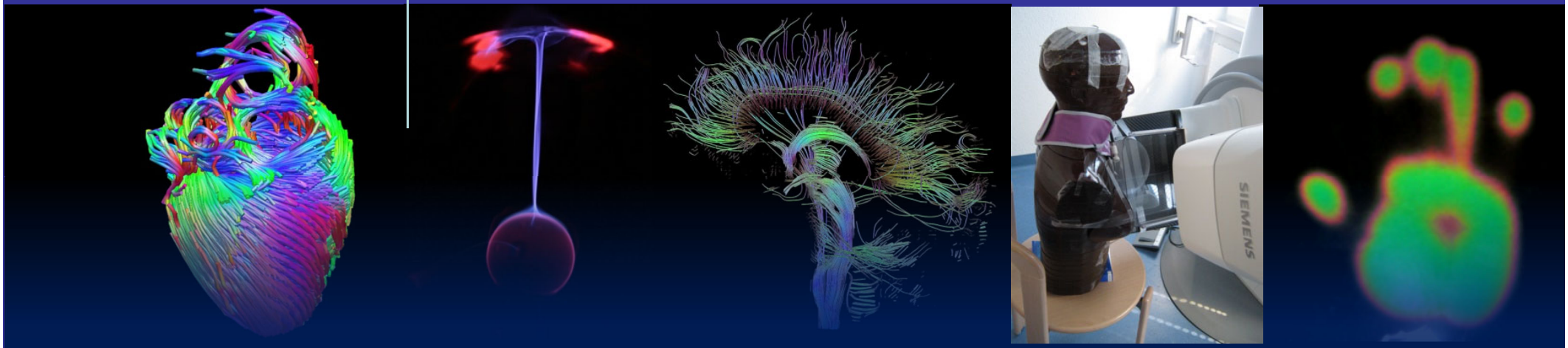
Medical Biophysics Group ZHAW
2024



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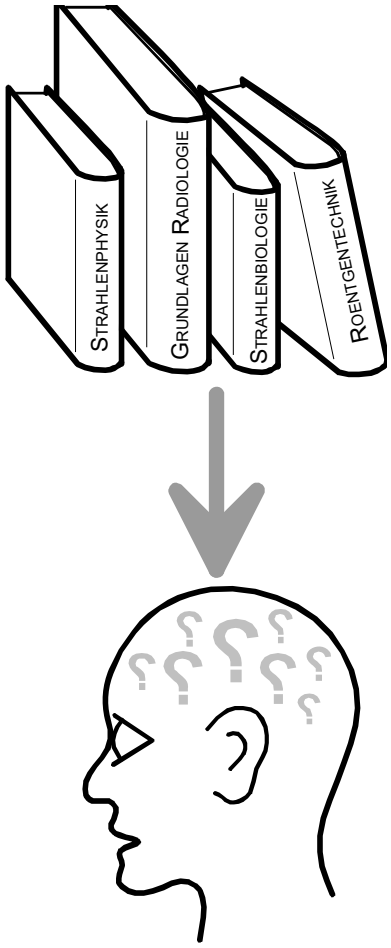


Model-based data analysis for clinical application – Modelling and Biological Systems:

Day 1

0920-1100: Modelling and Biological Systems
1320-1400: Using Graphical Model Editors
1400-1450: Using Python for Model Fitting

Day 2

1110-1200: Biokinetic / Biodynamic Modelling (→ Lab2: Model-based Data Analysis of PET Images)

Day3

0900-1100: Radiobiological Models

CONTENT

Bio- & Pharmacokinetics:

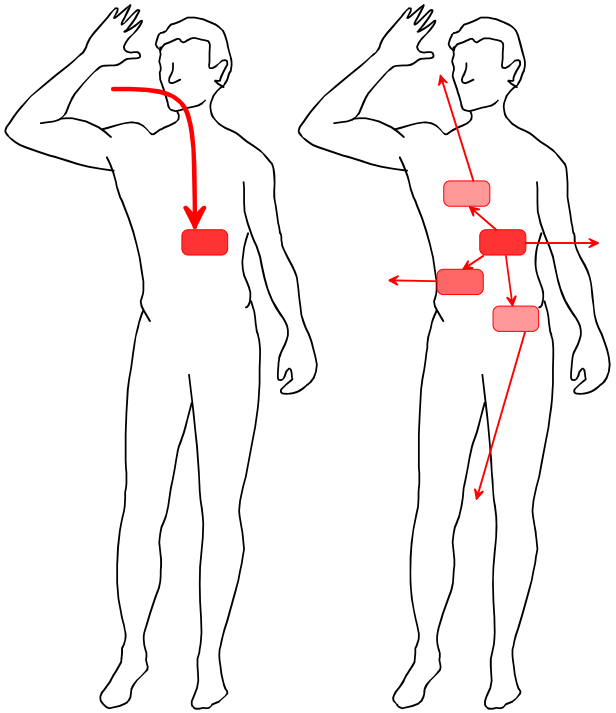
Definition of a compartment
Single compartment and elimination
Clearance
Clearance and different elimination pathways
Resorption
2-compartment models
Non-linear kinetics, Michaelis-Menten kinetics

Learning Objectives

Students are able to

- to implement multi-compartmental bio-kinetic models
- to calculate the clearance based on elimination measurements
- to model enzymatic activity or carrier systems
- to model kinetics of radio-isotopes
- to calculate the effective half life of an isotope (bound to a tracer)

Bio- and Pharmacokinetics

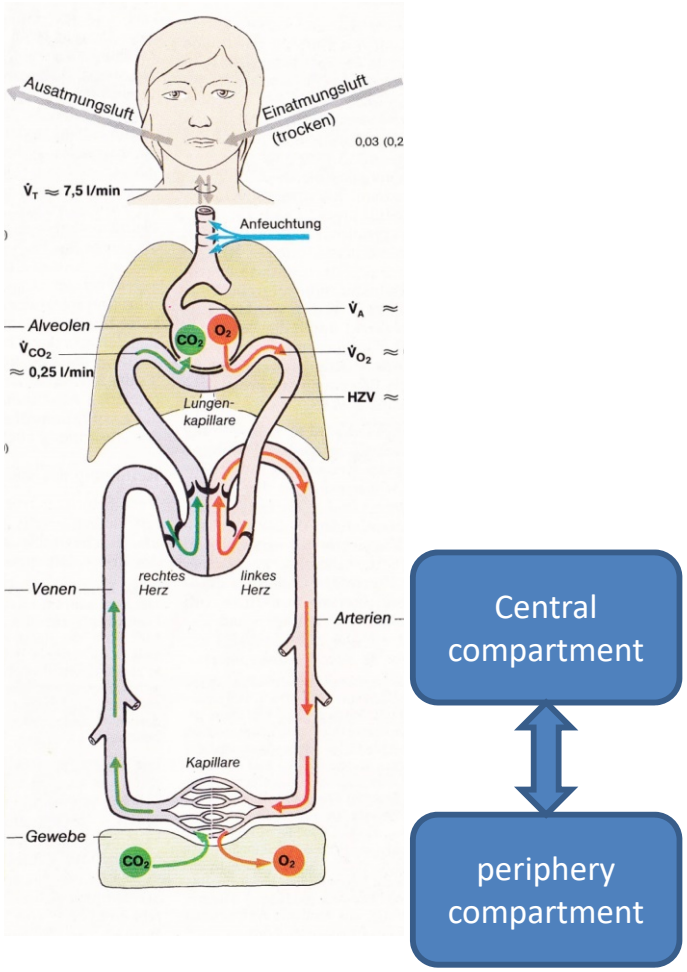


The human body can be regarded as a compartmental system. Biokinetics can be considered as the exchange of substances (drugs) between these compartments. Key processes are:

- Resorption
- Transfer
- Elimination

Fig.1. Human body as a compartmental system

Bio- and Pharmacokinetics

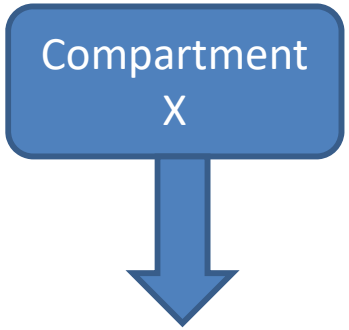


Definition of a compartment:

- Exchange with environment (neighboring compartments) much slower than equilibration of concentration inside
- Depending on the speed of resorption-, distribution and elimination, compartments may not correspond to a specific organ in all cases (e.g. contrast-media in the blood circulation vs. plasma concentration of drugs)

Fig.2. blood circulation and compartmental system (Faller & Schünke, 1988; modified)

Bio- and Pharmacokinetics



$$c = \frac{X}{V_d}$$

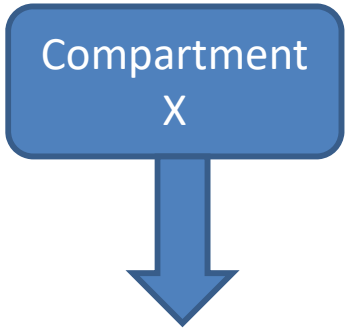
$$\frac{dX}{dt} = -k_e X$$

Single compartment and elimiation:

- X = amount of drug, c = concentration inside compartment with volume V_d
- k_e = elimination constant, first order kinetics is assumed here

Fig.3. Flow chart for a simple 1-compartment system with elimination only

Bio- and Pharmacokinetics

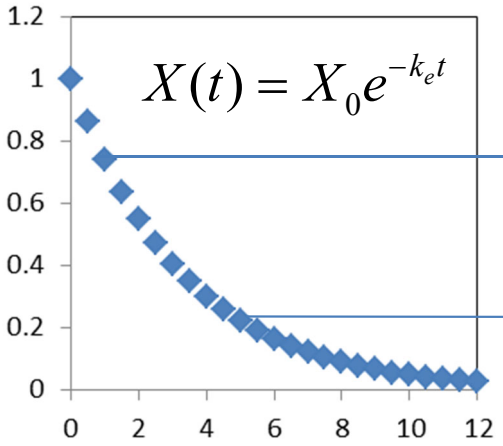


$$c = \frac{X}{V_d}$$

$$\frac{dX}{dt} = -k_e X$$

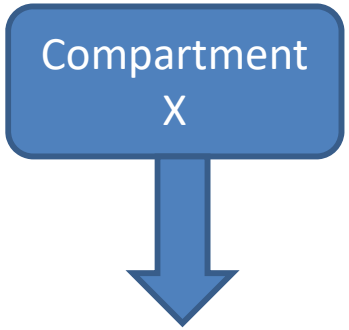
The elimination constant k_e = can be determined by the measurement of the concentration at two different time points:

$$k_e = \frac{\ln\left(\frac{c_p(t_1)}{c_p(t_2)}\right)}{t_2 - t_1} = \frac{\ln\left[c_p(t_1)\right] - \ln\left[c_p(t_2)\right]}{\Delta t}$$



Bio- and Pharmacokinetics

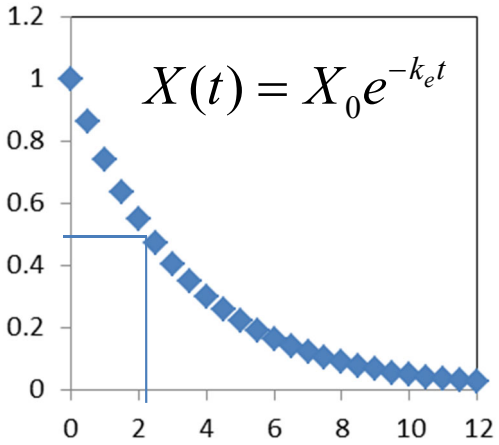
The half life is given by:



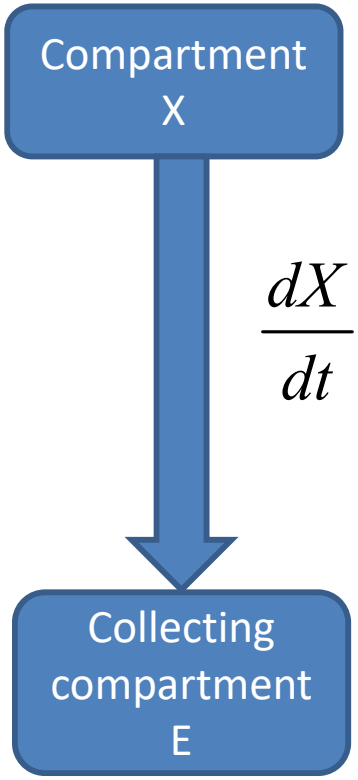
$$c = \frac{X}{V_d}$$

$$T_{1/2} = \frac{\ln(2)}{k_e}$$

$$\frac{dX}{dt} = -k_e X$$



Bio- and Pharmacokinetics



$$c = \frac{X}{V_d}$$

$$\frac{dX}{dt} = -k_e X$$

$$CL = \frac{\left(\frac{dE}{dt}\right)}{c}$$

Clearance *CL*:

- is a measure for the elimination speed (in case of first-order kinetics)
- corresponds to the volume which is cleared from the drug
- In case of complete renal elimination, the (renal) clearance gives the renal blood perfusion rate

Biokinetics

Main elimination pathways are:

- Renal elimination via kidneys
- expiration
- Biliary elimination via GIT
- Metabolic pathway, mainly via liver

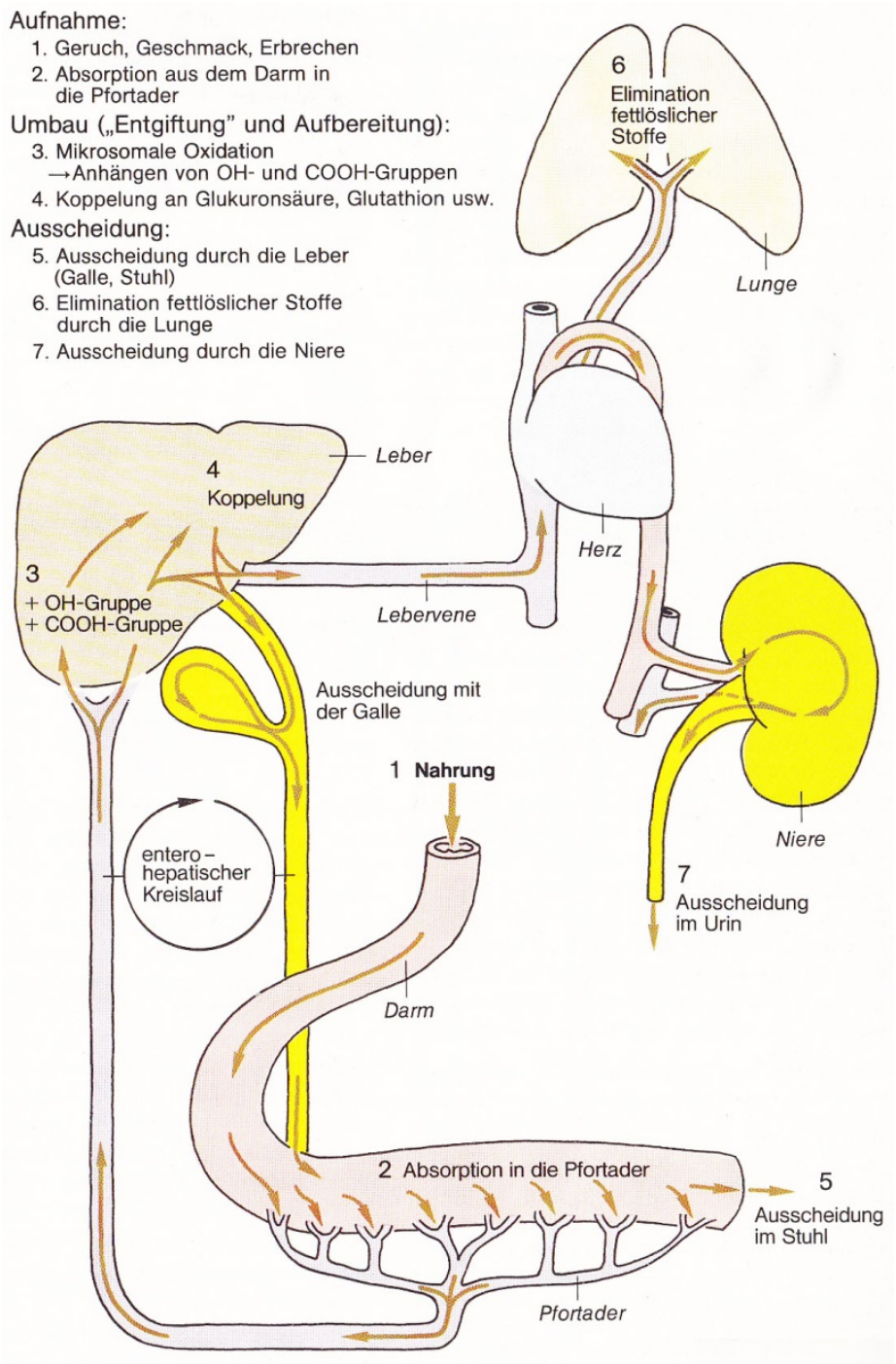
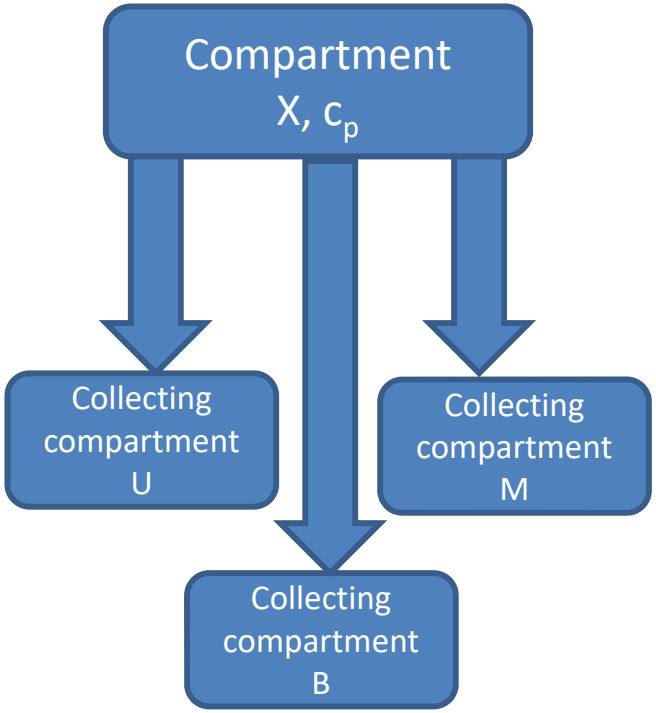


Fig.4. elimination pathways (Silbernagel & Despopoulos, 1979)

Bio- and Pharmacokinetics



Clearance in case of different elimination pathways:

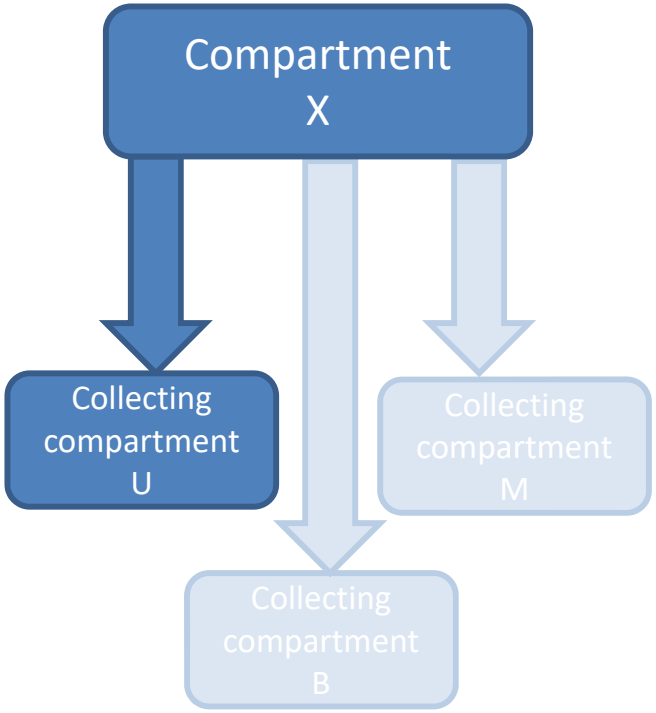
- Renal elimination: $U(t)$
- Biliary elimination: $B(t)$
- Metabolic elimination: $M(t)$

$$\frac{dX}{dt} = -k_e \cdot X \qquad \frac{dB}{dt} = k_B \cdot X$$

$$\frac{dU}{dt} = k_R \cdot X \qquad \frac{dM}{dt} = k_M \cdot X$$

Fig.5. Compartmental system with different elimination pathways

Bio- and Pharmakokinetics



Clearance in case of different elimination pathways:

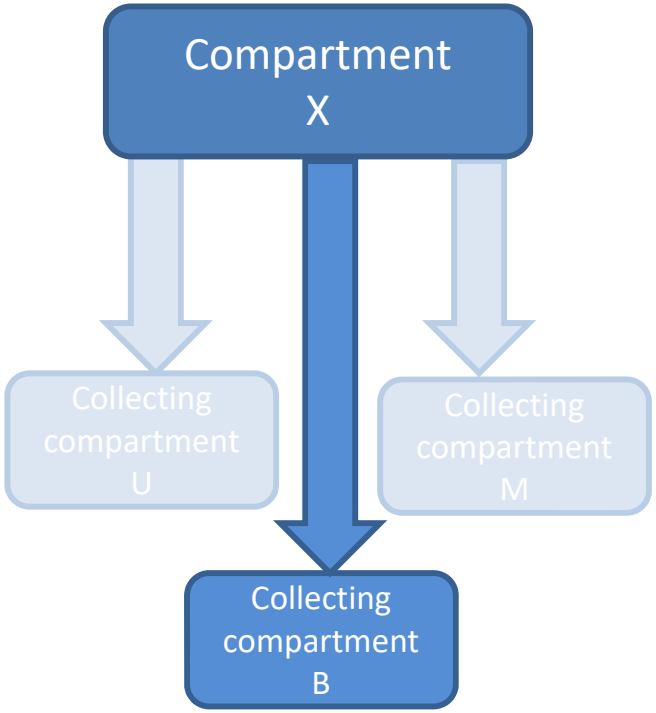
- Renal elimination → renal clearance CL_R:

$$U(t) = \frac{k_R}{k_e} D \cdot \left(1 - e^{-k_e \cdot t}\right)$$

$$CL_R = \frac{1}{c_p} \cdot \left(\frac{dU}{dt}\right) = k_R \cdot V_d$$

Fig.5. Compartmental system with different elimination pathways

Bio- and Pharmakokinetics



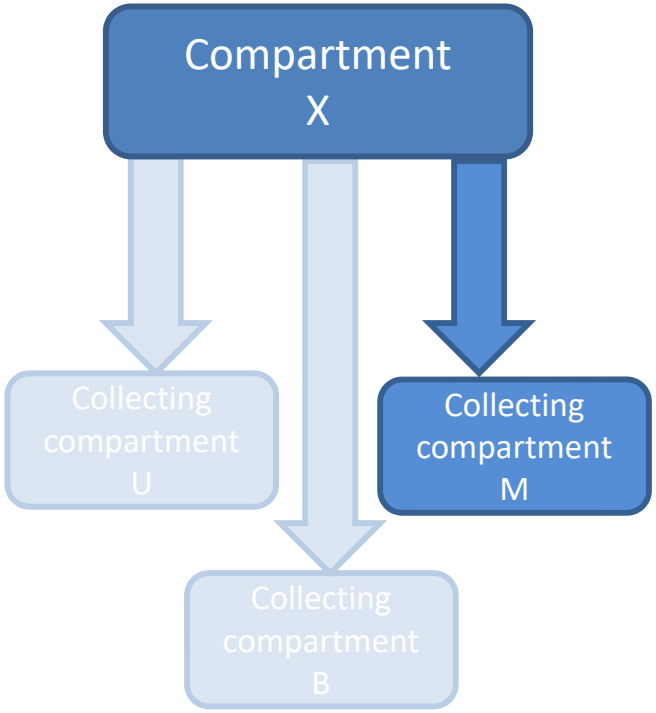
Clearance in case of different elimination athways:

- Biliary elimination → biliary clearance CL_B:

$$CL_B = \frac{1}{c_p} \cdot \left(\frac{dB}{dt} \right) = k_B \cdot V_d$$

Fig.5. Compartmental system with different elimination pathways

Bio- and Pharmacokinetics



Clearance in case of different elimination athways:

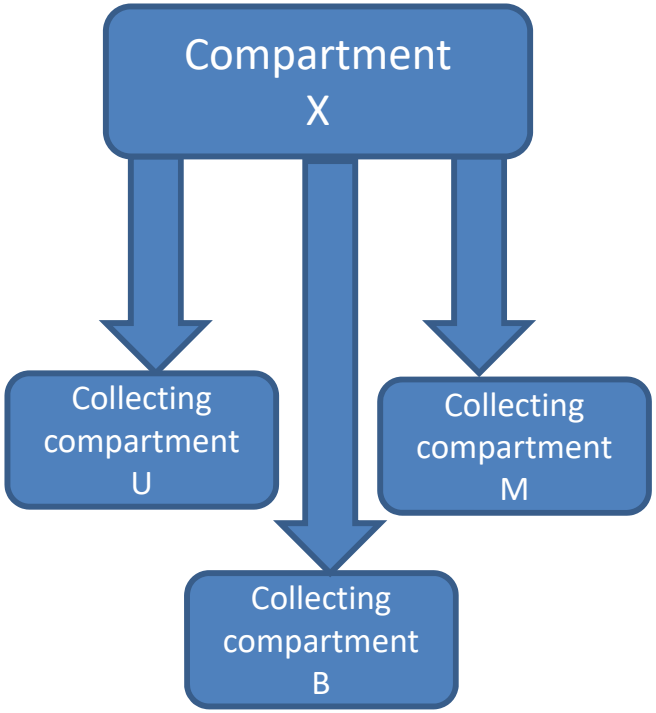
- Metabolic elimination → metabolic clearance CL_M:

$$M(t) = \frac{k_M}{k_e} \cdot D \cdot (1 - e^{-k_e t})$$

$$CL_M = \frac{1}{c_p} \cdot \left(\frac{dM}{dt} \right) = k_M \cdot V_d$$

Fig.5. Compartmental system with different elimination pathways

Bio- and Pharmacokinetics



The total clearance is the sum of:

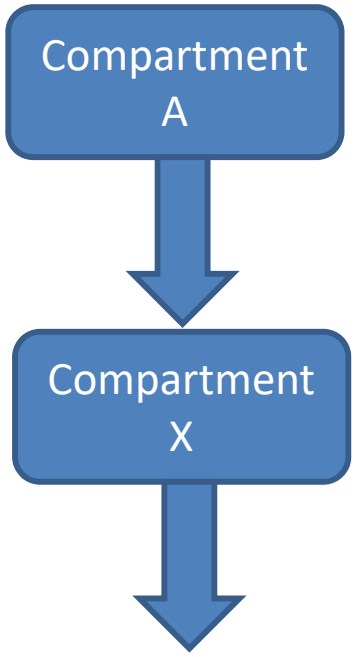
- Renal clearance
- Biliary clearance
- Metabolic clearance

$$CL_{tot} = \frac{\dot{E}}{c_p} = \frac{k_e X}{c_p} = \frac{\left(k_R + k_B + k_M\right) \cdot X}{c_p}$$

$$\Rightarrow \quad CL_{tot} = CL_B + CL_M + CL_R$$

Fig.5. Compartmental system with different elimination pathways

Bio- and Pharmacokinetics



$$\frac{dA}{dt} = -k_a A$$

$$\frac{dX}{dt} = -k_e X + k_a A$$

Resorption can be modelled by adding a resorption compartment, which can represent the GIT, subcutaneous drug depot etc. In most of the cases, the compartment with the amount X is the plasma (central) compartment.

Fig.6. Flow chart for a “1”-compartment system with resorption and elimination

Bio- and Pharmacokinetics

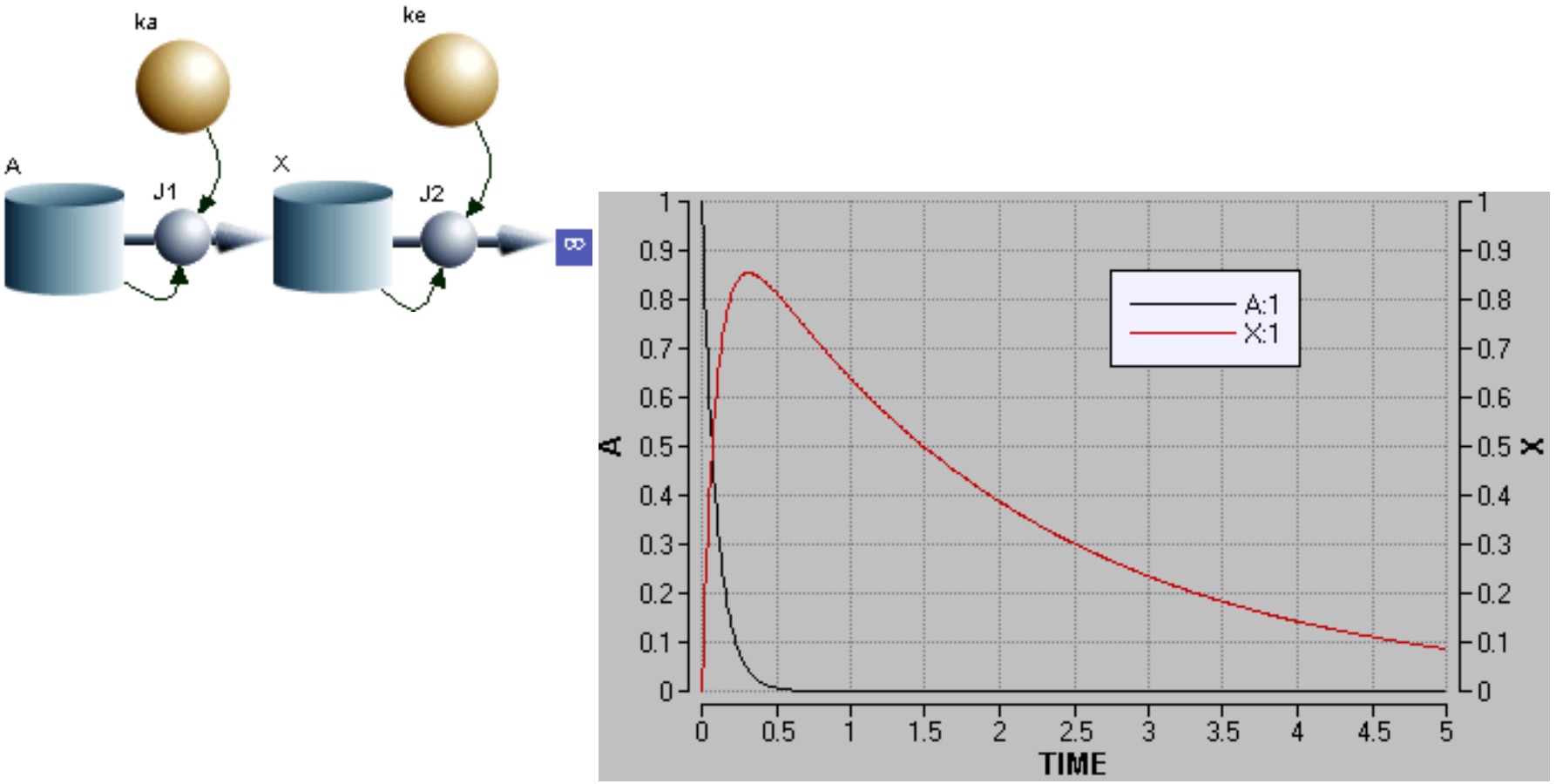
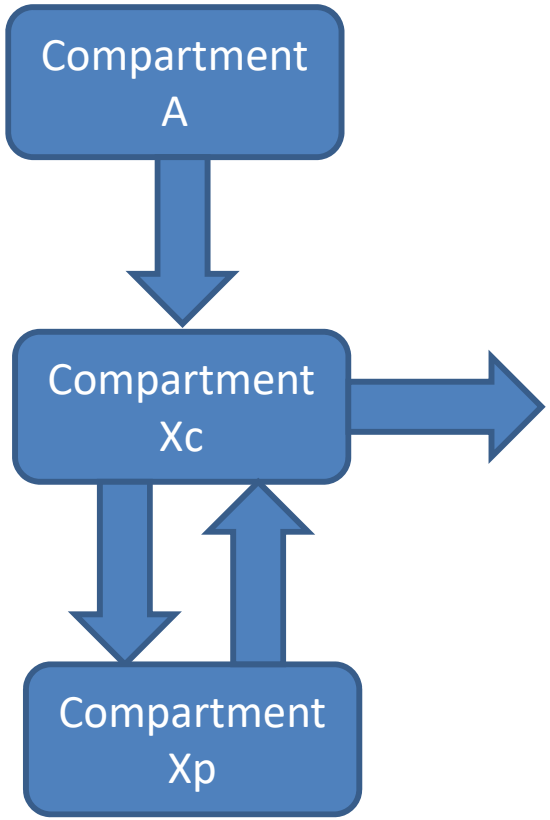


Fig.7. BM-Flow chart for a “1”-compartment system with resorption and elimination (left) and numerical solutions (left)

Bio- and Pharmacokinetics



2-compartment model:

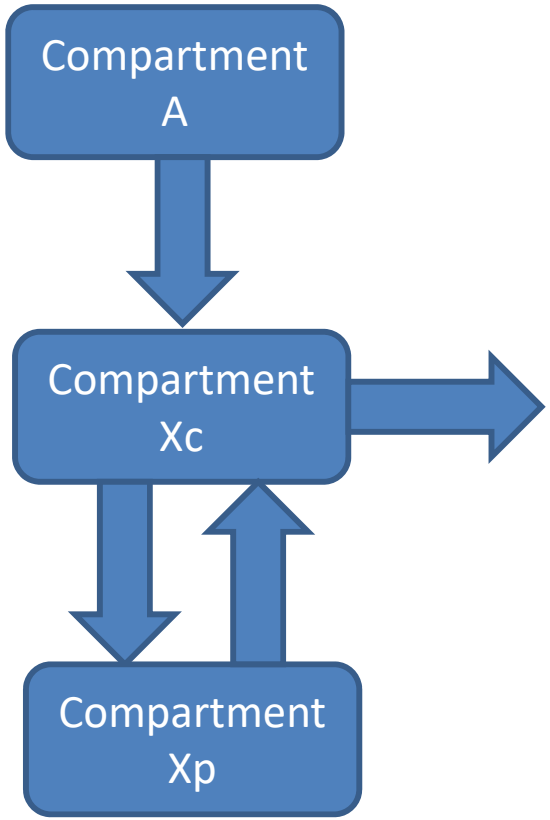
$$\frac{dA}{dt} = -k_a A$$

$$\frac{dX_c}{dt} = k_a A + k_{pc} X_p - (k_{cp} + k_e) \cdot X_c$$

$$\frac{dX_p}{dt} = k_{cp} X_c - k_{pc} X_p$$

Fig.8. Flow chart for a 2-compartment system with resorption and elimination

Bio- and Pharmacokinetics



2-compartment model with non-linear kinetics:

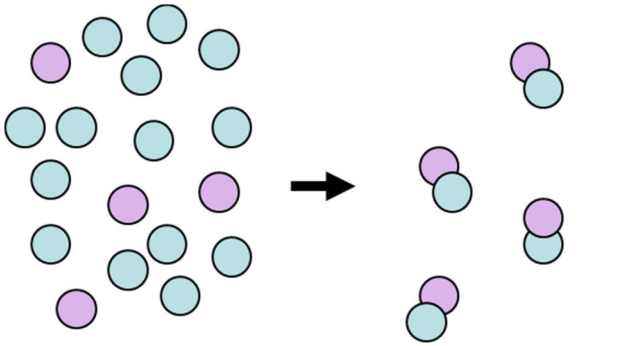
$$\frac{dA}{dt} = -f(A)$$

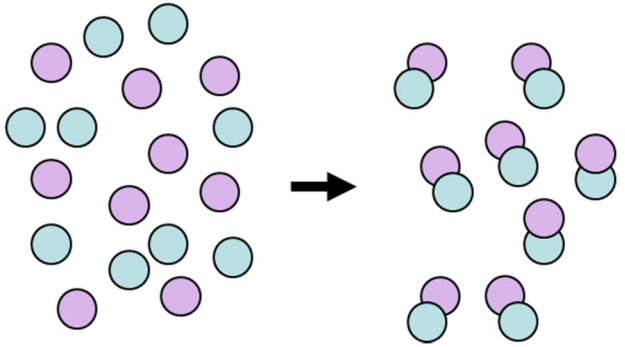
$$\frac{dX_c}{dt} = f(A) + g_{pc}(X_p) - g_{pc}(X_c) - h(X_c)$$

$$\frac{dX_p}{dt} = -g_{pc}(X_p) + g_{pc}(X_c)$$

Fig.8. Flow chart for a 2-compartment system with resorption and elimination

Enzymatic Reactions & Carrier Transport





Enzymatic (catalytic) reactions follow the so-called Michaelis-Menten kinetics:

$$\frac{dc}{dt} = -\frac{v_m \cdot c}{(k_m + c) \cdot V_d}$$

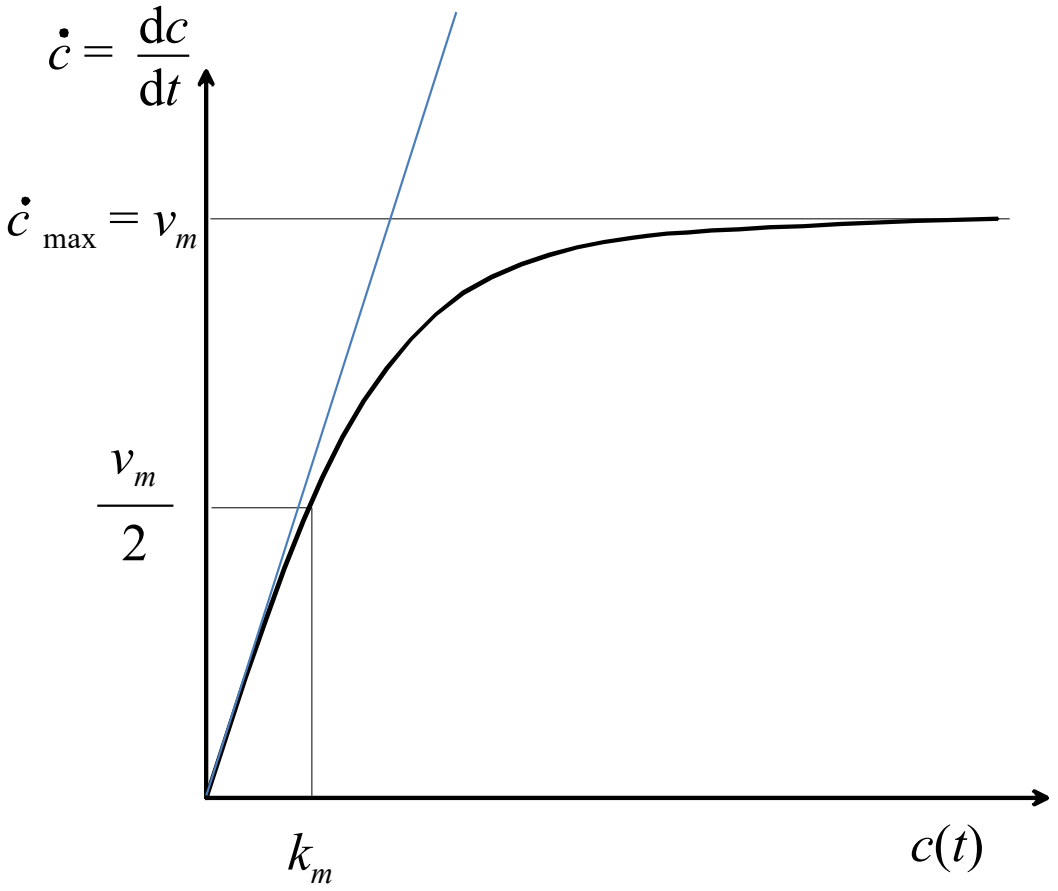
$$\lim_{c \to 0} \left(\frac{v_m \cdot c}{(k_m + c) \cdot V_d} \right) = \frac{v_m}{k_m \cdot V_d} \cdot c$$

$$\lim_{c \to \infty} \left(\frac{v_m \cdot c}{(k_m + c) \cdot V_d} \right) = \frac{v_m}{V_d}$$

Enzymatic Reactions & Carrier Transport

$$\lim_{c\to\infty}\left(\frac{v_m \cdot c}{(k_m + c)\cdot V_d}\right) = \frac{v_m}{V_d}$$

$$\lim_{c\to 0}\left(\frac{v_m \cdot c}{(k_m + c)\cdot V_d}\right) = \frac{v_m}{k_m \cdot V_d}\cdot c$$



Bio- and Pharmacokinetics

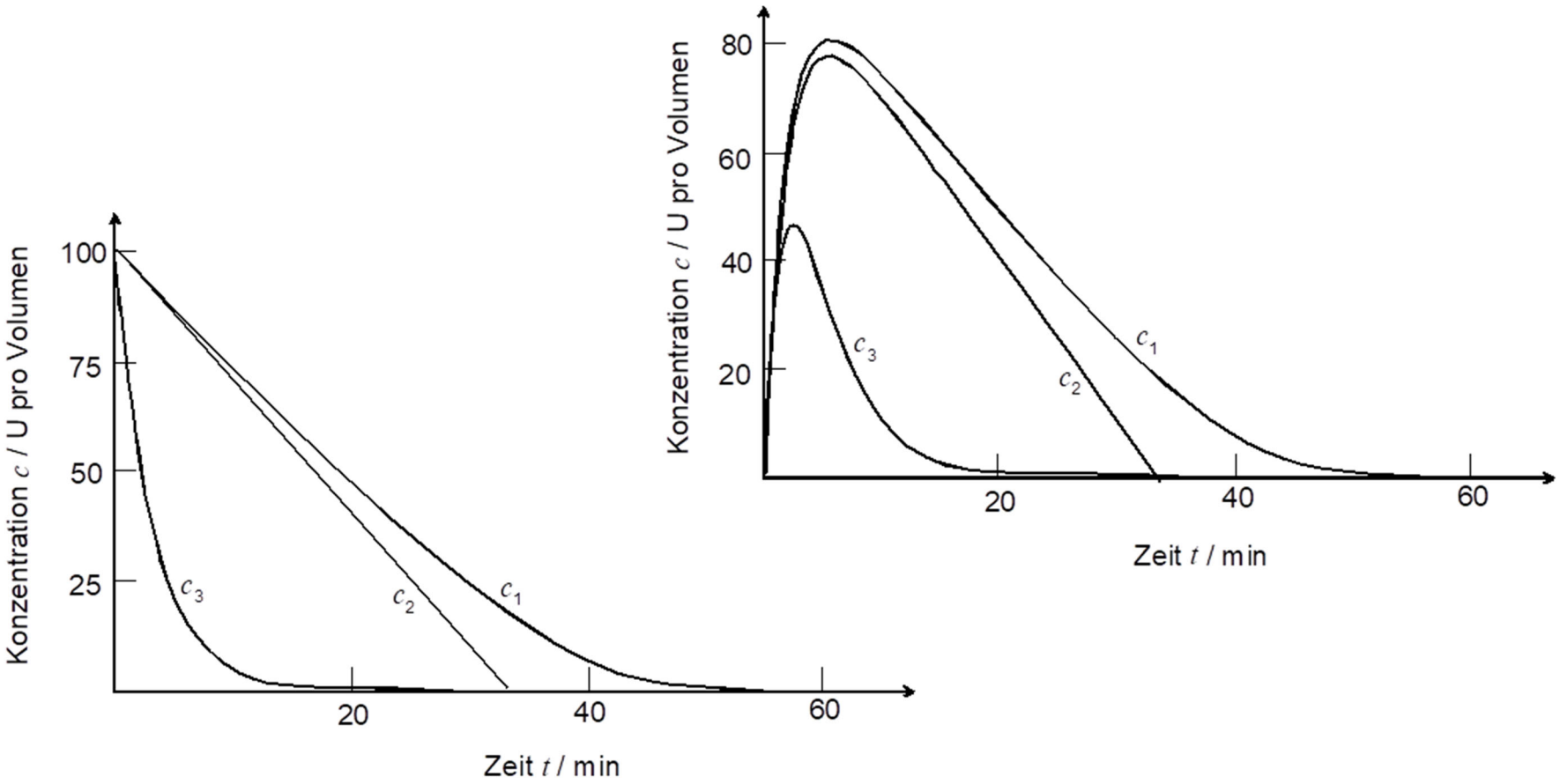


Fig.9. first-order and Michaelis-Menten kinetics without (lower left) and with resorption (upper right)

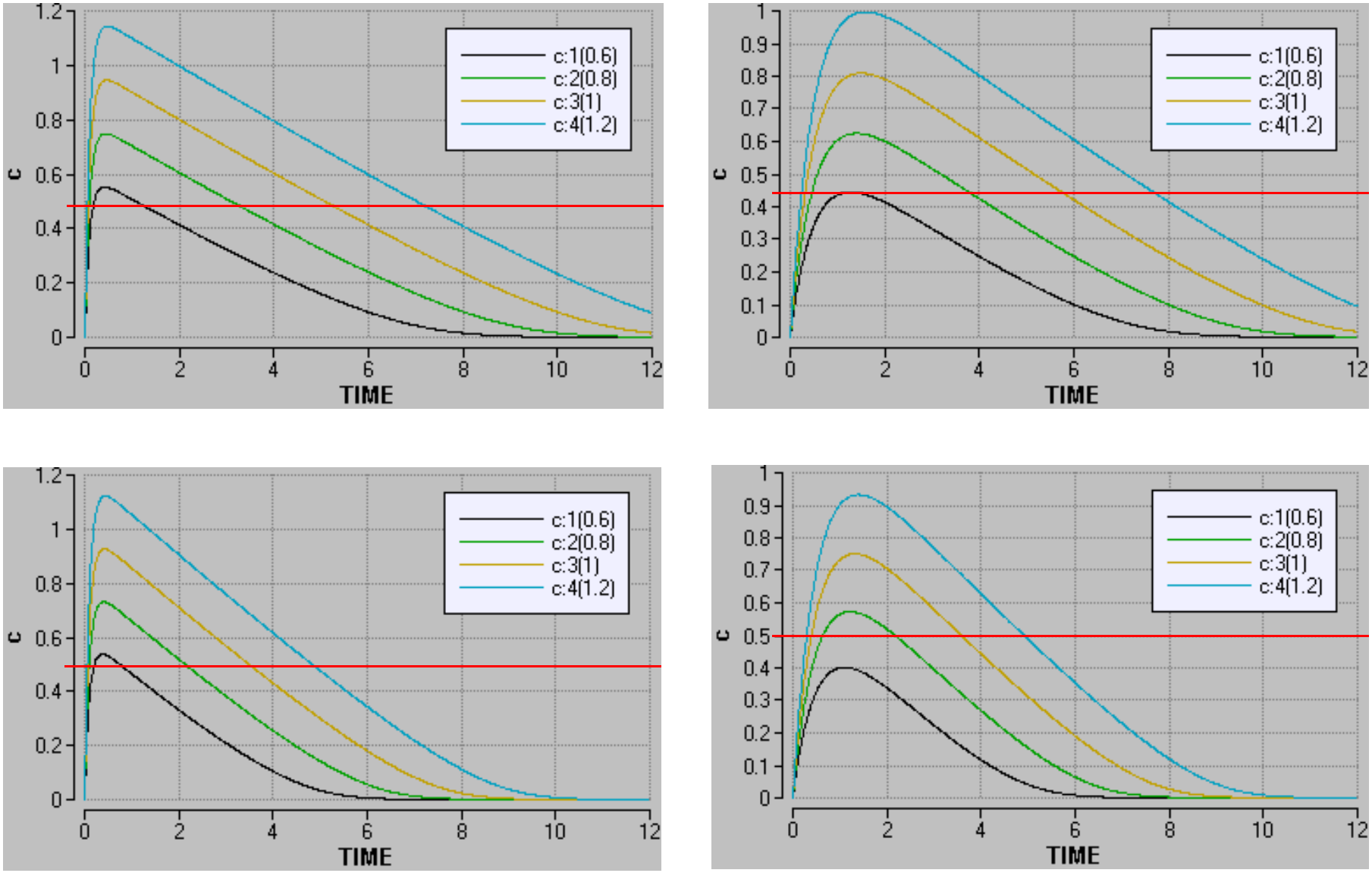
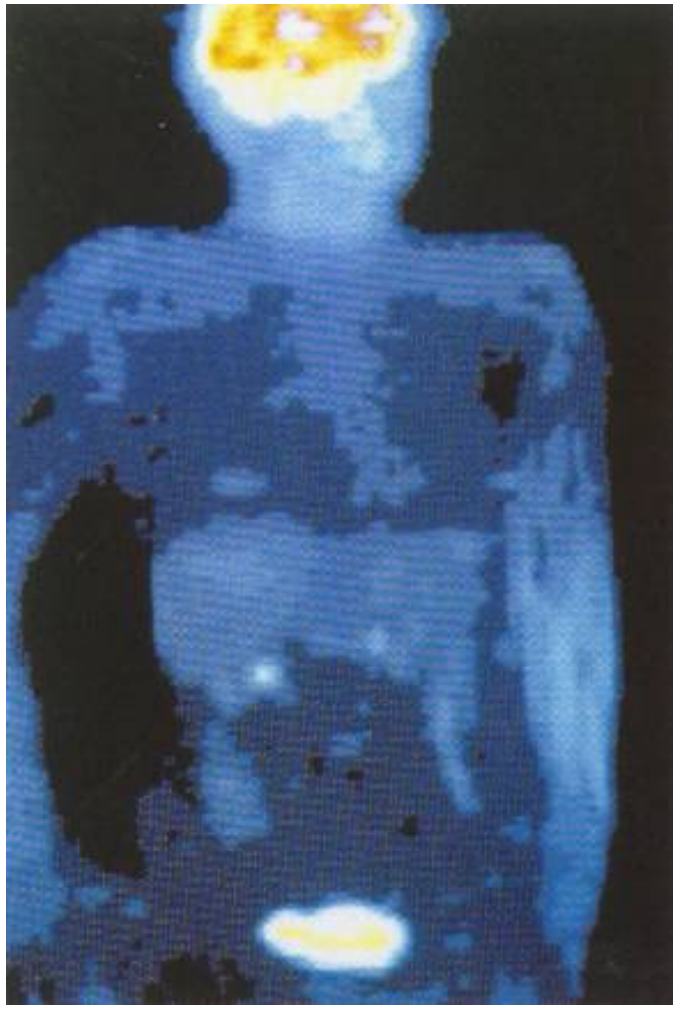


Fig.10. elimination of alcohol in dependence of the initial blood concentration for different resorption - and elimination parameters (left: k_a = 10 h^{-1}; right: k_a = 2 h^{-1}) and v_m = 0.55 (upper) and 0.8 bap·l/h (lower)

Imaging in uclear medicine – a way to catch bio-kinetics

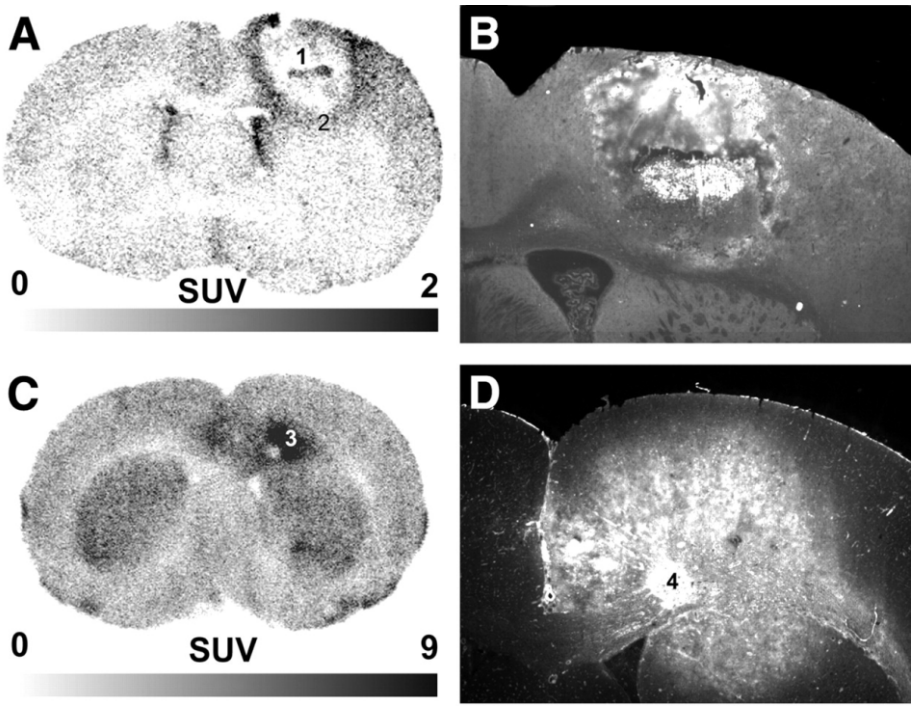
PET & SPECT: Tomography in Nuclear Medicine



Applications / Indications:

- → Metabolic information (tracer priciple)
- → ^{19}F-FDG for PET brain imaging or cancer metastasis search
- → $^{99m}TcO_4$ for bone micro fractions or metastasis search
- → Cardiology
- → Theranostics

PET & SPECT: Tomography in Nuclear Medicine



Types of Tracers / Molecules that can be labelled with radioisotopes:

→ Glucose

→ Neurotransmitters (neoronal activity)

→ Hormones (endocrine system)

→ Cytokines (immune system)

Uptake of ^{18}F-FET (A) and ^{18}F-FDG (C), together with the corresponding (B and D, respectively) Evans blue fluorescence scans.

Spaeth, N, Wyss, MT, Weber, B, Scheidegger, S, Lutz, A, Verwey, J, Radovanovic, I, Pahnke, J, Wild, D, Westera, G, Weishaupt, D, Hermann, DM, Kaser-Hotz, B, Aguzzi, A, Buck A (2004): Uptake of ^{18}F-Fluorocholin, ^{18}F-Fluoroethyl-L-Tyrosine, and ^{18}F-FDG in Acute Celebral Radiation Injury in the Rat: Implications for Separation of the Radiation Necrosis from Tumor Recurrence. *J. Nucl. Med.*, **45**, 1931-1938

PET & SPECT: Tomography in Nuclear Medicine

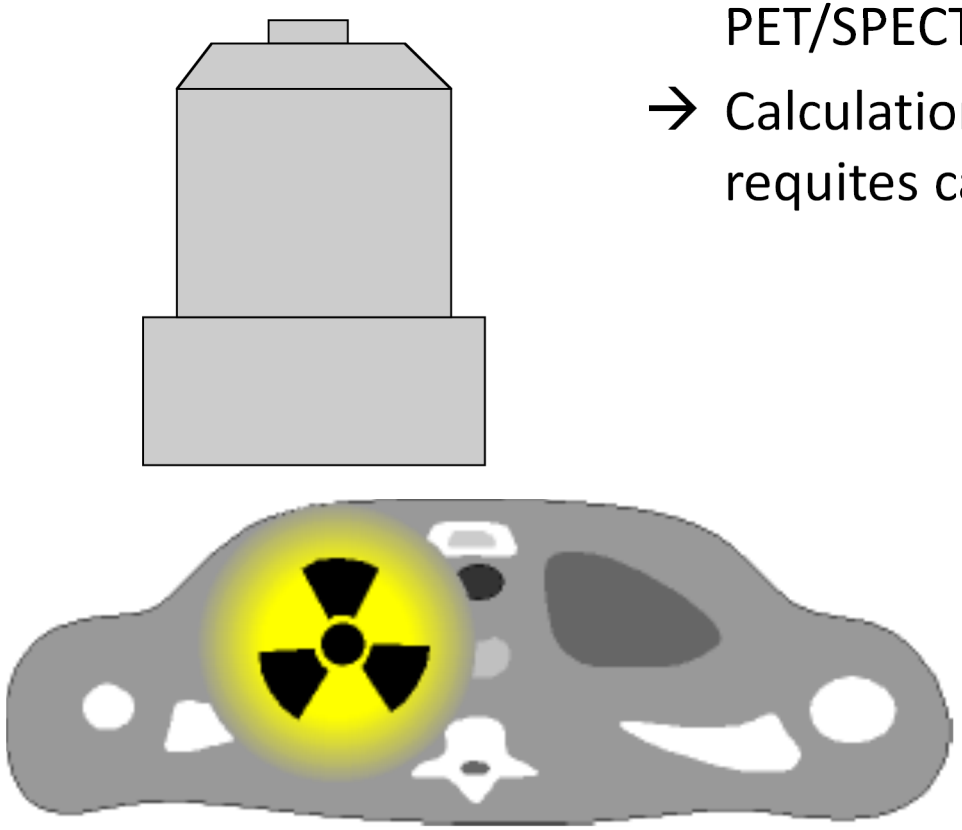
Priciple of tracer and imaging:

→ Tracer (specific molecule defines biokinetics)

→ Tracer accumulates in certain structures (e.g. metastasis or activ brain region)

→ Isotope defines radiation energy and characteristics: For PET, a positron emitter has to be used

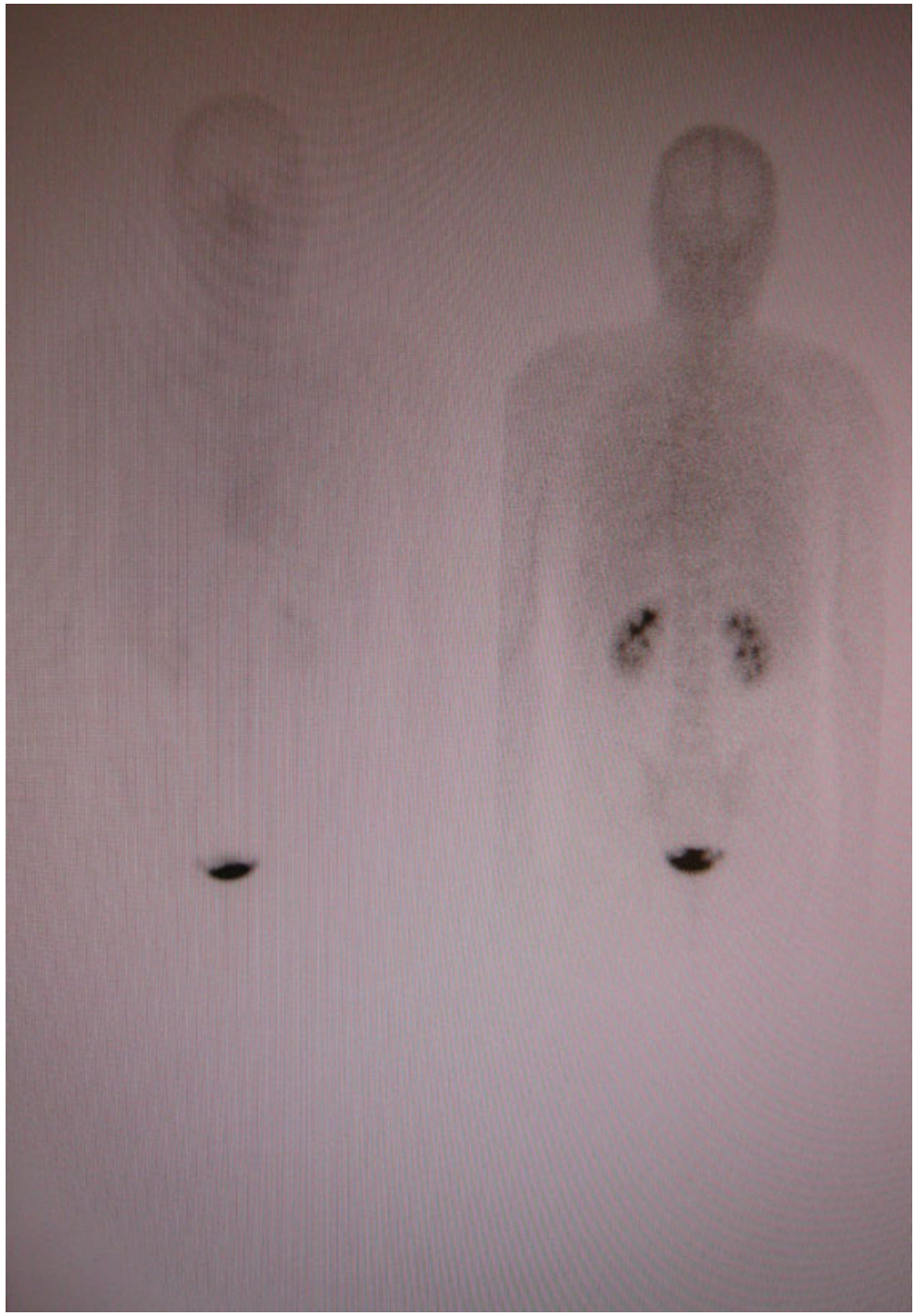
PET & SPECT: Tomography in Nuclear Medicine

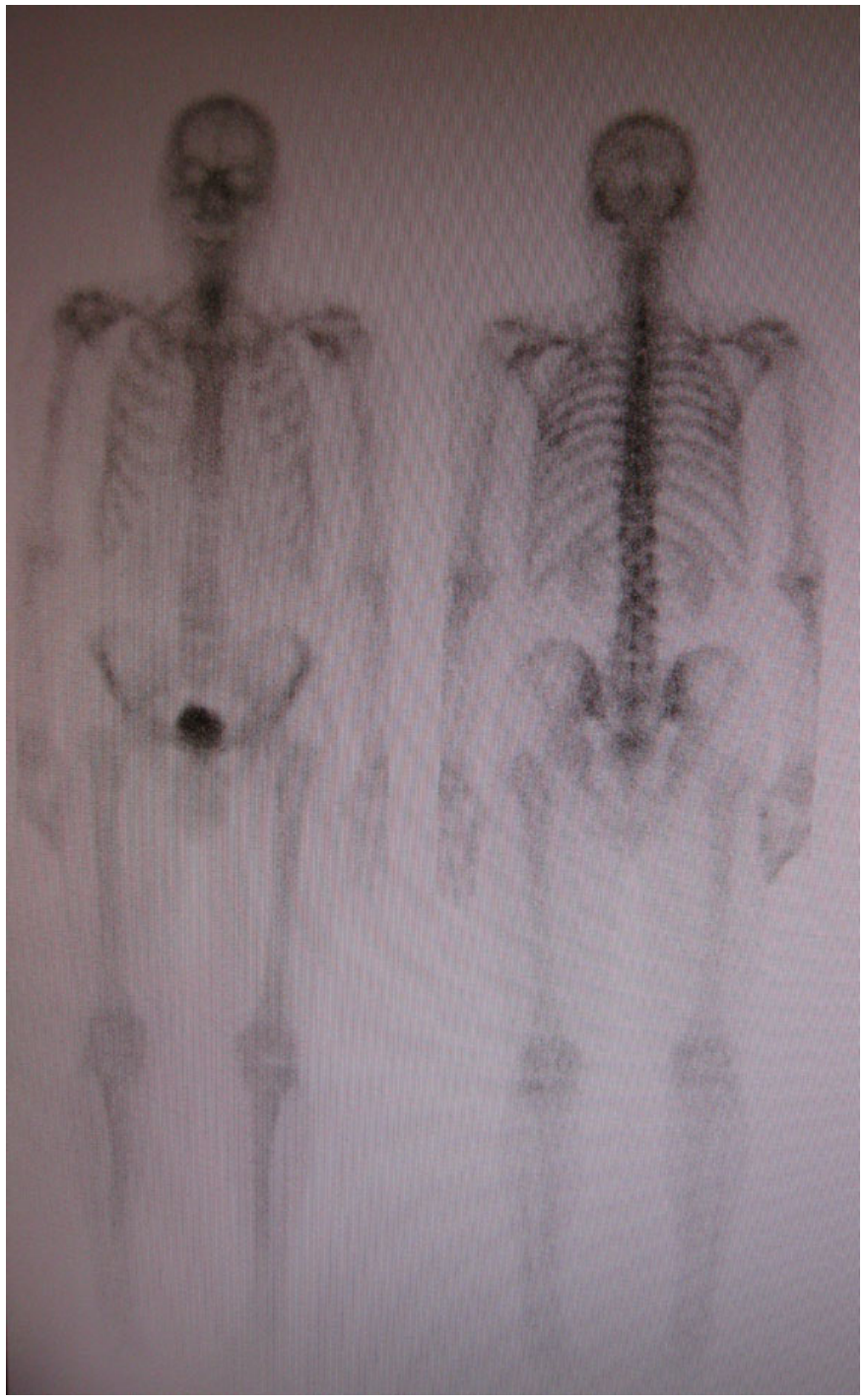


Principle of measurement:

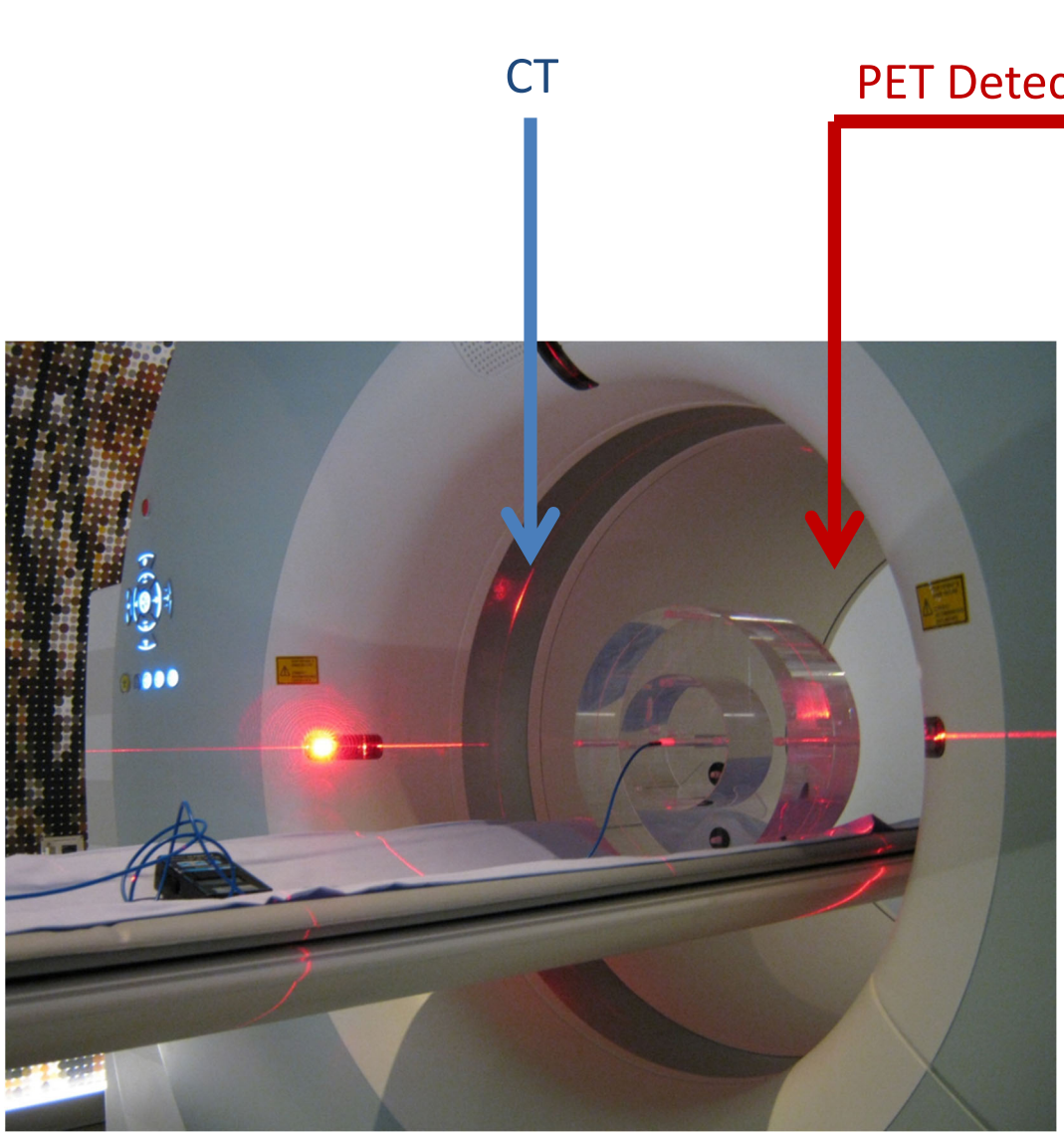
→ Measurement of γ-radiation emitted by isotopes by a Gamma Camera or PET/SPECT

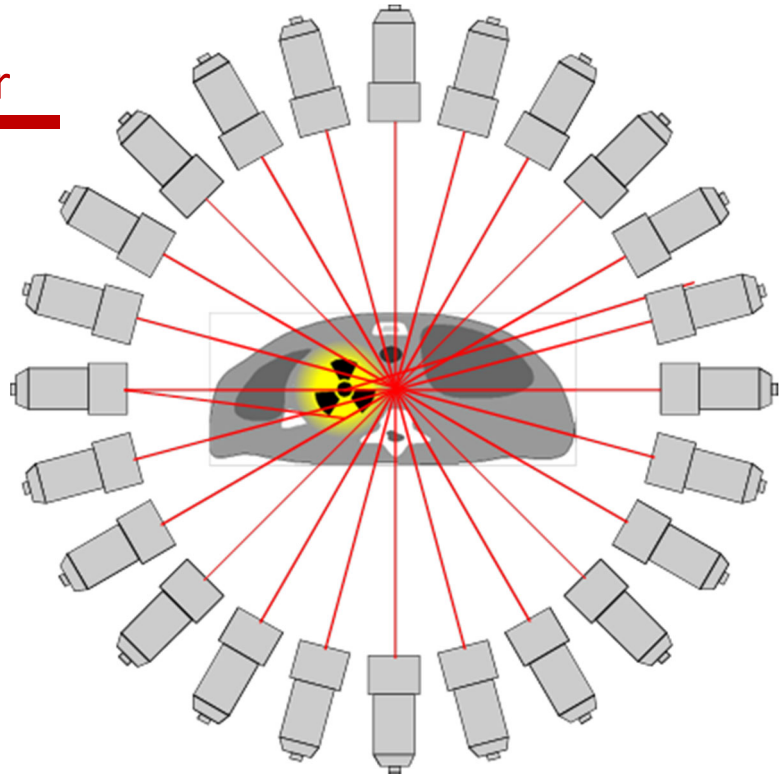
→ Calculation of activity distribution requites calibration

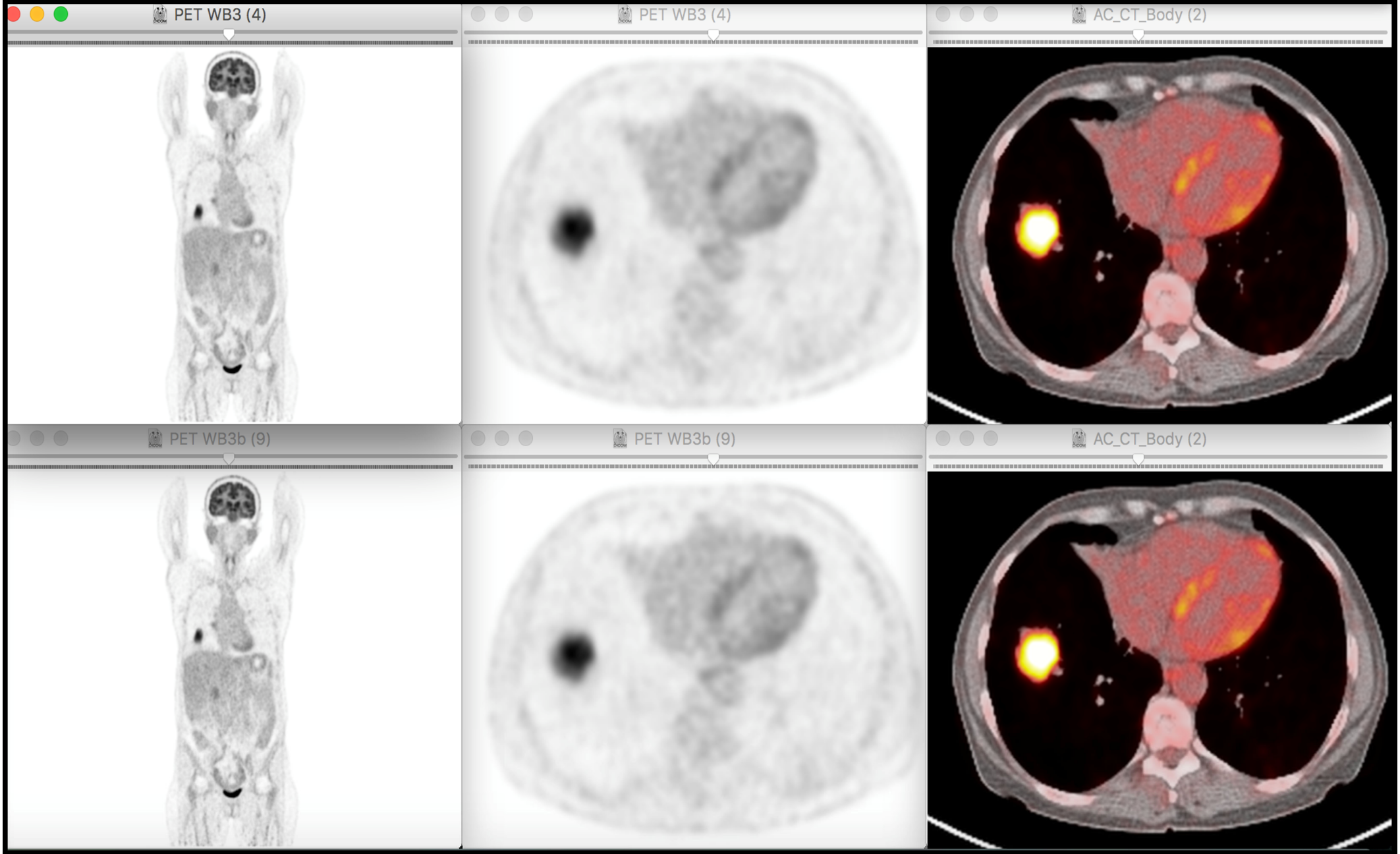




PET: Positron Emission Tomography






PET WB3 (4)
PET WB3 (4)
AC_CT_Body (2)
PET WB3b (9)
PET WB3b (9)
AC_CT_Body (2)

Nuclear Medicine: Radioactive Decay

$$\frac{dN}{dt} = -\lambda N$$

$$A(t) = \dot{N}$$

$$A(t) = -\lambda N(t)$$

$$\frac{dA}{dt} = -\lambda A$$

Modelling of decay:

→ Activity *A* [Bq] = number of decaying nuclei *dN* per second (time *dt*)

→ Probability of decay is given by quantum mechanics of the nucleus and is independent from neighboring nuclei

→ Decay is directly proportional to the number of remaining nuclei *N*

Nuclear Medicine: Radioactive Decay

$$\frac{dA}{dt} = -\lambda A$$

$$\frac{dA}{dt} = -(k_e + \lambda) A$$

$$A(t) = A_0 \cdot e^{-(k_e+\lambda)t}$$

Modelling of decay:

→ In addition to the radioactive (physical) decay, radio-isotopes are eliminated by biological processes of the body (elimination rate constant k_e)

→ This contribution has to be added to the physical decay constant λ

→ The solution $A(t)$ can be found vy separation and integration and is described by an exponential decay

Nuclear Medicine: Radioactive Decay

$$A(t) = A_0 \cdot e^{-(k_e+\lambda)t}$$

Modelling of decay:

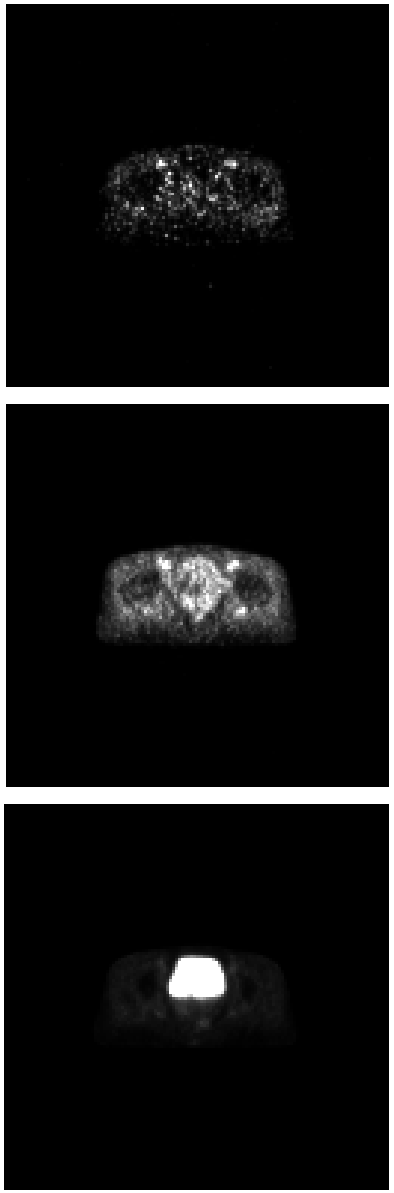
$$T_{1/2}^{eff} = \frac{\ln 2}{k_e + \lambda}$$

→ The effective half-life is dependent on the physical- and biological half-life

$$\frac{1}{T_{1/2}^{eff}} = \frac{k_e + \lambda}{\ln 2} = \frac{k_e}{\ln 2} + \frac{\lambda}{\ln 2} = \frac{1}{T_{1/2}^{bio}} + \frac{1}{T_{1/2}^{phy}} = \frac{T_{1/2}^{bio} + T_{1/2}^{phy}}{T_{1/2}^{bio} \cdot T_{1/2}^{phy}}$$

$$T_{1/2}^{eff} = \frac{T_{1/2}^{bio} \cdot T_{1/2}^{phy}}{T_{1/2}^{bio} + T_{1/2}^{phy}}$$

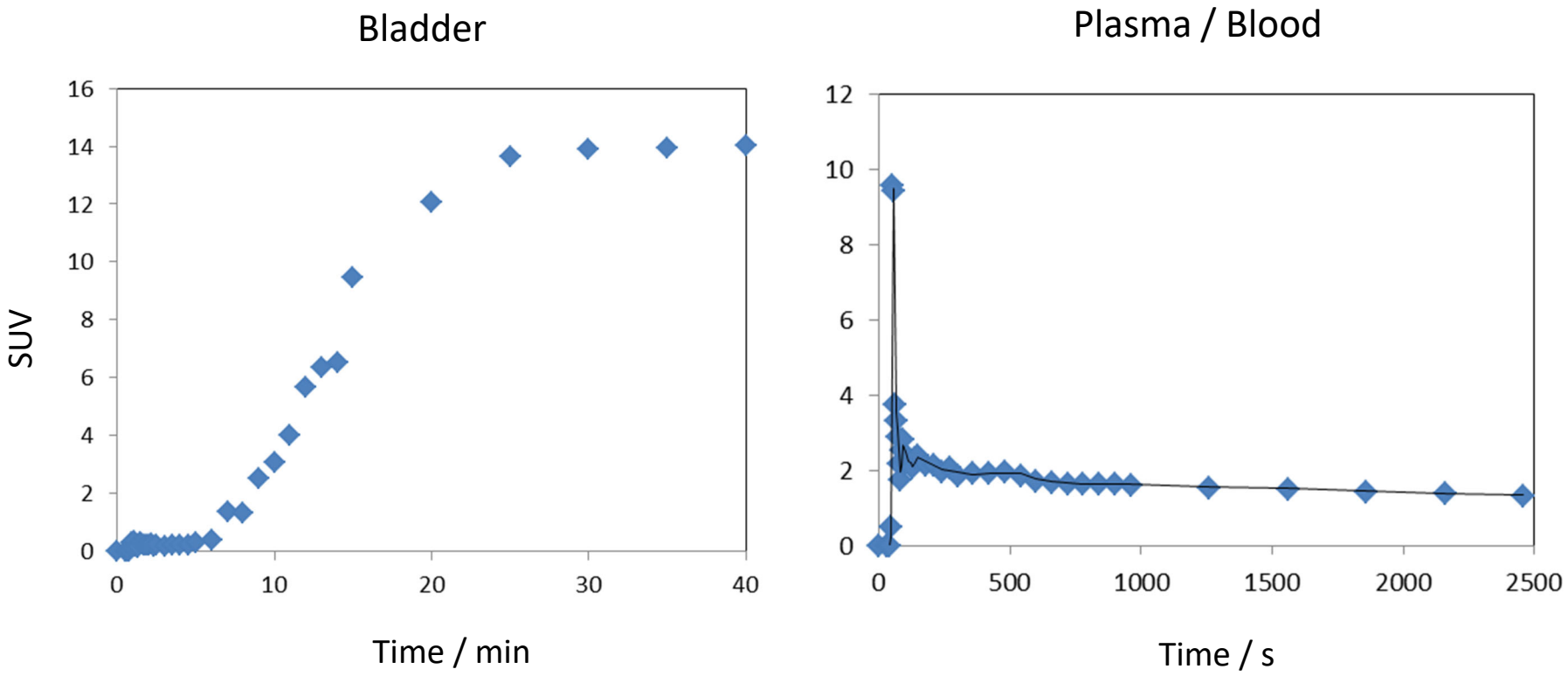
Problems



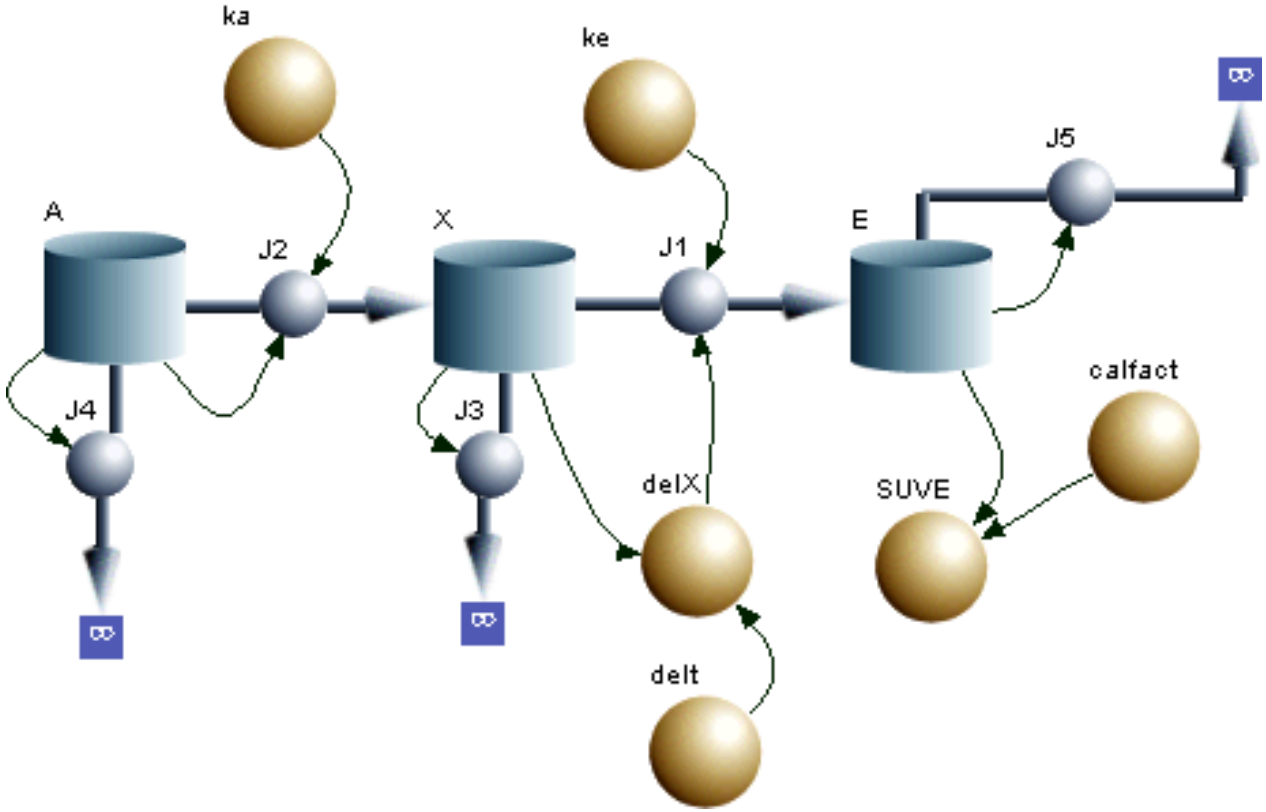
Model-based data analysis of Tracer accumulation and elimination (s. data set provided by materials week 6)

- Implementation of 2-Compartiment model
- Calibration
- Fit of measured activities (measurements of SUV by a DICOM viewer)

Measurements of SUV in Bladder and Plasma Compartment



Modelling of SUV in Bladder and Plasma Compartment



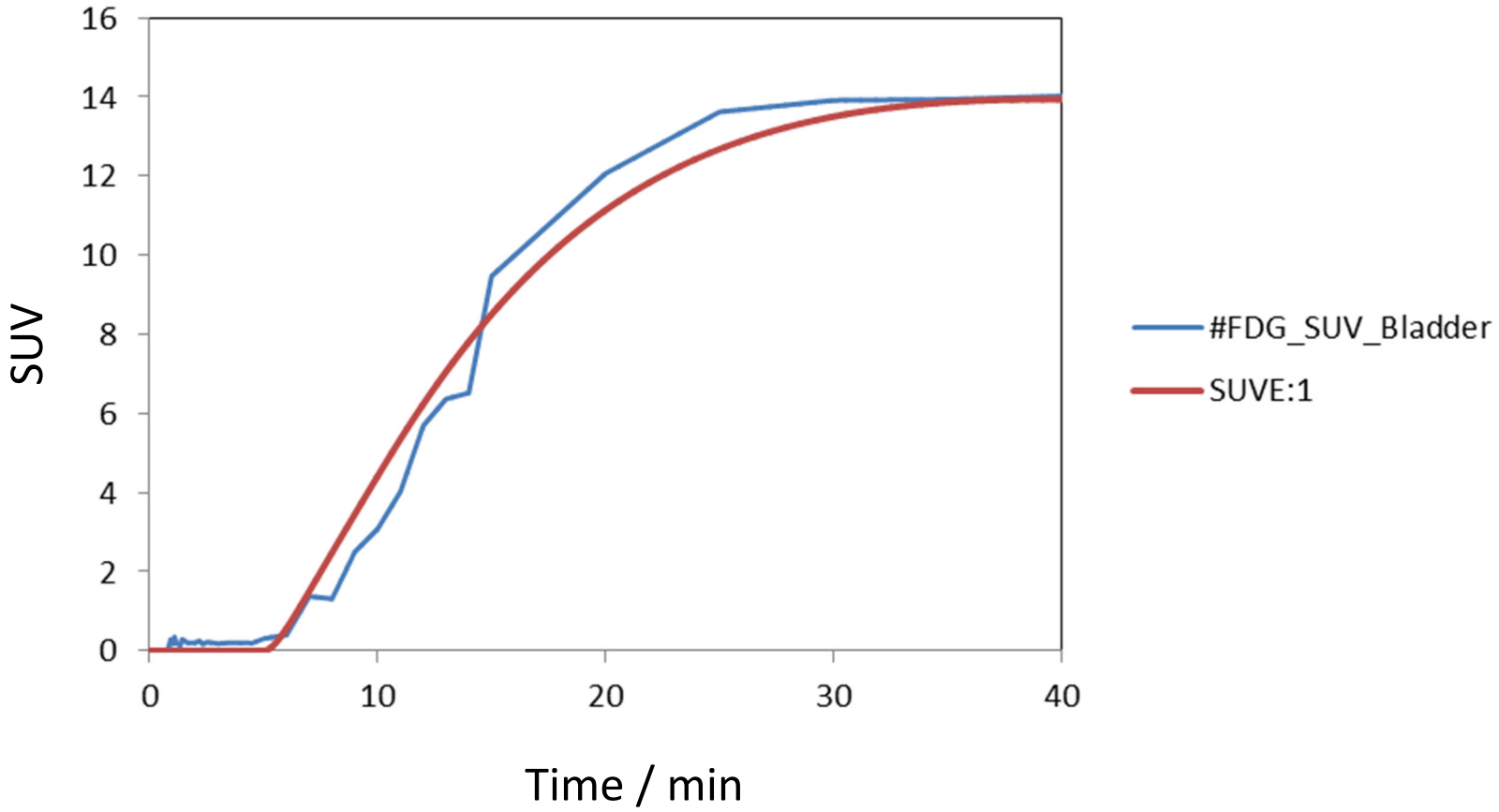
{Top model}

{Reservoirs}
d/dt (X) = - J1 + J2 - J3
INIT X = 0
d/dt (E) = + J1 - J5
INIT E = 0
d/dt (A) = - J2 - J4
INIT A = 1

{Flows}
J1 = ke*delX
J2 = ka*A
J3 = kr*X
J4 = kr*A
J5 = kr*E

{Functions}
ke = 0.1
ka = 2
SUVE = calfact*E
calfact = 19
delt = 5
delX = DELAY(X,delt)
{Globals}
kr = logn(2)/109
{End Globals}

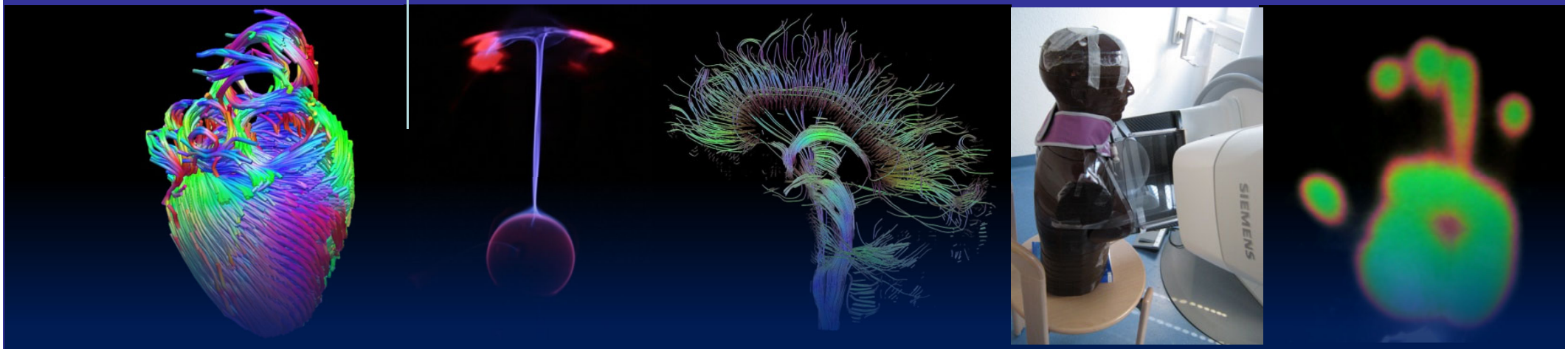
Simulation of SUV in Bladder $E(t)$



Pharmacodynamics

Hyperboost Training Course Model-based Data Analysis for Clinical Applications

Stephan Scheidegger
Medical Biophysics Group ZHAW
2024



CONTENT

Pharmacodynamics

Introduction: PK-PD models

Different types of PD-models

- Fixed effect models
- Linear and loglinear models
- Emax models
- Sigmoidal Emax models
- LQ models
- TCP and NTCP

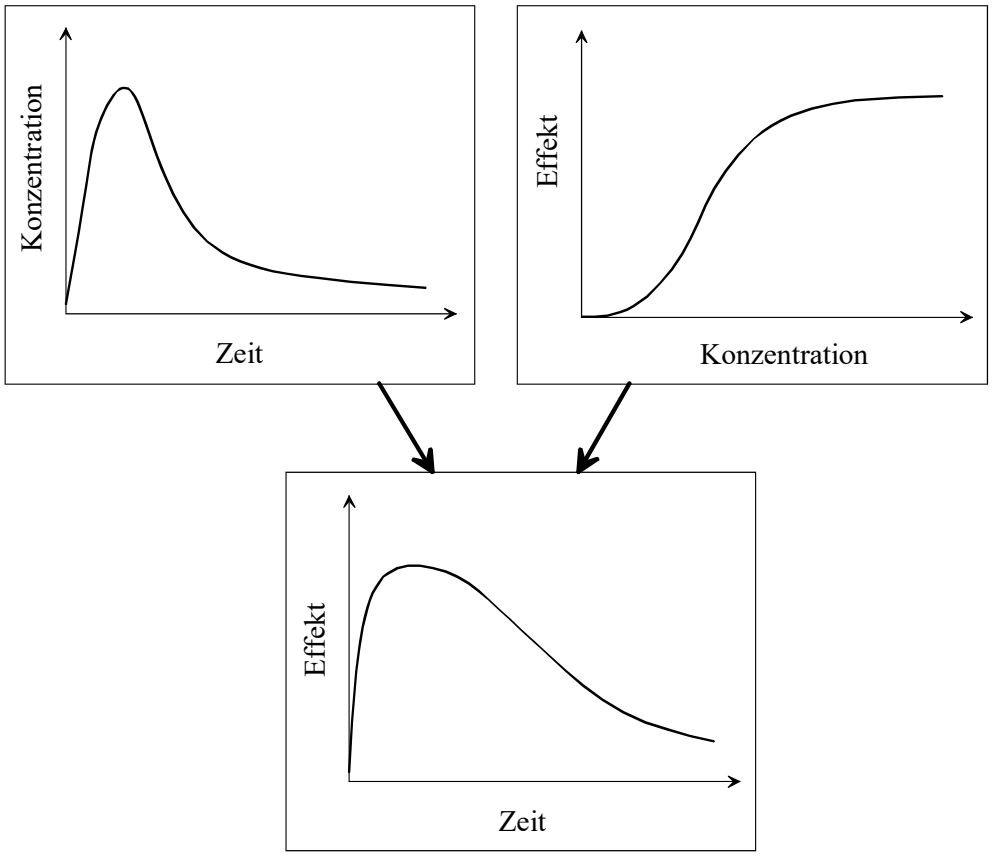
Combined PK-PD models for therapy simulation

Learning Objectives

Students are able

- to explain the different PD models and their limitations
- to analyze biological data
- to model biological combined PD-PK systems

Pharmacodynamics

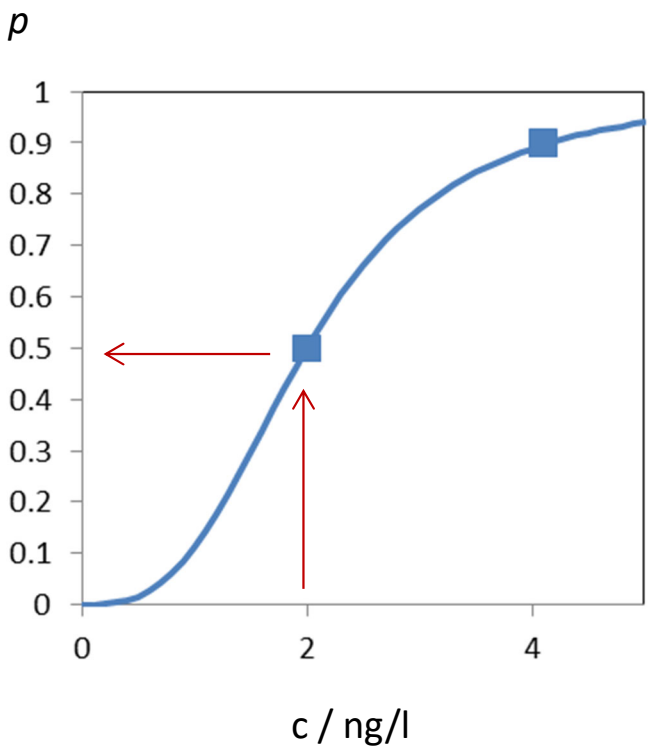


Modelling the effect of therapies: Pharmacodynamics (PD) consider the effect of a drug to the body, pharmacokinetics (PK) model the effect of the body to the drug.

To model the dynamic response during a treatment, pharmacokietic and pharmacodynamic models can be connected to a combined PK-PD model.

Fig.1. Therapy response as a combination of a PD and a PK model

Pharmacodynamics

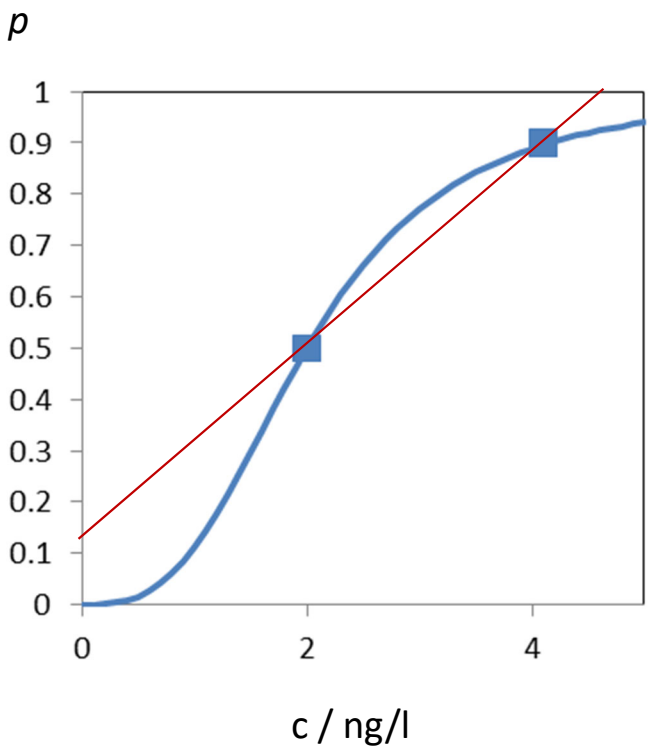


Different types of PD-models:

- fixed effect models give a probability for adverse reactions at a defined plasma concentration.
- Example for a fixed effect model: A plasma concentration of 2 ng/l digoxin is related to a probability of 50% and 4.1 ng/l to a probability of 90% adverse reaction.

Fig.2. Probability *p* for adverse reactions as a function of the plasma concentration *c*.

Pharmacodynamics



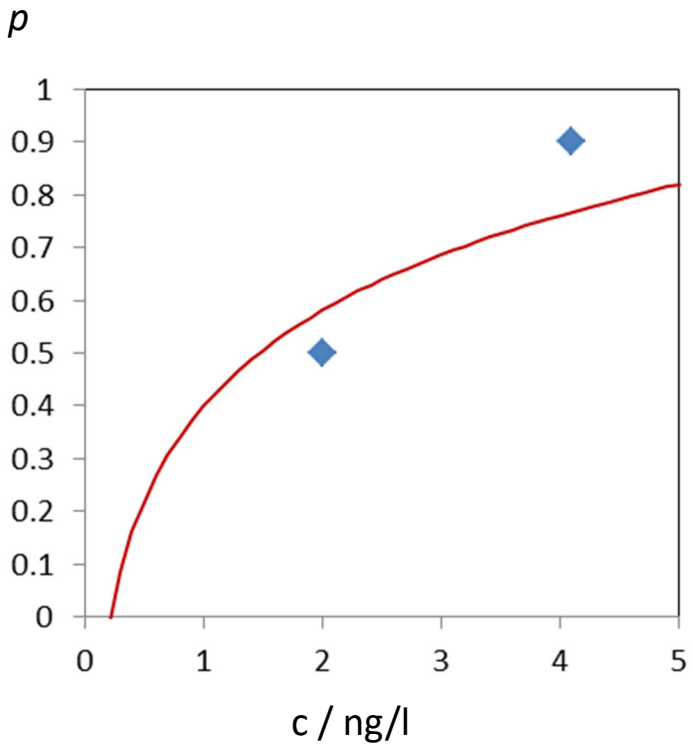
Different types of PD-models:

- Linear models: In most of the cases, the linear relation does not describe the data as soon as more concentrations are measured.

$$E = k \cdot c + E_0$$

Fig.3. Probability *p* for adverse reactions (= effect *E*) as a function of the plasma concentration *c* and with linear model.

Pharmacodynamics



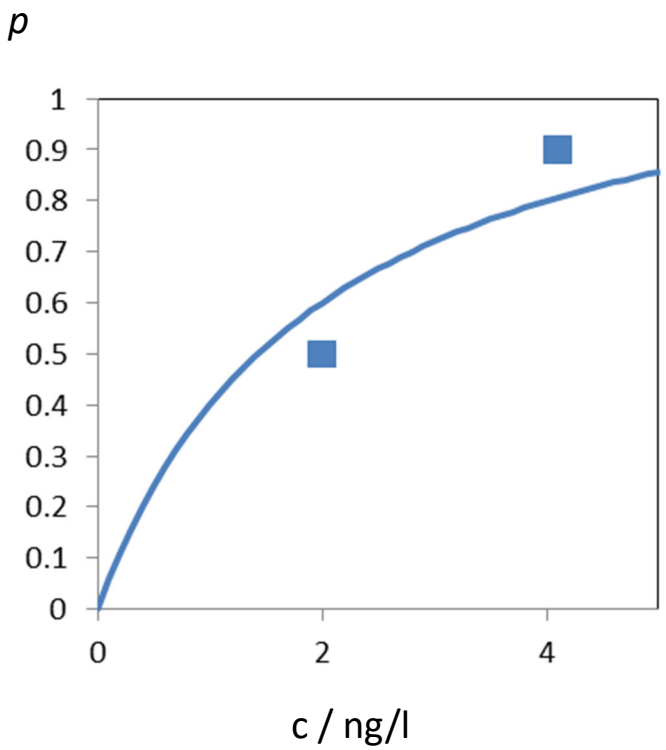
Different types of PD-models:

- logLinear models: depending on the parameters b and k, the effect at c = 0 can be negative or positive, this do not correspond to the often observed sigmoidal relationship.

$$E = k \cdot \log c + b$$

Fig.4. Probability *p* for adverse reactions (= effect *E*) as a function of the plasma concentration *c* with a loglinear model.

Pharmacodynamics



Different types of PD-models:

- E_{max}- models: $E(c=0)$ or $p(c=0) = 0$; but often do not really represent the data.

$$E = \frac{E_{\max} \cdot c}{c(E_{50}) + c}$$

Fig.5. Probability *p* for adverse reactions (= effect *E*) as a function of the plasma concentration *c* with an E_{max} - model.

Pharmacodynamics

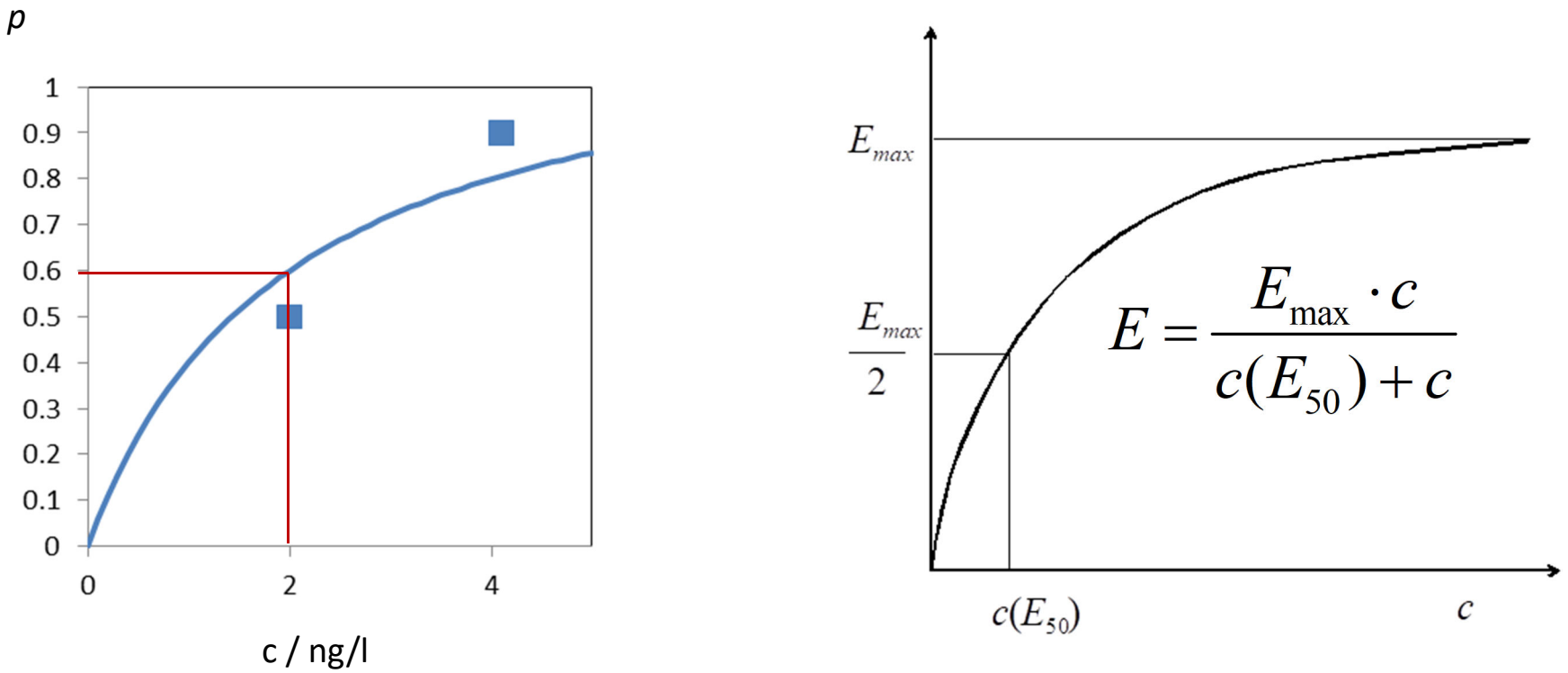
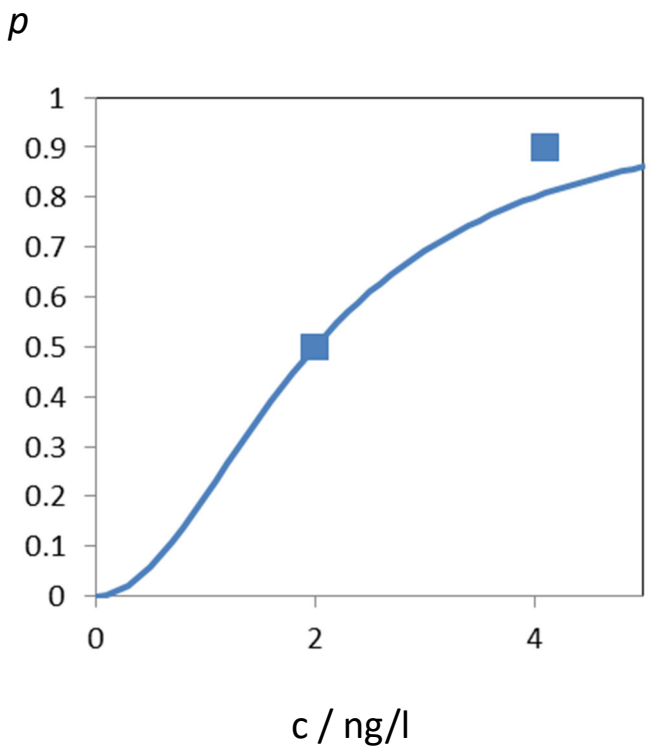


Fig.6. Probability *p* for adverse reactions (= effect *E*) as a function of the plasma concentration *c* with an E_{max} – model: The meaning of the parameter values is visible in the right diagram.

Pharmacodynamics



Different types of PD-models:

- Sigmoidal E_{max}- models: $E(c=0)$ or $p(c=0) = 0$; depending on the hill factor n, these models show the often observed sigmoidal shape.

$$E = \frac{E_{\max} \cdot c^n}{c^n (E_{50}) + c^n}$$

Fig.7. Probability *p* for adverse reactions (= effect *E*) as a function of the plasma concentration *c* with an sigmoidal E_{max} – model with $n = 2$.

Pharmacodynamics

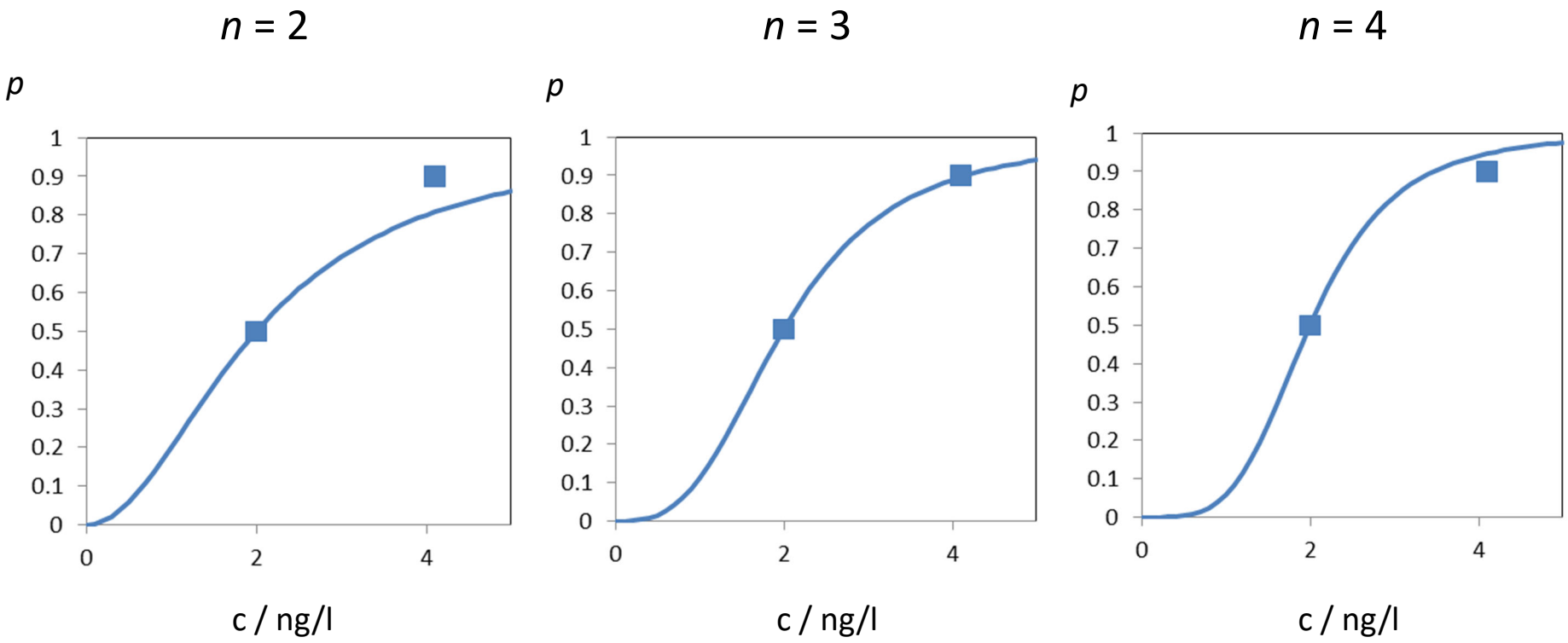
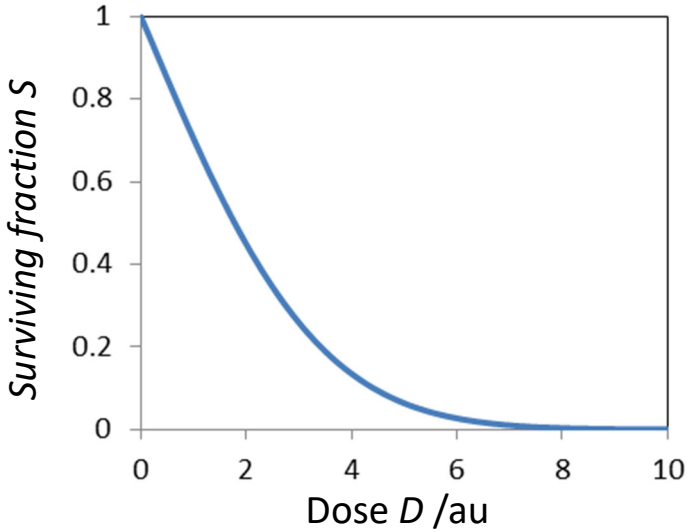


Fig.8. Probability *p* for adverse reactions (= effect *E*) as a function of the plasma concentration *c* with an sigmoidal E_{max} – model with varying *n*.

Pharmacodynamics



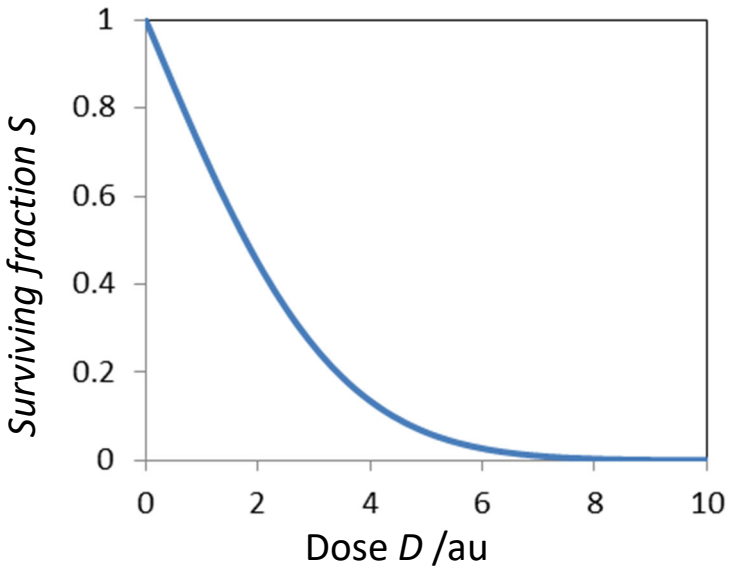
Different types of PD-models:

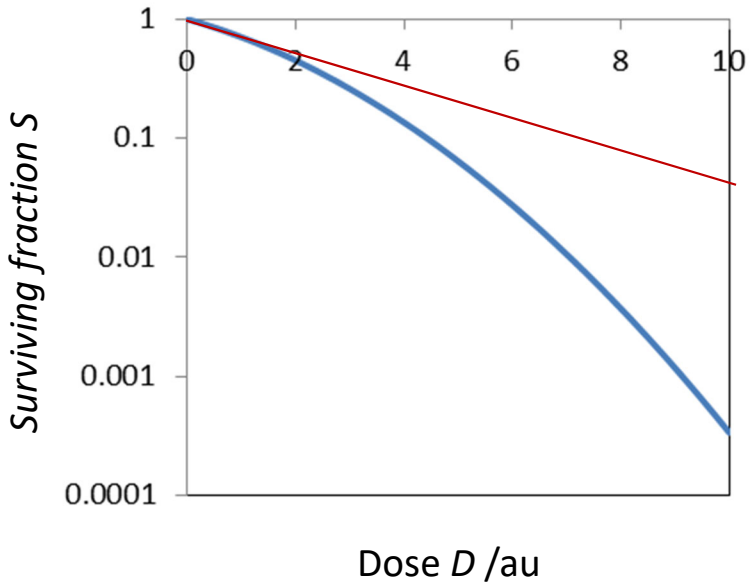
- Linear-quadratic (LQ) models: Often used for anticancer treatments using chemo- or radiation therapy.
- Survival (surviving fraction of cancer cells *S*) is modelled as function of the dose *D*:

$$S = \frac{N}{N_0} = e^{-(\alpha D + \beta D^2)}$$

Fig.9. Surviving fraction *S* as a function of the dose *D* with a linear quadratic model (linear scales).

Pharmacodynamics



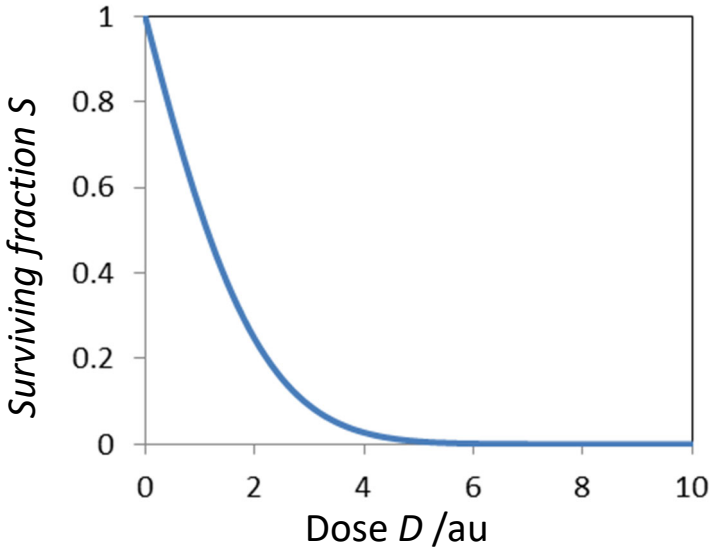


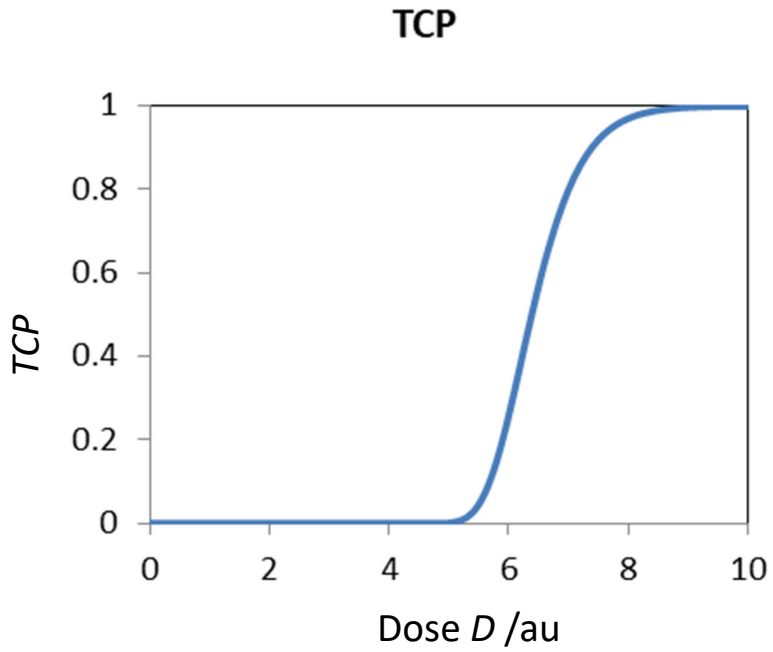
$$S = \frac{N}{N_0} = e^{-(\alpha D + \beta D^2)}$$

$$\log S = -\left(\alpha D + \beta D^2\right)$$

Fig.10. Surviving fraction *S* as a function of the dose *D* with a linear quadratic model, left: linear scale, right: log-scale; α = 0.3 / au; β = 0.05 / au^2.

Pharmacodynamics



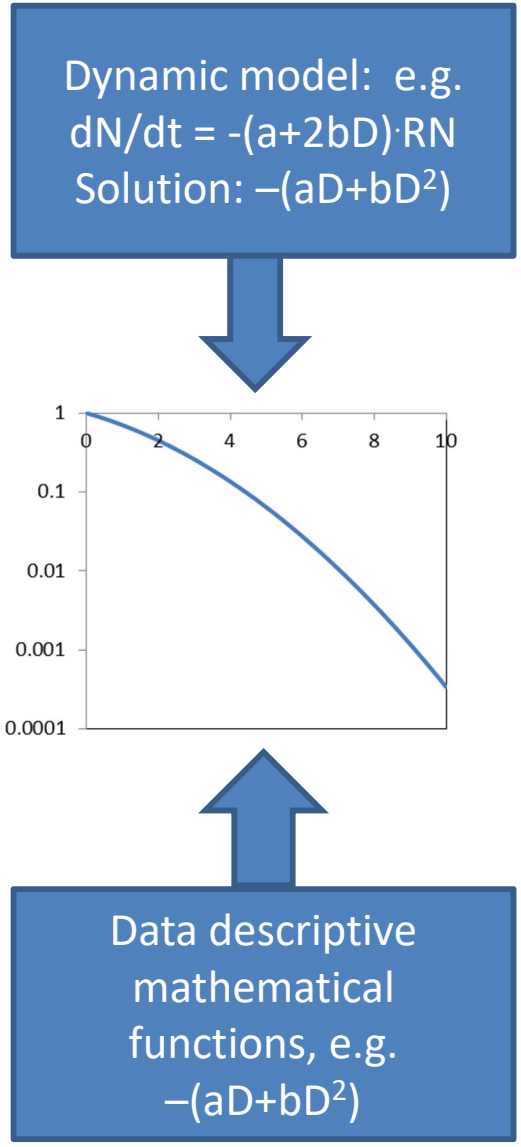


$$S = \frac{N}{N_0} = e^{-(\alpha D + \beta D^2)}$$

$$TCP = e^{-N} = e^{-N_0 S}$$

Fig.11. Surviving fraction *S* (left) and the Tumour Control Probability TCP (right) as a function of the dose *D*; α = 0.5 / au; β = 0.1 / au^2.; N_0 = 1000 cells (for solid tumours, N_0 can exceed 10^{12} cells!).

Pharmacodynamics



Different types of PD-models:

- Direct link models: the momentarily concentration leads to a momentarily effect.
- Indirect link models: momentarily plasma concentration does not correspond to the effect in time → hysteresis.
  → the discussed PD models are all data descriptive models using a fitting formula and DO NOT describe the dynamic process behind the effect!