PHARMACOKINETICS

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Basic principles of pharmacokinetics

Pharmacokinetics is aimed on this processes:

absorption

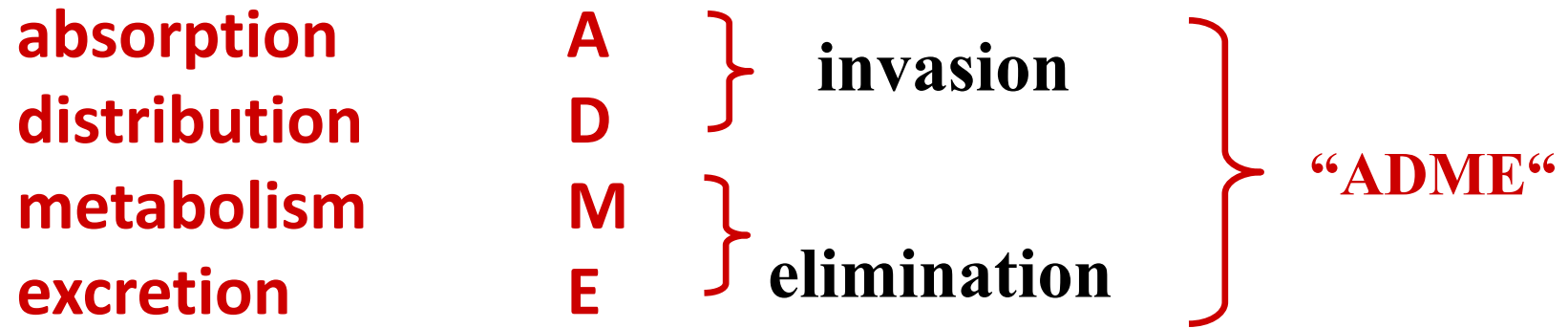distribution

biotransformation

excretion of drugs

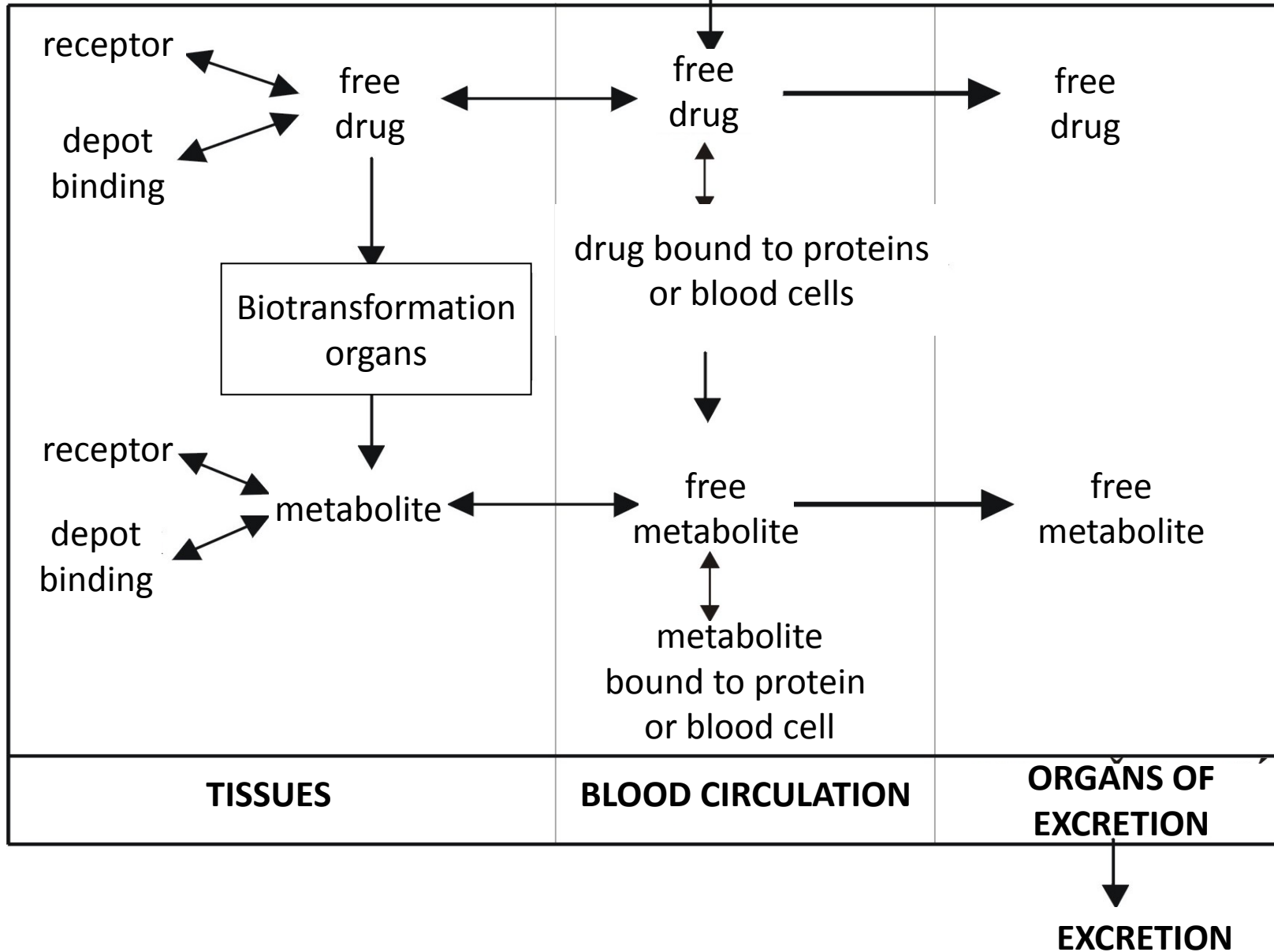and their relation to pharmacologic (therapeutic or toxic) effects

Pharmacokinetics

absorption   A ⎱ invasion
distribution   D ⎰
                              ⎱ "ADME"
metabolism   M ⎱ elimination
excretion   E ⎰

- processes of **ADME**

General features of drug movement across the body

1. **Physical-chemical characteristic of drug**

    lipophilic vs hydrophilic, MW, charge, pKa, solubility

2. **Drug transmission through biological barriers**

    lipophilic - pasive diffusion

    hydrophilic- pore transmission

    active transport, vesicular transport – pinocytosis, phagocytosis

3. **Drug binding**

    plasmatic prote

    blood cells
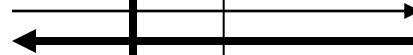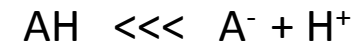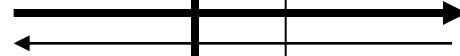
    tissue binding

4. **Tissue perfusion**

    brain, heart, liver and kidney

    adipose tissue

Stomach pH 1-2   Parietal cell+ vascular endothelial cell
                                          pH 7.2-7.4

AH >>> H$^+$+A$^-$ $\longrightarrow$ AH <<< A$^-$ + H$^+$
                             $\longleftarrow$

BH$^+$ >>> B + H$^+$ $\longrightarrow$ BH$^+$ <<< B + H$^+$
                             $\longleftarrow$

http://icp.org.nz/icp_t11.html

Absorption – routes of administration

penetration of dissolved drug from the site of administration to blood (systemic circulation) – necessary for general effect– **systemic effect**

Local effect:
on skin, mucosas or ventricles
absorption is undesirable – possible AE
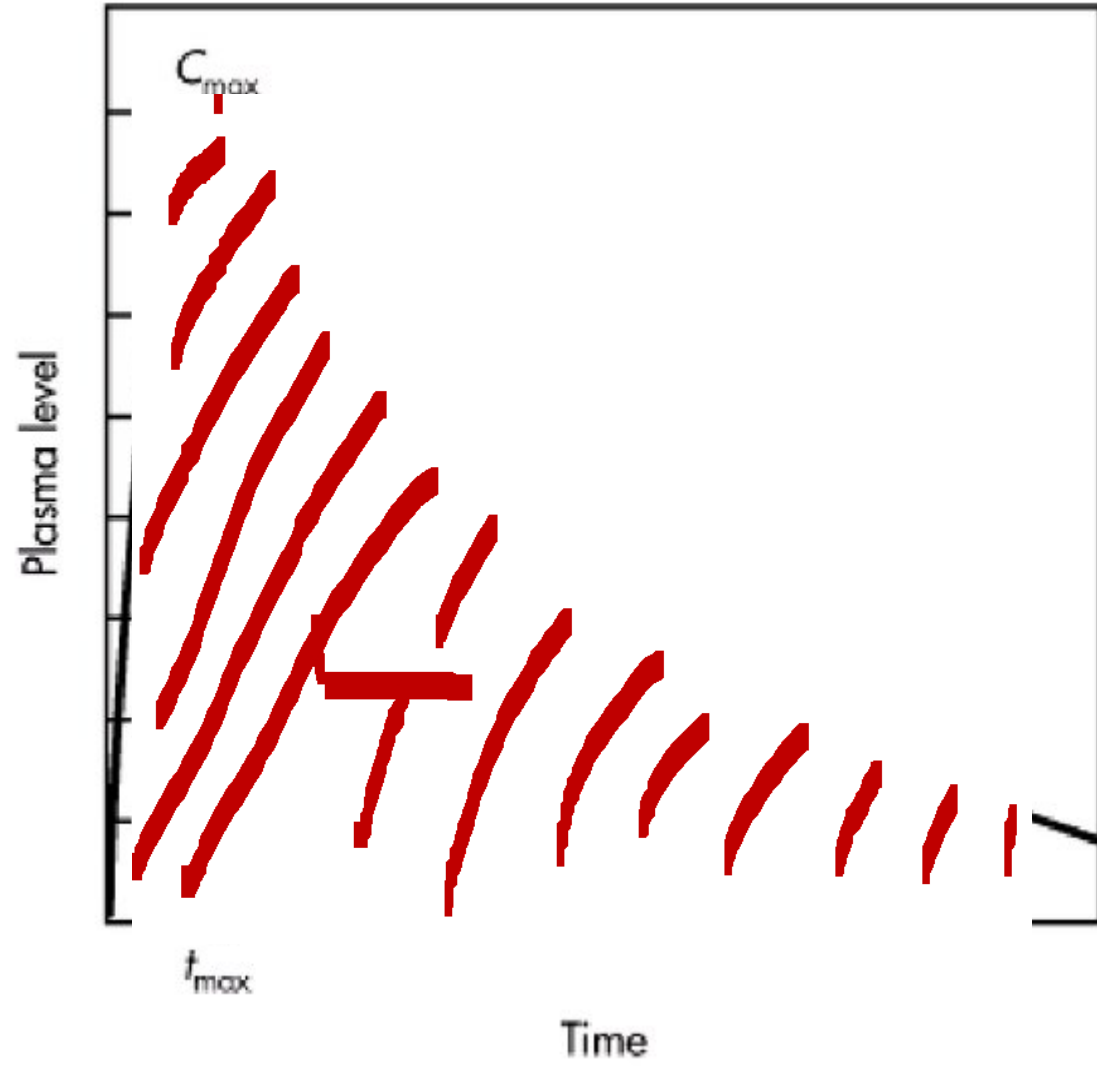ie. local corticoids, local anesthetics

Speed and **extent** of absorption are described by P-kinetic parameters:

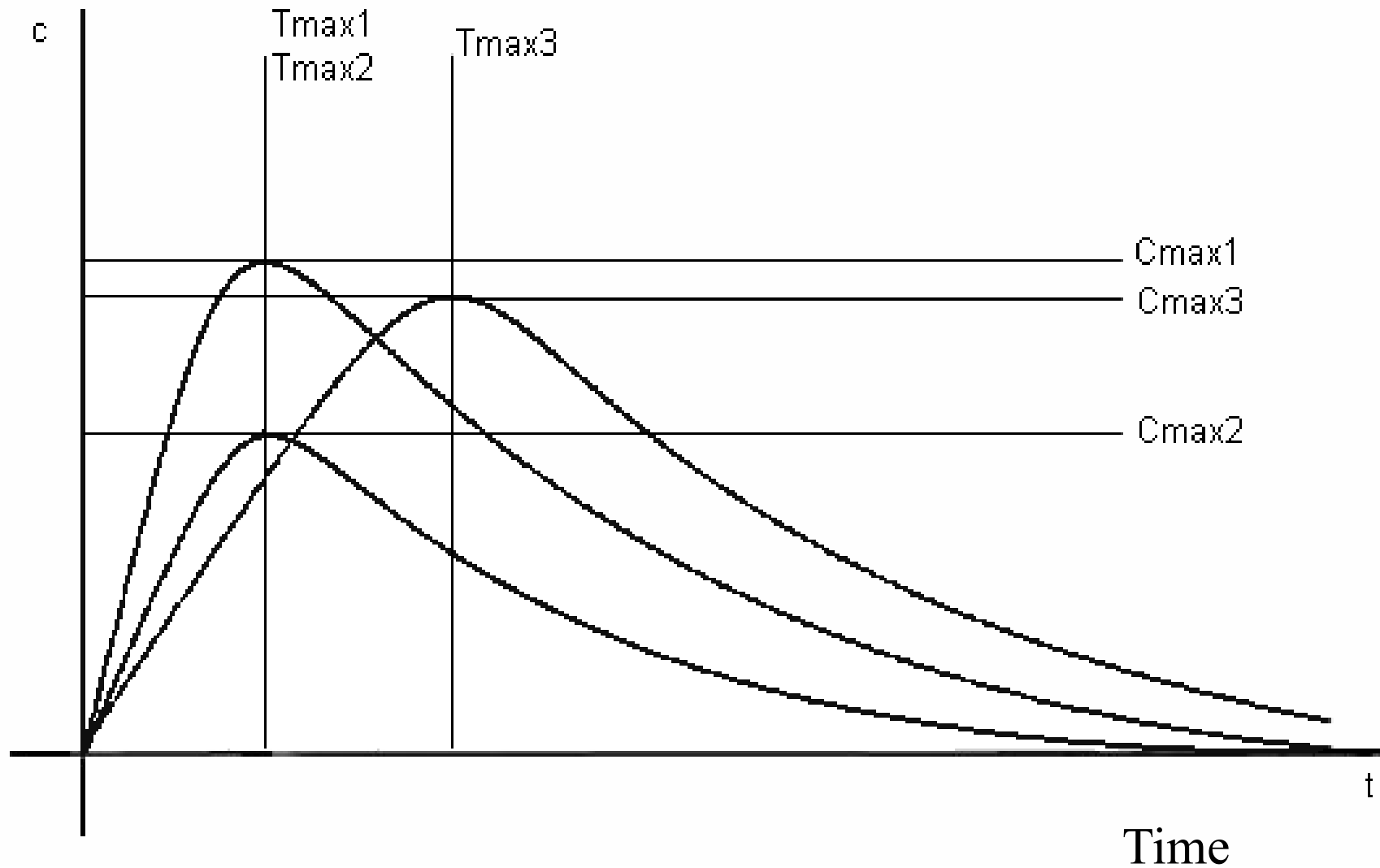C_{max} max. concentration of drug in plasma after single dose

T_{max} time, when drug reach c_{max} (speed)

F   bioavailability (extent)

Concentration of drug

Time

Bioavailability- F

how much from the administered dose get to circulation

extravascular administration - 0-100% (resp. 0-1)

intravenous (intravascular) - 100% = 1

if F is < 20 % = 0 - 0,2 – it not worth to administer the drug by this way (some of them are administered through that - SET, bisfosfonates)
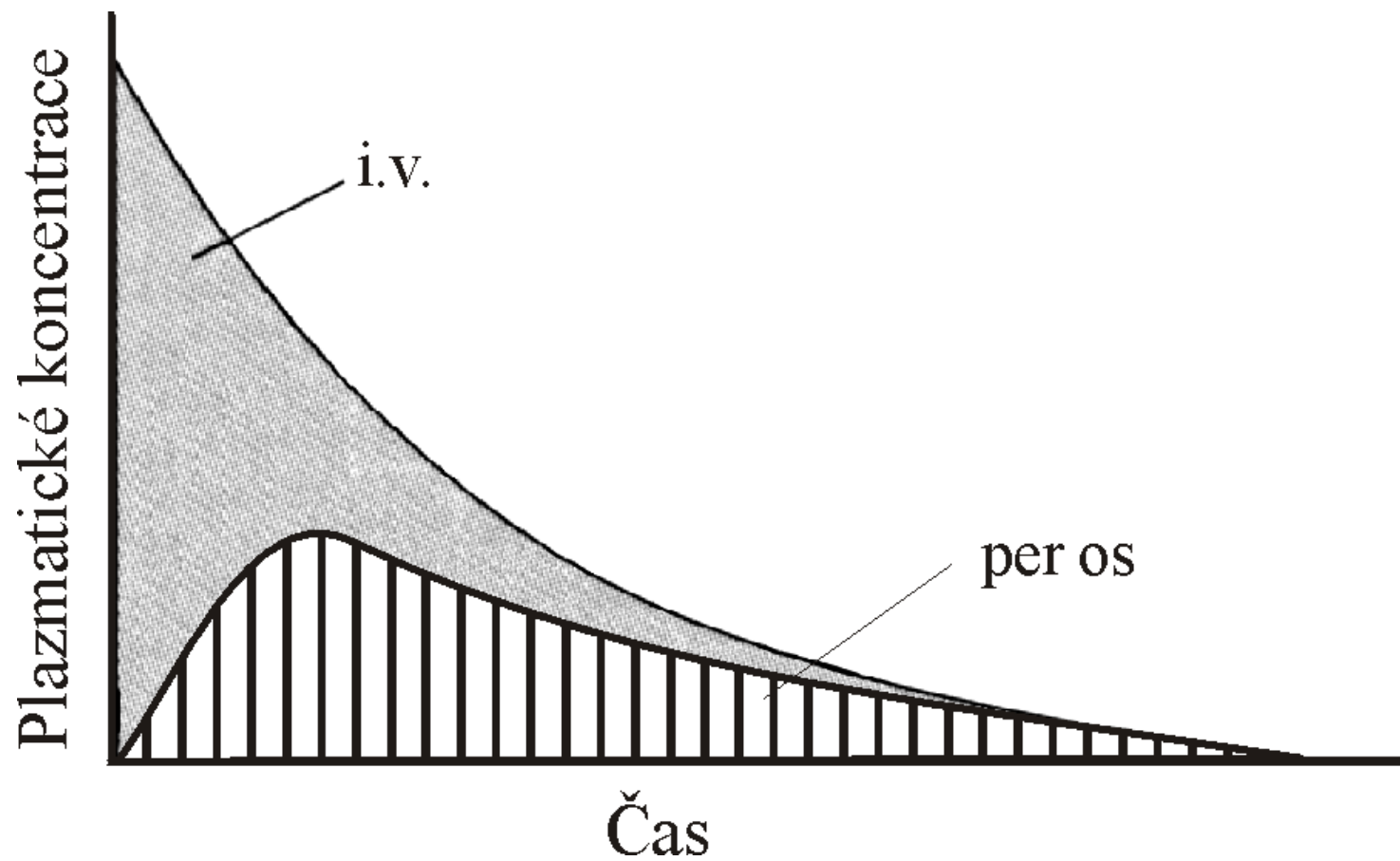
the measure of bioavailability is the **area under the curve** (AUC)
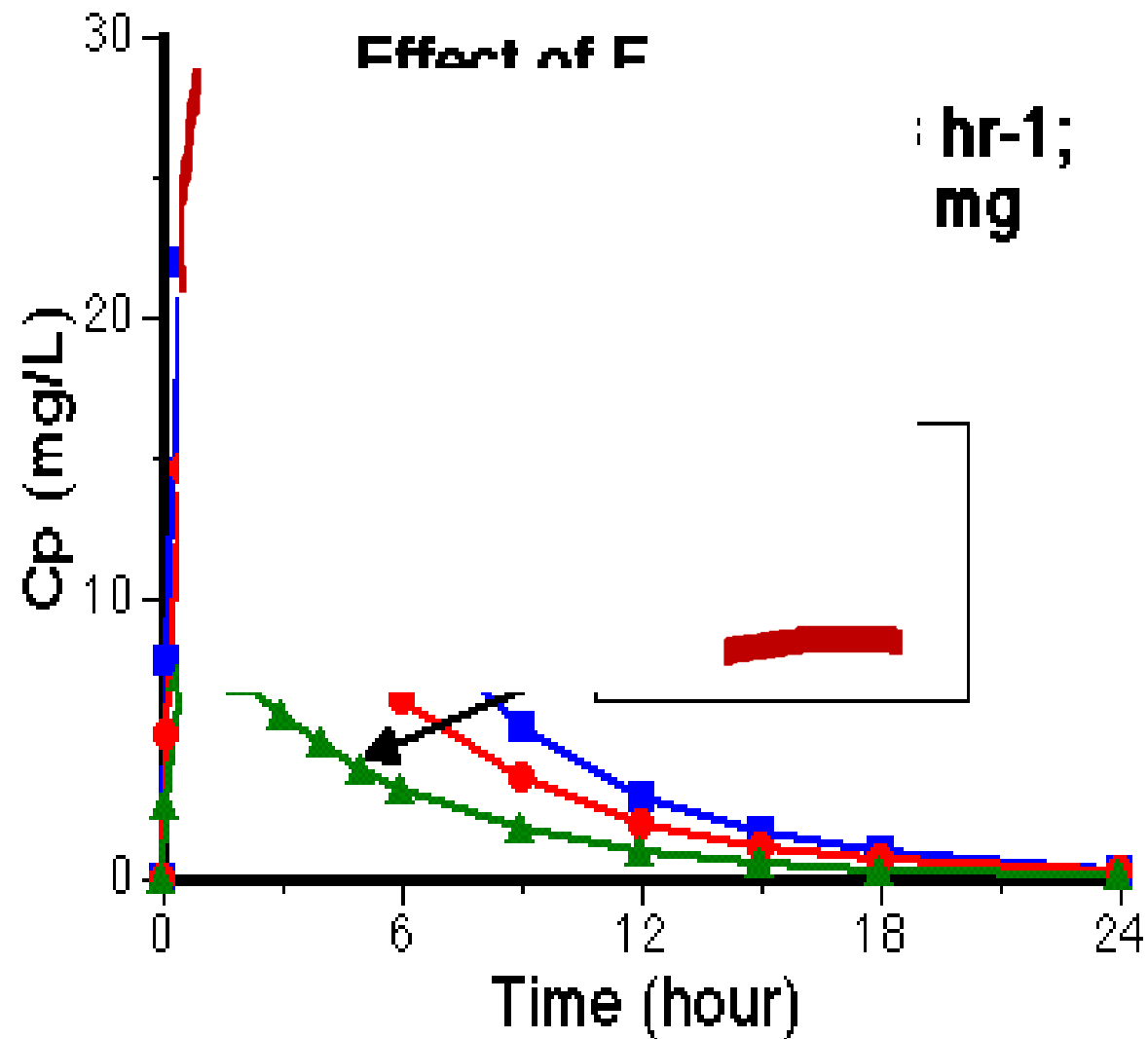
$$F = \frac{AUC_{po}}{AUC_{iv}}$$

http://icp.org.nz/icp_t6.htm

AUC – area under the curve

Effects of different bioavailability (F) on the pharmacokinetics

Bioavailability- F
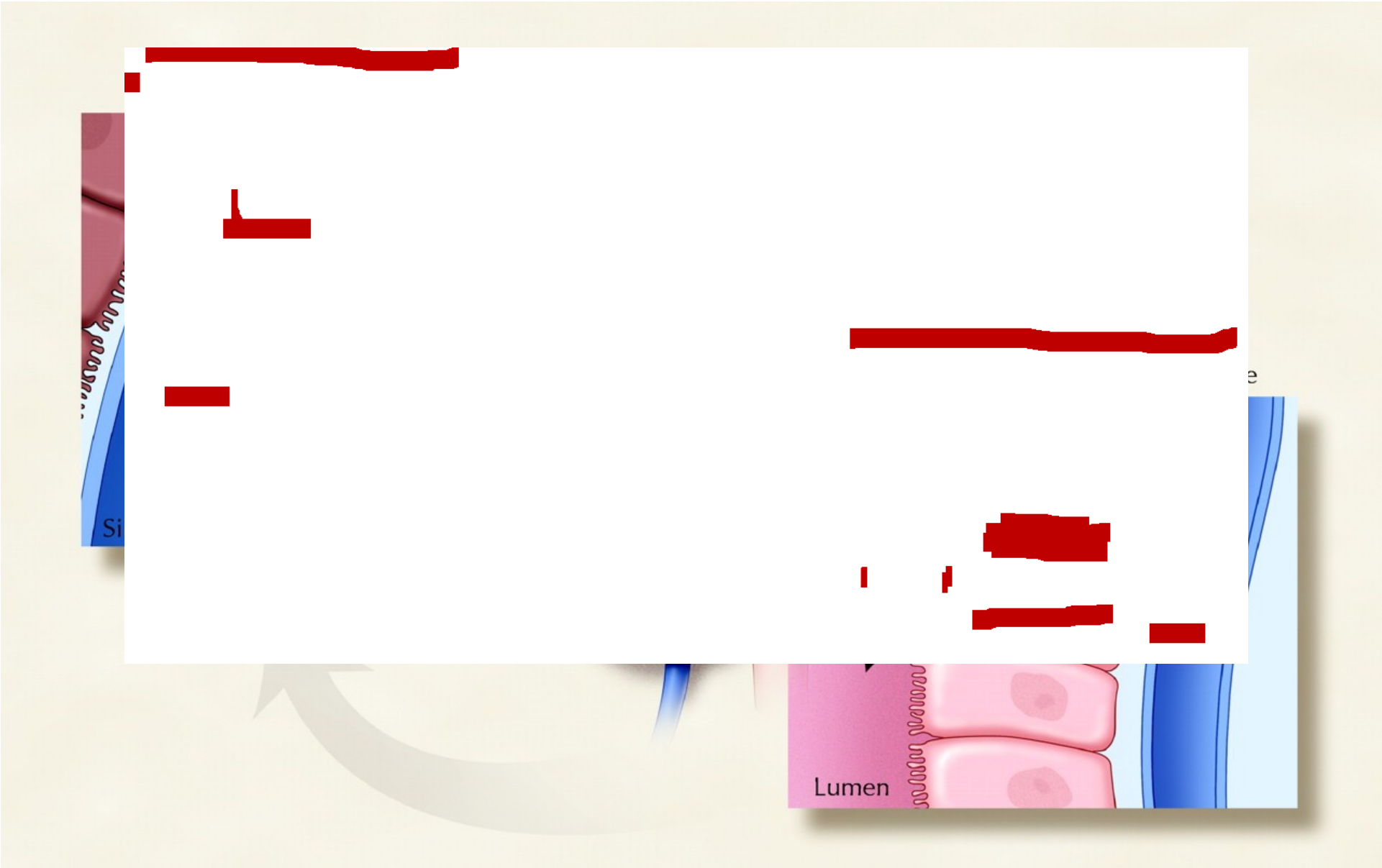
Absolute bioavailability

comparing the AUC of administered drug in the test dosage form and the AUC after i.v. drug administration

Relative bioavailability

assess the expected biological equivalence of two preparations of a drug
if the relative bioavailability = 1 (100%) → tested preparation is bioequivalent to the reference

Transporters

ABC - **A**TP-**B**INDING **C**ASSETTE

active efflux pumps

ATP-dependent transport of xenobiotics, lipids, metabolites

SLC Solute carrier family
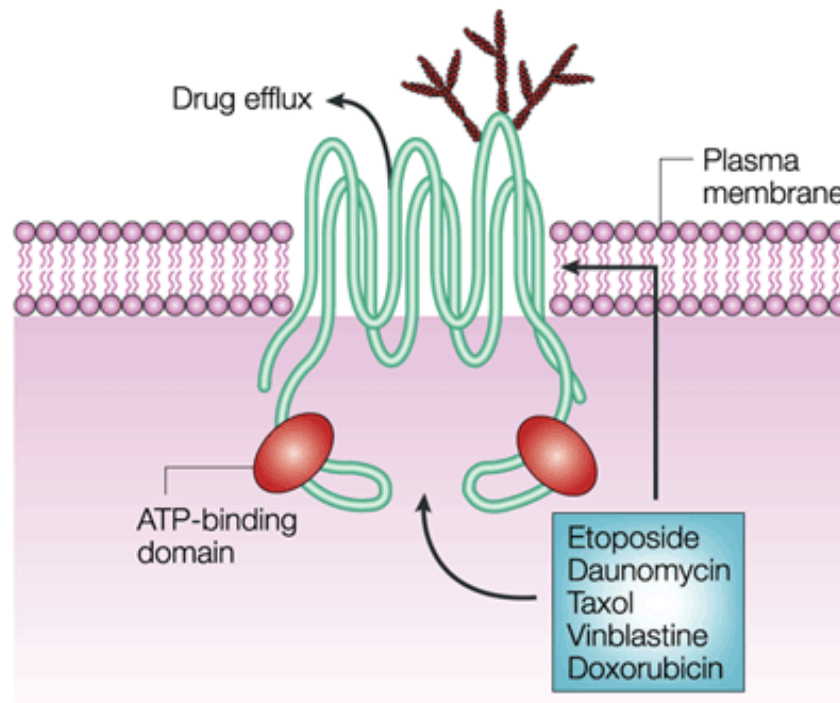
transport of endogenous substances within the body

heterogeneous, 1-14 transmembrane units

- dependent on the ion gradient (especially Na^+, Cl^- and H^+)
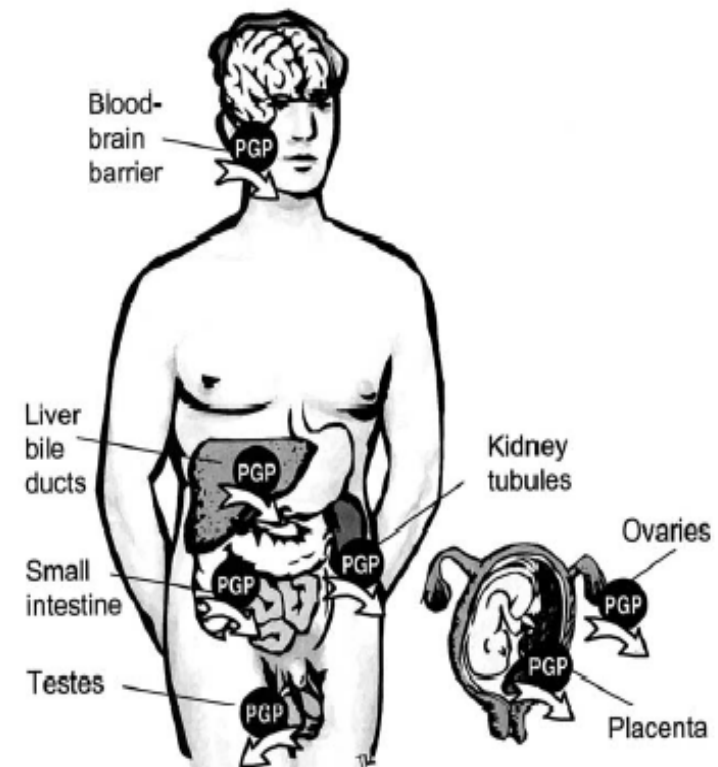- equilibration transport proteins

P-glycoprotein

- transmembrane pump encoded by *MDR1, ABCB1*
- drug efflux pump for xenobiotics
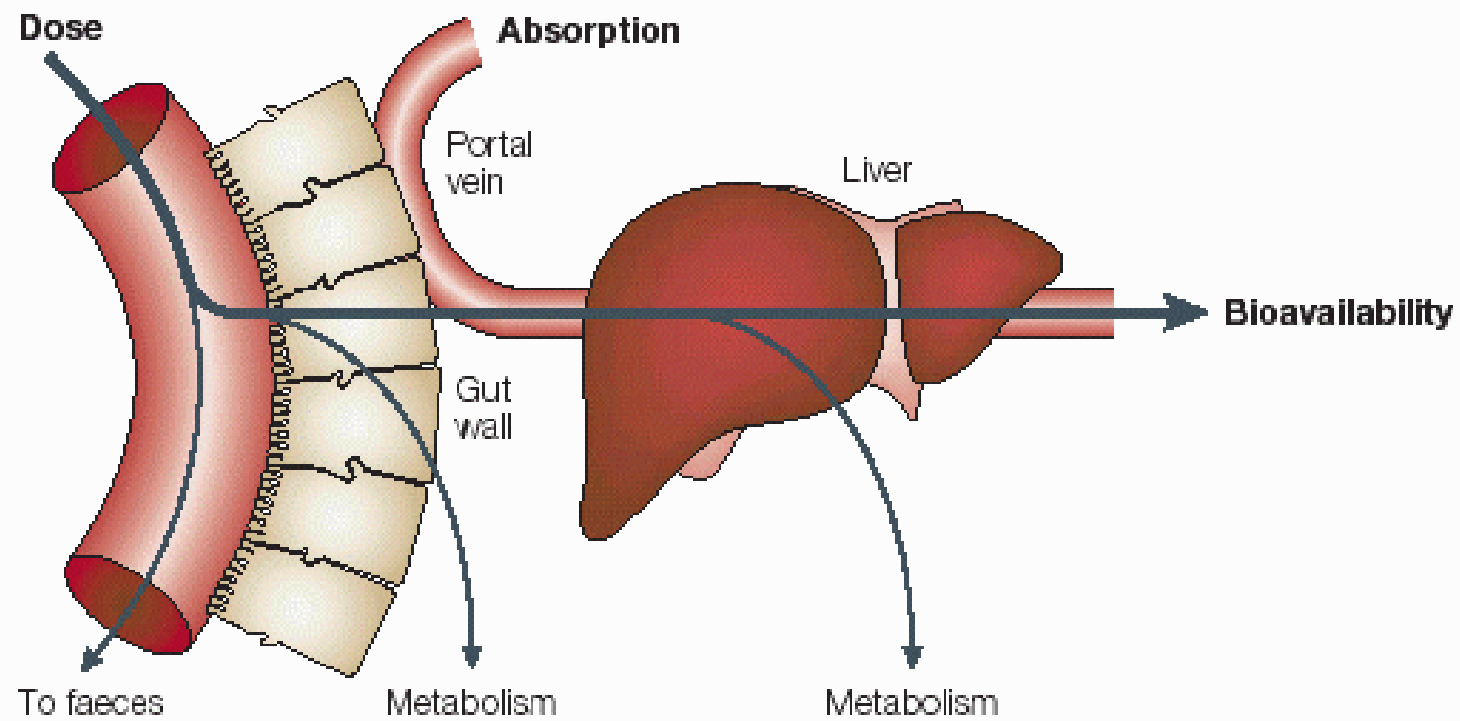- multidrug resistence to chemotherapeutics

Nature Reviews | Cancer

Presystemic elimination

First pass effect

SLC

52 rodin
- OCT
- OAT
- OATP
- MATE

Other factors influencing drug absorption

gender, weight, plasmatic volume, speed of gastric discharging
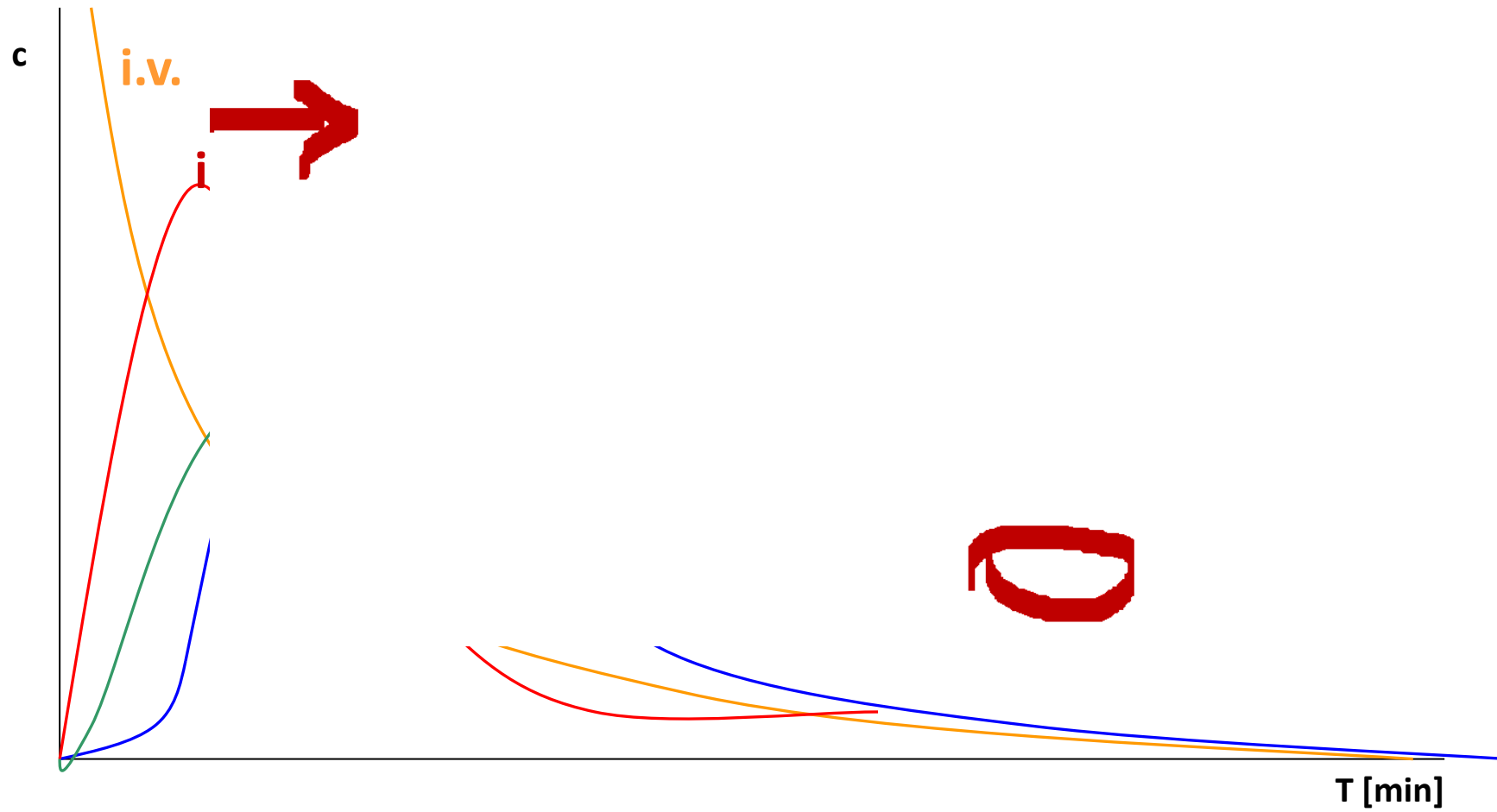
age - pH, bile, enzymes

pathophysiological de   es of liver, inflammation ...

Body constitution (B

diet

- acceleration/ decceleration

- chemical incompatibilities

- GIT functionality

Distribution

Penetration of drug from blood to tissues, dynamic proces where we are interested in:

> **speed of distribution**- depends on:
>
> > bindings
> >
> > membrane penetration
> >
> > organ perfusion
> >
> > **status-** distribution balance, free fractions of drug are equal in   blood and tissue

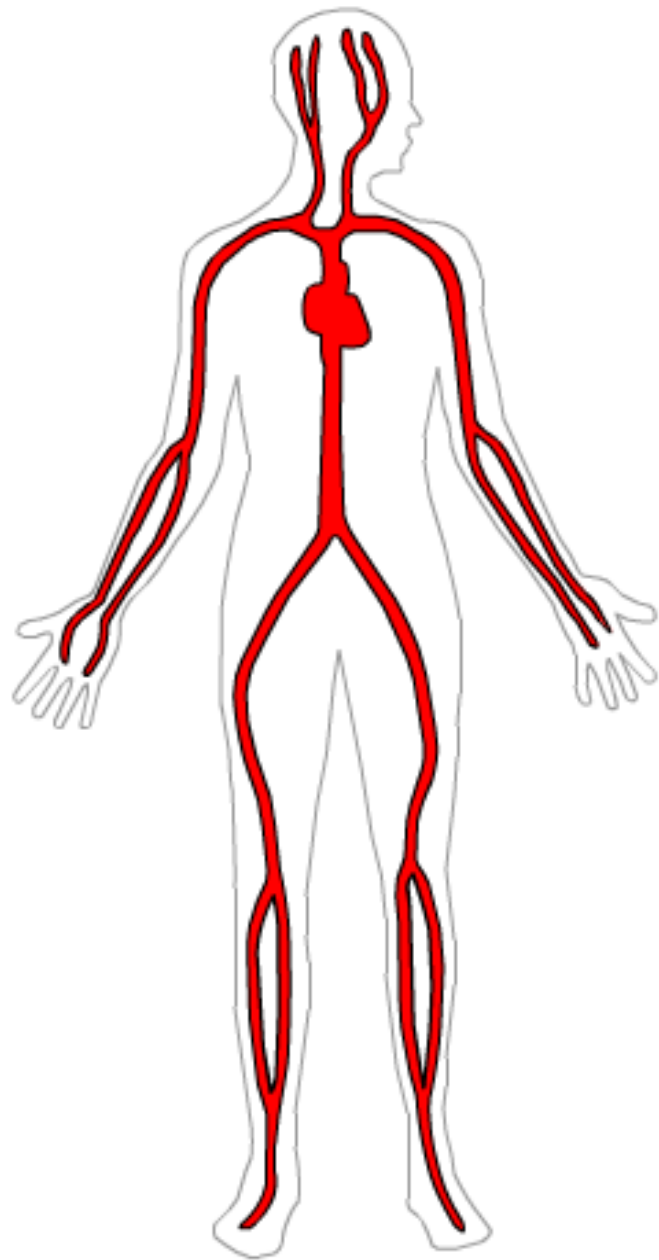## Volume of distributionV_d

hypothetic, theoretical volume

rate between amount of drug in organism and plastmatic concentration

$$Vd = \frac{D \cdot F}{C_0} \, [l]$$

http://icp.org.nz/icp_t3.html?htmlCond=0

The apparent volume of distribution, V_d, is defined as the volume that would contain the total body content of the drug at a concentration equal to that present in the plasma

Vd

5 L

Drug concentrated
in blood stream

Drug in blood and
extracellular space

Drug equally distributed
in blood and tissues
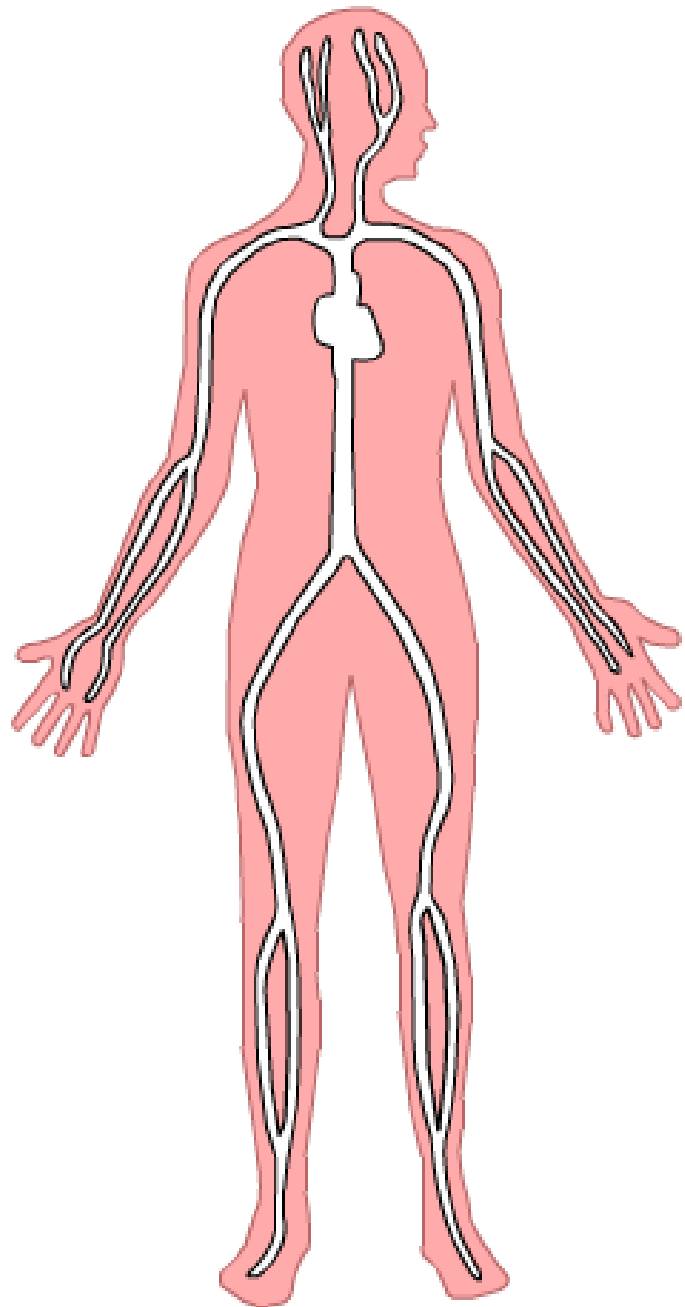
Drug moderately
concentrated in tissues

Drug highly concentrated
in tissues
(usually adipose)

10,000 L

Amount in body = Vd x plasma concentration

Ab = Vd x Cp

Vd

5 L

10,000 L

Drug concentrated
in blood stream

Drug in blood and
extracellular space

Drug equally distributed
in blood and tissues

Drug moderately
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**Drug highly concentrated
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Amount in body = Vd x plasma concentration
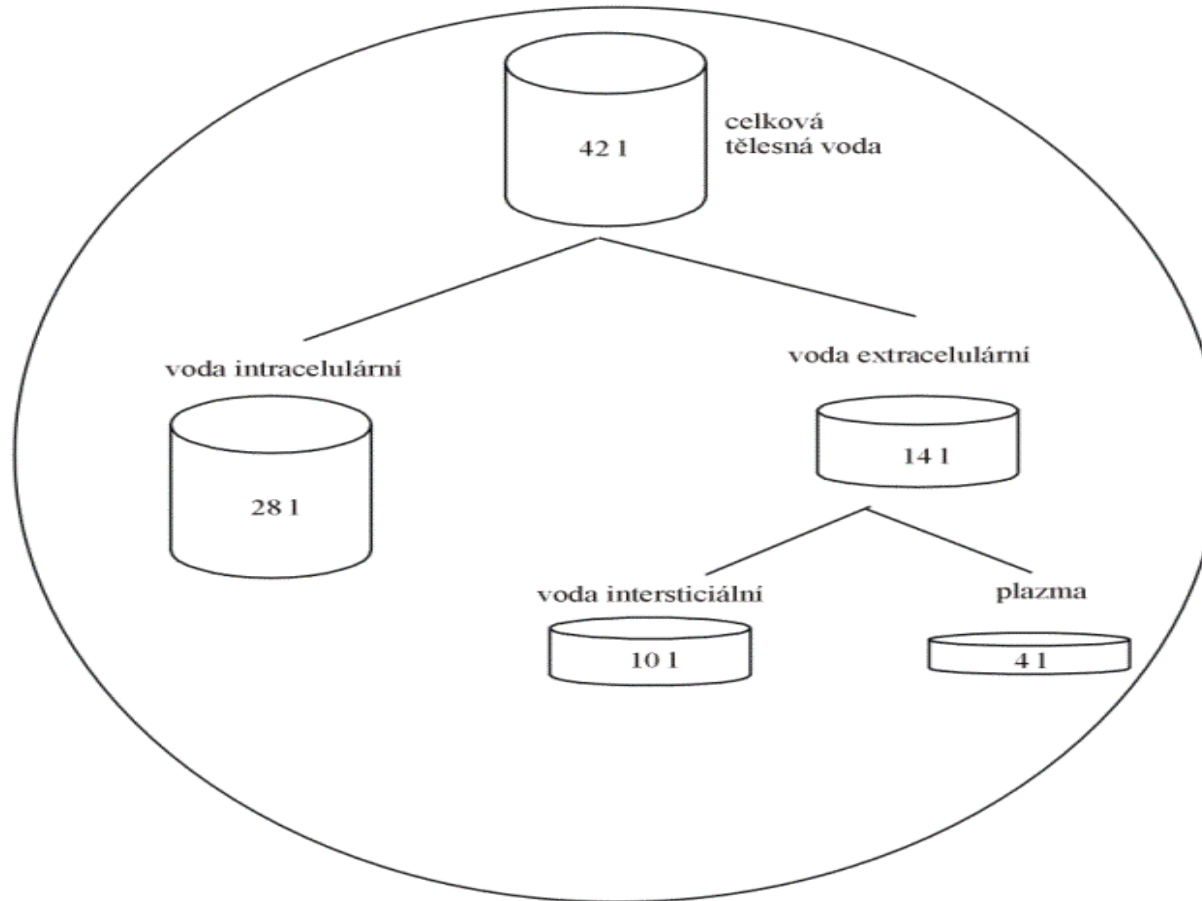
$$Ab = Vd \times Cp$$

$$Vd = \frac{Ab}{Cp}$$

Vd = **hypothetical volume**,

Final value of Vd can be even 50000 liters (antimalarial drugs).
What does this value tell us:

We can assess distribution of the drug in the body.

Distribution

Distribution volume - use:
Calculation of loading dose:

$$D = Vd \cdot c_T$$
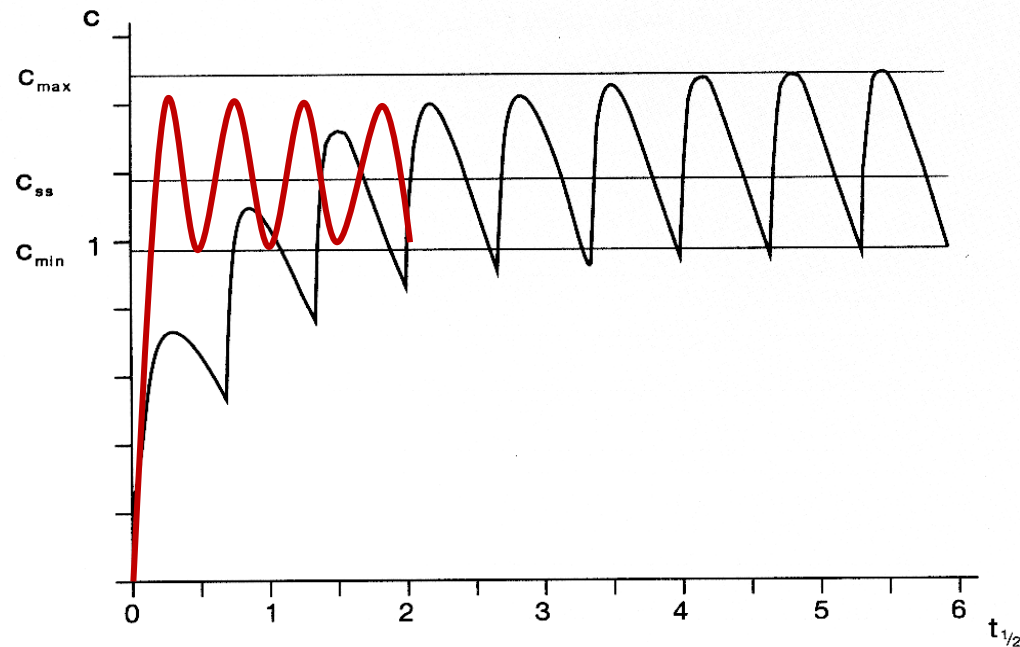
Distribution

Estimate the amount of drug in the body

M = Vd . C

Assessment of the effect of hemodialysis and hemoperfusion

drugs with higher Vd can not be eliminate from the body by these technics

Elimination of drugs

First-order elimionation

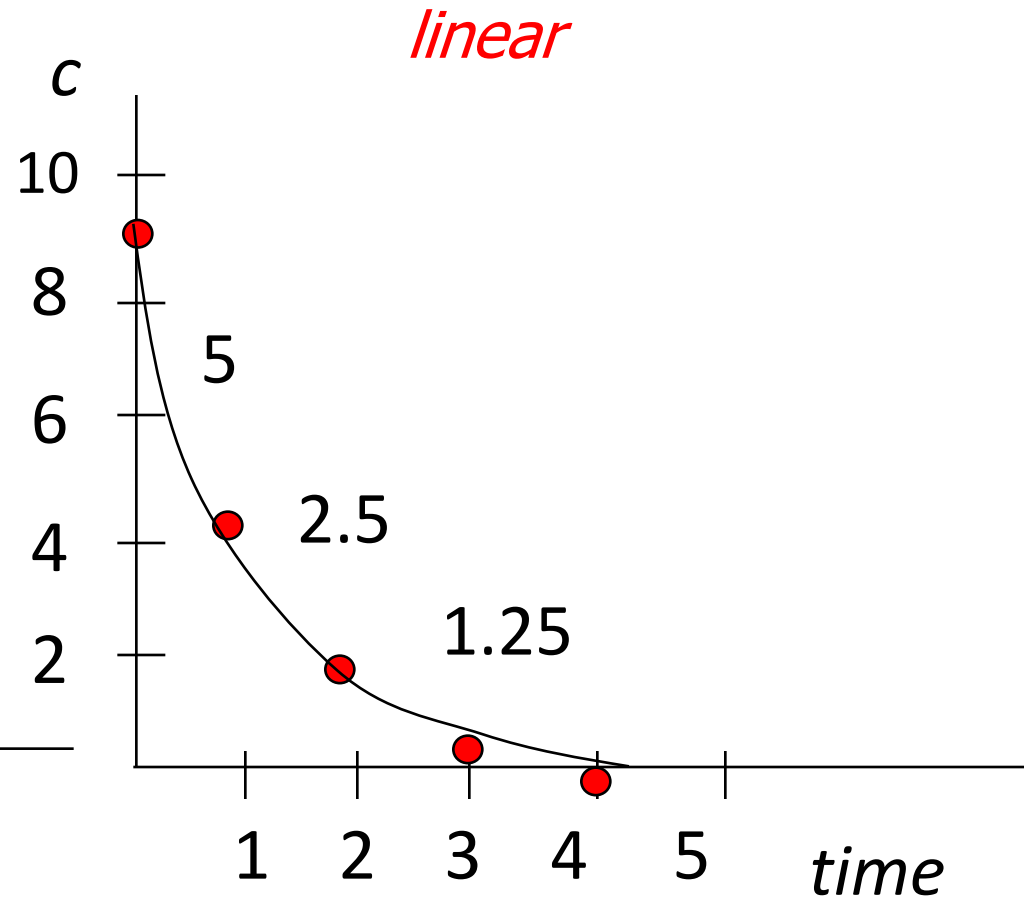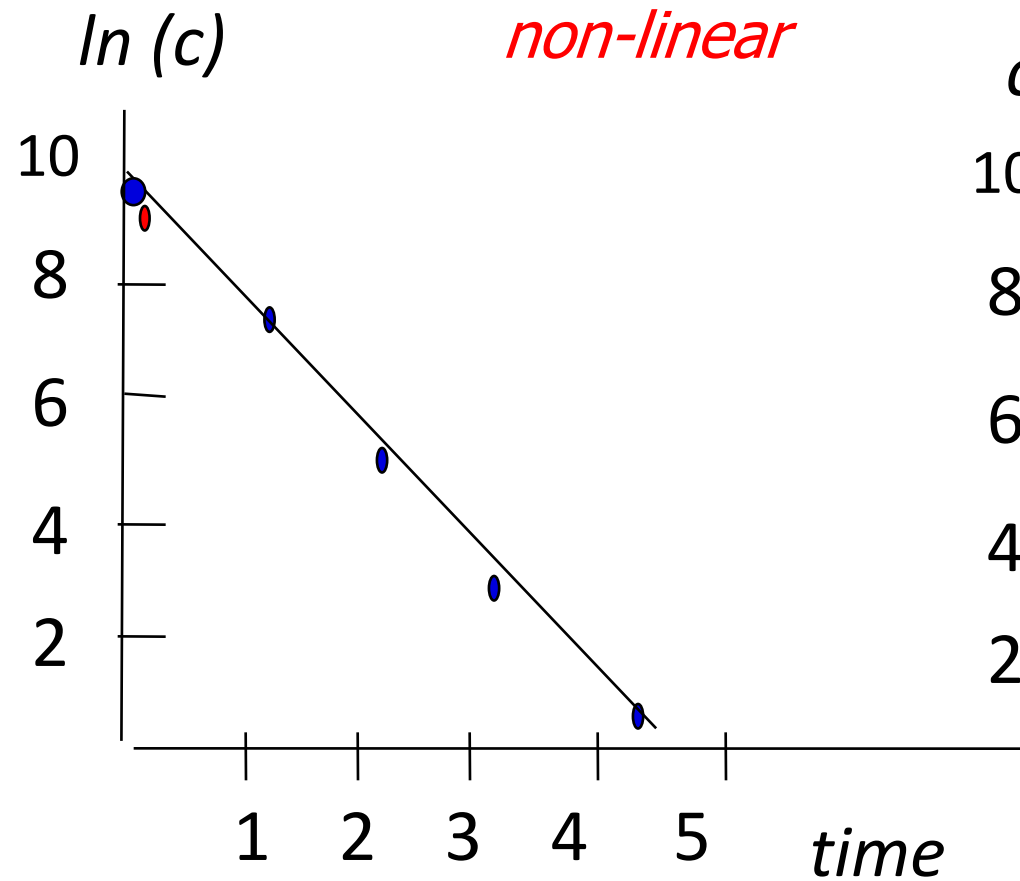Rate of elimination is influenced by plasmatic concentration

Linear kinetics

Zero-order elimination

Elimination rate is not influenced by plasmatic concentration

Non-linear kinetics

0 and 1st.-order elimination

Biotransformation - metabolism

Predominantly in liver, but also in other organs and parts of body

Enzymatic processes

bioactivation (prodrug)

      tamoxifen – endoxifen

      cyclophosphamide – phosphoramide

biodegradation

Biotransformation - metabolism

1. **Phase:**

   oxidation, hydrolysis → drug is still partly lipophilic
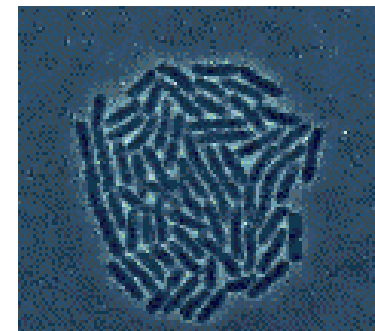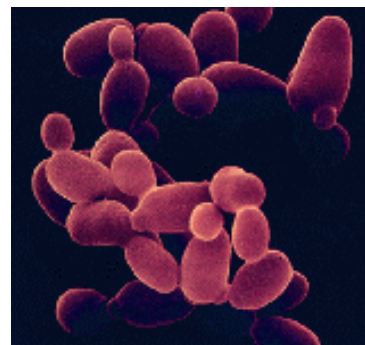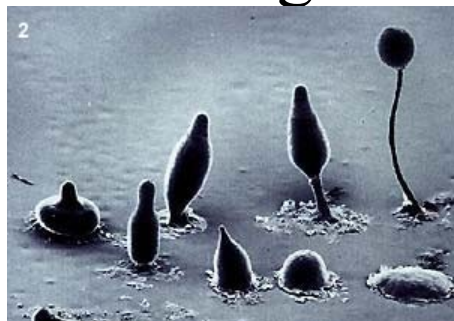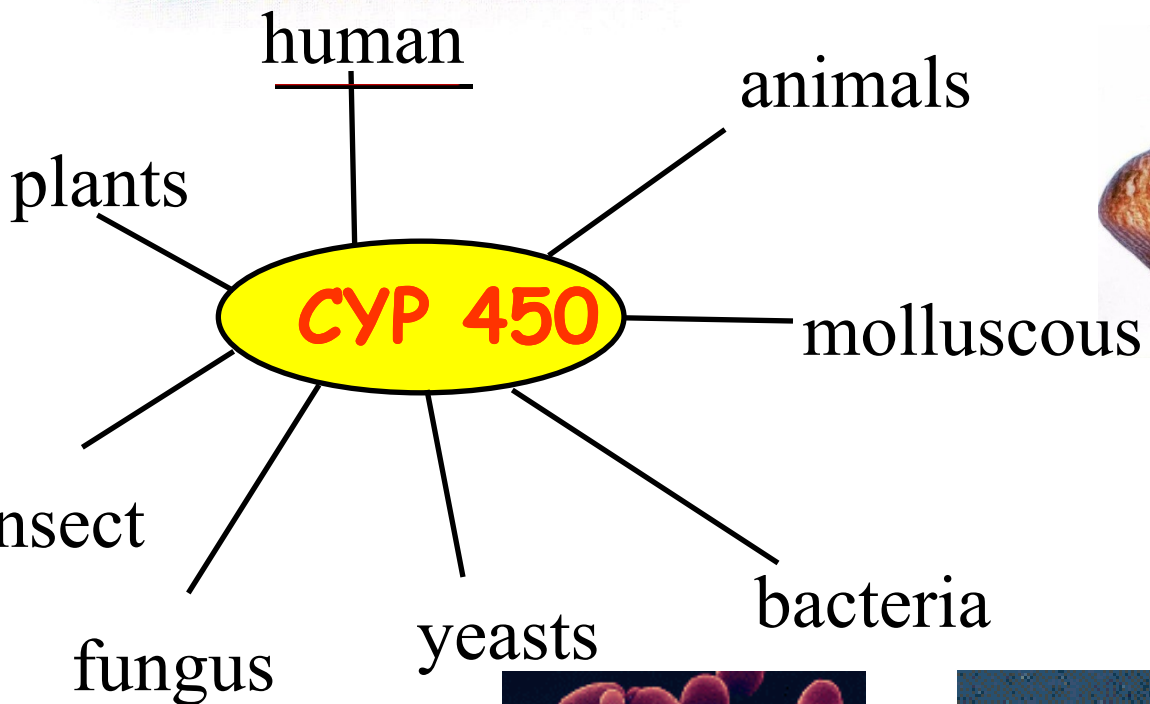
   cytochromes P450, dehydrogenases

2. **Phase:**

   conjugation → molecules becomes hydrophilic

Metabolites

- effective („more/less")

- inneffective

- toxic

human

animals

plants

CYP 450

molluscous

insect

bacteria

yeasts

fungus
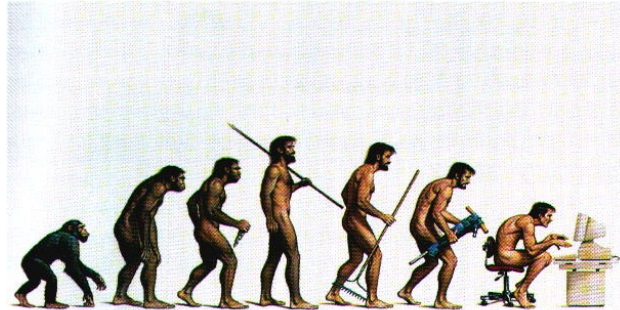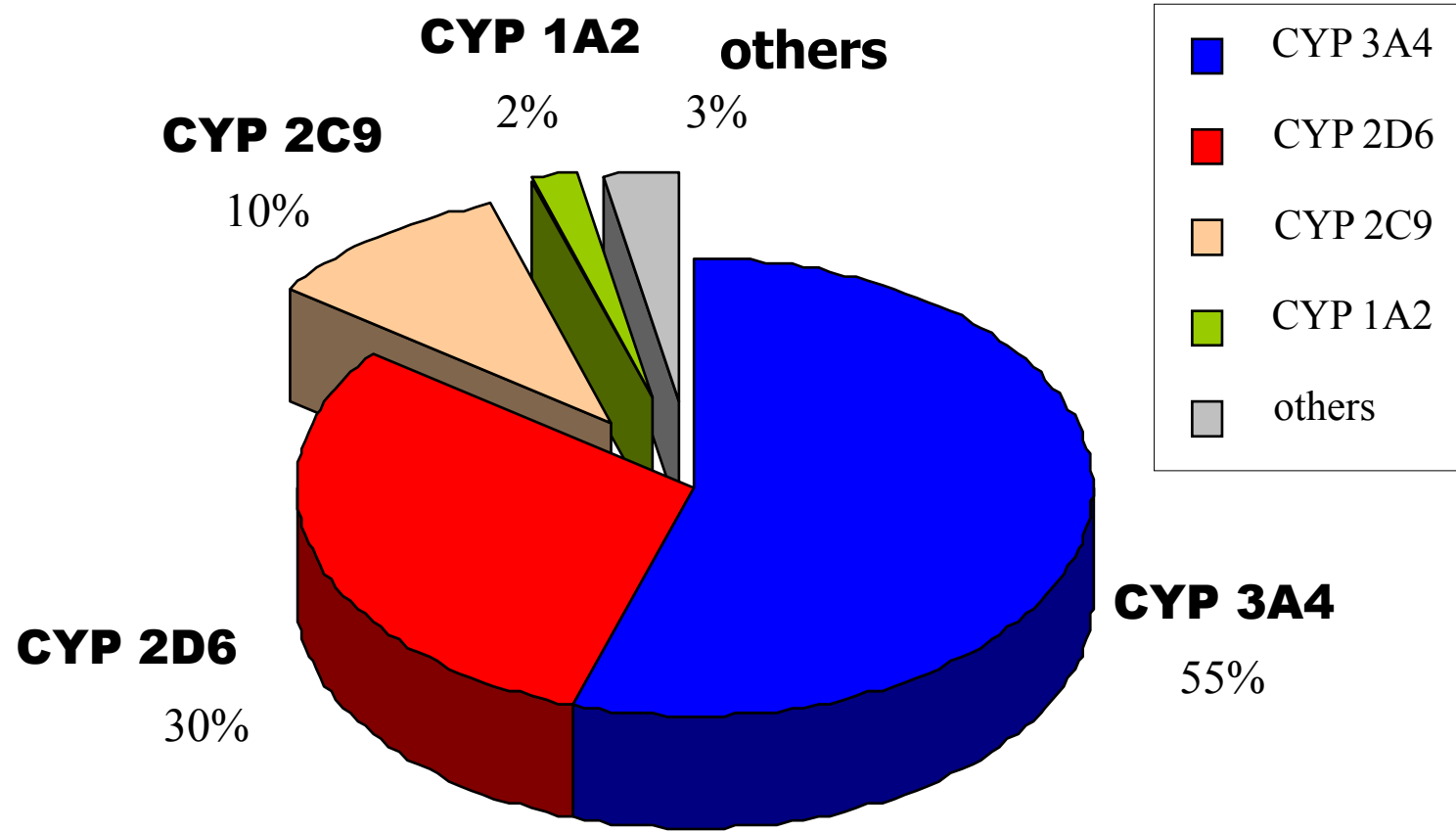
Inducers of CYP450

- **dexametazon**
- **fenobarbital**
- **rifampicine**
- **phenytoin**
- **St. John´s worth (Hypericum *perforatum)***
- ***Ginkgo biloba***

Inhibitors of CYP450

- **antidepressants (fluoxetin, fluvoxamin, paroxetin)**
- **chinin, chinidin**
- **chloramphenicol, erytromycine**
- **ketokonazol, itrakonazol**
- **grapefruit juice**

Excretion

kidneys
bile
lungs

saliva, skin, hair, milk…

Excretion by kidney

MW < 60.000 D (MW of albumin = 68.000 D)

glomerular filtration

tubular secretion

organic acids

> furosemide
> thiazide diuretics
> penicilins
> glukuronids
> organic bases
> morfin

alkalization

natrium hydrogencarbonate

tubular reabsorption

> diazepam

acidification

ammonium chloride

Excretion by liver

Substances permeate through 2 membranes of hepatocytes – basolateral and apical (canalicular)

Metabolites are excreted primary by **pasive diffusion**, further by **active transport** (glucuronides, bile acids, penicillins, tetracyclines, etc.)
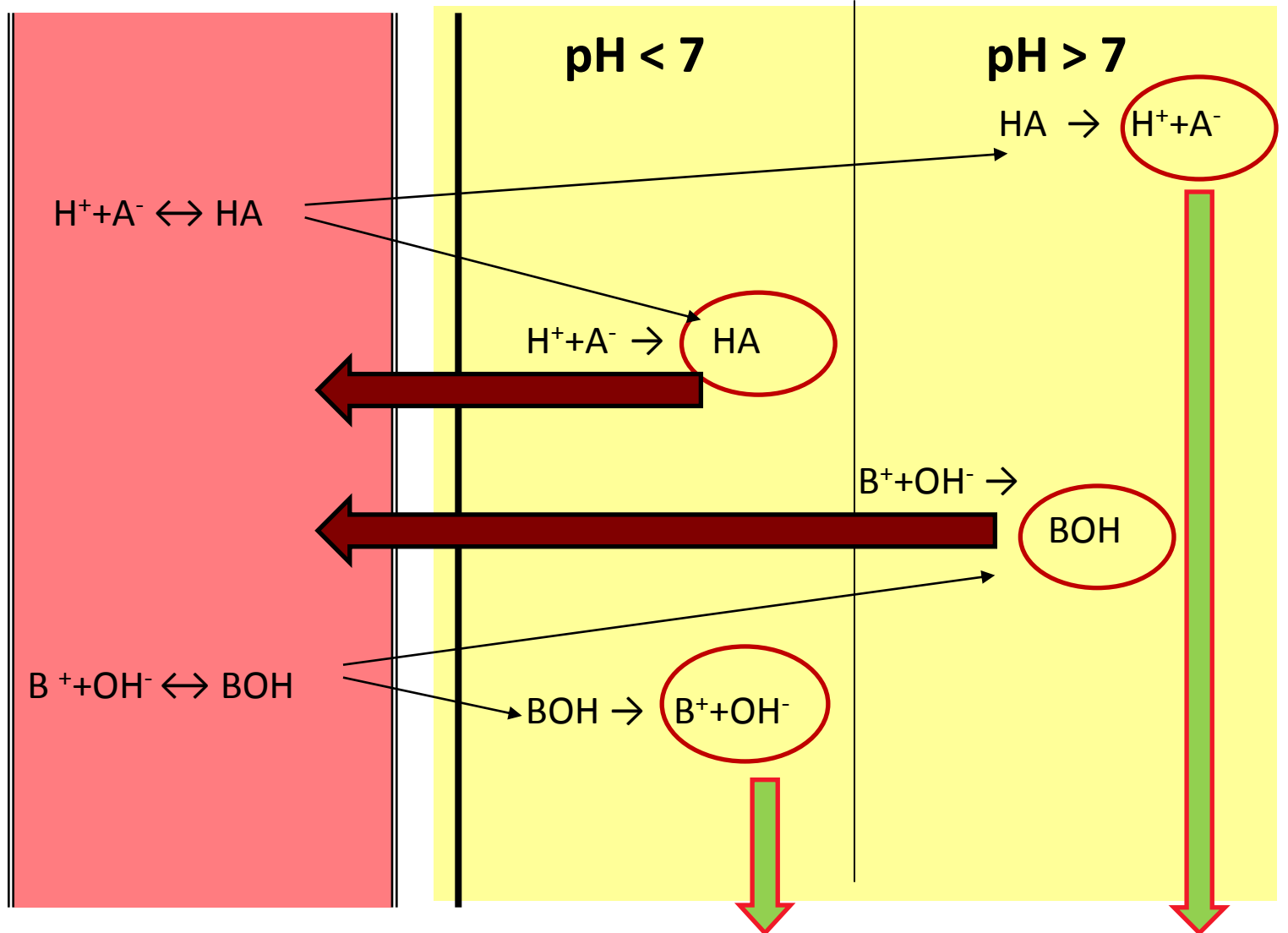Metabolites can be deconjugated by bacterial enzymes in intestine → release of lipophilic molecule → **re-absorption**

= ENTEROHEPATIC CIRCULATION
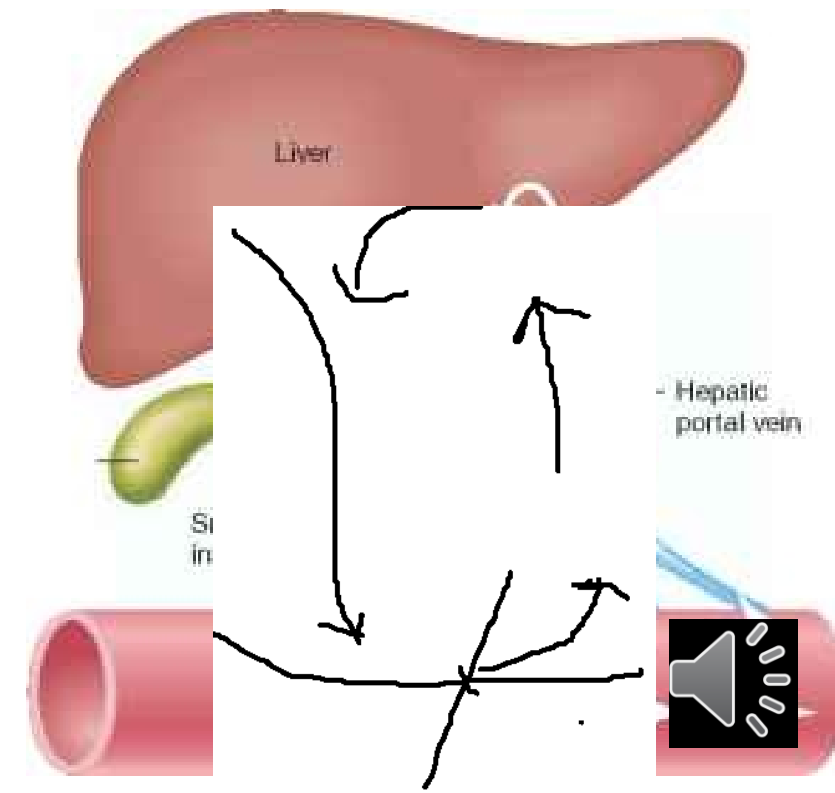
Glomerular capillary   Proximal tubulus

pH < 7   pH > 7

$HA \rightarrow$ $H^{+}+A^{-}$

$H^{+}+A^{-} \leftrightarrow HA$

$H^{+}+A^{-} \rightarrow$ HA

$B^{+}+OH^{-} \rightarrow$ BOH

$B^{+}+OH^{-} \leftrightarrow BOH$

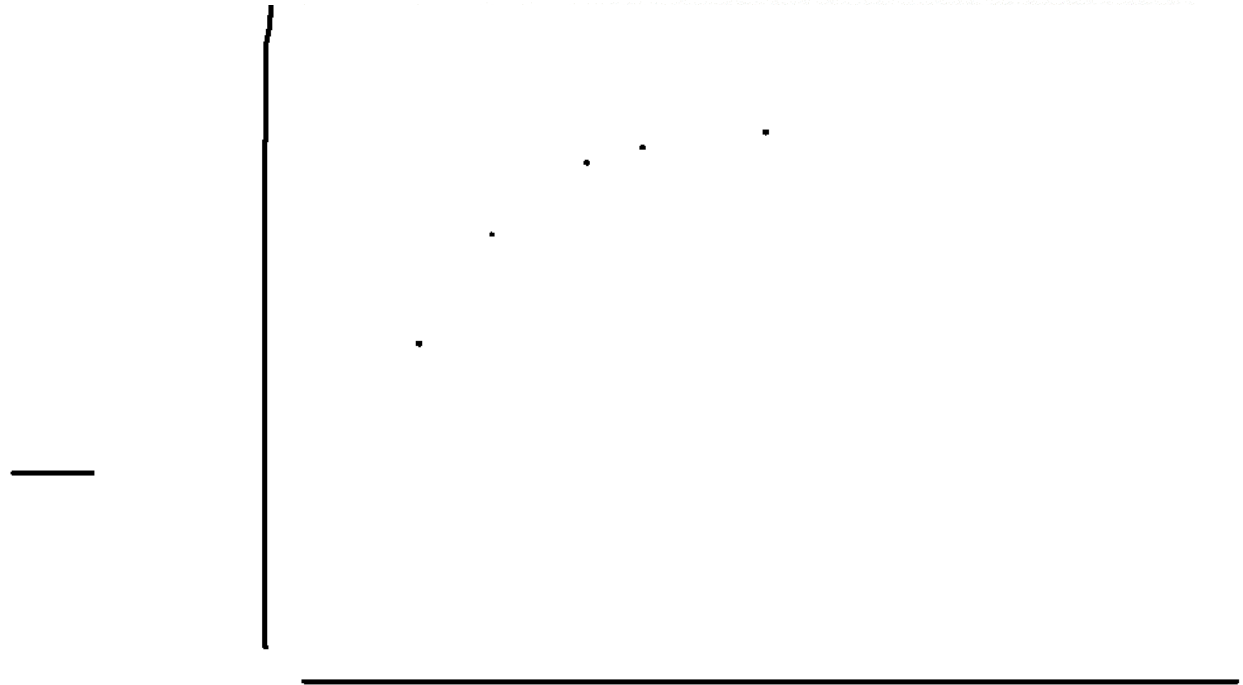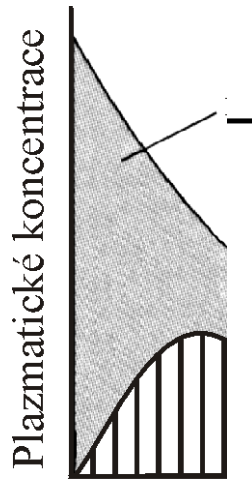$BOH \rightarrow$ $B^{+}+OH^{-}$

http://icp.org.nz/icp_t11.html

Pharmacokinetic parameters

Mathematic description of pharmacokinetic processes and its use in drug dosage

The guide for evaluation of pharmacokinetics in clinical practise is **plasma concentration/time curve** – problems with measuring in vivo

- In accordance with concentration-time curves we determine **pharmacokinetic parameters** – model values, which proviídes us to describe P-kinetic processes

- There are three possible manners of drug administration with regards to concentration-time curves:

  single dose

  continuous administration

  repeated dose

Single dose

Invasion phase

C _{max}

T _{max}

Bioavailability - F

$$F = \frac{AUC_{po}}{AUC_{iv}}$$

Volume of distribution - Vd

$$Vd = \frac{D \cdot F}{C_0}$$

Relationship of plasmatic conc. on time

C [mg/ml]

lag time   Tmax
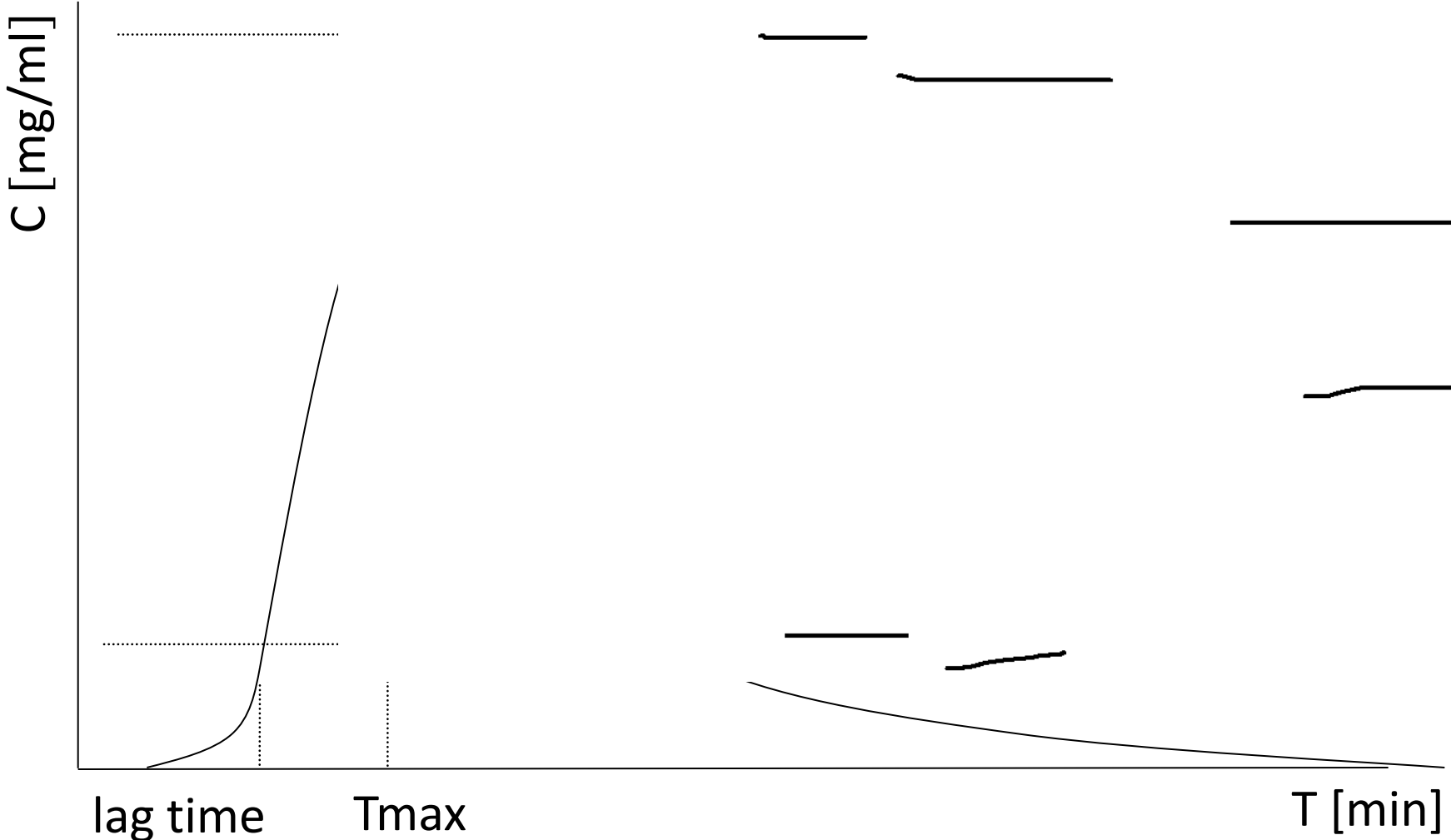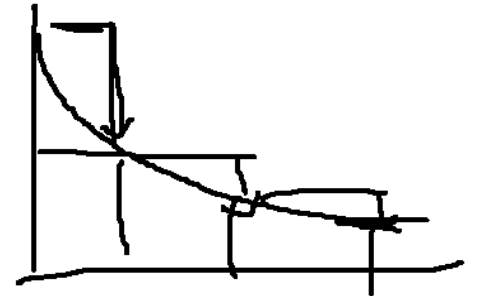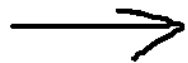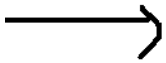
INVASION   ELIMINATION
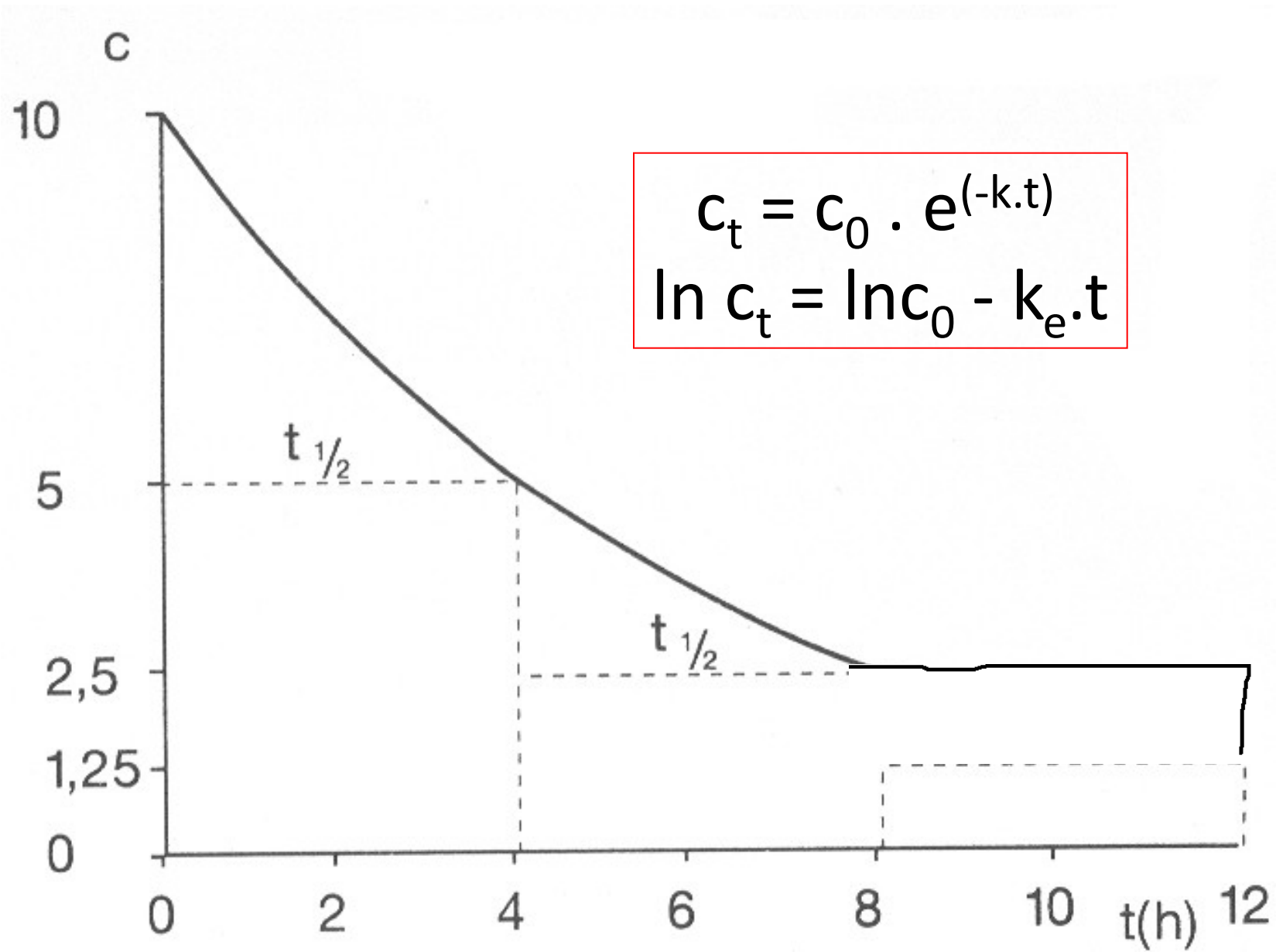
T [min]

Single dose

Elimination phase

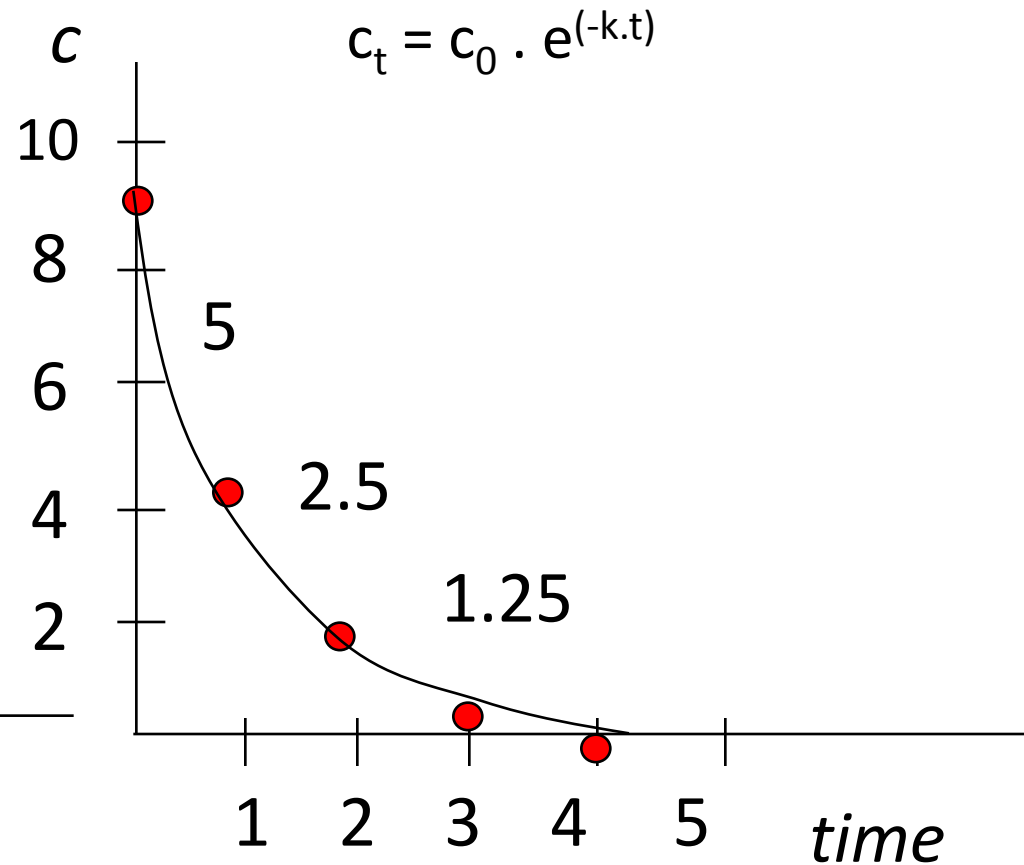Drug is eliminated from the organism with speed determined by:

$$\ln c_1 - \ln c_2$$

Cl_{PUL} ...

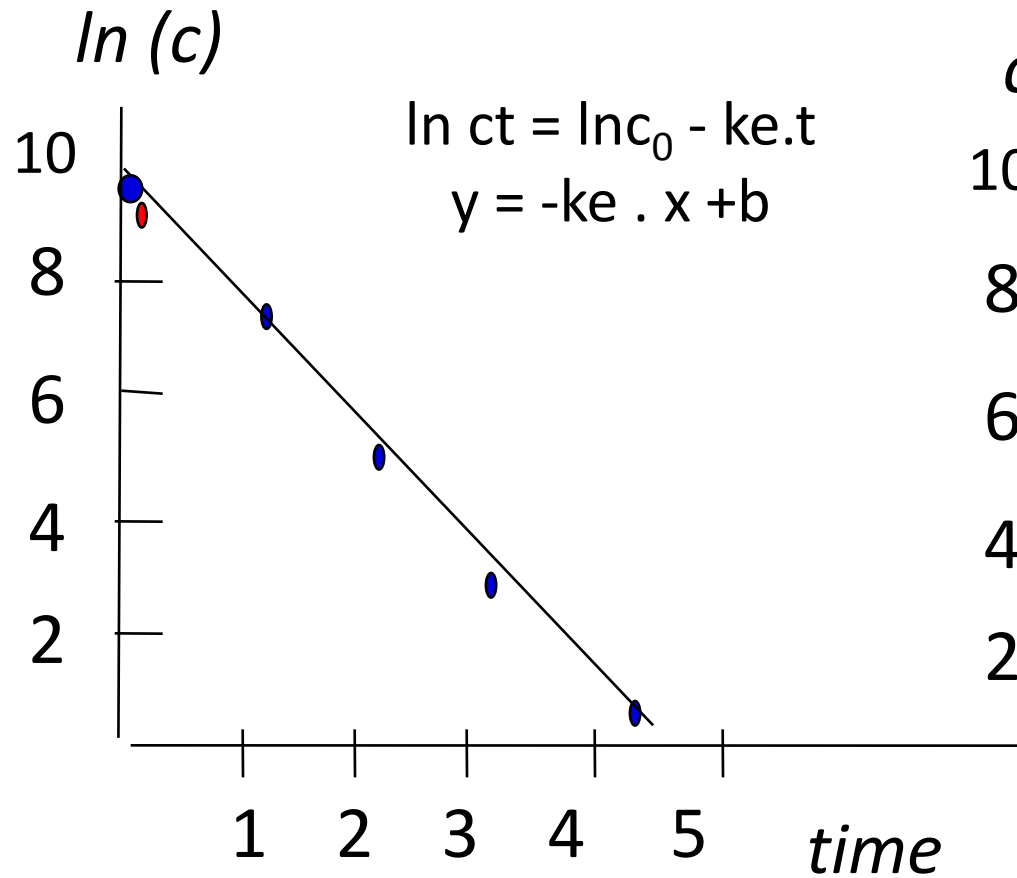$$c_t = c_0 \cdot e^{(-k \cdot t)}$$
$$\ln c_t = \ln c_0 - k_e \cdot t$$
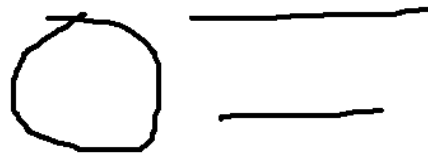
First-order kinetics – semilogaritmic plot (i.v.)

$ln (c)$

$\ln c_t = \ln c_0 - k_e.t$

$y = -k_e . x + b$

c

$c_t = c_0 . e^{(-k.t)}$

A Nor...   s

Plasma concentration (μmol/l)

150
100 - - - -
50 - - - -
0

0   2   4   6   8   10
Days

20

15

10

Therapeutic range | 10 | Dose (units = μmol/kg)
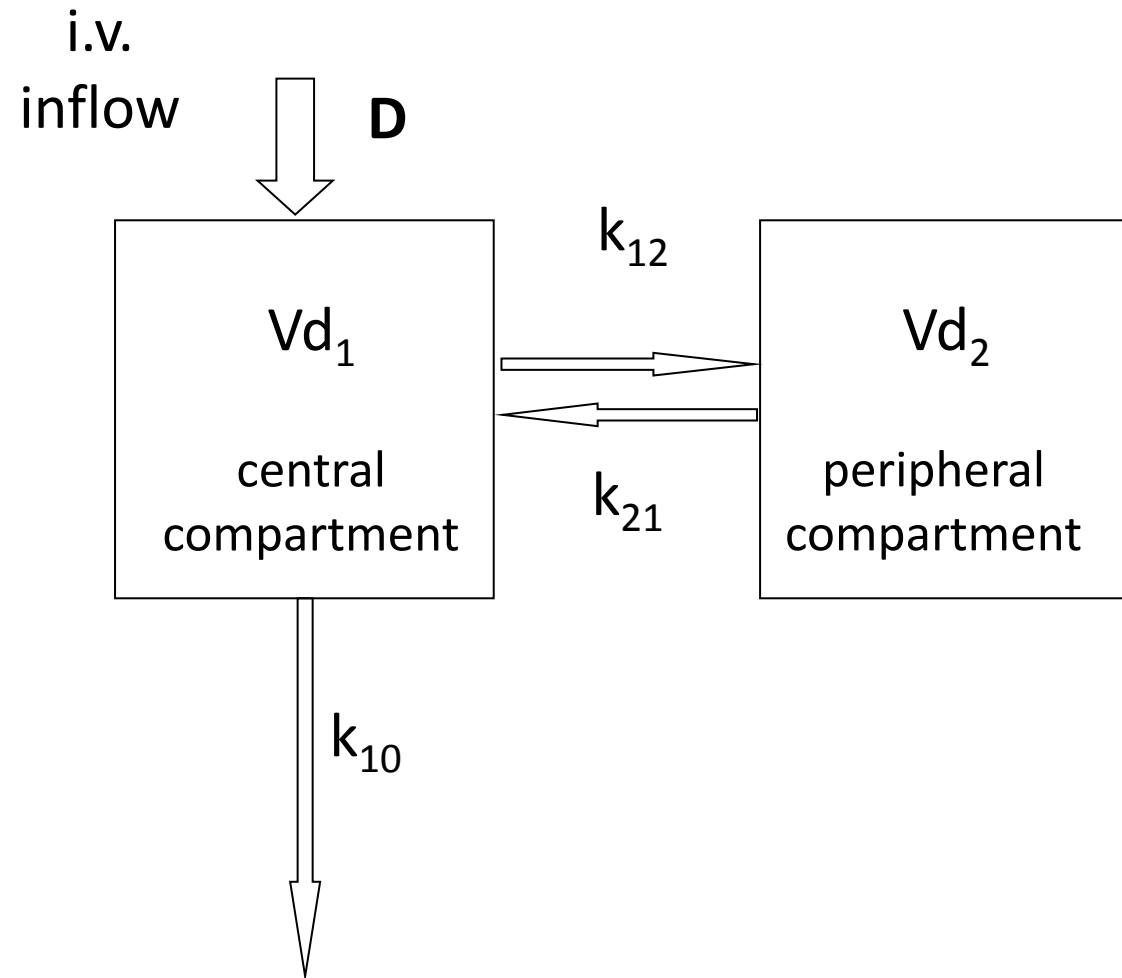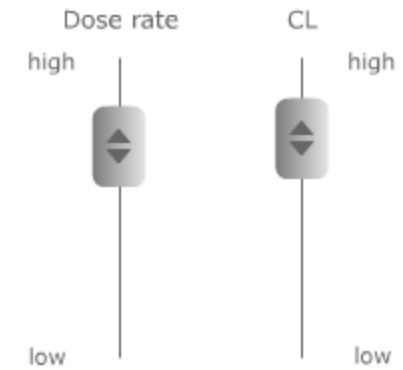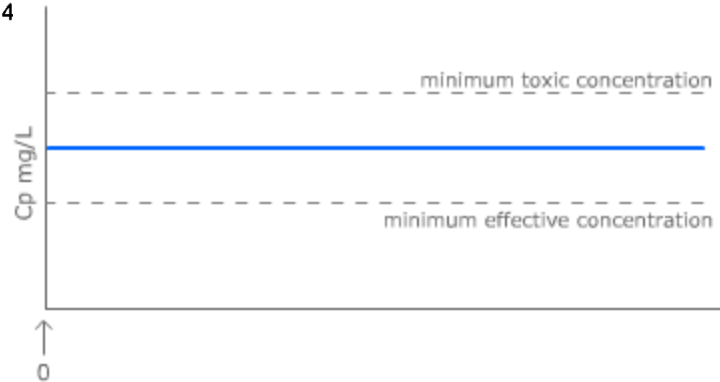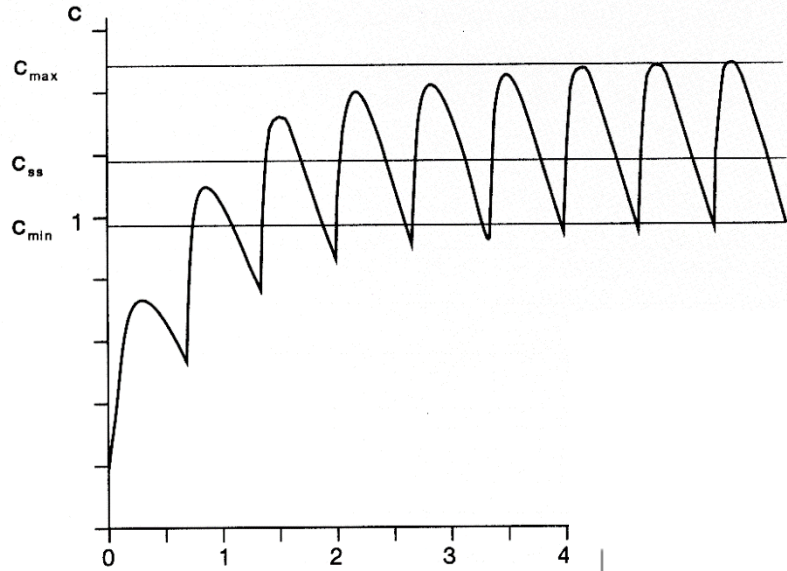
O. ഓൾ

Compartment models

D

i.v.
intake

A (GIT)
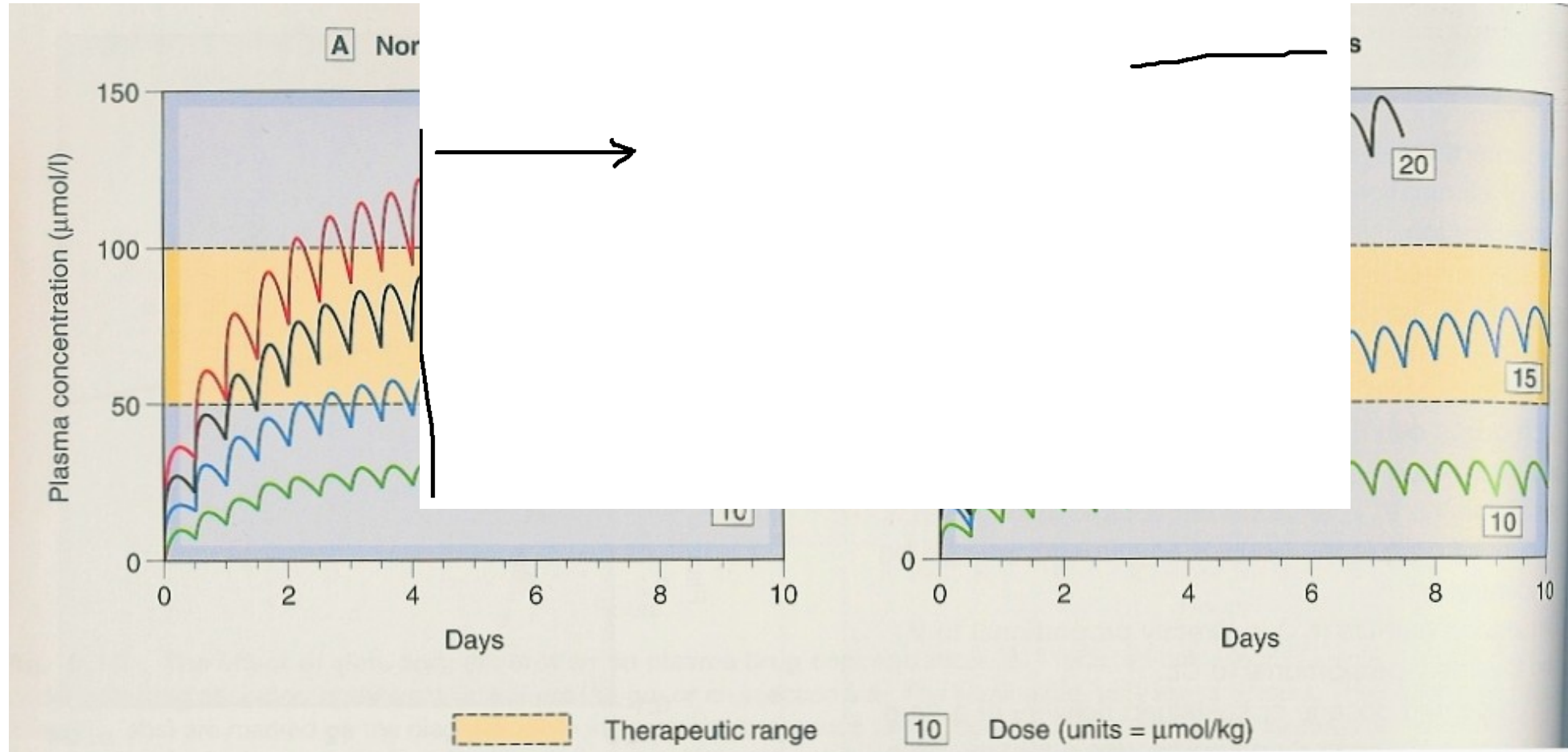
Compartment models– block schema
2- compartment model

Continuous and repeated administration of drugs

$$Cpss = \frac{Dose\ rate}{CL}$$

$$Dose\ rate = Cpss \times CL$$

Continuous administration

- **Intravenous** (e.g. by infusio pump), **transdermal** (TTS), **implant** → administration of drug with constant speed (mg/min)

- If duration of infusion is long enought, concentrations are increasing until the speed of elimination and inflow are the same – plato state is reached (concentration of plato is expressed as **Css**)
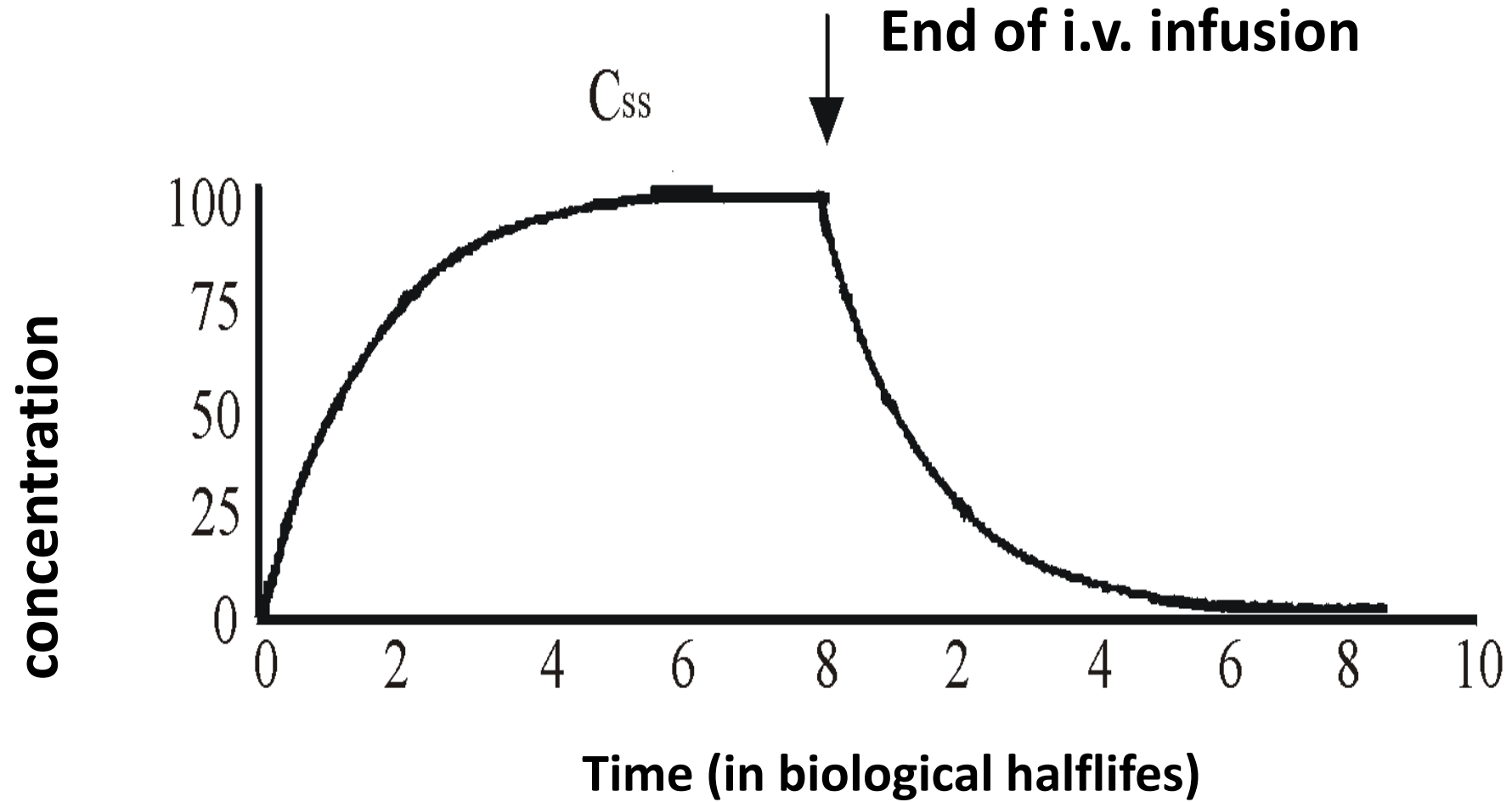
Continuous administration
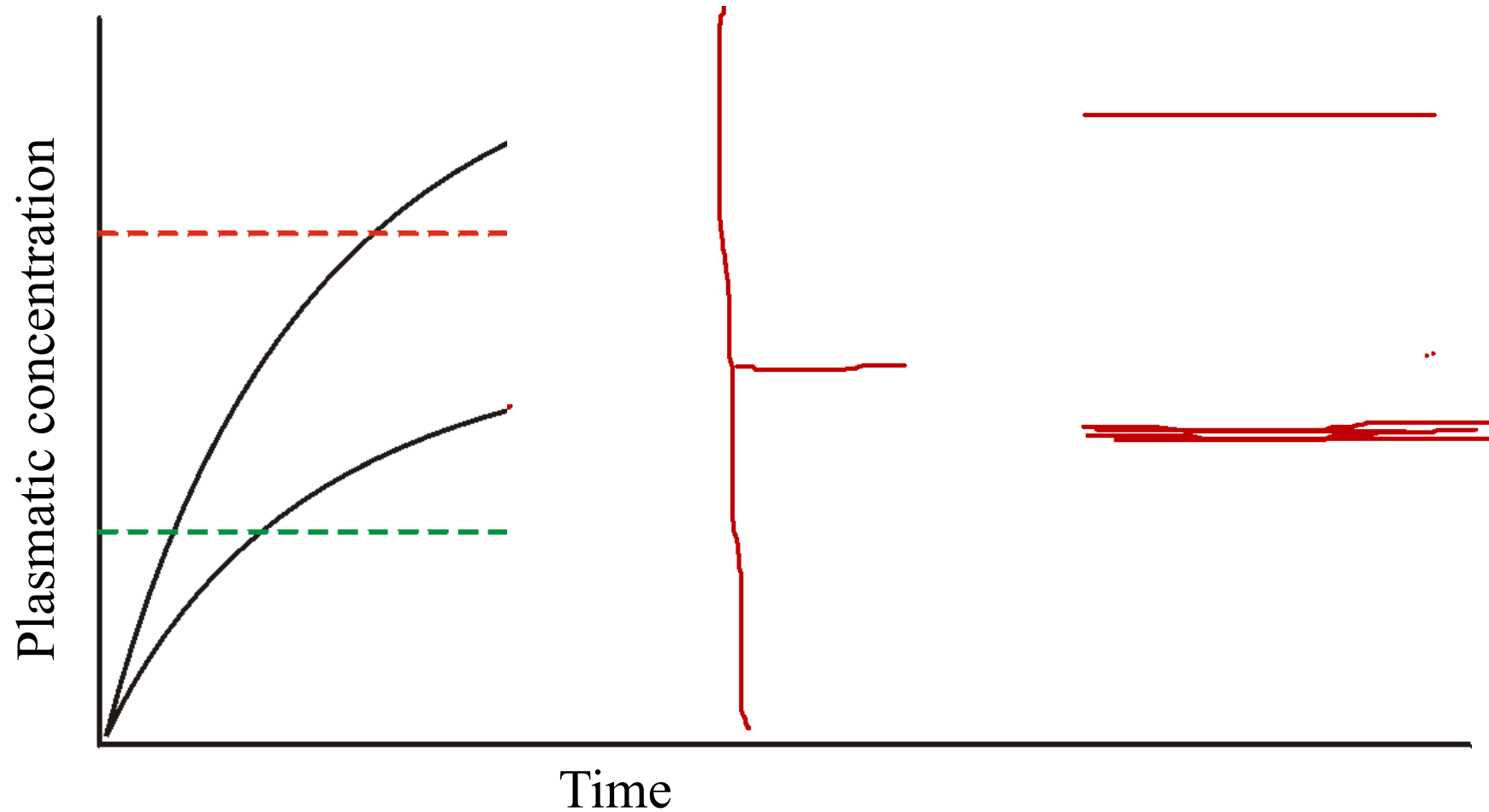
Continuous administration

In plato:

- Drug is binded to all binding sites, which can be occupied

- constant infusion rate **supplements amount, which is eliminated from organism in same time frame**

- **rate of drug administration [mg/min] = rate of elimination [mg/min]**

Continuous administration

Repeated administration

1) **F – bioavailability** – repeated administration is typical for p.o. administration

2) **τ – dosage interval** – plasmatic concentrations are fluctuating among minimal and maximal numbers – after reaching steady state this fluctuation is stabilized between **$Cmax_{plato}$** and **$Cmin_{plato}$**

$$\frac{D \cdot F}{\tau} = Cl \cdot css_{plateau}$$

Repeated administration

intra- (repeated intravascular injection) or **extravascular** (i.e. per os)
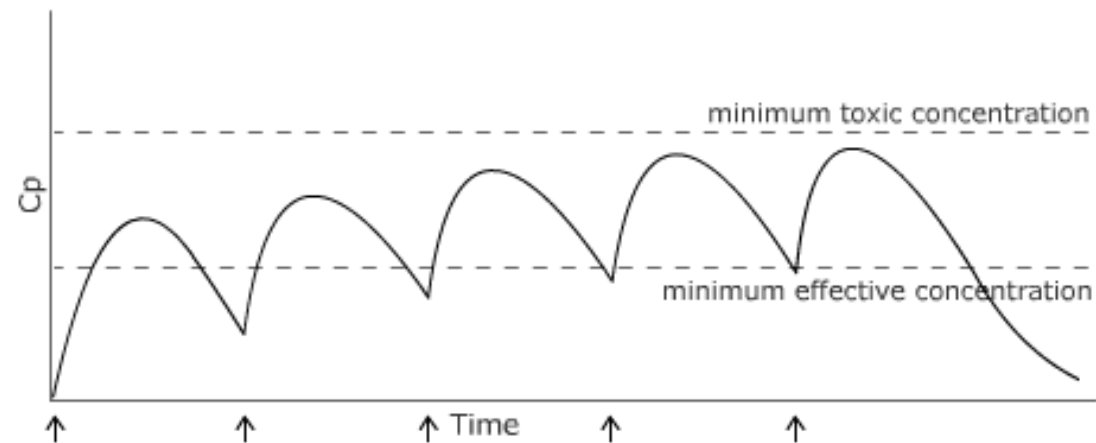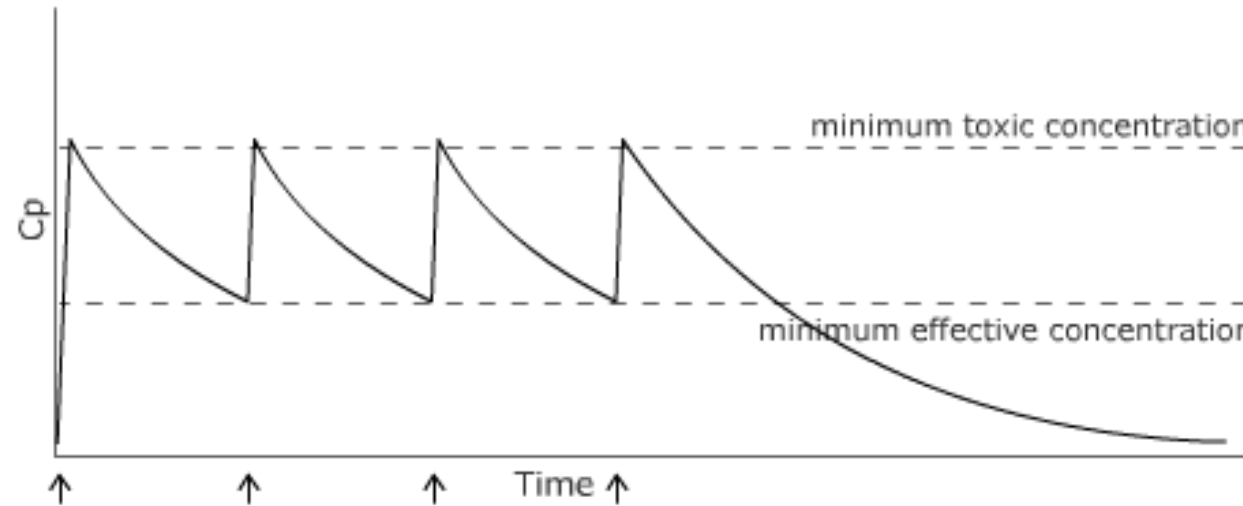
Basic pharmacokinetic parameters (+ computations)

c_{max} = maximal plasmatic concentration

t_{max} = time when c_{max} is reached

k_a = absorption rate constant

k_e = elimination rate constant

$t_{1/2}$ = biological halflife

Vd = volume of distribution

Cl = clearance

$$AUC = \frac{D}{Cl} = \frac{c_0}{k_e} = \frac{D}{k_e \cdot Vd} \ [mg \cdot l^{-1} \cdot h]$$

$$k_e = \frac{\ln c_1 - \ln c_2}{t_2 - t1} \ [h^{-1}]$$

$$t_{1/2} = \frac{\ln 2}{k_e} = \frac{0,7}{k_e} \ [h]$$

$$Vd = \frac{D \cdot F}{C_0} = \frac{F \cdot D}{AUC \cdot ke} \ [l]$$

$$Cl_{TOT} = \frac{D}{AUC} = ke \cdot Vd = Cl_{REN} + Cl_{HEP} + Cl_{PUL} \ ... [l \cdot h^{-1}]$$