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PHARMACOKINETICS

General principles of the fate of the drug in the body

Overview of pharmacokinetic processess: Drug absorption, distribution, metabolism and excretion

Jan Juřica, PharmD. Ph.D.

Basic principles of pharmacokinetics

Pharmacokinetics is aimed on this processes:

absorption

distribution

biotransformation

excretion of drugs

and their relation to pharmacologic (therapeutic or toxic)

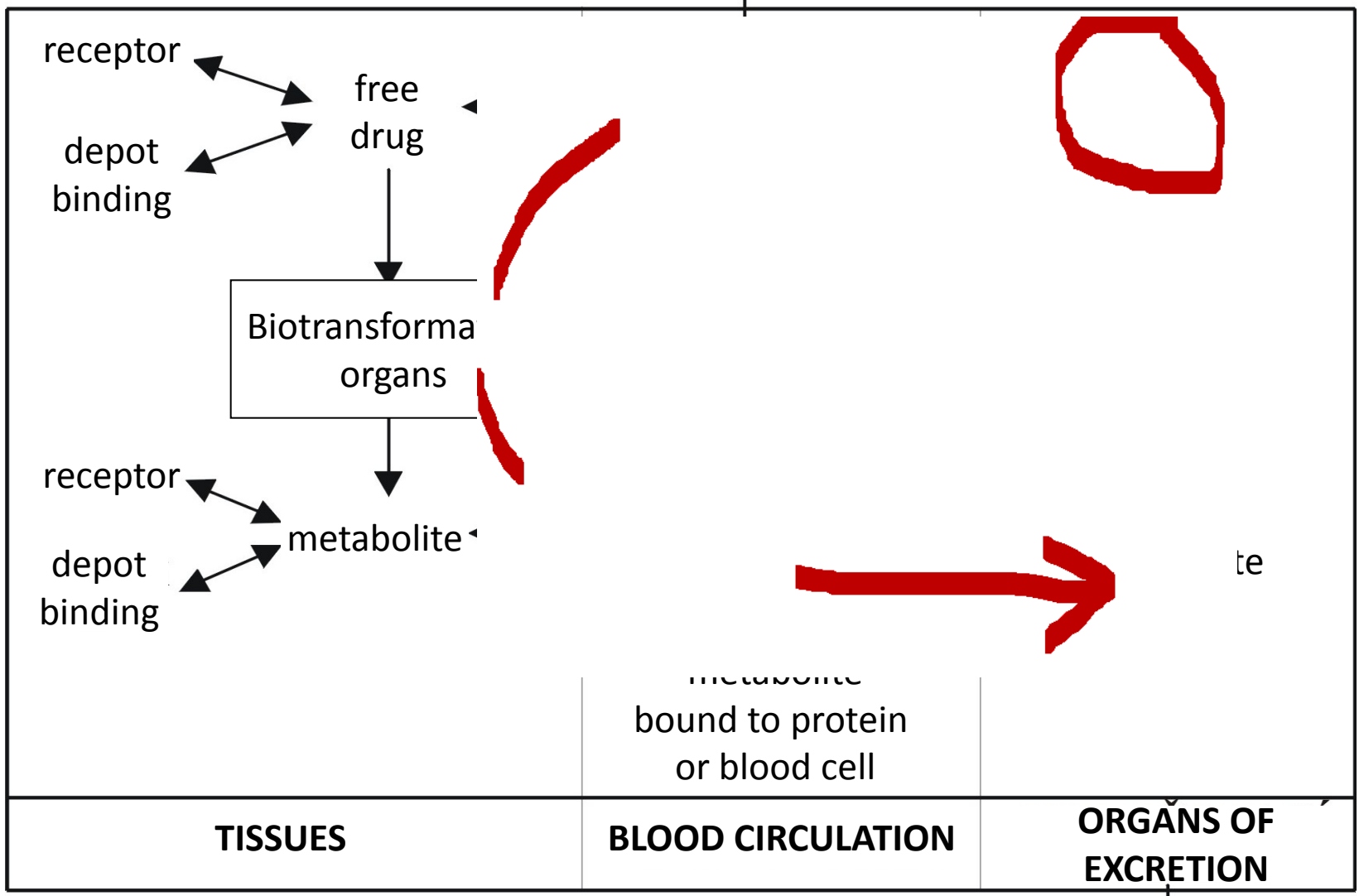
effects

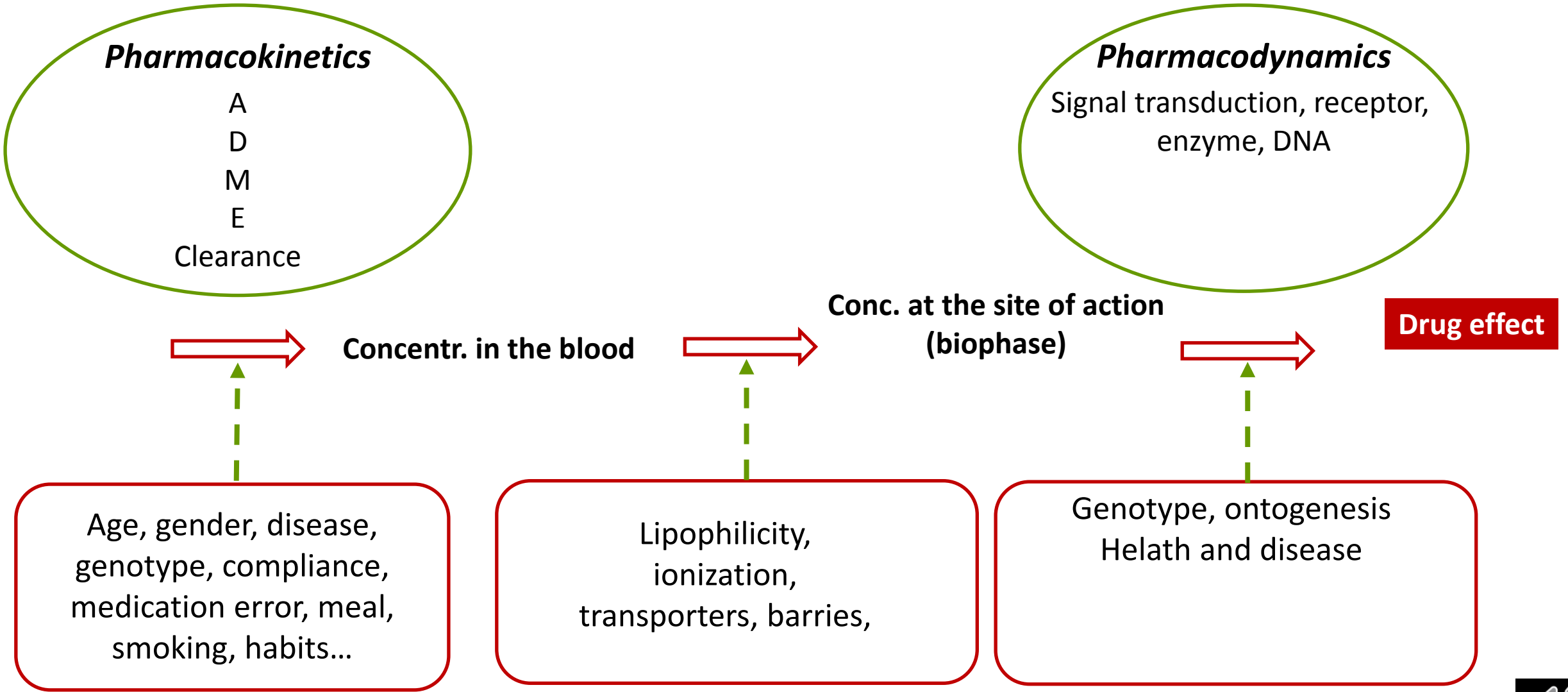
Pharmacokinetics

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

- processes of **ADME**

Administration of drug → Absorption




Pharmacokinetics
A
D
M
E
Clearance
Pharmacodynamics
Signal transduction, receptor, enzyme, DNA
Concentr. in the blood
Conc. at the site of action (biophase)
Drug effect
Age, gender, disease, genotype, compliance, medication error, meal, smoking, habits…
Lipophilicity, ionization, transporters, barries,
Genotype, ontogenesis
Helath and disease

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

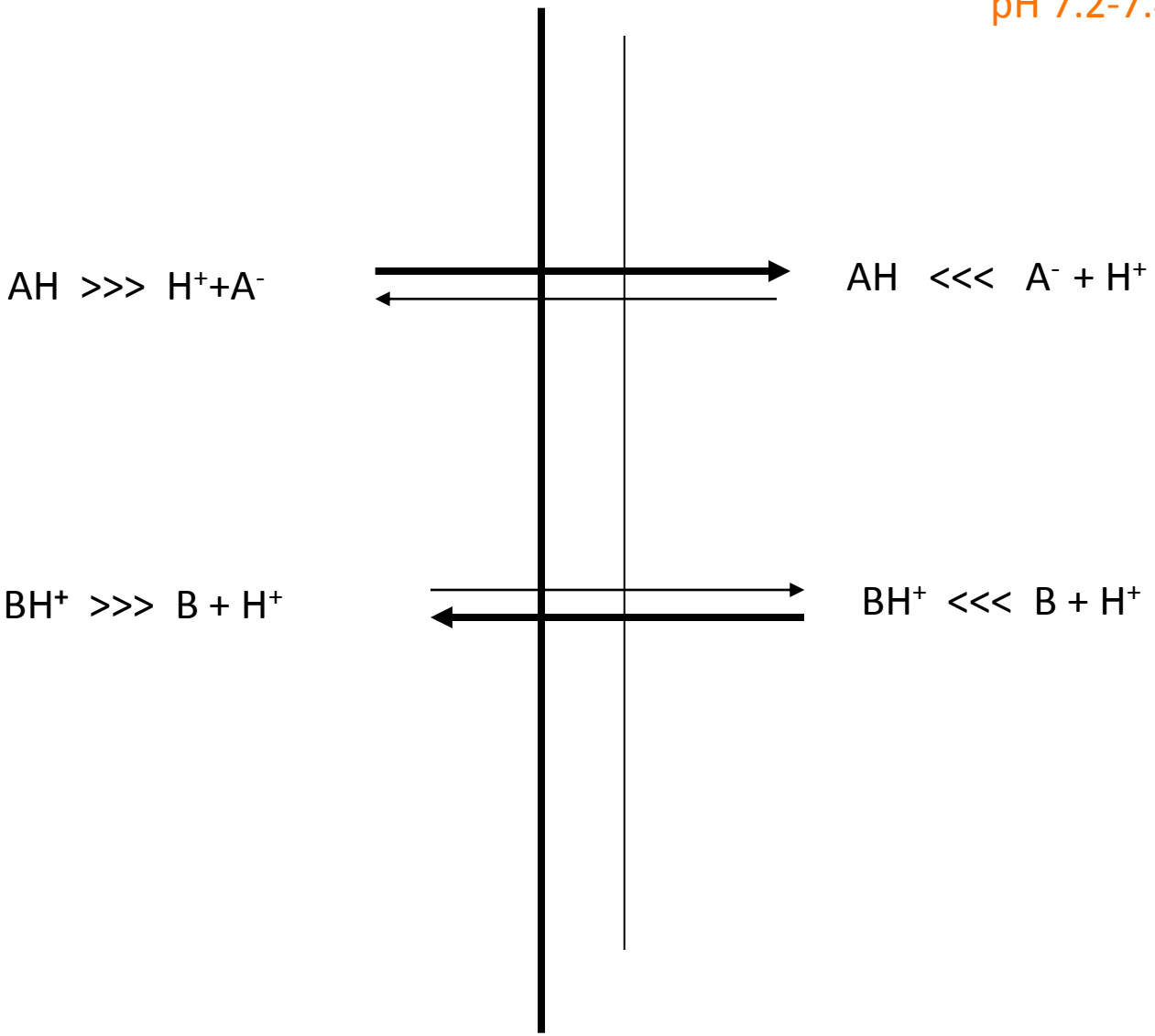
4. **Tissue perfusion**

   brain, heart, liver and kidney

   adipose tissue

Stomach pH 1-2

Parietal cell+ vascular endothelial cell
pH 7.2-7.4



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:

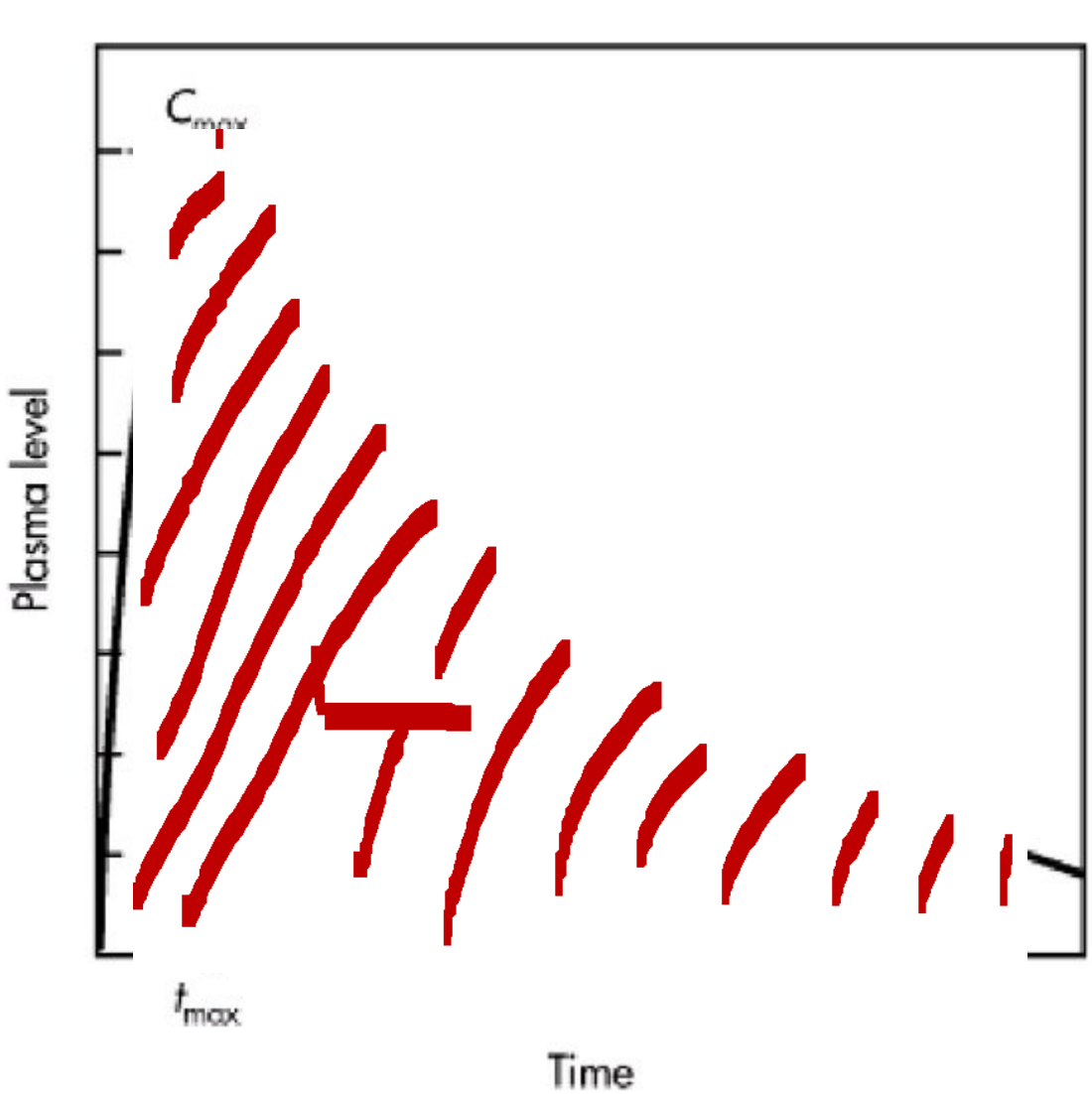
on skin, mucosas or ventricles
absorption is undesirable – possible AE
ie. local corticoids, local anesthetics

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

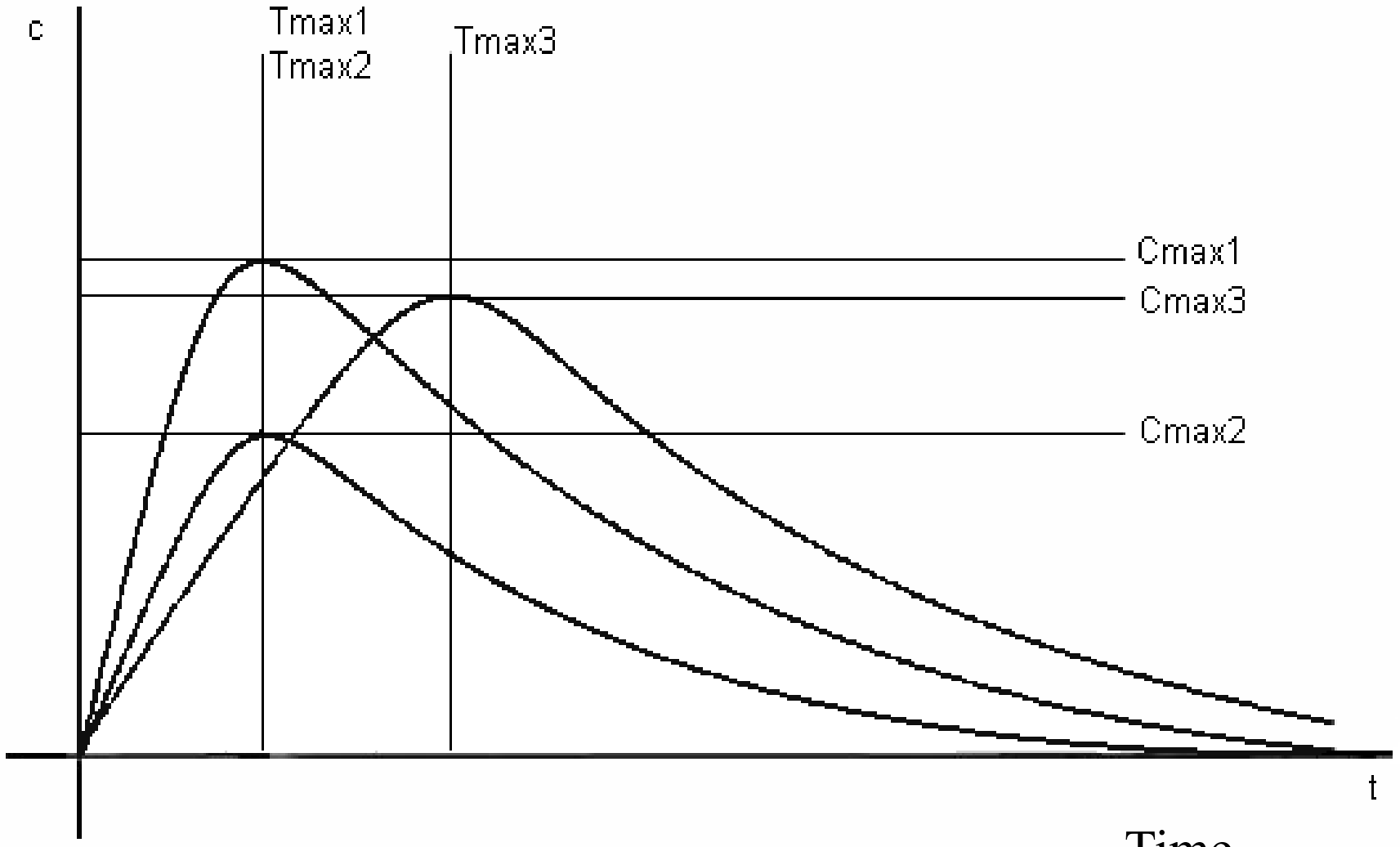
C_{max} max. concentration of drug in plasma after single dose

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

bioavailability (extent)


C_{max}
Plasma level
t_{max}
Time

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

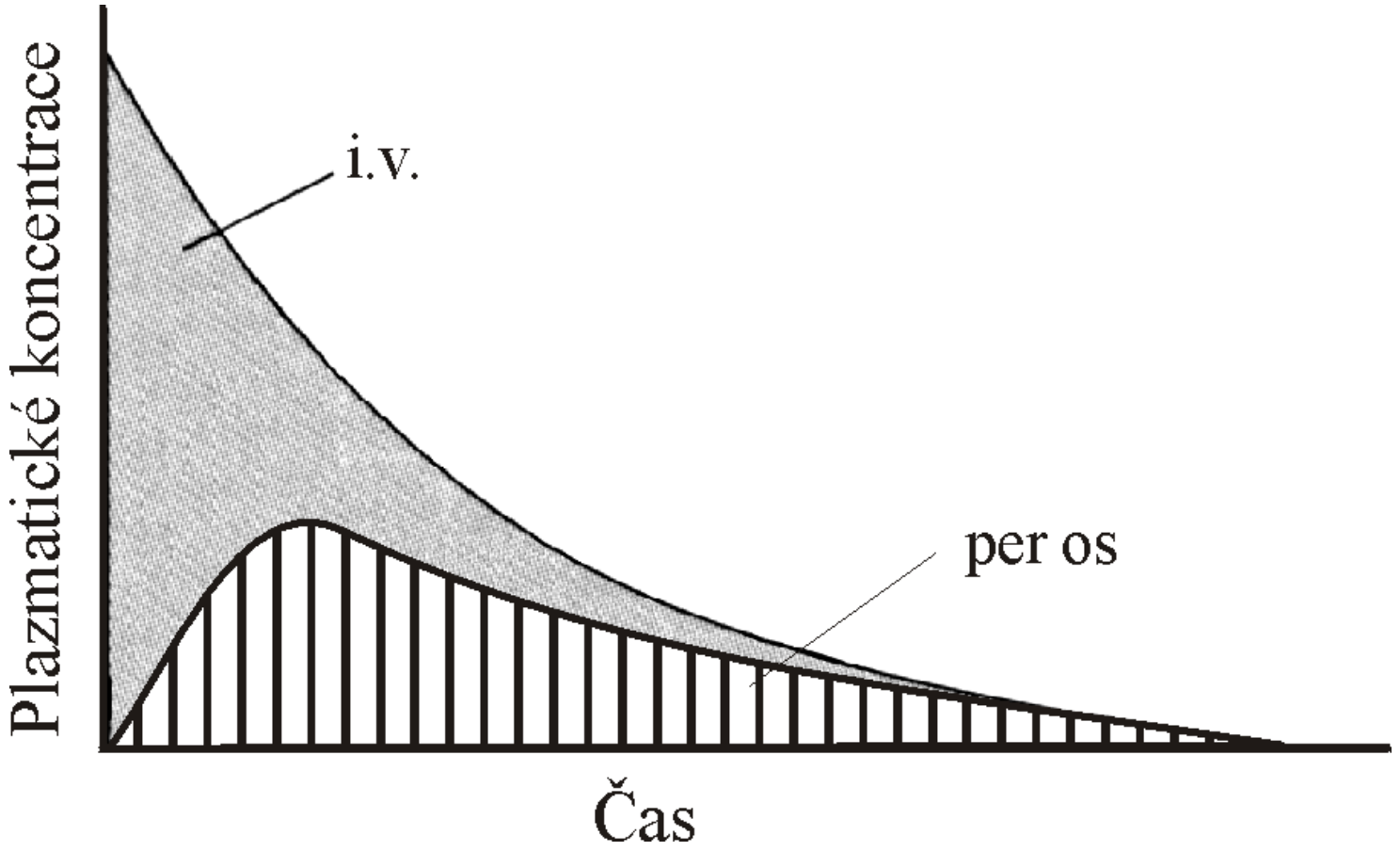
if F is < 20 % = 0 - 0,2 – it not worth to administer the drug by this way (some of them are administered through that - SET, bisfosfonates)

the measure of bioavailability is the **area under the curve** (AUC)

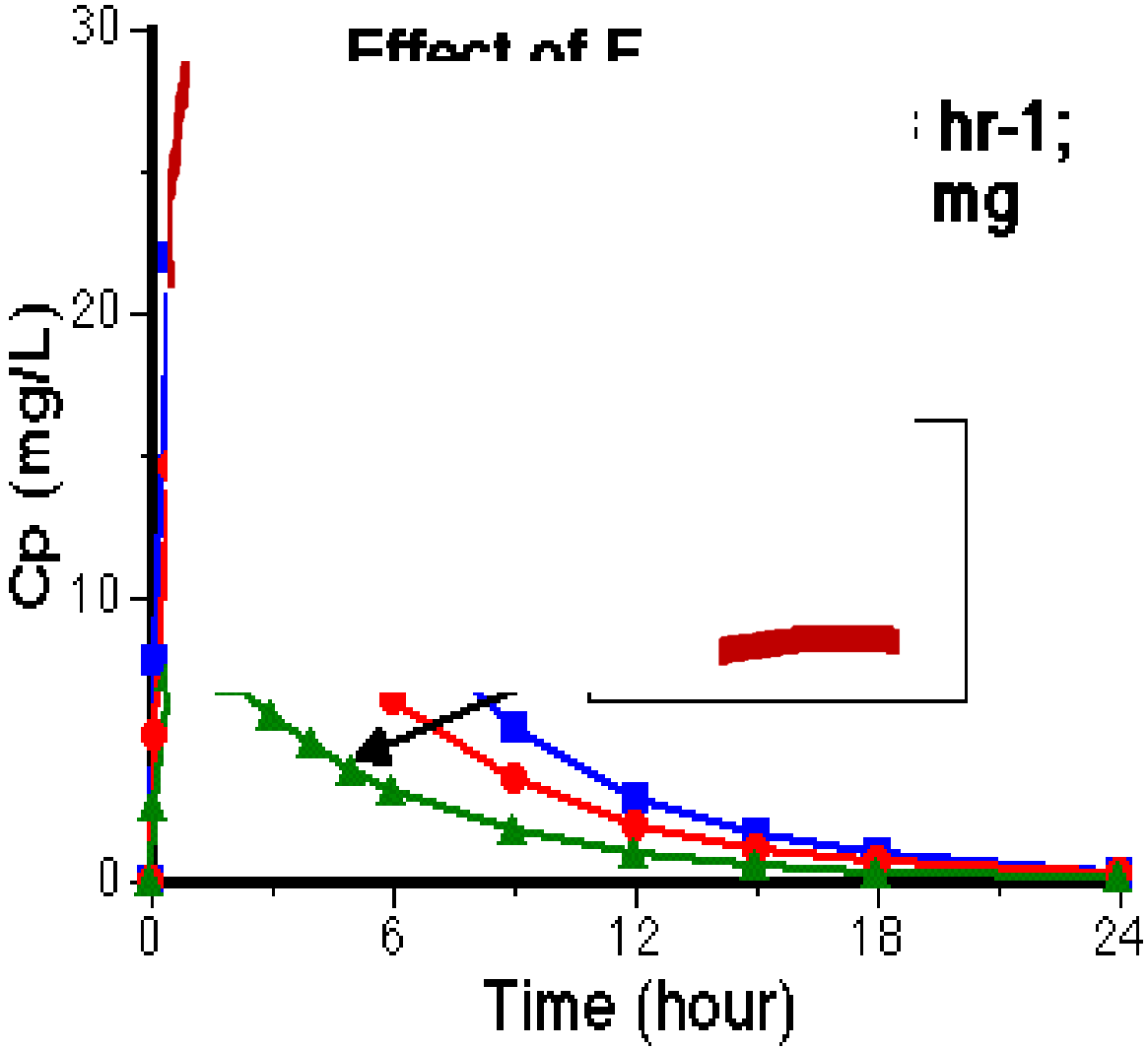
$$F = \frac{AUC_{po}}{AUC_{iv}}$$

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

AUC – area under the curve



Effects of different bioavailability (F) on the pharmacokinetics



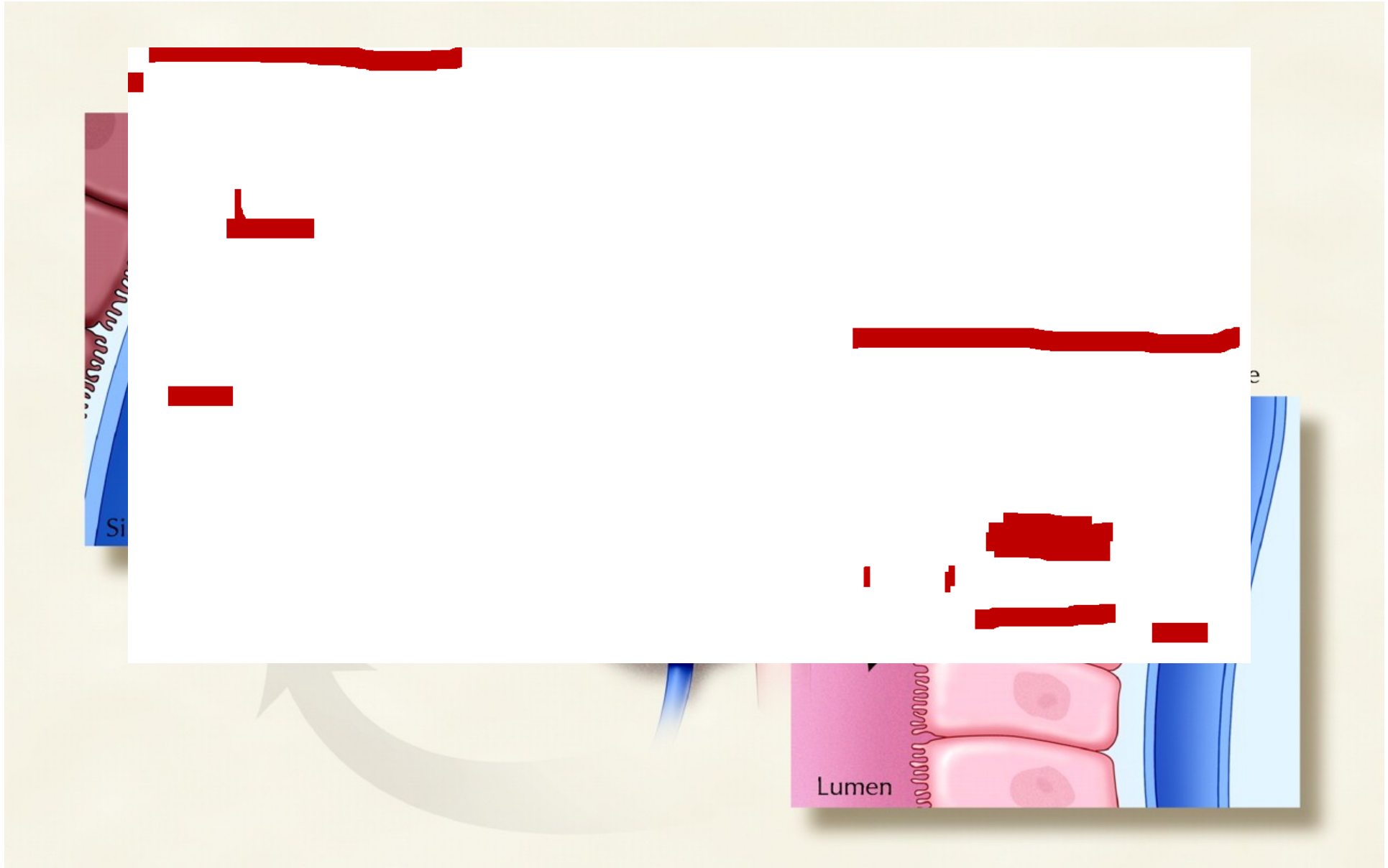
Bioavailability- F

Absolute bioavailability

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

Relative bioavailability

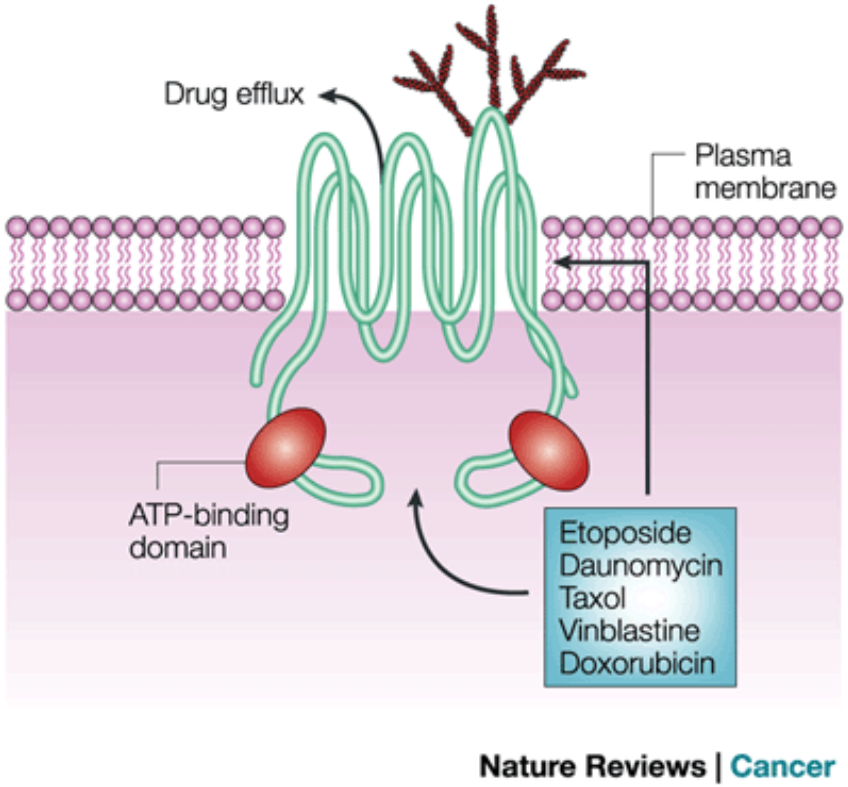
assess the expected biological equivalence of two preparations of a drug
if the relative bioavailability = 1 (100%) → tested preparation is bioequivalent to the reference

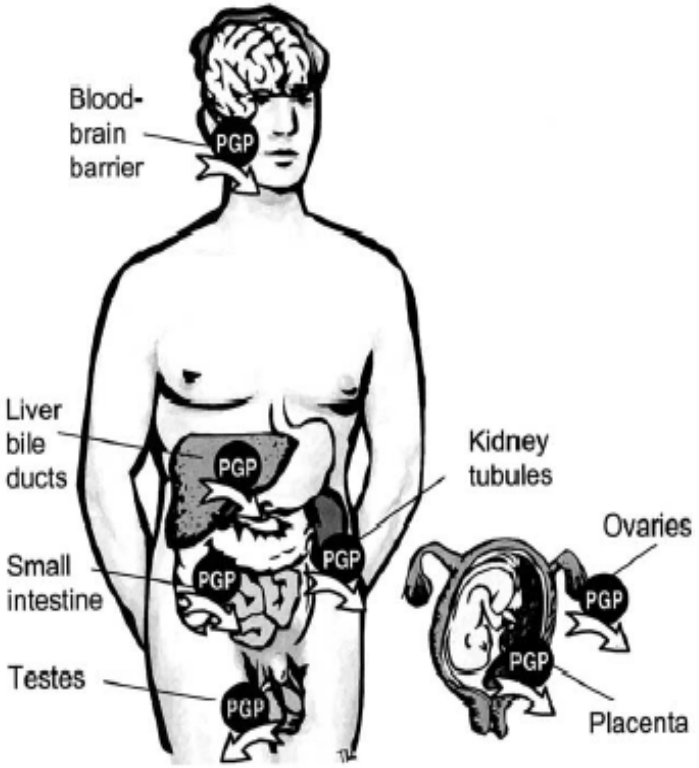


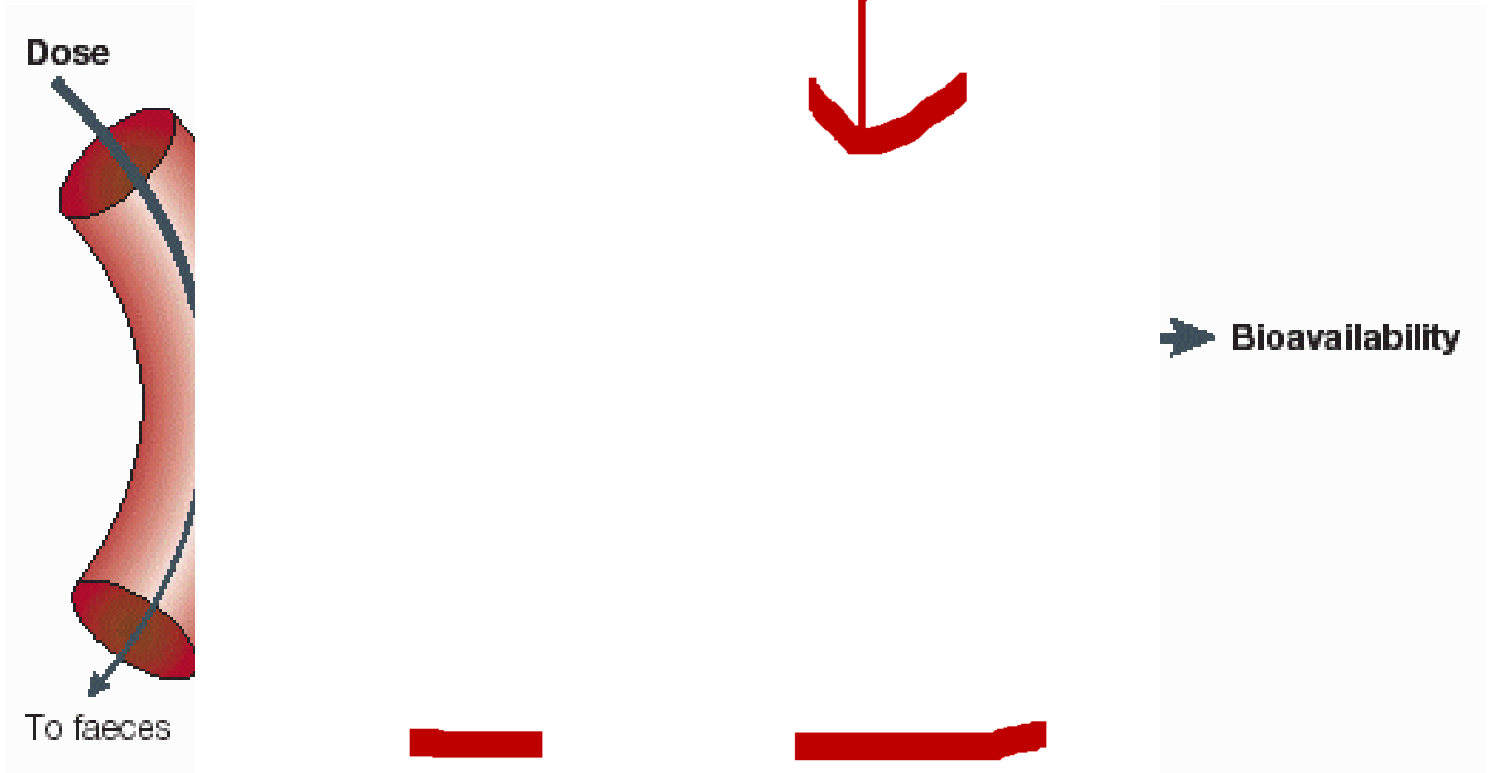
David G. Bailey, and George K. Dresser CMAJ 2004;170:1531-1532

P-glycoprotein

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







http://icp.org.nz/icp_t6.html?h

Other factors influencing drug absorption

gender, weight, plasmatic volume, speed of gastric discharging

age - pH, bile, enzymes

pathophysiological d[illegible] es of liver, inflammation ...

Body constitution (B\[illegible]

diet

- acceleration/ decceleration

- chemical incompatibilities

- GIT functionality

c
i.v.
i.m.

T [min]

Distribution

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

speed of distribution- depends on:

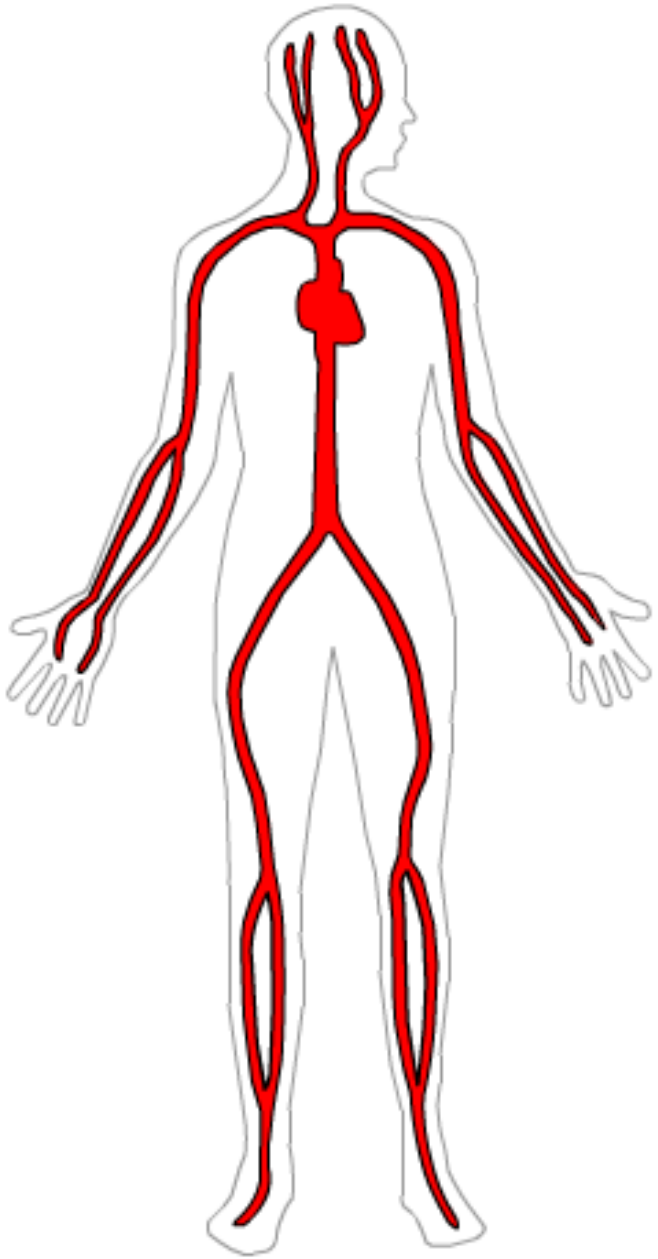
free fractions of drug are equal

l plastmatic concentration

[1]

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

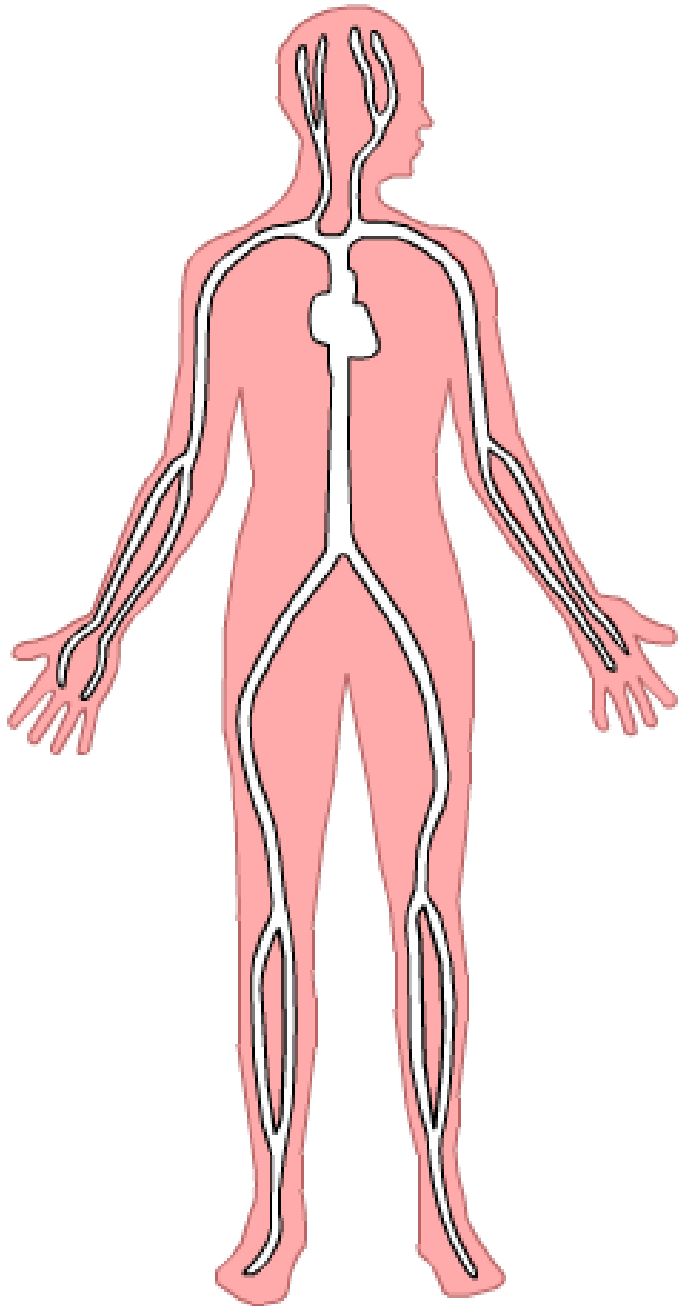
Drug moderately concentrated in tissues

Drug highly concentrated in tissues (usually adipose)

10,000 L

Amount in body = Vd x plasma concentration

Ab = Vd x Cp



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10,000 L

Amount in body = Vd x plasma concentration

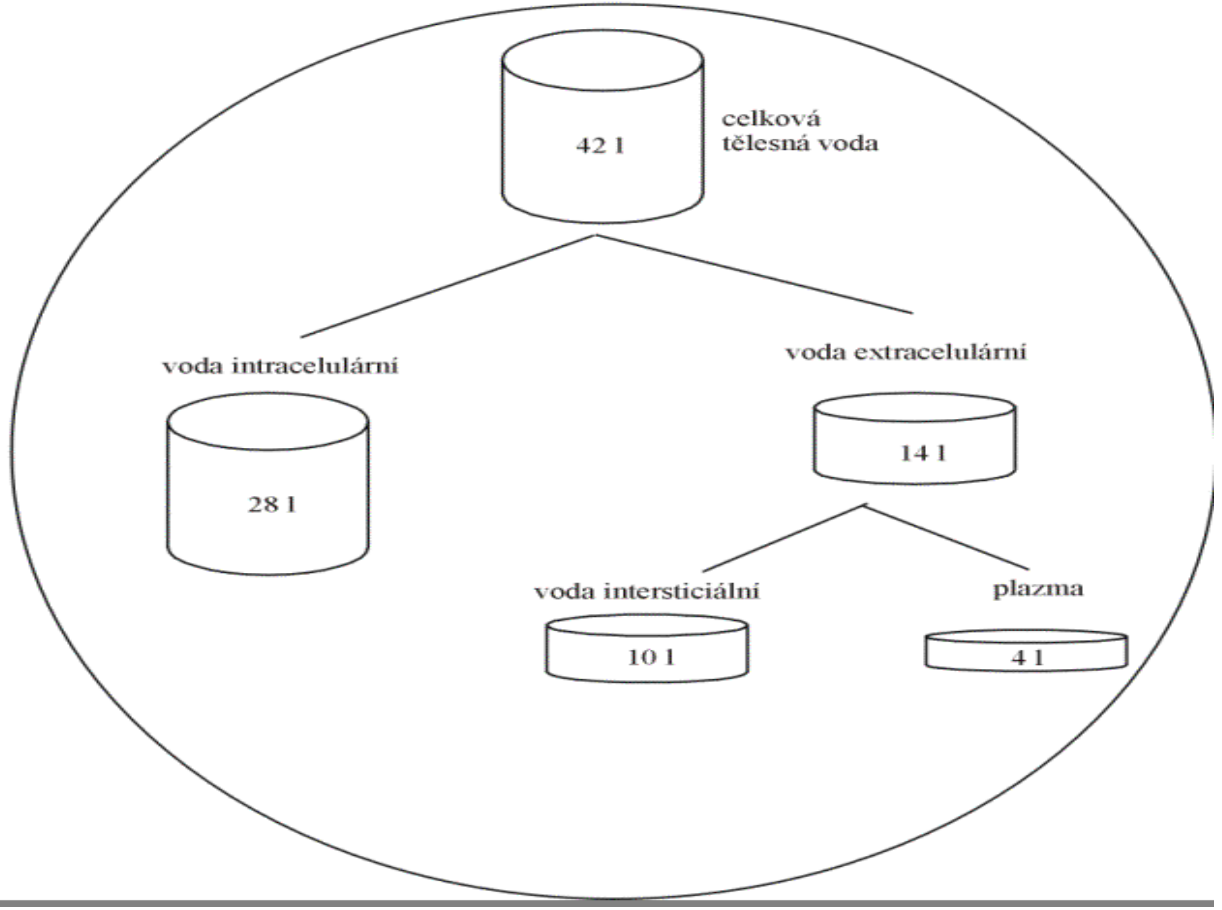
$$Ab = Vd \times Cp$$

$$\uparrow \quad \frac{\uparrow Ab}{\downarrow Cp}$$

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.

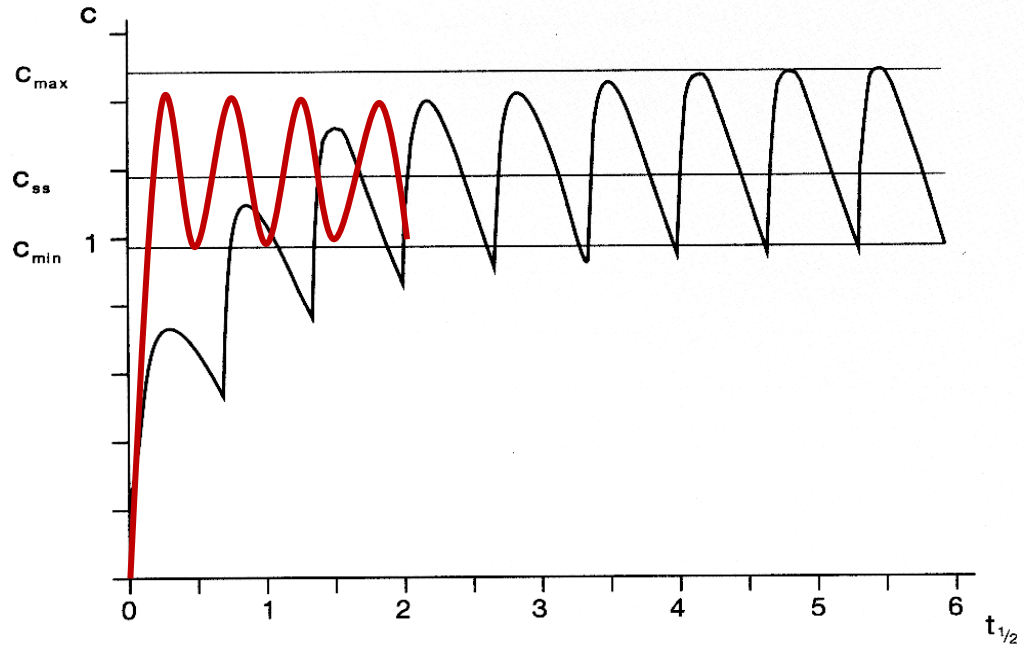


Distribution

Distribution volume - use:

Calculation of loading dose:

$$D = Vd \cdot c_T$$



Distribution

Estimate the amount of drug in the body

$$M = Vd \cdot C$$

Assessment of the effect of hemodialysis and hemoperfusion

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

Elimination of drugs

First-order elimionation

Rate of elimination is influenced by plasmatic concentration

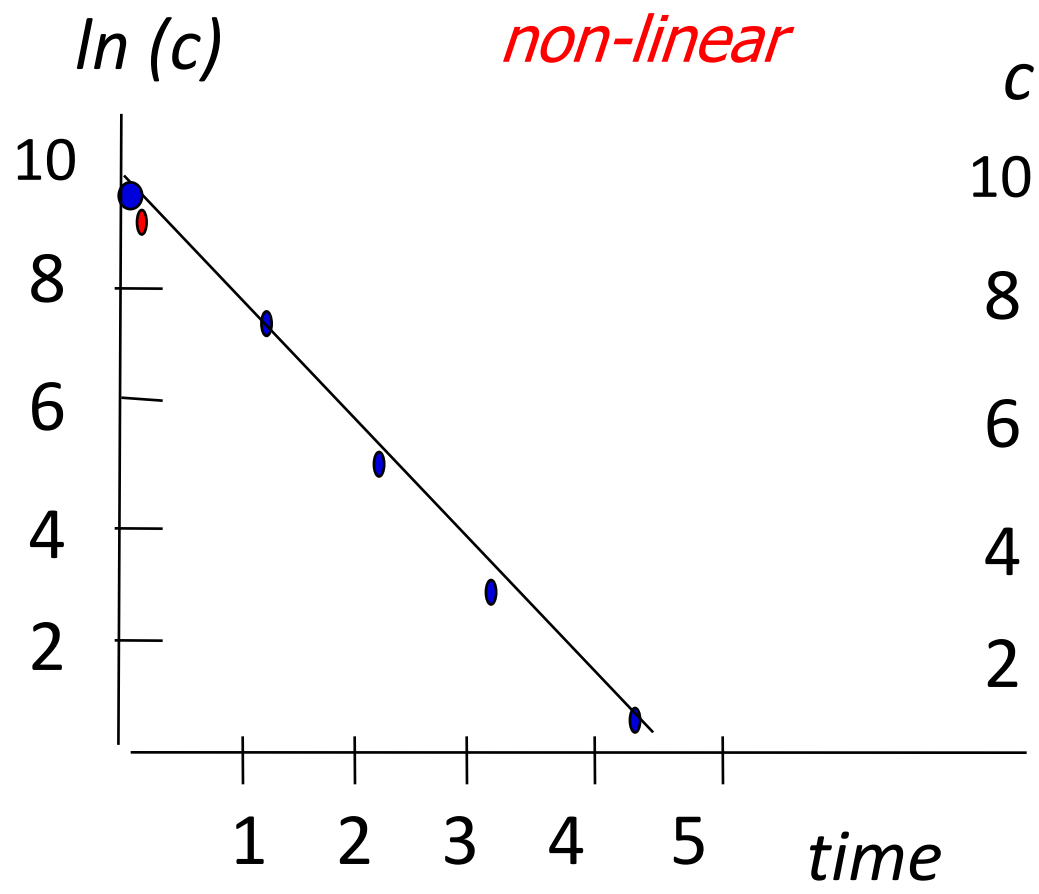
Linear kinetics

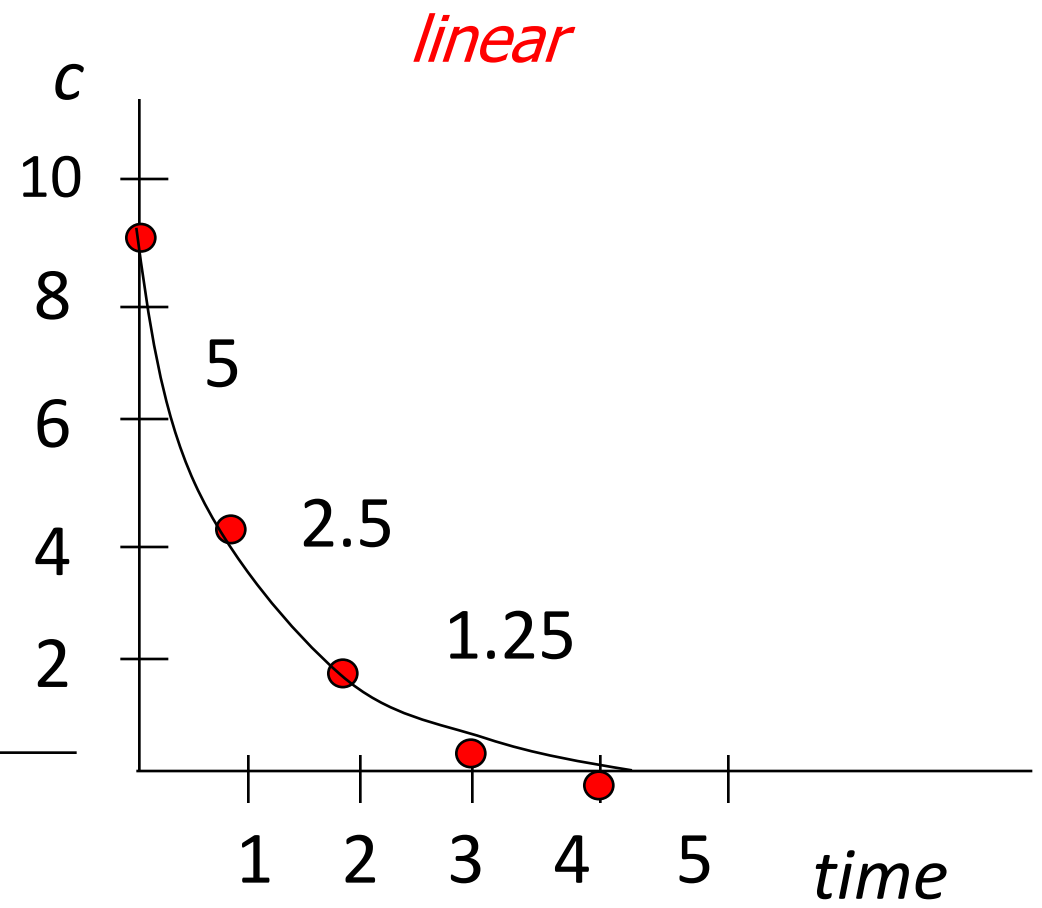
Zero-order elimination

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

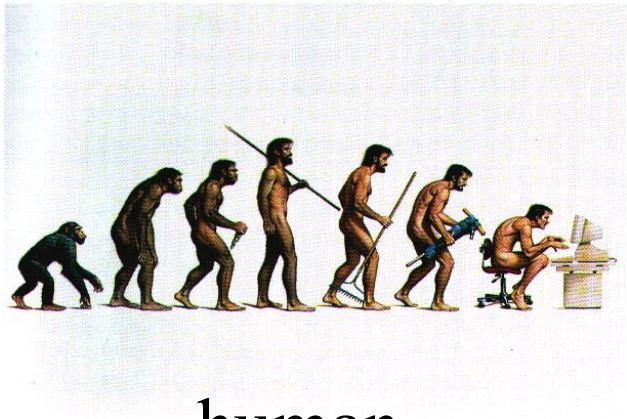
   cytochromes P450, dehydrogenases

2. **Phase:**

   conjugation → molecules becomes hydrophilic

Metabolites

- effective („more/less“)
- inneffective
- toxic



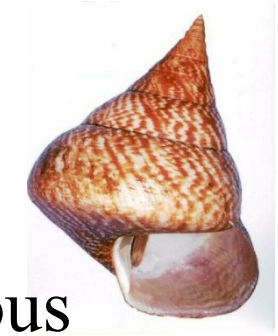
human

animals

plants

CYP 450

molluscous

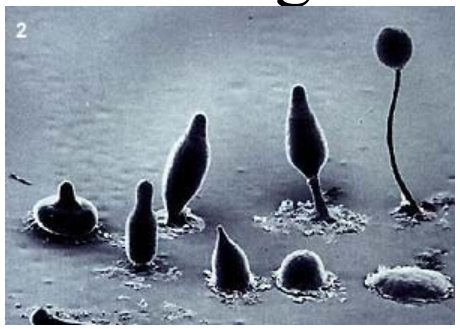


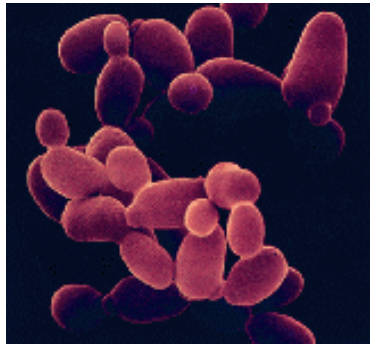
insect

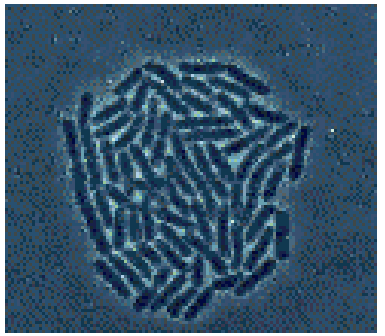
fungus

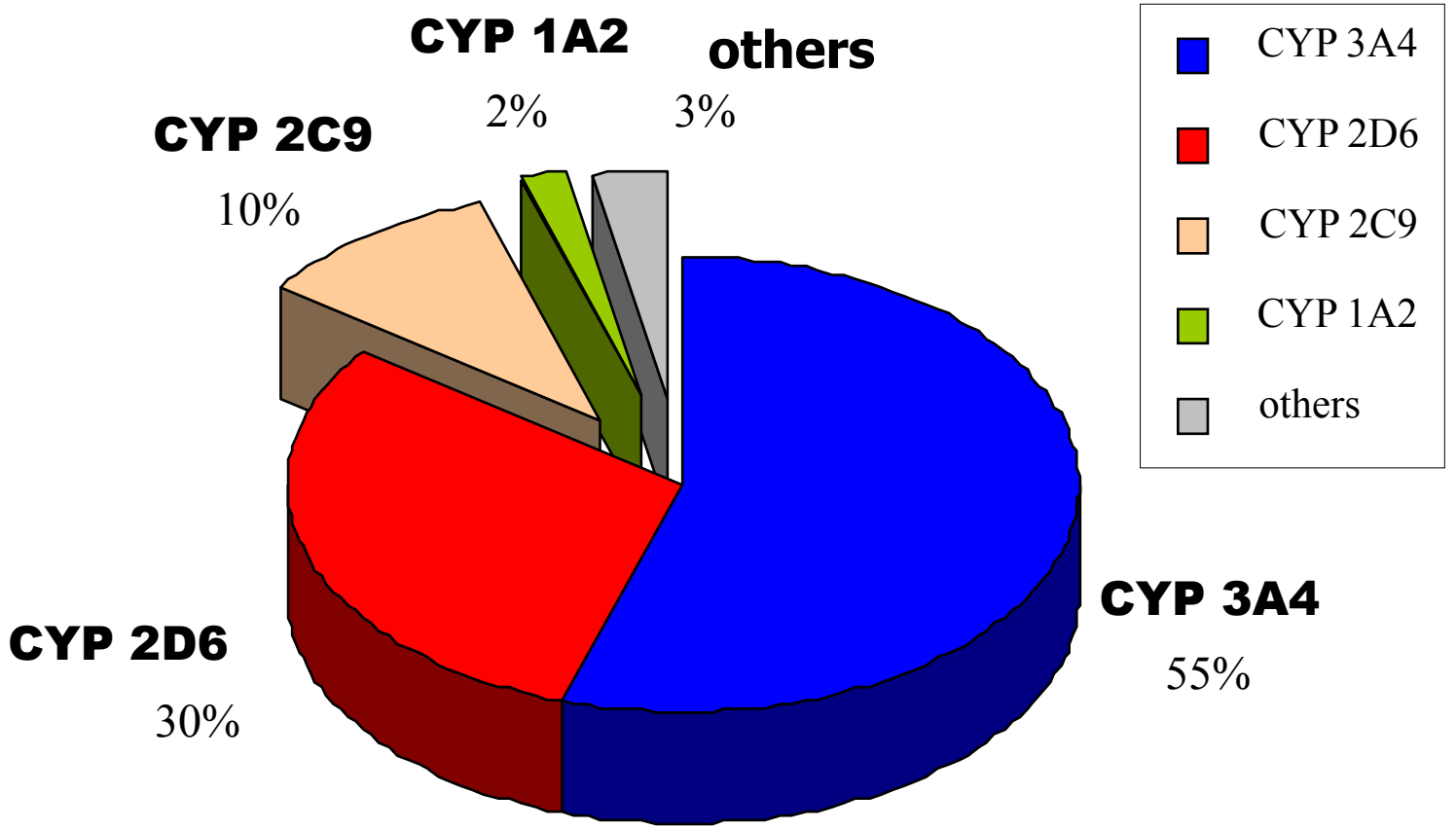
yeasts

bacteria








CYP 1A2
2%
others
3%
CYP 2C9
10%
CYP 2D6
30%
CYP 3A4
55%
CYP 3A4
CYP 2D6
CYP 2C9
CYP 1A2
others

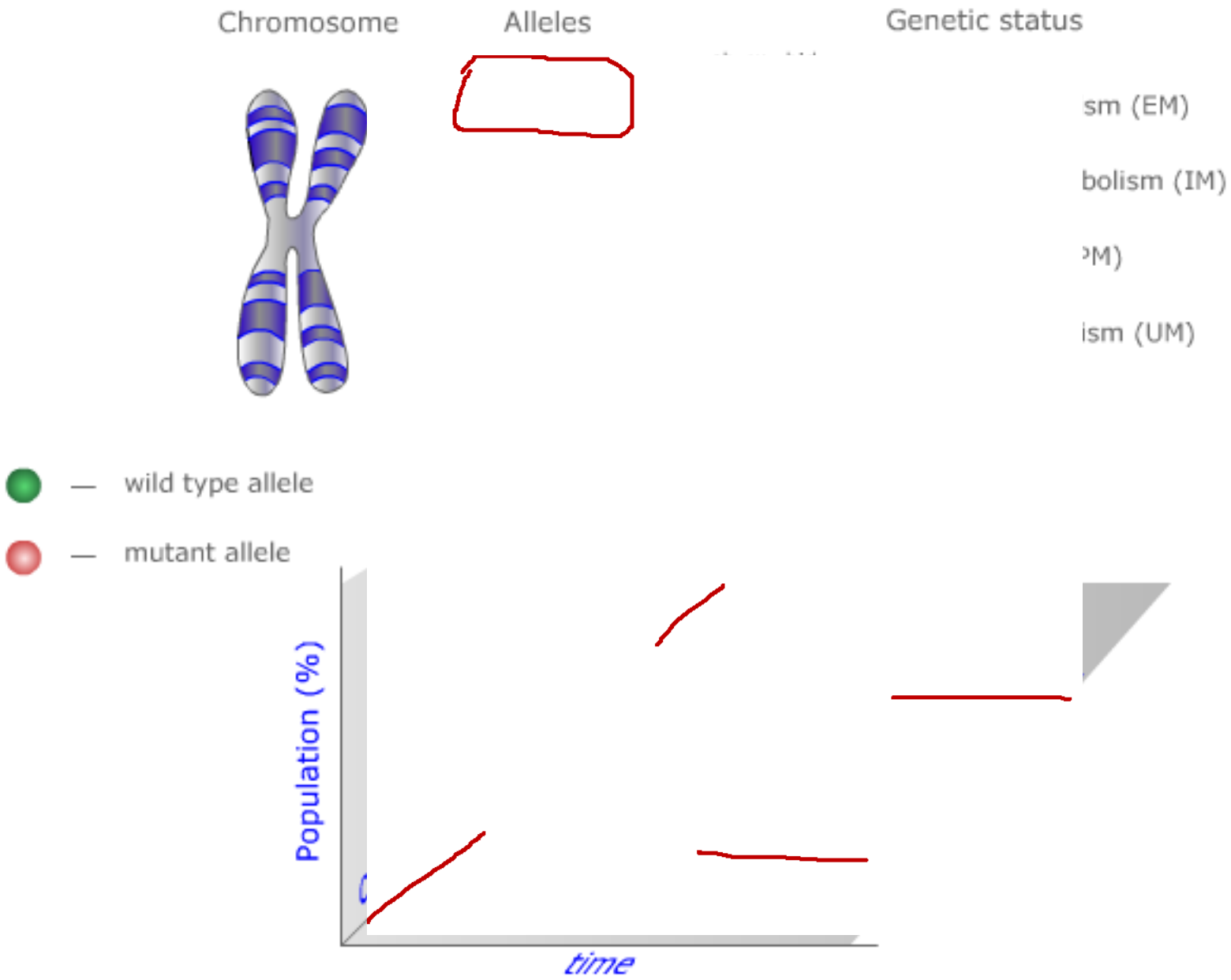
Inducers of CYP450

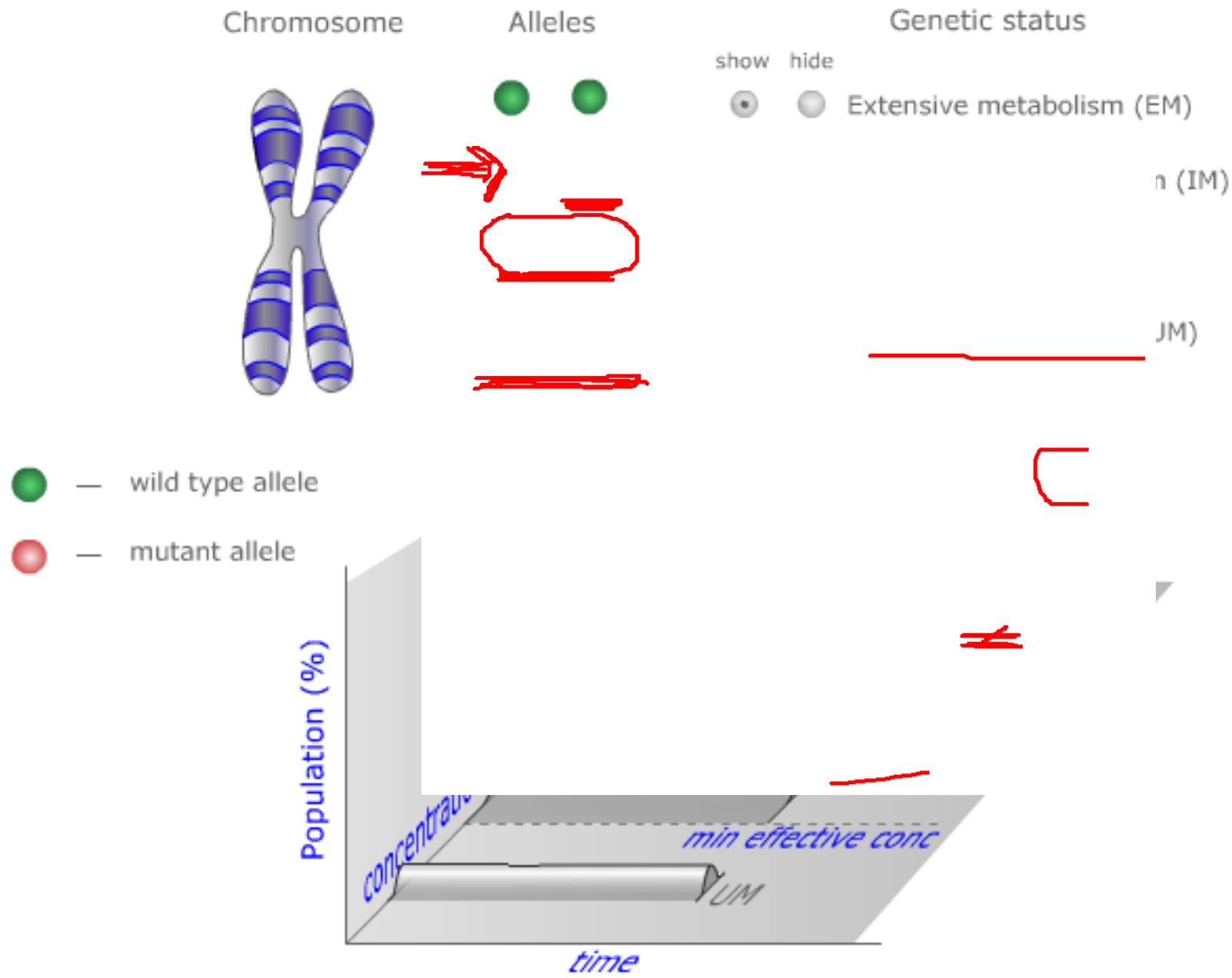
- **dexametazon**
- **fenobarbital**
- **rifampicine**
- **phenytoin**
- **St. John´s worth (Hypericum *perforatum)***
- ***Ginkgo biloba***

Inhibitors of CYP450

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

Genetic polymorfism of CYP 450




Chromosome
Alleles
Genetic status
show
hide
Extensive metabolism (EM)
n (IM)
JM)
wild type allele
mutant allele
Population (%)
min effective conc
UM
time

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

tubular reabsorption
- diazepam

alkalization

natrium hydrogencarbonate

acidification

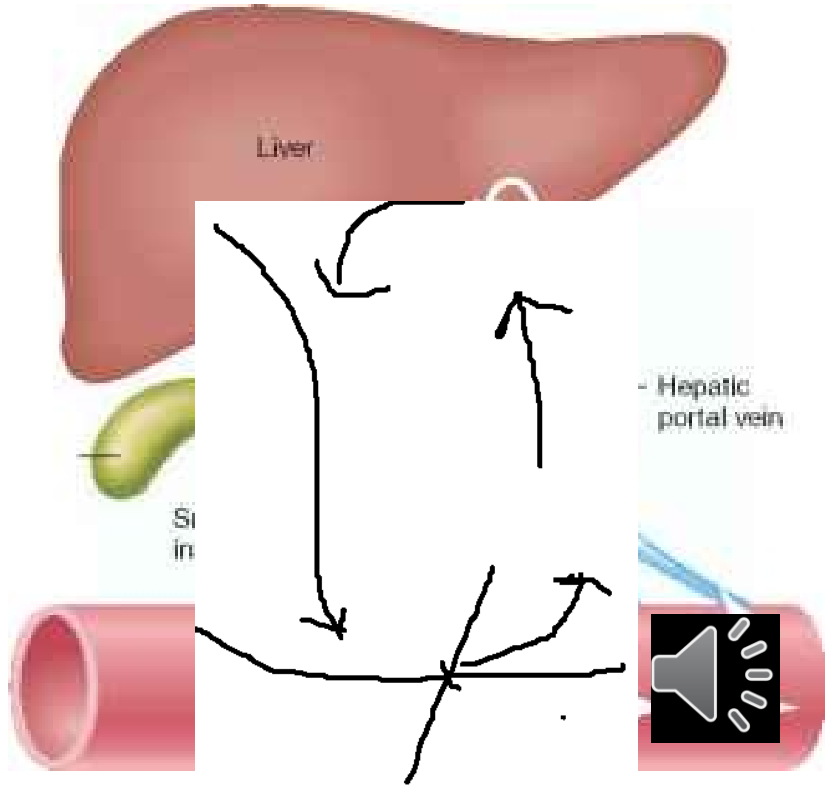
ammonium chloride

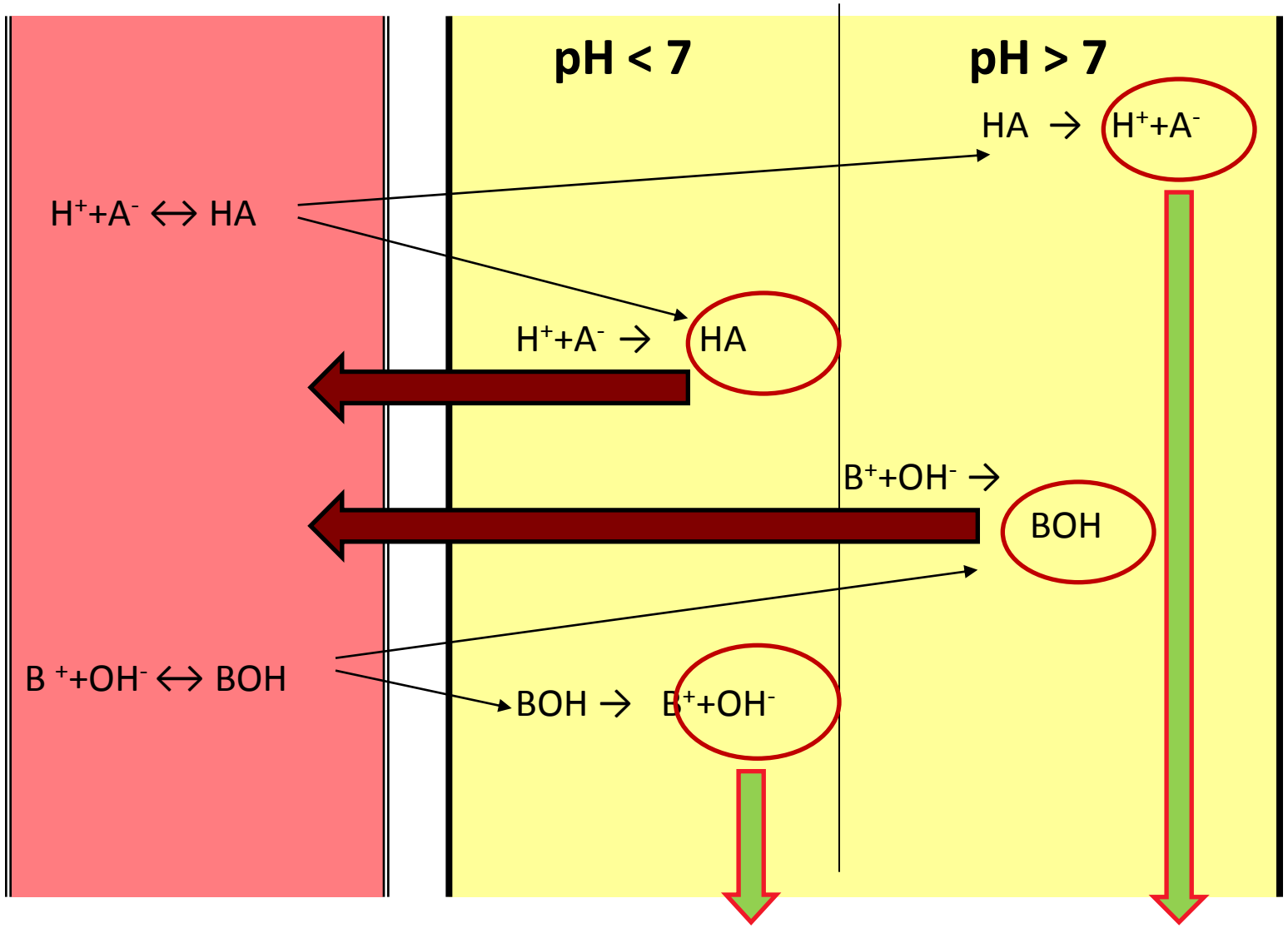
Excretion by liver

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





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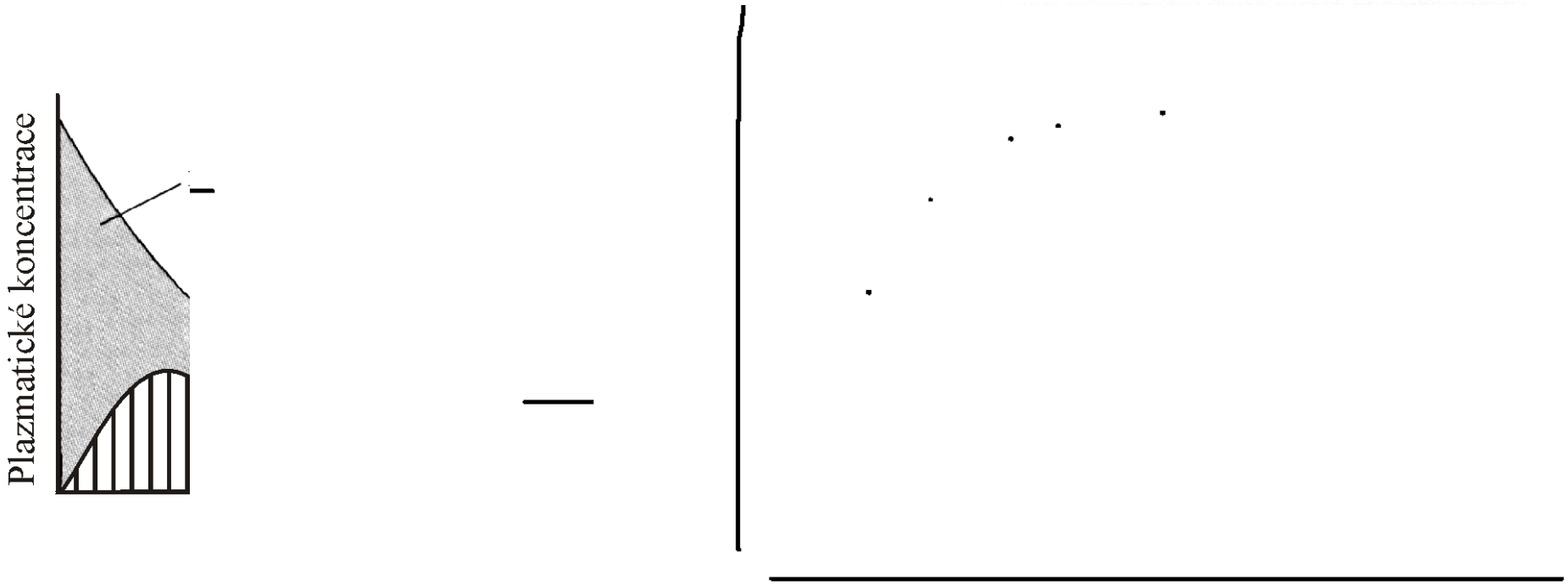
Pharmacokinetic parameters

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}

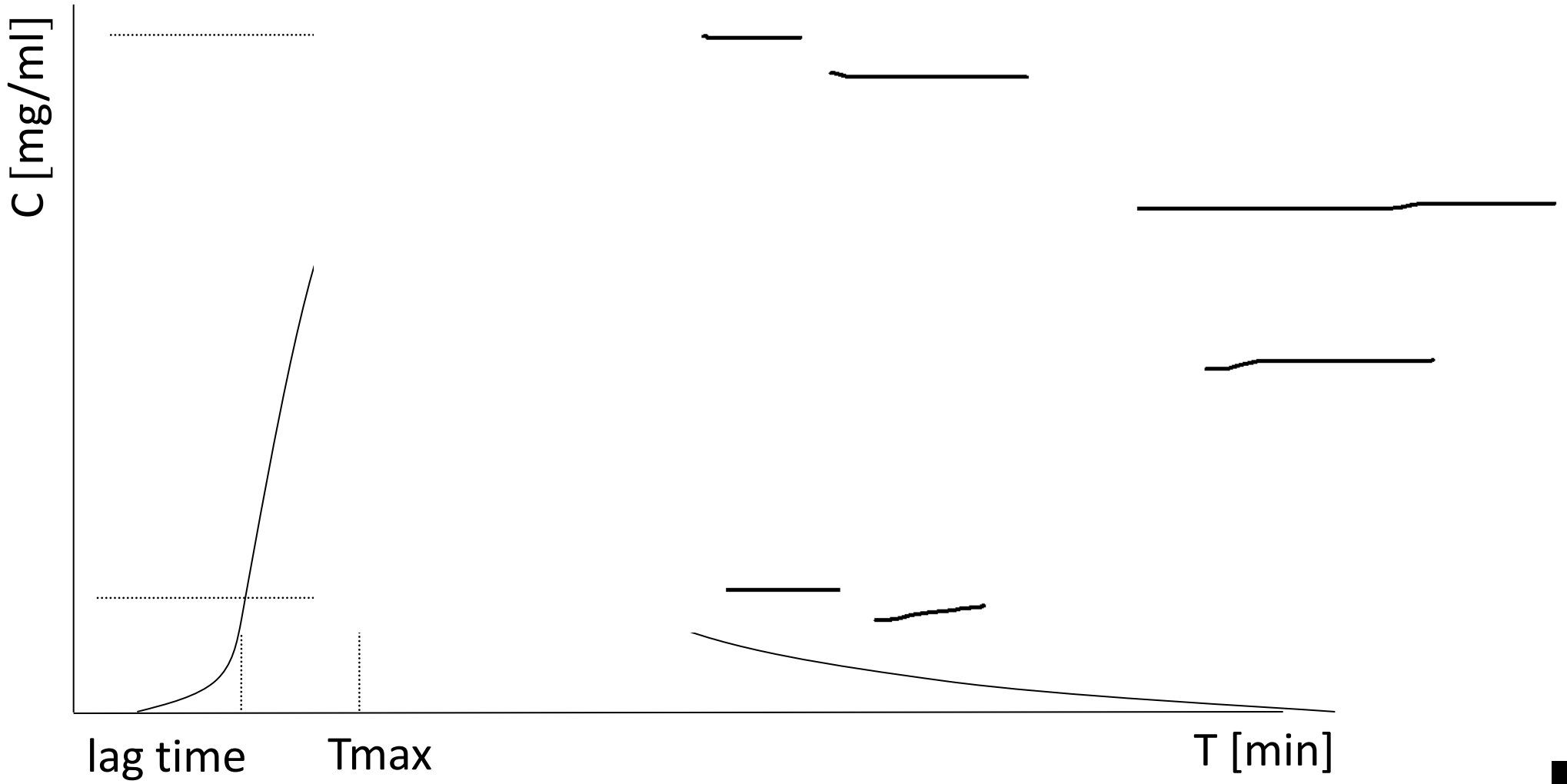
Bioavailability - F

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

Volume of distribution - Vd

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

Relationship of plasmatic conc. on time



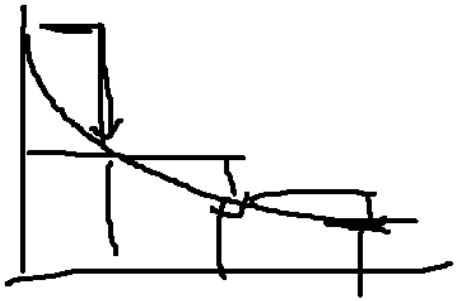
INVASION ELIMINATION

Single dose

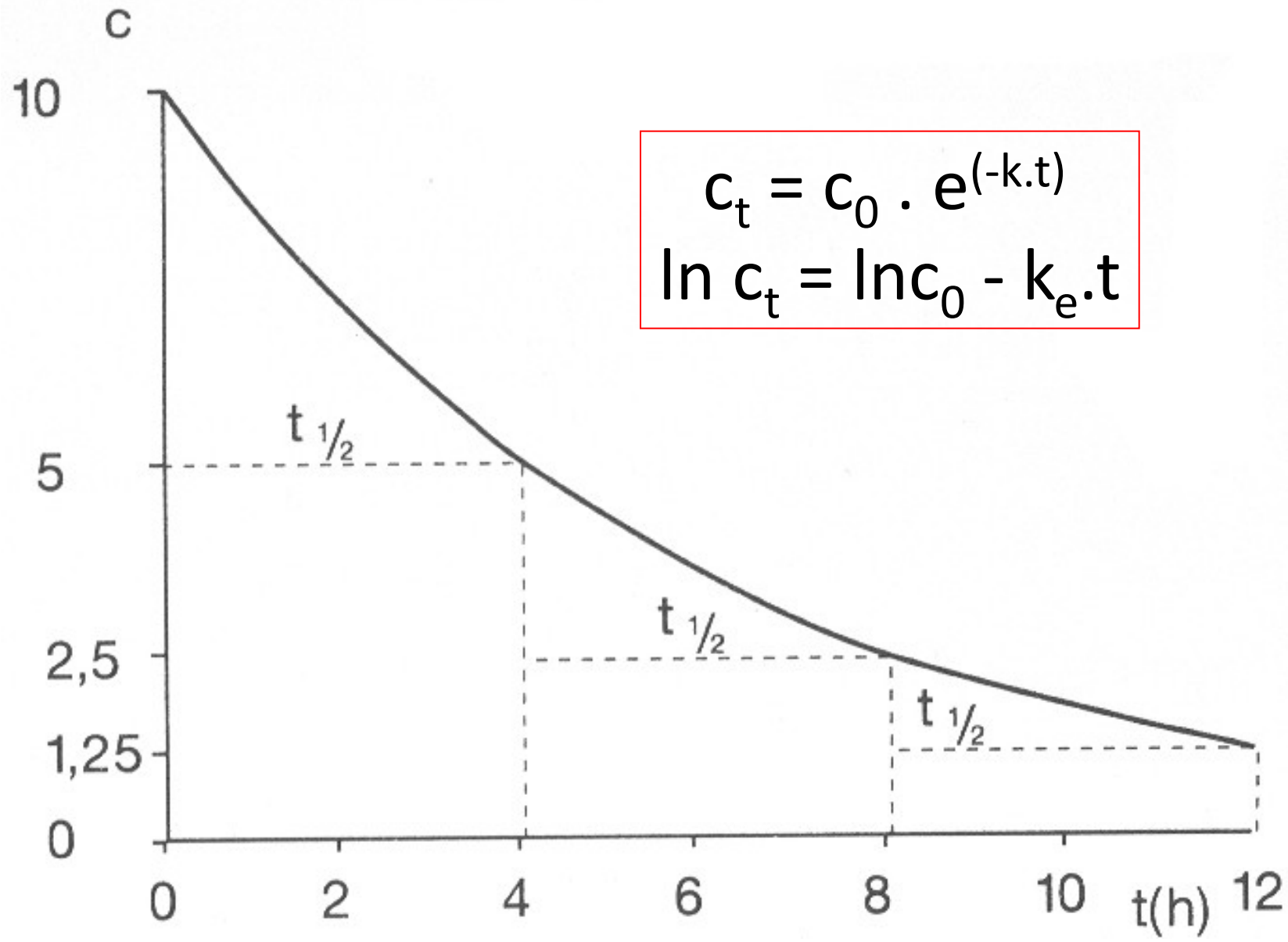
Elimination phase

Drug is eliminated from the organism with speed determined by:

$\ln c_1 - \ln c_2$



Cl_{PUL} ...



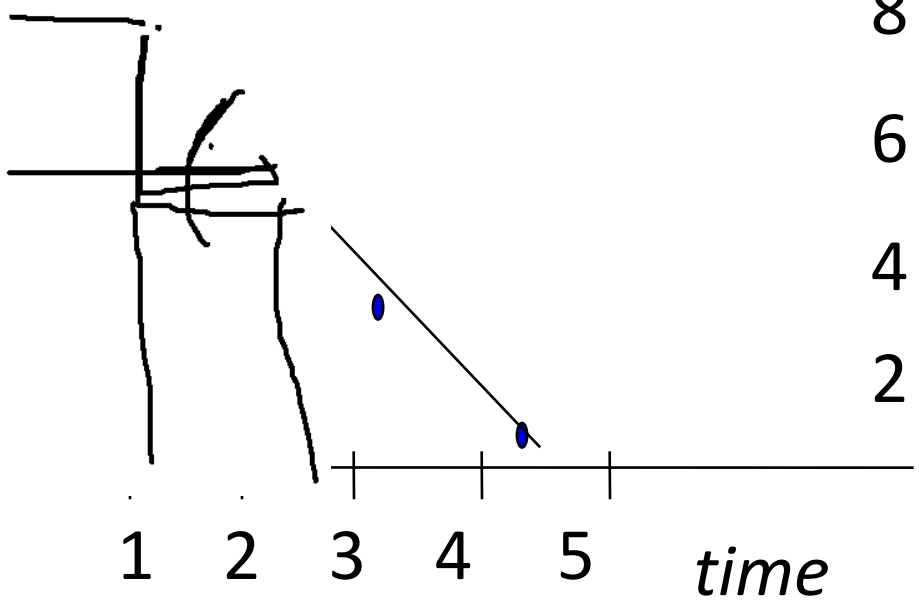
$$c_t = c_0 \cdot e^{(-k.t)}$$

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

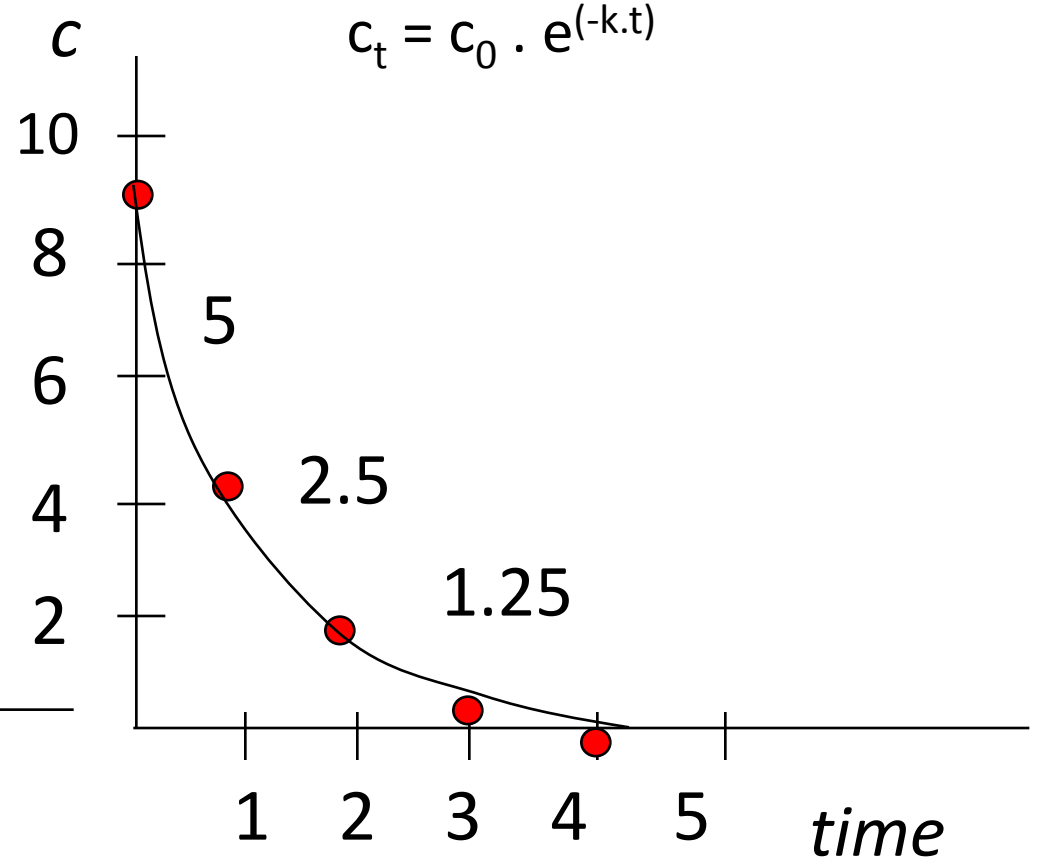
First-order kinetics – semilogaritmic plot (i.v.)

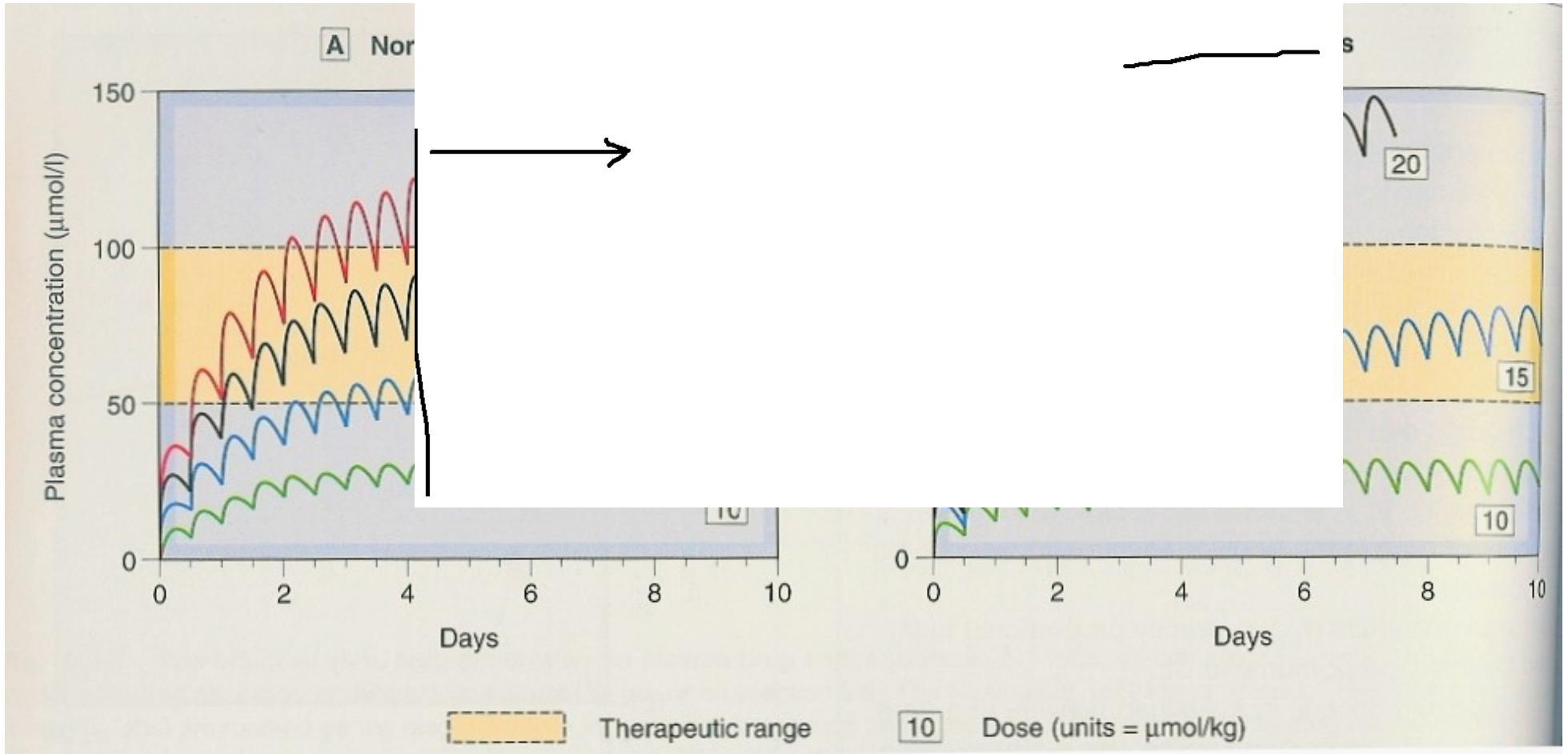
$ct = \ln c_0 - ke.t$

$y = -ke \cdot x + b$



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




A Nor
150
100
50
0
Plasma concentration (µmol/l)
0
2
4
6
8
10
Days
20
15
10
Therapeutic range
10
Dose (units = µmol/kg)

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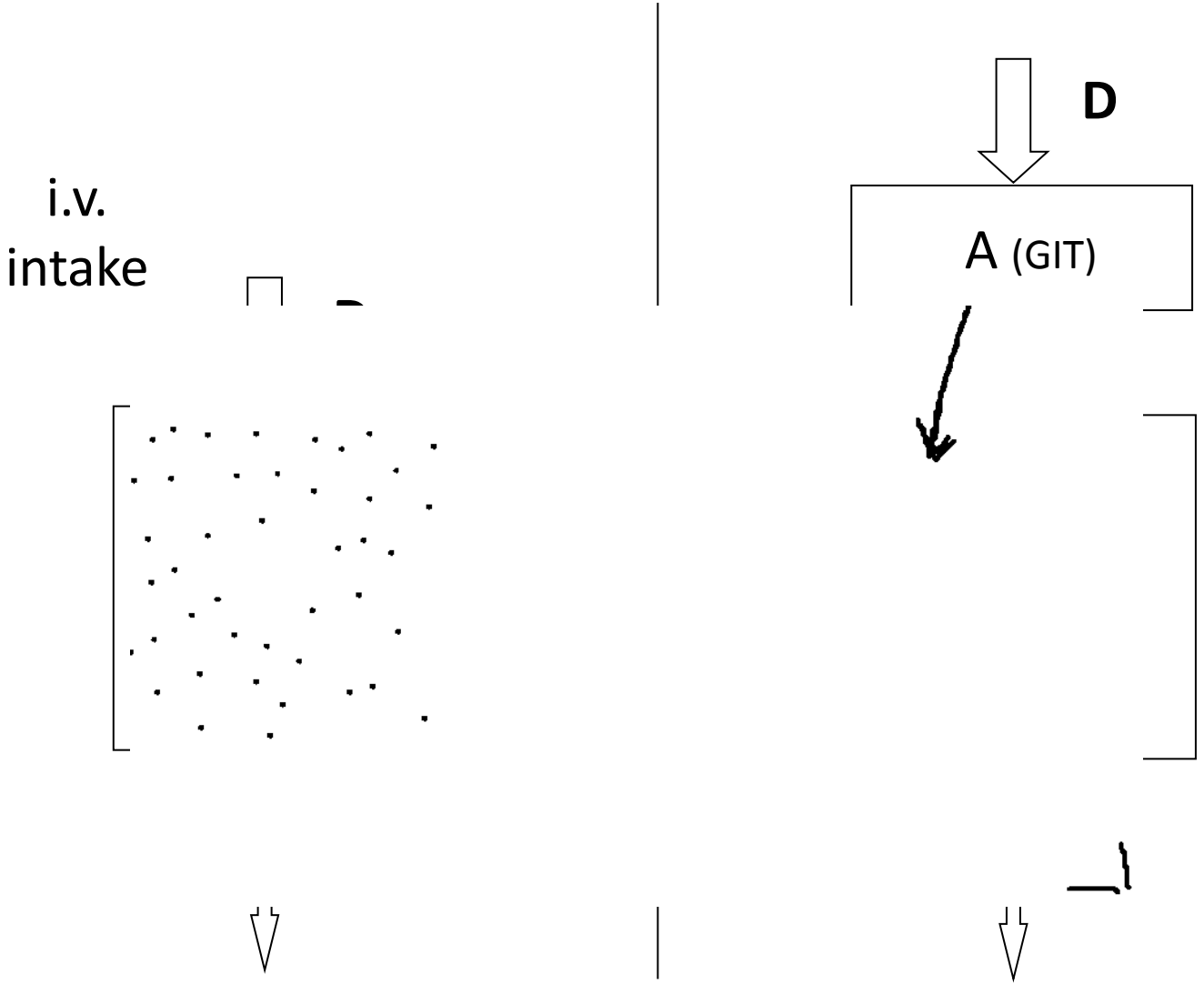
Compartment models

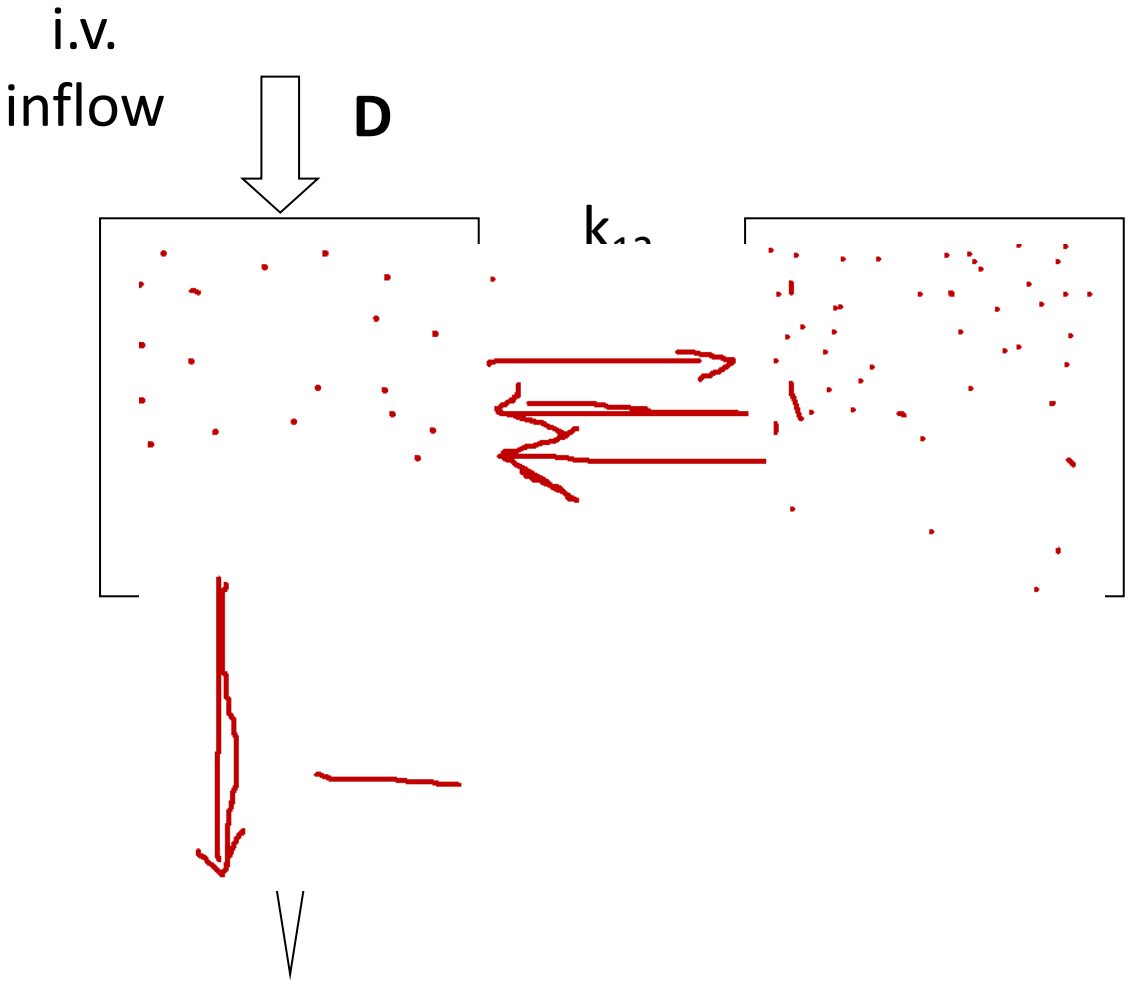
Compartment models– block schema

1- compartment model

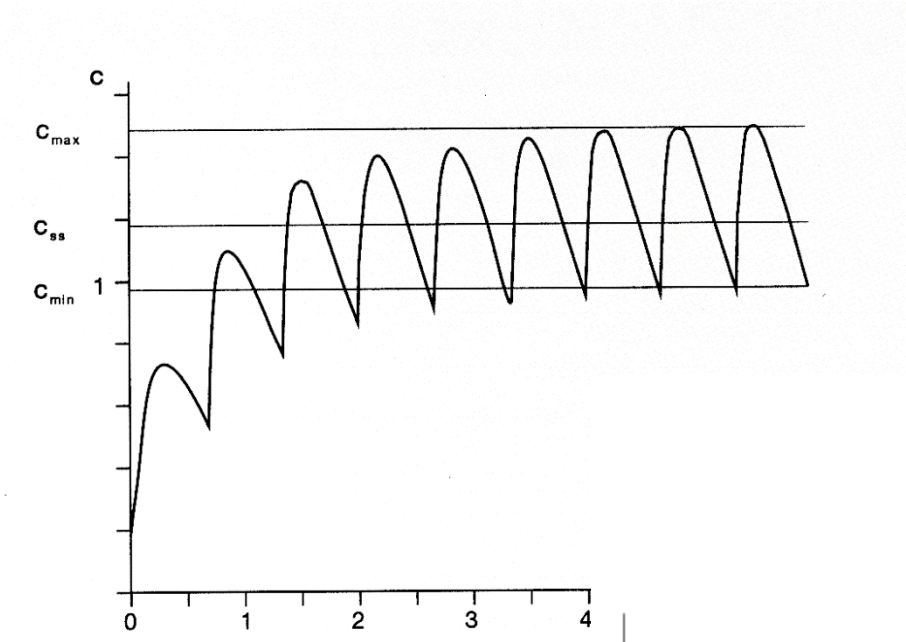


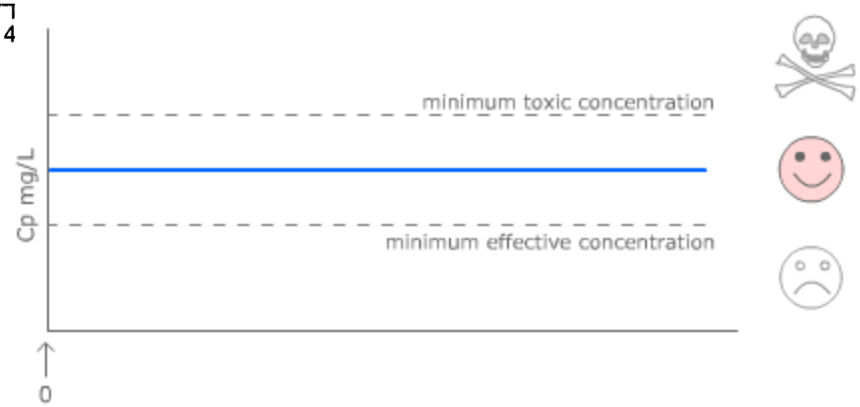
Compartment models– block schema

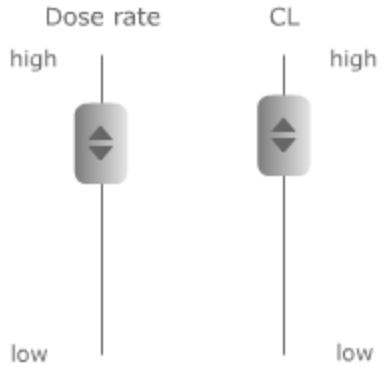
2- compartment model



Continuous and repeated administration of drugs







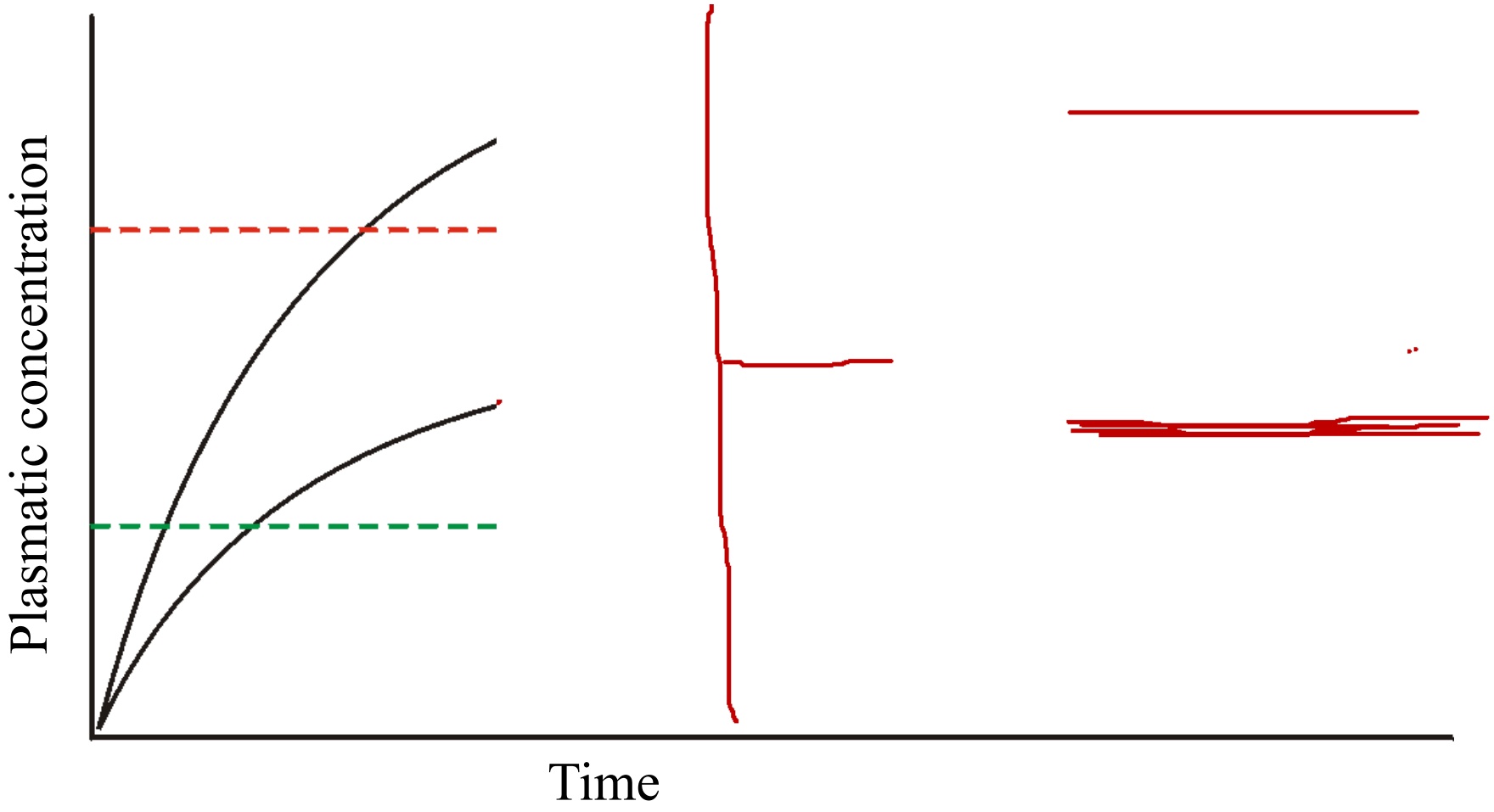
$$Cpss = \frac{\text{Dose rate}}{CL}$$

$$\text{Dose rate} = Cpss \times CL$$

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

Continuous administration

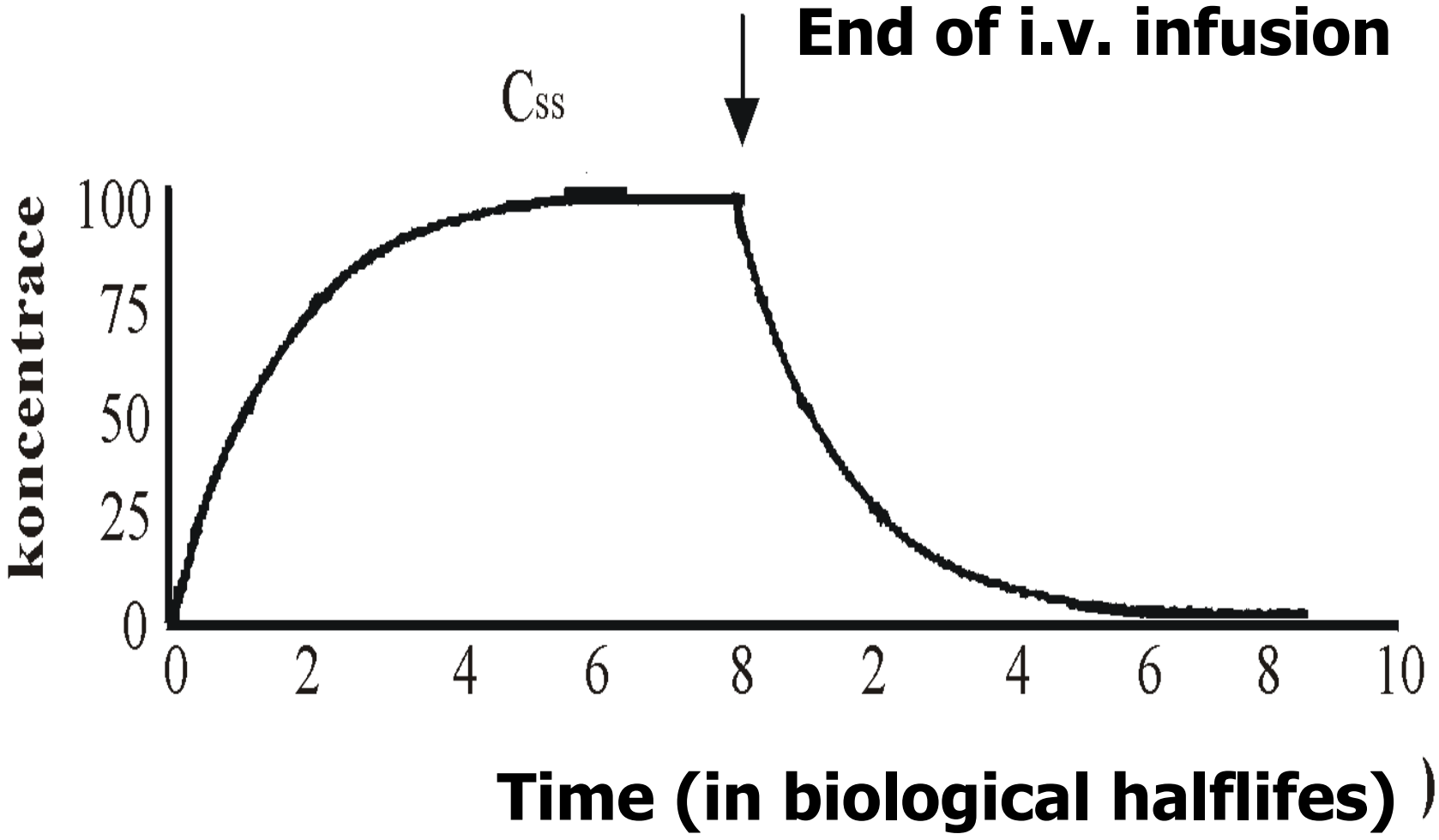


Continuous administration

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

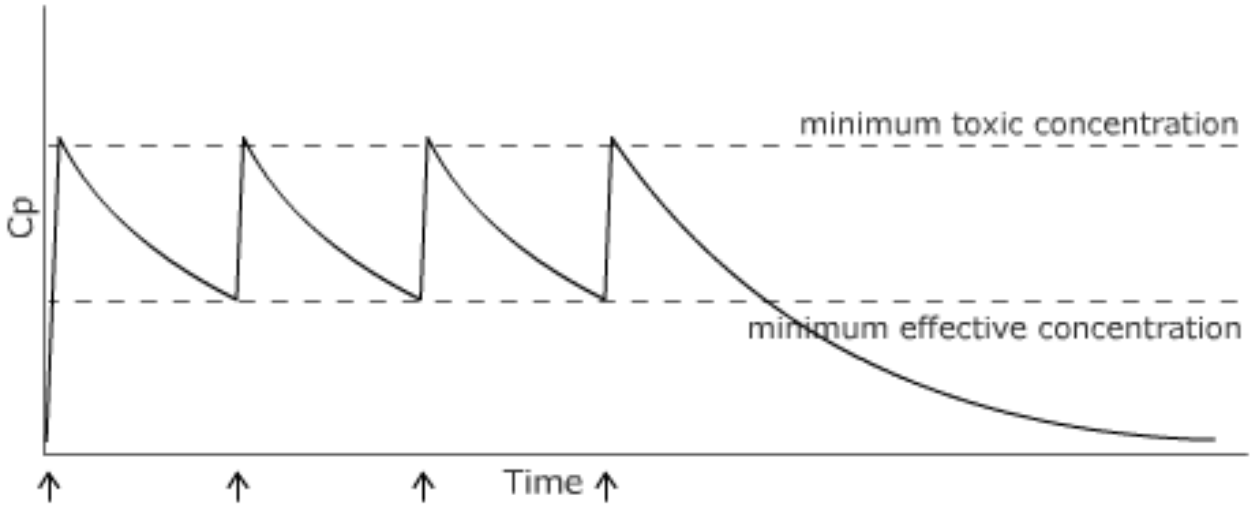
1) F – bioavailability – repeated administration is typical for p.o. administration

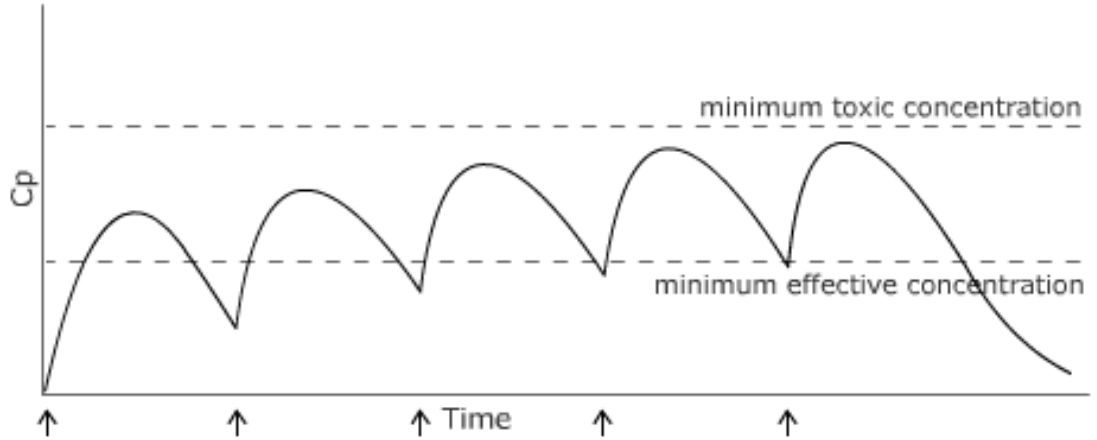
2) τ – dosage interval – plasmatic concentrations are fluctuating among minimal and maximal numbers – after reaching steady state this fluctuation is stabilized between $Cmax_{plato}$ and $Cmin_{plato}$

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

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

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

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

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

$t_{1/2}$ = biological halflife

Vd = volume of distribution

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

Cl = clearance

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