

# The General Concepts of Pharmacokinetics and Pharmacodynamics

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# PHARMACOKINETICS

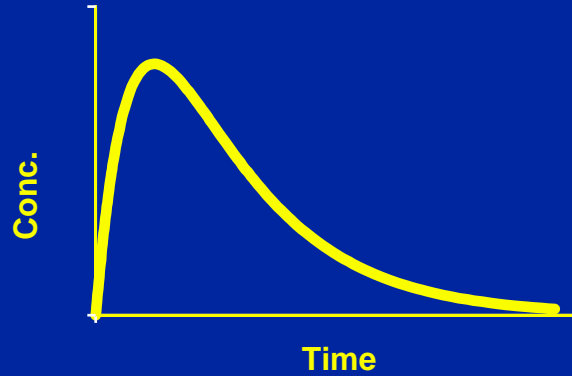
what the body does to the drug

# PHARMACODYNAMICS

what the drug does to the body

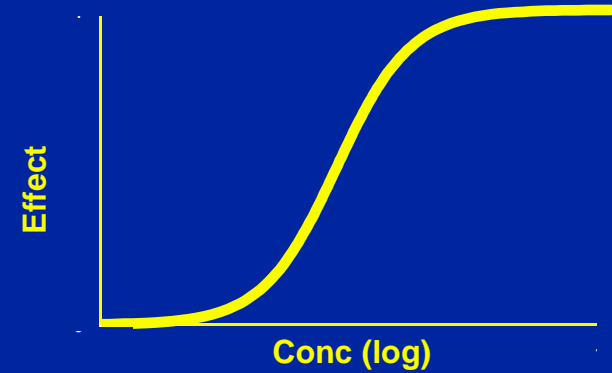
## Pharmacokinetics

conc. vs time



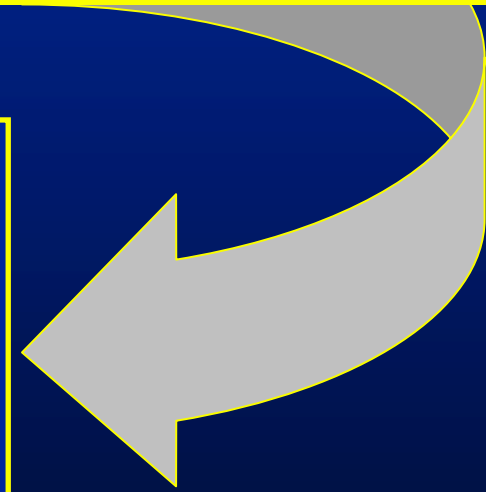
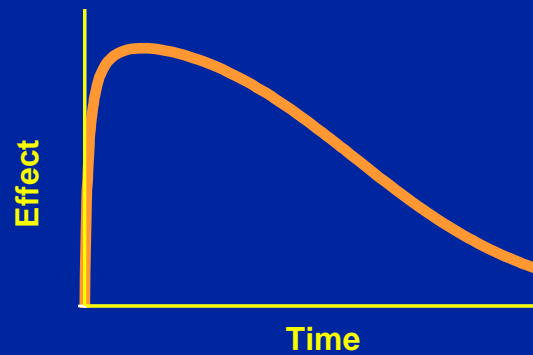
## Pharmacodynamics

conc. vs effect



## PK/PD

effect vs time



# Pharmacokinetics

**the time course of drug and metabolite  
concentrations in the body**

# Pharmacokinetics helps to optimize drug therapy:

- dose
- dosage regimen
- dosage form

# What happens to a drug after its administration ?

("Fate of drug")

Liberation

Absorption

Distribution

Metabolism

Excretion

# Pharmacokinetic Parameters

**Clearance**

**Volume of distribution**

**Half-life**

**Bioavailability**

**Protein Binding**

# Clearance

- quantifies **ELIMINATION**
- is the volume of body fluid cleared per time unit (L/h, mL/min)
- is usually constant

# Clearance

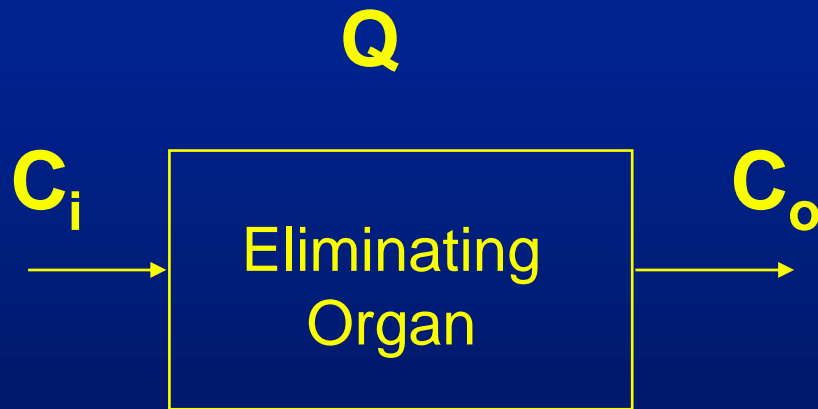


$$CL = Q \cdot E$$

Q Blood Flow

E Extraction Ratio

# Clearance



$$E = \frac{C_i - C_o}{C_i}$$

$$CL = Q \cdot E$$

$$CL = \frac{Q \cdot f_u \cdot CL_{\text{int}}}{Q + f_u \cdot CL_{\text{int}}}$$

**Parameters: Blood Flow, intrinsic clearance, protein binding**  
**Good prediction of changes in clearance**  
**Steady state**

# High-extraction drugs

$$CL = \frac{Q \cdot f_u \cdot CL_{\text{int}}}{Q + f_u \cdot CL_{\text{int}}}$$

$$Q \ll f_u \cdot CL_{\text{int}}$$



$$CL = Q$$

# Low-extraction drugs

$$CL = \frac{Q \cdot f_u \cdot CL_{\text{int}}}{Q + f_u \cdot CL_{\text{int}}}$$

$$Q \gg f_u \cdot CL_{\text{int}}$$



$$CL = f_u \cdot CL_{\text{int}}$$

# Clearance

Clearance can be calculated from

- Excretion rate / Concentration

e.g.  $(\text{mg/h}) / (\text{mg/L}) = \text{L/h}$

- Dose / Area under the curve (AUC)

e.g.  $\text{mg} / (\text{mg}\cdot\text{h/L}) = \text{L/h}$

# Clearance

Total body clearance is the sum of the individual organ clearances

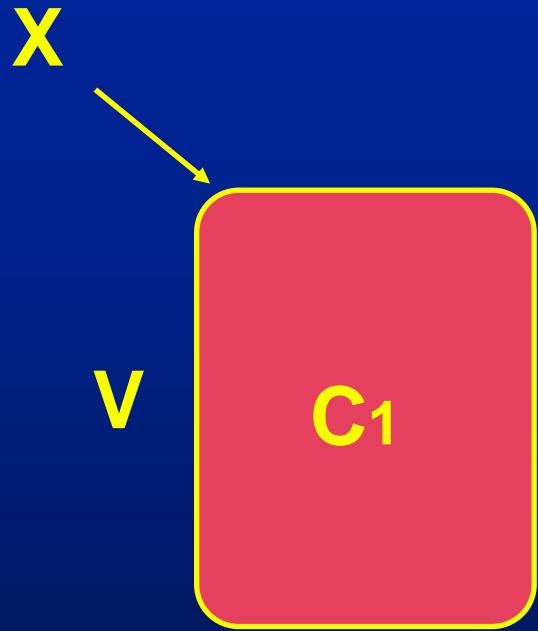
$$CL = CL_{\text{ren}} + CL_{\text{hep}} + CL_{\text{other}}$$

# Volume of Distribution

$$V_d = X / C_p$$

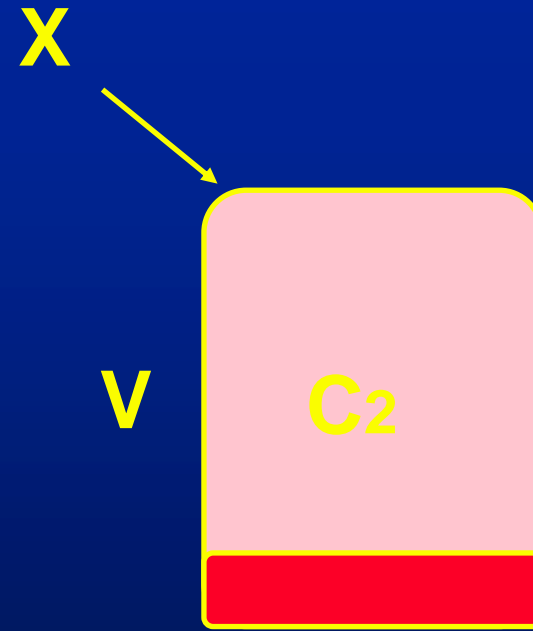
- quantifies **DISTRIBUTION**
- relates drug concentration ( $C_p$ ) to amount of drug in the body ( $X$ )
- gives information on the amount of drug distributed into the tissues

# Apparent Volume of Distribution



$$C_1 = X / V$$

$$V = X / C_1$$



$$C_2 = X / V_d$$

$$V_d = X / C_2$$

$$C_1 > C_2$$

$$V < V_d$$

# Volume of Distribution

<b>Dicloxacillin</b>	<b>0.1 L/kg</b>
<b>Gentamicin (ECF)</b>	<b>0.25 L/kg</b>
<b>Antipyrine (TBW)</b>	<b>0.60 L/kg</b>
<b>Ciprofloxacin</b>	<b>1.8 L/kg</b>
<b>Azithromycin</b>	<b>31 L/kg</b>

# Half-Life

$$t_{1/2} = \frac{0.693 \cdot Vd}{CL}$$

**Half-life is the time it takes for the concentration to fall to half of its previous value**

**Half-life is a secondary pharmacokinetic parameter and depends on clearance and volume of distribution**

# Half-Life

$$t_{1/2} = \frac{\ln 2}{k} = \frac{0.693}{k}$$

$$CL = k \cdot Vd$$

<b>k</b>	<b>elimination rate constant</b>
<b>CL</b>	<b>clearance</b>
<b>Vd</b>	<b>volume of distribution</b>

# Bioavailability

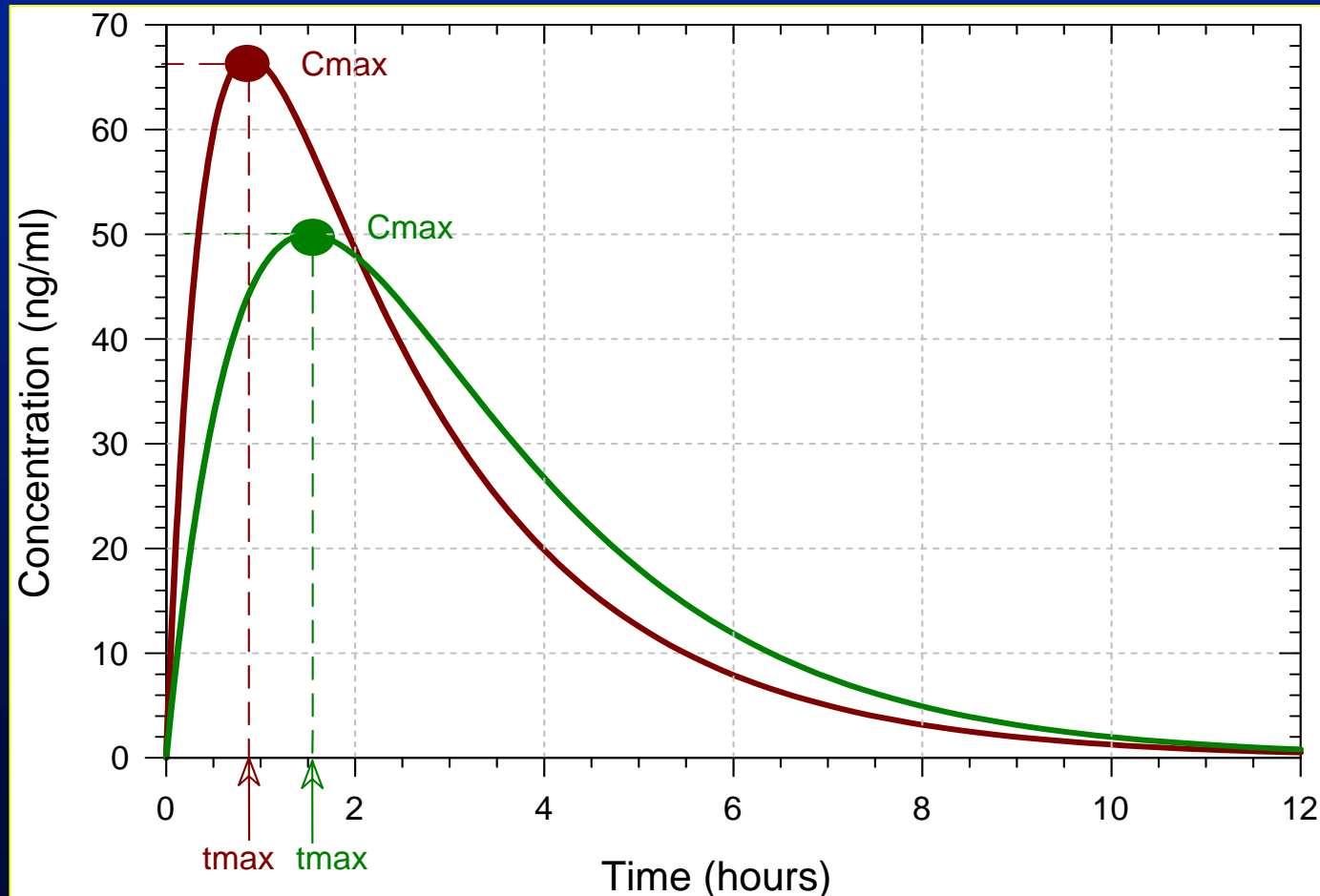
$$F = \frac{AUC_{po}}{AUC_{iv}}$$

- quantifies **ABSORPTION**

f is the fraction of the administered dose that reaches the systemic circulation

# Bioavailability

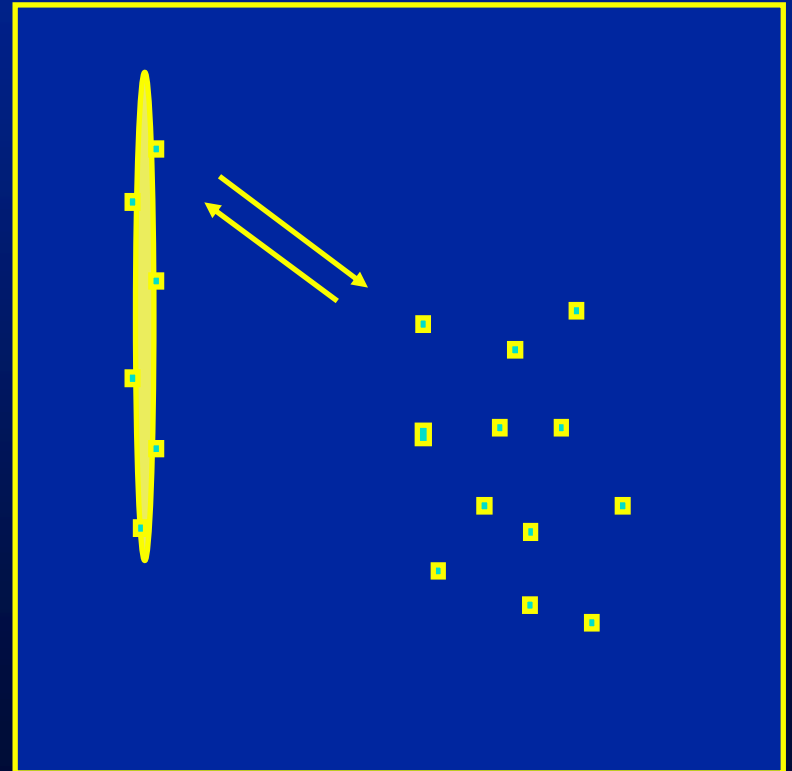
## Rate and Extent of Absorption



# Protein Binding

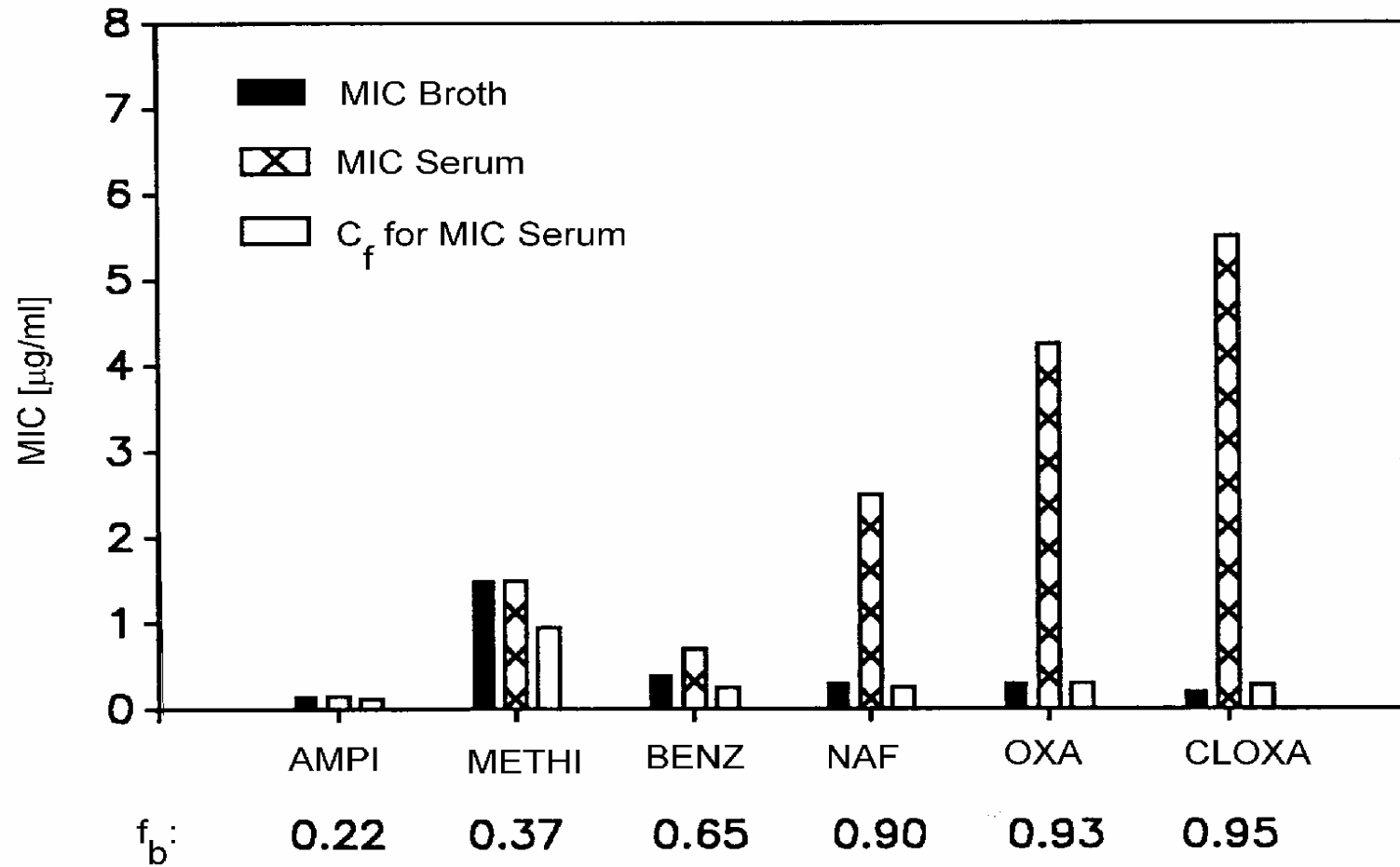
- **reversible** vs. irreversible
- **linear** vs. nonlinear
- **rapid** equilibrium

The **free (unbound)** concentration of the drug **at the receptor site** should be used in PK/PD correlations to make prediction for pharmacological activity



## Effect of Protein Binding on Antimicrobial Activity

MICs of *Staphylococcus aureus* (Data from Kunin et al. (1973))



# vascular space

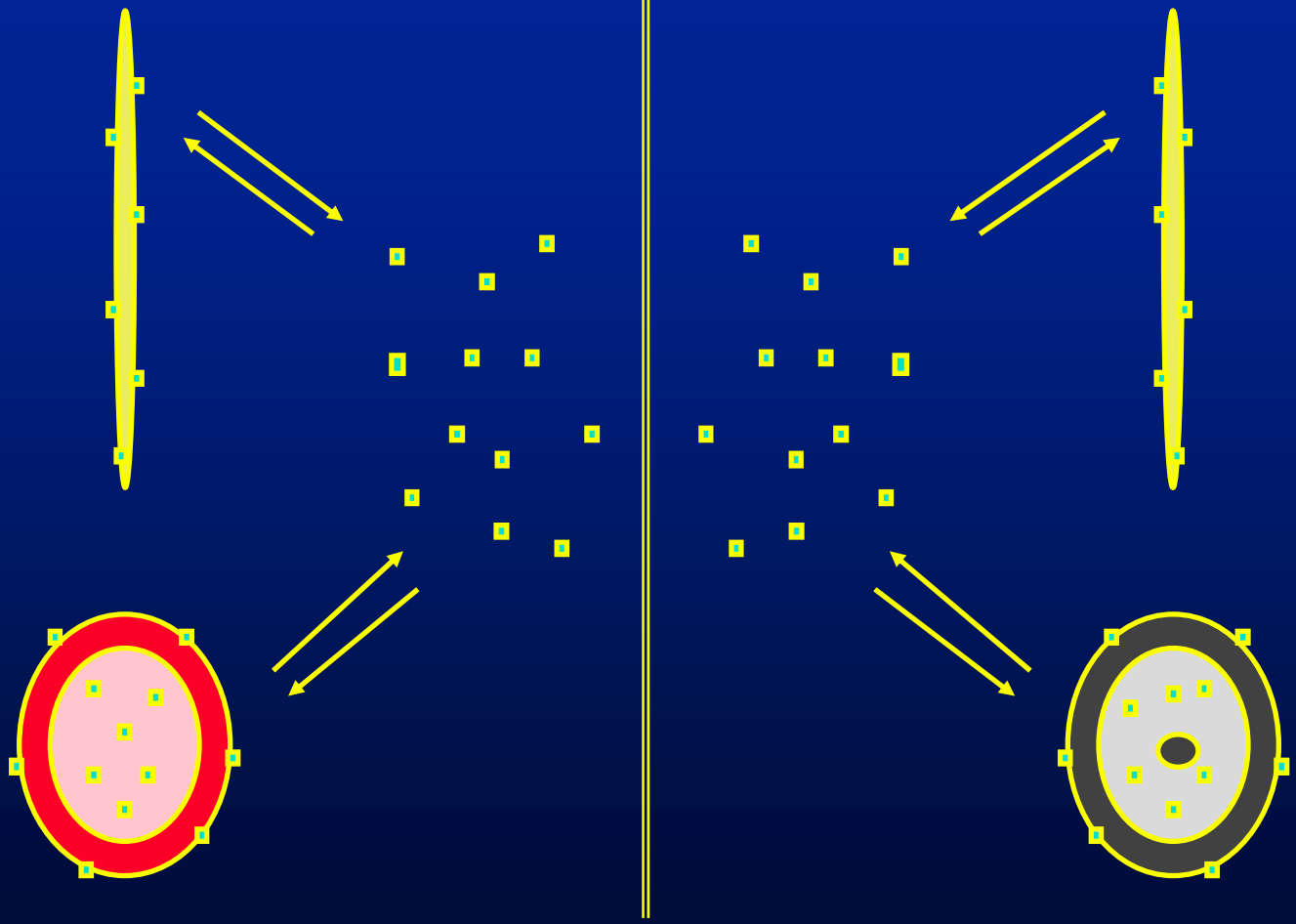
# extravascular space

plasma protein binding

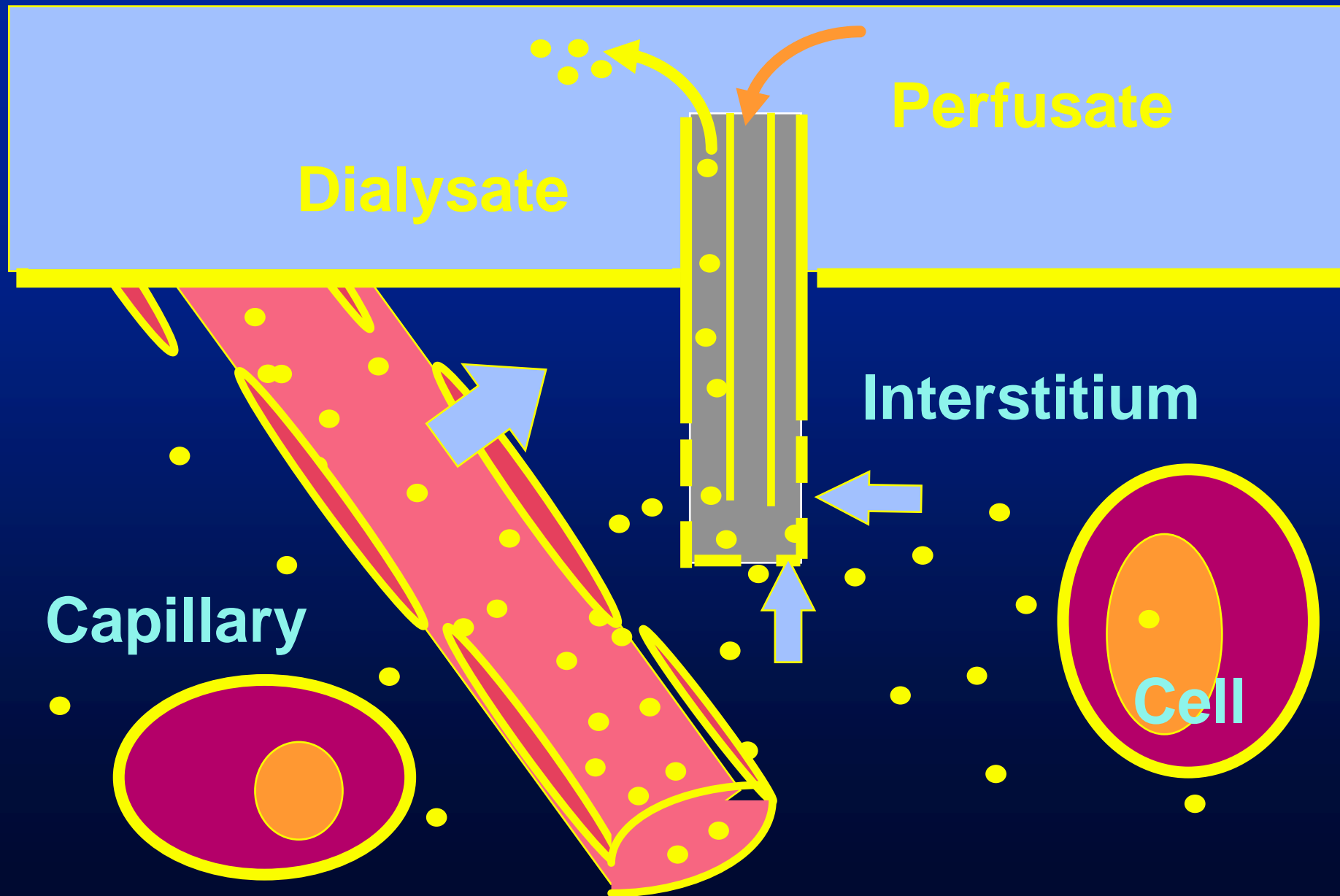
binding to extracellular biological material

blood cell binding,  
diffusion into blood cells,  
binding to intracellular biological material

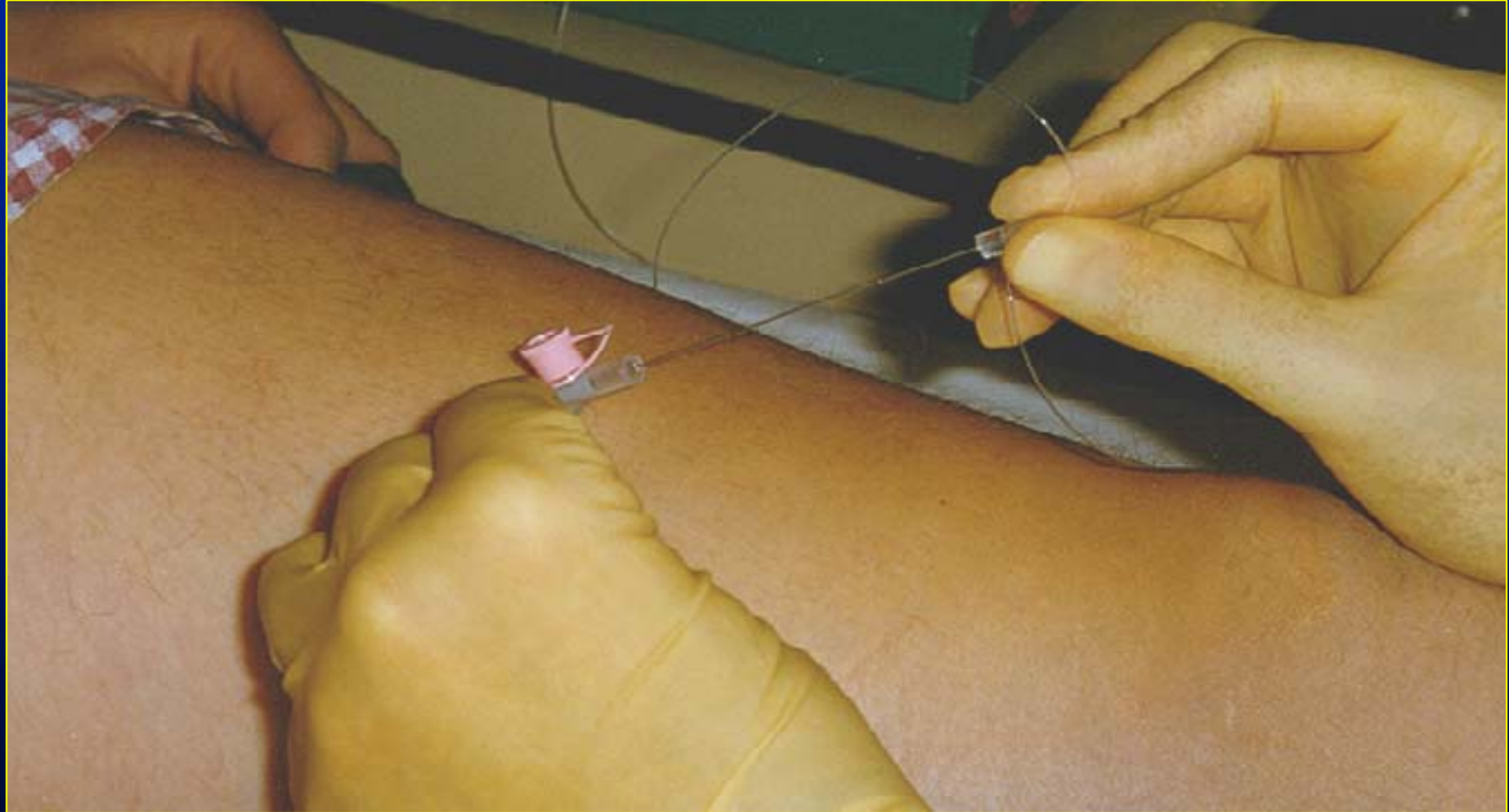
tissue cell binding,  
diffusion into tissue cells,  
binding to intracellular biological material



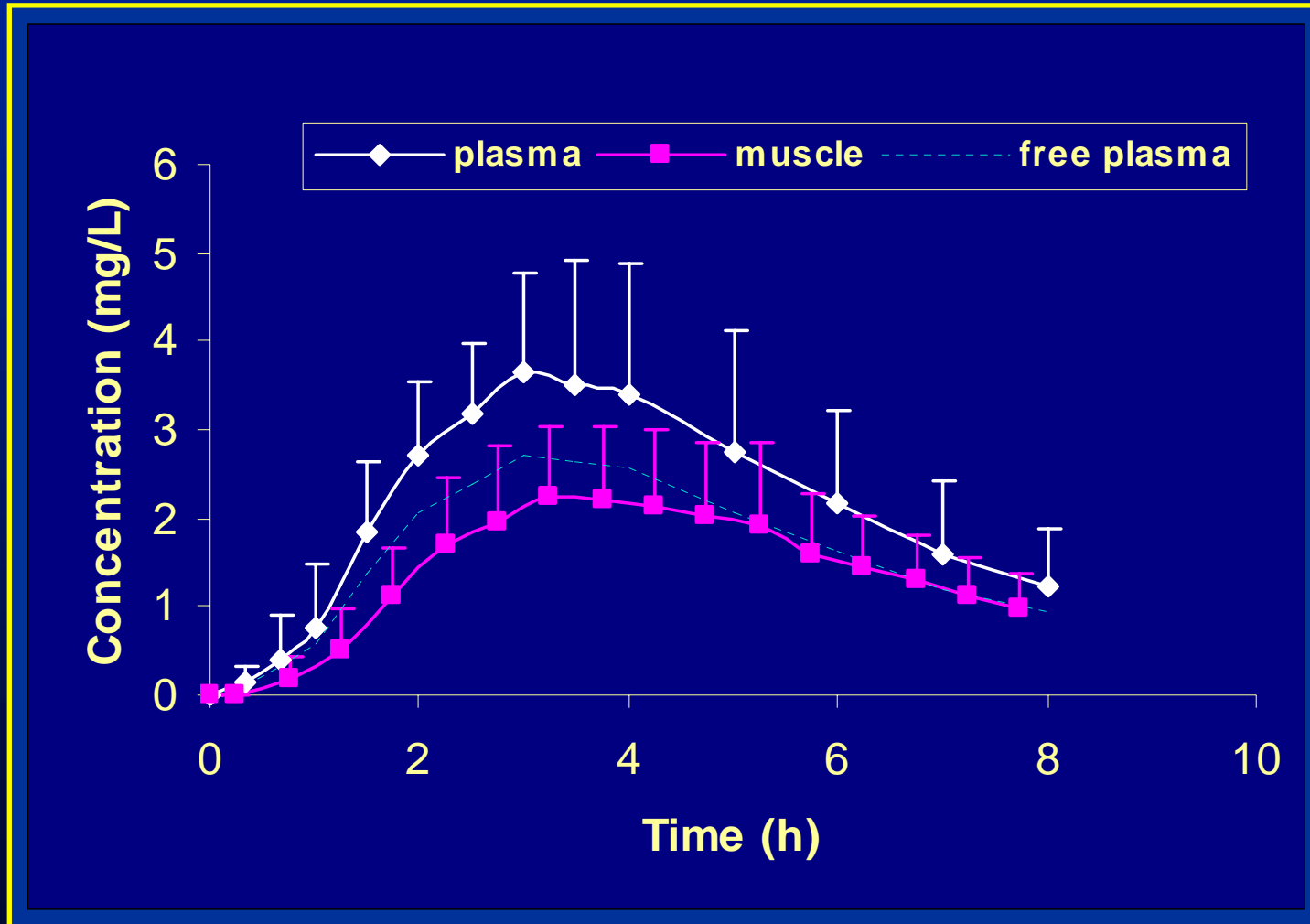
# Microdialysis



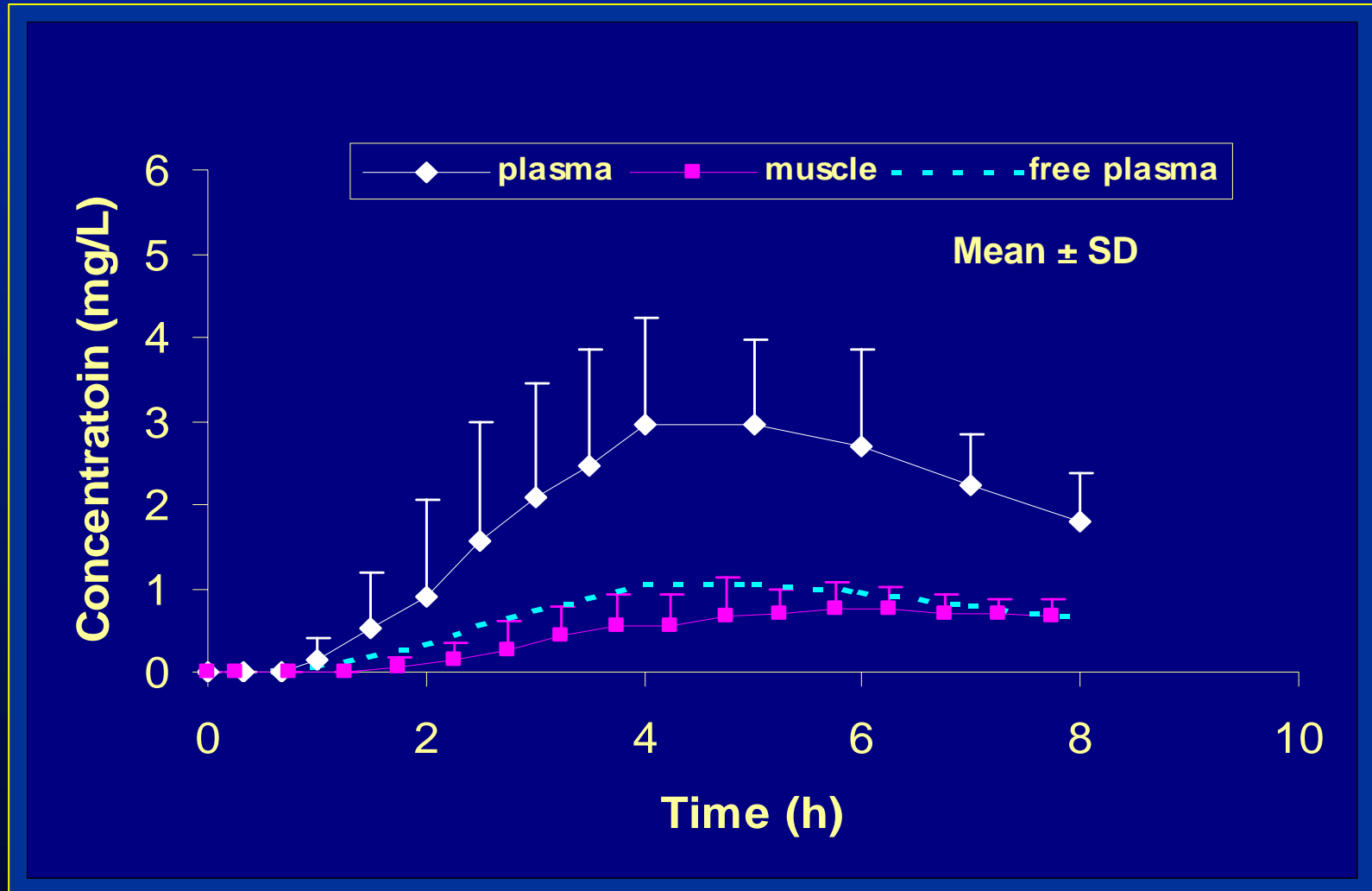
# Microdialysis



# Pharmacokinetic profile of cefpodoxime (400 mg oral dose, n = 6)



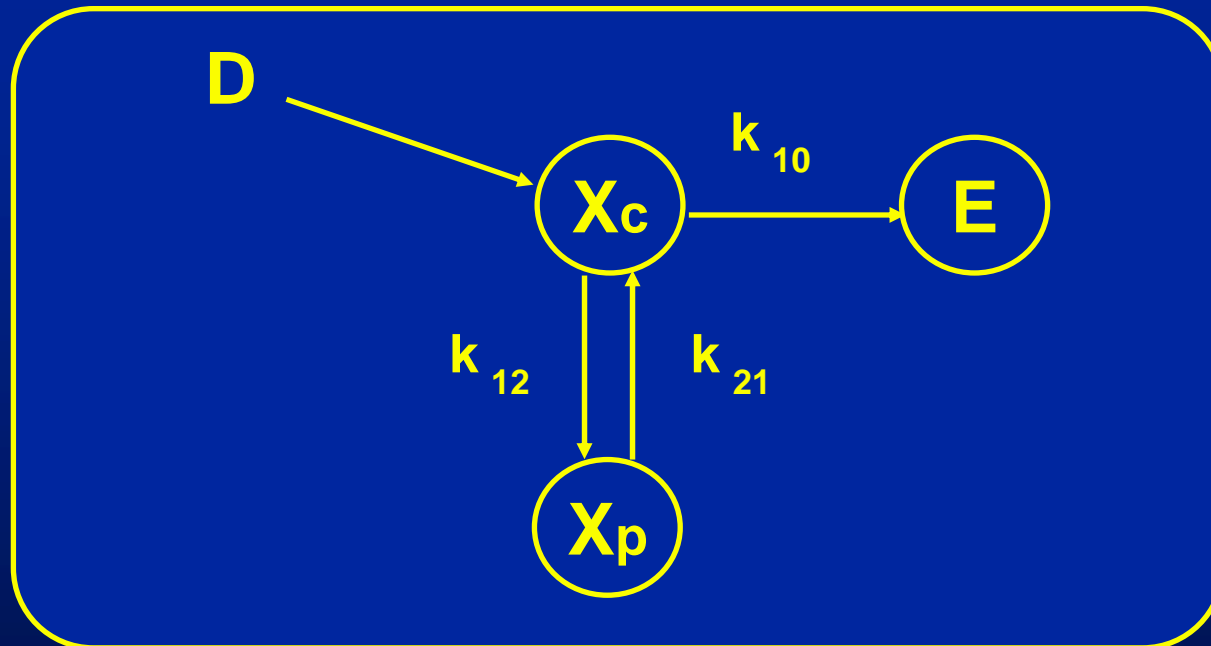
# Pharmacokinetic profile of cefixime (400 mg oral dose, n = 6)



# Pharmacokinetics

	Cefpodoxime	Cefixime
<b>AUC<sub>P</sub> [mg*h/L]</b>	22.4 (8.7)	25.7 (8.4)
<b>AUC<sub>T</sub> [mg*h/L]</b>	15.4 (5.2)	7.4 (2.1)
<b>C<sub>max, P</sub> [mg/L]</b>	3.9 (1.2)	3.4 (1.1)
<b>C<sub>max, T</sub> [mg/L]</b>	2.1 (1.0)	0.9 (0.3)

# Two-compartment model



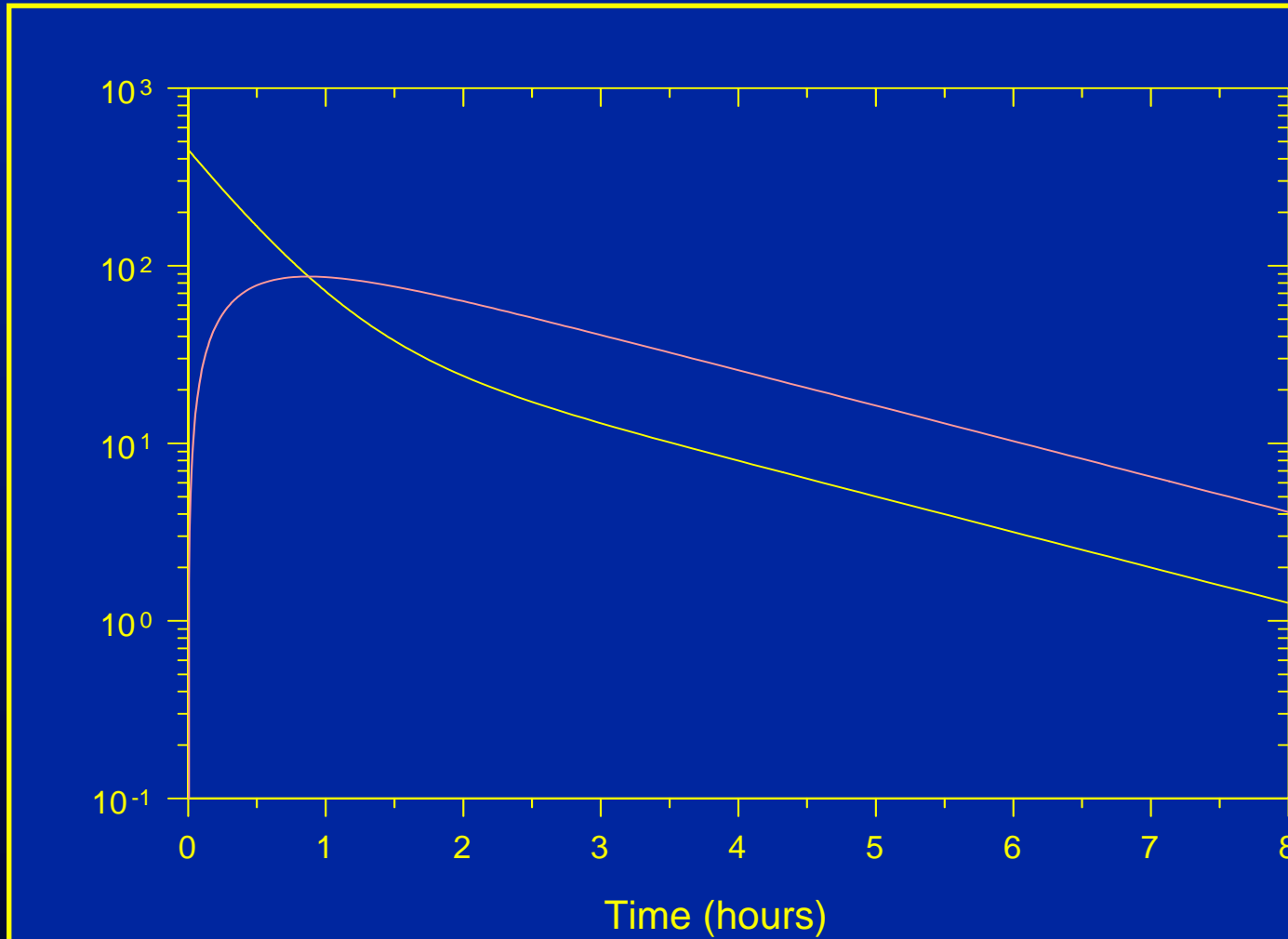
Dose

$X_c$  Drug in the central compartment

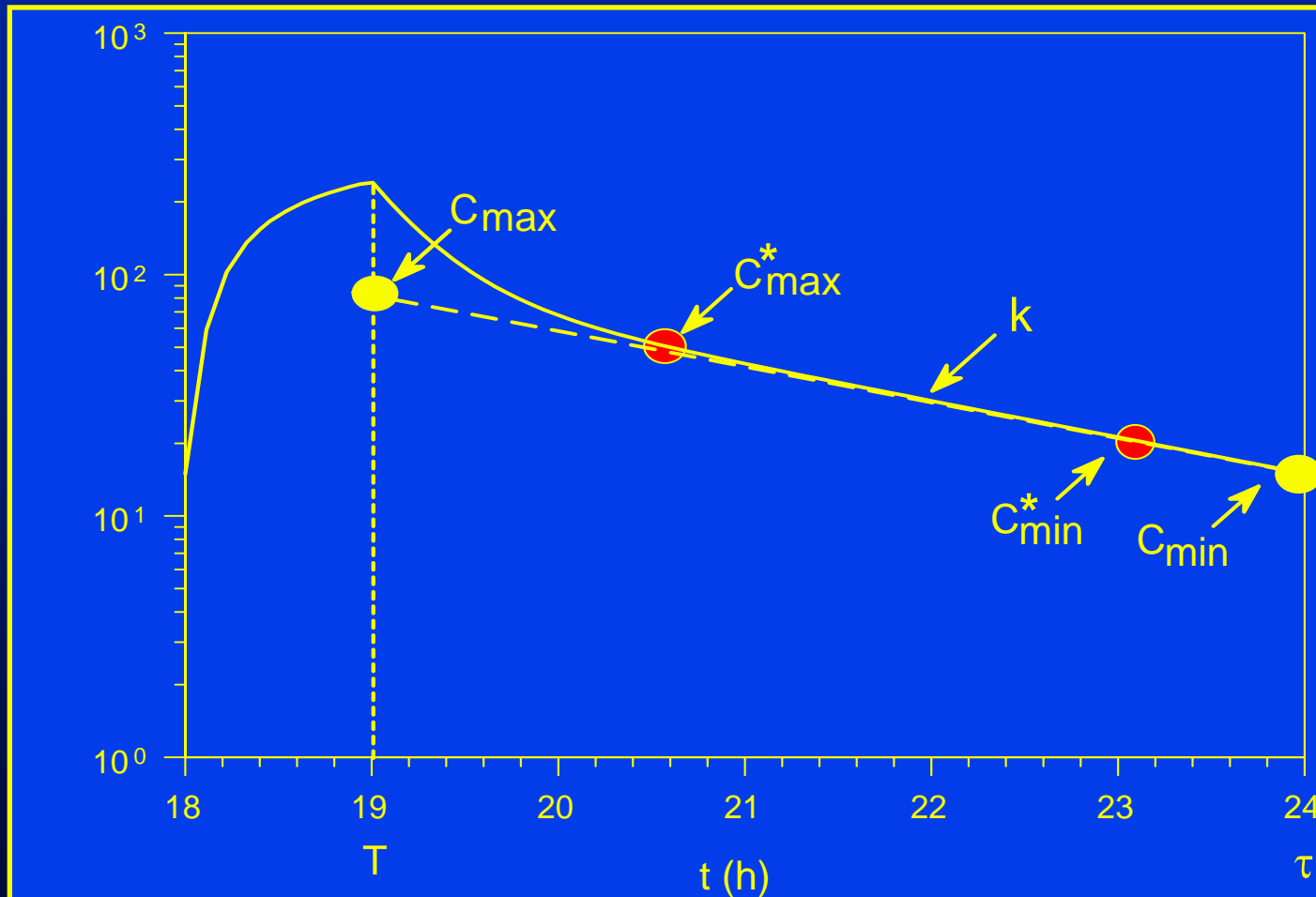
$X_p$  Drug in the peripheral compartment

Drug eliminated

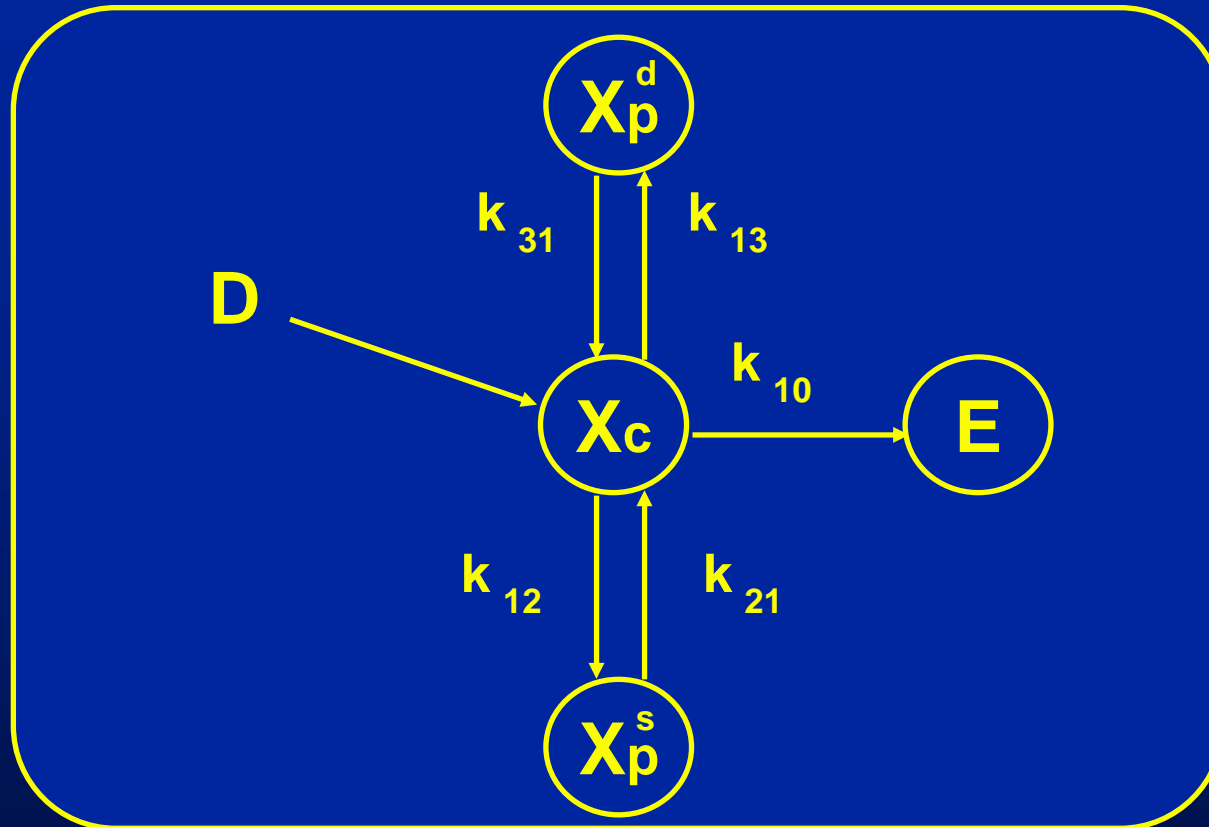
# Two-compartment model



# Short-term infusion



# Three-compartment model



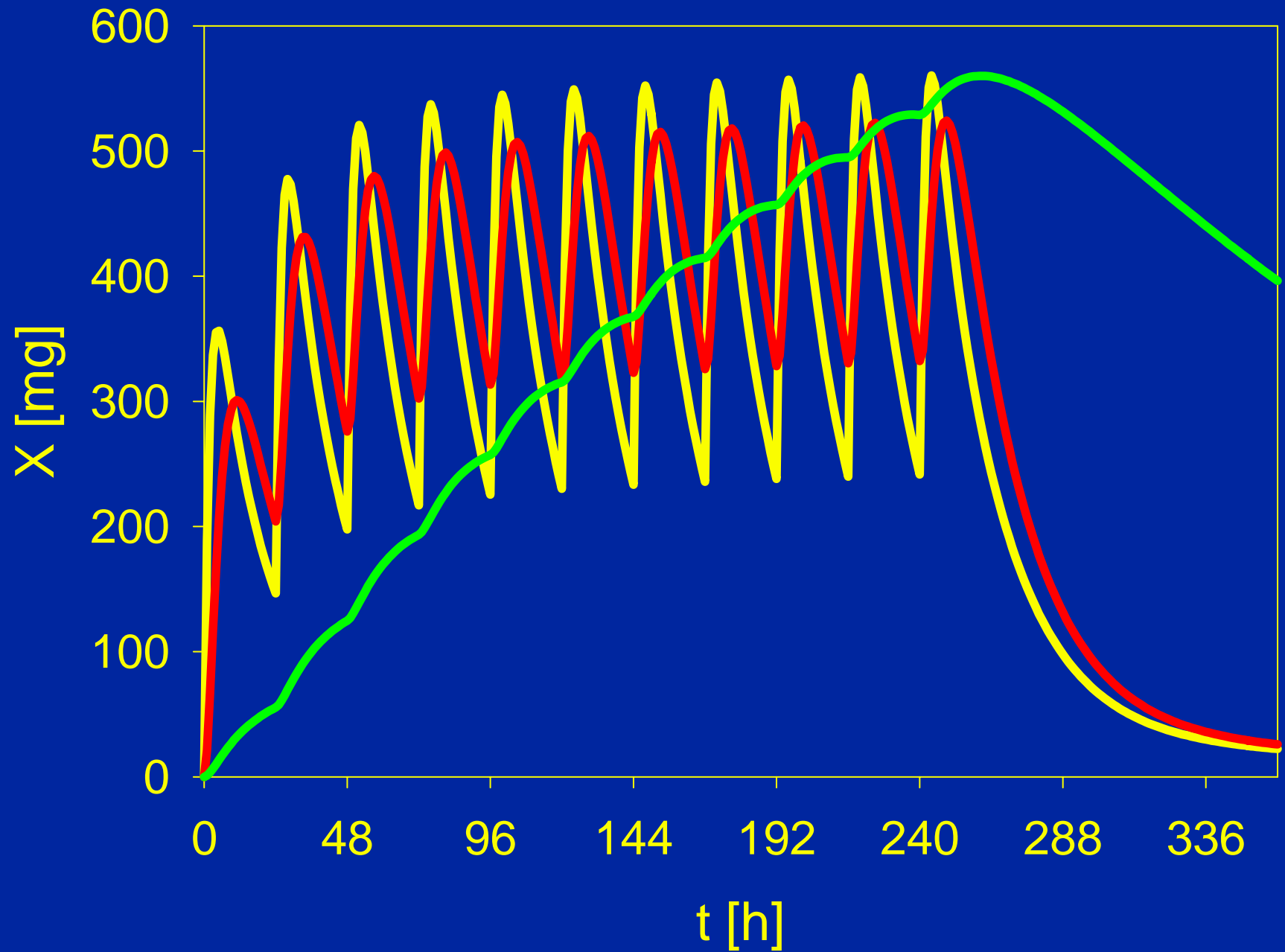
D Dose

E Drug eliminated

$X_c$  Drug in the central compartment

$X_{ps}$  Drug in the shallow peripheral compartment

$X_{pd}$  Drug in the deep peripheral compartment



# Drug Delivery

?



Biopharmaceutics

# Pharmacokinetics

?



PK-PD-Modeling

# Pharmacodynamics

# Questions

- **What are the effects of protein binding on antibiotic activity and interpretation of plasma levels?**
- **What are the effects of a change in protein binding on unbound concentrations?**
- **Why do we monitor post-distribution peaks as indicators of aminoglycoside activity?**
- **Why do we monitor troughs as indicators of aminoglycoside toxicity?**
- **How do you interpret a high tissue level of a macrolide?**