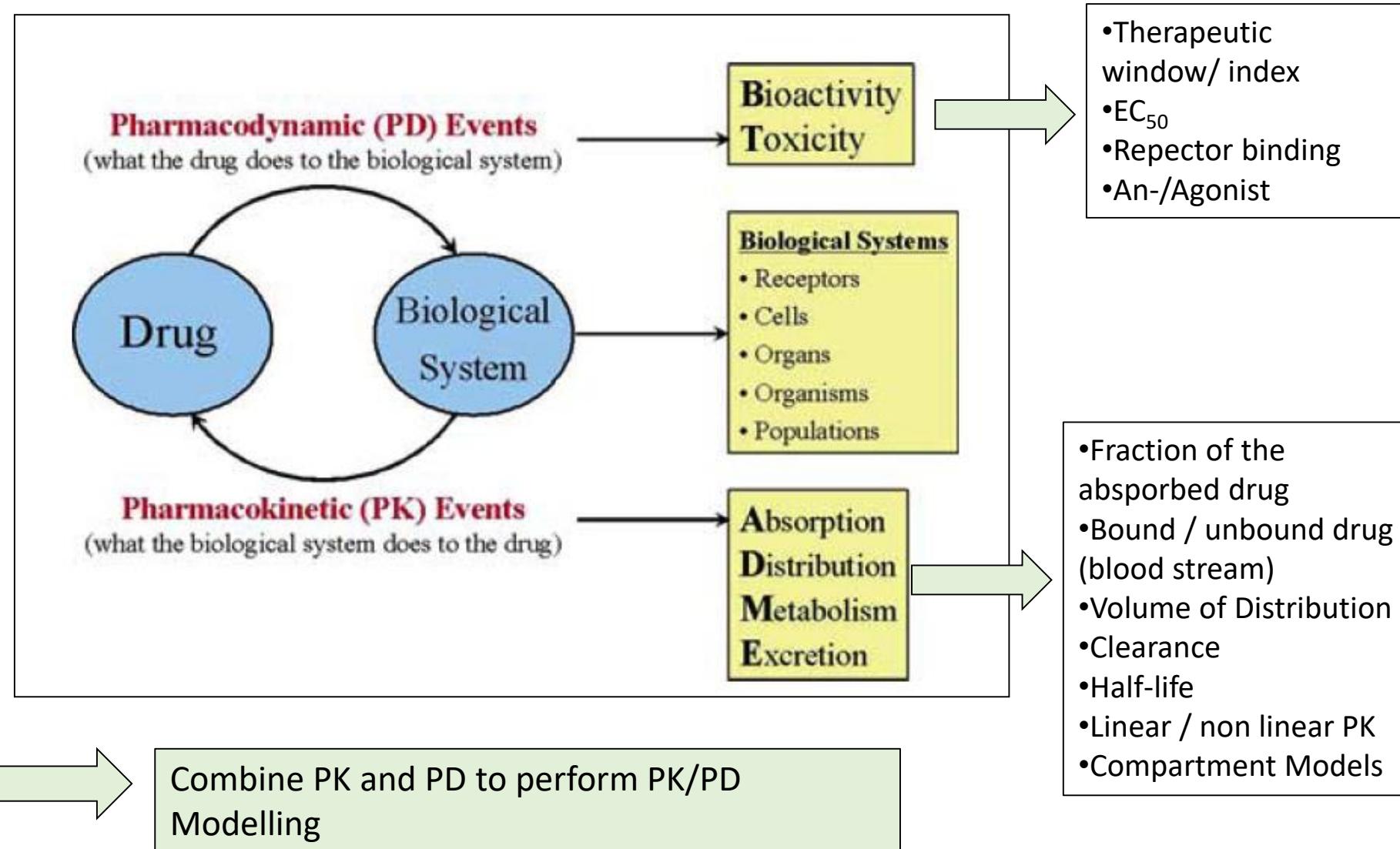
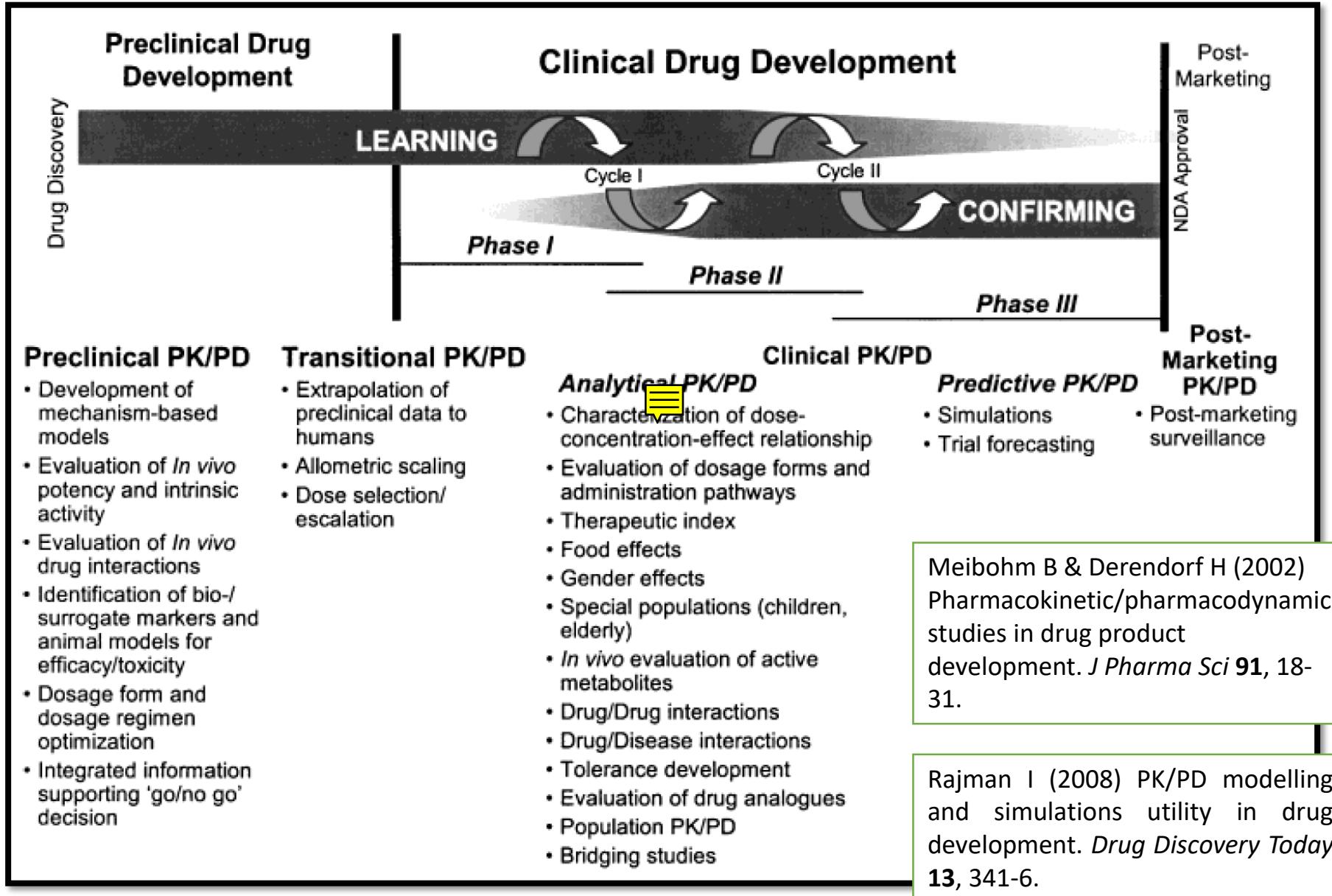


# 6. PK/PD MODELING





## 6.1 General framework

« All models are wrong,  
some are useful »

« A theoretical model can not account  
for all the experimental data because  
some of them are false »

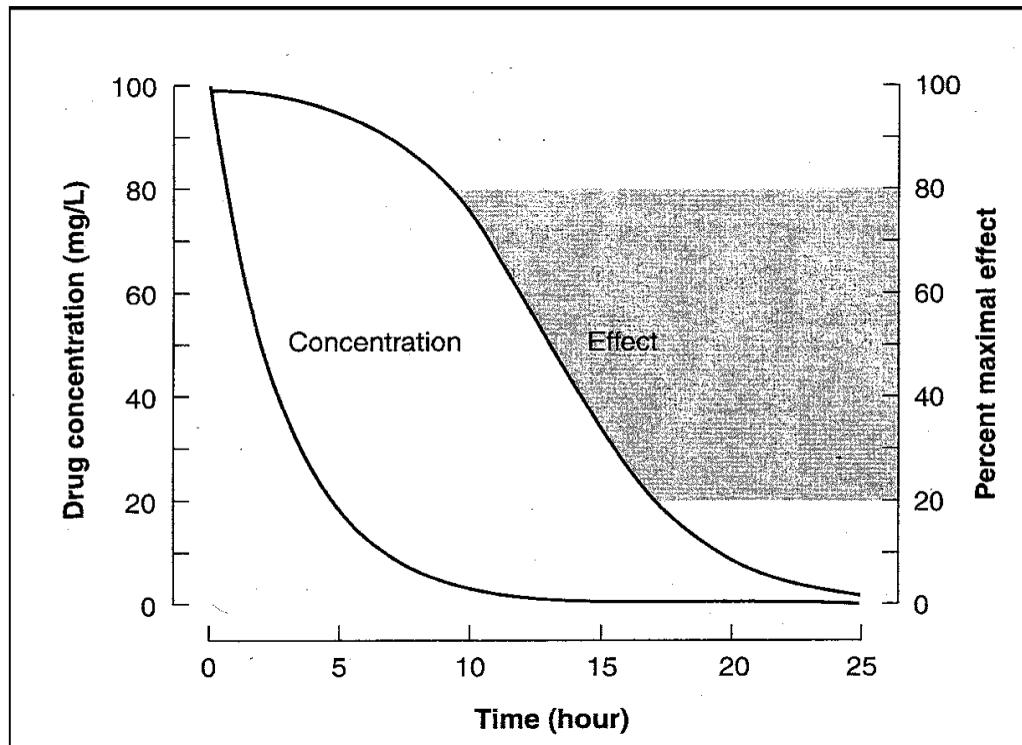
A PK/PD model can be viewed as a model for  
the response (effect E) of a system to an input  
(time of input and drug concentration).

$$E(t) = G[t, C]$$

$$E(t) = G[t, C]$$

1° Static or dynamic systems

$$\begin{array}{c} E(t) = G[t, C(t)] \\ \swarrow \quad \searrow \\ E(t) = G[t, C(-\infty, t)] \end{array}$$



$$E(t) = G[t, C]$$

1° Static or dynamic systems

$$\begin{array}{c} \nearrow \\ E(t) = G[t, C(t)] \\ \searrow \\ E(t) = G[t, C(-\infty, t)] \end{array}$$

2° Relaxed (at rest) or unrelaxed (not at rest)

$$G[t, 0] = 0, \quad -\infty < t < \infty$$

3° The response of a relaxed system to an input  
=> linear or non-linear

$$G[t, \alpha C_1(-\infty, t) + \beta C_2(-\infty, t)] = \alpha G[t, C_1(-\infty, t)] + \beta G[t, C_2(-\infty, t)]$$

4° The system can be time-invariant or time-variant

## Direct vs indirect models

Most **PK/PD Models** can be built by composing cascades of dynamic linear and static non-linear sub-systems.

Nonlinear dynamic systems can be built up by combining dynamic and static functions, obtaining so-called **cascade structure models**, where the output of one function is the input to another

### Direct-Response (Action) Models

- Dynamic linear model

**FOLLOWED BY**

- Static nonlinear sub-model

### Indirect-Response (Action) Models

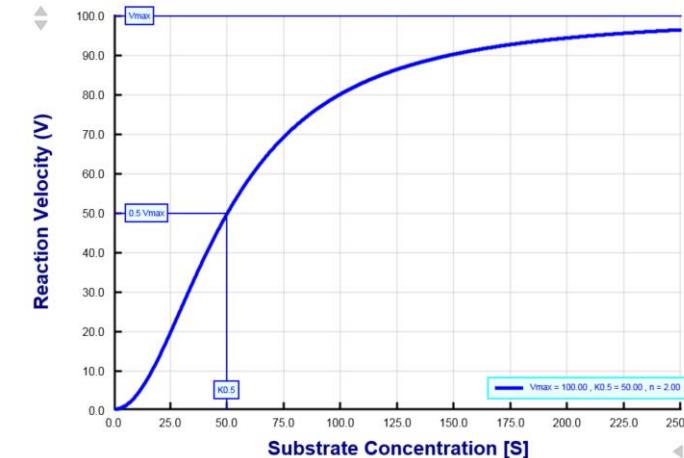
- Static nonlinear model

**FOLLOWED BY**

- Dynamic linear sub-model

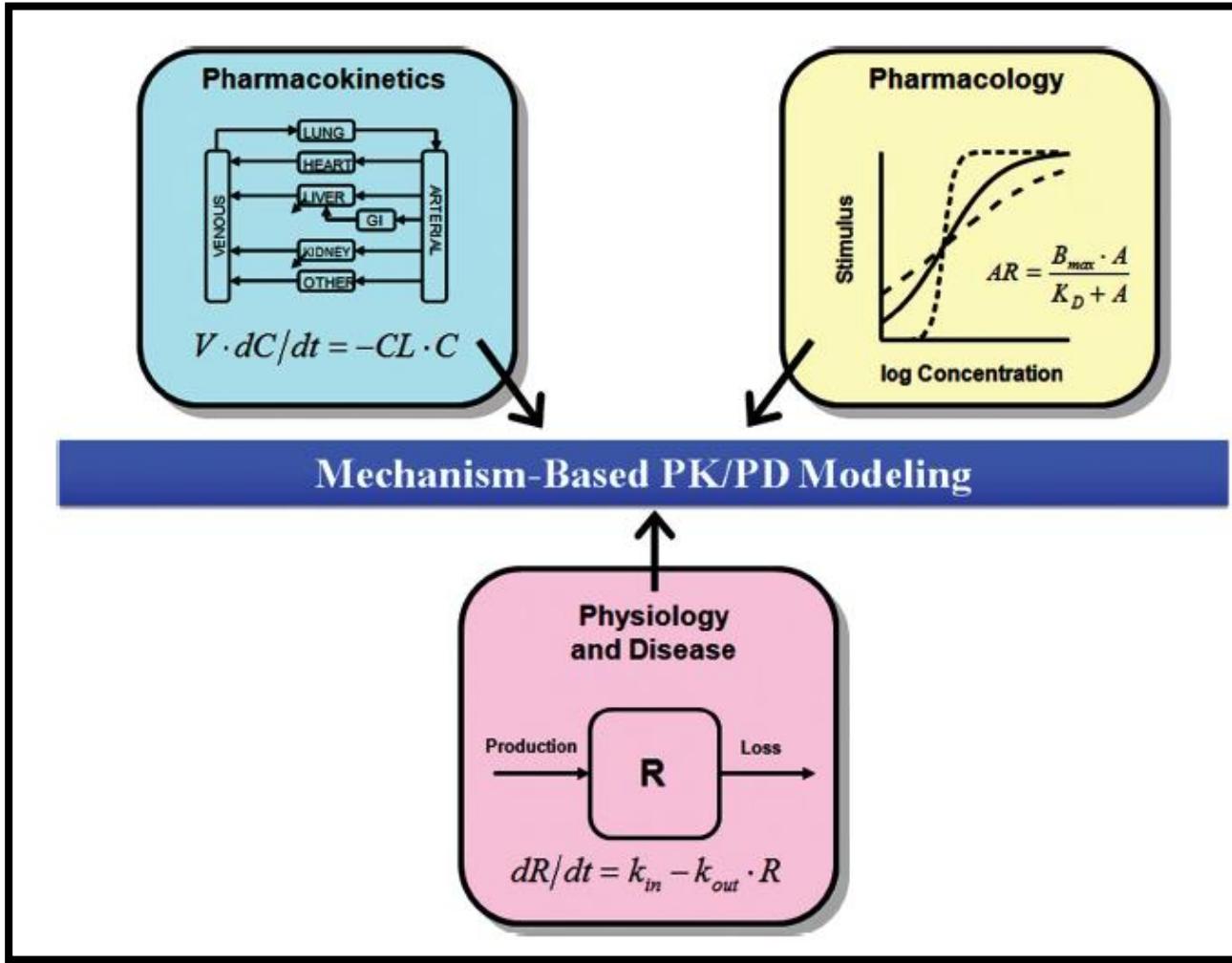
# PK/PD Modeling

**1) Empirical Models** traditional approach; uses rather empirical models such as the Hill equation to describe *in vivo* PA concentration effects.



# PK/PD Modeling

2) **Mechanism Based Models** based on a molecular understanding of the biochemical reactions of the drug inside the body (for example drug-receptor interactions).

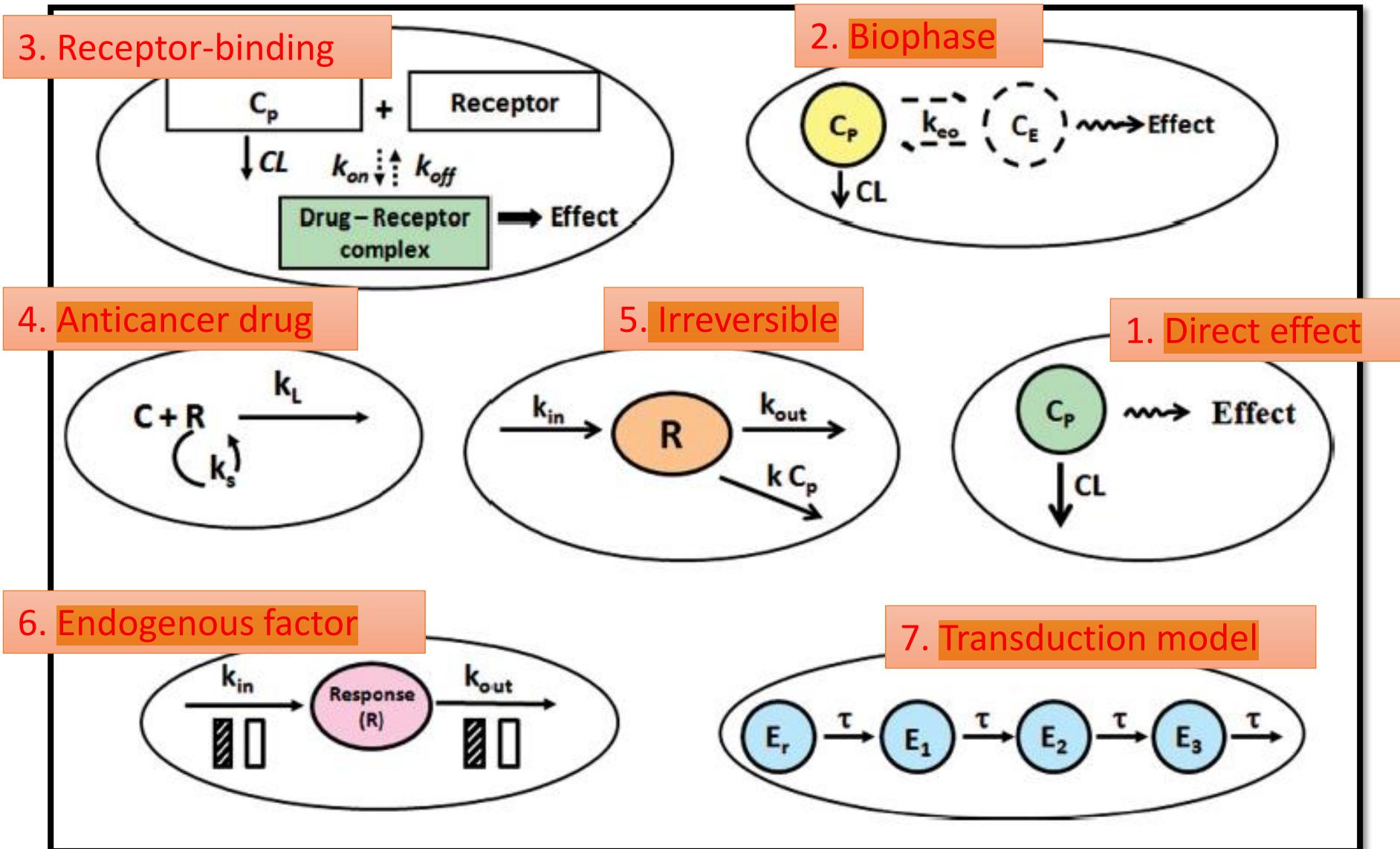


# PK/PD Modeling – Mechanism Based Models

## Major Classes of Mechanism Based Model:

1. Basic Turnover Models
  - Direct effect
  - Biophase
  - Receptor-binding
  - Anti-cancer drugs
  - Irreversible
  - Endogenous factor modulation
  - Transduction Model
2. Enhanced Models
3. System Models

# PK/PD Modeling – Basic Turnover Models



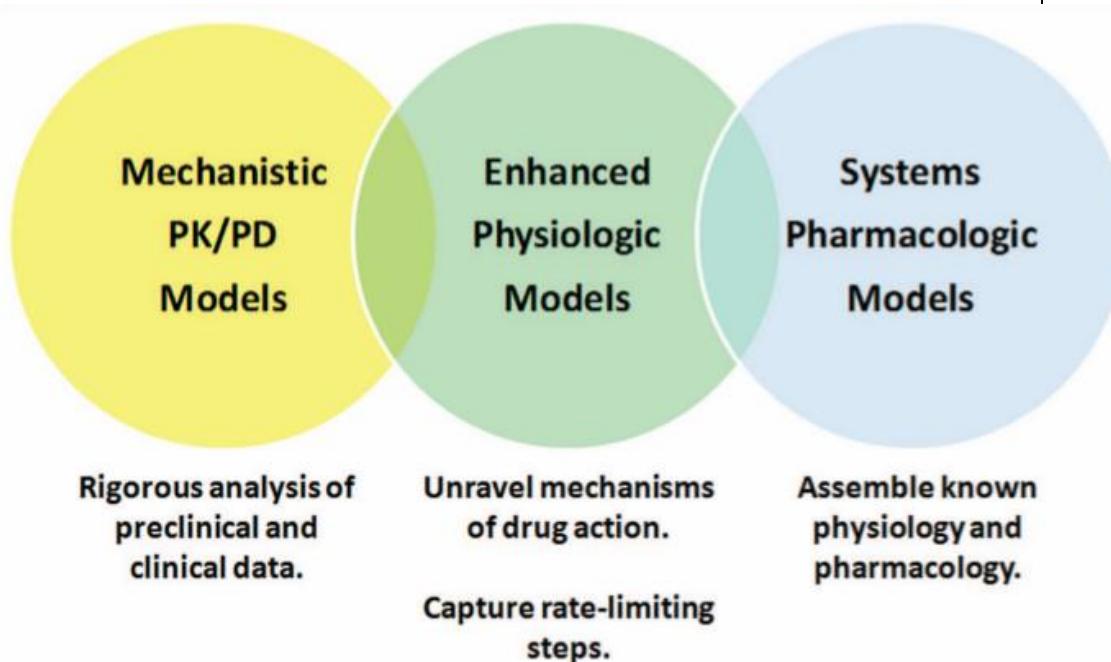
# PK/PD Modeling – Mechanism Based Models

## Major Classes of Mechanism Based Model:

1. Basic Turnover Models
  - Direct effect
  - Biophase
  - Receptor-binding
  - Anti-cancer drugs
  - Irreversible
  - Endogenous factor modulation
  - Transduction model

2. Enhanced Models

3. System Models



# Major types of PK models

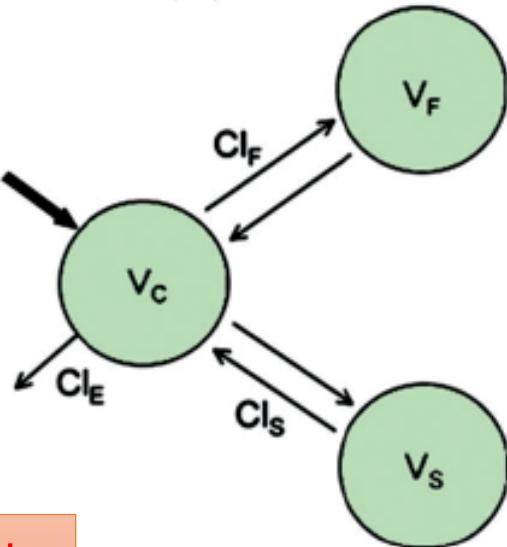
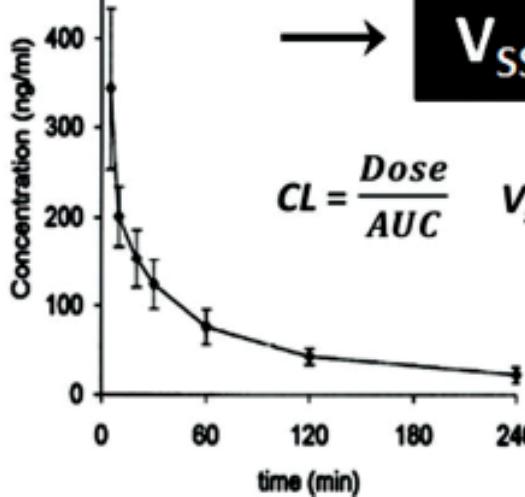
Noncompartmental

NCA

$V_{ss}$

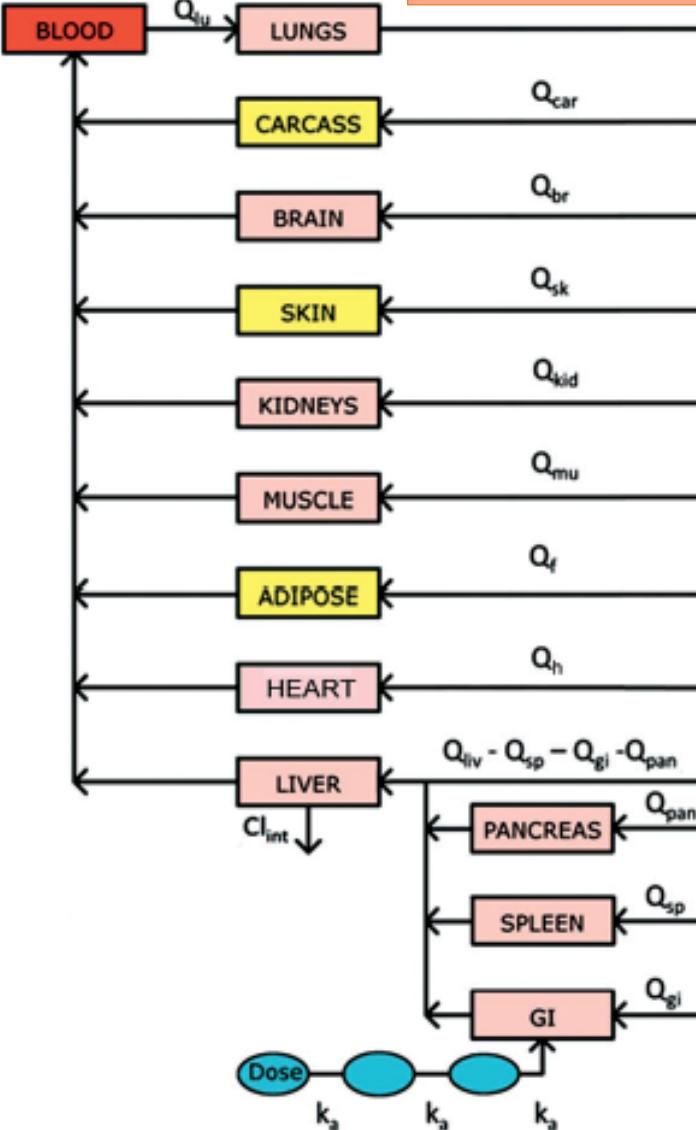
$\xrightarrow{CL}$

$$CL = \frac{Dose}{AUC} \quad V_{ss} = \frac{AUMC}{AUC} \cdot CL$$



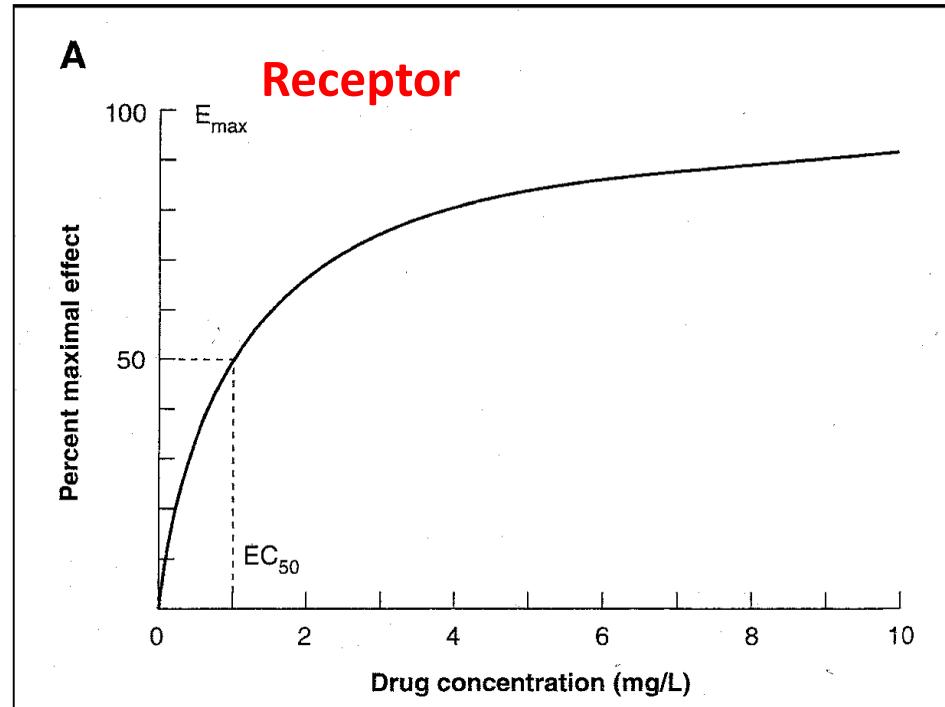
Compartmental

Physiologically based



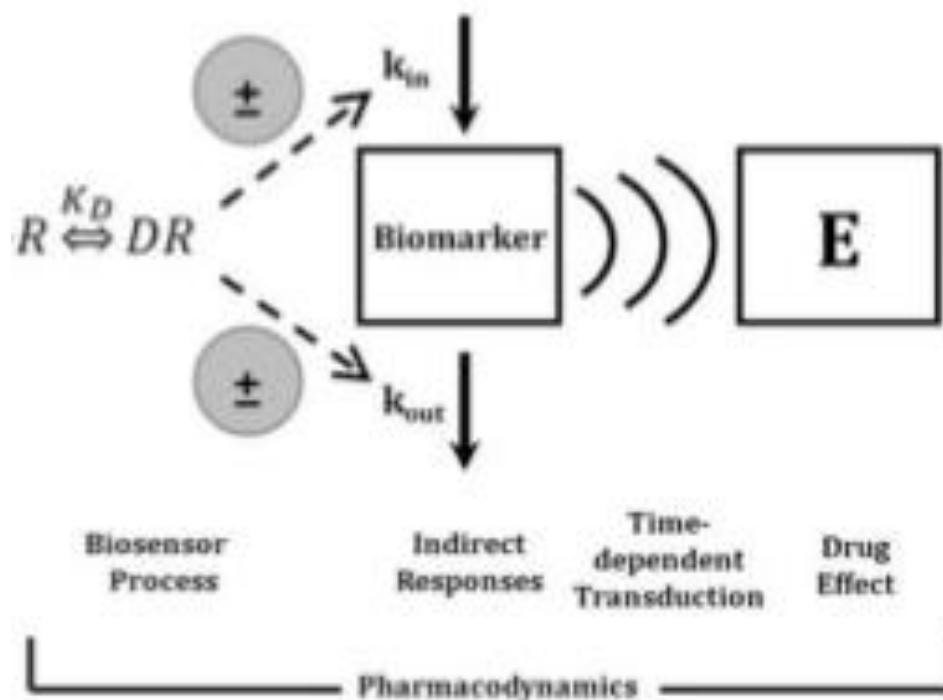
## Different types of PD models

- Simple models



## Different types of PD models

- Simple models
- More advanced models



→ depends on

- the time-scale of the drug effect
- Indirect / direct effect
- Turnover

# PK/PD Modeling

## Biological Turnover Rates of Structures or Functions



Fast



Slow



- Electrical Signals (msec)
- Neurotransmitters (msec)
- Chemical Signals (min)
- Mediators, Electrolytes (min)
- Hormones (hr)
- mRNA (hr)
- Proteins / Enzymes (hr)
- Cells (days)
- Tissues (mo)
- Organs (year)
- Person (1 century)

B  
I  
O  
M  
A  
R  
K  
E  
R  
S

CLINICAL  
EFFECTS

# PK/PD Modeling

- **Surrogate endpoint** as "a **biomarker** intended to **substitute for a clinical endpoint** ». Surrogate markers are used when the primary endpoint is undesired (e.g., death), or when the number of events is very small, thus making it impractical to conduct a clinical trial to gather a statistically significant number of endpoints.

## Definition **Biomarker**:

A characteristic that is objectively measured and evaluated as an indicator of normal processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention

Examples: blood pressure, plasma glucose concentration, heart rate, etc.

## Definition **Clinical Endpoint**:

A characteristic or variable that reflects how a patient feels, functions or survives

Examples: Death, stroke, bone fracture, cure or failure etc.

→ may be difficult/impossible to evaluate

# PK/PD Modeling

## How to chose the PK/PD model?

- Amount of experimental data
- Details known about the mechanism
- Concentration-effect relationship?
- Model used for similar drugs

## 6.2. Direct action models

### 6.2.1. Linear E vs Dose/C relationships

- The **Fixed Effect Model** (Quantal Effect Model) is a statistical approach based on a logistic regression analysis that relates a certain drug concentration with the statistical likelihood of one (or several) effects to be present or absent. *Major limitations of this model deal with the prediction of complete effect-time profiles.*

- The **Linear Model** assumes a direct proportionality between drug concentration and drug effect. *This model erroneously assumes that the effect can increase with concentrations without limits.*

$$E = S \cdot C + E_0$$

- The **Log-Linear Model** was conceived on the observation that when the concentration-effect is hyperbolic, the log-concentration-effect relationship is roughly linear in the range of 20 to 80% of maximal effect. *Obvious disadvantages of this model are that it is neither possible to predict the value of E when C = 0, nor to predict a maximum effect.*

$$E = S \cdot \log C + E_0$$

## TP Exercise 1: Check the linear model

The rapid equilibrating medicament A is given intravenously and the C<sub>0</sub> concentration is 200 µg/l. The elimination constant is 0.231 and the half-life 3 hours. Please choose the appropriate PK model and use the linear model to compute the effect-time curve. Please give the time-concentration and the time-effect curves and fill the table. The effect at t=0 is 2 (in %) and S is 0.49 l/µg.

Time	CP	Effect
0		
1		
2		
3		
4		
5		
7		
9		
12		
24		

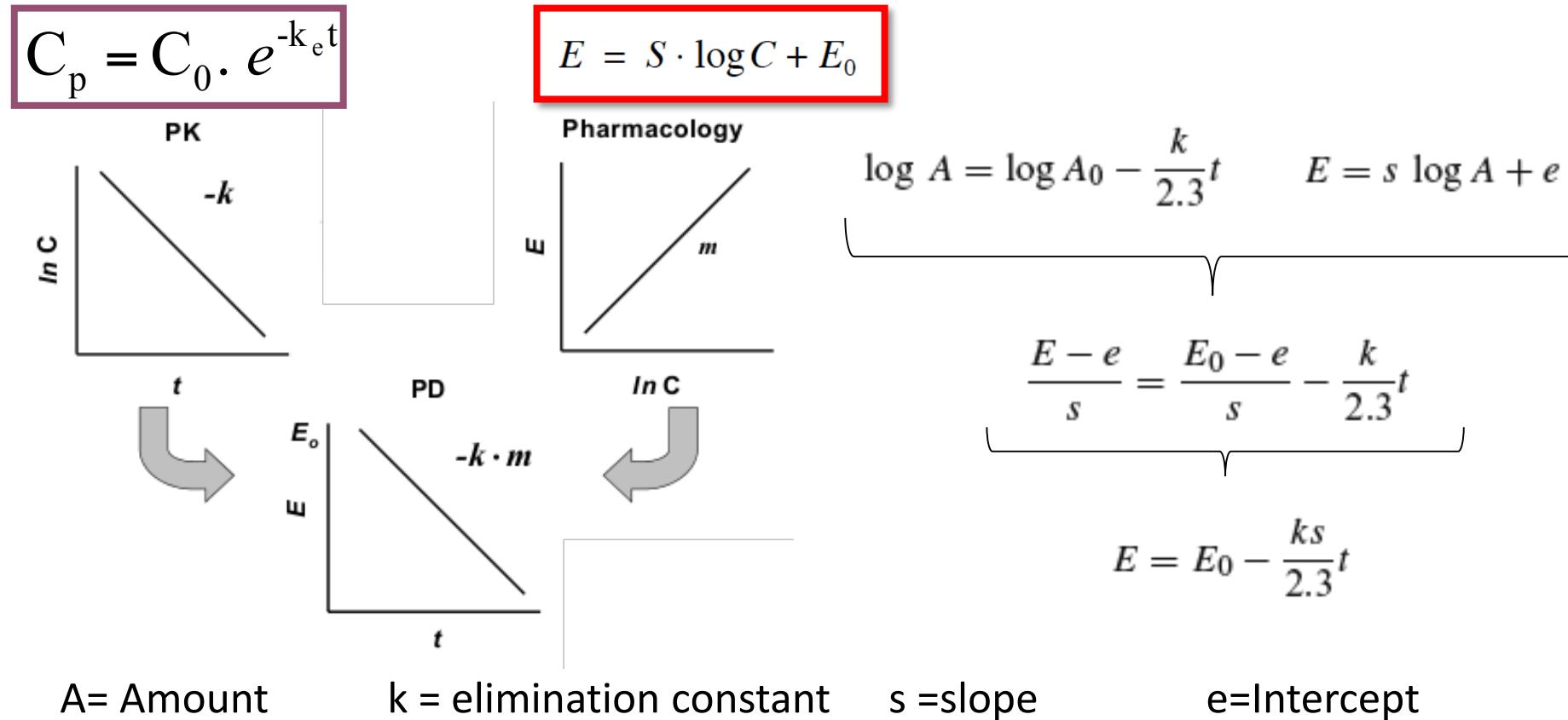
## TP Exercise 2: Check the log-linear model

The rapid equilibrating medicament A is given intravenously and the C<sub>0</sub> concentration is 200 µg/l. The elimination constant is 0.231 and the half-life 3 hours. Use the PK model as in TP1 and use the log-linear model to compute the effect-time curve. The effect at t=0 is 5 (in %) and S is 40.

Time	CP	Effect
0		
1		
2		
3		
4		
5		
7		
9		
12		
24		

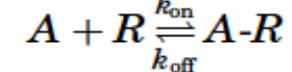
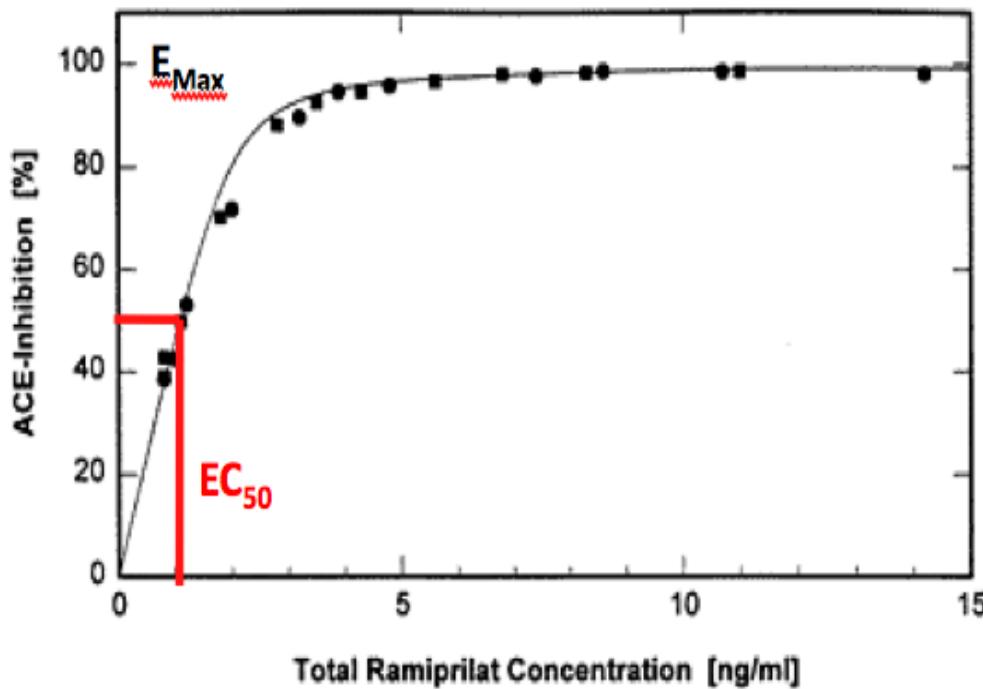
## 6.2.1. Linear E vs Dose/C relationships

The **Levy “k-m” equation** (1965) described the time course of pharmacological activity of a drug to its first-order elimination, and provided for the first time the connection between PK (the  $k$  reflecting the monoexponential elimination rate constant) and pharmacology (the  $s$  being the slope of the Effect versus log drug concentration function).



## 6.2.2. Non linear E vs Dose/C relationships

- The E<sub>MAX</sub> Model was originally derived from the **classical theory of drug-receptor interaction**. This is a simple PK-PD model broadly used to characterize a myriad of pharmacologic effects.

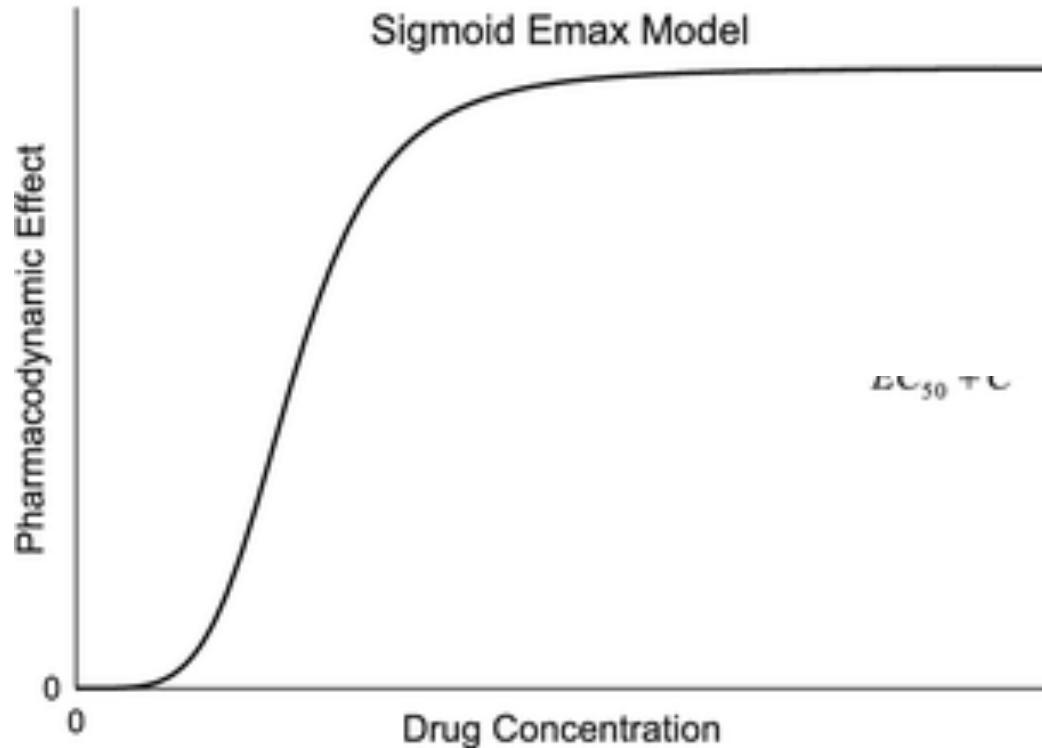


$$\frac{dAR}{dt} = k_{on} \cdot A \cdot R - k_{off} \cdot AR$$

$$E = \frac{E_{MAX} \cdot C}{EC_{50} + C} + E_0$$

## 6.2.2. Non linear E vs Dose/C relationships

- The **Sigmoidal E<sub>MAX</sub> Model** is a generalization of the E<sub>MAX</sub> model.



$$E = \frac{E_{\text{MAX}} \cdot C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}} + E_0$$

## 6.2.2. Non-linear E vs Dose/C relationships

**Example of Phase II drug development :** The tacrine\* data together with phase 1 PK and preclinical data for CI-1017\*\* were used to simulate various clinical trial scenarios to determine the optimal clinical trial design.



\* Tacrine = an approved drug for the treatment of Alzheimer's disease symptoms.

\*\* CI-1017 = an M1-muscarinic acid agonist tested for AD.

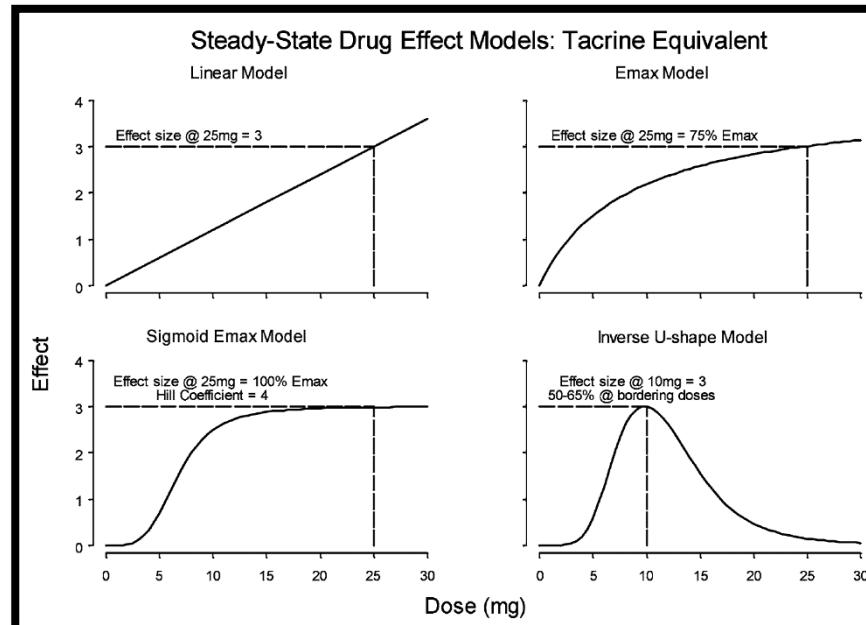


Table II. Estimated Power to Detect a Significant ( $\alpha = 0.05$ ) Treatment Effect (ref. 5)

Trial design	Parallel	4 x 4	4 x 4	6 x 6
Period length (weeks)	12	4	3	2
Dose response shape				
Linear	29	84	51	41
Emax	28	88	67	43
Sigmoid E <sub>max</sub>	43	96	85	68
Inverse U-Shape	21	57	49	39
Average	30	81	63	48

Go/no-go decision !!!

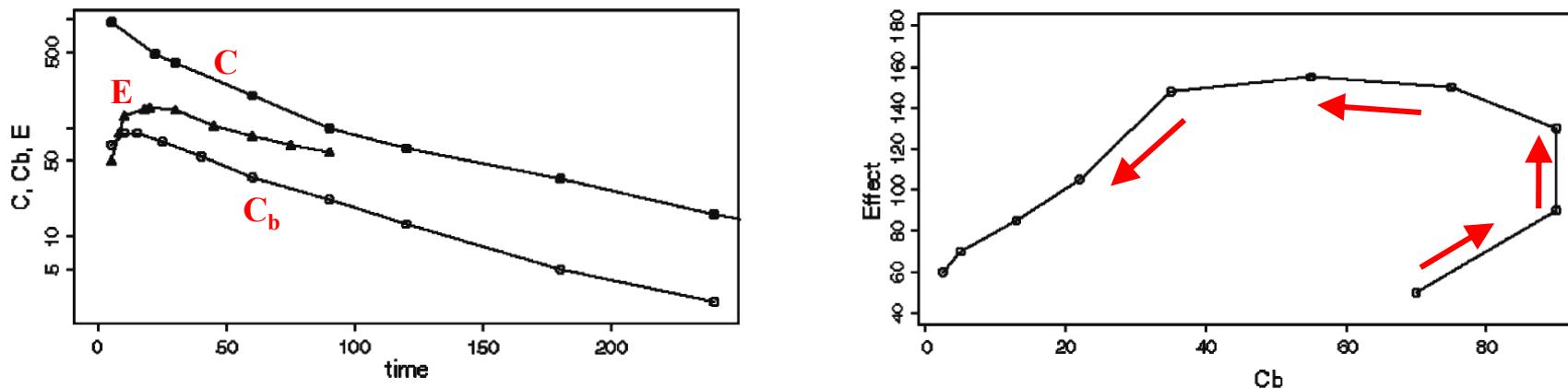
## 6.2.2. Non-linear E vs Dose/C relationships

Maximum effects are predicted to occur simultaneously with peak drug concentrations, since obviously if C is the maximum observed drug concentration, the maximum observed effect E is :

$$E = \frac{E_{MAX} \cdot C^\gamma}{EC_{50}^\gamma + C^\gamma} + E_0$$



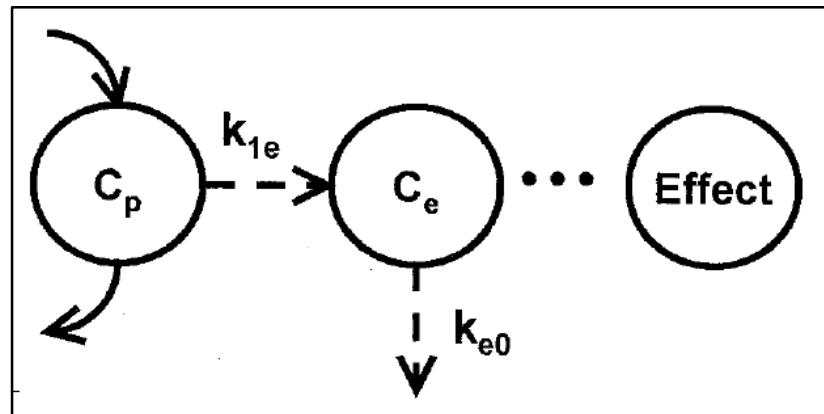
!!! For many responses E lags behind or ahead of C !!! => HYSTERESIS



**Fig. 1.** Morphine plasma, brain concentrations and effect obtained graphically from (23). The delay between plasma concentrations  $C$  (circles), brain concentrations  $C_b$  (open circles) and response  $E$  (diamonds) (upper panel) gives rise to a counterclockwise hysteresis loop in the  $C_b - E$  relationship (lower panel).

### 6.2.3. Biophase distribution models

- **1968**, concept of **biophase compartment** where “*it indicates a space containing the receptors, or to be interposed between the receptors and extracellular fluid*”. This **hypothetical** compartment is driven by plasma concentrations and directly related to the effect. The model is capable of describing the **time delay** between plasma concentrations and effect time curves.

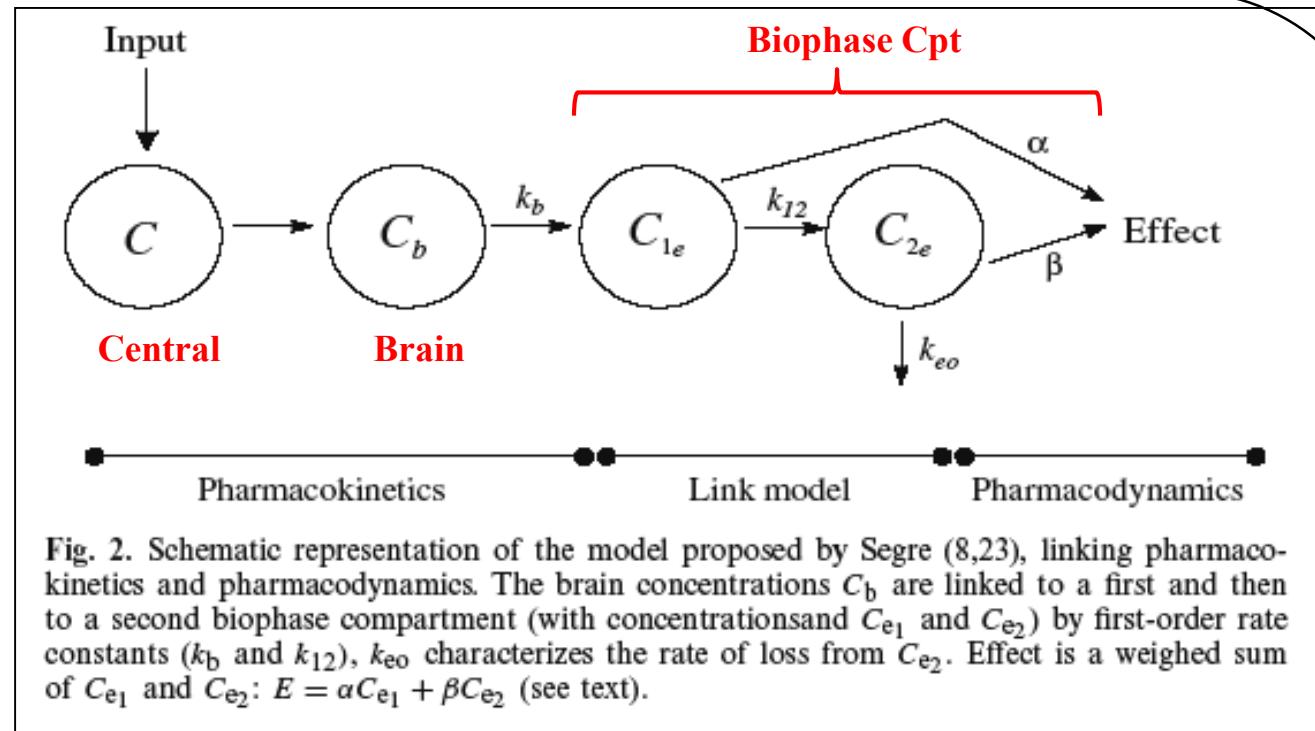


$$\frac{dC_e}{dt} = k_{1e} \cdot C_p - k_{e0} \cdot C_e$$

!!! This model is known as the “**effect compartment model**” (or link model) and is used to explain the hysteresis in the C-E plot of many drugs. !!!

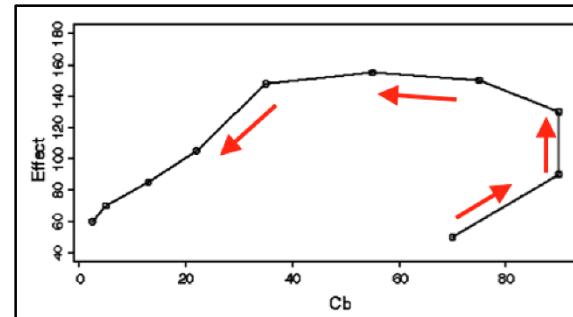
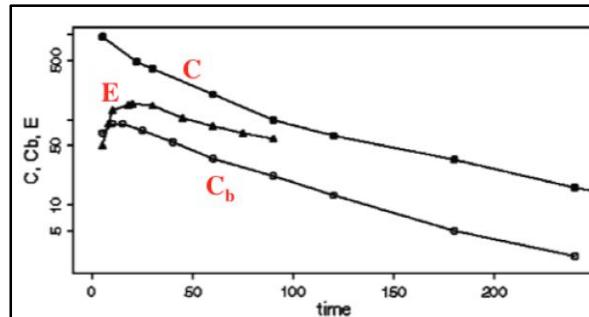
### 6.2.3. Biophase distribution models

Model to explain hysteresis in the Morphine concentration-effect curve



$$\begin{aligned}\frac{dC_{e1}}{dt} &= k_b C_b - k_{12} C_{e1} \\ \frac{dC_{e2}}{dt} &= k_{12} C_{e1} - k_{eo} C_{e2}\end{aligned}$$

$$E = \alpha C_{e1} + \beta C_{e2}$$



Dahlstrom et al. (1978)

### 6.2.3. Biophase distribution models

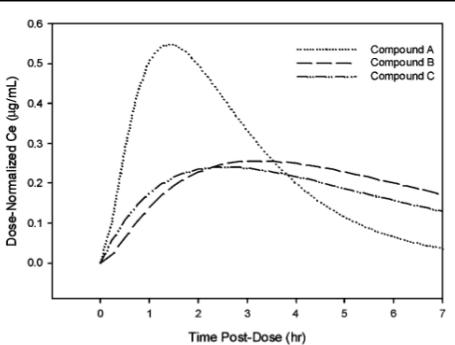
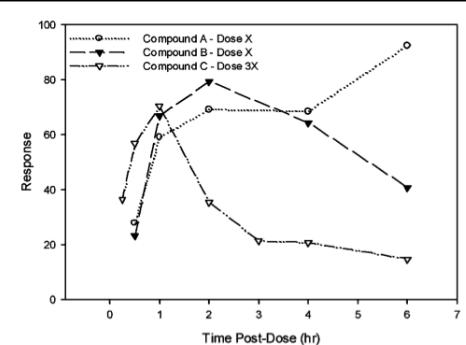
**Example :** PK/PD modeling in predicting response in phase I study and assessing the potential for differentiation between compounds.

$$\frac{dC_e}{dt} = k_{1e}C_p - k_{e0}C_e$$

$$E = \frac{C_e^\gamma}{C_e^\gamma + EC_{50}^\gamma}$$

**Table I.** Parameter Estimates of the PK-PD Modeling of Preclinical and Clinical Data

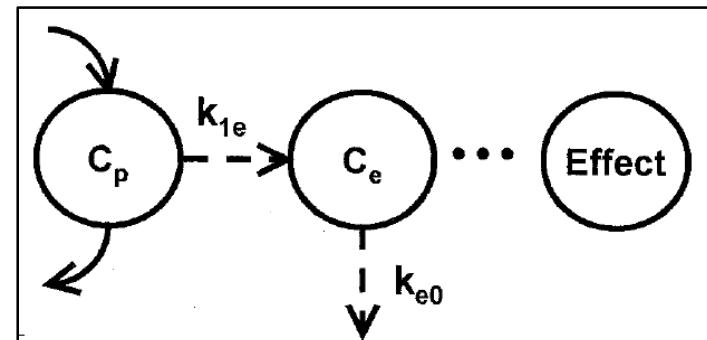
PD Parameter	Compound A	Compound B	Compound C
Preclinical Data			
$k_{e0}$ ( $\text{hr}^{-1}$ )	0.32	0.23	3.84
EC <sub>50</sub> ( $\mu\text{g/mL}$ )	2.00	0.634	7.52



**Fig. 1.** Time course of pharmacologic response (Left Panel) and dose-normalized concentrations in the effect compartment (Right Panel) and effect compartment for compounds A, B and C.

Preclinical

Left Panel) and  
Compounds A, B and C.



### 6.2.3. Biophase distribution models

**Example :** PK/PD modeling in predicting response in phase I study and assessing the potential for differentiation between compounds.

$$\frac{dC_e}{dt} = k_{1e}C - k_{e0}C_e$$

$$E = \frac{C_e^\gamma}{C_e^\gamma + EC_{50}^\gamma}$$

**Table I.** Parameter Estimates of the PK-PD Modeling of Preclinical and Clinical Data

PD Parameter	Compound A	Compound B	Compound C
Preclinical Data			
$k_{e0}$ ( $\text{hr}^{-1}$ )	0.32	0.23	3.84
EC <sub>50</sub> ( $\mu\text{g/mL}$ )	2.00	0.634	7.52
Clinical Data			
$k_{e0}$ ( $\text{hr}^{-1}$ )	1.05	0.45	5.63
EC <sub>50</sub> ( $\mu\text{g/mL}$ )	1.21	0.405	29.5

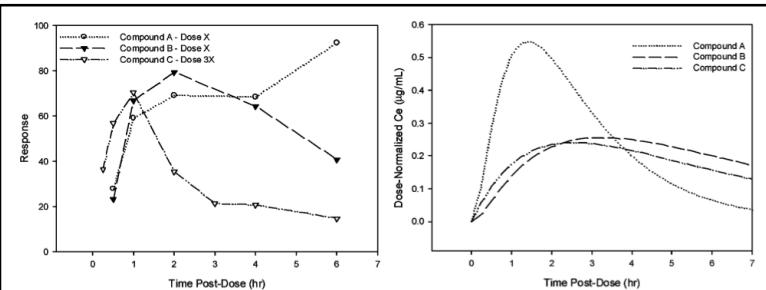


Fig. 1. Time course of pharmacologic response in preclinical studies (Left Panel) and Dose-Normalized concentrations in the effect site (Right Panel) for compounds A, B and C.

Preclinical

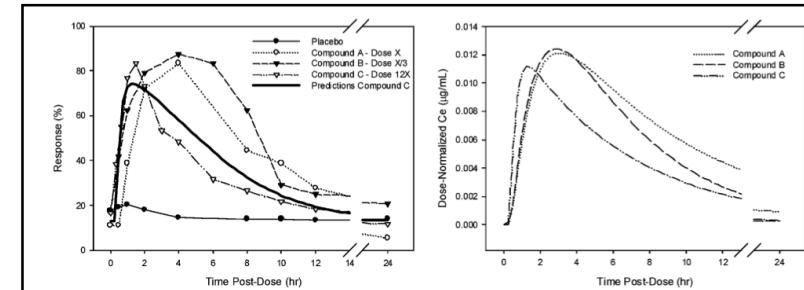


Fig. 2. Time course of pharmacologic response in Phase 1 study (Left Panel) and Dose-Normalized concentrations in the effect site (Right Panel) for compounds A, B and C.

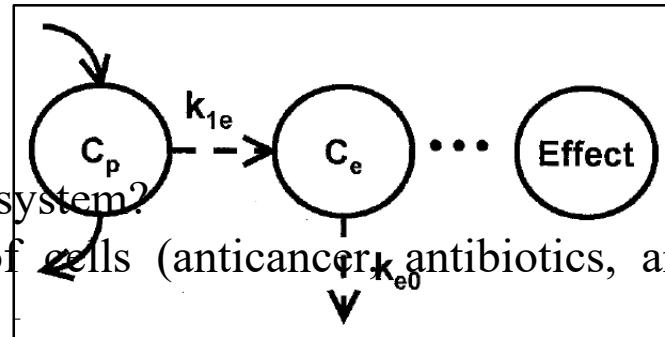
Phase I

### 6.2.3. Biophase distribution models

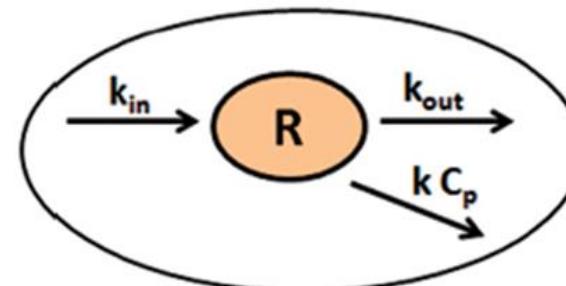
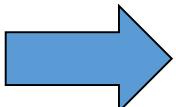
- takes into account for the time-delay between the effect and the plasma concentration

$$\frac{dC_e}{dt} = k_{1e} \cdot C_p - k_{e0} \cdot C_e$$

- How to model changes in the turnover of a system?
- Like the change in the self-replication of cells (anticancer antibiotics, antimalarial drugs?)

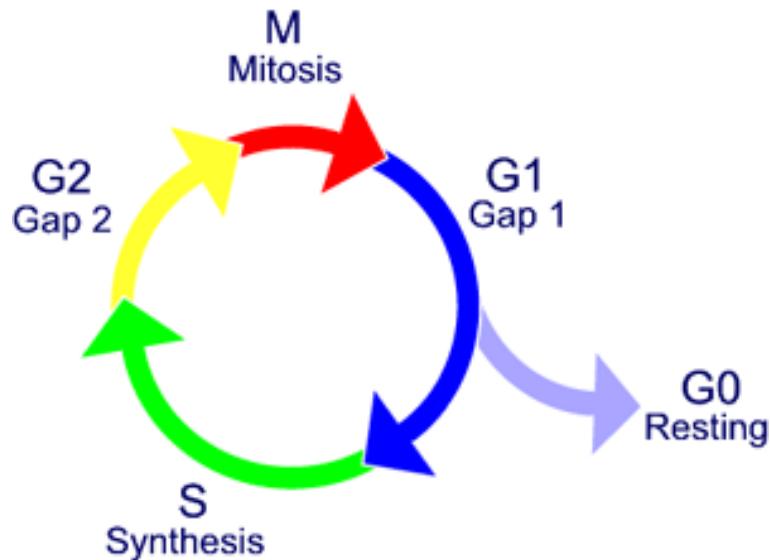


Irreversible effects



#### 6.2.4. Irreversible effects

##### Tumor / Cancer

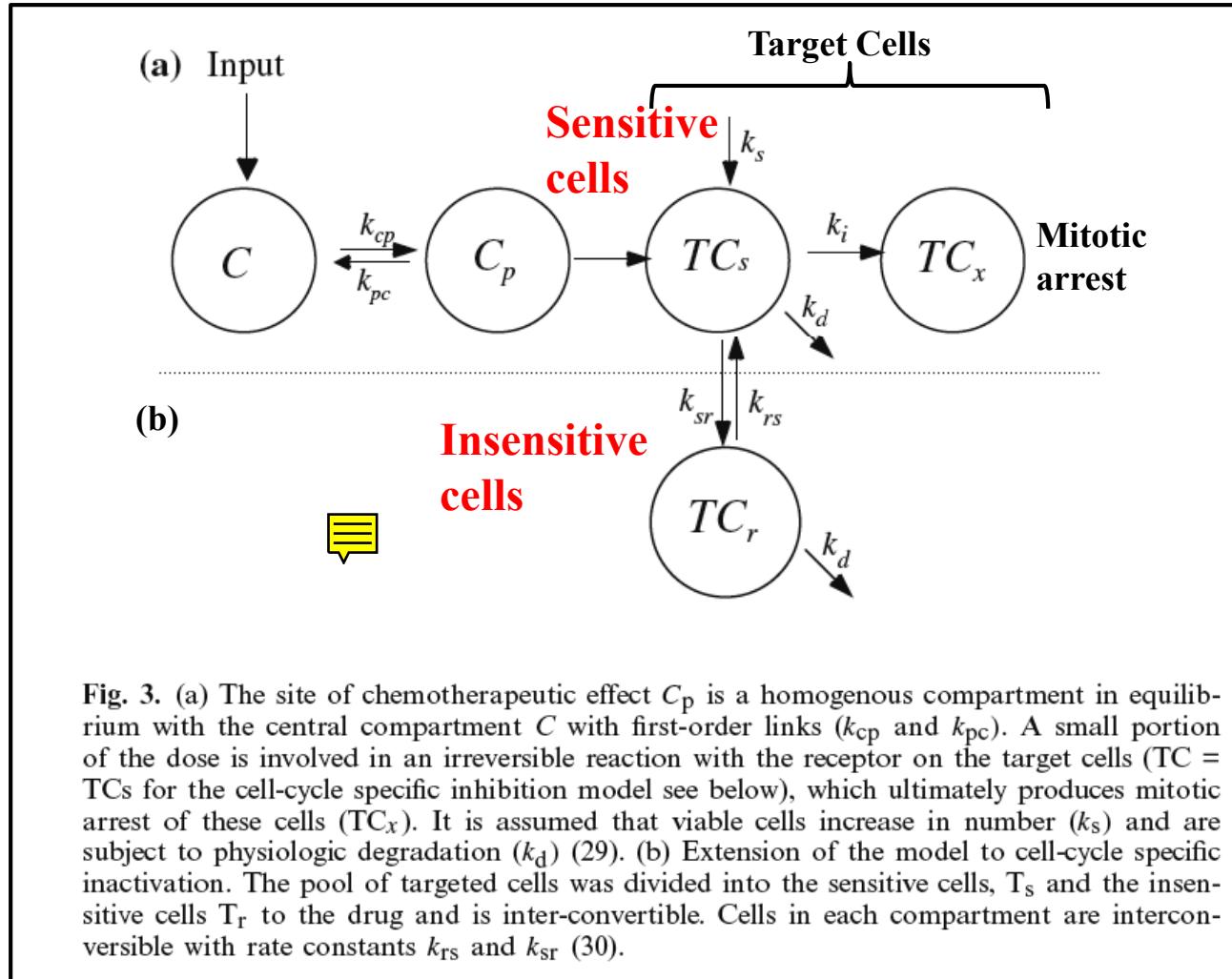


→ Cell-cycle nonspecific drugs act against cancer cells in any phase of the cell cycle

- Normal cells know to stop dividing when they come in contact with other cells
- In the case of tumor cells this stop mechanism is not working
- Chemotherapeutic drugs kill or stop cells in a specific part of the cell cycle

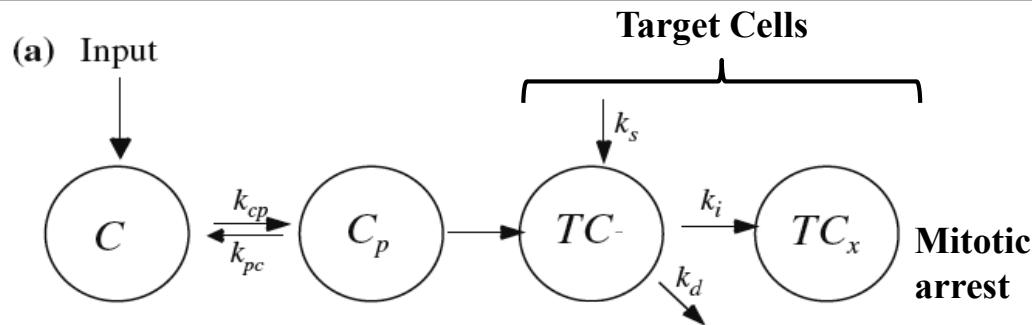
## 6.2.4. Irreversible effects

- Model of Jusko (1973) : Cell-cycle non-specific chemotherapeutic drug.



## 6.2.4. Irreversible effects

1



- The rate of change in quantity of target cells (TC) with time :

$$\frac{dTC}{dt} = (k_s - k_d)TC - k_i TCA_p$$

$k_s$  formation rate  
 $k_d$  elimination rate  
 $k_i$  inhibition rate

*Amount of the drug in the peripheral chemotherapeutic compartment (receptor site)*

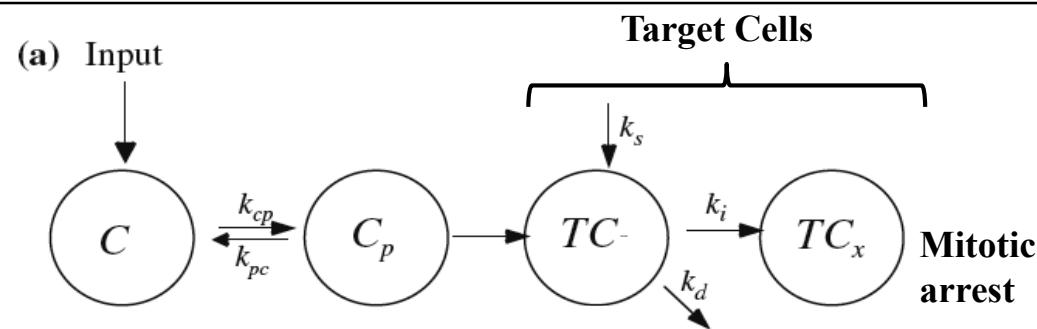
- If F is the fraction of surviving cells ( $TC/TC_0$ ) :

$$\log(F) = (k_s - k_d)t/2.3 - k_i \int_0^t A_p(t) dt$$

!!! Predicts a log-linear relationship between the fraction of surviving cells and the dose of the drug !!!

## 6.2.4. Irreversible effects

1



- After all the drug is eliminated :

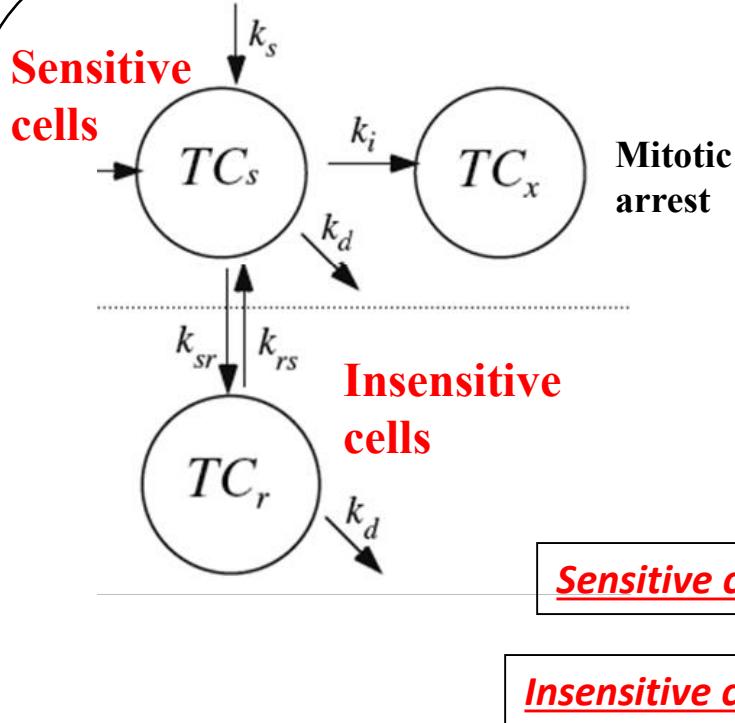
$$\log(F) \approx (k_s - k_d)/2.3t - k_{12}/k_{10}k_i \text{ dose} = \alpha - K \text{ dose}$$



Used to quantify the chemotherapeutic efficacy of different drugs.

## 6.2.4. Irreversible effects

2



$k_s$  formation rate  
 $k_d$  elimination rate  
 $k_i$  inhibition rate  
 $k_{sr}$  rate of sensitive  $\rightarrow$  insensitive cells  
 $k_{rs}$  rate of insensitive  $\rightarrow$  sensitive cells

$$\frac{dTC_s}{dt} = k_{rs}TC_r + (k_s - k_{sr})TC_s - k_iTC_sA_p$$

$$\frac{dTC_r}{dt} = (k_{sr}TC_s - k_{rs})TC_r - k_dTC_r$$

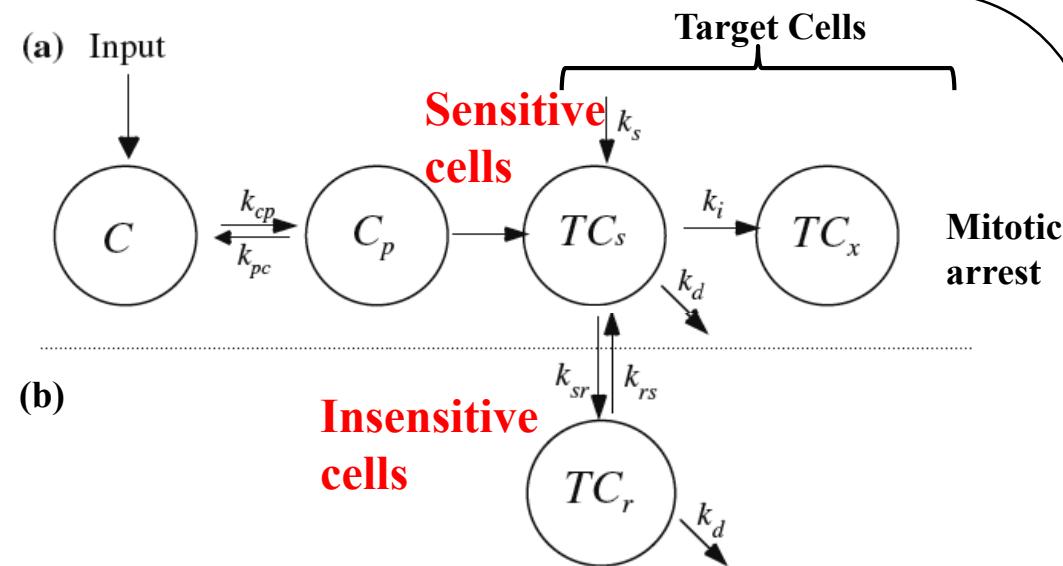
**Sensitive cells**

**Insensitive cells**

## 6.2.4. Irreversible effects

$k_s$  formation rate  
 $k_d$  elimination rate  
 $k_i$  inhibition rate  
 $k_{sr}$  rate of sensitive  $\rightarrow$  insensitive cells  
 $k_{rs}$  rate of insensitive  $\rightarrow$  sensitive cells

$TC_s$  sensitive cells  
 $TC_r$  insensitive cells



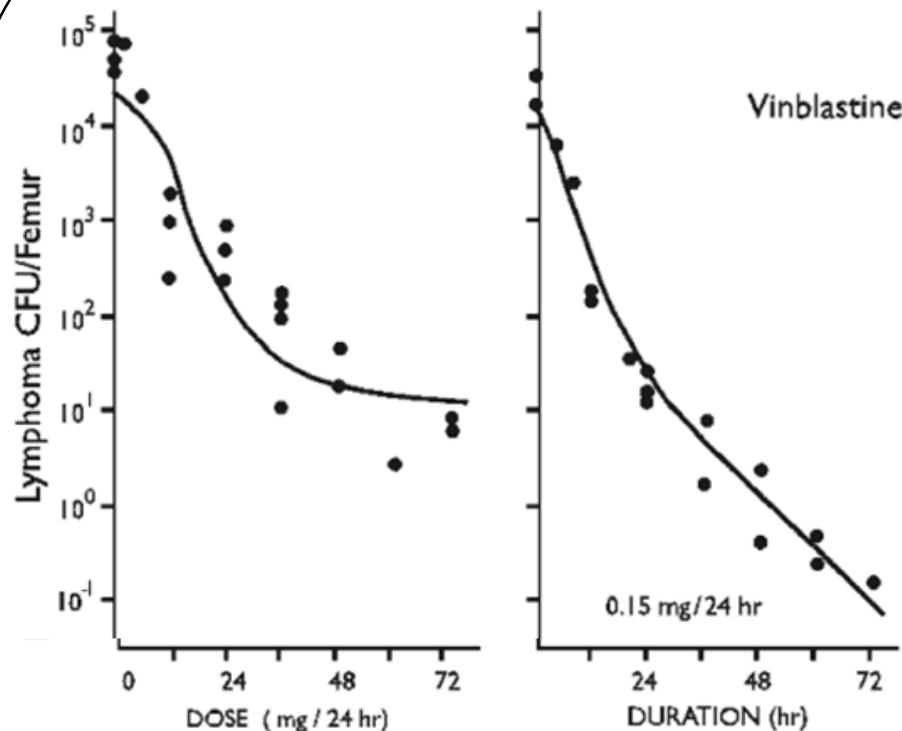
$$\frac{dTC_s}{dt} = k_{rs}TC_r + (k_s - k_{sr})TC_s - TC_s K \text{ dose } N$$

$$\frac{dTC_r}{dt} = k_{sr}TC_s - k_{rs}TC_r - k_dTC_r$$

Total number of given doses

#### 6.2.4. Irreversible effects

2



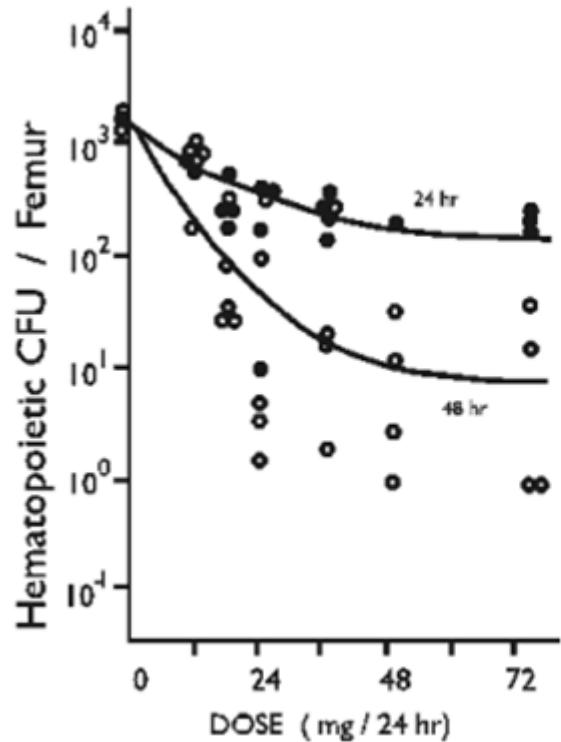
- Lymphatic cells are part of the lymph system
- Vinblastine : cell-cycle non-specific chemotherapeutic drug

• Exp. value

— PK/PD prediction

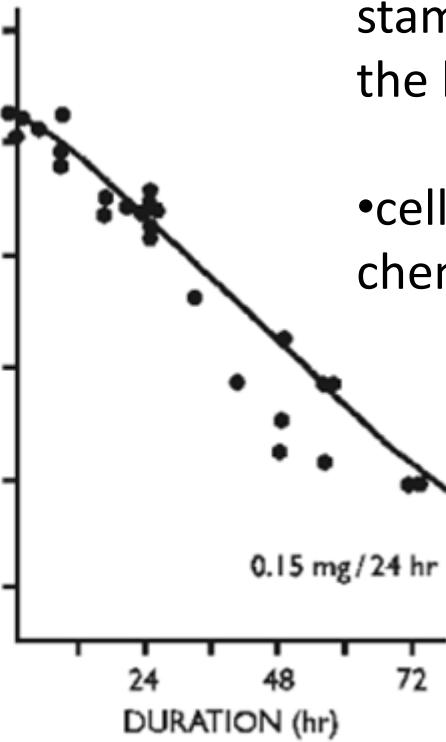
#### 6.2.4. Irreversible effects

2



• Exp. value

— PK/PD prediction

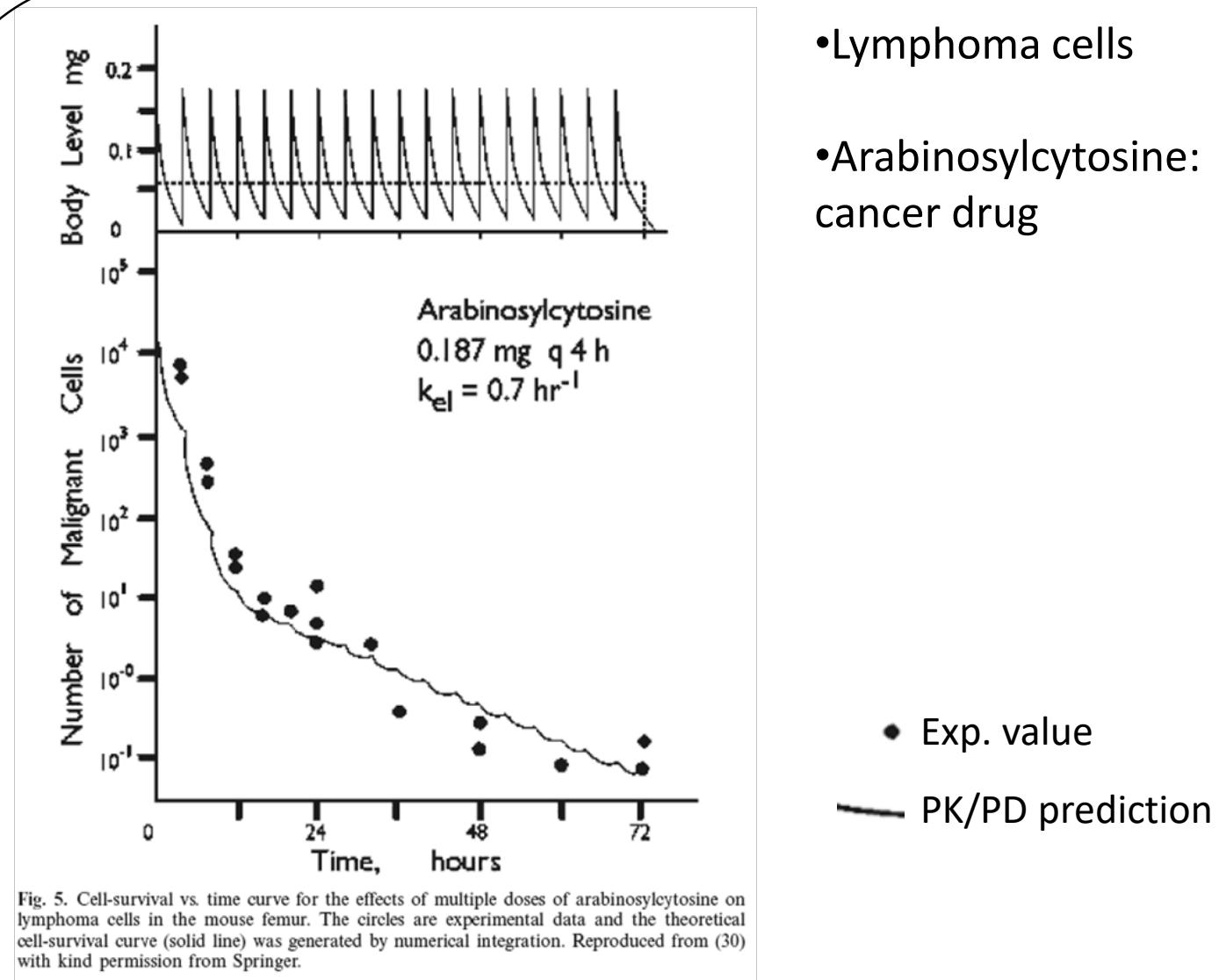


- Hematopoietic cells are stem cells that give rise to all the blood cells

- cell-cycle non-specific chemotherapeutic drug

## 6.2.4. Irreversible effects

2



- Lymphoma cells

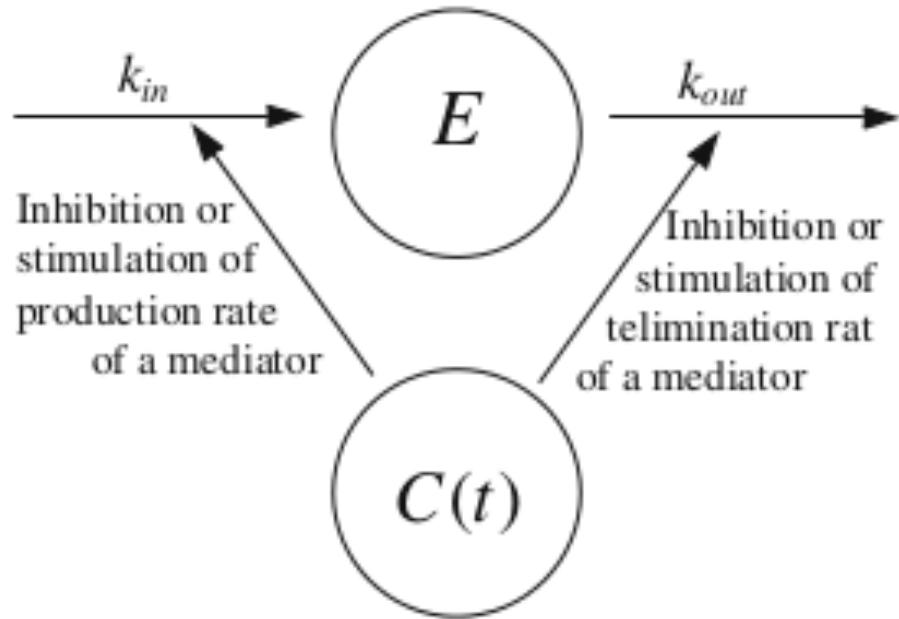
- Arabinosylcytosine: anti-cancer drug

## Direct Action against Indirect Action Models

Two basic conceptual approaches have been developed for analysing hysteresis between drug plasma levels and pharmacodynamic response.

- 1) **Direct Action Models:** The pharmacological effect is considered as a direct consequence of drug action and the *delay* in response is thought to reflect the *time required for the drug to reach its site* of pharmacological action.
- 2) **Indirect Action Models:** The drug receptor interaction initiates a series of *downstream biochemical events* that account for the observed *time lag*. Indirect mechanisms of action involve primarily the modulation of endogenous factors that mediate the drug effect.

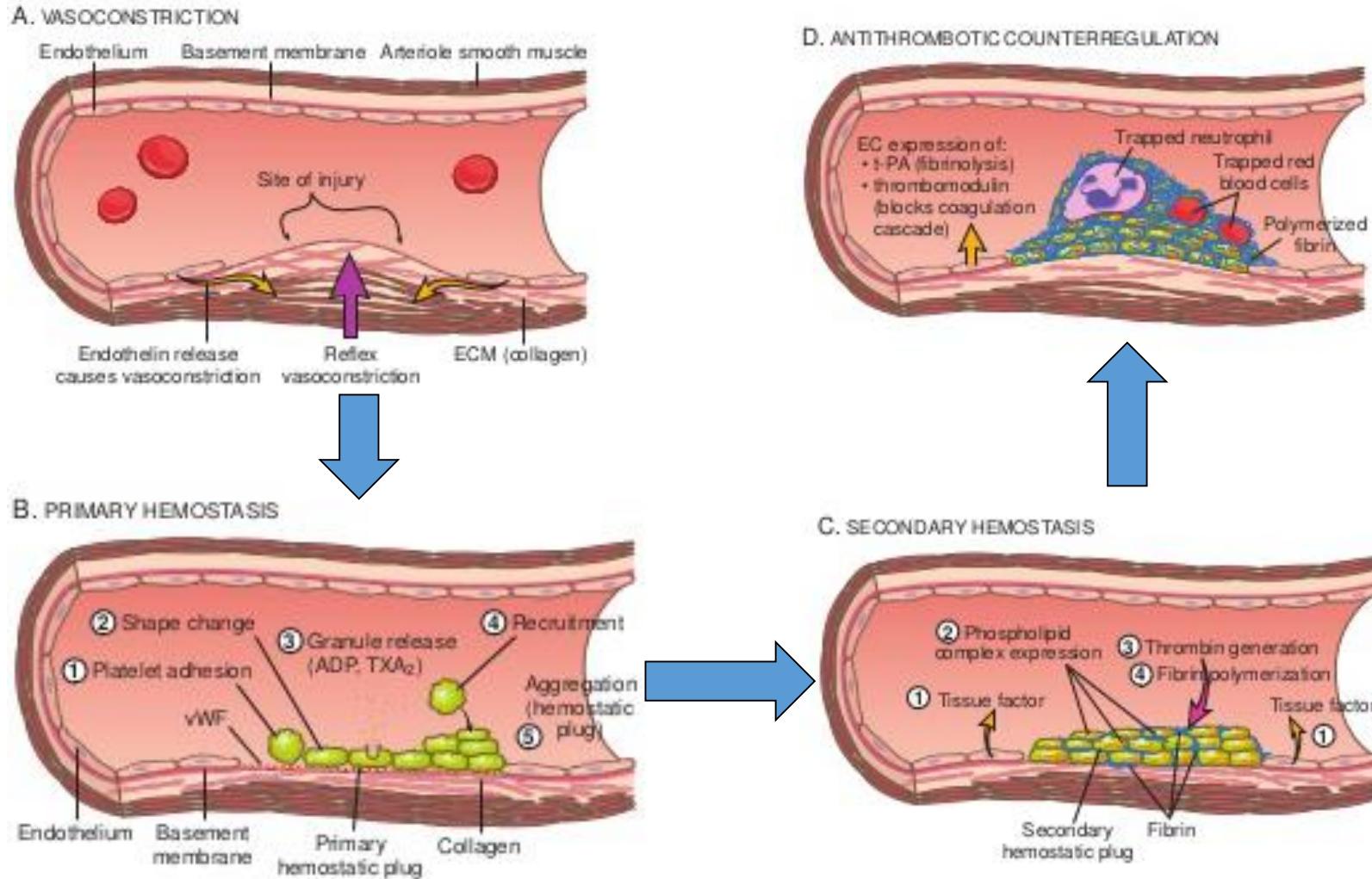
## 6.3. Indirect action models



- Modulation of endogenous factors
- Models for cell trafficking
- Transduction models

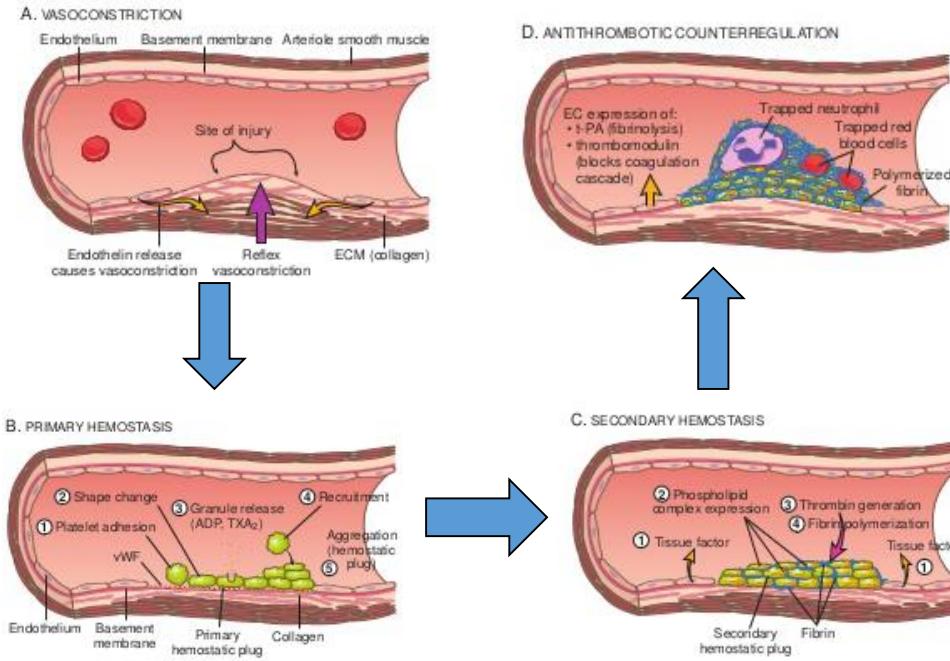
### 6.3.1. Modulation of endogenous factors

#### Normal Blood clotting



### 6.3.1. Modulation of endogenous factors

#### Normal Blood clotting



#### Treatment

- with Anticoagulants that prevent the clotting of blood

#### Thrombosis

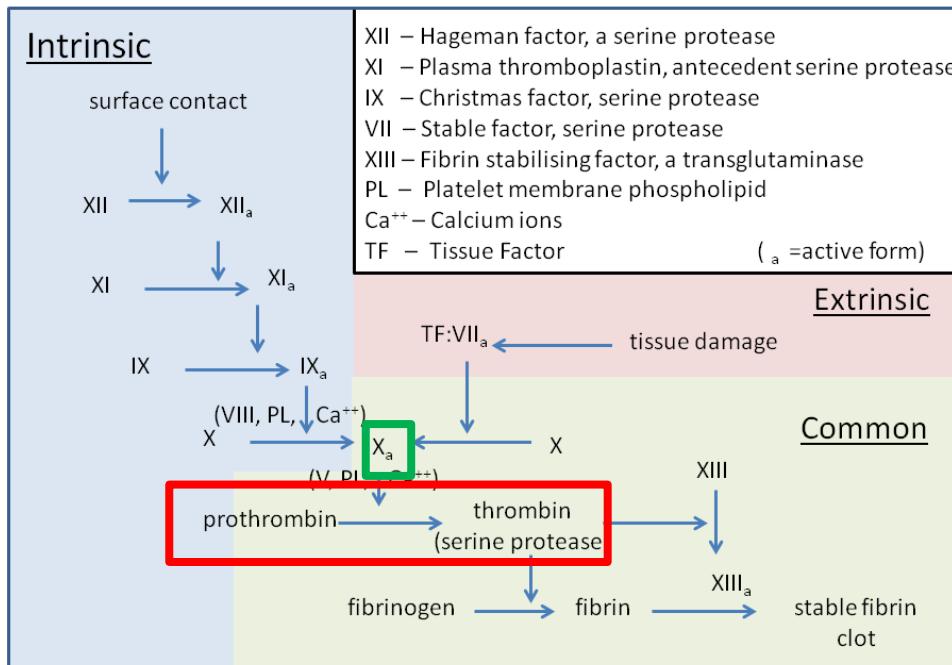
- Blood clotting even occurs in the absence of an injury
- Clots obstruct the veins
- Embolism: moving clots
- May lead to greater obstruction  
-> deprivation of oxygen, infarction, tissue death
- Can be acquired or a genetic effect

### 6.3.1. Modulation of endogenous factors

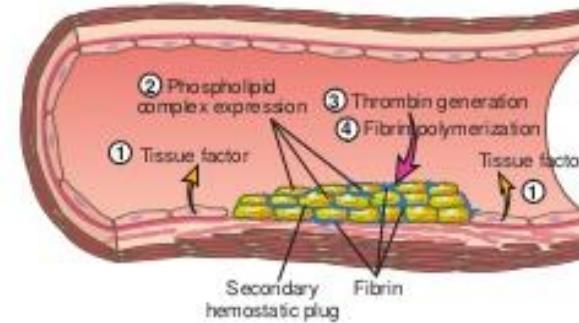
What is a possible biomarkers for thrombosis / blood clotting?



The three pathways that makeup the classical blood coagulation pathway



C. SECONDARY HEMOSTASIS



### Prothrombin activity

Factor Xa cleaves prothrombin

-> Warfarin inhibits Vitamin K dependent synthesis of active Factor II, VII, IX, X.

### 6.3.1. Modulation of endogenous factors

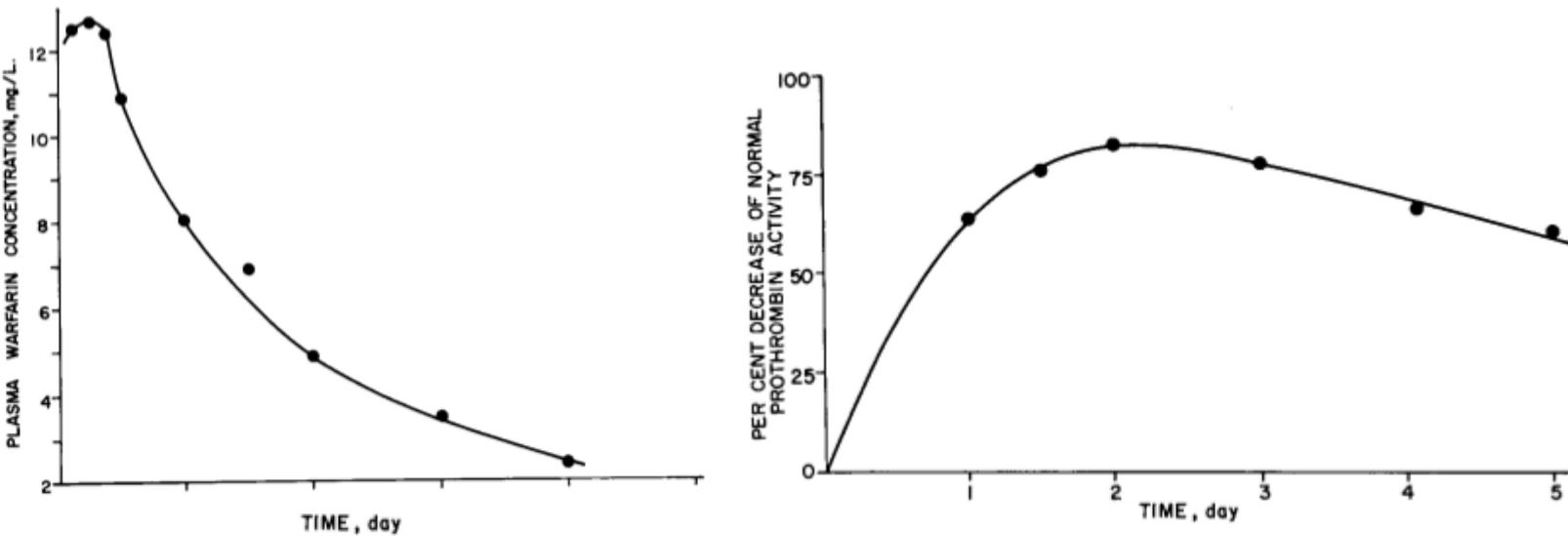


Fig. Plasma-warfarin concentration and depression of prothrombin complex activity as function of time after oral administration of 1.5 mg warfarin per kilogram body weight. Average of 5 normal subjects.

### 6.3.1. Modulation of endogenous factors

- First outline of an indirect action model (Nagashima *et al.*, 1968) : Effect of oral dose of warfarin on prothrombin complex activity, P, in the blood (role on blood coagulation) :

Introduction of two processes, prothrombin synthesis and degradation  
=> The net change of prothrombin complex activity,  $P_{\text{net}} =$

The diagram illustrates the derivation of the differential equation for prothrombin complex activity  $P$  over time  $t$ . It starts with the equation  $P_{\text{net}} = P_{\text{syn}} + P_{\text{deg}}$ . This is shown to be equal to the initial level of prothrombin  $P_{\text{syn}}^0$  minus a term involving the slope  $s$  and the ratio of current concentration to minimum extrapolated concentration  $C/C_{\min}$ . This leads to the differential equation  $\frac{dP}{dt} = k_{\text{deg}} P^0 - s \log \frac{C^0}{C_{\min}} + \frac{sk}{2.3}t - k_{\text{deg}} P$ .

$P_{\text{net}} = P_{\text{syn}} + P_{\text{deg}}$

*Level of prothrombin before drug administration*

$P_{\text{syn}} = P_{\text{syn}}^0 - s \log C/C_{\min}$

*slope*

*Min. extrapolated [warfarin]  
From effect-concentration curve*

$\frac{dP}{dt} = k_{\text{deg}} P^0 - s \log \frac{C^0}{C_{\min}} + \frac{sk}{2.3}t - k_{\text{deg}} P$

### 6.3.1. Modulation of endogenous factors

Described a computer program for warfarin dosage adjustment in patient

- **1969**, Scheiner used a linear model with a clotting factor :

$$\frac{dP}{dt} = -k_{\text{deg}} P + (1 - xC)k_{\text{syn}} \quad \text{for } 1 - xC > 0, \quad P < 1$$

$$\frac{dP}{dt} = -k_{\text{deg}} P \quad \text{for } 1 - xC < 0 \text{ or } P = 1$$

x=sensitivity factor

The model was fitted to the available patient-response data and then used for dosage individualization.

ksyn=max synthesis rate of the clotting factor P

- **1973**, Theophanus, same PK model for warfarin elimination BUT modeled the effect of warfarin on the prothrombin complex activity :

$$\frac{dP}{dt} = -k_{\text{syn}} \ln \frac{C}{C_{\max}} - k_{\text{deg}} P$$

C<sub>max</sub> = concentration of warfarin which produced total inhibition of prothrombin complex synthesis.

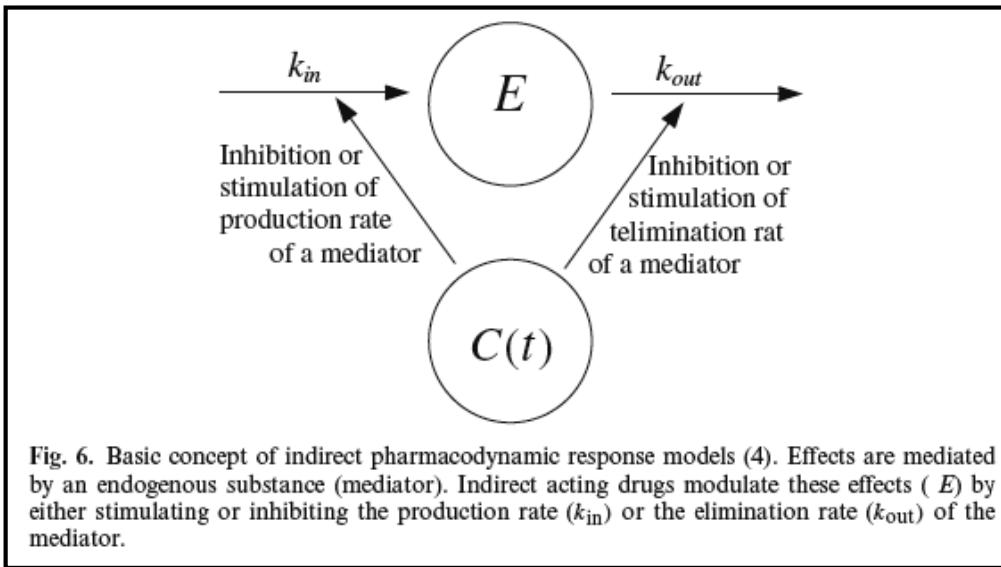
- **1981-82**, Abbrecht & O'Leary, more physiological model.

The time-dependent prothrombin activity =  $\frac{dP}{dt} = k_{\text{syn}} \left(1 - \frac{C}{C + EC_{50}}\right) - k_{\text{deg}} P$

Michaelis-Menten

### 6.3.1. Modulation of endogenous factors

- **1990s**, Dayneka *et al.*, four indirect models based on drug effects that either stimulate or inhibit the production or loss of a mediator :



Inhibititon/Stimulation of a production factor of the response

$$\frac{dE}{dt} = k_{in}[1 \pm g(C)] - k_{out}E$$

Inhibition/Stimulation of a dissipation factor of the response

$$\frac{dE}{dt} = k_{in} - k_{out}[1 \pm g(C)]E$$

$g(C)$  for Inhibititon

$$I(C) = \frac{I_{max}C}{C + EC_{50}}$$

$g(C)$  for Stimulation

$$S(C) = \frac{E_{max}C}{C + EC_{50}}$$

### 6.3.2. Models for cell trafficking

-Corticosteroids such as methylprednisolone (MP) have immunosuppression and anti-inflammation effects (among other effects).

-They for example alter the circulating patterns of leukocytes such as basophils

-Basophils are major contributors to allergic and anaphylactic reactions

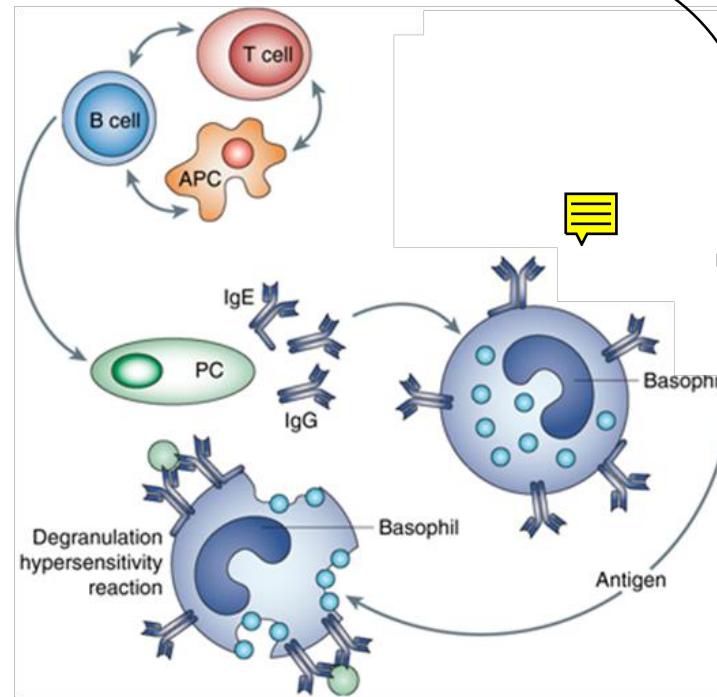


Fig. The classical primary immune response (1) is initiated with the presentation of the Antigen (Ag) by the APC. Following the production of IgG and IgE by plasma cells (PC) the basophil binds these antibodies and degranulates releasing histamine to the surrounding leading to a hypersensitive reaction.

### 6.3.2. Models for cell trafficking

- Basophils are major contributors to allergic and anaphylactic reactions
- 98% of circulating histamine is contained in basophiles
- MP leads to a depletion of basophils from blood to other body compartments

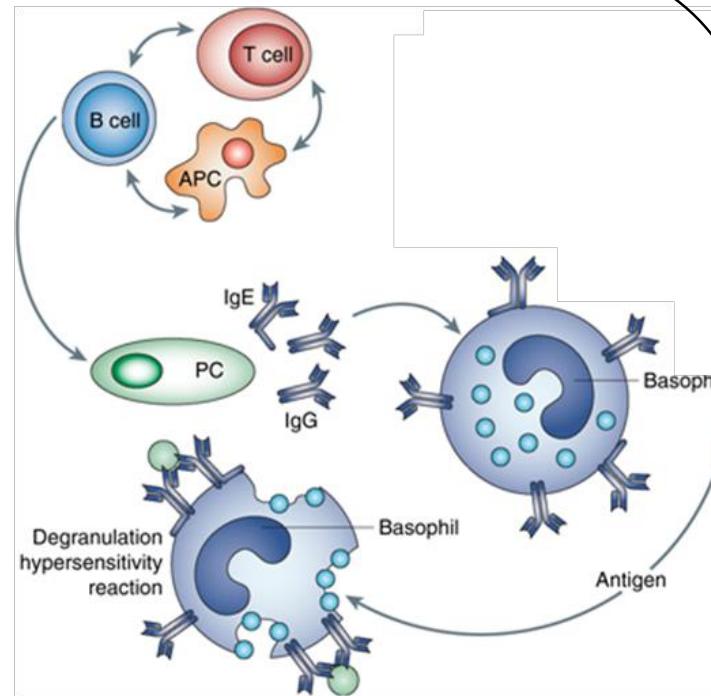
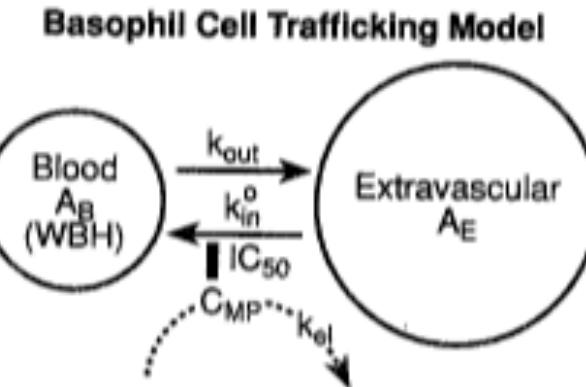


Fig. The classical primary immune response (1) is initiated with the presentation of the Antigen (Ag) by the APC. Following the production of IgG and IgE by plasma cells (PC) the basophil binds these antibodies and degranulates releasing histamine to the surrounding leading to a hypersensitive reaction.

### 6.3.2. Models for cell trafficking

- **1991**, Wald et al. used a cell trafficking model to more accurately define and extrapolate corticosteroids-induced alterations in the distribution of circulating cells and provide parameters for steroid sensitivity following corticoid administration.



*Amount of basophil cells in the blood*

$$\begin{aligned}\frac{dB_B}{dt} &= +I(t)k_{in}B_E - k_{out}B_B \\ \frac{dB_E}{dt} &= -I(t)k_{in}B_E - k_{out}B_B\end{aligned}$$

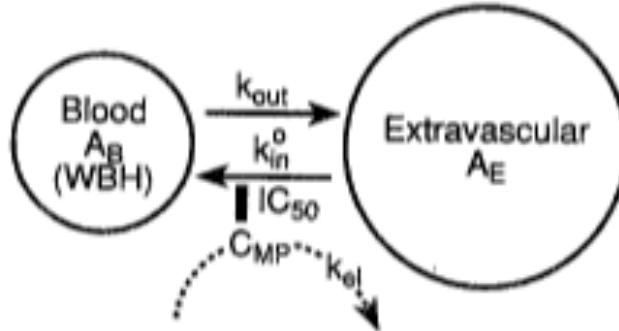
*Movement from the blood to extravascular sites*

$$I(t) = 1 - \frac{C}{C + EC_{50}}$$

*Extravascular sites*

### 6.3.2. Models for cell trafficking

**Basophil Cell Trafficking Model**



*Amount of basophil cells in the blood*

$$\begin{aligned}\frac{dB_B}{dt} &= +I(t)k_{in}B_E - k_{out}B_B \\ \frac{dB_E}{dt} &= -I(t)k_{in}B_E - k_{out}B_B\end{aligned}$$

*Movement from the blood to extravascular sites*

$$I(t) = 1 - \frac{C}{C + EC_{50}}$$

*Extravascular sites*

$$B_E \gg B_B, B_E \approx Cst \approx B_E^{ss}$$

$$\frac{dB_B}{dt} = +I(t)k_{in}^0 - k_{out}B_B \quad \text{where } k_{in}^0 = k_{in}B_E^{ss}$$

### 6.3.2. Models for cell trafficking

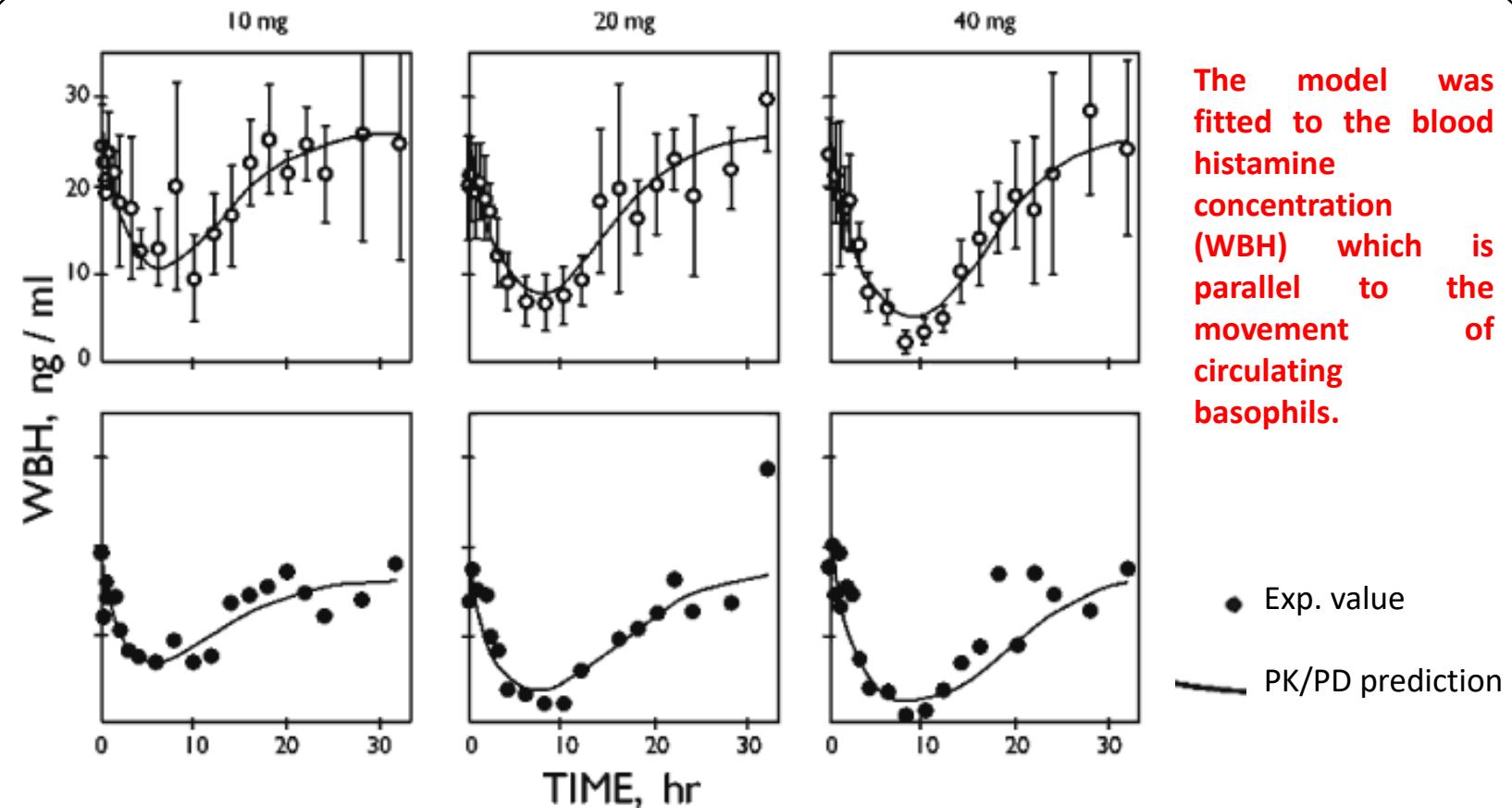


Fig. 7. Composite graph showing whole blood histamine (WBH) vs. time for 3 dosage levels of methylprednisolone with depiction of the average data ( $\pm$ SD) for 5 subjects (top) and one individual subject (bottom). Solid lines were generated by using nonlinear least-squares regression to fit the model to data from all dosage levels simultaneously. Reproduced from (38) with kind permission from Springer.

### 6.3.2. Models for cell trafficking

The pharmacological effect of many drugs and hormones are often mediated by time-dependant transduction, whereby the final response is a result of a **signalling cascade** controlled by secondary messenger.

When these post-receptor events are rate limiting, drug effects can lag considerably behind plasma concentrations.



-This is often the case for glucocorticoids (steroids), which bind to glucocorticoid receptors (GR)



-GR regulate genes controlling the development, metabolism, and immune response

-GR activity can be monitored by hepatic tyrosine aminotransferase (TAT) activity



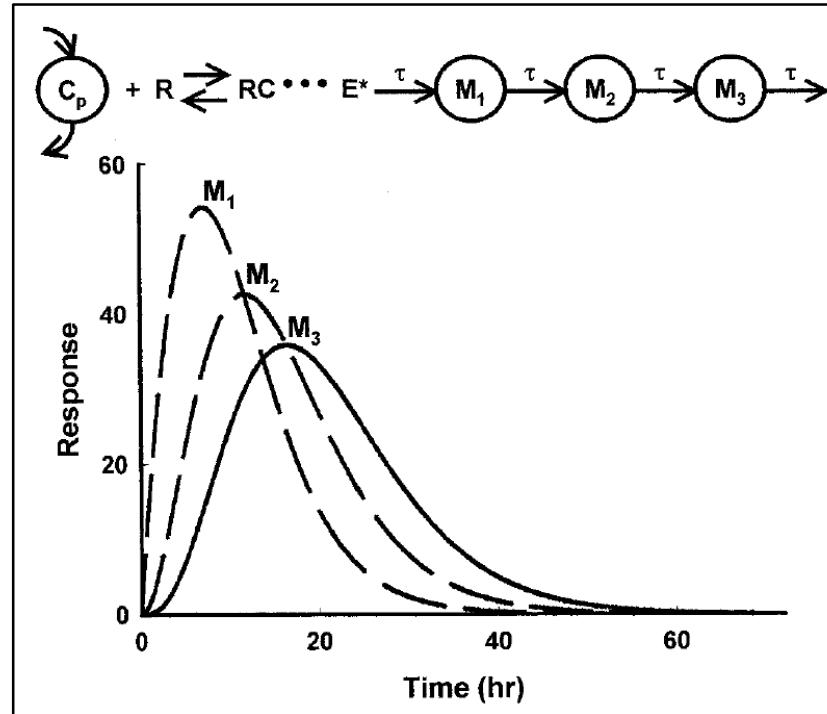
Need for transduction models

### 6.3.3. Transduction models

- **First generation** models proposed to examine steroid response in relation to plasma prednisolone concentrations (Boudinot, 1986).



several restrictions & weaknesses limited its applicability

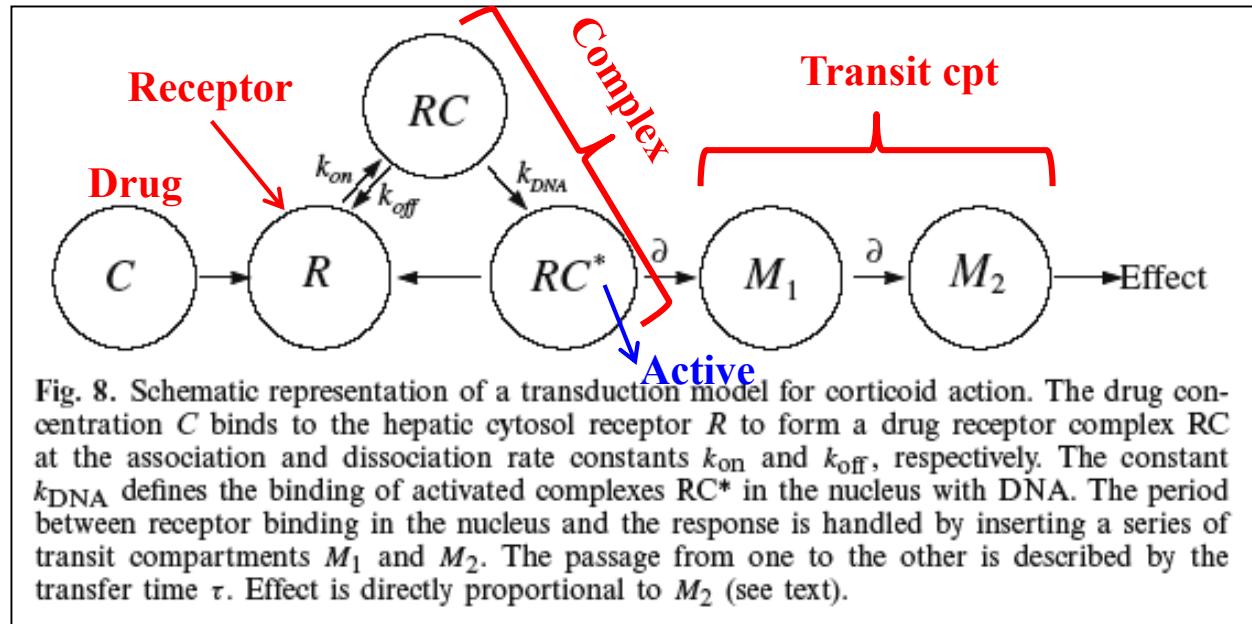


Example of steroids which exhibit a delay of several hours between max responses and peak steroids concentrations. This delay has been attributed to the induction of protein synthesis following steroid receptor binding.

### 6.3.3. Transduction models

- **Second generation** model for prednisolone PKPD in rats (Nichols, [1989](#)).

**Steroid response**  
= activity of the  
hepatic enzyme  
tyrosine  
aminotransferas  
e (TAT)



$$\frac{d(R)}{dt} = -k_{on}RC + k_{off}RC + RC^*$$

$$\frac{dRC}{dt} = -k_{on}RC - (k_{off} + k_{DNA})RC$$

$$\frac{dRC^*}{dt} = (k_{DNA}RC - RC^*)/\tau_1$$

$$\frac{dM_1}{dt} = \frac{RC^* - M_1}{\tau_1}$$

$M_1, M_2$  = Secondary messengers

$$\frac{dM_2}{dt} = \frac{M_1 - M_2}{\tau_1}$$

$$\frac{dTAT}{dt} = \kappa M_2^\gamma - k_{deg} TAT$$

$\tau_1$  = time of transfer for  $M_1-M_2$

### 6.3.3. Transduction models

- If more than 2 transit compartments (Sun & Jusko, **1998**)

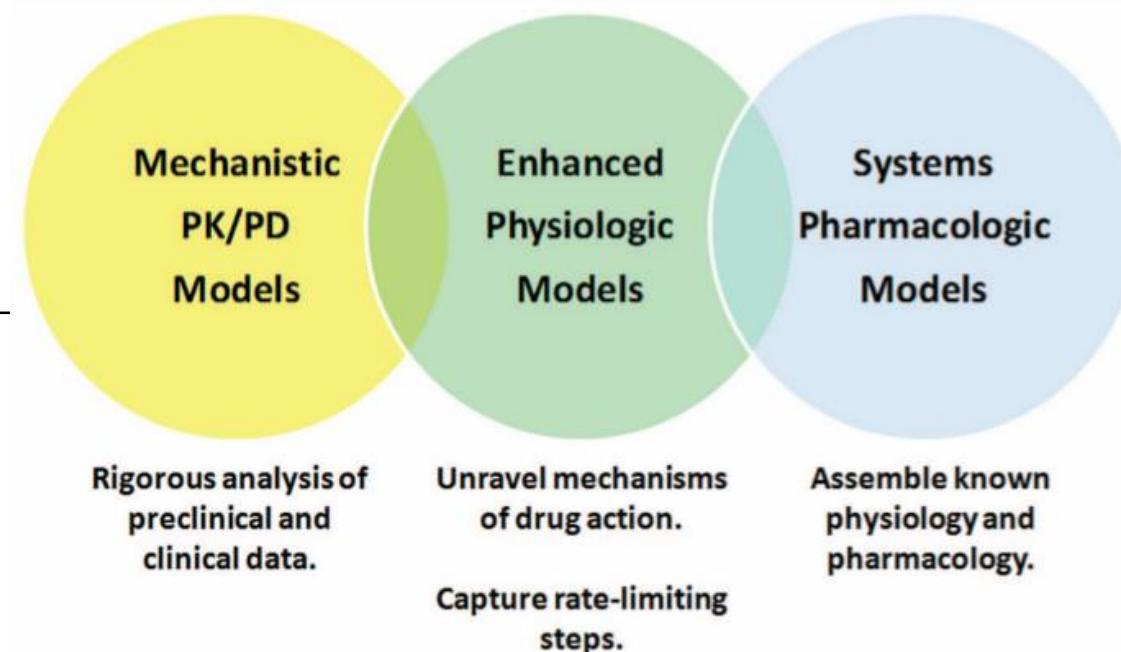
$$\frac{dM_1}{dt} = \frac{RC^* - M_1}{\tau_1}$$

$$\frac{dM_2}{dt} = \frac{M_1 - M_2}{\tau_1}$$

$$\frac{dM_i}{dt} = \frac{M_{i-1}}{\tau_{i-1}} - \frac{M_i}{\tau_i}, \quad i = 2, \dots, n$$

## Major mechanism-based PK/PD models

- Basic models can be clustered into direct action and indirect action models
- In a lot of cases these models are sufficient
- They fail in cases of tolerance development  
(for example: caffeine and the heart rate)  
further models are needed (such as tolerance models)



## 6.4. Enhanced models

### 6.4.1. Tolerance models

- First model for tolerance used a **time-series model** where the effect is function of the recent history of plasma concentration (Zahler, **1982**)

$$E(t) = E_0 + s_0 C_0(t) + s_1 C(t - 1) + s_2 C(t - 2) + \cdots + s_m C(t - m)$$

$S_i$  and  $C_i$  are coefficients and drug concentration corresponding to  $m$  previous periods determined at equispaced time.

- Semi-mechanistic model for tolerance with a more physiologic interpretation (Ekbad & Licko, **1984**) :

**Transformation of a hypothetical substance R to a substance RC.**

- Model for tolerance of caffeine on heart rate (Chow *et al.*, **1989**) :  
Use of a **function that declined exponentially** as a function of time.

$$E = E_0 + \alpha C_e(t) e^{-kt}$$

### 6.4.1. Tolerance models

- Model to describe the development of tolerance to furosemide-induced diuresis (Hammarlund *et al.*, 1985) : The Hill model was used to describe the excretion-response relationship.

$$E = E_0 + \frac{E_{\max} U(t)^{\gamma}}{U(t)^{\gamma} + U(t)_{50}}$$

*Urinary excretion rate of furosemide*

*Sensitivity of the system to the drug*

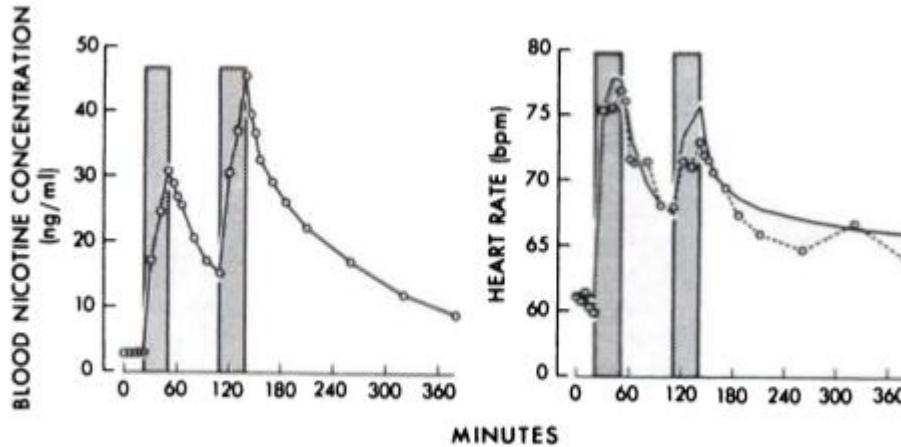
- To model tolerance,  $U(t)_{50}$  was modified such as it decreased exponentially as a function of the cumulative excretion of furosemide :

$$U(t)_{50} = U_{0,50} e^{k \int_0^t U(t) dt}$$

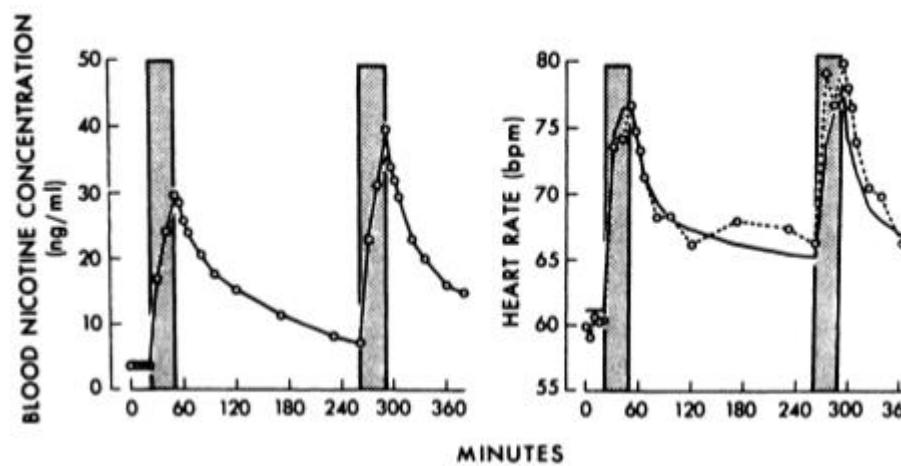
*Initial value of the excretion rate when no tolerance has developed*

### 6.4.1. Tolerance models

- Compartmental PKPD model for nicotine tolerance (Porchet *et al.*, **1988**) :



Motivation:  
Model the acute  
tolerance to  
nicotine



### 6.4.1. Tolerance models

- Compartmental PKPD model for nicotine tolerance (Porchet *et al.*, 1988) : Generation of a hypothetical substance  $C_m$  in a “**tolerance compartment**” that acted as a non-competitive antagonist of the effects of nicotine.

$$\frac{dC_m}{dt} = k_{mo}(C - C_m), \quad C_m(0) = 0$$

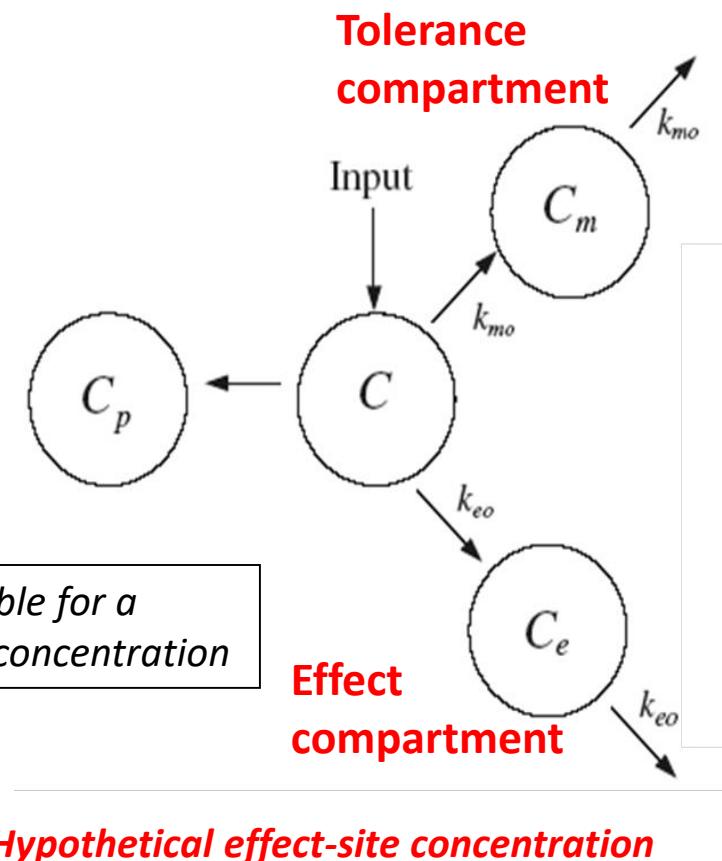
- Using a standard non-competitive antagonist model :

$$E = E_0 + E_{max} \frac{C}{C + EC_{50}(1 + C_m/C_{m,50})}$$

*Simplification*

*Degree of tolerance attainable for a given steady-state nicotine concentration*

$$E = E_0 + \frac{\alpha C}{C + C_m/C_{m,50}}$$



### 6.4.1. Tolerance models

- Extension of the model of Porchet (Chi *et al.*, 1993) :
- Tolerance of caffeine to its cardiovascular effects

$$\frac{dC_m}{dt} = k_{mo}(C - C_m), \quad C_m(0) = 0$$

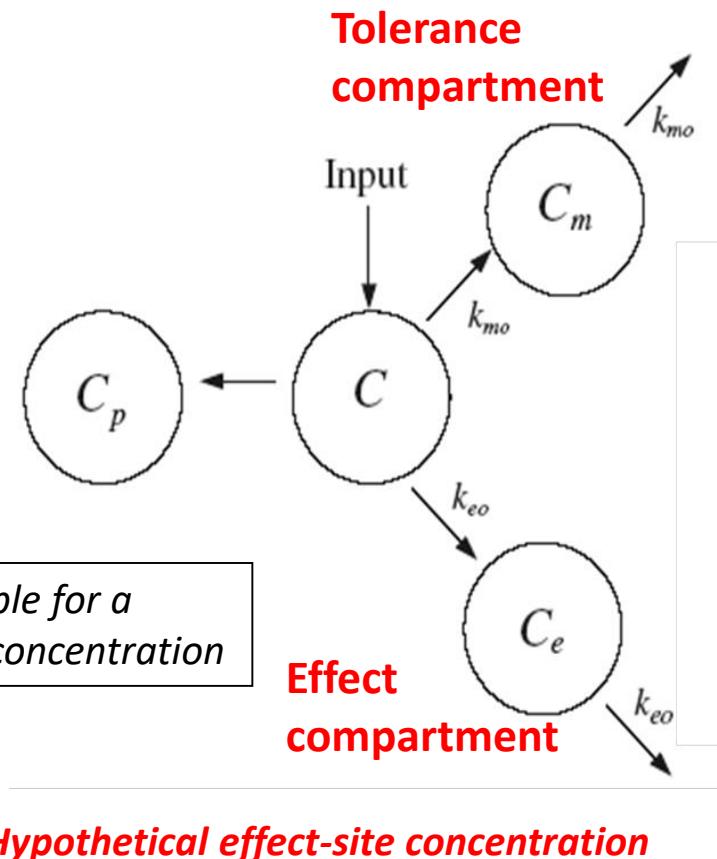
- Using a standard non-competitive antagonist model :

$$E = E_0 + E_{max} \frac{C}{C + EC_{50}(1 + C_m/C_{m,50})}$$

*Simplification*

*Degree of tolerance attainable for a given steady-state caffeine concentration*

$$E = E_0 + \frac{\alpha C_e}{C + C_m/C_{m,50}}$$



### 6.4.1. Tolerance models

More physiological models for tolerance (hyper-sensitization) typically involve some regulatory feedback mechanism which “dumps” (or “amplifies”) the response as a function of current response level.

- An example of such model is proposed by Mandema ([1995](#)) where acute tolerance development of alfentanil electroencephalographic effects in rats.

$$E = E_0 + E_{\max} \frac{C_e^\gamma}{C_e^\gamma + EC_e^\gamma} + \alpha X$$



$X = \text{Feedback response}$

$$X = k_f E(t)^* k_j e^{-k_f t}$$

$\uparrow$   
*Rate of feedback development*

### 6.4.1. Tolerance models

- Tolerance models were developed to model acute (fast occurring) and chronic tolerance (slow occurring)
- These models will allow to predict how the dose regime has to be adapted to observe an effect
- There are drugs which need to be taken at a particular point in time
- Reason: spontaneous changes in the hormone plasma level throughout the day resulting from hormone secretion fluctuations



Time-variant models

## 6.4.2. Time-variant models

- Model that integrated the **hormone secretion fluctuation** for the description of the hormone-lowering effect of a drug and account for the variation in response observed after administration of a **placebo** (Francheteau *et al.*, 1991).
- Change with time in the physiological response during the placebo periods resulted from fluctuations in the concentration of auxiliary variables, which are analogous to the concentrations of two hypothetical endogenous molecules E1 and E2 with opposite action.

Mean level of  $E(t)$  over time after placebo administration

$$E(t) = E_m(t)(1 + E_{max_1}C_1(t) + E_{max_2}C_2(t))$$

Maximal positive and negative effect elicited by the concentrations of  $C_1$  of  $E_1$  or  $C_2$  of  $E_2$

## 6.4.2. Time-variant models

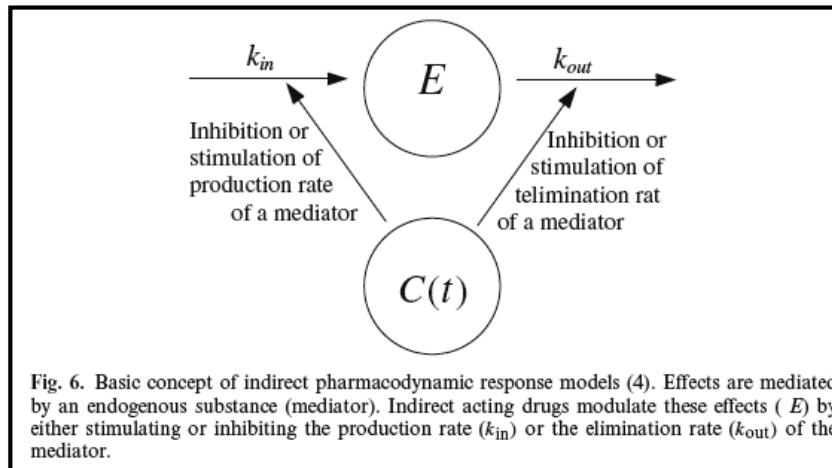
- Indirect response model for the **circadian rhythm** of endogenous cortisol concentrations (Lew *et al.*, 1993) with the production rate parameter,  $k_{in}$ , replaced with a time-dependant function involving the use of a single cosine function.

$$k_{in} = I_m + I_a \cos [(t - t_z)2\pi/24]$$

*Amplitude of the input rate*

*Mean input rate*      *Peak time*

Classical indirect model



## 6.4.2. Time-variant models

- Chronopharmacokinetics of nicotine : modeling the effect of **both meal and circadian** influences on the clearance of nicotine (Gries et al., 1996).

$$Cl(t) = Cl_0(1 + \text{circadian}(t))(1 + \text{meal}(t))$$

Parametric approach :

$$\text{circadian}(t) = A \sin[(t - \varphi)2\pi/\omega]$$

$$\text{meal}(t) = \sum_{k=1}^m \text{Ind}(t - t_k \geq 0) \frac{\alpha\beta}{\beta - \chi} \left( e^{-\beta(t-t_k)} - e^{-\chi(t-t_k)} \right)$$

Non-parametric approach :

Cosine + Exponential functions => Cubic splines

$$\text{meal}(t) = \sum_{k=1}^m \text{Ind}(t - t_k \geq 0) S(t - t_k)$$

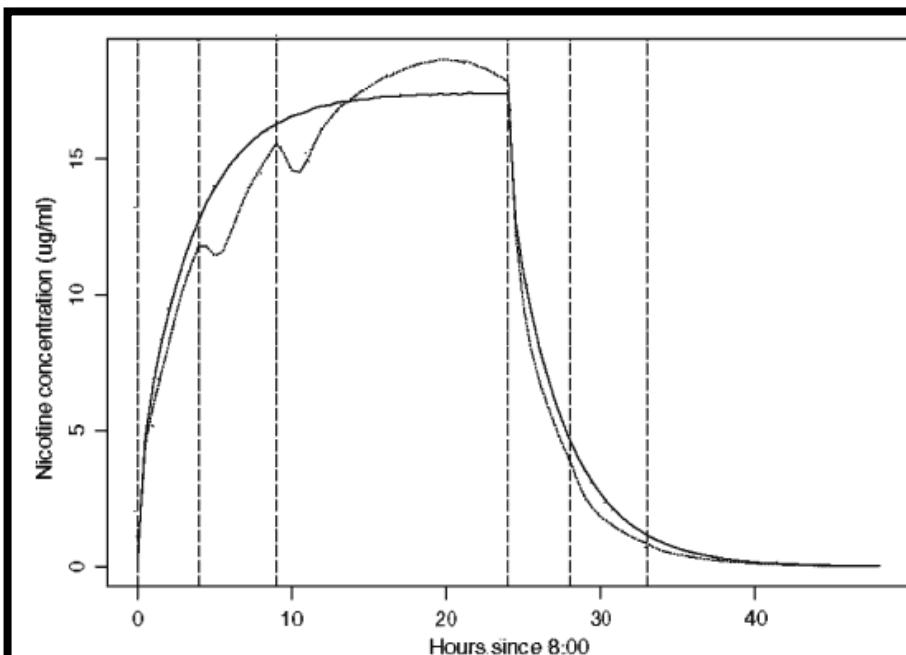


Fig. 10. Influence of time-varying clearance on simulated nicotine concentrations during intravenous infusion of nicotine. Nicotine is assumed to be dosed by constant infusion of 1.25 mg/h for 12 h. The solid line indicates the simulated nicotine concentration assuming constant clearance, the broken line the nicotine concentration assuming time-varying clearance. The vertical dashed lines are times of meal. (Circadian and meal related changes in nicotine clearance could influence cigarette smoking behaviour, smokers typically smoke after meals, and a decline in plasma nicotine concentration due to an increase in clearance could contribute to the urge to smoke. Some smokers smoke less in the evenings, and that behaviour might be contributed to by the lower clearance in the evening compared to the morning).

## 6.4.2. Time-variant models

- Since the concentrations in plasma rather than at the effect site are usually measured, the  $C_e$ -E relationship is obscured by equilibration delays that intervene between the two concentrations, and the plot of E vs. C often shows hysteresis
- For some drugs no model can be identified to fit the experimental data
- For example because the molecular mechanism was unknown



non-parametric and semi-parametric models

### 6.4.3. Non-parametric and semi-parametric models

(a) Non-parametric approach to correct hysteresis (Hull *et al.*, [1978](#)) : The effect site was linked to the plasma by a first-order process represented by a single rate constant ( $k_{eo}$ ), but no assumption regarding the form of the pharmacodynamic model was required.

(b) Model based on Hull *et al.* approach (Fuseau & Sheiner, [1984](#))

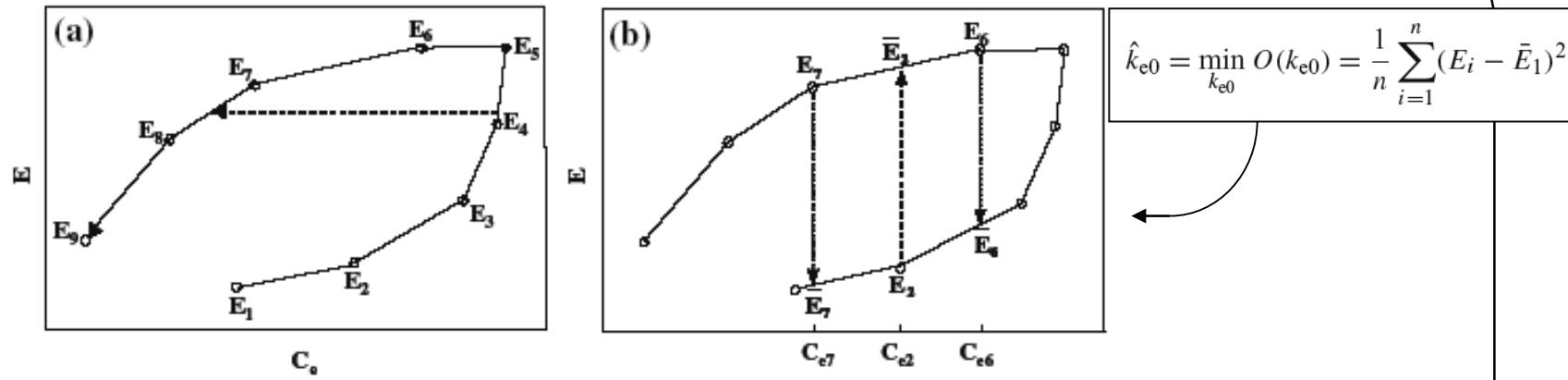


Fig. 11. Effect vs. predicted  $C_e$ . (a) The degree of superposition of the two limbs of the hysteresis is chosen as the horizontal distance at a particular chosen  $E$ .  $k_{eo}$  is adjusted to make  $C_e$  identical at these two times (64). (b) The distance between the two limbs of the curve is evaluated by the vertical difference between each pair of observed ( $E_i$ ) and interpolated ( $\bar{E}_i$ ) effect at the same  $C_{ei}$ .  $k_{eo}$  is chosen to minimize the mean of those squared differences (65).

### 6.4.3. Non-parametric and semi-parametric models

- Unadkat *et al.*, **1986** : Further elaboration which eliminated the requirement of parametric PK model in favour of a non-parametric representation of the concentrations using simple linear interpolating splines.
- Verotta & Sheiner, **1987** : Further extension of the algorithm described by Fuseau (1984) by allowing the simultaneous analysis of multiple data sets.

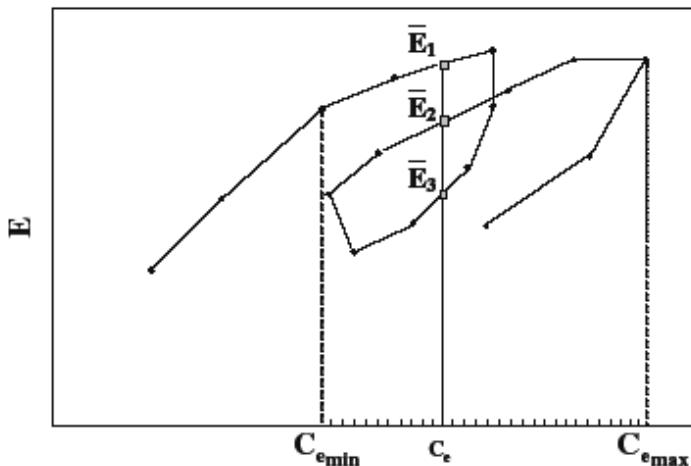


Fig. 12. Collapsing a complex hysteresis loop. (i) The range of overlap  $[C_{e\min}, C_{e\max}]$  is determined, (ii) a grid of equispaced points is defined over the grid, (iii) for each point on the grid predictions are obtained for each limb and (iv) the average of the squared distances between all pairwise combinations of these predictions is obtained and summed for all points of the grid.

### 6.4.3. Non-parametric and semi-parametric models

- Verotta *et al.*, **1989** : Implementation of a procedure to describe both proteresis and hysteresis.

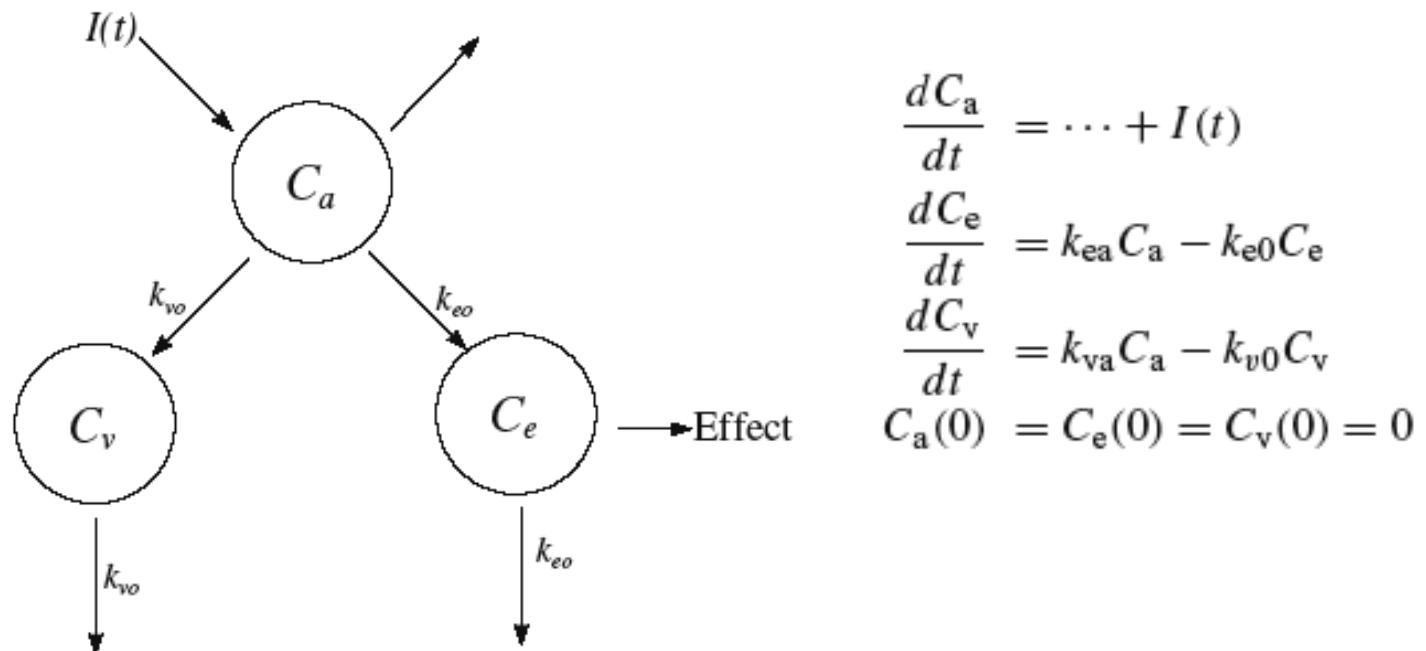


Fig. 14. The concentration in the venous sampling compartment ( $C_v$ ) is deconvoluted to predict the unobserved concentrations in the arterial compartment ( $C_a$ ). Predicted concentrations in the effect compartment ( $C_e$ ) are obtained by numerical convolution of  $C_a$  (see text).  $k_{vo}$  is the first-order loss rate from  $C_v$ .  $I(t)$  is the input function.

#### 6.4.4. Population PK/PD modeling

!!! Variability of response among individuals in a population !

- When individual response data are available (limited number of individuals in the same design and number of measurements as large as possible) => **Standard Two-Stage Method**
- When data derive from studies performed on a greater number of individuals in a different design usually with sparse and unbalanced data => **Nonlinear Mixed-Effect Regression Model**
- (**Bayesian hierarchical model**)

##### 1) The **Standard Two-Stage Method** :

This method supposes a **first stage** in which the **parameters** of each **individual** are estimated by minimizing an **objective function** and assuming identical effect variances.

Using those estimates, the **second stage** calculates **population** mean values and **interindividual** variability of parameters.

#### 6.4.4. Population PK/PD modeling

##### 2) The **NONlinear Mixed-Effect regression Model** :

This approach allows simultaneous analysis of all data in the studied population, using PK or PD models to describe typical trends (population means) and individual profiles.

In these models, the parameters of each individual are modeled in terms of both fixed and random effects. **Fixed effects** account for large intra- and interindividual differences in the value of parameter and covariates. **Random effects** are applied to account for unexplained inter- and intraindividual variability.

General representation of these models is

$$y_{ij} = f(\phi_i, D, t_{ij}) + \varepsilon_{ij}$$

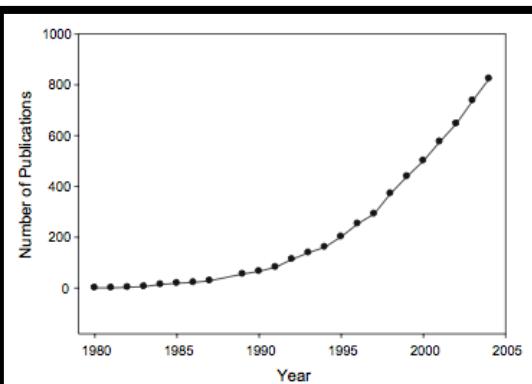


Figure 1. Number of articles published each year as reported by MEDLINE using the keywords “population pharmacokinetics” or “NONMEM.”

Bonate (2005) AAPS J

⇒ Development of **NONMEM** computer programs :  
NONMEM V/VI/VII/..., WinNonmix®, ADAPT,  
PKBugs, MONOLIX, PopKinetics, ...

#### 6.4.4. Population PK/PD modeling

NONMEM

**PROS** : few measurements per subjects, easily applied in the clinic and drug development, specific populations of patients, drug interactions or tolerances to treatment, ...

**CONS**: statistical complexity !

- use of **many models** (structural, interindividual, intraindividual and covariate);
- **numerous statistical assumptions** (random and fixed effects distribution);
- **variety of estimation methods** (algorithms and approximations).

## 6.4.4. Population PK/PD modeling NONMEM

Criteria used for selecting the final model were

- graphics (visual inspection)
- Akaike criterion (estimates the quality of one each model relative to the other models; has a penalty term for the number of parameters)
- Bayesian information criteria (partially based on likelihood, and closely related to Akaike criterion; penalty term for the number of parameters higher as in Akaike)
- Likelihood (gives the probability of one model compared to the other)
- objective function (gives an overall error in the prediction using a single model based on the experimental data)
- likelihood ratio test (expresses how many times more likely the data are under one model compared to the other)
- residuals distribution (residuals are estimates of experimental error using the calculated data of a model as reference).