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Delayed Effect Models

Division of Pharmacokinetics & Drug Therapy
Department of Pharmaceutical Biosciences
Uppsala University, Sweden

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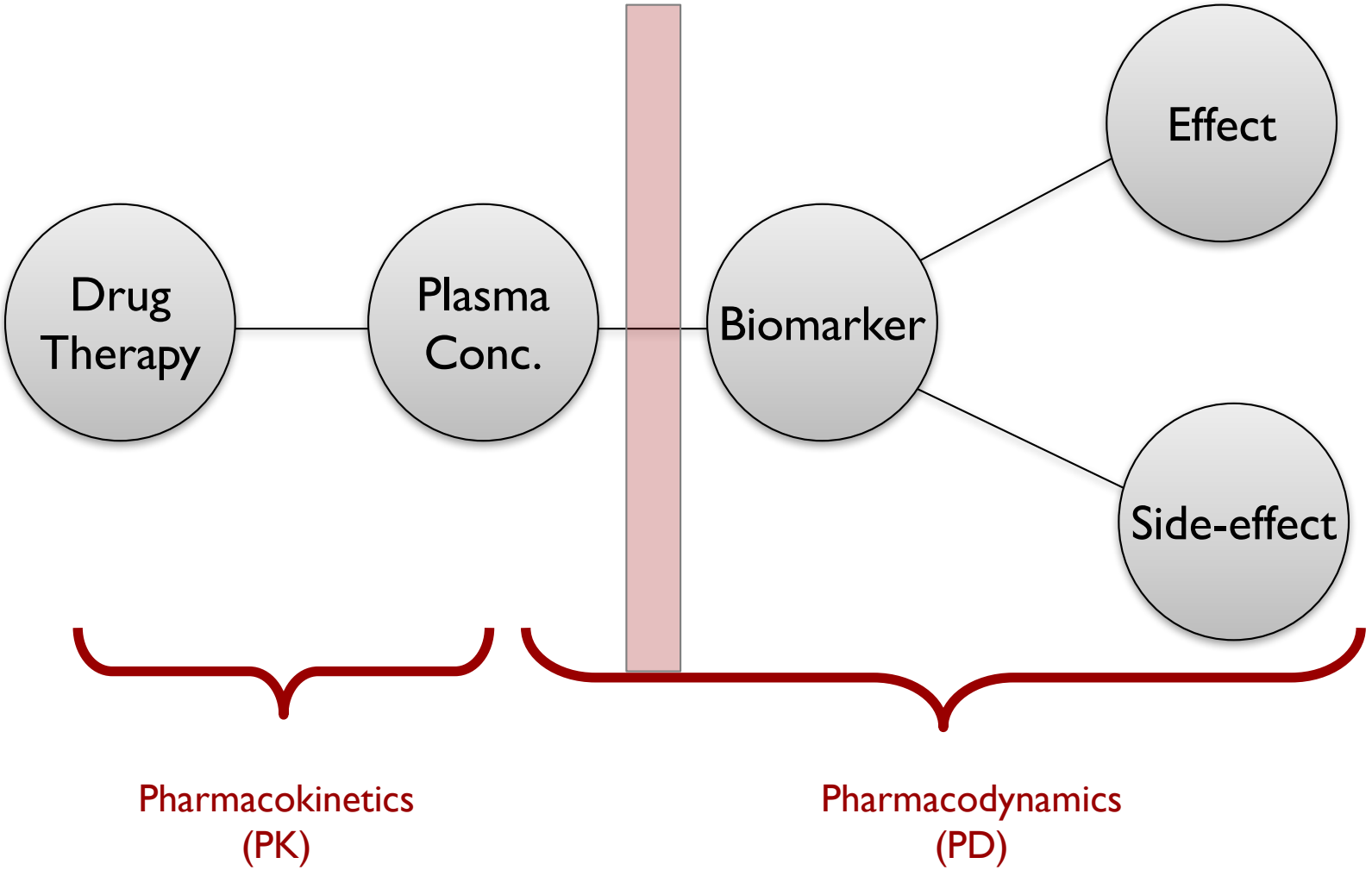
PKPD relationship

Effects of a drug could be delayed compared to PK



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Outline

- Diagnosing delayed effects
- Reasons for delayed effects
- Models for delayed effects
  - Effect compartment model
  - Binding model
  - Indirect response model
  - Transduction model

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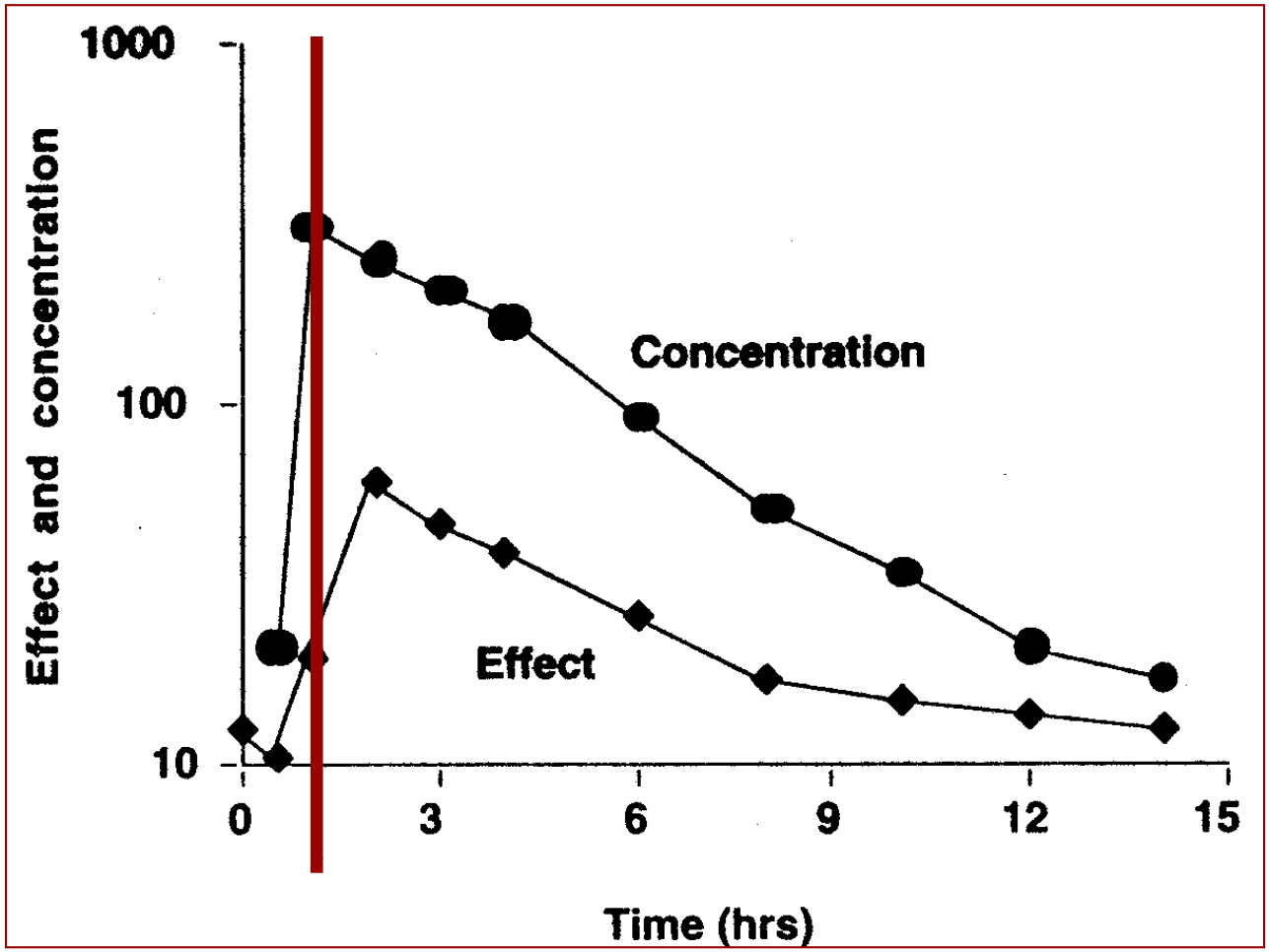
Diagnosing delayed effect

We talk of delayed effects when PK peak comes before PD peak

Plasma concentration and effect versus time



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Reasons for effect delay

Several reasons for effect delay are possible

- Active metabolite
- Non equilibrium
  - Slow delivery of drug to site of action (effect compartment)
  - Receptor interaction (dR*/dt) may be slow (binding model)
- Indirect response
  - Drug influences synthesis/degradation of endogenous substance
  - Slow transducer process lead to observed effect

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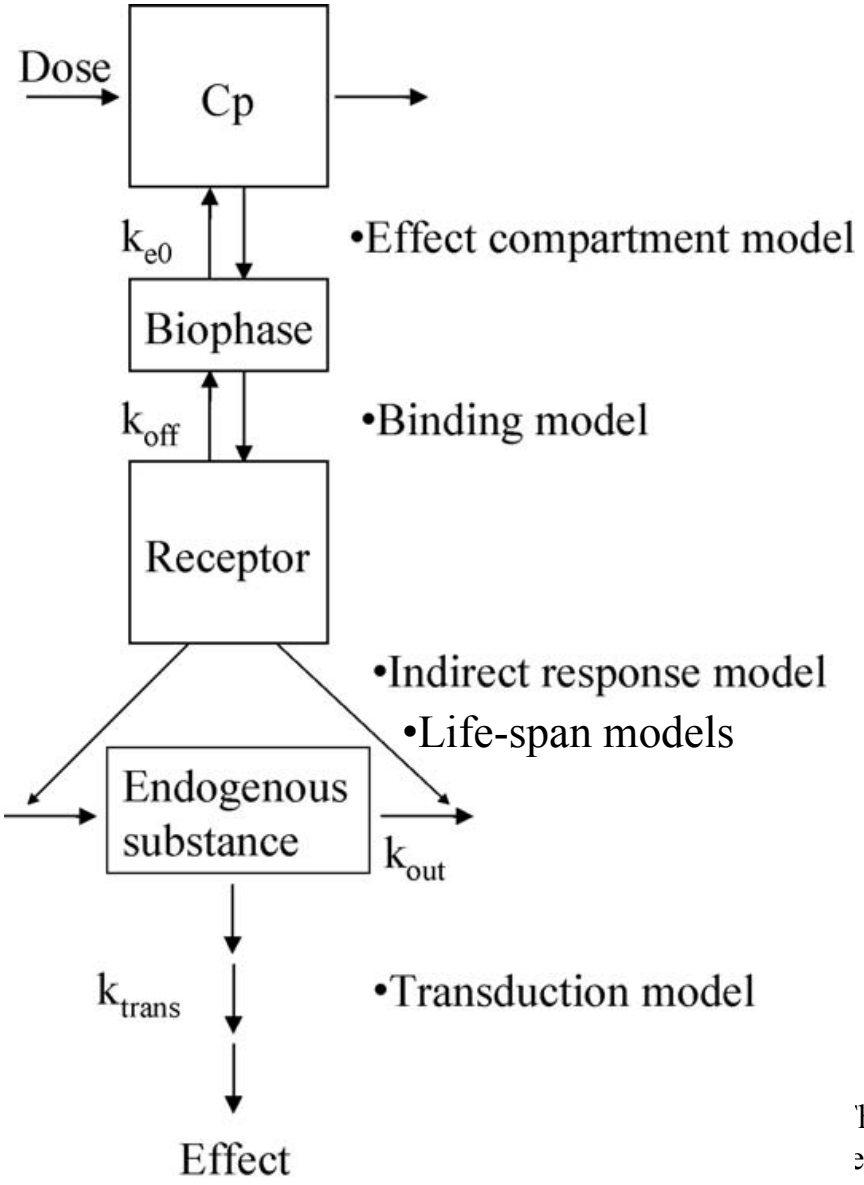
Drug effect delays



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Effect compartment (link) model

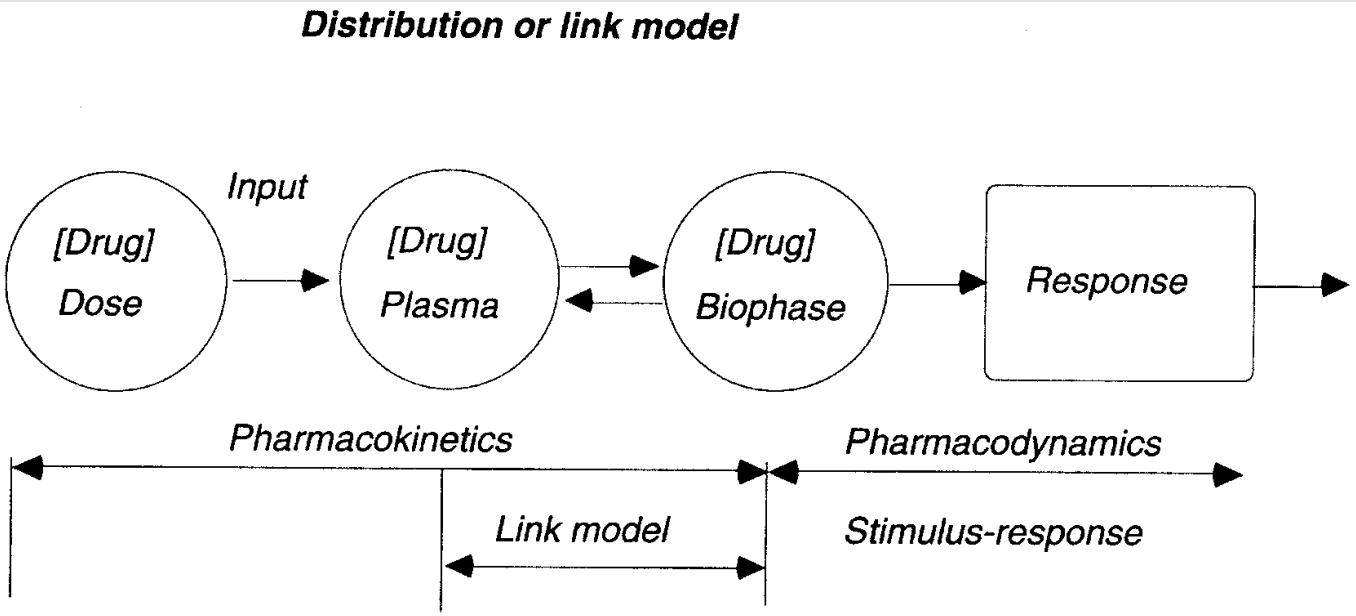

Figure 4.33 *Schematic presentation of the relationship between drug kinetics, the link and drug dynamics.*

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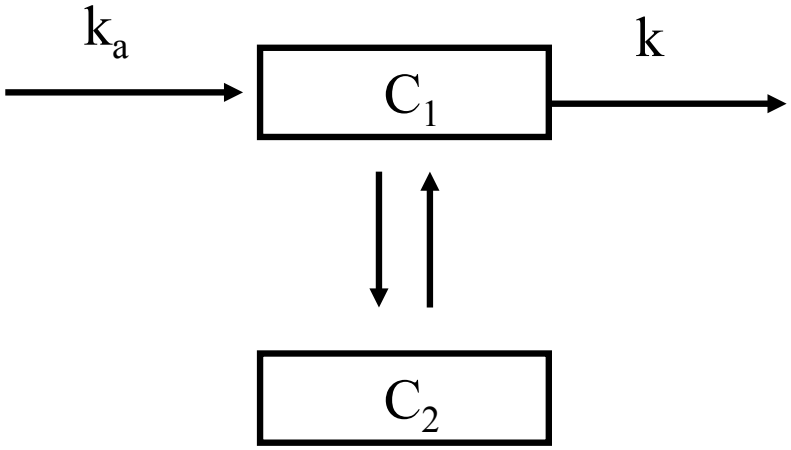
Effect compartment (link) model

Drug conc measured in the target tissue is used to predict PD

Drug effect related to the concentration in the peripheral compartment



$$E = \frac{C_2 \cdot E_{max}}{C_2 + EC_{50}}$$

Example: Pulmonary and cardiac effects of fenoterol
*Hochhaus *et al.*, 1992.

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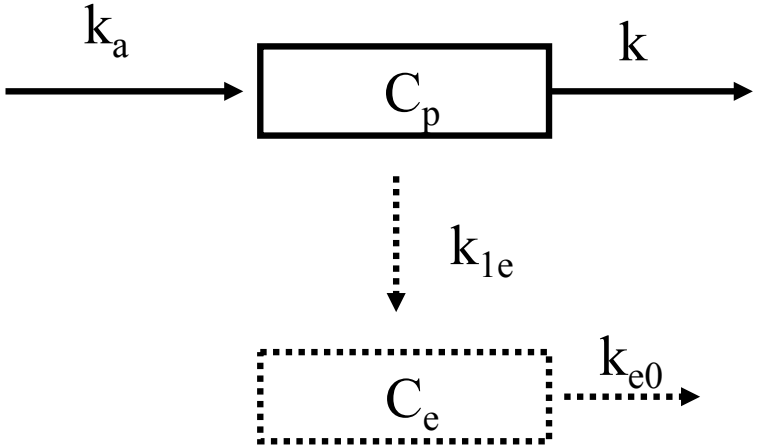
Effect compartment (link) model

Target tissue conc rarely available, use PD to predict target PK

Drug effect related to the concentration in the effect compartment



$$E = \frac{C_e \cdot E_{max}}{C_e + EC_{50}}$$

Example: Paralytic effect of d-tubocurarine
*Sheiner *et al*. 1979.

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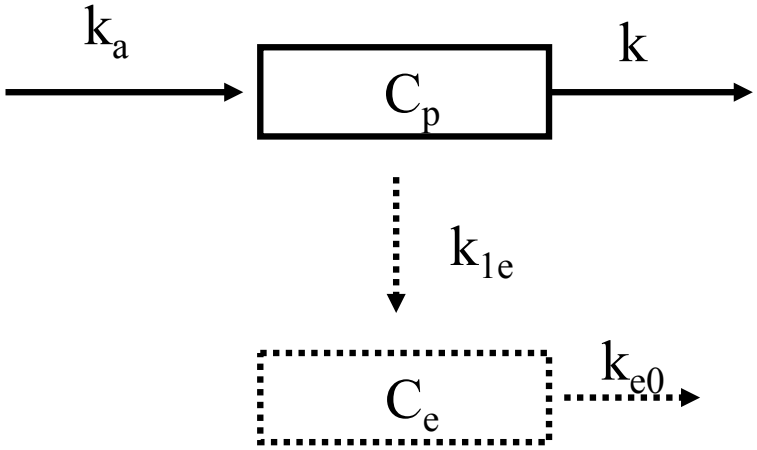
Effect compartment (link) model

Assumptions with the model

Changes in dose does not influence the time of maximum effect (unless non-linear PK)

The mass transfer to and from the effect compartment is negligible and does not affect the pharmacokinetics



$$dA/dt = dose \cdot ka - k \cdot A, Cp = \frac{A}{Vc}$$

$$dCe/dt = k_{1e} \cdot Cp - k_{e0} \cdot Ce$$

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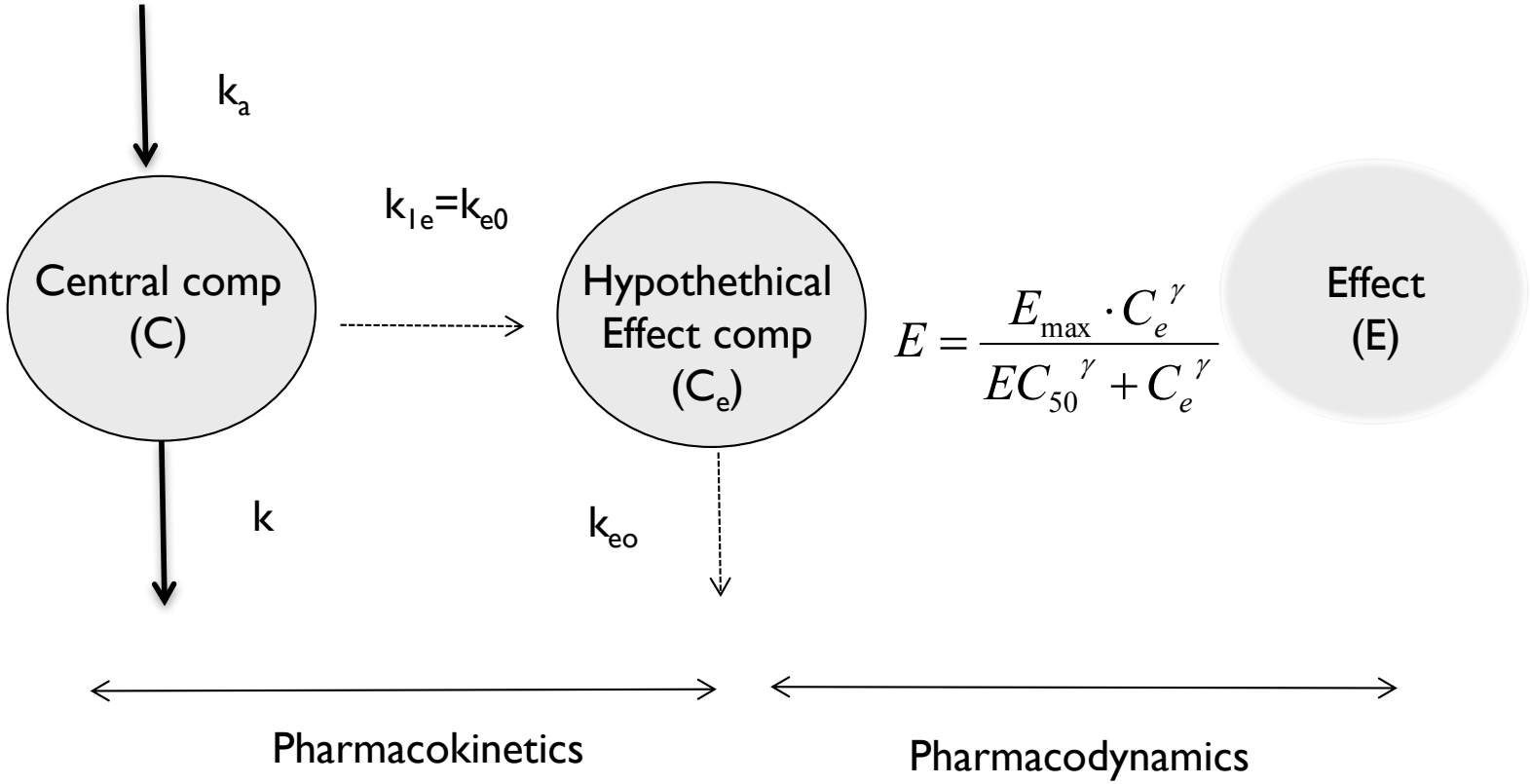
Effect compartment model



$$\frac{dC_e}{dt} = k_{e0} \cdot C - k_{e0} \cdot C_e = k_{e0} \cdot (C - C_e)$$

Sheiner et al CPT 1979

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Effect compartment model

Different ways to model Ce:

1. Differential equation of Ce(t)

$$\frac{dC_e}{dt} = k_{e0} \cdot C - k_{e0} \cdot C_e = k_{e0} \cdot \left(C - C_e\right)$$

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Effect compartment model

Different ways to model Ce:

2. Closed form of Ce (analytical approach)

1-comp disposition PK model

$$C_e = \frac{D \cdot k_{e0}}{V \cdot (k_{e0} - k)} \cdot \left[e^{-k \cdot t} - e^{-k_{e0} \cdot t} \right]$$

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Effect compartment model

1-comp disposition + 1st order abs single PK model

$$C_e = \frac{F \cdot D \cdot k_a \cdot k_{e0}}{V} \cdot \left[\frac{e^{-k \cdot t}}{(k_a - k)(k_{e0} - k)} + \frac{e^{-k_a \cdot t}}{(k - k_a)(k_{e0} - k_a)} + \frac{e^{-k_{e0} \cdot t}}{(k - k_{e0})(k_a - k_{e0})} \right]$$

2-comp disposition + 1st order abs PK model

$$C_e = \frac{F \cdot D \cdot k_a \cdot k_{e0}}{V_c} \cdot \left[\begin{array}{l} \frac{(k_{21} - \alpha) e^{-\alpha \cdot t}}{(k_a - \alpha) \cdot (\beta - \alpha) \cdot (k_{e0} - \alpha)} + \frac{(k_{21} - k_a) \cdot e^{-k_a \cdot t}}{(\alpha - k_a) \cdot (\beta - k_a)(k_{e0} - k_a)} + \\ \frac{(k_{21} - \beta) \cdot e^{-\beta \cdot t}}{(k_{e0} - \beta) \cdot (k_a - \beta) \cdot (\alpha - \beta)} + \frac{(k_{21} - k_{e0}) \cdot e^{-k_{e0} \cdot t}}{(\alpha - k_{e0}) \cdot (\beta - k_{e0})(k_a - k_{e0})} \end{array} \right]$$

Colburn J Pharmcokin Biopharm 1981

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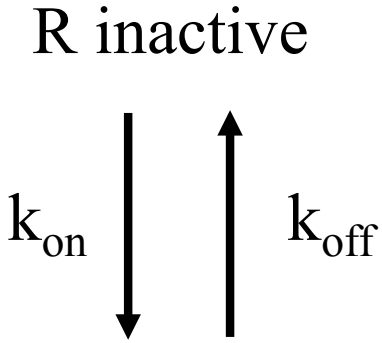
(Receptor) Binding model



$$\mathbf{K_D} = k_{off} / k_{on}$$

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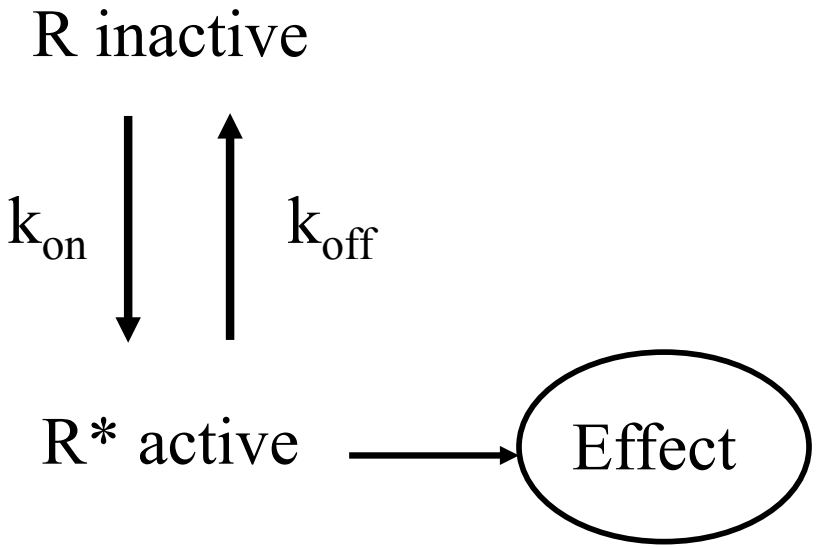
(Receptor) Binding model

Effects are observed when "R" is active



$$\mathbf{K_D} = k_{off} / k_{on}$$

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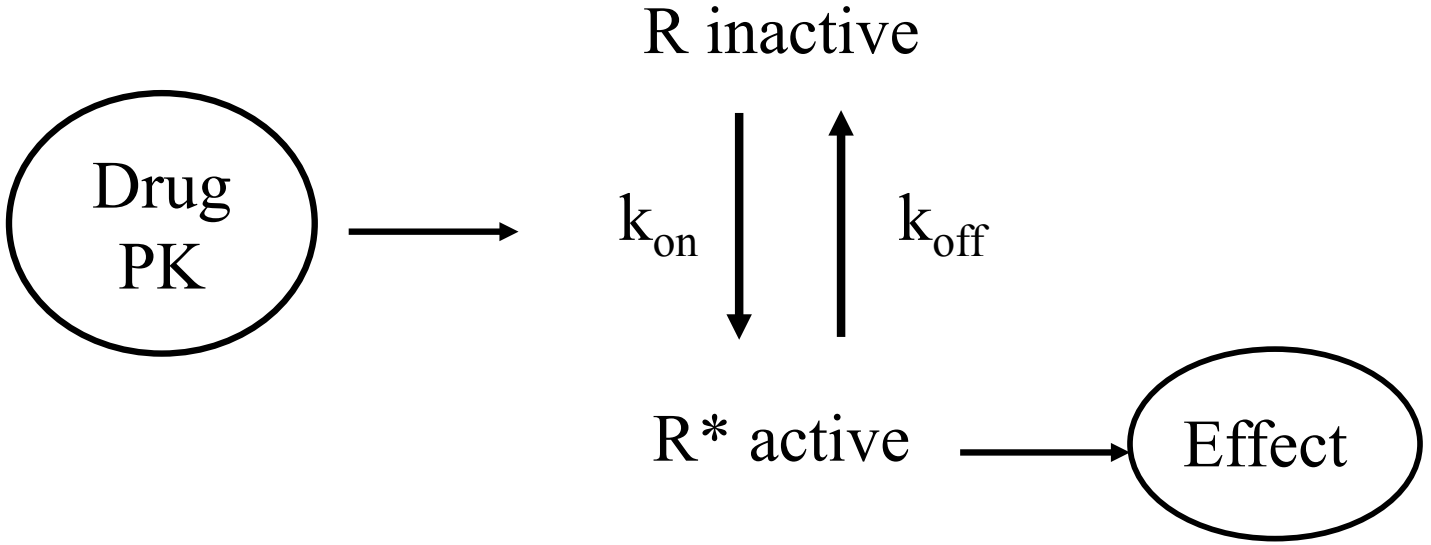
(Receptor) Binding model

Drug may act as agonist or antagonist

$$\mathbf{K_D} = k_{off} / k_{on}$$



For example for agonist:

dRinact/dt = -Kon*CP*Rinact + Koff*Ract

dRact/dt = Kon*CP*Rinact - Koff*Ract

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Indirect response (turnover) models

$$dR/dt = k_{in} - R \cdot k_{out}$$

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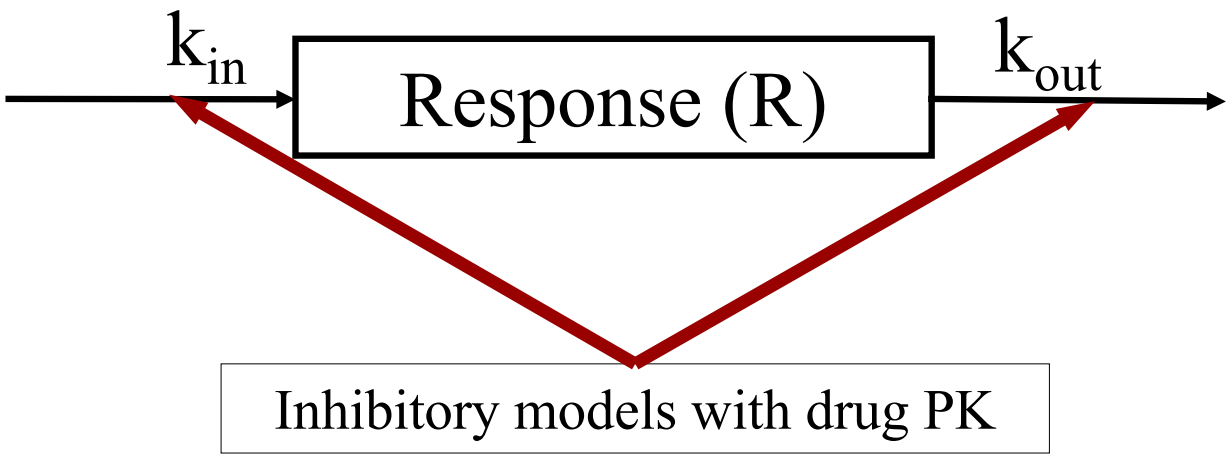
Indirect response (turnover) models

Four basic model for indirect response

Inhibition of k_{in} or k_{out}



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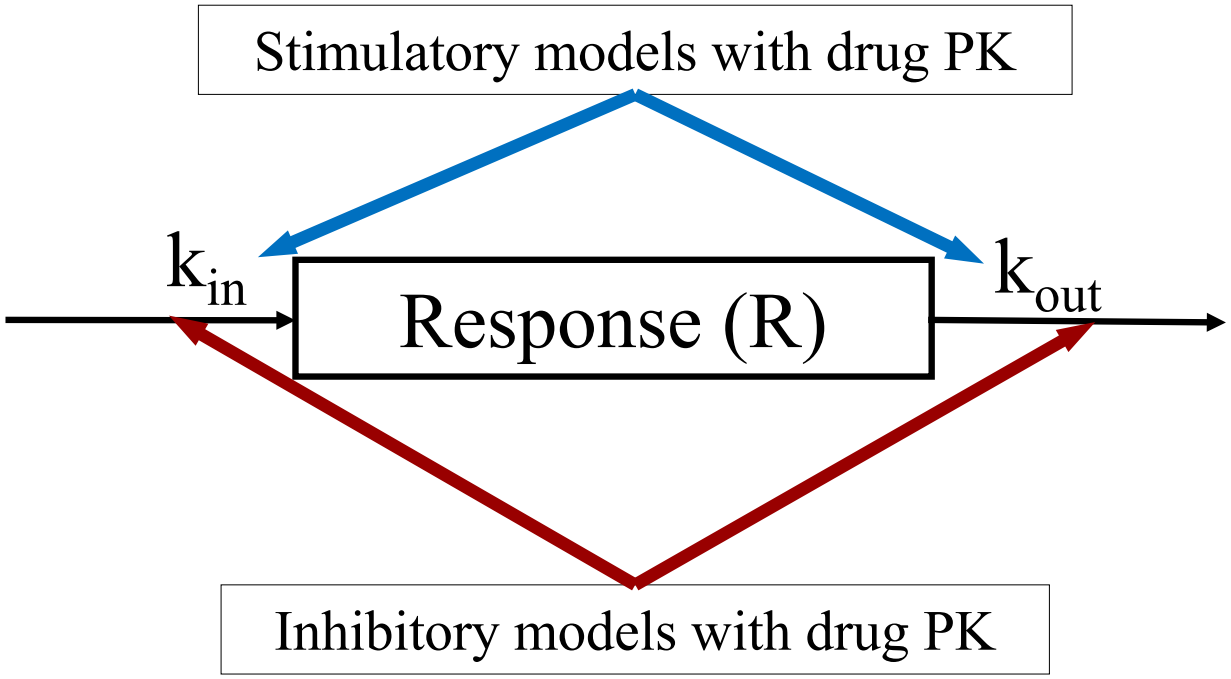
Indirect response (turnover) models

Four basic model for indirect response

Stimulation of k_{in} or k_{out}



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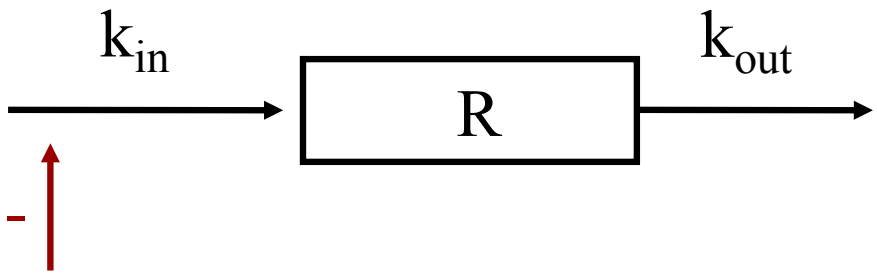
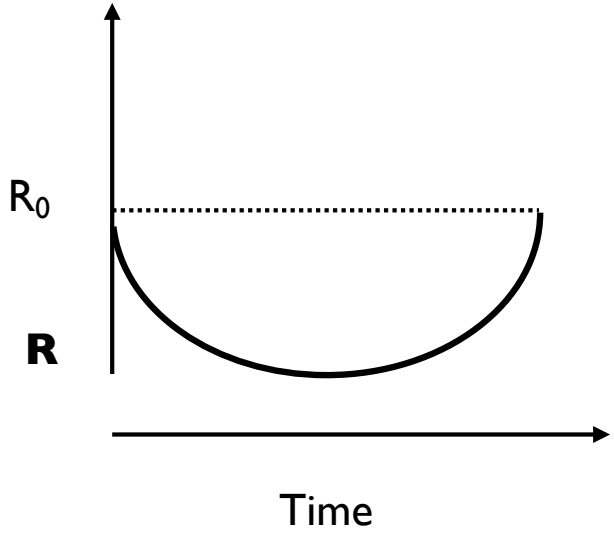
Indirect response (turnover) models

A drug could inhibit the production of "R"



$$dR/dt = k_{in} \left(1 - \frac{C_p}{C_p + IC_{50}}\right) - k_{out} \cdot R$$



Example: Warfarin on the prothrombin complex activity

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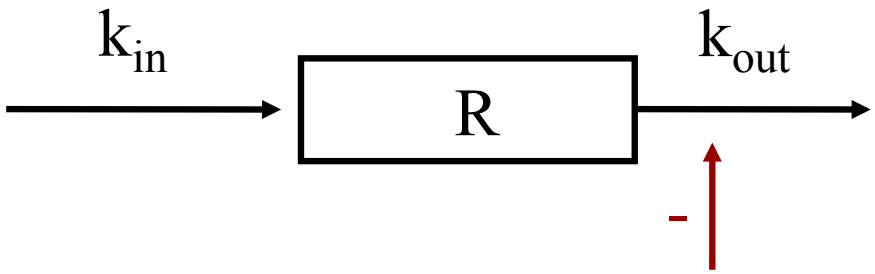
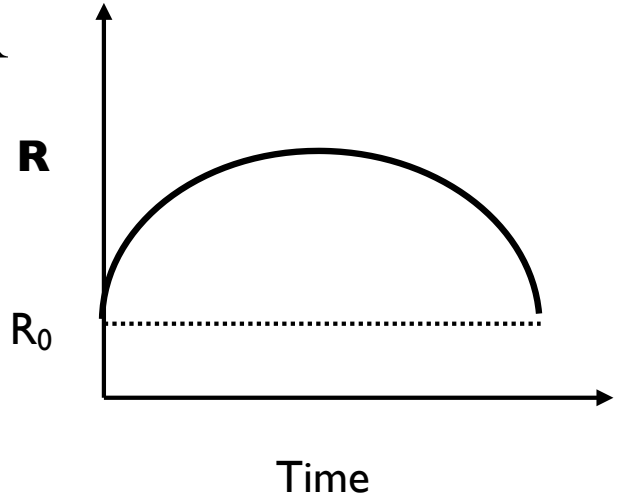
Indirect response (turnover) models

A drug could inhibit the removal of "R"



$$dR/dt = k_{in} - k_{out} \left(1 - \frac{C_p}{C_p + IC_{50}}\right) \cdot R$$



Example: Cholinesterase inhibitors SSRIs /cocaine

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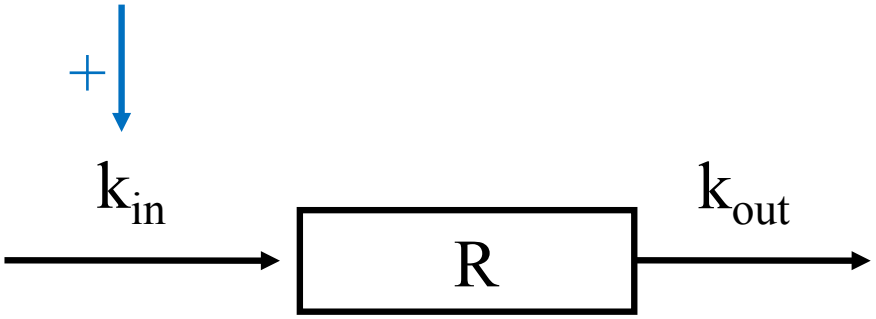
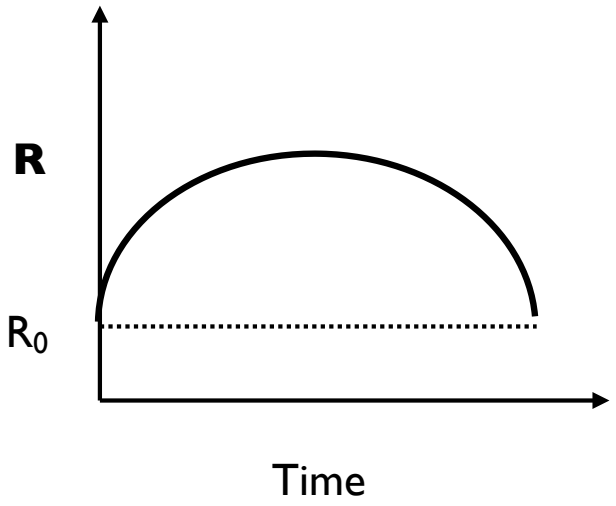
Indirect response (turnover) models

A drug could stimulate the production of "R"



$$dR/dt = k_{in} \left(1 + \frac{Emax \cdot C_p}{C_p + EC_{50}}\right) - k_{out} \cdot R$$



Example: Terbutaline on cAMP in smooth musculature

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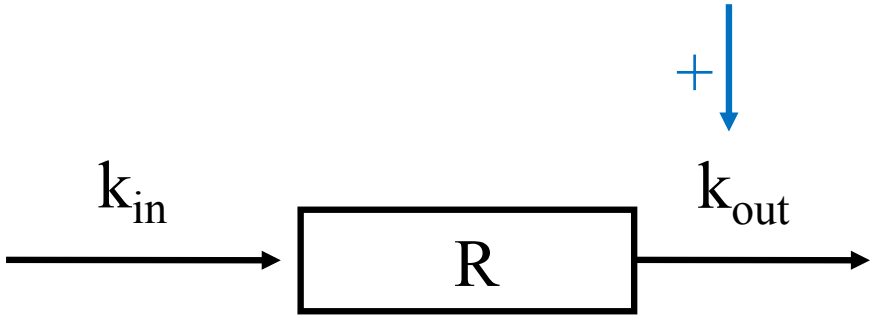
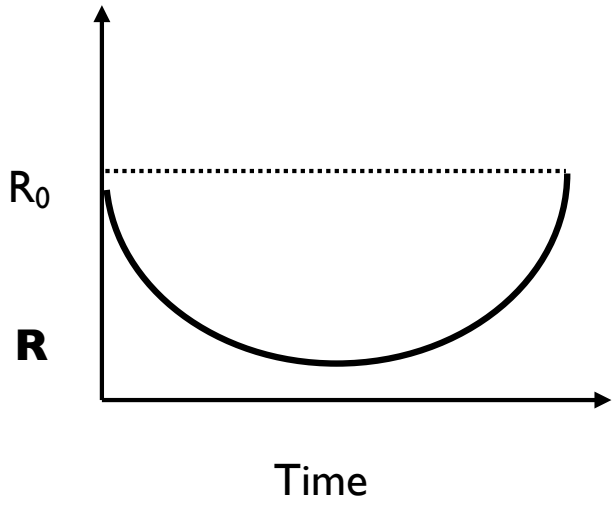
Indirect response (turnover) models

A drug could stimulate the removal of "R"



$$dR/dt = k_{in} - k_{out} \left(1 + \frac{Emax \cdot C_p}{C_p + EC_{50}}\right) \cdot R$$



Example: Terbutaline (on plasma potassium levels)

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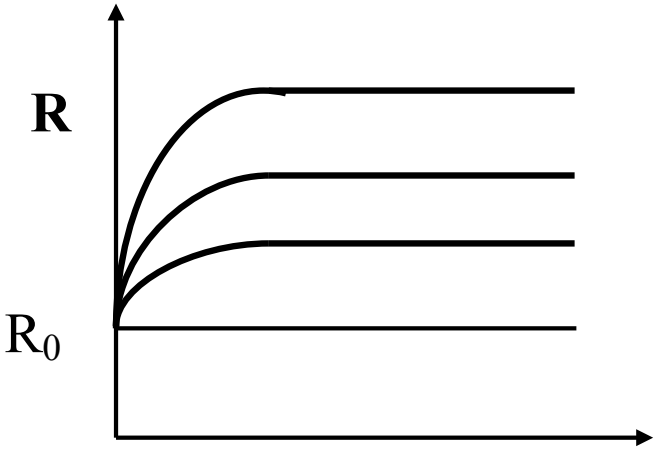
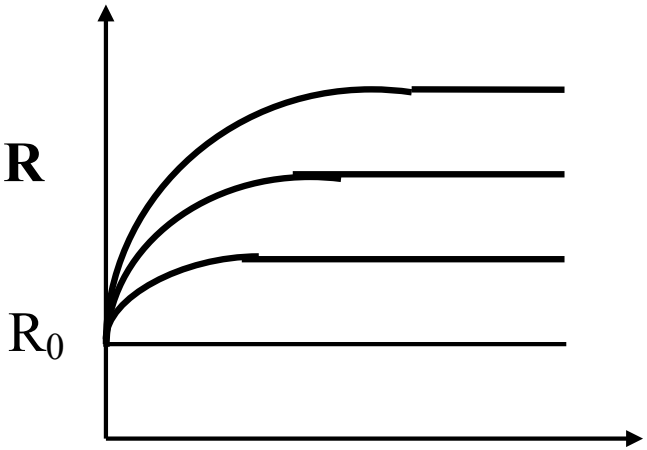
Indirect response (turnover) models

Stim. on k_{in} and inhib. of k_{out}, similar effect with different delay

$$dR/dt = k_{in} - R \cdot k_{out}$$



Stimulation of k_{in}



Inhibition of k_{out}

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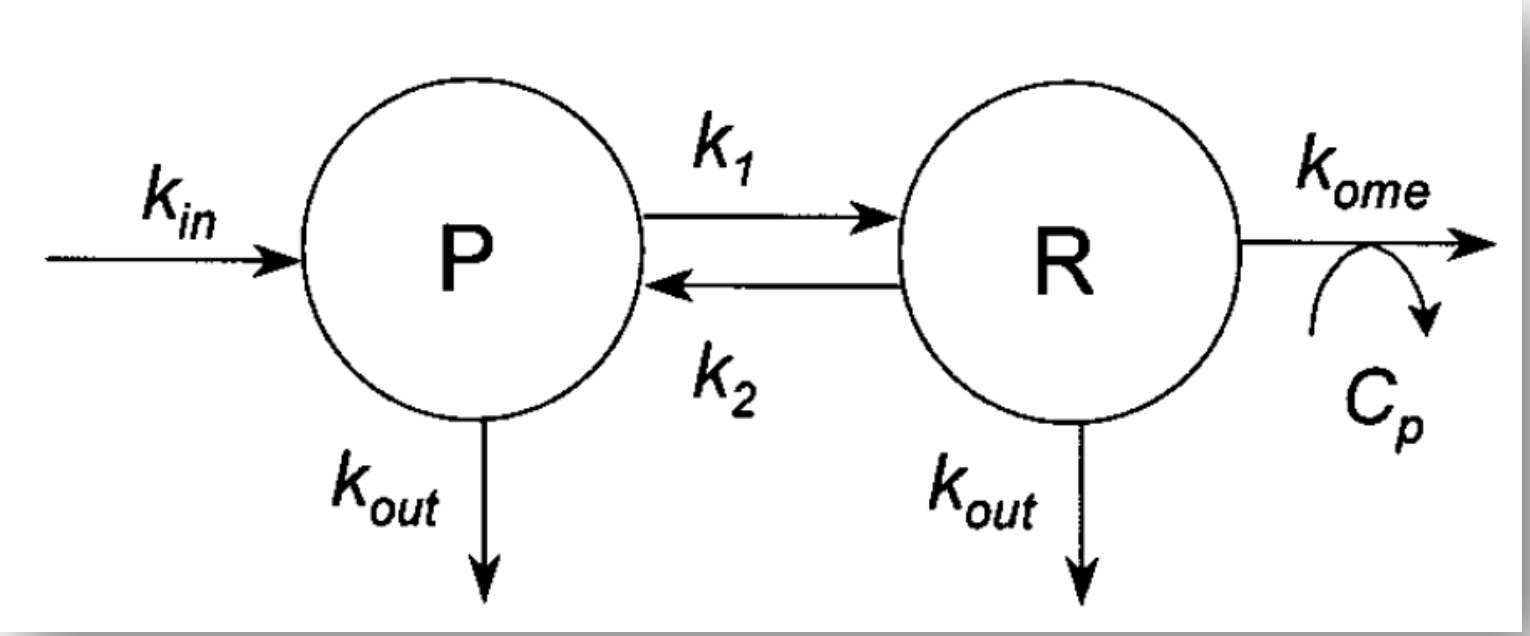
Indirect response (turnover) models

Example of model - omeprazol

A Turnover model of Irreversible Inhibition of Gastric Acid Secretion by Omeprazole in the Dog

*Äbelö *et al*



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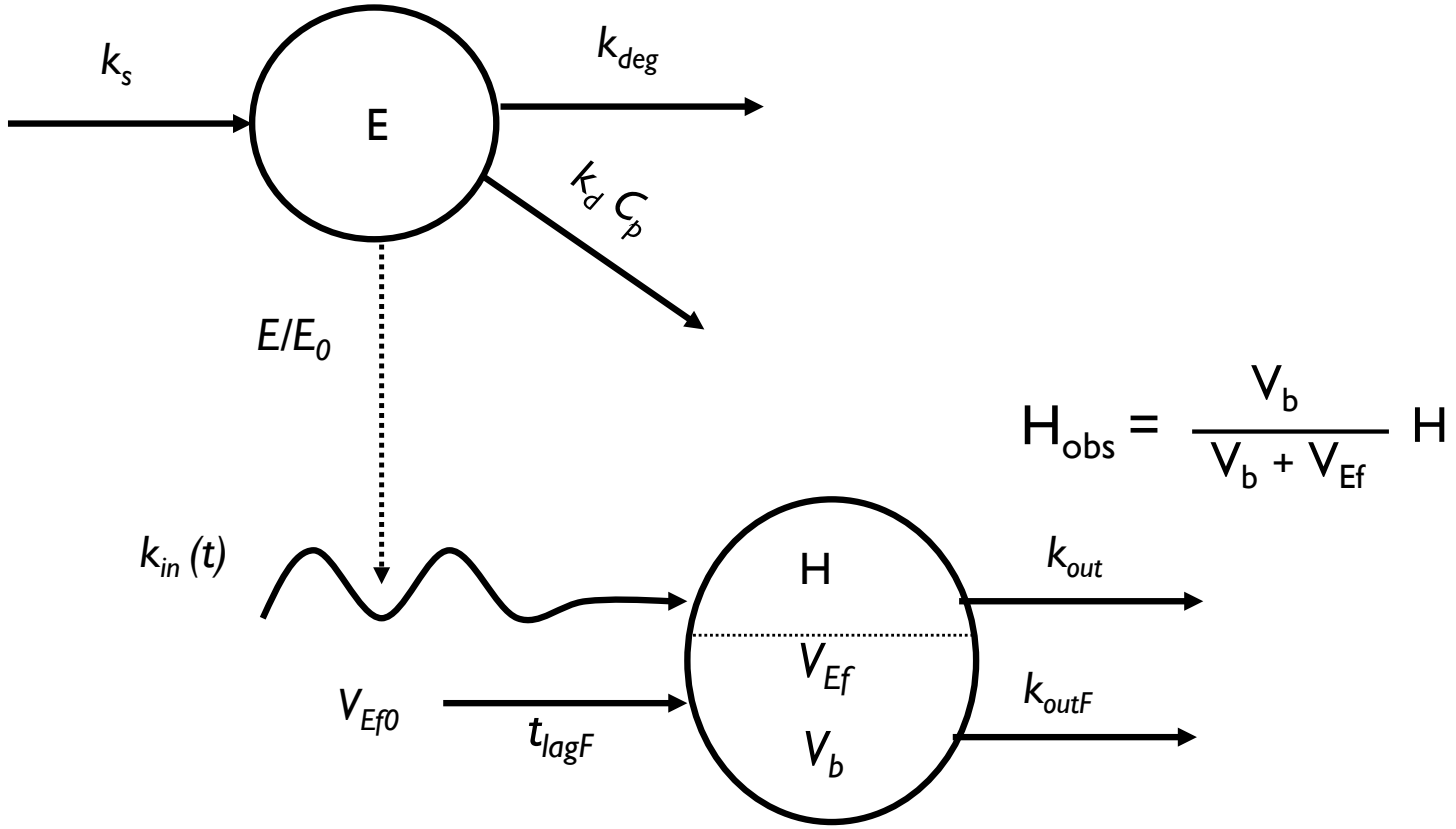
Indirect response (turnover) models

Example of model - lanzoprazol

Pharmacodynamic Modelling of Lansoprazole using an Indirect Irreversible Response Model

*Puchalski *et al*



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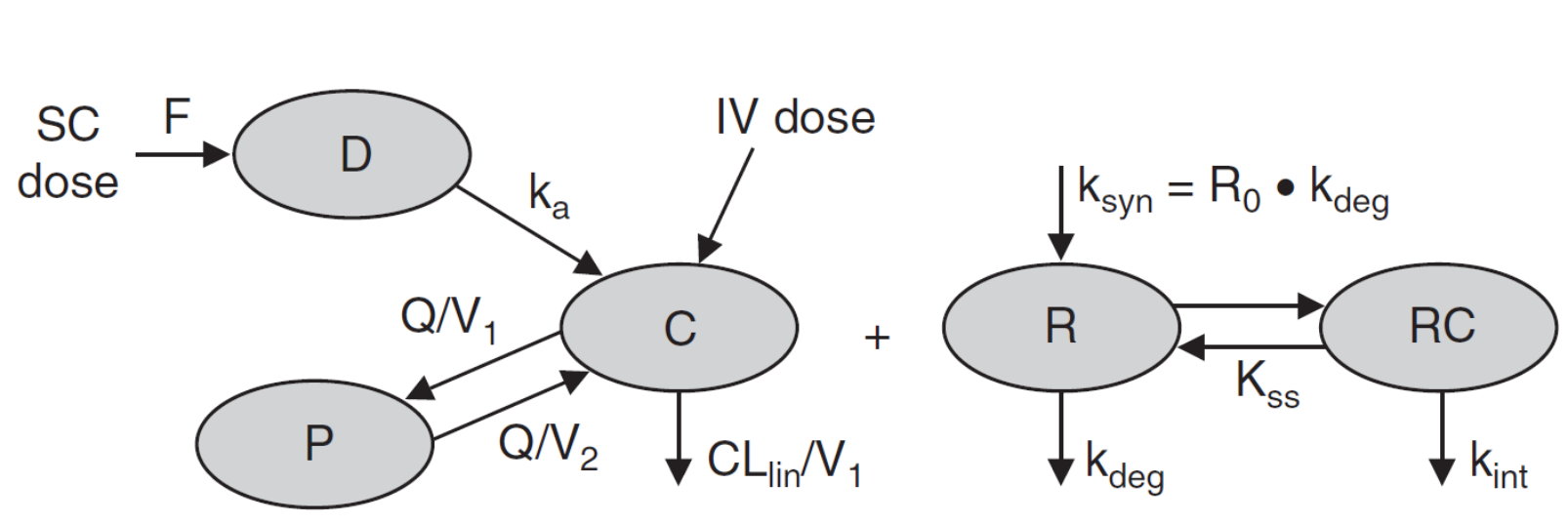
Target mediated drug disposition

Example of model with receptor binding and indirect response



*Gibiansky, 2012

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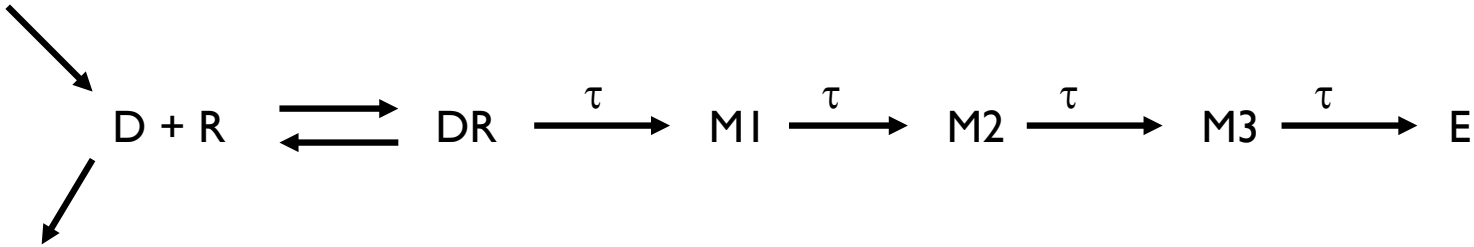
Transduction models

Pharmacological effects produced by signal transduction (cascade responses)



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Transduction models

Effect delay differs if signaling in cell membrane or nuclear

Two classes of receptors involved

Cellmembrane

- e.g. insulin → insulin receptor on cellmembrane → phosfolipases, nucleotidcyclases (cAMP, cGMP) → glucose carrier, Ca-ion channel etc. → → observed effect.

Cytosolic/nuclear

- e.g., corticosteriods → receptor in cytoplasm → translocation to nucleus → interacts with GRE on DNA → transcription/translation controlled → → observed effect.

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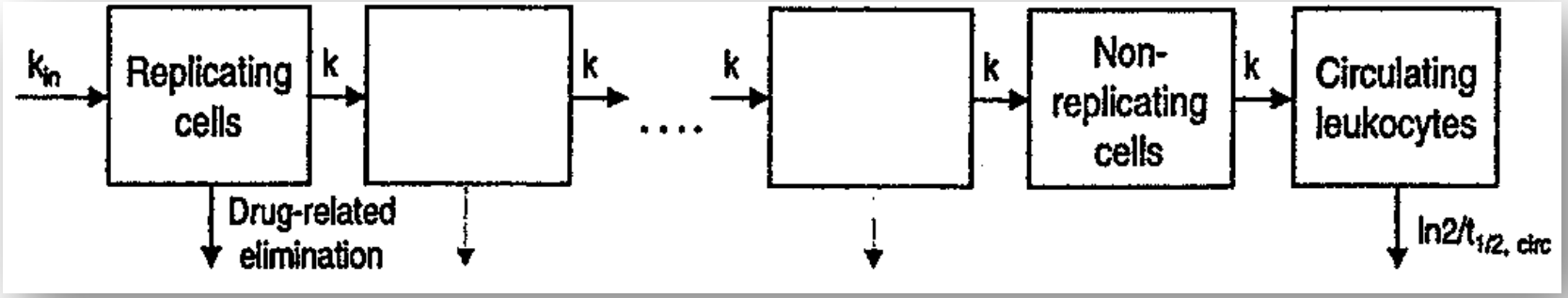
Transduction models

Example of transduction model with transit compartments

Semi-physiological model for the time course of leukocytes.

*Friberg *et al.* 2000



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Discrimination between models

Prior

- knowledge of mechanisms
- knowledge of rate limiting step(s)
- knowledge of parameter values
- empirical experience

Goodness-of-fit of model to data

- Numerical (likelihood of model given data)
- Graphical (agreement between predictions/simulations and observed data)

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Summary

Multiple reasons why effects could be delayed (compared to plasma PK)

- Slow equilibration to target tissue
  Effect compartment model
- Slow activation of receptor
  Binding model
- Drug affecting production/removal of endogenous substance
  Indirect response model
- Drug activates a cascade of events leading to effect
  Transit compartment model

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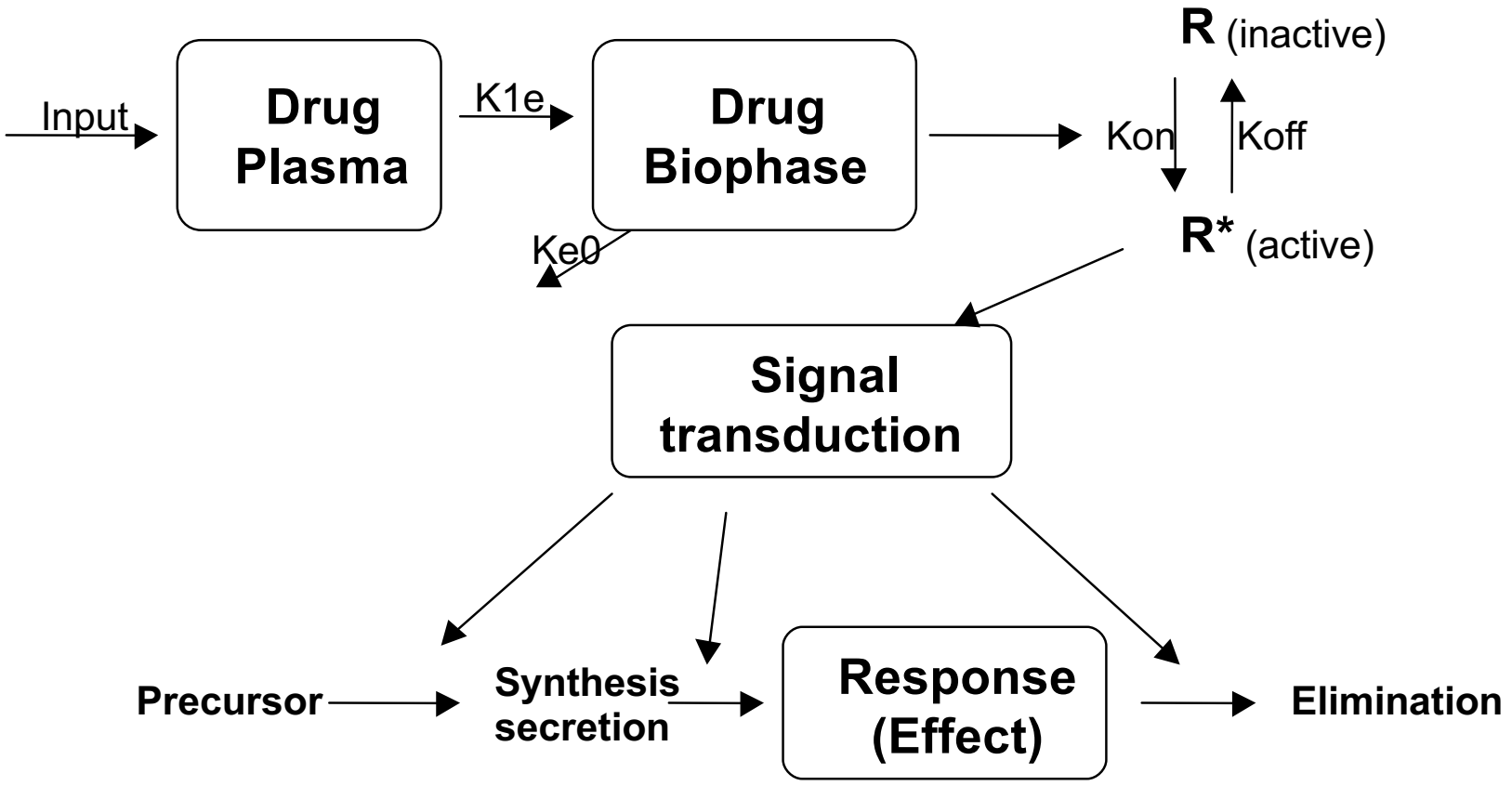
The full model of effect delay



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