Some principles of modeling and simulation in preclinical research and drug development

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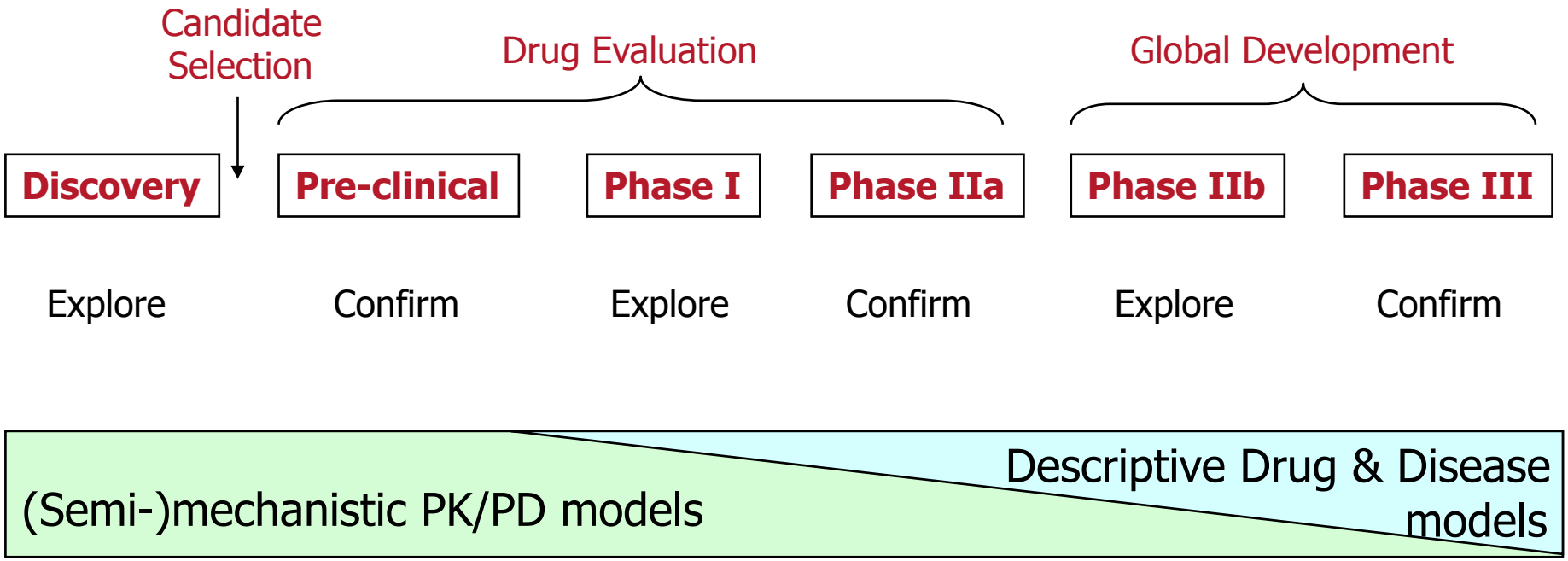
Exprimo

Modelling and simulations throughout drug development:

Objectives of M&S should focus on the next phase(s) of development to support decisions that need to be made



Mechanistic *versus* descriptive (empirical) models:

Mechanistic

- Early stages of development
- Good understanding of system
- Interpretable parameters
- Interpolation and extrapolation
- May require less data

Descriptive

- Late stages of development
- Fair understanding of system (grey box)
- Less meaningful parameters
- Interpolation
- Usually requires a lot of data

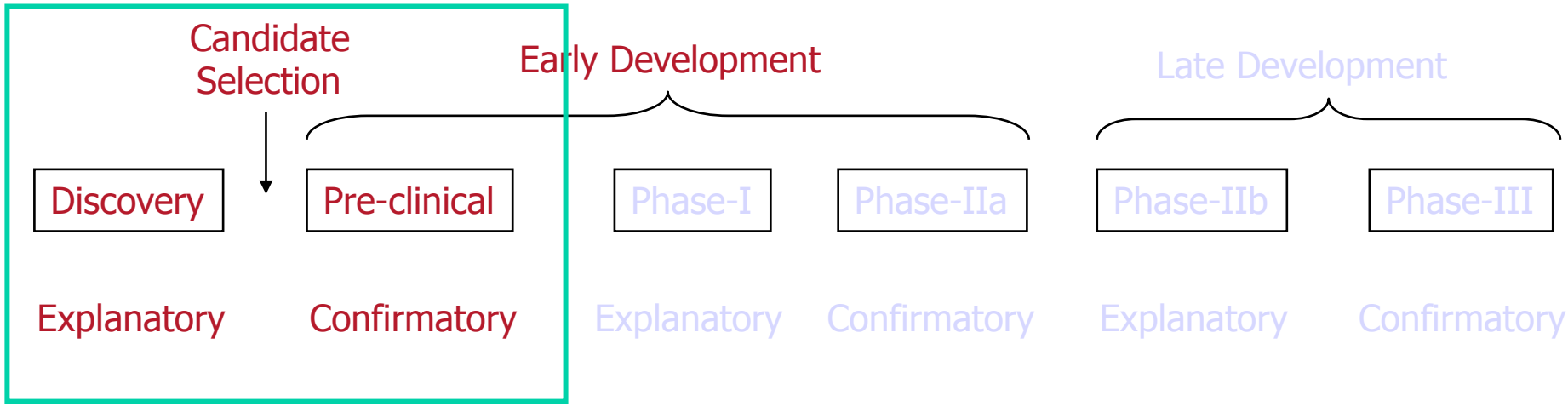
M&S throughout Discovery and Pre-clinical:

Current phase

- Feasibility assessment mechanism of action
- Define metrics candidate selection
- Assess safety margin
- Combined meta-analysis and objective review of all discovery and pre-clinical data

Next phase

- Evaluation and selection appropriate biomarker(s)
- Optimize designs of early ph-I studies with biomarkers

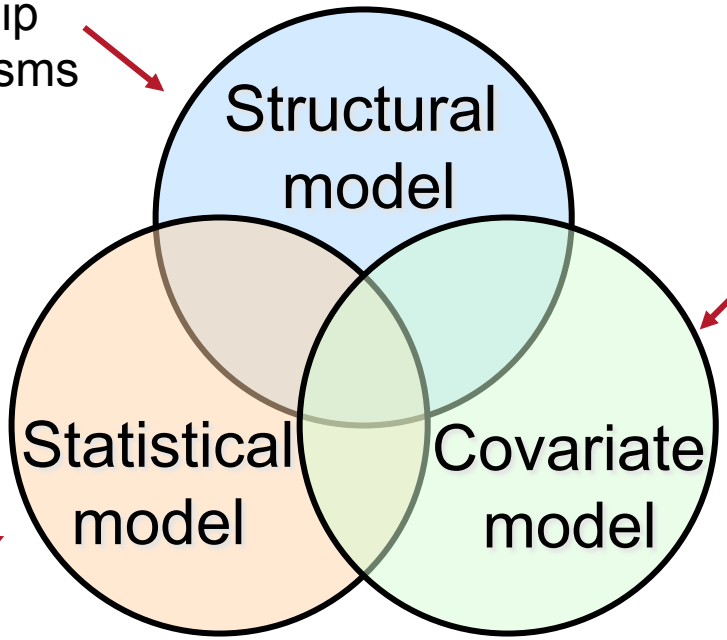


Why do we model in drug development?

1. The systems are complex
    - Nonlinearity and/or time dependency
    - Complex data (multiple sources, noisy, errors...)
2. To integrate information
    - Across time, dose-levels, drugs and systems
3. To predict and extrapolate
    - We are not only interested in the specific observation
    - We are often not primarily interested in the setting studied
4. To optimize further studies
5. The model can be used as a "knowledge repository"
    - Describe what is currently known about mechanism of action and system
6. The model might help to fill in the "gaps" in data
7. The model can help us identify and quantify uncertainty

Components of drug models

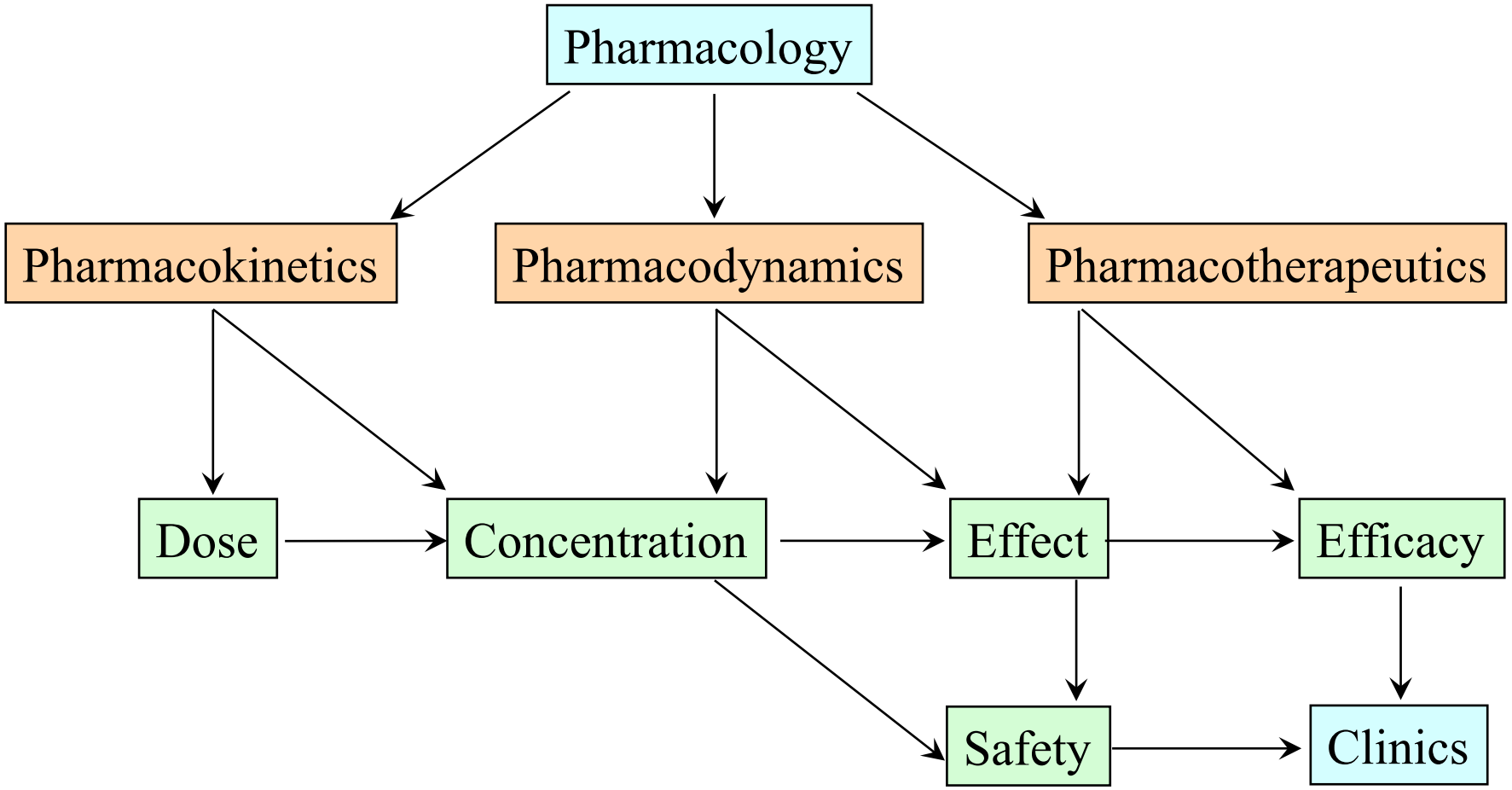
e.g. Dose-Conc. relationship
Conc.-Effect relationship
Physiological mechanisms
Maturation processes



Relationships between parameters and compound/ system characteristics

Inter-individual, inter-occasion and residual variabilities
Uncertainty and correlation

Pharmacokinetic-Pharmacodynamic modelling

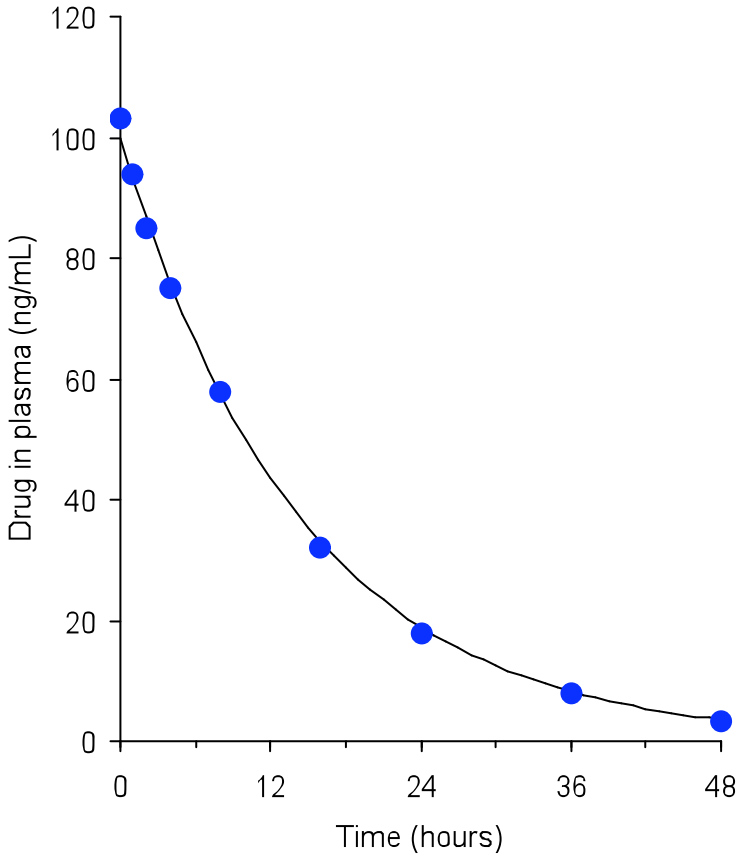


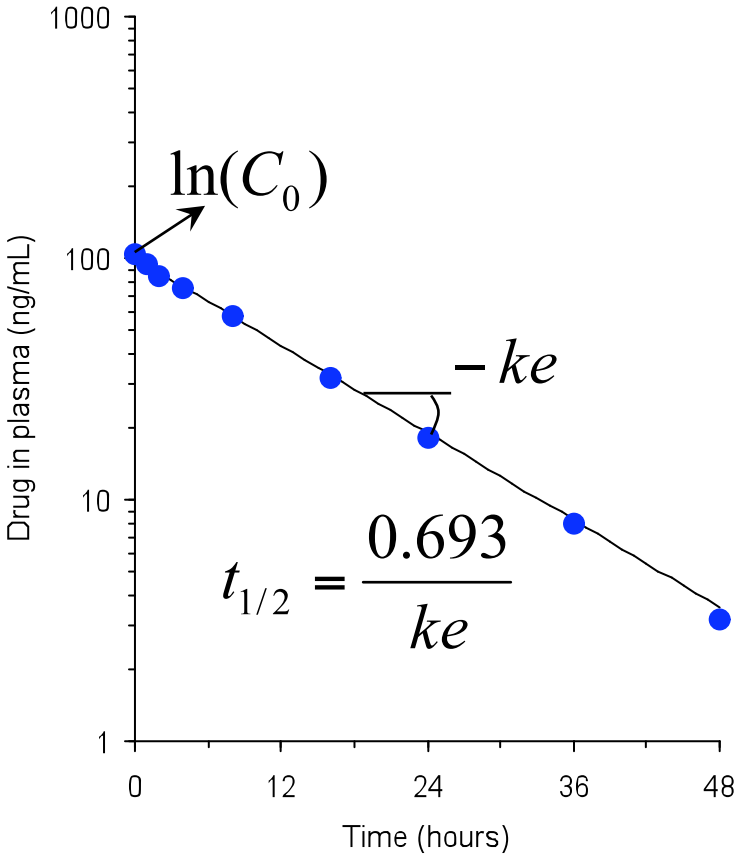
Pharmacokinetic models

What happens when a drug is administered as an intravenous bolus?

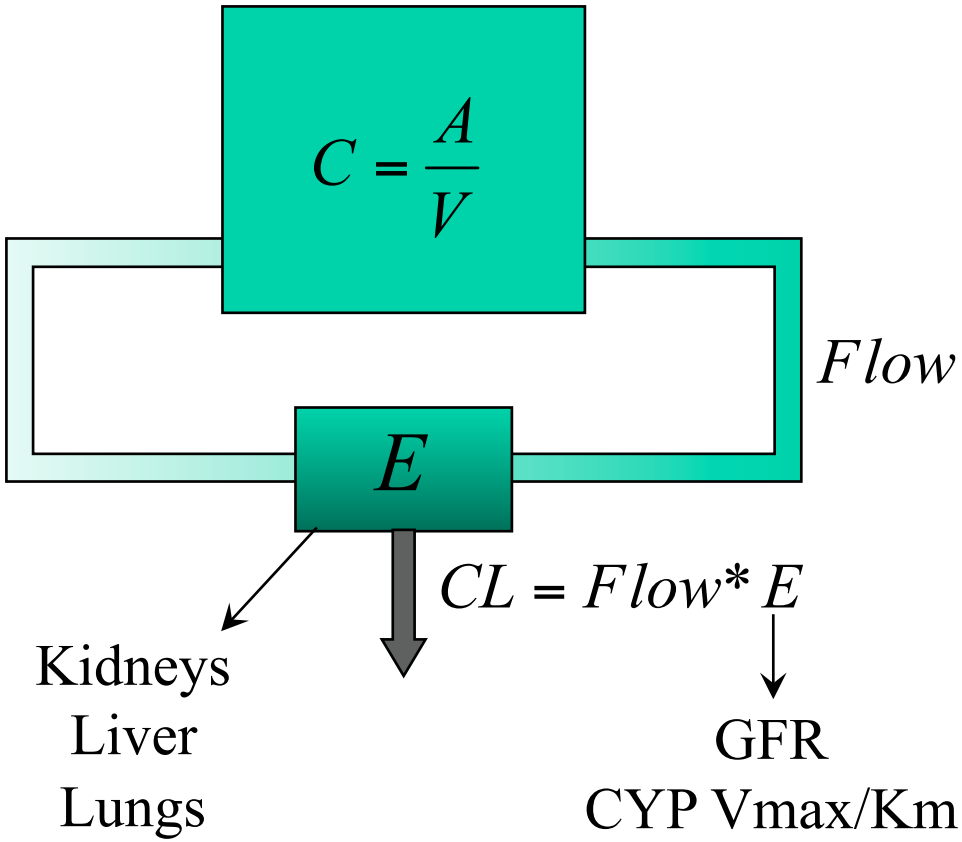
$$C_t = C_0 * \exp(-ke * t)$$

$$\ln(C_t) = \ln(C_0) - ke * t$$





From 'descriptive' to 'mechanistic' model based on flow dynamic systems



$$\frac{dA}{dt} = -CL * C$$

$$\frac{dA}{dt} = -CL * \frac{A}{V}$$

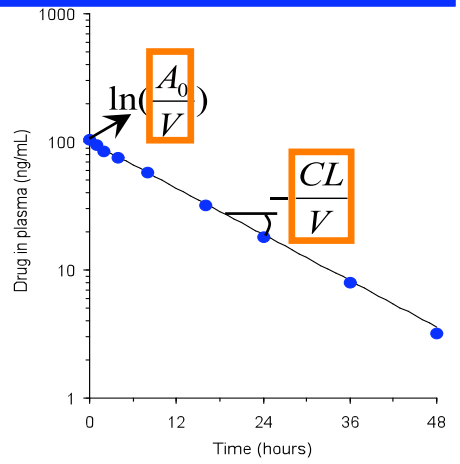
$$\frac{dA}{dt} = -\frac{CL}{V} * A$$

$$\frac{dA}{dt} = -ke * A$$

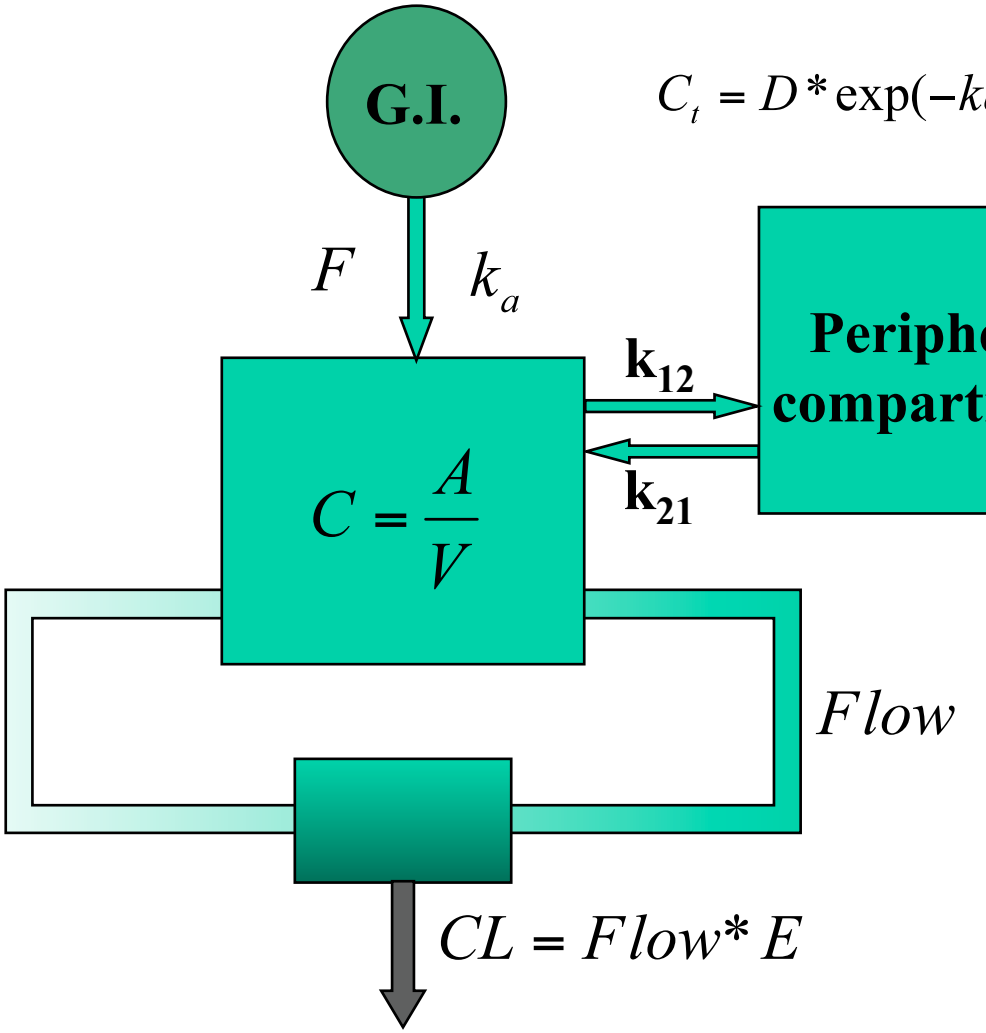
$$\frac{dC}{dt} = -ke * \frac{A}{V}$$

$$C_t = \frac{D}{V} * \exp(-\frac{CL}{V} * t)$$

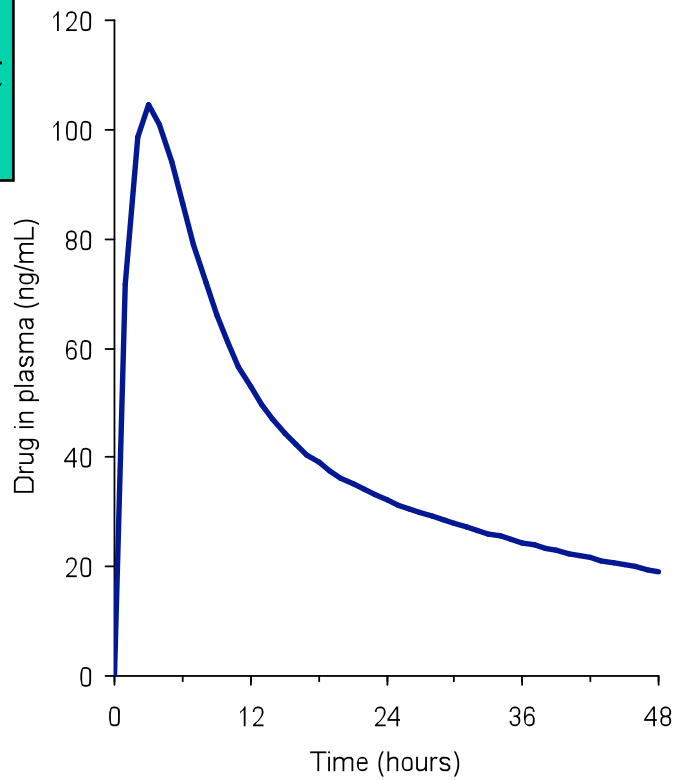
$$\ln(C_t) = \ln(\frac{A_0}{V}) - \frac{CL}{V} * t$$



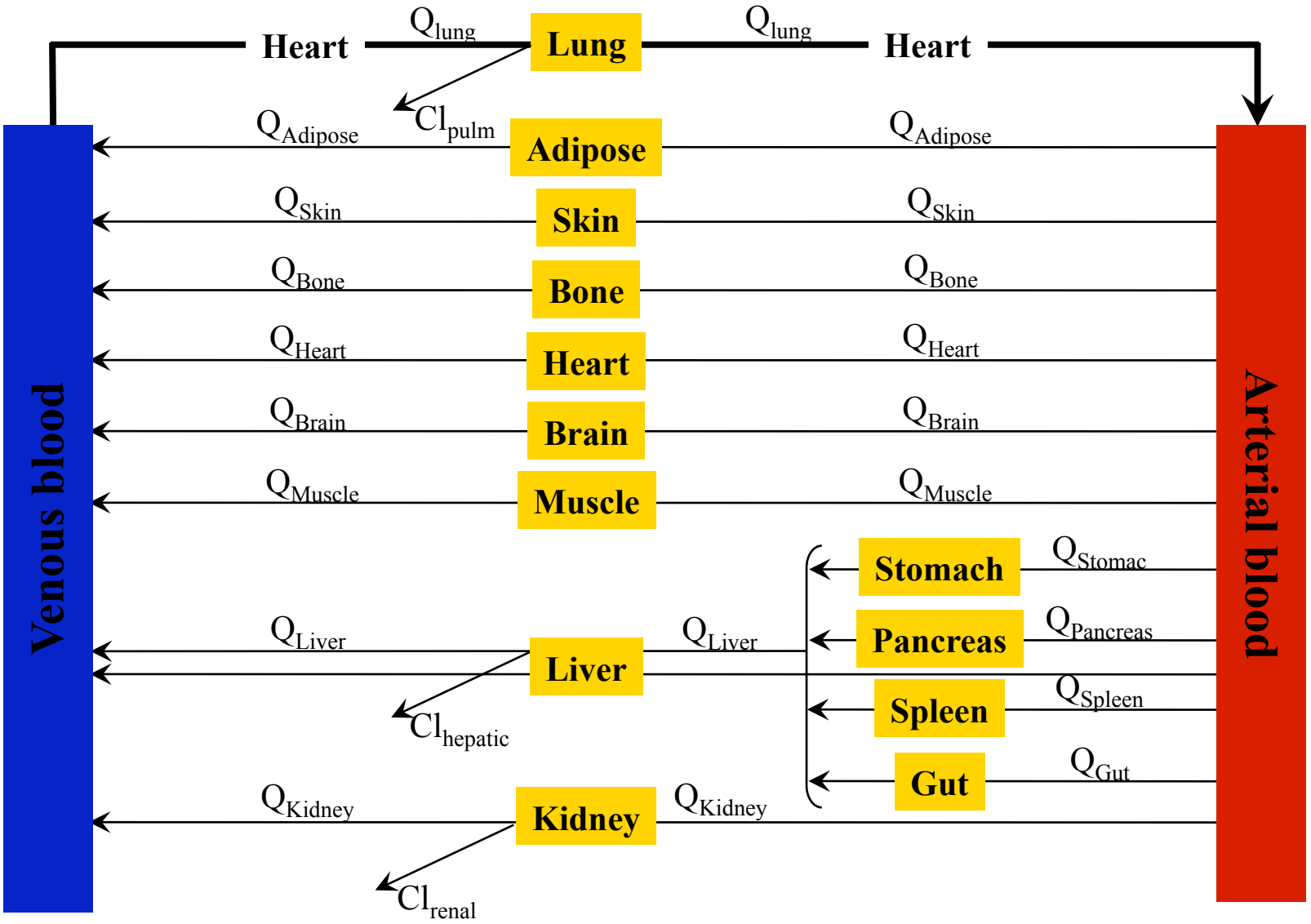
Model with oral absorption (first order) and peripheral compartment



$$C_t = D * \exp(-ka * t) + A * \exp(-\alpha * t) + B * \exp(-\beta * t)$$

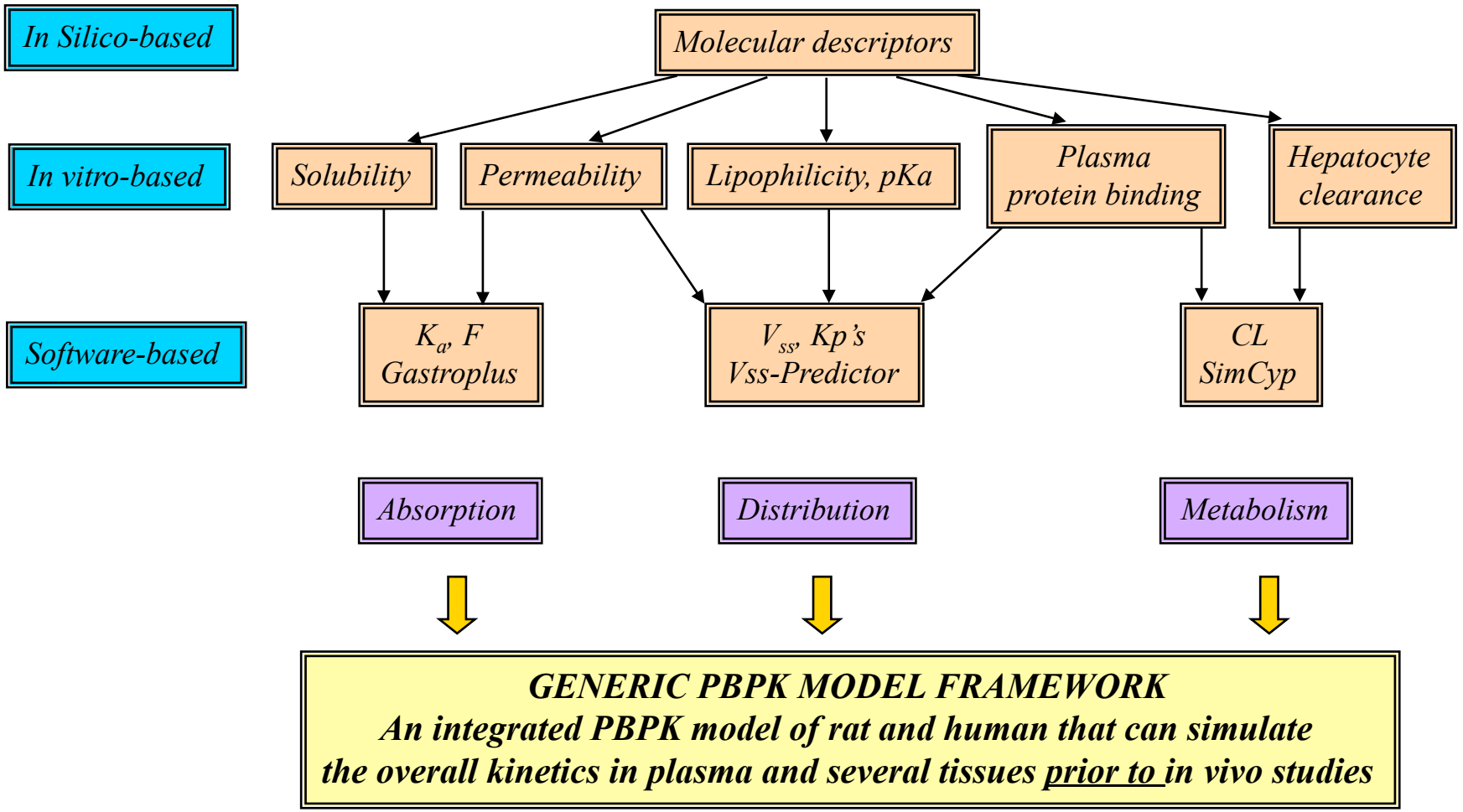


Physiologically-based pharmacokinetic model (PBPK)



http://edds.georgetown.edu/conferences/Theil.pdf

From in silico to in vivo



http://cdds.georgetown.edu/conferences/Theil.pdf

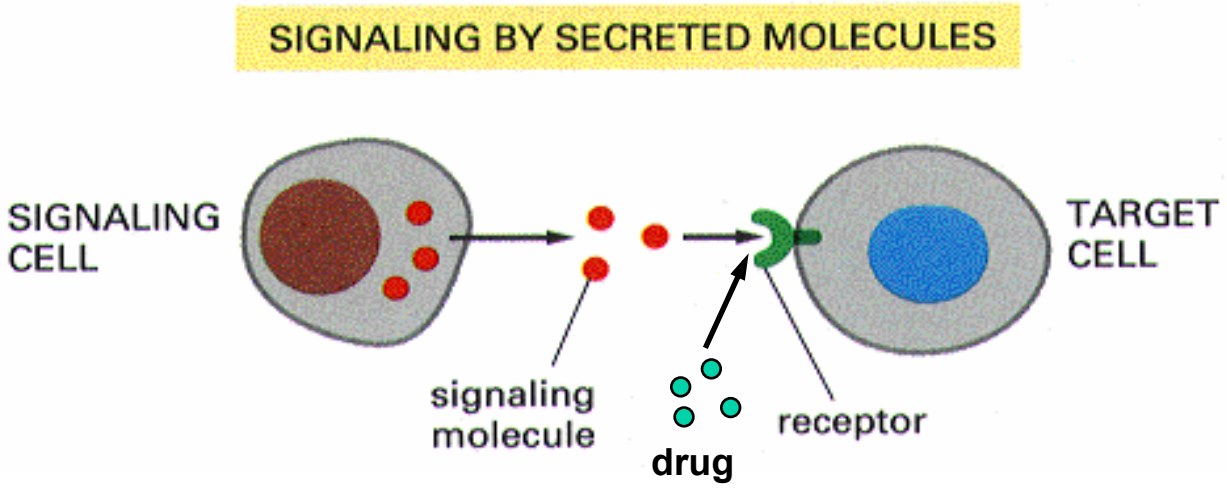
Pharmacodynamic models

The receptor theory

First postulated by John Langley (1820-1878)

Furthered by Paul Ehrlich (1854-1915)

"Corpora non agunt nisi fixata"



http://www.med.nyu.edu/Pharm/Levy2003.ppt

Clark's occupation theory

$$[R] + [D] \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [RD]$$

$$\frac{d[RD]}{dt} = k_1.[R].[D] - k_{-1}.[RD] = 0$$

$$k_1.[R].[D] = k_{-1}.[RD]$$

$$K_D = \frac{k_{-1}}{k_1} = \frac{[R].[D]}{[RD]}$$

$$[RT] = [R] + [RD]$$

$$K_D = \frac{[RT].[D]}{[RD]} - \frac{[RD].[D]}{[RD]}$$

$$K_D + [D] = \frac{[RT].[D]}{[RD]}$$

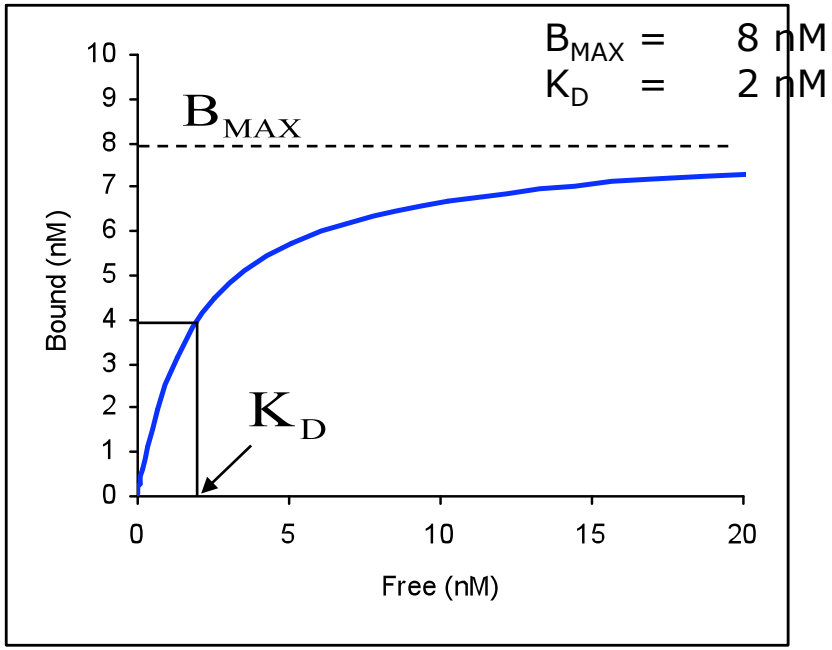
$$\boxed{[RD] = \frac{[RT].[D]}{K_D + [D]}}$$

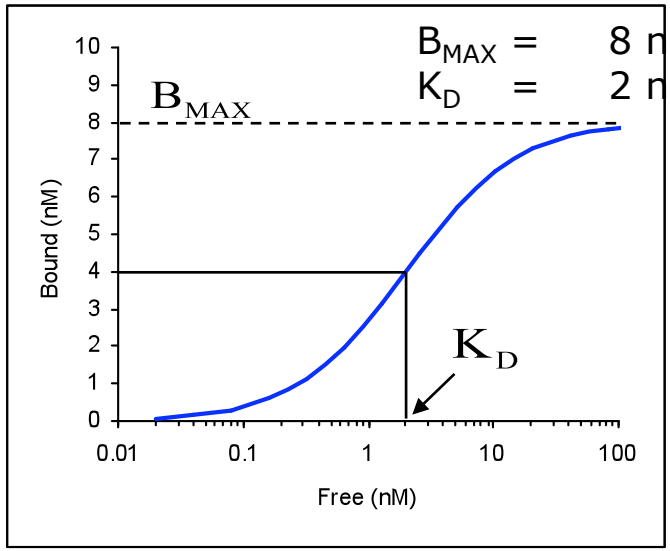
$$\boxed{Bound = \frac{B_{MAX}.Free}{K_D + Free}}$$

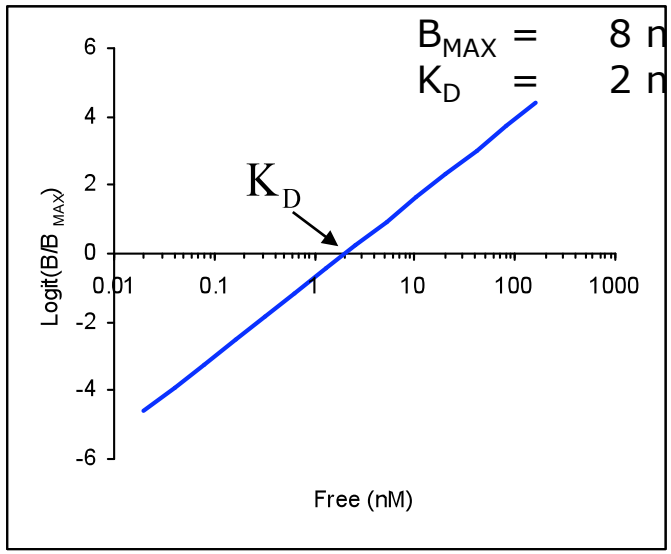
RT or B_{MAX} = Total amount of receptor (binding sites/mg protein or nM)
R = Free receptor (binding sites/mg protein or nM)
D or Free = Free drug (nM)
DR or Bound = complex drug-receptor (binding sites/mg protein or nM)
K_1 = association rate constant (min^{-1})
K_{-1} = dissociation rate constant (min^{-1})
K_A = Association constant
[ ] = concentration (nM)

Some graphical representations

$$\text{Bound} = \frac{B_{MAX} \cdot \text{Free}}{K_D + \text{Free}}$$







From receptor occupancy to pharmacological effect
A simple view: the E_{MAX} model

$$\frac{E_D}{E_{MAX}} = \frac{[RD]}{[RT]}$$

$$[RD] = \frac{[RT].[D]}{K_D + [D]}$$

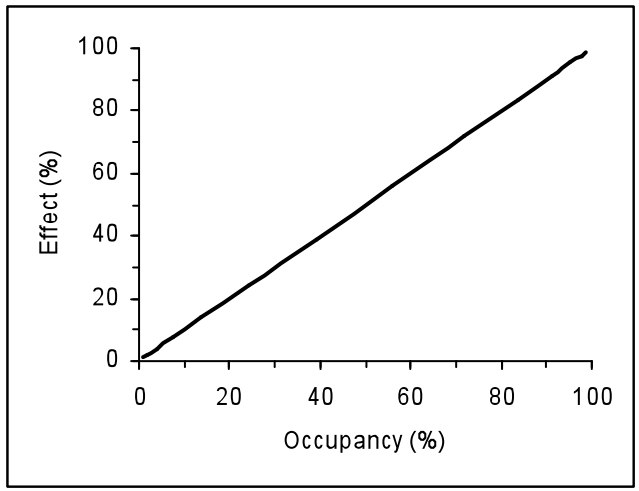
$$\frac{E_D}{E_{MAX}} = \frac{[D]}{K_D + [D]}$$

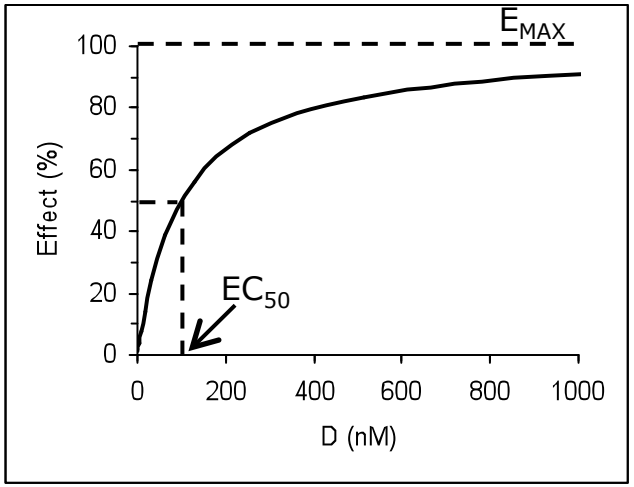
This assumed that:

The measured effect was linearly related to the number of receptor occupied by the drug

Maximum effect was attained at maximum binding

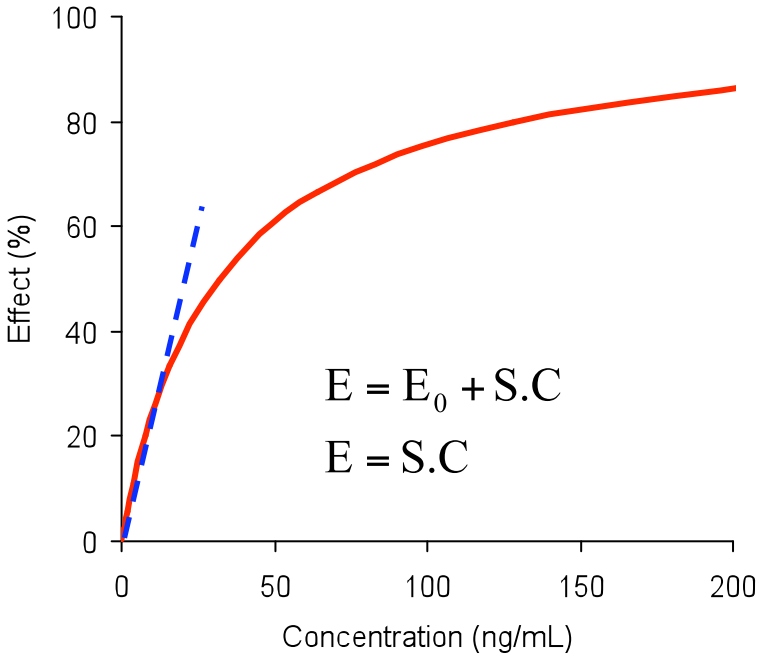
$$Effect = \frac{E_{MAX}.C}{EC_{50} + C}$$



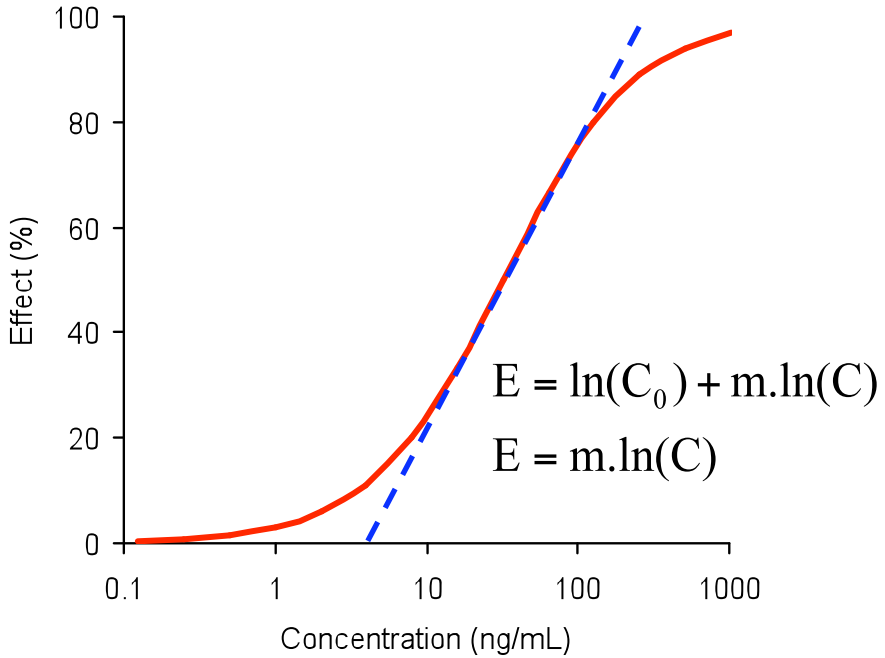


Some derived/simplified models

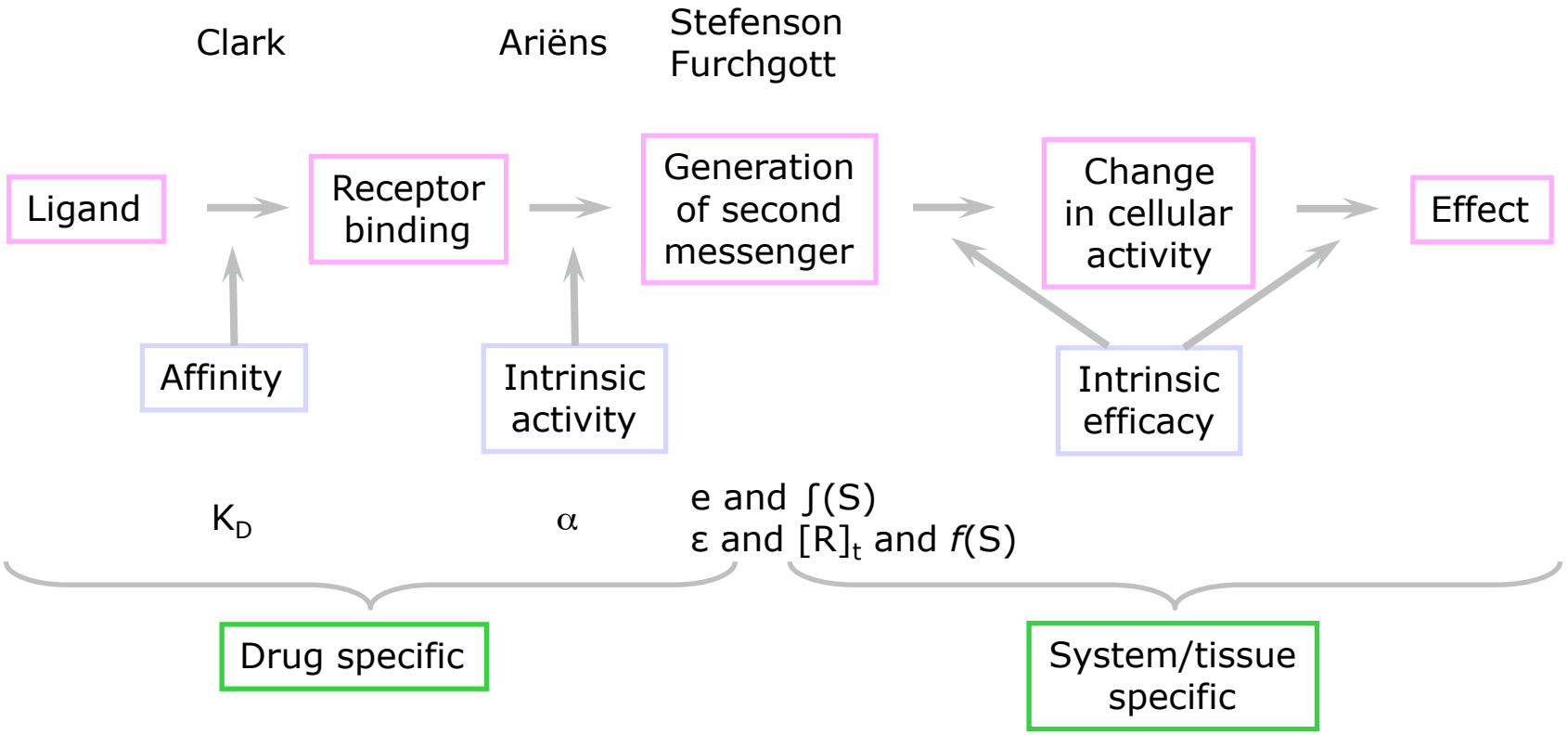
linear effect concentration model



log-linear effect concentration model

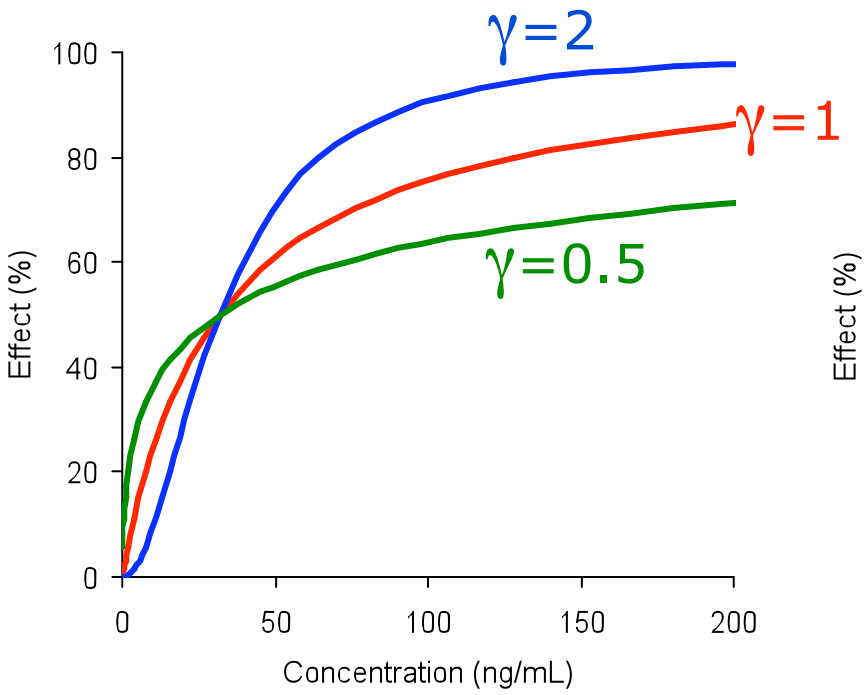


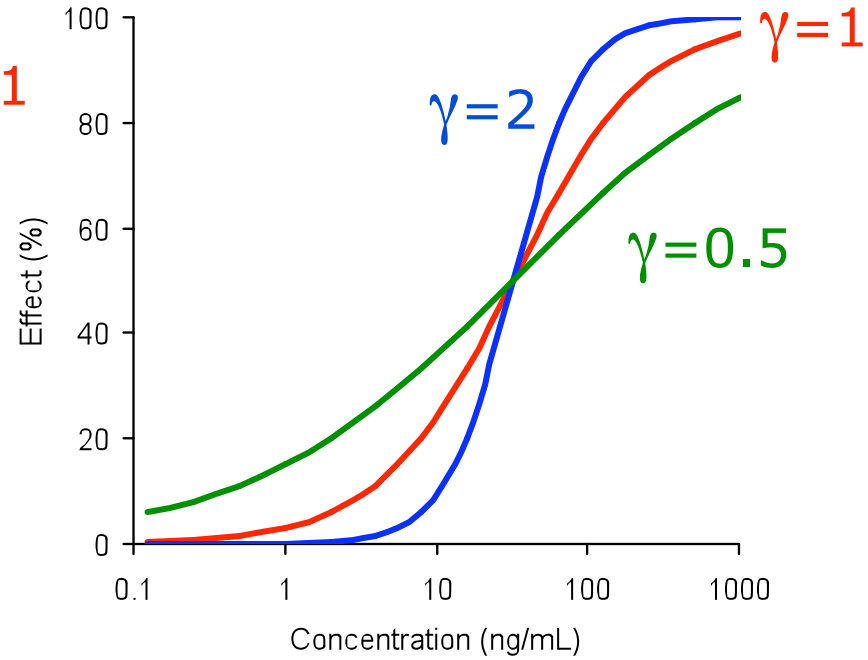
From receptor occupancy to pharmacological effect
A more complete view



E_{MAX} model and sigmoid E_{MAX} model

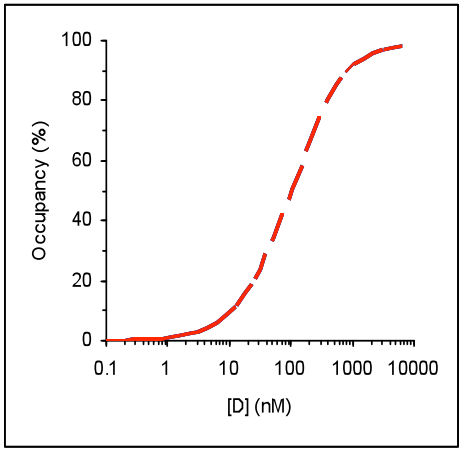
$$E = \frac{E_{MAX} \cdot C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}}$$

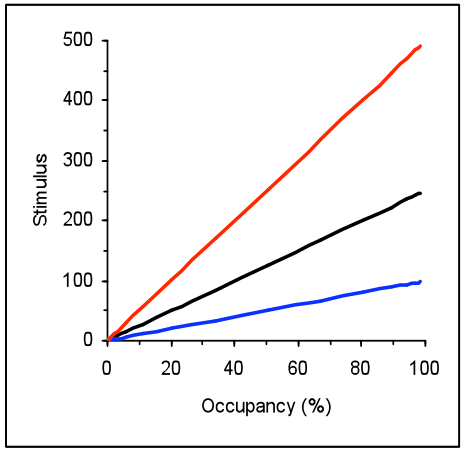




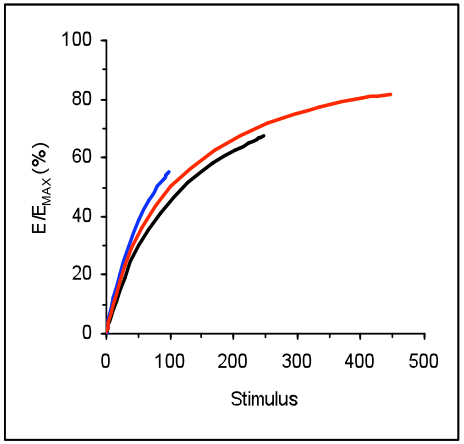
Operational model of agonism: effect of intrinsic activity (different drugs)

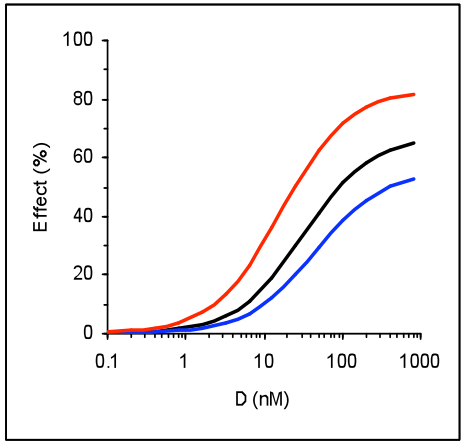
$$E_D = f\left[\frac{\varepsilon.[RT]_T.[D]}{[D]+K_D}\right] = f(S) \quad \text{and} \quad f(S) = \frac{S_D}{S_{50}+S_D}$$

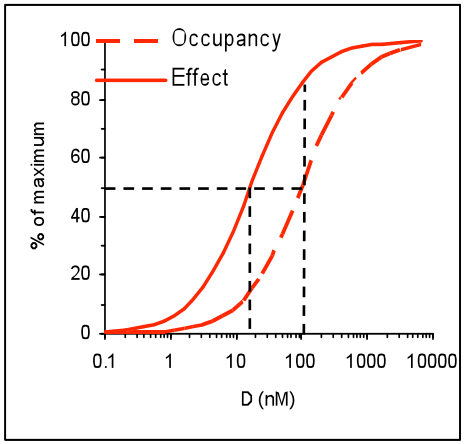




RT (nM)	KD (nM)	ε	S_{50} (nM)
100	100	2.5	120
100	100	1	80
100	100	5	100







Apparent dissociation between receptor occupancy and measured effect:

Production of glucose by β-adrenoreceptor stimulation

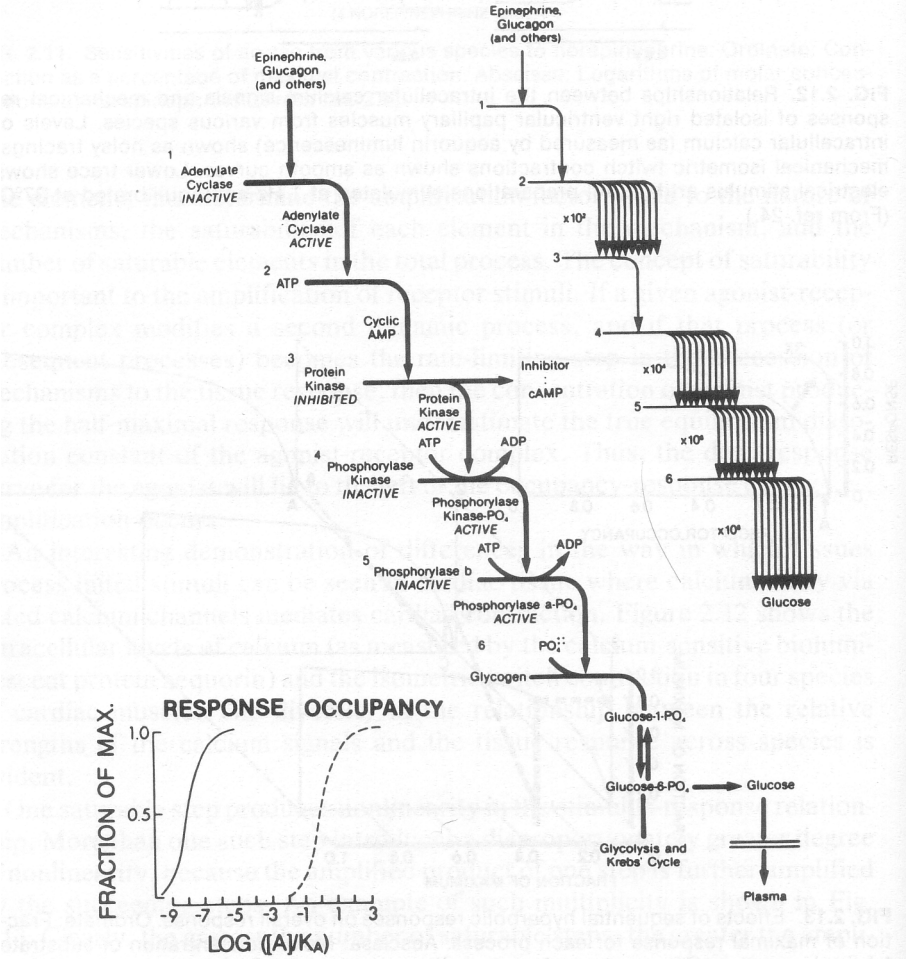
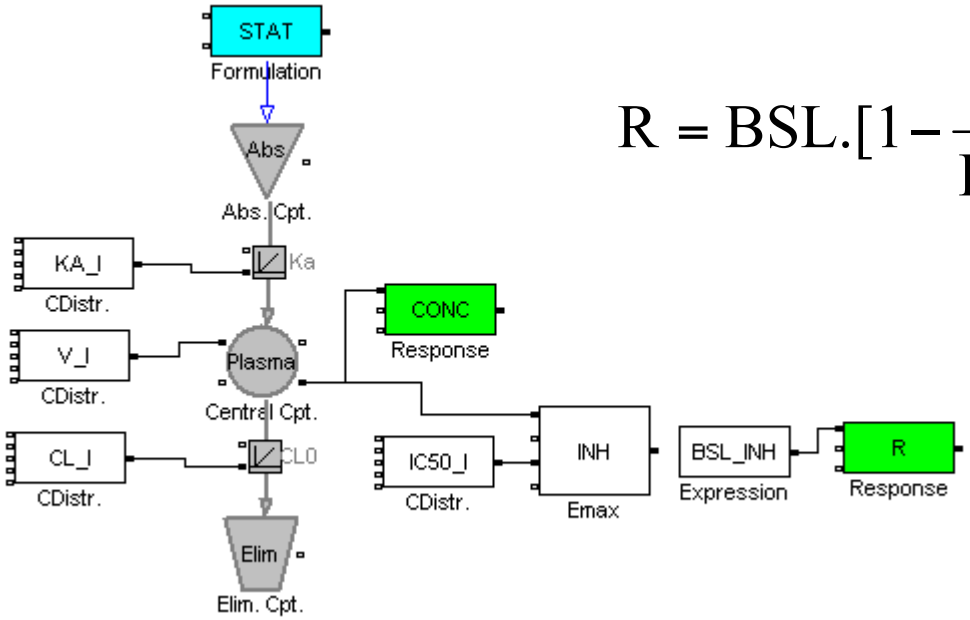


FIG. 2.15. Production of glucose by β-adrenoceptor or glucagon-receptor stimulation. **Inset:** A magnification factor of eight orders of magnitude is produced by the cascade of reactions. (From ref. 9.)

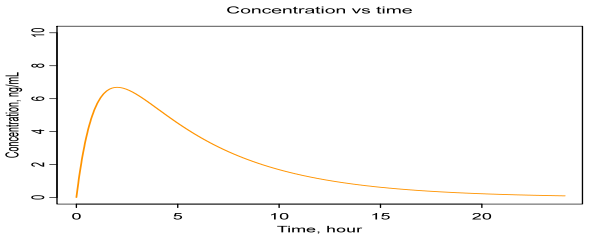
PK-PD models

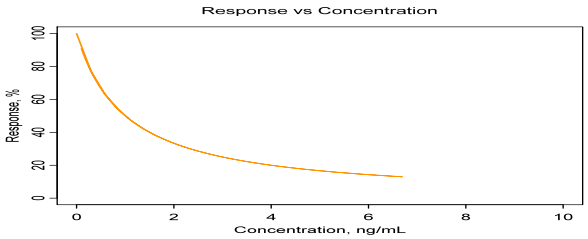
Concentration–effect–time relationship: direct response → inhibition

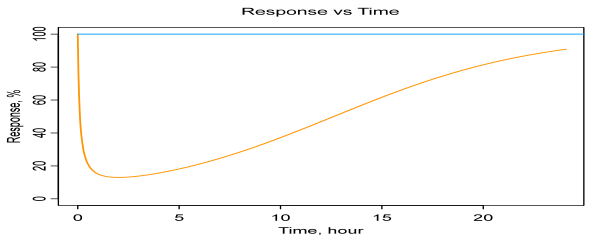


$$R = BSL.[1 - \frac{I_{max}.C^n}{IC_{50}^n + C^n}]$$

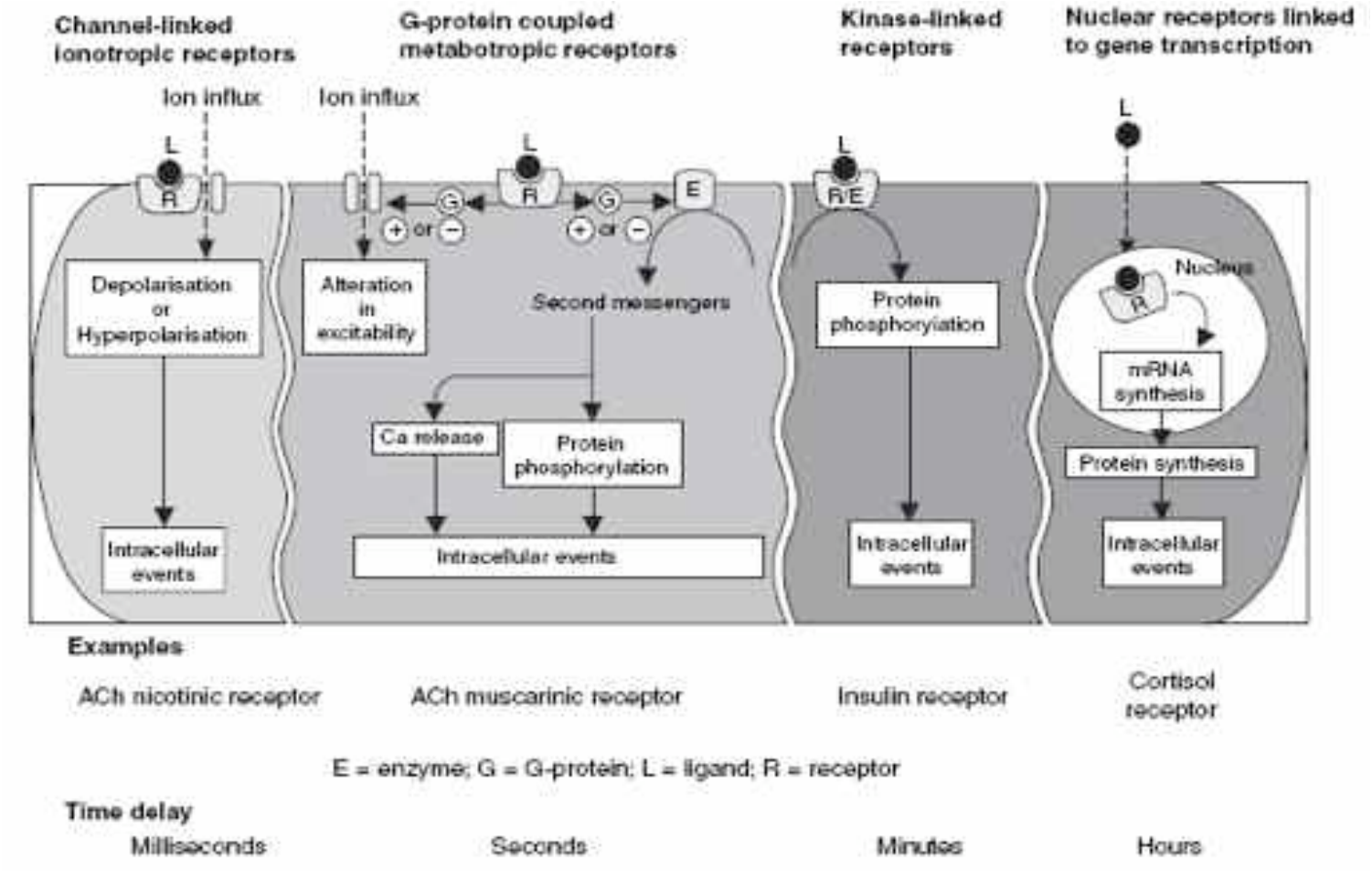
Dose	= 0.8 mg
KA	= 1 h^{-1}
V	= 80 L
CL	= 16 $L.h^{-1}$
IC_{50}	= 1.0 ng/mL
n	= 1.0
I_{max}	= 1.0
BSL	= 100





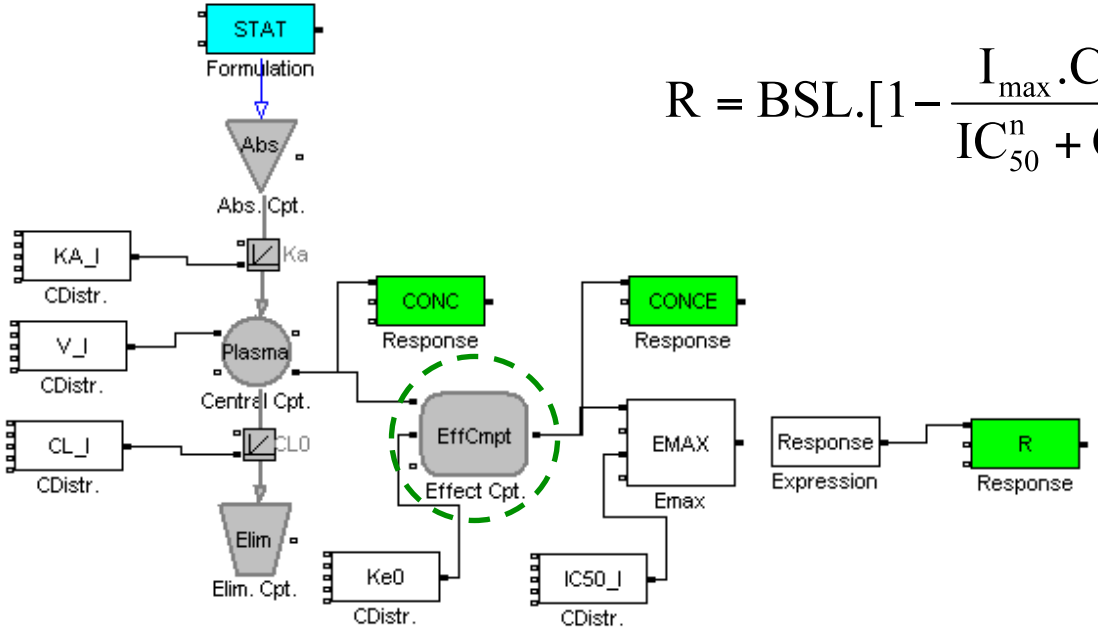


The time delay between receptor occupancy and effect also depends on the second messenger mechanism



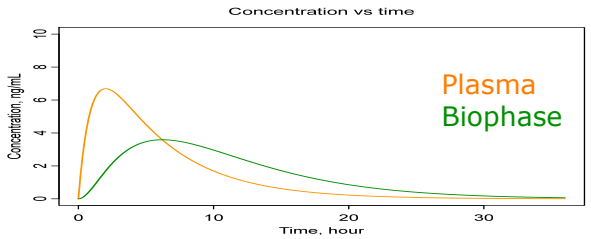
LEES, P., CUNNINGHAM, F. M. & ELLIOTT, J.
Principles of pharmacodynamics and their applications in veterinary pharmacology.
Journal of Veterinary Pharmacology & Therapeutics 27 (6), 397-414.

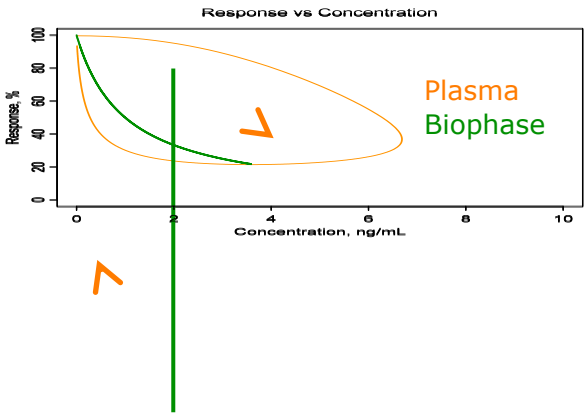
Effect compartment (or Link) model

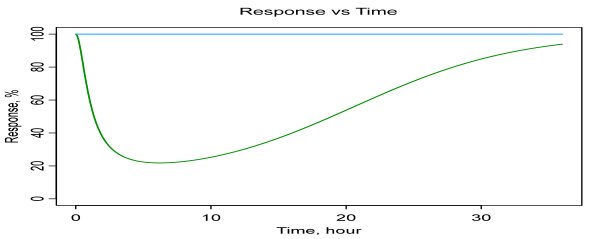


$$R = BSL.[1 - \frac{I_{max}.Ce^{n}}{IC_{50}^{n} + Ce^{n}}]$$

Dose	= 0.8 mg
KA	= 1 h^{-1}
V	= 80 L
CL	= 16 $L.h^{-1}$
IC_{50}	= 1.0 ng/mL
n	= 1.0
I_{max}	= 1.0
BSL	= 100
Ke0	= 0.2 h^{-1}



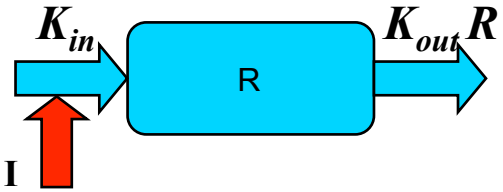




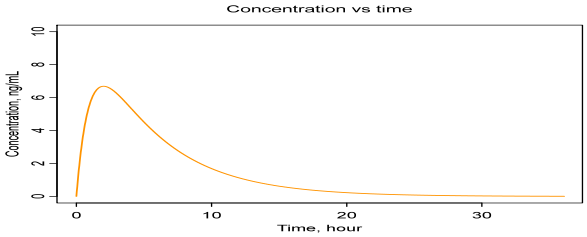
Biophase

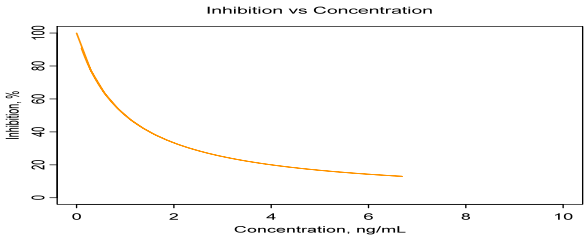
Concentration–effect–time relationship for an indirect response model with inhibition of build-up

Inhibition of build-up :

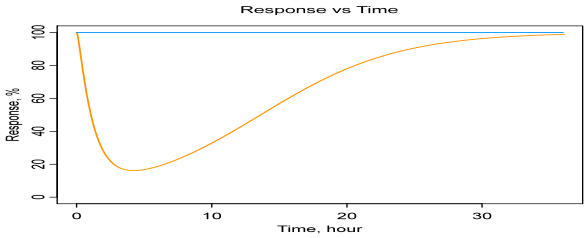


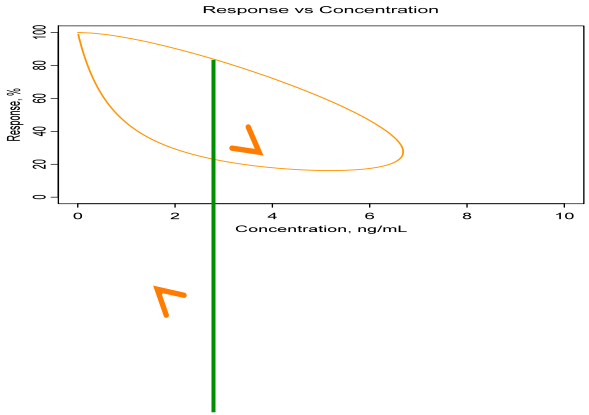
$$\frac{dR}{dt} = k_{in}.[1 - \frac{I_{max}.C^n}{IC_{50}^n + C^n}] - K_{out}.R$$





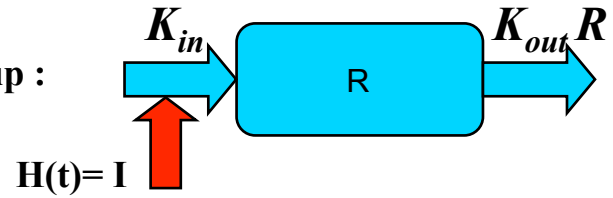
Dose	= 0.8 mg
KA	= 1 h^{-1}
V	= 80 L
CL	= 16 $L.h^{-1}$
IC_{50}	= 1.0 ng/mL
n	= 1.0
I_{max}	= 1.0
Kin	= 100 $Runits.h^{-1}$
Kout	= 1 h^{-1}





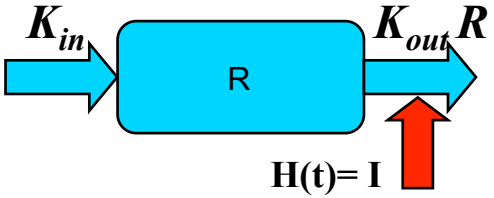
Indirect response models

Inhibition of build-up :



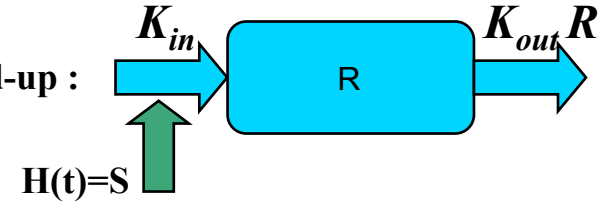
$$\frac{dR}{dt} = k_{in}.[1 - \frac{I_{max}.C^n}{IC_{50}^n + C^n}] - K_{out}.R$$

Inhibition of loss :



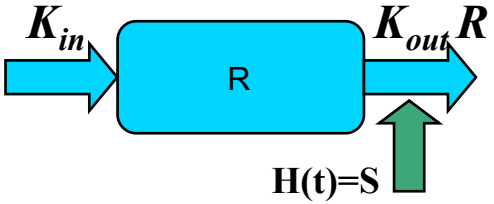
$$\frac{dR}{dt} = k_{in} - k_{out}.[1 - \frac{I_{max}.C^n}{IC_{50}^n + C^n}].R$$

Stimulation of build-up :



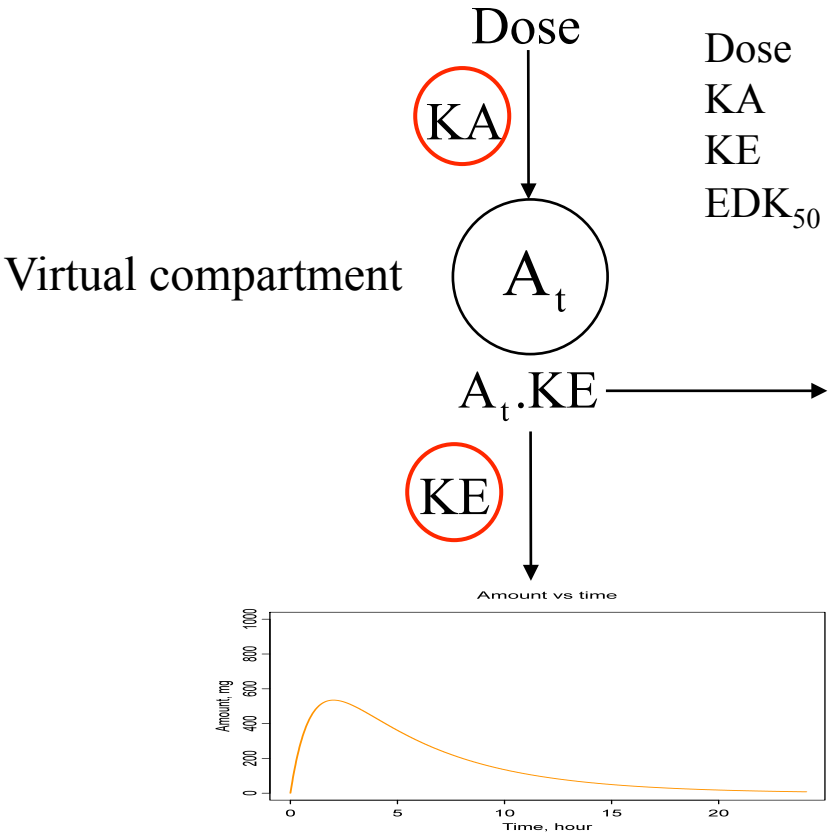
$$\frac{dR}{dt} = k_{in}.[1 + \frac{E_{max}.C^n}{EC_{50}^n + C^n}] - k_{out}.R$$

Stimulation of loss :



$$\frac{dR}{dt} = k_{in} - k_{out}.[1 + \frac{E_{max}.C^n}{EC_{50}^n + C^n}].R$$

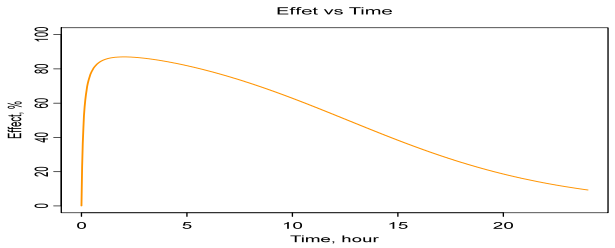
KPD model: analysis of effect-time profile in the absence of pharmacokinetic data



Dose = 800 mg
KA = 1 h^{-1}
KE = 0.2 h^{-1}
EDK_{50} = EC_{50} . CL = 1 $mg.L^{-1}$. 16 $L.h^{-1}$ = 16 $mg.h^{-1}$

$$E_t = E_{MAX} \frac{A_t.KE}{\underbrace{EC_{50}.CL}_{EDK_{50}} + A_t.KE}$$

Pharmacokinetic-pharmacodynamic potency of a drug



Mechanistic model: example of a viral kinetic model based on the predator-prey principle (Lotka-Volterra)

Target cell (activated CD4+ cells):

$dT/dt = b - d_1 \cdot T - (1\text{-}INH) \cdot i \cdot V \cdot T$

Actively infected cells (short-lived):

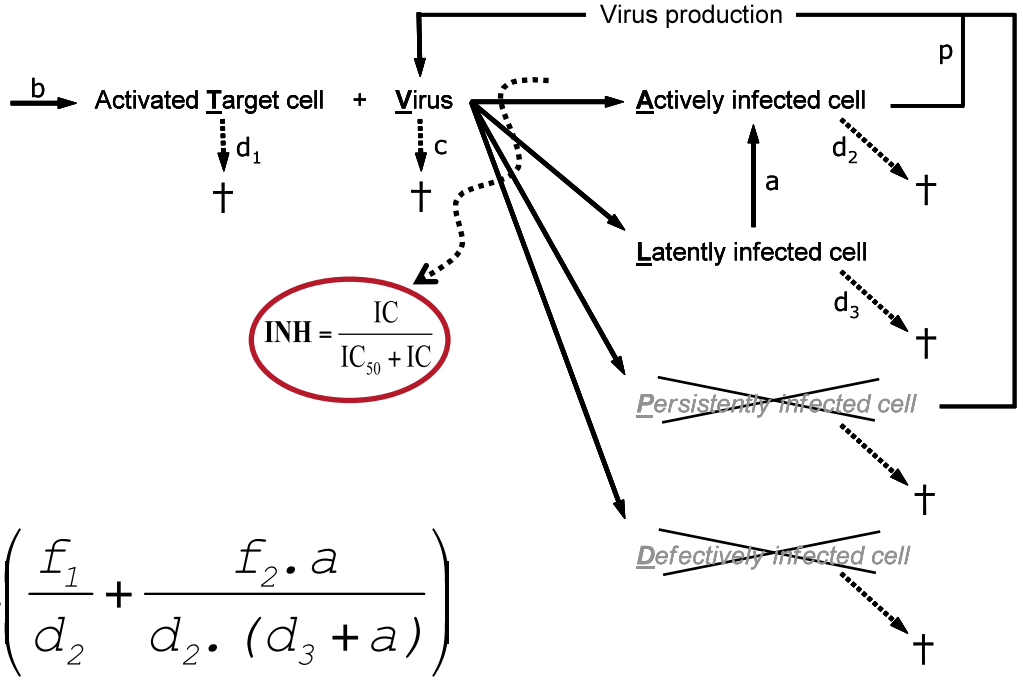
$dA/dt = f_1 \cdot (1\text{-}INH) \cdot i \cdot V \cdot T - d_2 \cdot A + a \cdot L$

Latently infected resting cells (long lived):

$dL/dt = f_2 \cdot (1\text{-}INH) \cdot i \cdot V \cdot T - d_3 \cdot L - a \cdot L$

Infectious virus (copies HIV-1 RNA):

$dV/dt = p.A - C.V$



$$RR0 = \frac{b}{d_1}.i.\frac{p}{c}.\left(\frac{f_1}{d_2} + \frac{f_2.a}{d_2.(d_3 + a)}\right)$$

$$RR0_{INH} = (1 - INH).RR0$$

$RR0_{INH}$>1 → growth
$RR0_{INH}$=1 → survival
$RR0_{INH}$<1 → extinction

$$RMIC = (RR0 - 1).IC_{50}$$

Pre-clinical application:

Modelling the anti-lipolytic effect of an adenosine A_1-receptor agonist

The data were obtained from:

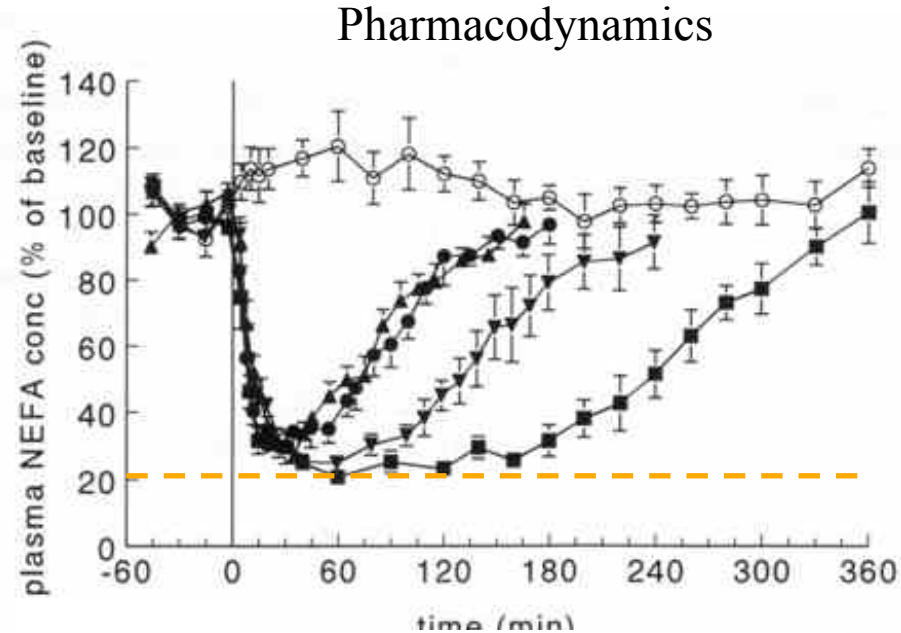
E.A Van Schaick,. H.J.M.M. De Greef, M.W.E. Langemeijer, M.J. Sheehan, A.P. IJzerman, and M. Danhof,:

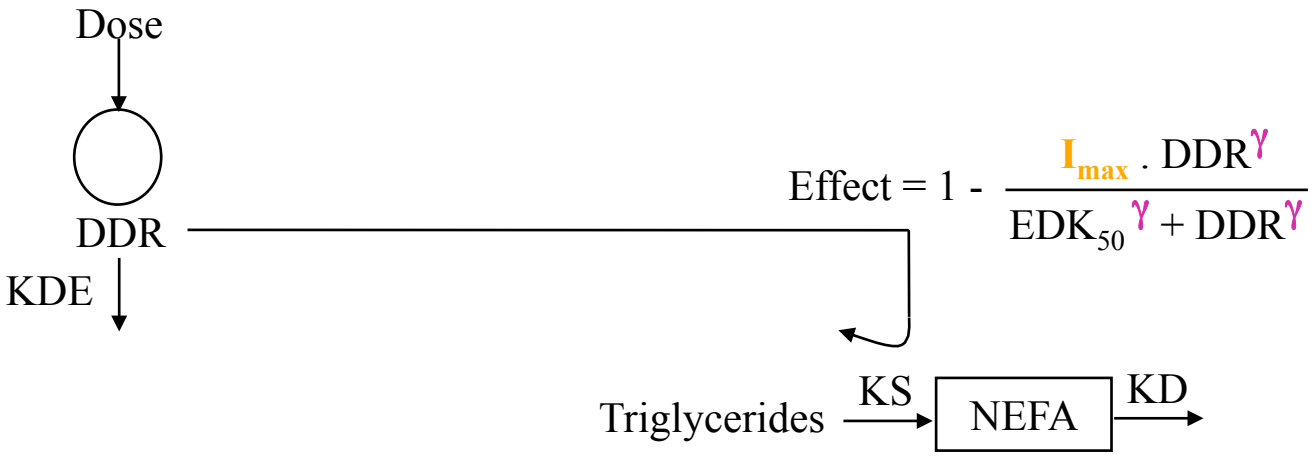
Pharmacokinetic-pharmacodynamic modeling of the anti-lipolytic and anti-ketotic effects of the adenosine A_1-receptor agonist N^6-(p-sulphophenyl)adenosine in rats.

Br. J. Pharmacol., **122**, 525-533 (1997)

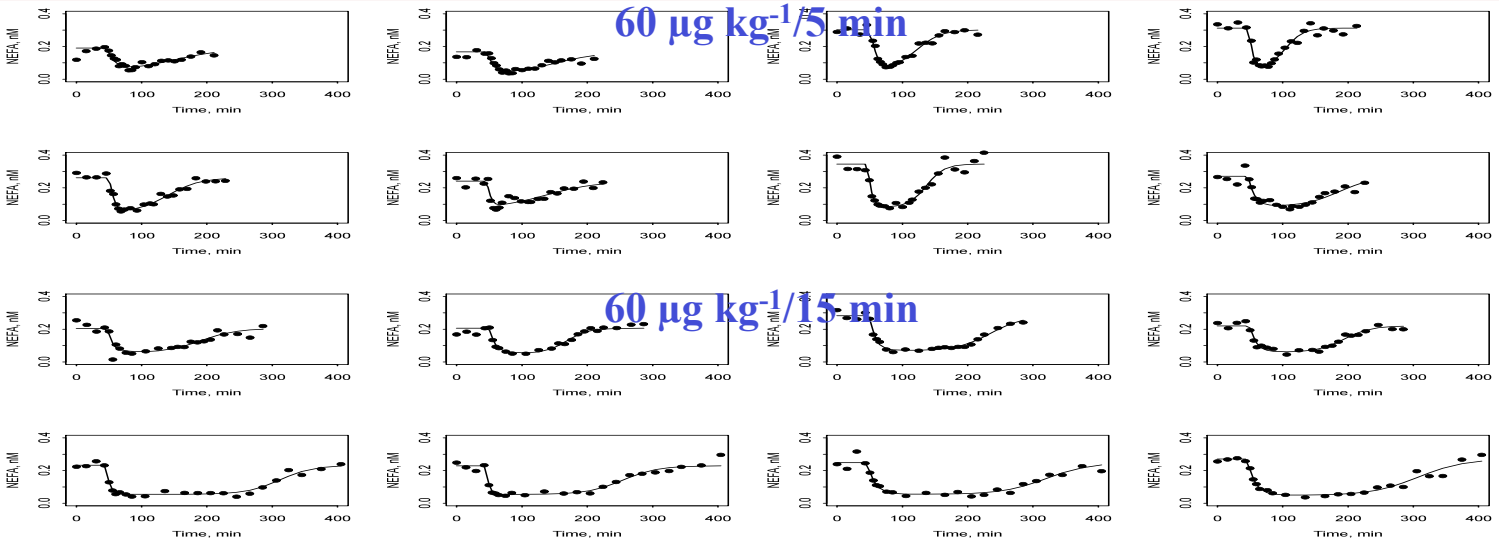
Exprimo

Would it be possible to analyse the dose-response-time data in absence of pharmacokinetics?





The individual NEFA plasma concentration-time profiles are fitted well with an adapted K-PD model



The parameters EDK_{50}, β/KDE, E_{max}, γ and baseline are similar

Differences in KD/K_{out} usually occur when the effect is directly linked to the central compartment and the compound follows a multi-compartmental distribution

PK-PD				K-PD			
Parameters	Mean		SE	Parameters	Mean		SE
(Pharmaco)kinetics							
Cl ($ml.min^{-1}$)	2.3	±	0.1				
β (min^{-1})	0.018	±	0.001	KDE (min^{-1})	0.020	±	0.002
Pharmacodynamics							
K_{in}* ($nM.mL^{-1}.min^{-1}$)	0.026	±	0.003	KS ($nM.mL^{-1}.min^{-1}$)	0.046	±	0.005
K_{out} (min^{-1})	0.105	±	0.009	KD (min^{-1})	0.165	±	0.01
BSL (nM)	0.26	±	0.01	BSL* (nM)	0.28	±	0.03
IC_{50} ($ng.mL^{-1}$)	22.4	±	1.8				
EDK_{50}* (µg min^{-1})	0.050	±	0.003	EDK_{50} (µg min^{-1})	0.056	±	0.004
I_{max}** (fraction of BSL)	0.80	±	0.01	I_{max} (fraction of BSL)	0.77	±	0.01
γ	2.2	±	0.2	γ	2.1	±	0.1

* Secondary parameters

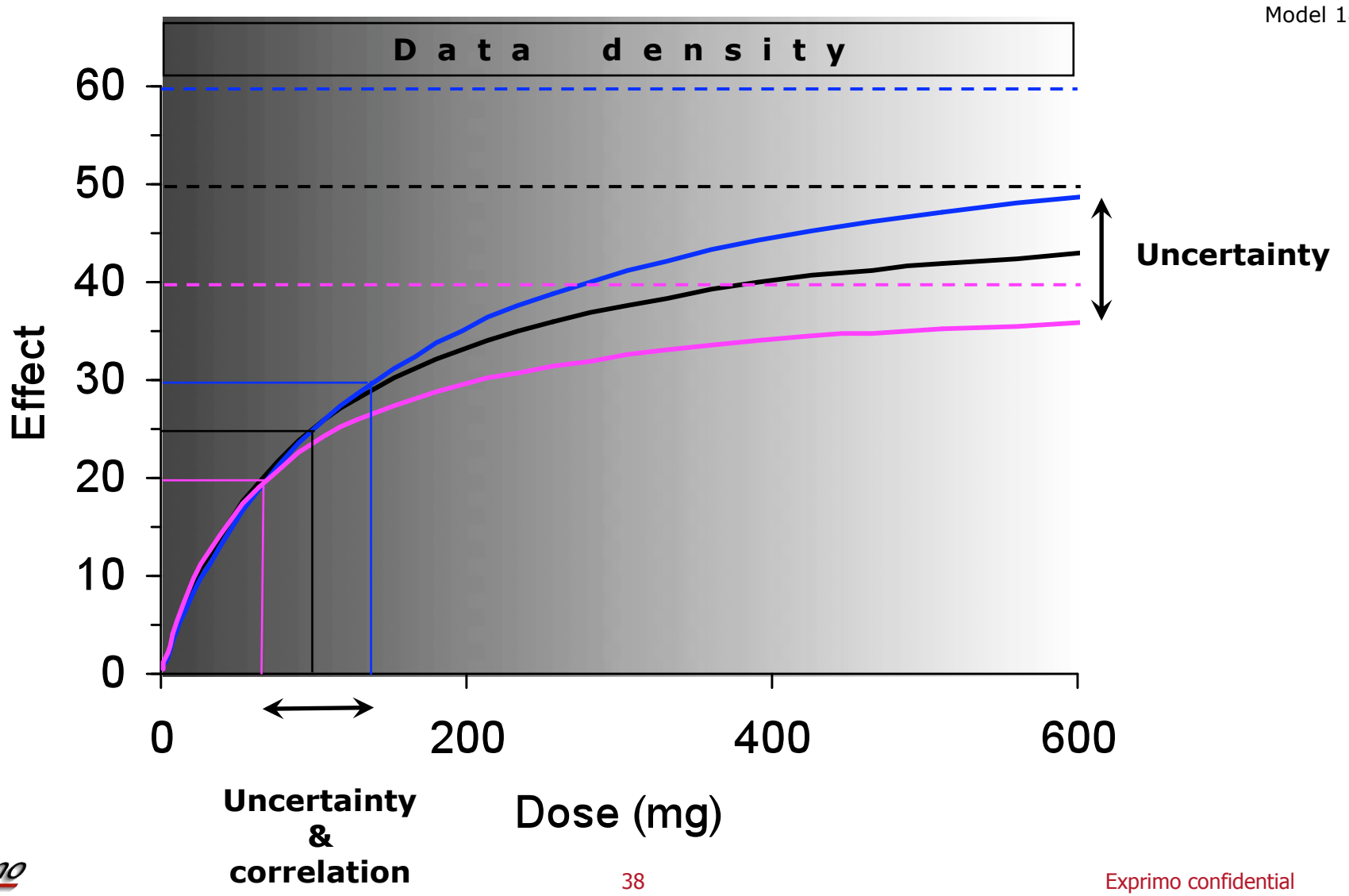
** I_{max} was fixed for the 15 µg in 5 min and 15 µg in 15 min treatments

Simulation

Some principles (1)

- Simulation models usually consist of
  - Structural model equations
  - Structural model parameters
    - Mean
    - Uncertainty
    - Correlation between parameter estimates
  - Random parameters
    - inter-individual variability
    - intra-individual variability
    - inter-occasion variability
- Simulations are usually performed at different levels
  - Typical subject
  - Entire (sub-)population
  - Study

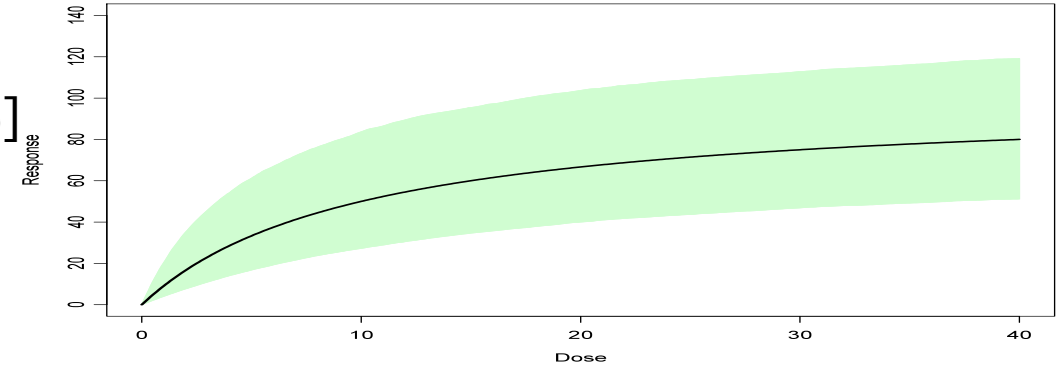
Uncertainty and correlation of parameter estimates



Simulations excluding correlation between the parameters

Model

- E_{max} dose-response model
- ED_{50} (mean [CV])= 10 mg [60%]
- E_{max} (mean [CV])= 100 [30%]
- Correlation not implemented



Simulations

- 1500 replicates

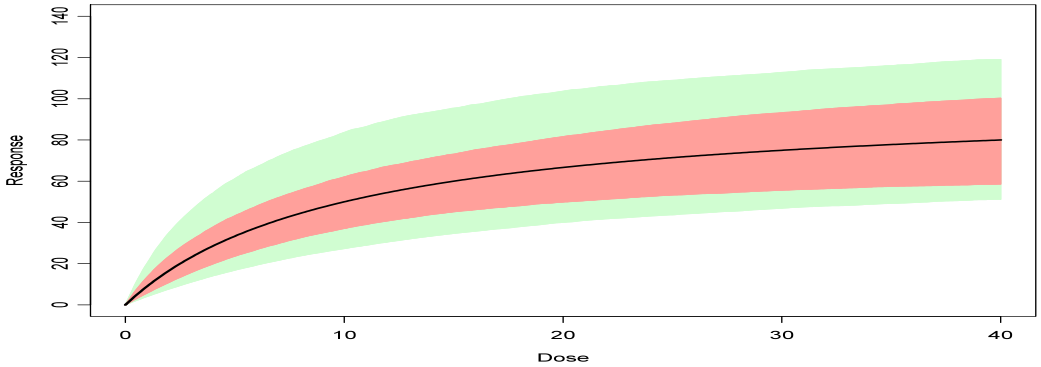
Results

- 10, 50 and 90 percentiles of response in function of dose

Simulations including correlation between the parameters

Model

- E_{max} dose-response model
- ED_{50} (mean [CV])= 10 mg [60%]
- E_{max} (mean [CV])= 100 [30%]
- Correlation implemented = 0.8



Desired effect

Simulations

- 1500 replicates

Results

- 10, 50 and 90 percentiles of response in function of dose

Some principles (2)

- Simulations can be performed to:
  - Describe observations
  - Explain observations
  - Understand the system
  - Interpolate and/or extrapolate
  - Estimate the risks associated to
    - Random effect
    - Uncertainty
    - Hypothesis
  - Evaluate different (if) scenarios or hypotheses
  - Optimize study designs
  - Others…

Conclusion/recommendation

Magritte 1929

Backup slides

Analysis of the PK-PD data

Parameterization: ensure that sampled parameters are meaningful and simulations realistic

- Estimate transformed parameters
  - e.g. estimating $\log(ED_{50})$ will ensure values of ED50 >0 when sampling from uncertainty

$$R = \frac{E_{MAX}.Dose}{e^{\log ED_{50}} + Dose}$$

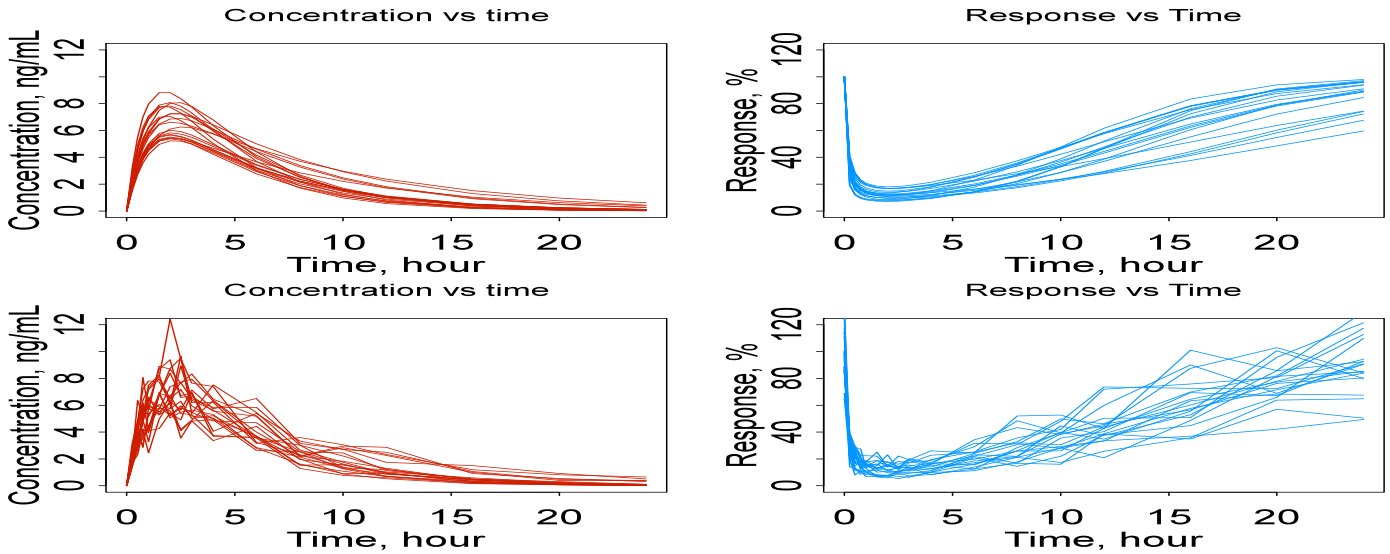
- Assume log-normal distribution when acceptable

$$P_{1i} = THETA_1 * \exp(\eta_{1i}) \text{ or } P_{1i} = \log(THETA_1) + \eta_{1i}$$

- If response needs to be between 0 and 1, use logit transformation

- Evaluate the correlation in the parameter estimates and in the inter-subject random effect

Non-linear (mixed effect) modelling is recommended to estimate the fixed (mean) and random (inter-individual and residual variability) parameters of PK-PD models



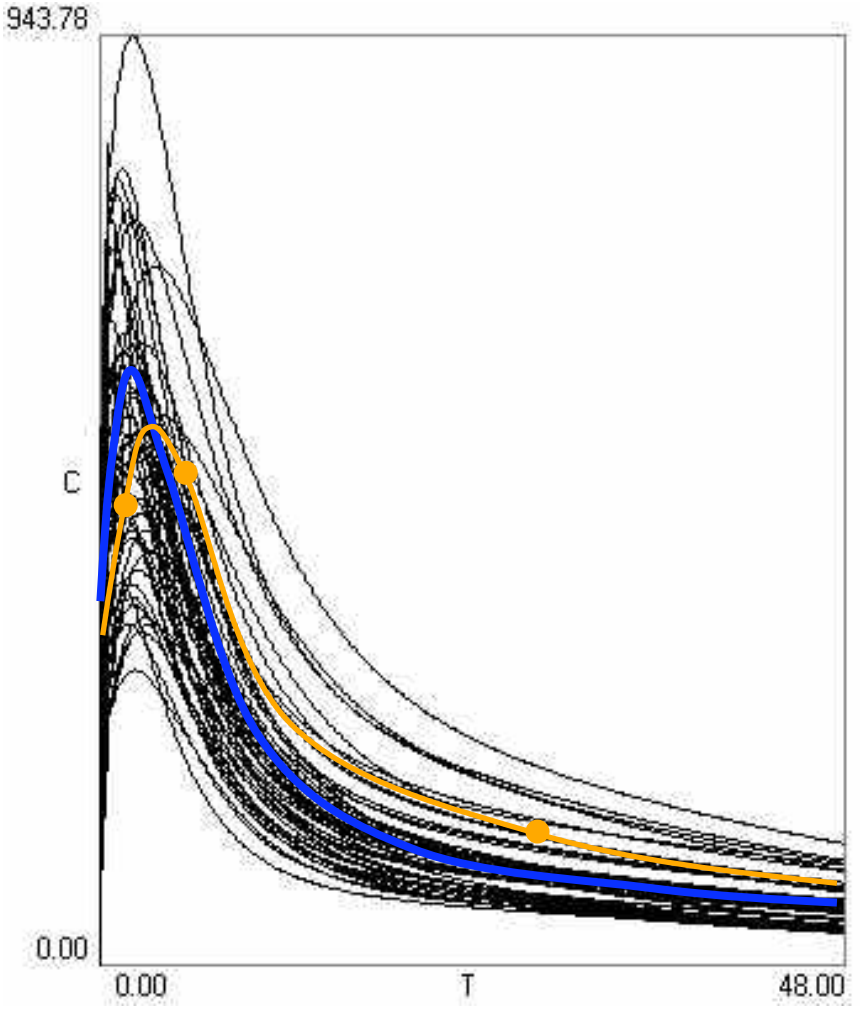
Empirical Bayesian Estimation is used to estimate the individual model parameters (e.g. POSTHOC function of NONMEM)

$$SS = \sum_{i=1}^{n} \frac{(C_p' - C_p)^2}{\delta^2} + \sum_{j=1}^{m} \frac{(P_j' - P_j)^2}{\omega_j^2}$$

Where:

m = number of parameters
n = number of data points
Cp' = predicted serum level
Cp = observed serum level
δ = standard deviation of drug assay
P' = revised population parameter
P = population parameter
ω = standard deviation of population parameter

http://www.rxkinetics.com/bayes.html



Available software for modeling in PK-PD

- NONMEM
- MONOLIX
- WinNonlin, WinNonMix
- SAS
  - PROC NLIN
  - PROC MIXED
- S-PLUS
  - lm, lmList
  - nls, nlminb
  - lme, nlme, etc

Available software for simulation in PK-PD

- NONMEM
- MONOLIX
- WinNonlin, WinNonMix
- SAS
- S-Plus
- MATLAB
- Pharsight Trial Simulator (TS2)
- Berkeley Madonna
- ACSL
- Adapt
- Stella
- P-Pharm
- Pspice
- Mathematica
- And many others …