CHAPT IV : Linear compartmental PKs

❶ The compartmental structure. Transfer rate constants. Open compartment mammillary models.

❷ Mathematic description : dynamic elementary model, states, parameters.

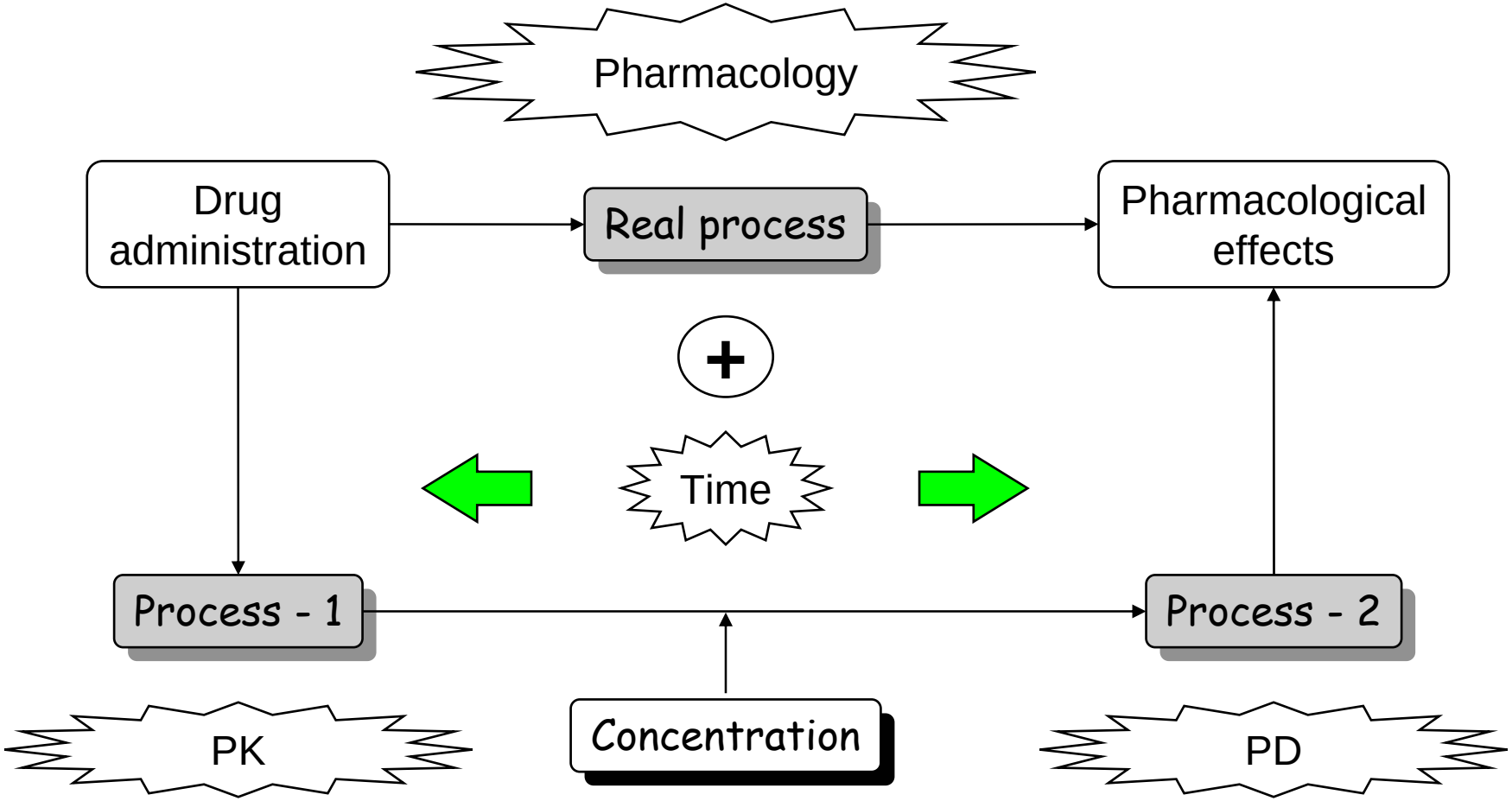
❸ Fundamental properties : superimposition principle. Clearance and administration schemes. Extravascular administrations.

❹ General analytic expression. Macro-rates and micro-rates. The phases of development : computing macro-exponents, normalized macro-coefficients, complex administration protocols, macro-coefficients, route of administration.

❺ Simulation of typical cases : flip-flop, repeated administrations. Sensitivity of the output to the model parameters. Initial conditions.

Functional scheme - Chapt IV

The context


Pharmacology
Drug administration
Real process
Pharmacological effects
+
Time
Process - 1
Process - 2
PK
Concentration
PD

States and unit processes

Systems are monitored by means of quantifiable measures (temperature, concentration, etc)

Use models to describe these quantifiable measures by means of the state variables

Basic laws govern changes in the real system

Mathematical descriptions expressed by differential equations

How the rate of change of one state variable depends on the current value of each of the state variables

?

$$\frac{dy_i}{dt} = f_i(y_1, y_2, \ldots, y_n)$$

- $f_i \quad i = 1, n$ can always be written as a sum of terms each of which represents a single or unit process which occurs in the system.

The order of the process

- Ex : Bimolecular reaction

$$A + B \underset{k_2}{\overset{k_1}{\rightleftarrows}} AB$$

★ Material Conc. State Var.

$$A \longrightarrow y_1$$
$$B \longrightarrow y_2$$
$$AB \longrightarrow y_3$$

★ Forward reaction rate $u_f = k_1 \cdot y_1 \cdot y_2$

★ Backward reaction rate $u_b = k_2 \cdot y_3$

□ The differential equations : $\frac{dy_1}{dt} = \frac{dy_2}{dt} = -\frac{dy_3}{dt} = u_b - u_f = k_2 \cdot y_3 - k_1 \cdot y_1 \cdot y_2$

- The order of a unit process :

It is the sum of the exponents of each of the state variables in the term describing the process

Linear and nonlinear models

- **Definition :** If the rates of change of all of the state variables of a model can be written as sums of processes of order 0 or 1, the model is linear otherwise nonlinear. These models are described by a set of linear or nonlinear differential equations, respectively.

- **Ex. linear models :**

  - Radioactive decay : The number of atoms decaying per unit of time is directly proportional to the number present at that time :

$$\begin{cases} \frac{dN}{dt} = -\lambda \cdot N \end{cases}$$

  - Diffusion : If there is a concentration gradient along x, Fick's law states that the rate at which material crosses a plane with surface S, perpendicular to the gradient , is :

$$\begin{cases} \frac{dq}{dt} = -D \cdot S \cdot \frac{\partial y}{\partial x} \end{cases}$$

    - ⋆ Material crosses a membrane between two spaces :

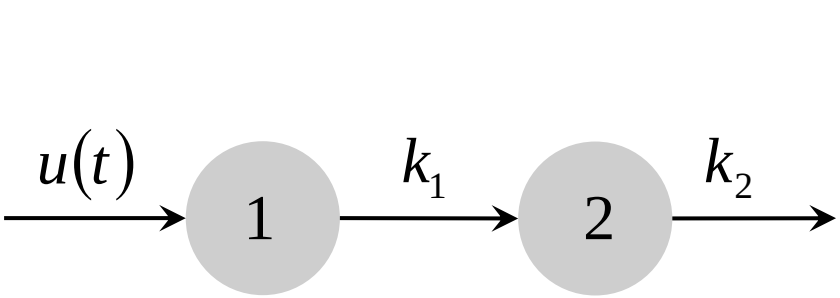
D ⟶ the diffusion coefficient,

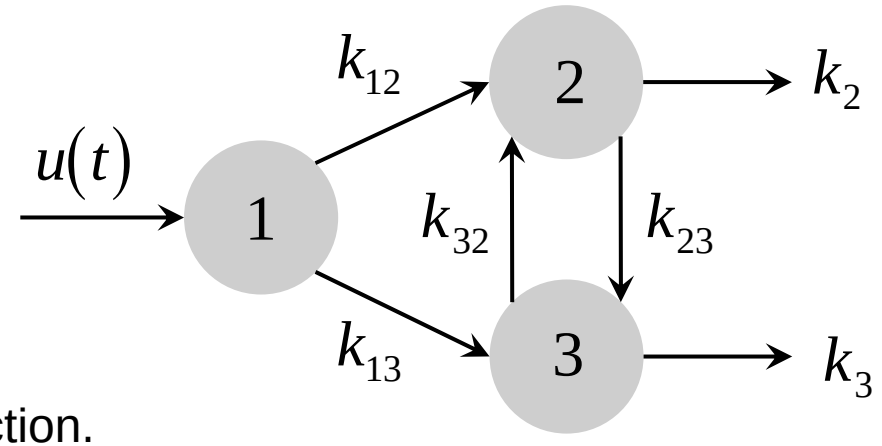
P ⟶ the permeability constant.

$$V_1 \cdot \frac{dy_1}{dt} = -V_2 \cdot \frac{dy_2}{dt} = P \cdot S \cdot (y_2 - y_1)$$

Space and compartments

- Biological space : may be well-stirred (homogeneous, ex. blood stream) or under-stirred (heterogeneous, ex. intracellular space).
- Compartment : is a biological space that acts kinetically like a distinct, homogeneous, well-stirred amount of material.
- Compartmental models : is a model which is made up of a finite number of compartments, and the compartments interact by exchanging material.





$u(t)$ is the administration rate or input function.

Linear modeling and ...

- Draw and connect compartments :
  - Volumes of distribution V_i characterizes the size of the compartment (units : volume).
  - Transfer rate constants k_{ij} connect compartments among them (units : time^{-1}).
- Mathematic description :
  - Modeling each connection pathway by first-order unit processes :

$$\begin{cases} \dfrac{dq}{dt} = -k_{ij} \cdot q \\ \dfrac{[dq/q]}{dt} = -k_{ij} \end{cases}$$

The elimination rate from a given compartment is proportional to the amount of material in this compartment

The relative decrease of material from a given compartment per unit time is constant

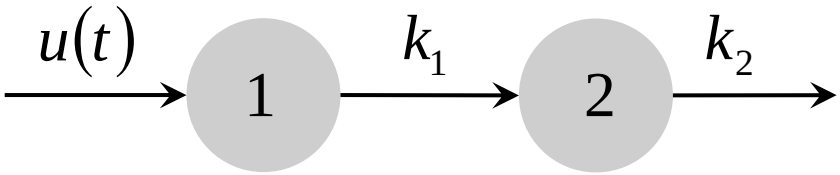
★ Transfer rate constants k_{ij} are involved in a first-order (linear) unit process.

★ For the sampled compartments introduce the volumes of distribution V_i .

... compartmental structure

- For a given compartmental structure :
  - express the rate of variation of material in each compartment, by assembling unit processes and establishing a system of linear differential equations (DE).

★ Ex :



$$\frac{dq_1}{dt} = -k_1 \cdot q_1 + u(t) \qquad q_1(0) = 0$$

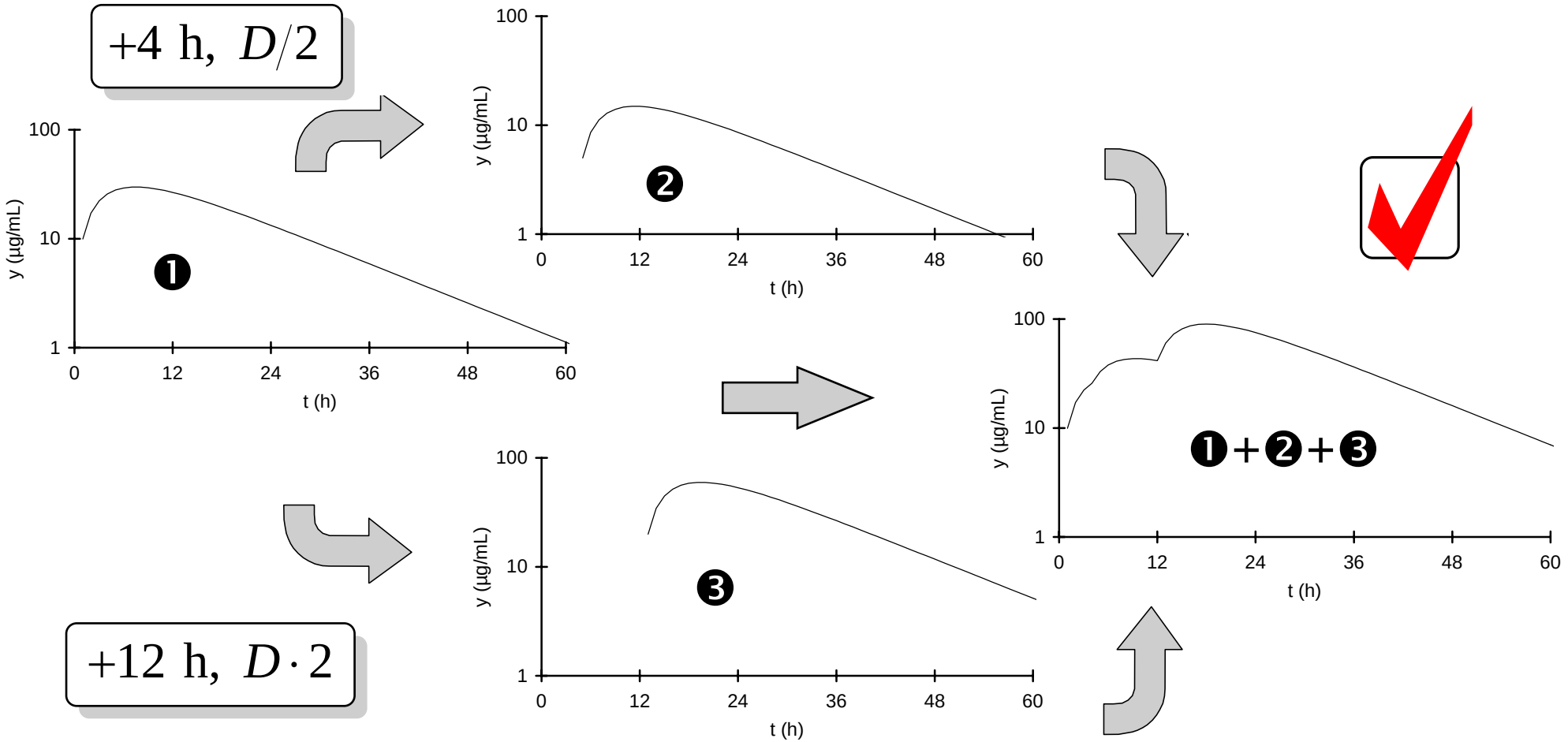
$$\frac{dq_2}{dt} = k_1 \cdot q_1 - k_2 \cdot q_2 \qquad q_2(0) = 0$$

  - V_i and k_{ij} are the parameters (called micro-rates, µrates).

- DE are linear : $y(t)$ is linear with respect to the administered amount, D .
  - Due to this linearity, the superimposition principle holds :

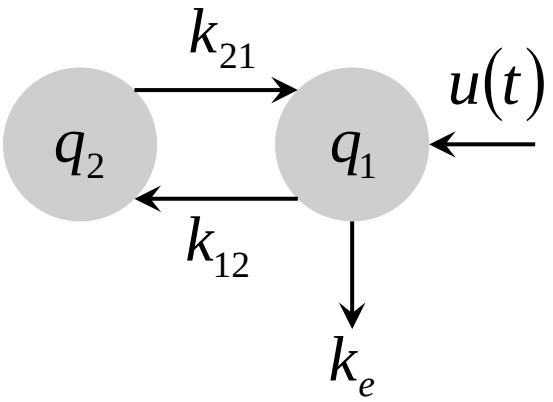
The resulting kinetic after various administration protocols could be evaluated by linearly combining the elementary kinetics obtained after each protocol

Superimposition principle



Compartment modeling

- Fick's diffusion law :



❶ central vs peripheral : $Q = P_d \cdot S_d$ inter-cpt clearance.

❷ central vs environment : $CL = P_e \cdot S_e$ total clearance.

- First order process :

☐ Define :

$$Q = k_{12} \cdot V_1 = k_{21} \cdot V_2$$

$$CL = V_1 \cdot k_e$$

Anatomic

$$\frac{dq_1}{dt} = -CL \cdot y_1 + Q \cdot (y_2 - y_1) + u(t)$$

$$\frac{dq_2}{dt} = Q \cdot (y_1 - y_2)$$

$$q_1 = V_1 \cdot y_1 \quad q_2 = V_2 \cdot y_2$$

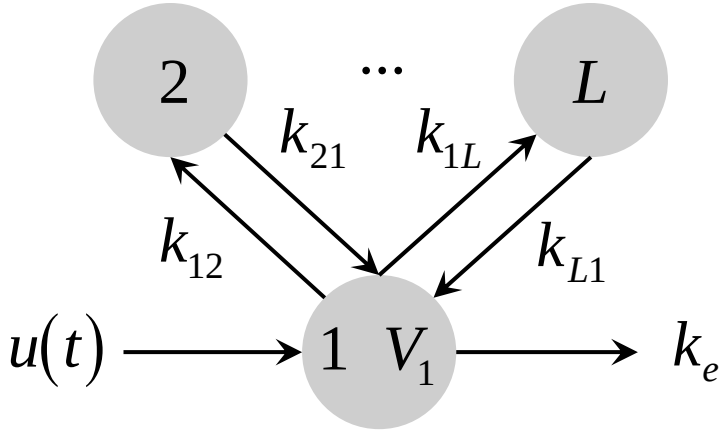
Metabolic

$$\frac{dy_1}{dt} = -k_e \cdot y_1 + k_{12} \cdot (y_2 - y_1) + \frac{u(t)}{V_1}$$

$$\frac{dy_2}{dt} = k_{21} \cdot (y_1 - y_2)$$

Compartment mammillary models

- The commonly used structure :
  1. The material is distributed and eliminated from the central cpt.
  2. No exchanges among peripheral cpts.
  3. Observations are made in the central cpt.



☐ The nbr of parameters in DE is twice L :

★ V_1, k_e and $k_{1i} - k_{i1}$ pairs.

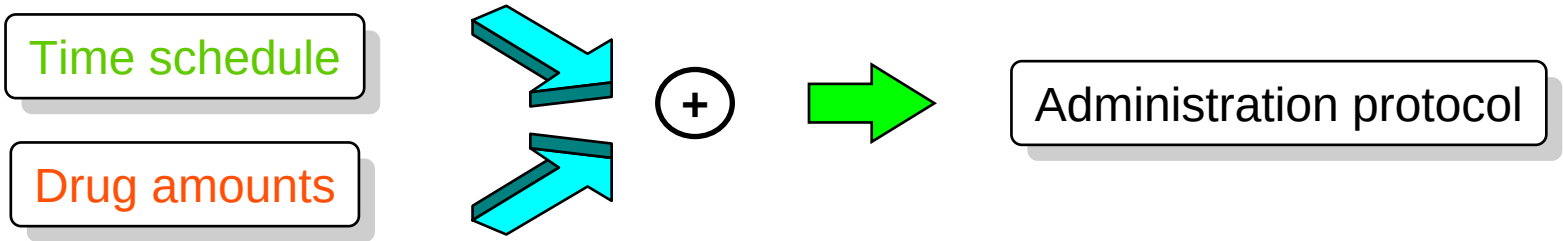
- Note : If peripheral cpts are not sampled, the corresponding V_i cannot be evaluated.

  To assess a fictitious volume, assume flux equality, then :

$$V_i = \left(k_{1i}/k_{i1}\right) \cdot V_1 \qquad i = 2, L$$ and the total $$V_T = V_1 \cdot \left[1 + \sum_{i=2}^{L} \left(k_{1i}/k_{i1}\right)\right]$$

Clearance and administration schemes

- Clearance definitions :
  - ★ Internal : The capacity of a live organism (e.g. liters of drug distribution volume) to eliminate the drug per time unit : $CL = V_1 \cdot k_e$
  - ★ External : The proportionality constant between D and its image at output, the area under the time-concentration curve : $CL = (D/AUC)$
- Administration protocols :
  - ★ Intra- (bolus IV or infusion) and extravascular (oral or intramuscular) routes have been considered in single or repeated dose protocols.
  - ★ Factors defining an administration protocol :



Complex administration protocols

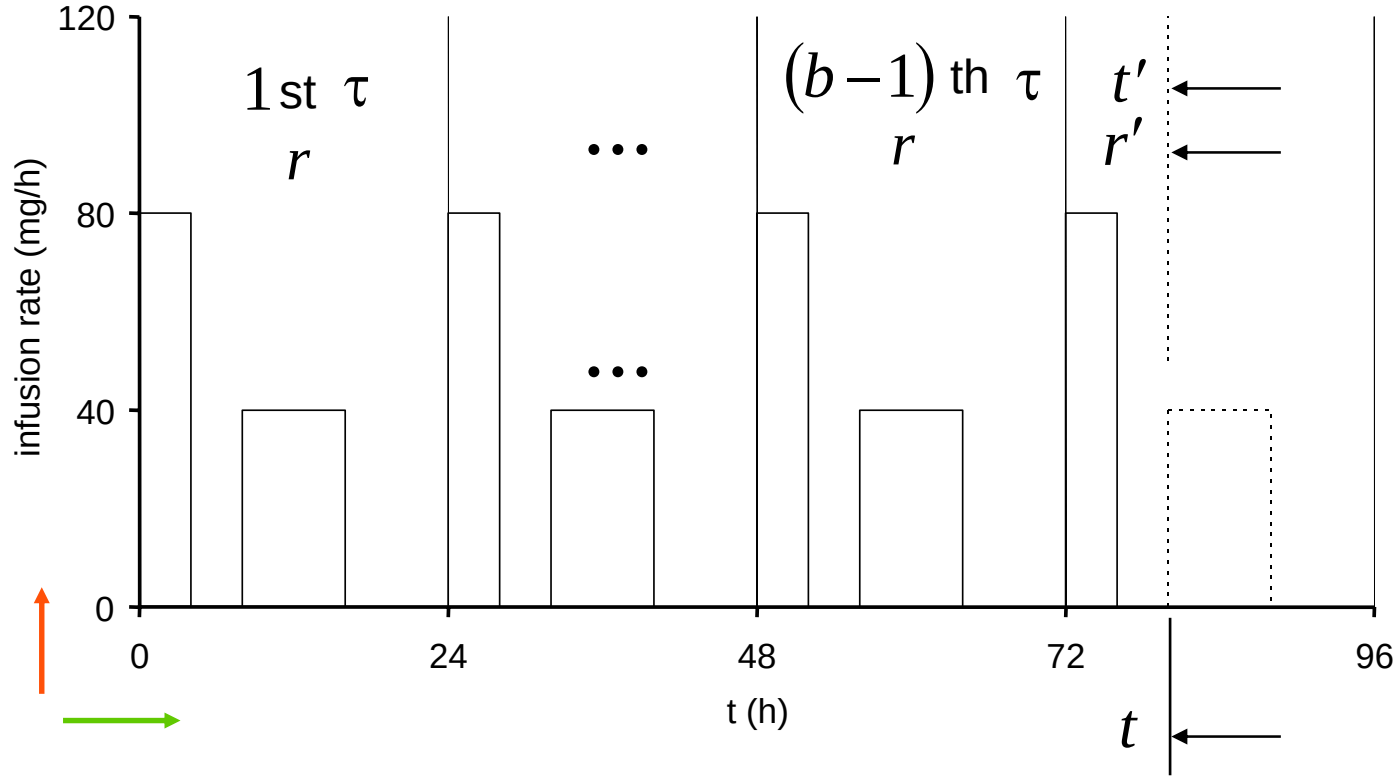
- Definition of terms :

τ : period

r : nbr. of components

b : n° of present period

t : elapsed time from origin



t' : elapsed time from the beginning of the p -th period

$$t' = t - (b-1)\cdot\tau$$

r': nbr. of components under the b-th period

Practical issues

- Special problems for extravascular administrations :
  - ☐ The drug goes through an "absorption compartment" before reaching the central one :
    - ★ Use two new parameters : bioavailability F_a (units : %) ;
      : absorption constant k_a (units : time^{-1}).
    - ★ F_a can be evaluated when drug was given by both intra- and extravascular routes. When data are lacking for one of these, assume complete bioavailability : volumes of distribution and clearance (called apparent) will be overestimated.
- Note : In the next developments, for practical reasons we assume a null initial state.
- Form of the mathematical model : Instead of solving DE for each particular application, develop an analytic generic formula from which the particular cases may be obtained by using a system of control indexes.

General analytic expression

- Analytic form of the generic model :

$$y_{Mi}(t', \underline{x}) = \underline{D}^T \cdot \sum_{j=1}^{L} \underline{h}(a_j, \tau, r, b, r') \cdot A_{ij} \cdot \exp(-a_j \cdot t') \quad \underline{D}\,(r \times 1)$$

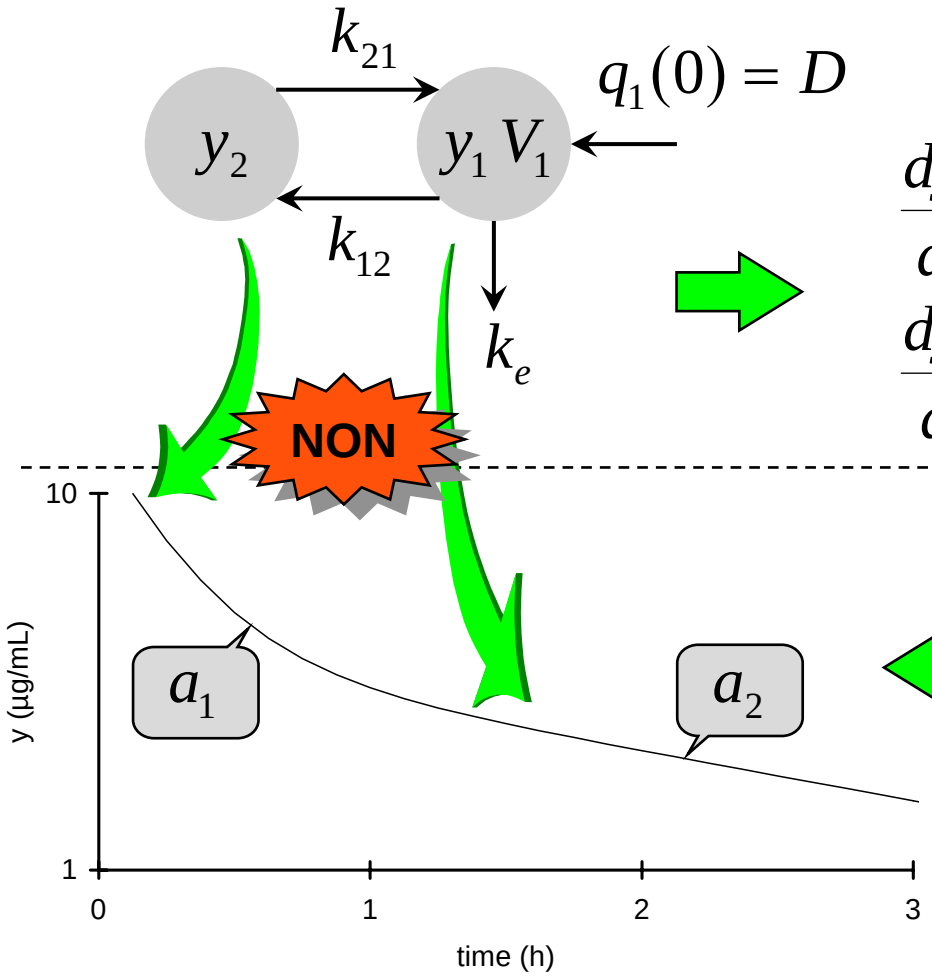
  - Indexes : i associated to the n° of cpt in which y_{Mi} is predicted.

    j associated to the n° of exponential term.
  - The number of exponential terms is equal to the number of compartments.
  - Coefficients A_{ij}, and exponents a_j are called macro-rates, Mrates. Mrates are the parameters to be estimated, components of $\underline{x}\,(p \times 1)$ with $p = 2 \cdot L$.
  - Algebraic relations make it possible to express Mrates as function of µrates and inversely.

- Parametric identifiability :

  How many compartments are they seen through the observed data?

Differential and analytic forms



Differential form, µrates

$$\frac{dy_1}{dt} = -k_e \cdot y_1 + k_{12}(y_2 - y_1) \qquad y_1(0) = \frac{D}{V_1}$$

$$\frac{dy_2}{dt} = k_{21} \cdot (y_1 - y_2) \qquad y_2(0) = 0$$

$$y_1(t) = D \cdot \left(A_{11} \cdot e^{-a_1 \cdot t} + A_{12} \cdot e^{-a_2 \cdot t}\right)$$

$$y_2(t) = D \cdot \left(A_{21} \cdot e^{-a_1 \cdot t} + A_{22} \cdot e^{-a_2 \cdot t}\right)$$

Analytic form, Mrates

Phases of the development

- Goal :
  - Given a compartment configuration (µrates) compute Mrates and then, predict in central and peripheral compartments, $y_{Mi}(t,\underline{x})$, (i indexing the compartment n°) for the specified administration conditions.
  - Let the normalization : $A_{ij} = \hat{A}_{ij} / V_i$
  - $\hat{A}_{ij}$ are normalized coefficients and $h(.)$, a function depending on the administration protocol.
- Steps :
  - ★ compute a_j and $\hat{A}_{ij}$ as function of µrates ;
  - ★ obtain $h(a,\tau,q,p,q')$ according to the administration protocol ;
  - ★ take into account the administration route.

Computing macro-exponents

- For an L-compartment mammillary model :

  ★ a_j are the negative solutions of the L-order algebraic equation :

$$\left[z+\left(k_e+\sum_{s=2}^{L}k_{1s}\right)\right]\cdot\prod_{s=2}^{L}(z+k_{s1})-\sum_{s=2}^{L}k_{1s}\cdot k_{s1}\cdot\prod_{\substack{w=2\\w\neq s}}^{L}(z+k_{w1})=0$$

  ★ **Ex** : 2-compartment model :

$$\left[z+\left(k_e+k_{12}\right)\right]\cdot\left(z+k_{21}\right)-k_{12}\cdot k_{21}=0$$

$$a_1=-z_1 \qquad \text{and} \qquad a_2=-z_2$$

- Note : Order a_j in decreasing order ($a_1 > a_j > a_L$).

Normalized macro-coefficients

- Normalized coefficients :

If $i = 1$:

$$\hat{A}_{1j} = \frac{\prod_{\substack{s=2}}^{L}\left(k_{s1} - a_j\right)}{\prod_{\substack{s=1 \\ s\neq j}}^{L}\left(a_s - a_j\right)}$$

If $i \neq 1$:

$$\hat{A}_{ij} = k_{1i} \cdot \frac{\prod_{\substack{s=2 \\ s\neq i}}^{L}\left(k_{s1} - a_j\right)}{\prod_{\substack{s=1 \\ s\neq j}}^{L}\left(a_s - a_j\right)}$$

Ex : 2-compartment model :

		$j = 1$	$j = 2$
★ Central :	$i = 1$	$\hat{A}_{11} = \left(k_{21} - a_1\right)/\left(a_2 - a_1\right)$	$\hat{A}_{12} = \left(k_{21} - a_2\right)/\left(a_1 - a_2\right)$
★ Peripheral :	$i = 2$	$\hat{A}_{21} = k_{12}/\left(a_2 - a_1\right)$	$\hat{A}_{22} = k_{12}/\left(a_1 - a_2\right)$

Some properties

- Properties of $\hat{A}_{ij}$:

  ❶ $\frac{1}{k_e} = \sum_{j=1}^{L} \frac{\hat{A}_{ij}}{a_j}$ ❷ if $i = 1$, $\sum_{j=1}^{L} \hat{A}_{ij} = 1$ else $\sum_{j=1}^{L} \hat{A}_{ij} = 0$

- Remember :

  ★ index i denotes the compartment n° for prediction ;

  ★ index j denotes the exponential term n°.

- Conclusion :

  ★ The terminal half-life is associated with a_L ,

  ★ There is no correspondence between i and j .

Computing macro-coefficients (1)

- Note : - set $\tau \to \infty$ for an irregular administration protocol ;
  - the steady state is obtained for $p \to \infty$.

  Ex : - single dose : $\tau \to \infty$ and $r = r' = 1$;
  - single dose repeated daily : $\tau = 24\ \text{h}$ and $r = r' = 1$.

- Form of the administration factor (units : mass) : superimposition principle.

$$h(a, \tau, r, p, r') = \underbrace{\text{Contribution of the } p-1 \text{ entirely administered periods}}_{} + \underbrace{\text{Contribution of the } r' \text{ components of the present period}}_{}$$

- Let :

$$R_0 = e^{-a\cdot\tau} \cdot \frac{1 - e^{-(p-1)\cdot a\cdot\tau}}{1 - e^{-a\cdot\tau}}$$

(R_0 cancels for irregular administrations)

Computing macro-coefficients (2)

- For the k – th intravascular administration :

  ❶ t_{sk} , t_{ek} : start and end infusion times, ❷ $T_k = t_{ek} - t_{sk}$: the duration of infusion.

  D_k : total infused drug amount.

$$R(r) = \sum_{k=1}^{r} \frac{D_k}{T_k} \cdot \left(e^{a \cdot t_{ek}} - e^{a \cdot t_{sk}} \right) \quad \text{and} \quad h(a, \tau, r, p, r') = \frac{1}{a} \cdot \left[R_0 \cdot R(r) + R(r') \right]$$

- For the k – th extravascular administration :

  t_k : the administration time,

  D_k : the administered drug amount.

$$R(r) = \sum_{k=1}^{r} D_k \cdot e^{a \cdot t_k} \quad \text{and} \quad h(a, \tau, r, p, r') = R_0 \cdot R(r) + R(r')$$

Route of administration

- Intravascular administration : with
  - ☐ After stopping infusion for the $r'-$ th component :

$$y_{Mi}^{(2)}(t',\underline{x}) = \frac{1}{V_i}\cdot\sum_{j=1}^{L}\hat{A}_{ij}\cdot h\left(a_j,\tau,r,p,r'\right)\cdot e^{-a_j\cdot t'}$$

$$t'\in\left]0,\tau\right]$$

  - ☐ During infusion time for the $q'-$ th component :

$$y_{Mi}^{(1)}(t',\underline{x}) = y_{Mi}^{(2)}(t',\underline{x}) + \frac{1}{V_i}\cdot\frac{D_{r'}}{T_{r'}}\cdot\sum_{j=1}^{L}\frac{\hat{A}_{ij}}{a_j}\cdot\left[1-e^{-a_j\cdot(t'-t_{sr'})}\right]$$

- Extravascular administration :

$$y_{Mi}(t',\underline{x}) = \frac{1}{V_i}\cdot\sum_{j=1}^{L}\hat{A}_{ij}\cdot\frac{k_a}{k_a-a_j}\cdot\left[h\left(a_j,\tau,r,p,r'\right)\cdot e^{-a_j\cdot t'} - h\left(k_a,\tau,r,p,r'\right)\cdot e^{-k_a\cdot t'}\right]$$

Repeated administrations

- Steady state :
  - Obtain a target average level C_{ave} by periodic administrations of D_R every τ :

$$u_o \equiv \frac{D_R}{\tau} = CL \cdot C_{ave}$$

Input-output balance over a period

  - Define : $AUC_R \equiv \frac{D_R}{CL} = C_{ave} \cdot \tau$ and $AUC_S \equiv \frac{D_s}{CL}$ in single dose.
  - If $D_R = D_S$ then : $AUC_R = AUC_S$

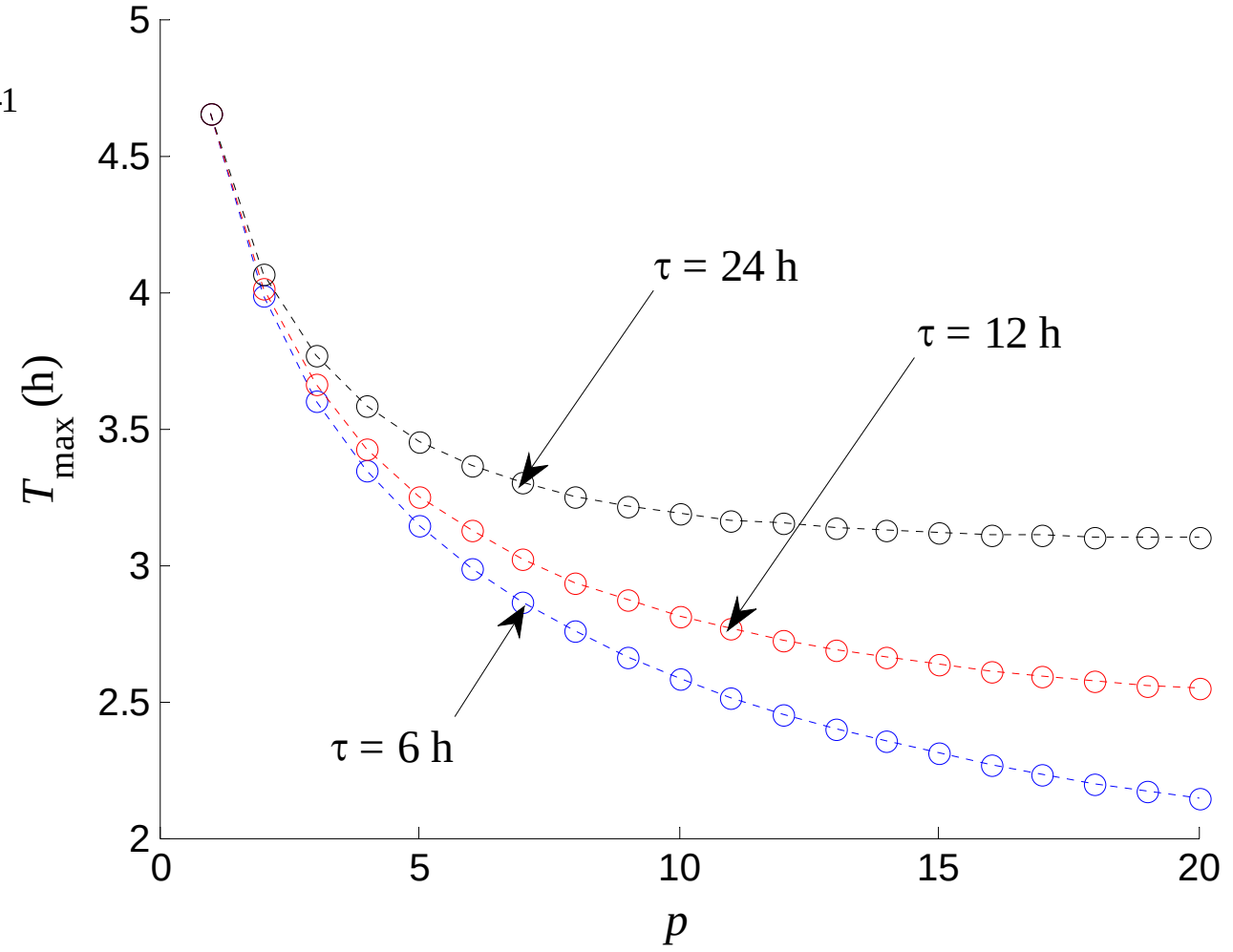
- Extravascular 1-cpt : $T_{\max}$ is moving …

$$T_{\max} = \frac{1}{k_a - a_1} \cdot \log\left[\frac{k_a}{a_1} \cdot \frac{1-e^{-p \cdot k_a \cdot \tau}}{1-e^{-p \cdot a_1 \cdot \tau}} \cdot \frac{1-e^{-a_1 \cdot \tau}}{1-e^{-k_a \cdot \tau}}\right]$$

T_{max} is p dependent

- $k_a = 1\,\mathrm{h}^{-1}$ $\quad a_1 = 0.01\,\mathrm{h}^{-1}$

- T_{max} :
  - is lower for τ low (reduce fluctuations).
  - appears early in RD for τ high (rule of $5 \cdot t_{1/2}$).



Intravascular, 1-cpt model …

- After stopping infusion :
  - ☐ Single administration : $$y_{M1}^{SD}(t,\underline{x}) = \frac{1}{V_1} \cdot \frac{D}{T \cdot a_1} \cdot \left[e^{-a_1 \cdot (t-T)} - e^{-a_1 \cdot t} \right]$$
  - ☐ Repeated administrations : $$y_{M1}^{RD}(t',\underline{x}) = \frac{1-e^{-p \cdot a_1 \cdot \tau}}{1-e^{-a_1 \cdot \tau}} \cdot y_{M1}^{SD}(t,\underline{x})$$ $a_1 \equiv k_e$
  - ☐ With : $$A(p) \equiv \frac{1-e^{-p \cdot a_1 \cdot \tau}}{1-e^{-a_1 \cdot \tau}}$$ for $\forall \quad t = t' \quad \in \quad [0 \quad \tau]$
  - ☐ Accumulation factor : $$A(p) \xrightarrow[p \to \infty]{} A^* \equiv \frac{1}{1-e^{-a_1 \cdot \tau}}$$
  - ⇒ $$y_{M1}^{RD}(t',\underline{x}) = A(p) \cdot y_{M1}^{SD}(t,\underline{x})$$
  - ☐ Steady-state kinetics : $p \to \infty$ $$y_{M1}^{SS}(t',\underline{x}) = A^* \cdot y_{M1}^{SD}(t,\underline{x})$$

Specific conditions

… min max concentrations …

- Single dose :

$$\max\left[y_{M1}^{SD}(T,\underline{x})\right]=\frac{D}{V_1}\cdot\frac{1-e^{-a_1\cdot T}}{T\cdot a_1} \qquad \min\left[y_{M1}^{SD}(\tau,\underline{x})\right]=\frac{D}{V_1}\cdot\frac{e^{a_1\cdot T}-1}{T\cdot a_1}\cdot e^{-a_1\cdot\tau}$$

- Steady state :

$$\max\left[y_{M1}^{SS}(T,\underline{x})\right]=A^*\cdot\max\left[y_{M1}^{SD}(T,\underline{x})\right] \qquad \min\left[y_{M1}^{SS}(\tau,\underline{x})\right]=A^*\cdot\min\left[y_{M1}^{SD}(\tau,\underline{x})\right]$$

- Intravascular bolus :
  - When $T\to 0$ then $\dfrac{1-e^{-a_1\cdot T}}{a_1\cdot T}=\dfrac{e^{a_1\cdot T}-1}{a_1\cdot T}\to 1$
  - Steady state :

$$\max\left[y_{M1}^{SS}(\underline{x})\right]=A^*\cdot\frac{D}{V_1} \qquad \min\left[y_{M1}^{SS}(\tau,\underline{x})\right]=A^*\cdot\frac{D}{V_1}\cdot e^{-a_1\cdot\tau}$$

… specific and general conditions

- Time to reach steady-state :
  - For δ small, determine p such that $(1-\delta)\cdot A^{*} = A(p)$:

$$p\cdot\tau = -\frac{\ln\delta}{\ln 2}\cdot t_{1/2}$$

Specific conditions

  - Ex : For $\delta = 0.03$ the time need to reach steady state is $p\cdot r \approx 5\cdot t_{1/2}$ and it may be covered by p repetitions of period τ .

- General conditions :
  - Intravascular during infusion, extravascular route, several components, multi-cpt configurations : The above approximately holds provided that $a_{i+1} >> a_i$.

- Reduce fluctuations :

Increase T for intra- or decrease k_a for extravascular

Loading dose

- Obtain optimum drug effects : The « loading dose » scheme
- Use the accumulation factor : $D^p = \dfrac{D_{SS}}{1 - e^{-p \cdot a_1 \cdot \tau}}$

$$\frac{D^{SS}}{D^1} = 1 - 2^{-\frac{\tau}{t_{1/2}}}$$

The smaller the ratio $\tau / t_{1/2}$, the larger the ratio D^1 / D^{SS}

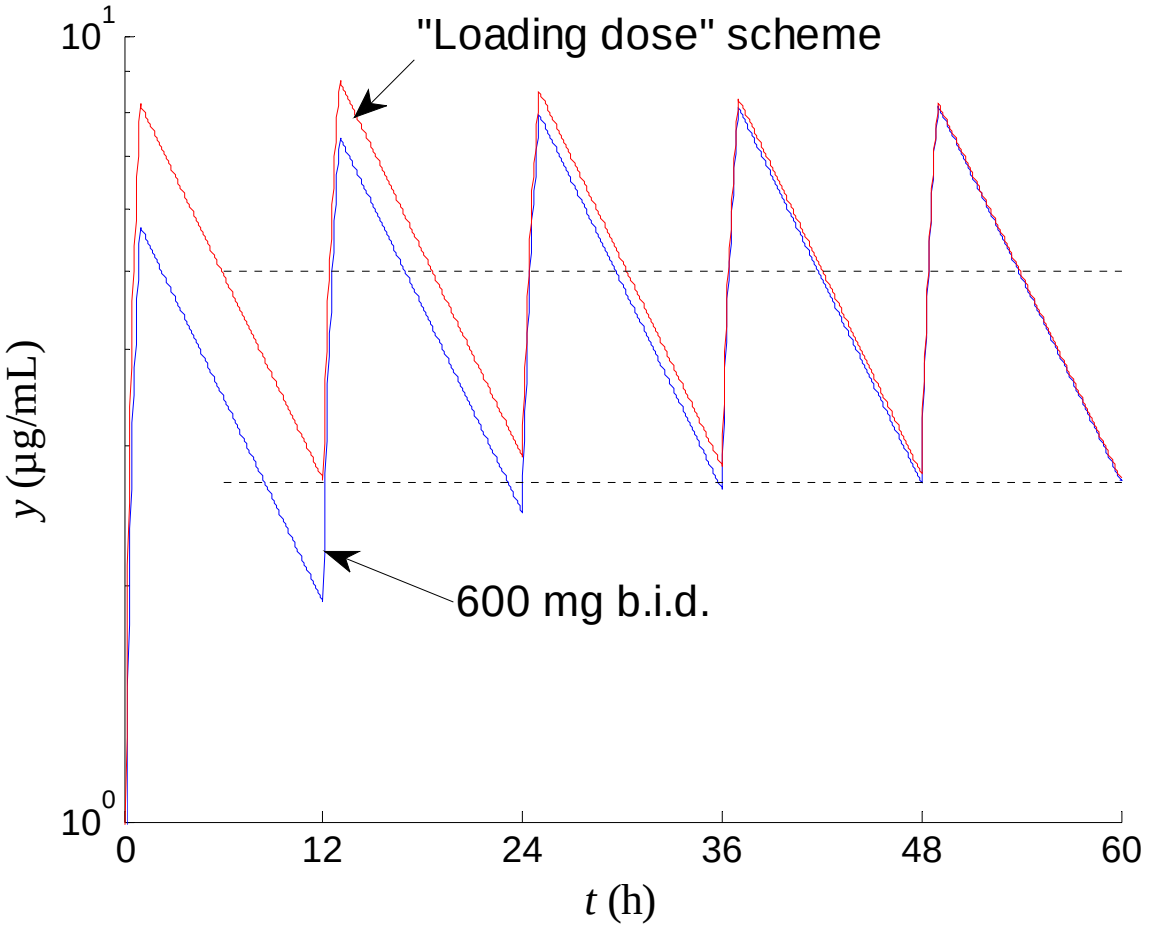
★ If $\tau \approx t_{1/2}$ then $D^1 = 2 \cdot D^{SS}$

- Ex : $V_1 = 100\,\mathrm{L}$ $k_e = 0.1\,\mathrm{h^{-1}}$
  $T = 1\,\mathrm{h}$ $\tau = 12\,\mathrm{h}$

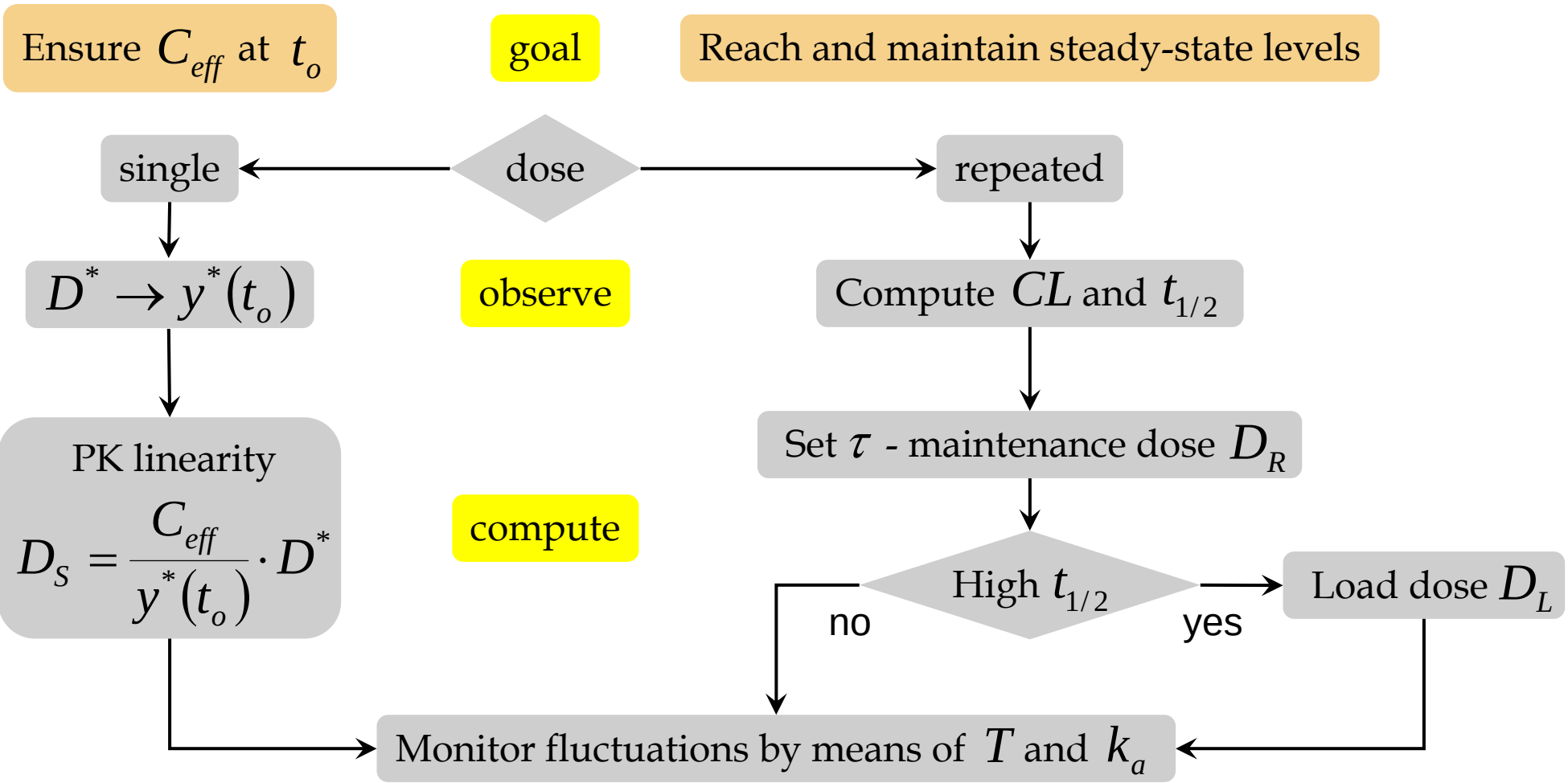
  □ $D^{SS} = 600\,\mathrm{mg}$ ensures $y_{ave}^{SS} = 5\,\mu\mathrm{g/mL}$

Dosage calculation

	p	D^p (mg)
Loading dose	1	859
Transient doses	2	660
	3	617
	4	605
Maintenance dose	5	600



Flowchart for dosage regimen



Equilibrium state

$$\text{Equilibrium state} \equiv \text{Steady state} \;/\; \tau \to 0$$

- Mammillary cpt model :

$$\frac{dy_1}{dt} = -k_e \cdot y_1 - k_{1i} \cdot (y_1 - y_i) + \frac{u(t)}{V_1} \qquad y_1(0) = 0$$

$$\frac{dy_i}{dt} = k_{i1} \cdot (y_1 - y_i) \qquad y_i(0) = 0$$

☐ Mass-balance for a peripheral compartment :

$$\frac{dy_i}{dt} = 0 \to y_1 = y_i$$

The intersection of time-concentration profiles behaves at the maximum concentration of y_i

☐ Mass-balance for the central compartment :

$$\frac{dy_1}{dt} = 0 \to u_o = V_1 \cdot k_e \cdot y_{1o} = CL \cdot y_{1o}$$

Reach y_{1o} at the equilibrium state depends simply on the CL

Conversion of μ-rates to M-rates

- Express A_1 A_2 a_1 a_2 as functions of V_1 k_e k_{12} k_{21} .

$$a_1 + a_2 = k_e + k_{12} + k_{21} \qquad A_1 = \frac{1}{V_1} \cdot \frac{k_{21} - a_1}{a_2 - a_1}$$

$$a_1 \cdot a_2 = k_e \cdot k_{21} \qquad A_2 = \frac{1}{V_1} \cdot \frac{k_{21} - a_2}{a_1 - a_2}$$

- Express V_1 k_e k_{12} k_{21} as functions of A_1 A_2 a_1 a_2 .

$$k_{21} = \frac{A_2 \cdot a_1 + A_1 \cdot a_2}{A_2 + A_1} \quad k_e = \frac{a_1 \cdot a_2}{k_{21}} \quad k_{12} = a_1 + a_2 - (k_e + k_{21}) \quad V_1 = \frac{1}{A_1} \cdot \frac{k_{21} - a_1}{a_2 - a_1}$$

- Application:

$$V_1 = 7.742\ \text{L} \quad k_e = 0.868\ \text{h}^{-1} \quad k_{12} = 1.856\ \text{h}^{-1} \quad k_{21} = 1.302\ \text{h}^{-1}$$

$$A_1 = 9.144 \cdot 10^{-2}\ \text{L}^{-1} \quad A_2 = 3.772 \cdot 10^{-2}\ \text{L}^{-1} \quad a_1 = 3.723\ \text{h}^{-1} \quad a_2 = 0.304\ \text{h}^{-1}$$

Summary, notes

- PK linearity was used to elaborate the previous formulas.
- The estimated parameters are macrorates in the identification task.
- Complex formula to predict $y_{Mi}(t, \underline{x})$ used :
  - ★ inside the criterion function J ;
  - ★ for simulation and dosage regimen applications.
- Main advantage : ⇨ very general conditions :
  1. multi-compartment configuration ;
  2. periodic or irregular protocols ;
  3. all possible routes of administration ;
  4. analytic forms (no DE, fast computing).

The reference experiment

- Intravascular route : 100 mg by bolus.
  - Fixed μ-rates :

$$V_1 = 7.742\ \mathrm{L}$$

$$k_e = 0.868\ \mathrm{h^{-1}}$$

$$k_{12} = 1.856\ \mathrm{h^{-1}}$$

$$k_{21} = 1.302\ \mathrm{h^{-1}}$$

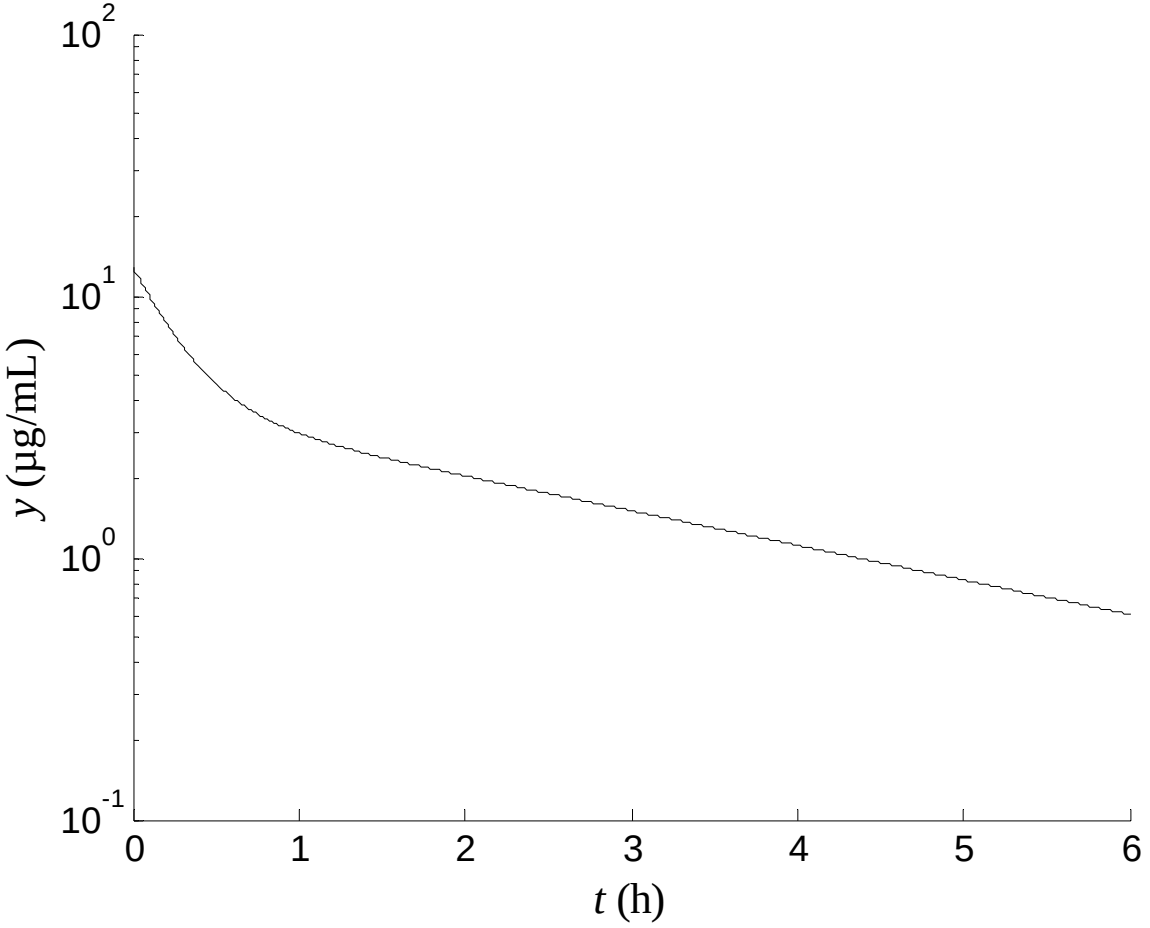
  - Computed M-rates :

$$A_{11} = 9.144 \cdot 10^{-2}\ \mathrm{L^{-1}}$$

$$A_{12} = 3.772 \cdot 10^{-2}\ \mathrm{L^{-1}}$$

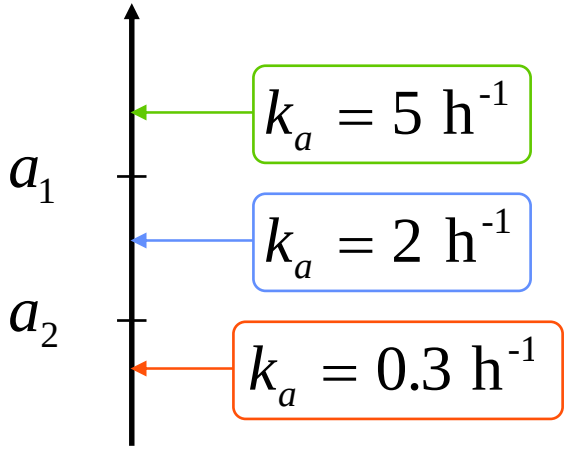
$$a_1 = 3.723\ \mathrm{h^{-1}}$$

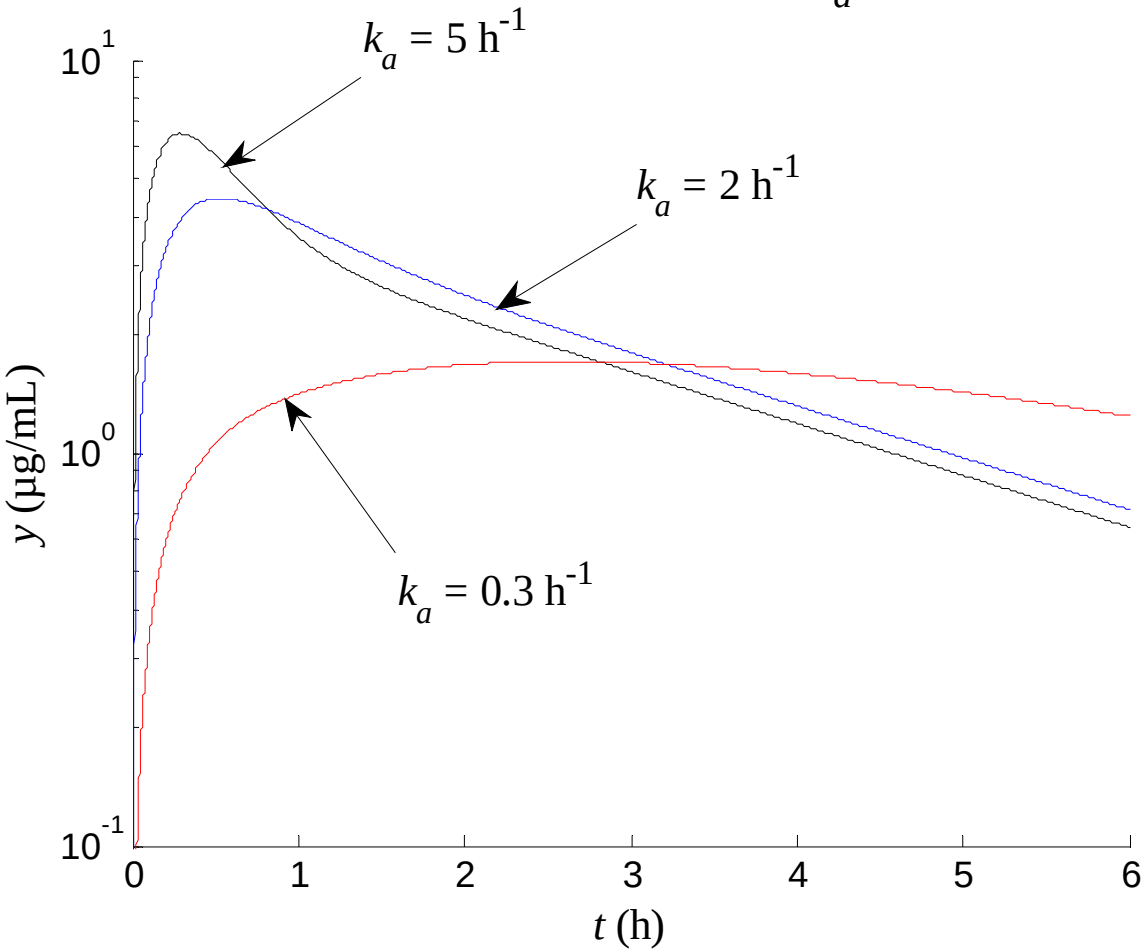
$$a_2 = 0.304\ \mathrm{h^{-1}}$$



The "flip-flop"

- Extravascular case : The influence of absorption rate constant, k_a .
  - ☐ Reference μ-rates.
  - ☐ Complete bioavailability.
  - ☐ Vary k_a :





Repeated administrations

- Intravascular case : The influence of the period τ (for the previous data).

❶ Administr. unit : 100 mg / 0.05 h.

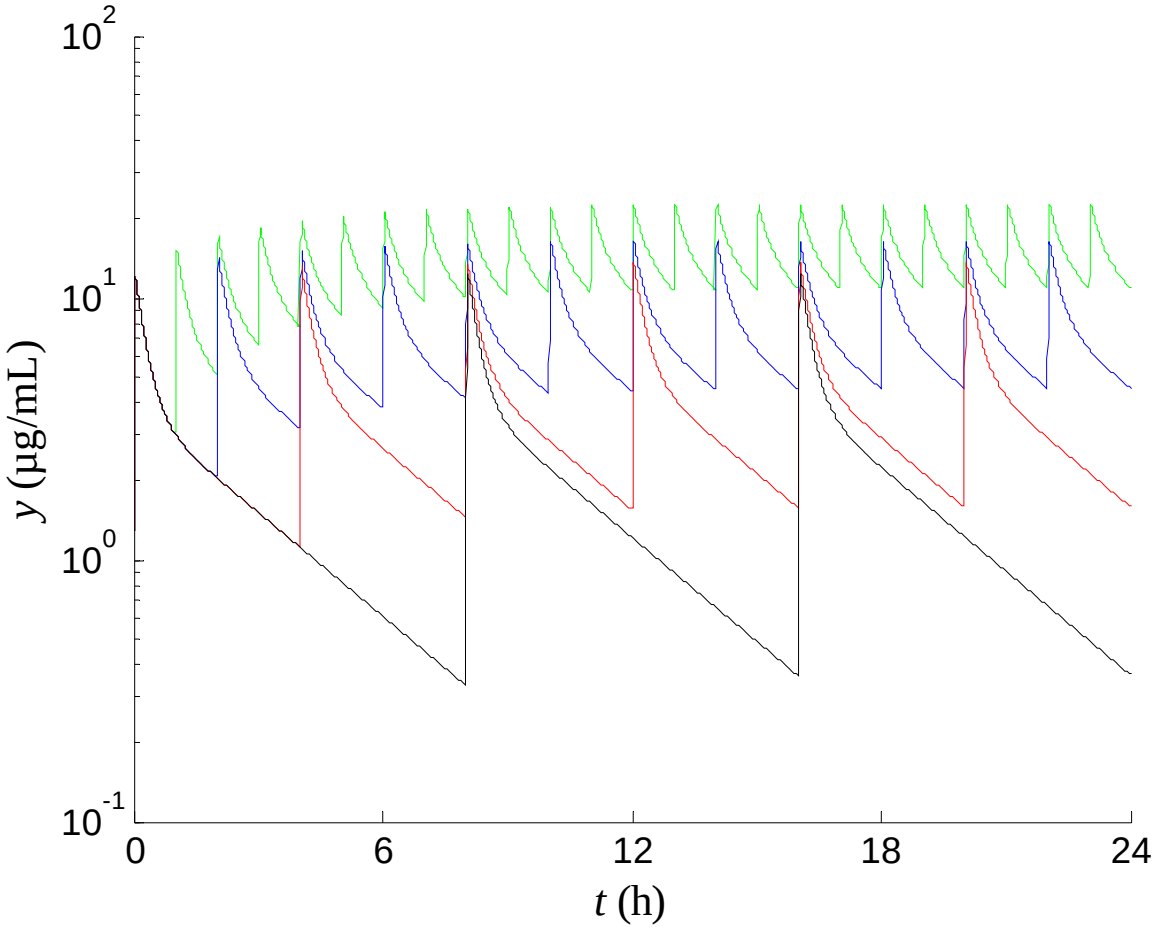
❷ $t_{1/2} \approx 2\,\text{h}$

τ	$y_{\min}$	$y_{\max}$
1	10.94	22.82
2	4.54	16.56
4	1.60	13.66
8	0.36	12.44

☐ with τ increasing :

★ $y_{\min}$ and $y_{\max}$ decrease,

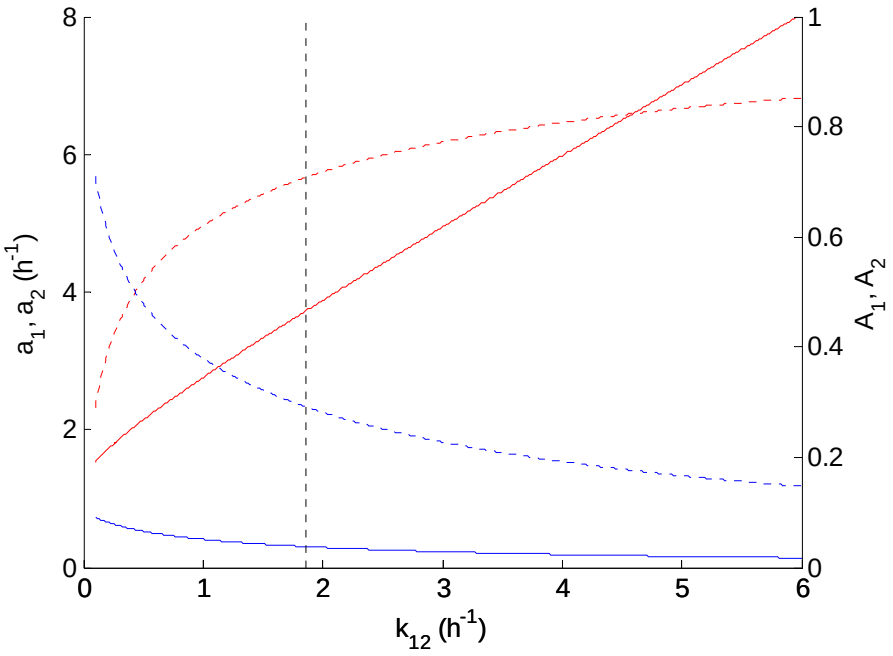
★ $\left(y_{\max} - y_{\min}\right)$ increases.

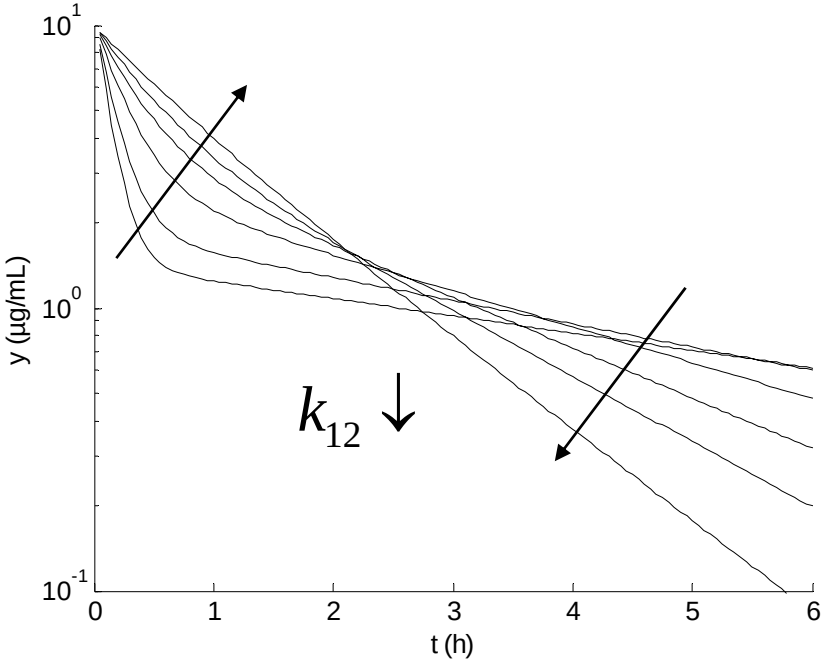


Sensitivity to the μ-rate k_{12}

- Intravascular case : 75 mg / 0.05 h
  - the same model as above : $k_{21} = 1.302\ \text{h}^{-1}$
  - variable $k_{12} \in [0.1 - 6]\ \text{h}^{-1}$

for $k_{12} << k_{21}$ the kinetic becomes mono-phasic

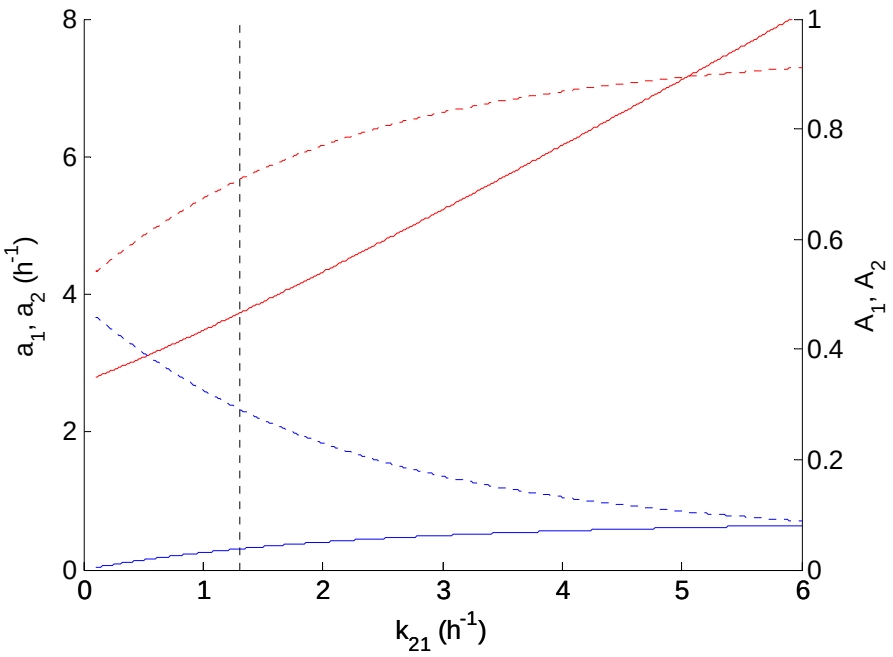


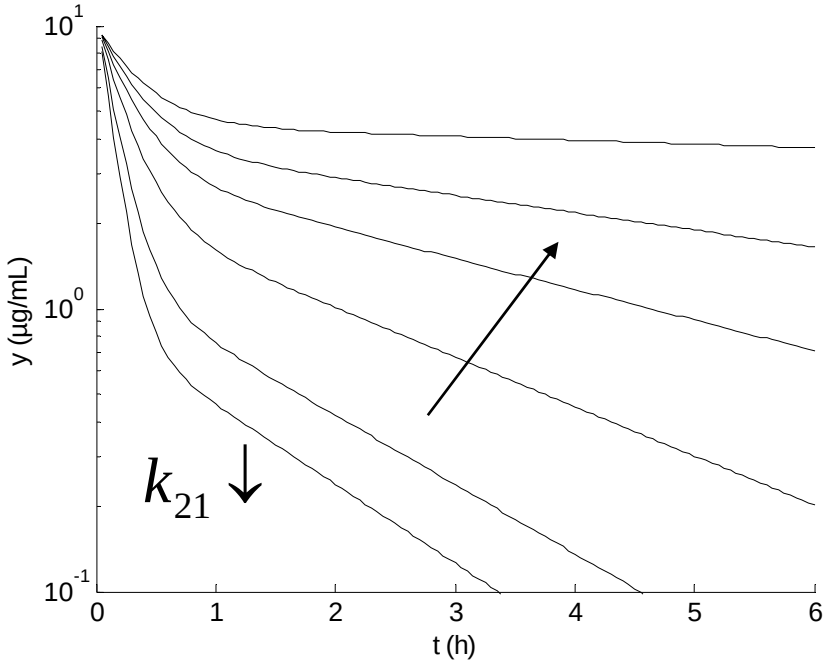


Sensitivity to the μ-rate k_{21}

- Intravascular case : 75 mg / 0.05 h
  - the same model as above : $k_{12} = 1.856\ \text{h}^{-1}$
  - variable $k_{21} \in [0.1 - 6]\ \text{h}^{-1}$

decreasing k_{21} decelerates the slopes of phases

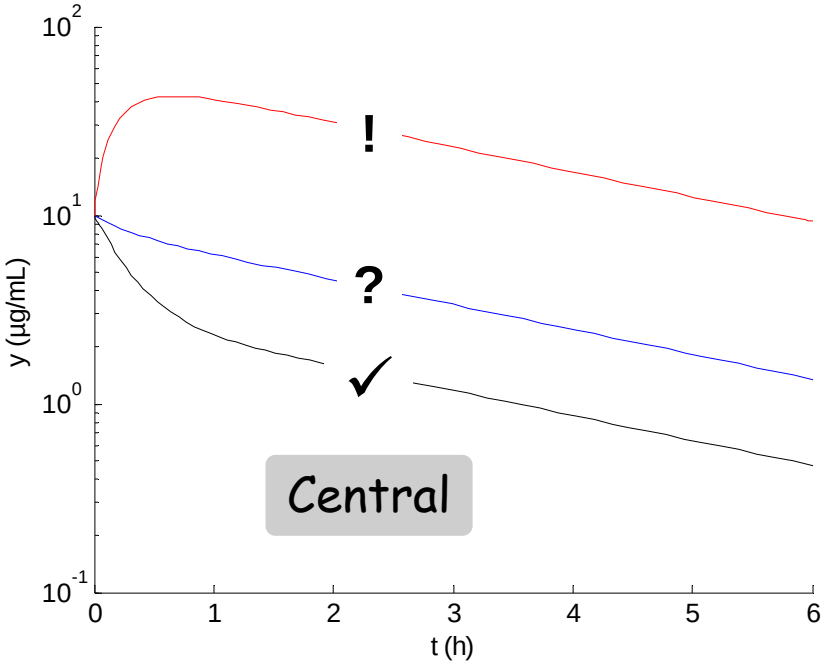


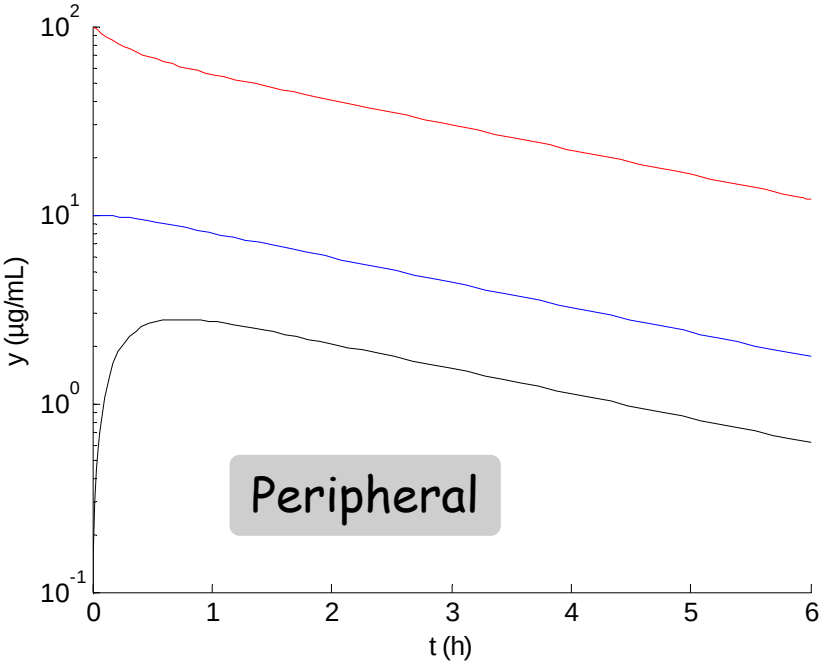


Sensitivity to the initial conditions

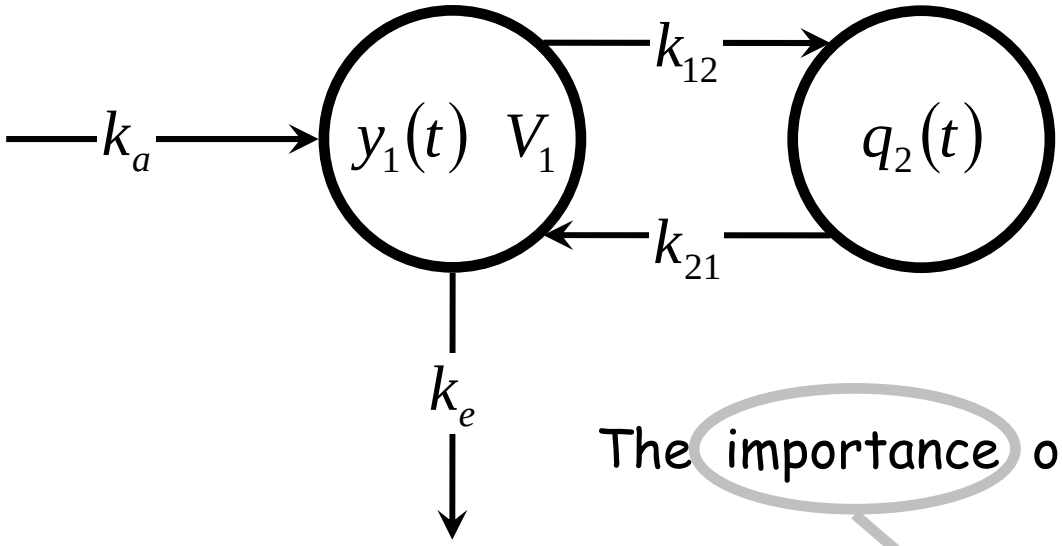
- Configuration with initial conditions : (the same model as above)
  - Central cpt : $y_1(0) = 10\ \mu g \cdot mL^{-1}$
  - Peripheral cpt : $y_2(0) = 0 \quad 10 \quad 100\ \mu g \cdot mL^{-1}$

  ⇩ for $y_1(0) \approx y_2(0)$ the quick decline disappears ⇩





The need for a functional modeling



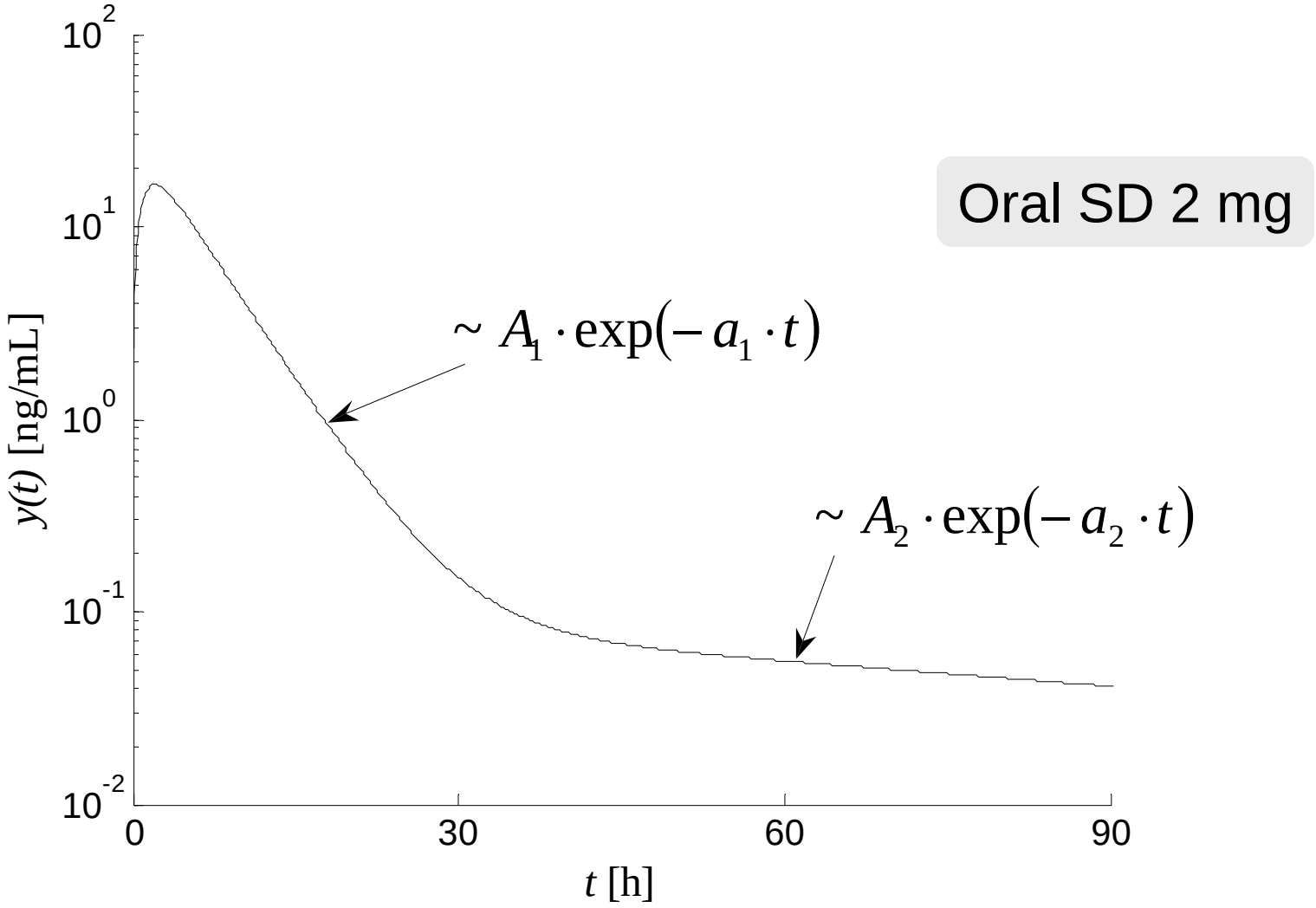
The importance of the elimination rate

Clearance $CL = V_1 \cdot k_e$

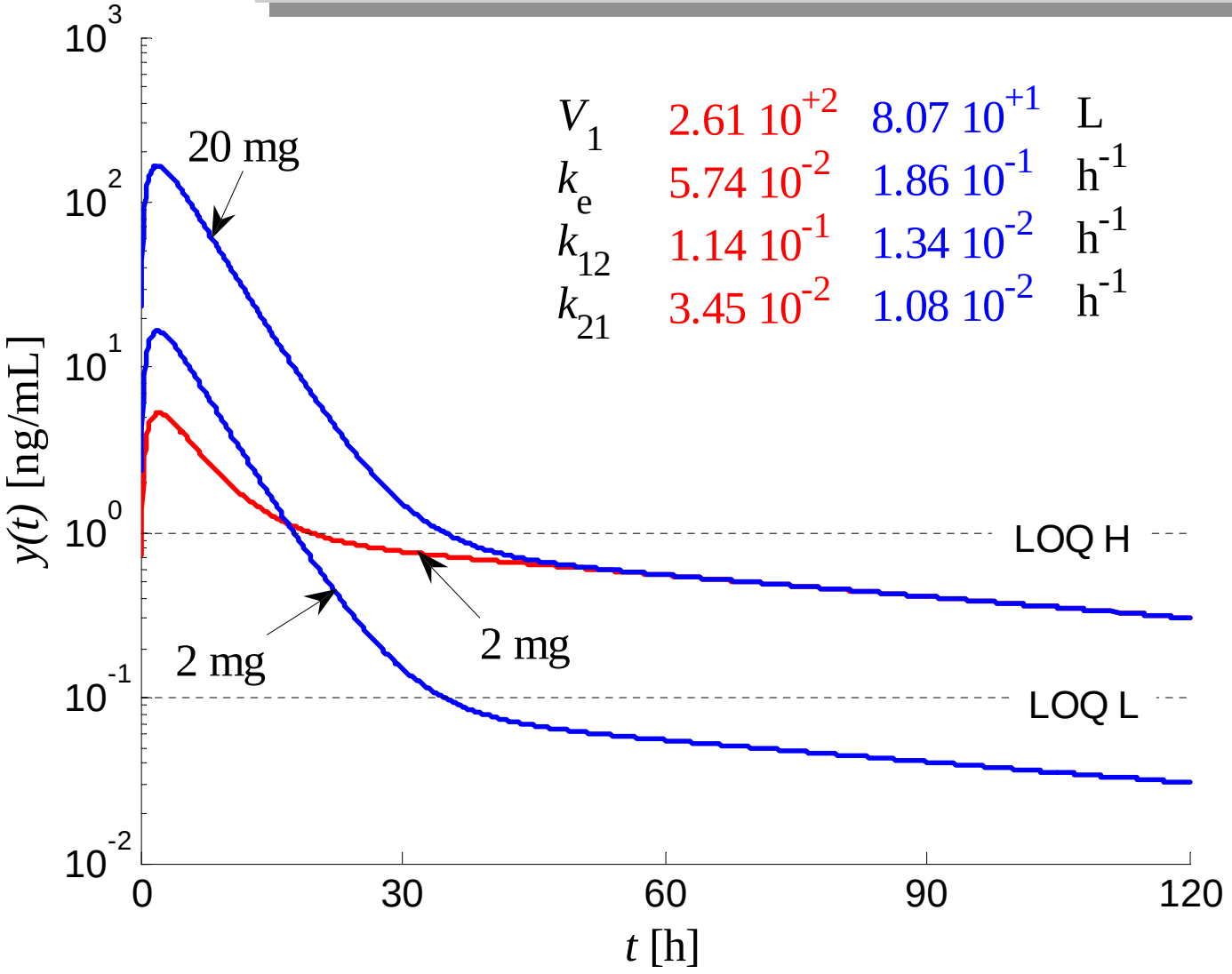
Half-life $t_{1/2} = \dfrac{\ln 2}{a_2}$

$$y_1(t) \propto \begin{cases} A_1 \cdot \exp(-a_1 \cdot t) + \\ A_2 \cdot \exp(-a_2 \cdot t) - \\ (A_1 + A_2) \cdot \exp(-k_a \cdot t) \end{cases}$$

Time-concentration profile



Profiles and LOQ



V_1	$2.61\ 10^{+2}$	$8.07\ 10^{+1}$	L
k_e	$5.74\ 10^{-2}$	$1.86\ 10^{-1}$	h^{-1}
k_{12}	$1.14\ 10^{-1}$	$1.34\ 10^{-2}$	h^{-1}
k_{21}	$3.45\ 10^{-2}$	$1.08\ 10^{-2}$	h^{-1}

$$CL = 15\,\mathrm{L}\cdot\mathrm{h}^{-1}$$

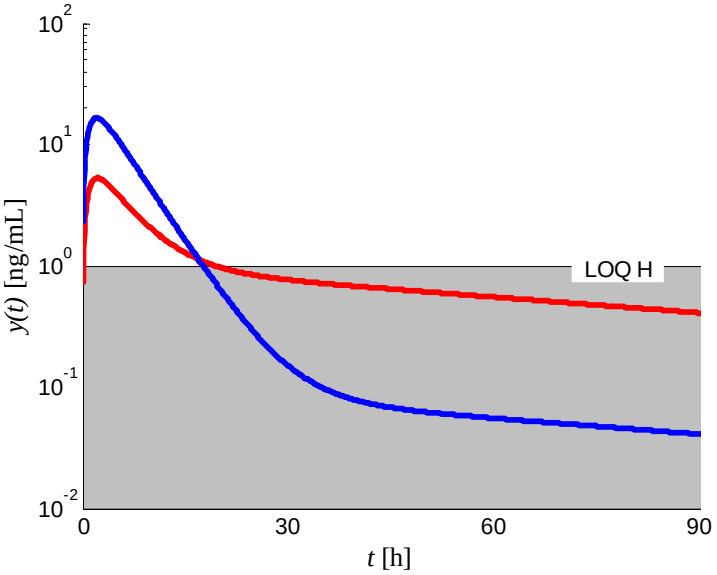
$$t_{1/2} = 70\,\mathrm{h}$$

$$k_a = 1\,\mathrm{h}^{-1}$$

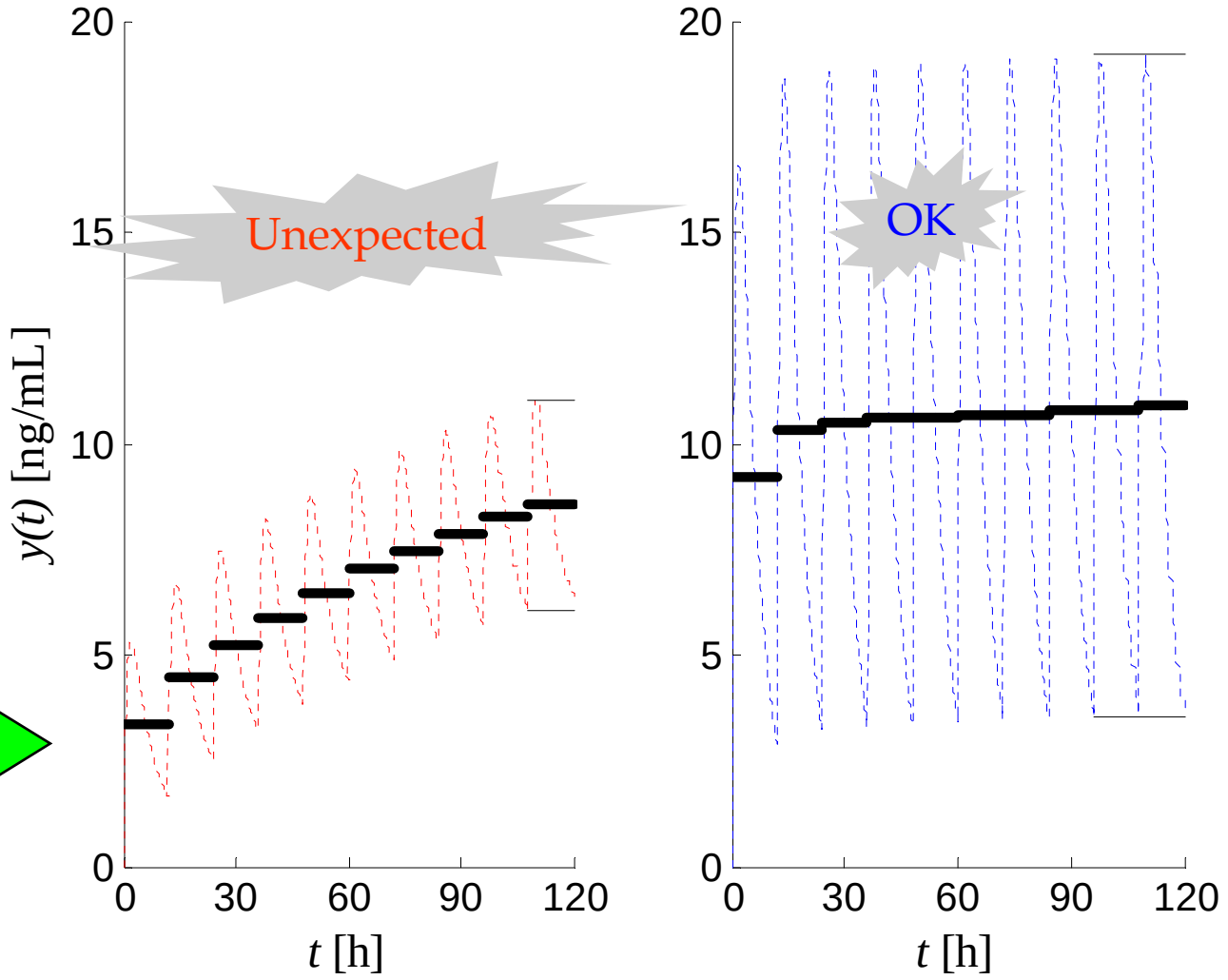
$$\frac{A_1}{A_2} \approx 6$$

$$\frac{A_1}{A_2} \approx 250$$

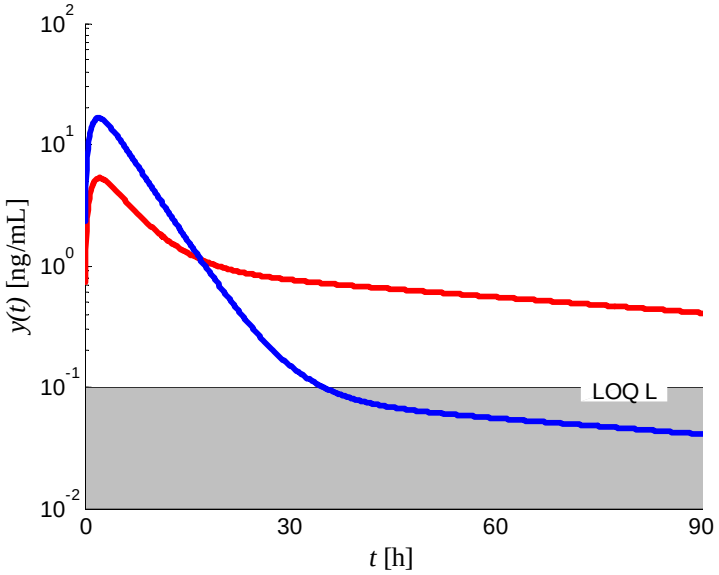
High LOQ , [2 vs. 2 mg], RD



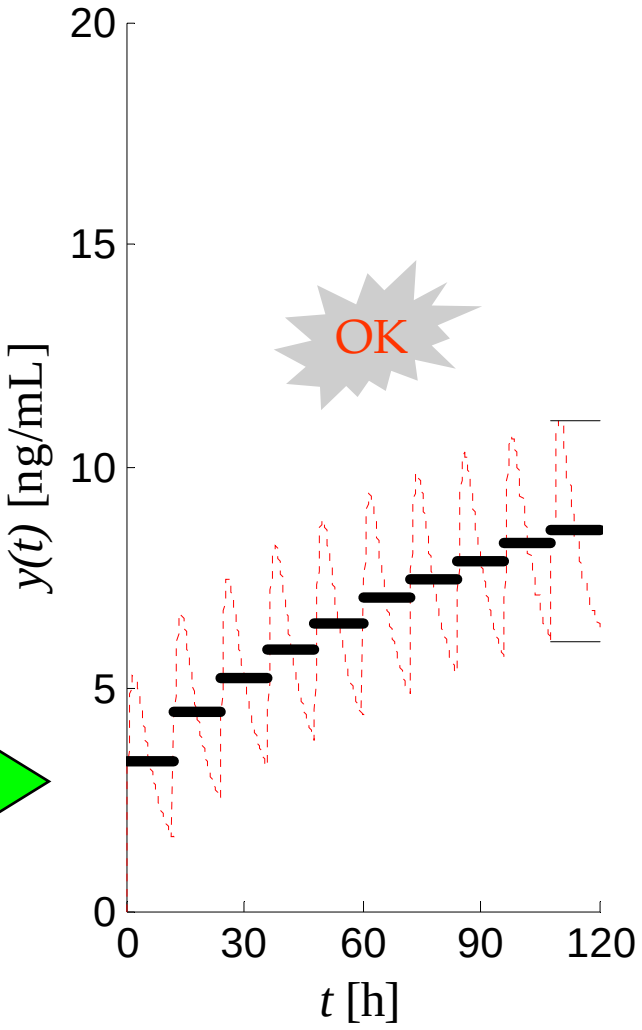
Oral RD 2 mg bid

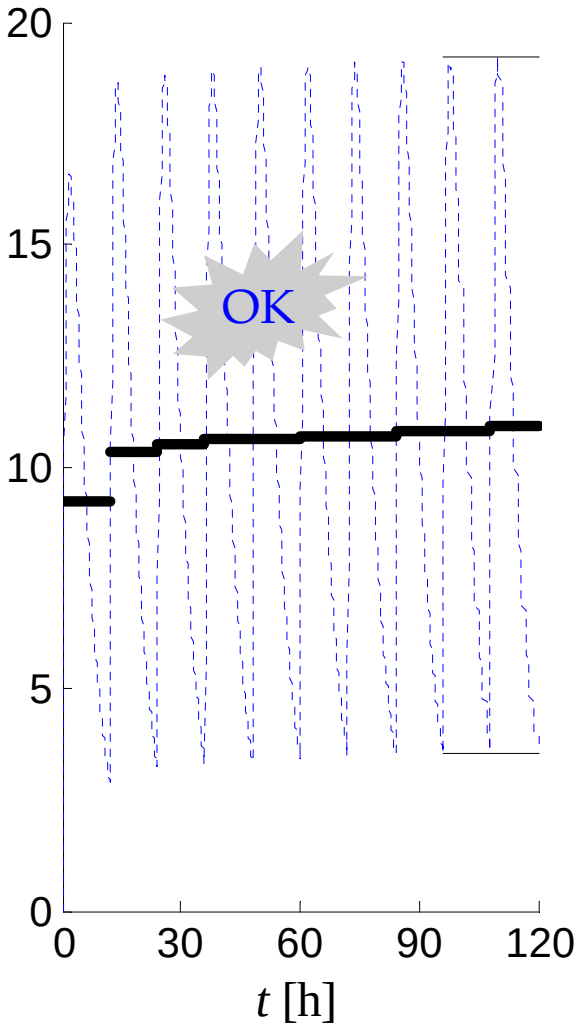


Low LOQ, [2 vs. 2 mg] , RD

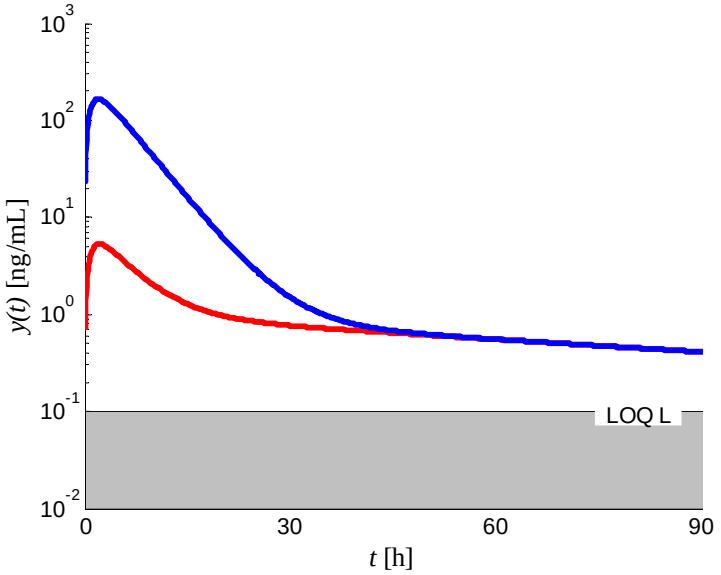


Oral RD 2 mg bid

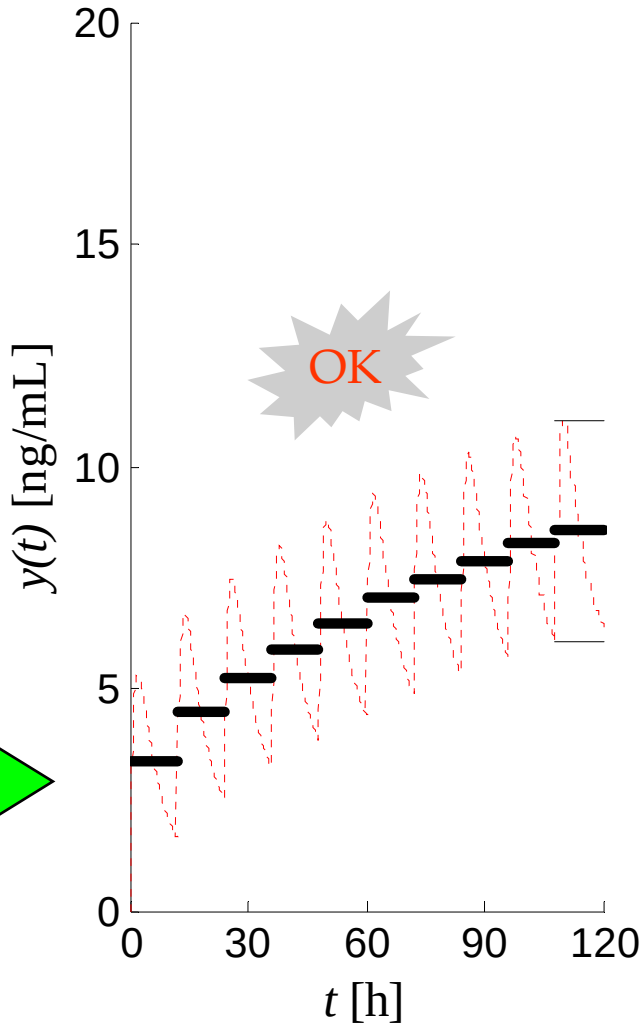


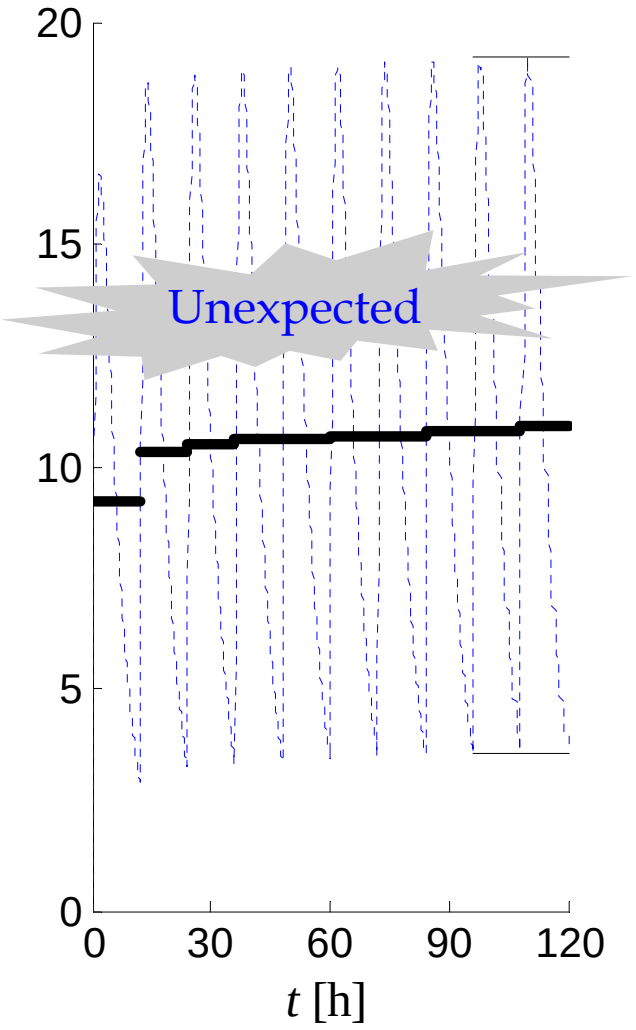


Low LOQ, [2 vs. 20 mg] , RD

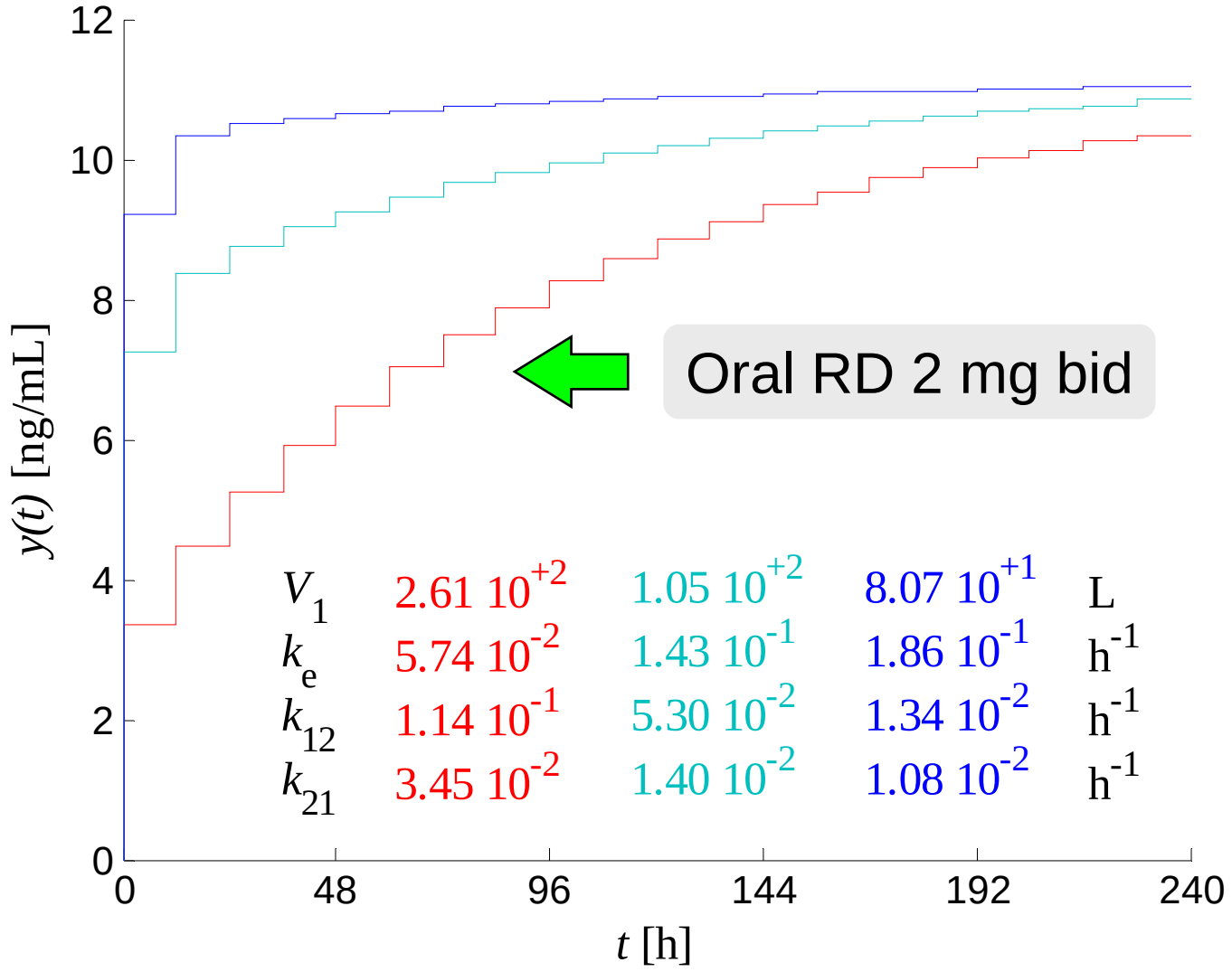


Oral RD 2 mg bid





Average concentration in RD



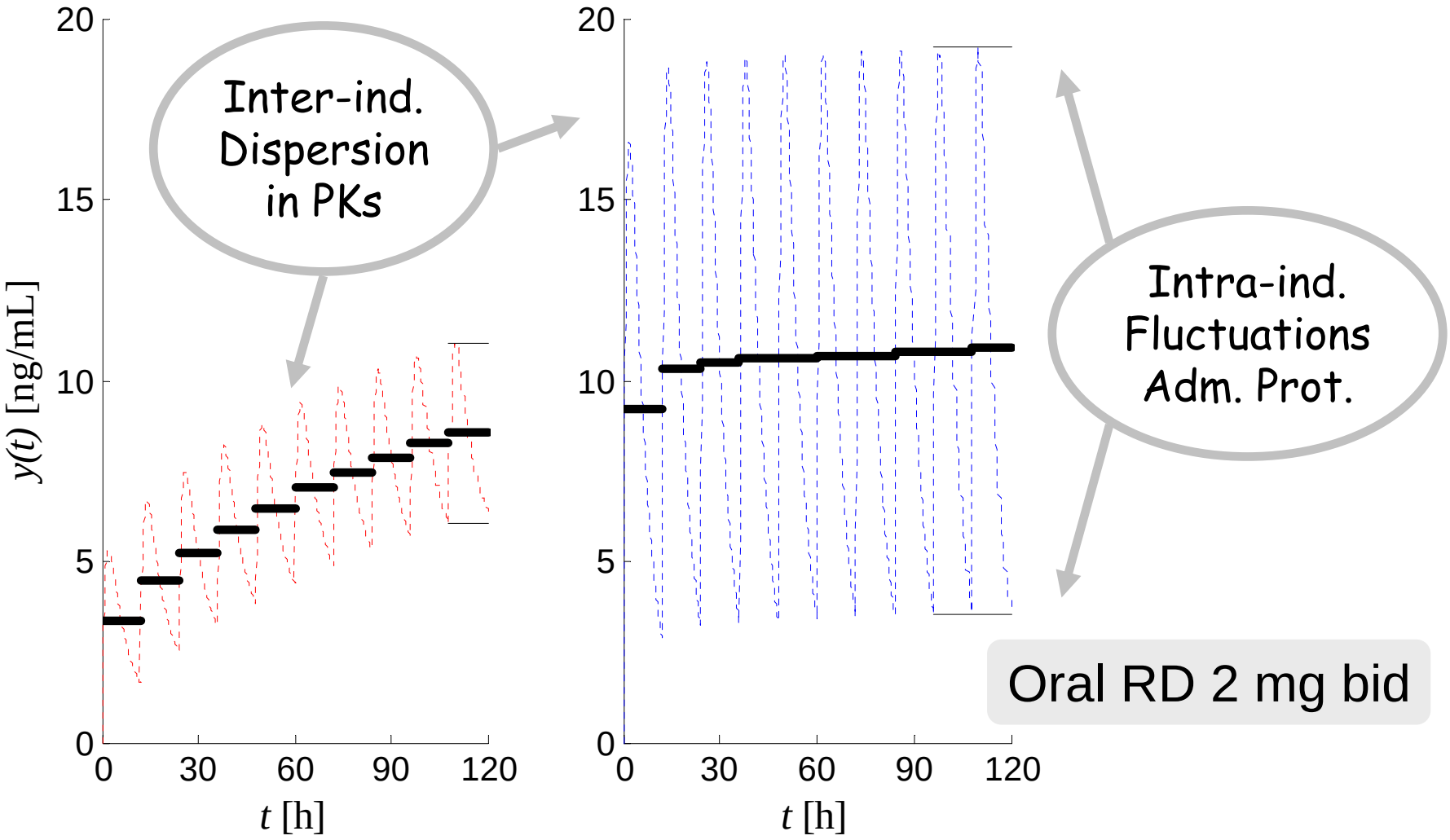
$CL = 15\,\mathrm{L}\cdot\mathrm{h}^{-1}$

$t_{1/2} = 70\,\mathrm{h}$

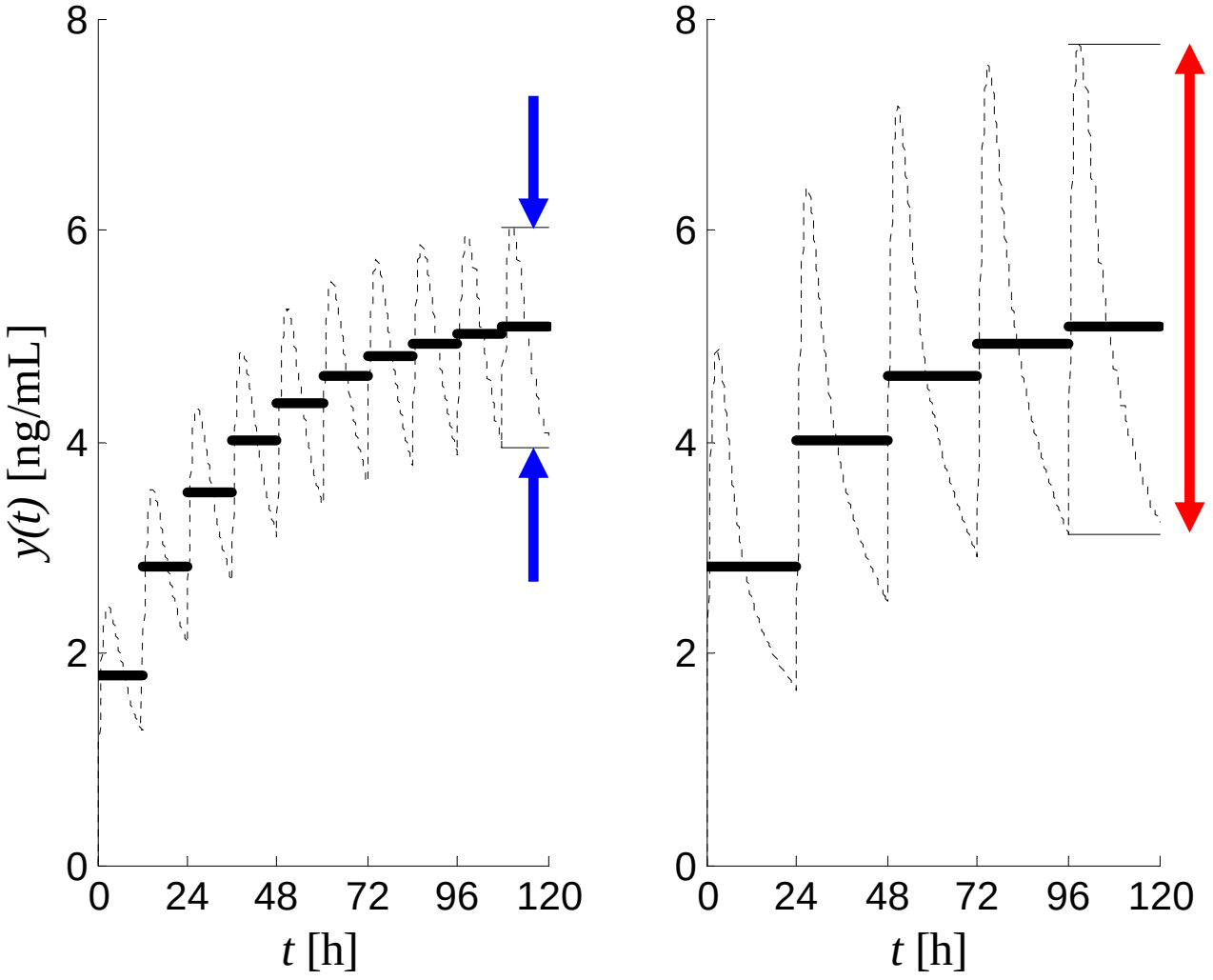
$k_a = 1\,\mathrm{h}^{-1}$

- $\frac{A_1}{A_2} \approx 6$
- $\frac{A_1}{A_2} \approx 45$
- $\frac{A_1}{A_2} \approx 250$

Variability in drug levels



Reduce fluctuations



Oral RD 2 mg / d

1 mg **bid**
vs.
2 mg **oid**

Schedule controls fluctuations

4 mg / d