CHAPT VI : Dosage adjustment

❶ Dosage adjustment. The possible solutions. Optimal conditions.

❷ Static and dynamic dosage adjustment.

❸ Simulated data : Mexiletin, Amiodarone.

❹ Real data : Methotrexate, Amikacin.

❺ Follow a reference signal : Isosorbite dinitrate and metabolite kinetics.

❻ Optimal control in clinical PKs : Minimal transient time.

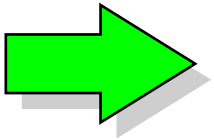
❼ Describing point, phase plane, trajectory. Controllability, stability. Reachable area.

Functional scheme - Chapt VI

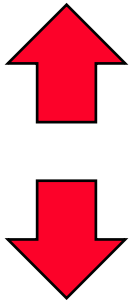
Before the dosage adjustment...

- Goal : Safely administer drugs having :

  ★ narrow therapeutic window + wide inter-individual dispersion.



PK process



- 7.5 mg / kg
- dose # 29.39 %
- T = 30 min / 12 h

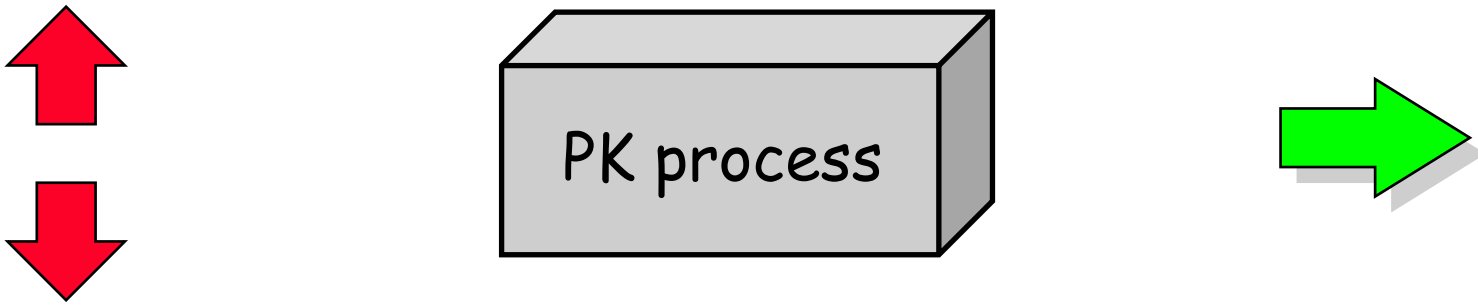
- CL # 46.17%
- V_T # 48.75 %

- min, max violated
- y_{moy} # 89.28 %

The observed variability is an image of the inter-individual dispersion

... after the dosage adjustment

Obtain individual PK parameters and, then
use highly variable inputs to offset the dispersion of the process parameters

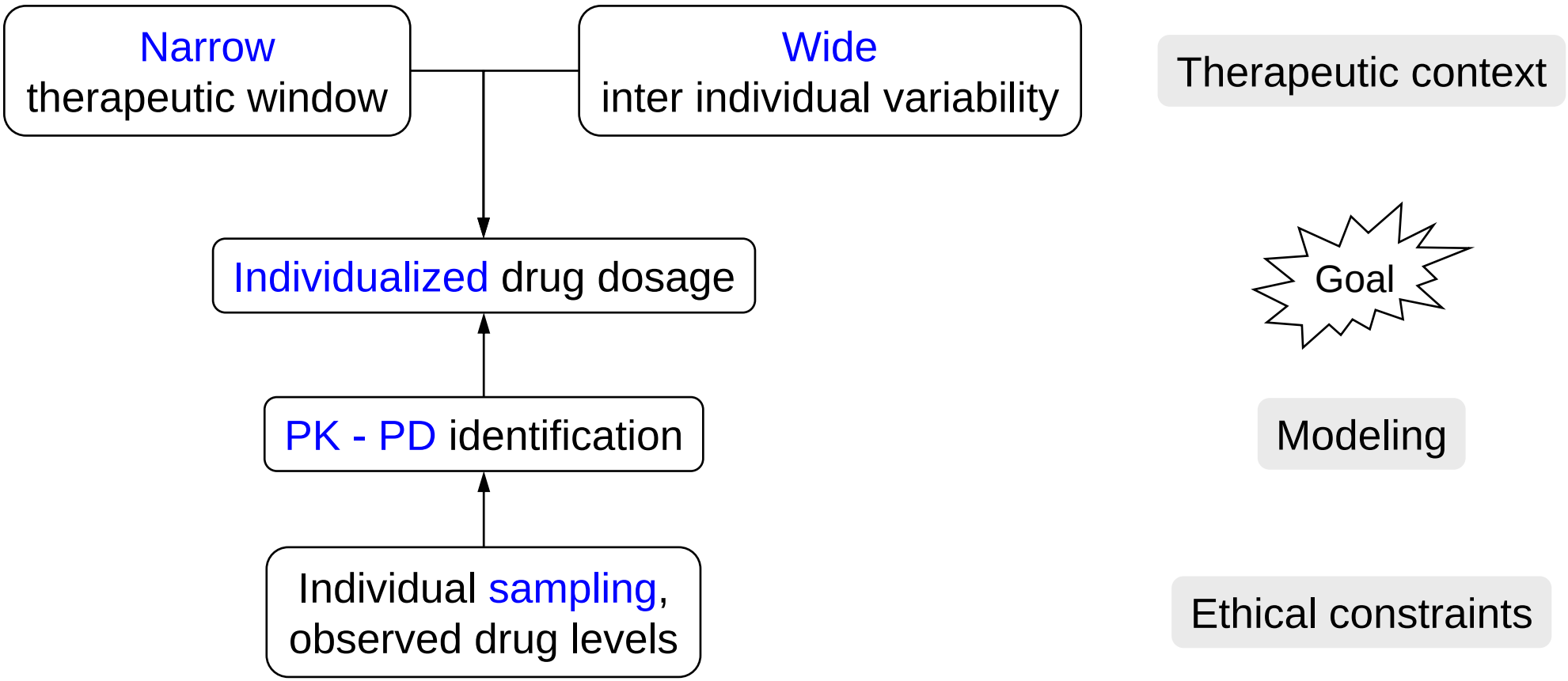


- load dose # 49.39 %
- maint. - # 46.19 %
- T= [1-8] h / [8-48] h

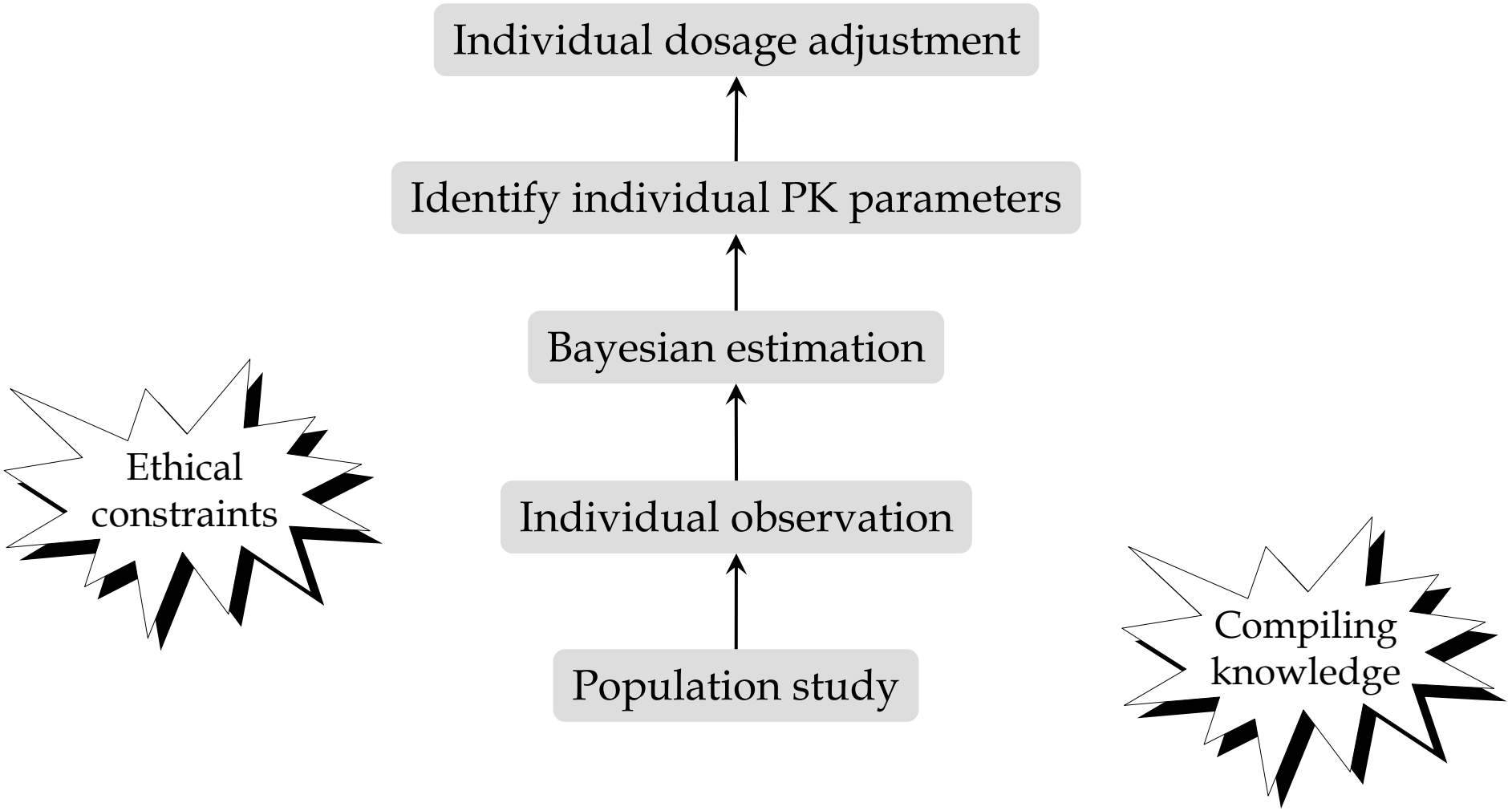
- CL # 46.17%
- V_T # 48.75 %

- min, max respected
- y_{moy} < 5 %

Why and how dosage adjustment



Functional flowchart



Naive dosage adjustment

- Hypotheses :
  - ☐ linear PK systems,
  - ☐ concentrations are directly related to the individual pharmacological response.
- Goal : concentration profile inside the therapeutic window (assumed known !).
- Possible solutions :

Problem	Time schedule	Drug amounts
1st	Set	Compute
2nd	Compute	Set

★ the 1st problem has a simple solution using the PK linearity property ;

★ the 2nd problem is more complex and requires tools from control theory.

Optimal conditions

- Optimality (1) : For a given route and schedule of drug administrations, the adjustment will be said optimal if :

  ★ minimum levels $y_{\min} > C_{\text{eff}}$

  ★ mean levels $y_{\text{moy}} = C_{\text{ave}}$

  ★ maximum levels $y_{\max} < C_{\text{tox}}$

  Goal - 1

  for each administration.

- Steps :

  ❶ Set C_{eff} C_{ave} C_{tox} ;

  ❷ Identify individual PK parameters $\underline{x}$;

  ❸ Propose a time-schedule for drug administration ;

  ❹ Specify the $t_{\min}$ and $t_{\max}$ for each administration ;

  ❺ Compute : $y_{\min} = y_{Mi}(t_{\min}, \underline{x})$ $y_{\text{moy}} = y_{Mi}(\underline{x})$ $y_{\max} = y_{Mi}(t_{\max}, \underline{x})$.

The solution

- Computation :
  - Using linearity, factorize $y_{\min}$ y_{moy} $y_{\max}$ expressions as :
    - ★ $y_{\min} = D_{\min} \cdot g(t_{\min}, \underline{x}) > C_{\text{eff}}$
    - ★ $y_{\text{moy}} = D_{\text{moy}} \cdot g(\underline{x}) = C_{\text{ave}}$
    - ★ $y_{\max} = D_{\max} \cdot g(t_{\max}, \underline{x}) < C_{\text{tox}}$
  - Solve these inequalities to obtain the optimal amounts $D_{\min}$, D_{moy} and $D_{\max}$.
  - Actual choice :

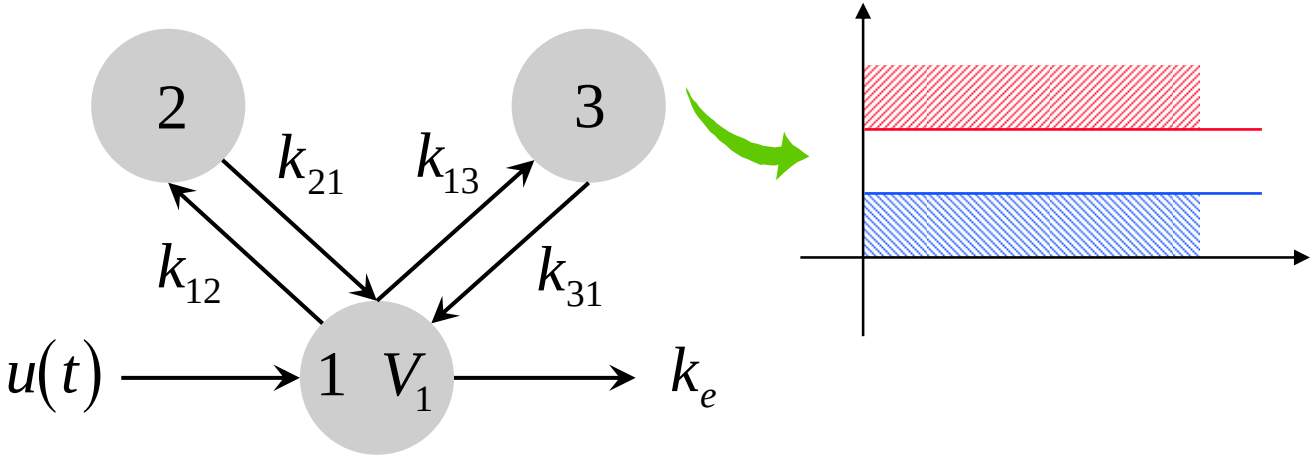
$$D_{\min} < D_{OPT} \approx D_{\text{moy}} < D_{\max}$$

Warning :

If no reliable solution can be found (ex : $D_{\min} > D_{\max}$) a new time-schedule is proposed and the procedure is repeated.

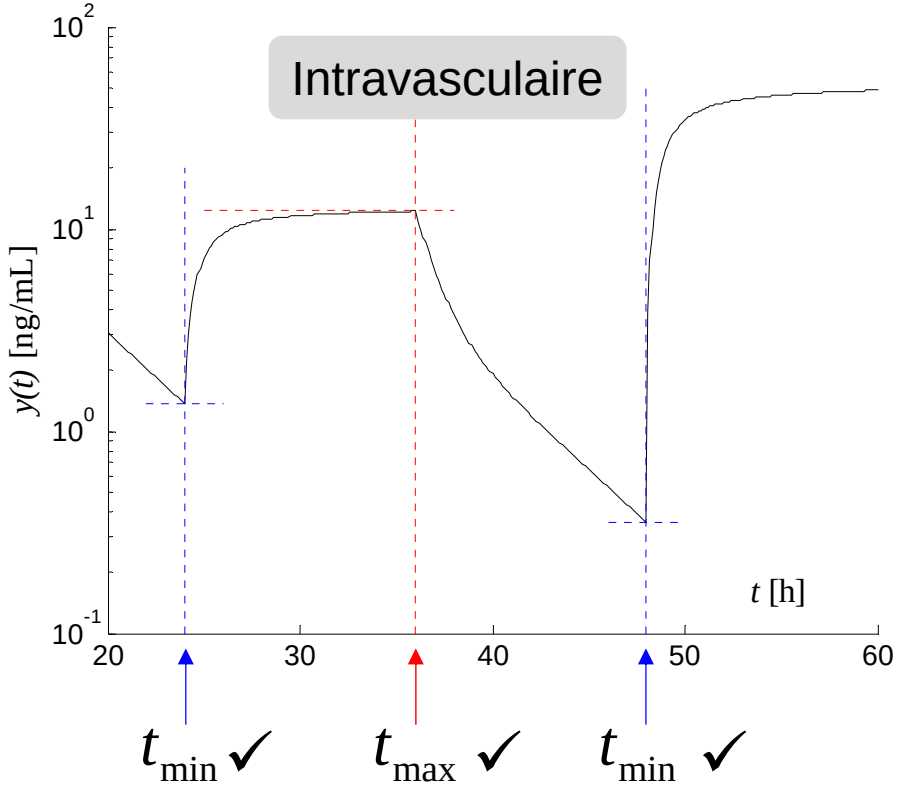
Practical issues

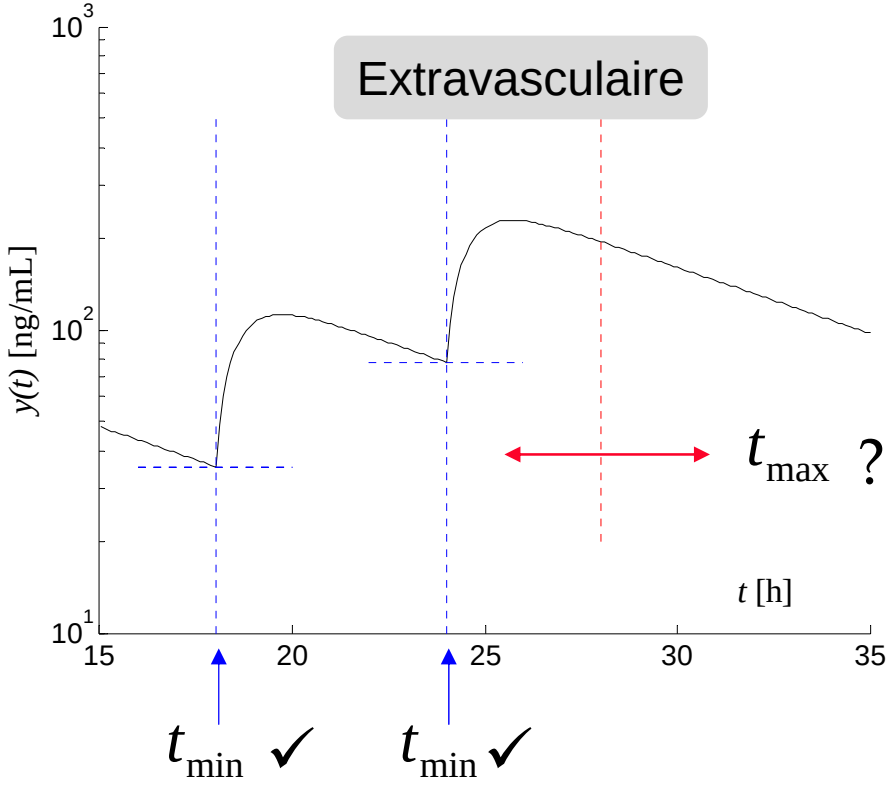
- Options :
  - Possible association of constraints with a peripheral compartment, as for the central.



  - The basic approach is adapted to :
    - ★ long-term treatment (static) : optimize at the stationary state, and
    - ★ emergency treatment (dynamic) : adapt as soon as possible, (ex : loading and maintenance amounts).

Determine times of extrema





- ☐ t_{min} before a new administration,
- ☐ t_{max} at the end of infusion,

- ☐ t_{min} before a new administration,
- ☐ compute t_{max} as solution of a transcendental equation (using iterative algorithms).

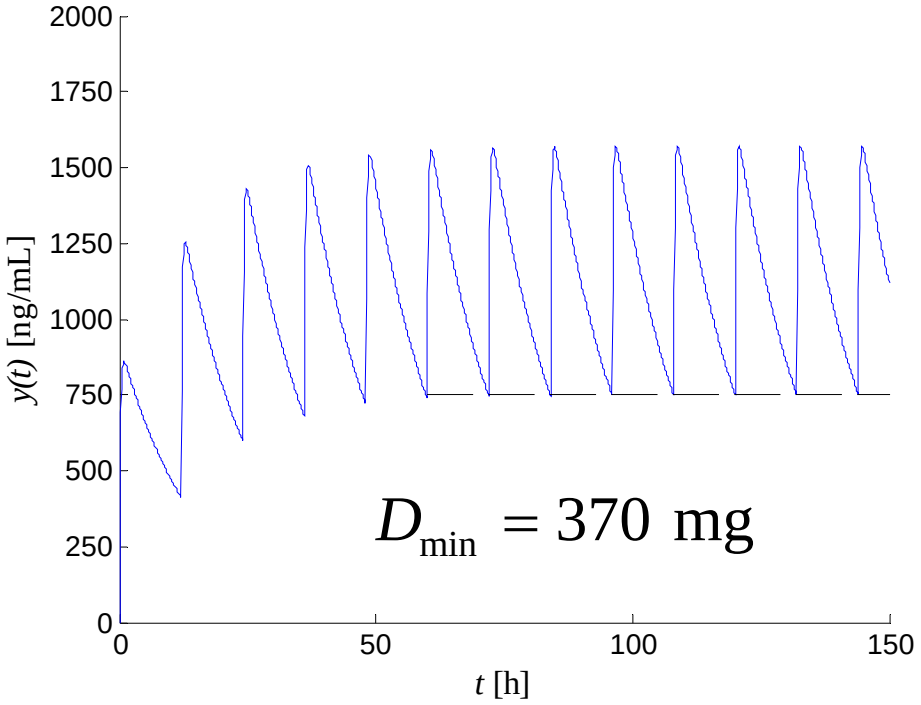
Static dosage

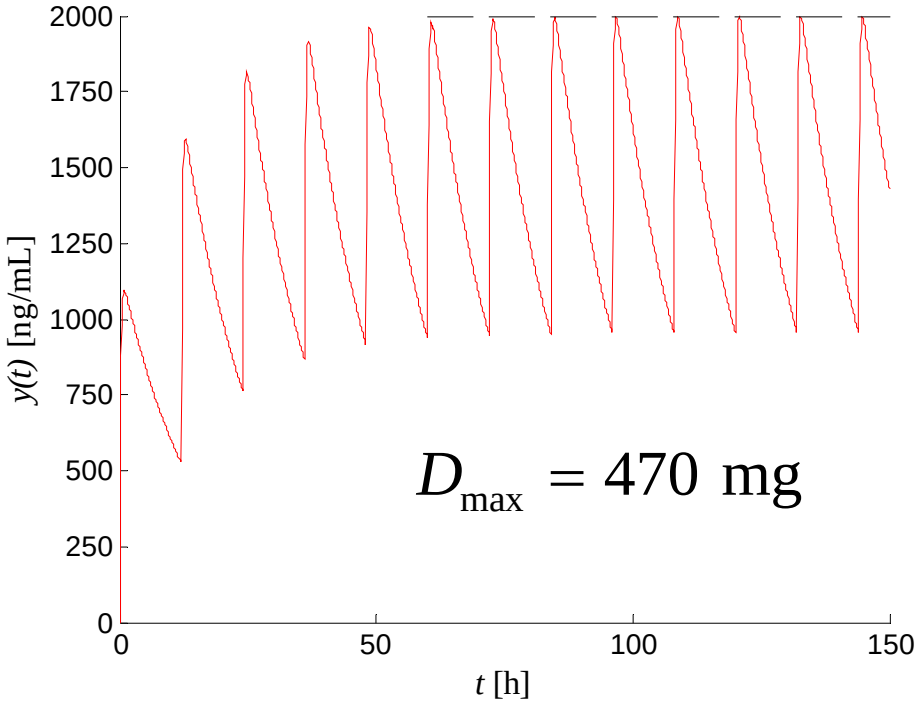
- Let :

1°) $C_{\min} = 750\ \text{ng} \cdot \text{mL}^{-1}$ $C_{\max} = 2\ \mu\text{g} \cdot \text{mL}^{-1}$,

2°) $V_1 = 406\ \text{L}$ $k_e = 0.067\ \text{h}^{-1}$ $k_a = 4.85\ \text{h}^{-1}$,

3°) 12-h regular dosage schedule.





Dynamic dosage

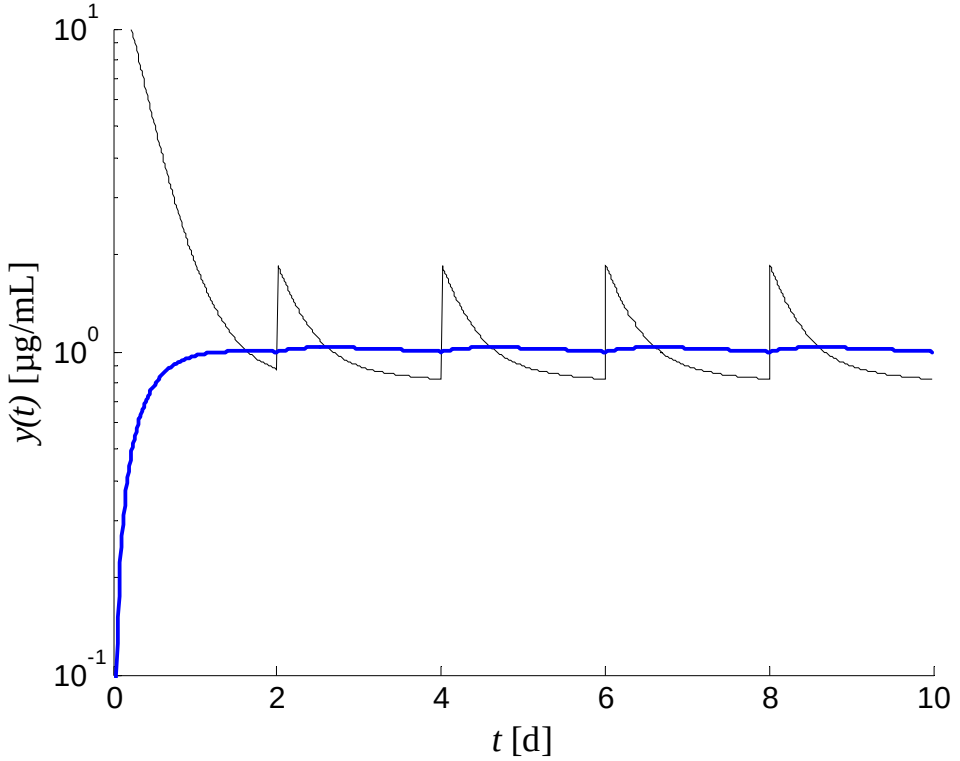
- Let :

1°) $C_{min} = 1\ \mu g \cdot mL^{-1}$ in the peripheral compartment,

2°) $V_1 = 400\ L \quad k_e = 0.509\ d^{-1} \quad k_{12} = 2.17\ d^{-1} \quad k_{21} = 0.165\ d^{-1}$,

3°) 15-min infusions every 2 days.

Administer in the central cpt :
- a loading dose of 7.192 g at d0,
- a transition dose of 390 mg at d2,
- maintenance doses of 415 mg / 2 d.



Real data - Methotrexate

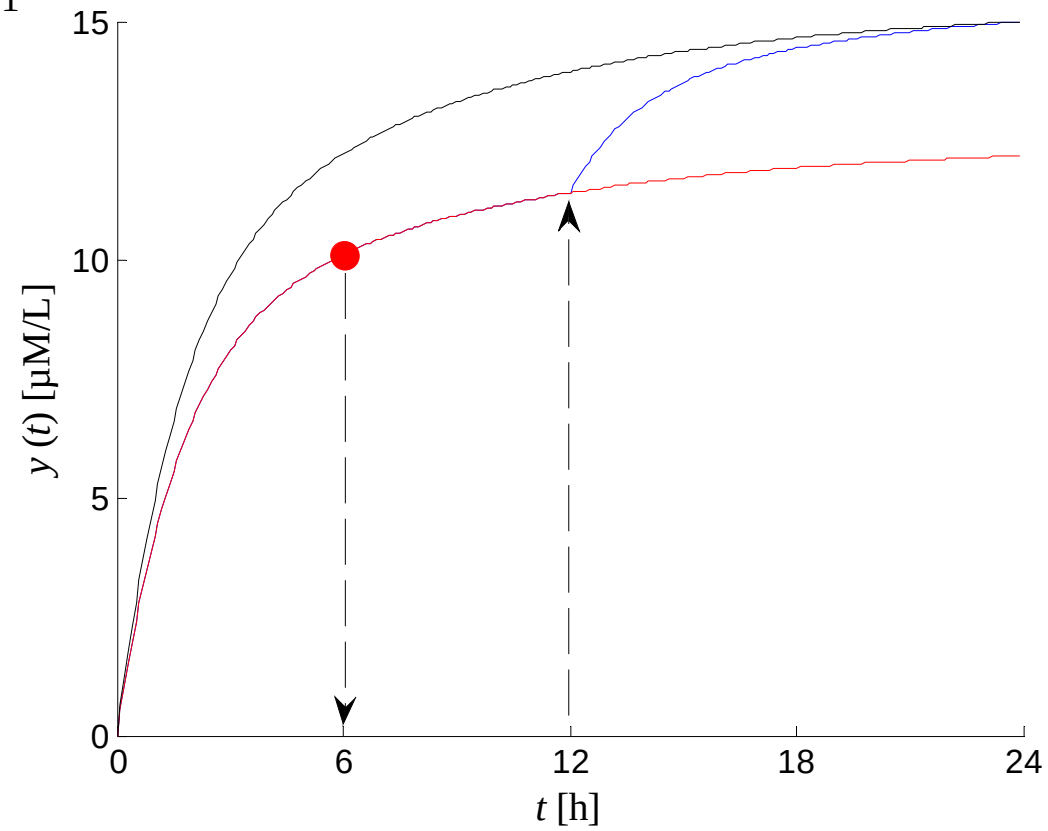
- Goal : For an individual (i), reach $P = 15\ \mu\text{M} \cdot \text{L}^{-1}$ at the steady state by infusion.

❶ Compute the infusion rate $R_0 = CL_{\text{moy}} \cdot P = 0.1075\ \text{mM} \cdot \text{h}^{-1}$
using the mean $CL_{\text{moy}} = 7.167\ \text{L} \cdot \text{h}^{-1}$

❷ Begin the infusion for the i -th individual with R_0 : *Discrepancy* { P target / actual levels }.

❸ Sample at 6 h, assay, estimate using MAP $CL_i = 8.675\ \text{L} \cdot \text{h}^{-1}$
Compute $R_i = 0.134\ \text{mM} \cdot \text{h}^{-1}$

❹ Stop the infusion with R_0 at 12 h and begin a new one with R_i .



Real data - Amikacin

- Intravenous infusion. Std protocol : Dose = 7.5 mg/kg, T = 30 min.
- Goals : $y_{\min} < C_{\text{toxA}} = 3 \quad y_{\text{moy}} = C_{\text{ave}} \approx 8 \quad y_{\max} < C_{\text{toxR}} = 25\ \mu\text{g}\cdot\text{mL}^{-1}$

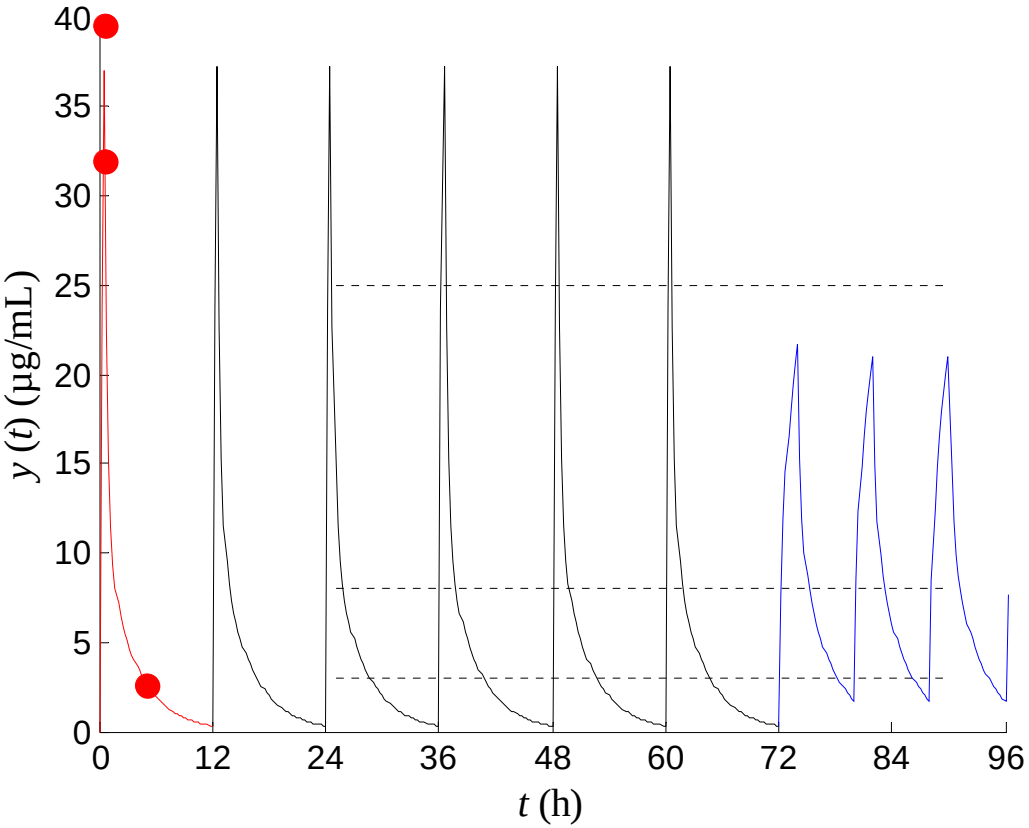
1. MAP identification : 525 mg, 3 samples :

$V_1 = 8.39\ \text{L} \quad k_e = 1.145\ \text{h}^{-1}$

$k_{12} = 1.38\ \text{h}^{-1} \quad k_{21} = 0.833\ \text{h}^{-1}$

2. Observation interval :
   - [T = 0.5 h / 12h] * 6
3. Adjusted dosage at 72 h :
   - Schedule : [T = 2h / 8h]
   - Load and maintenance

     doses = 658 and 615 mg.



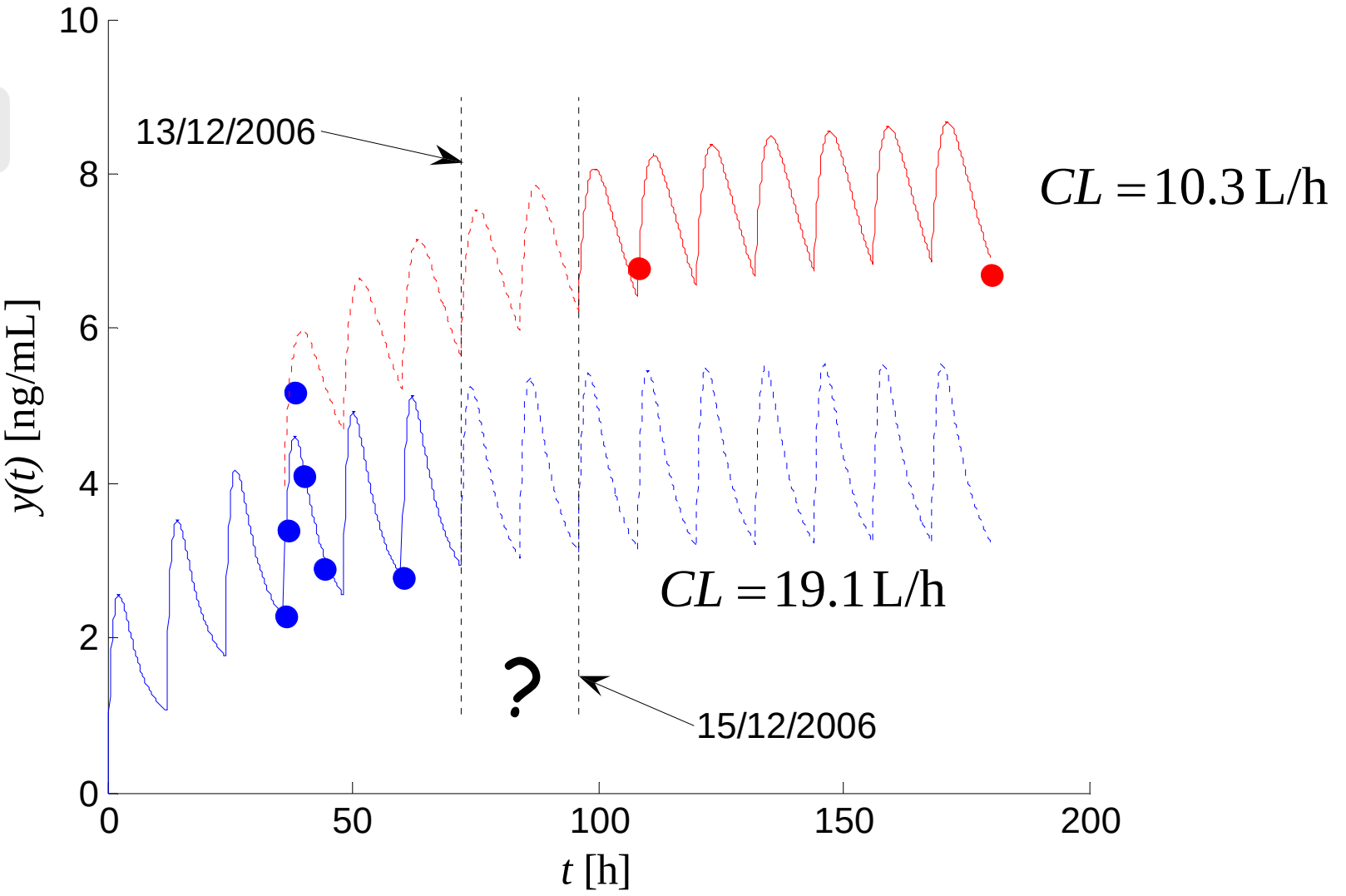
Real data - Sirolimus

- 16 patients out of $n = 19$ were monitored.
- 7 patients out of 16 were stable.
- 9 patients presented CL changes and therefore dosage regimen was updated.
- Therapeutic range :

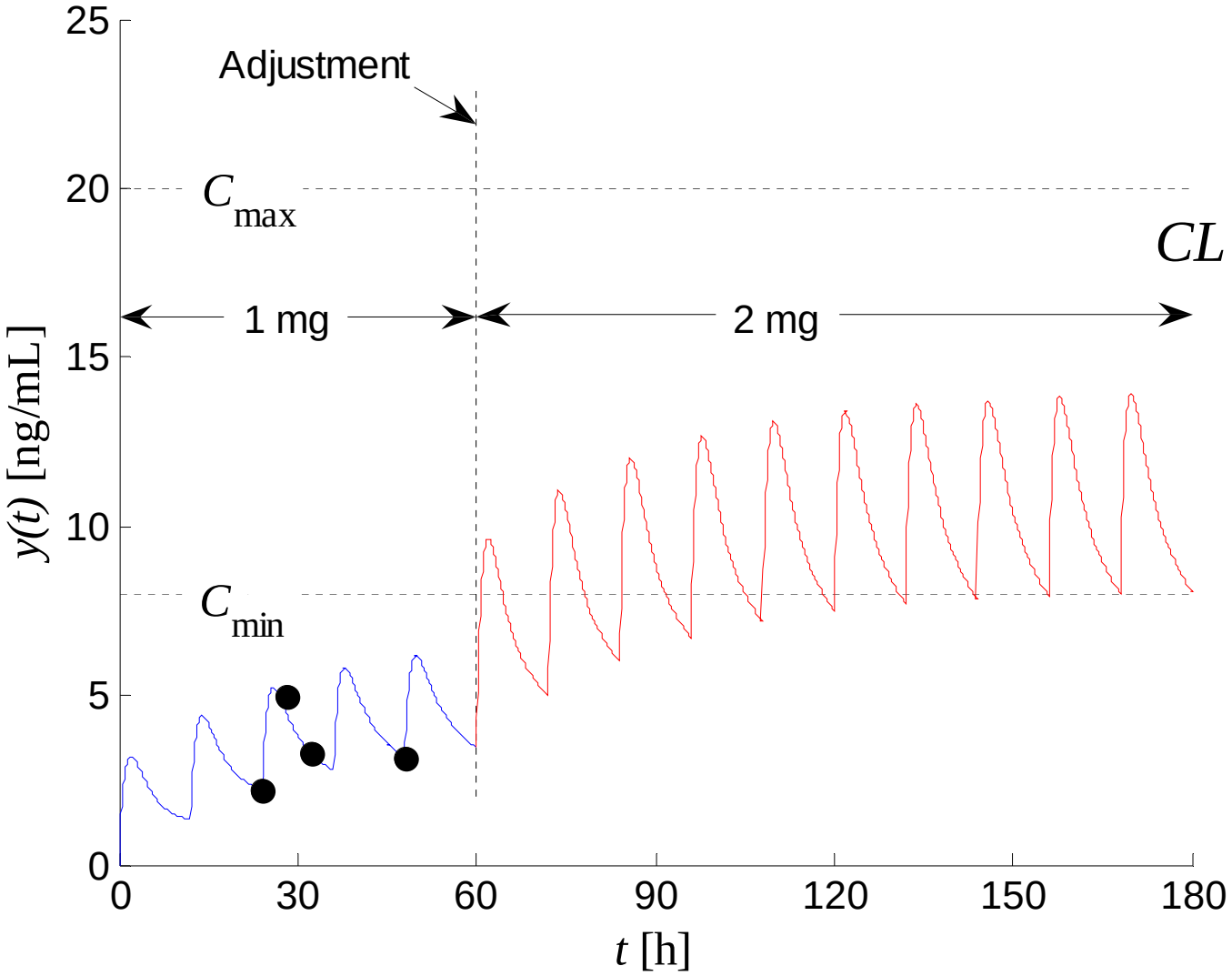
$$\left.\begin{aligned} C_{\min} &= 8 \\ C_{\text{ave}} &= 12 \\ C_{\max} &= 20 \end{aligned}\right\} \text{ng} \cdot \text{mL}^{-1}$$

Modification of clinical status ?

1 mg - bid

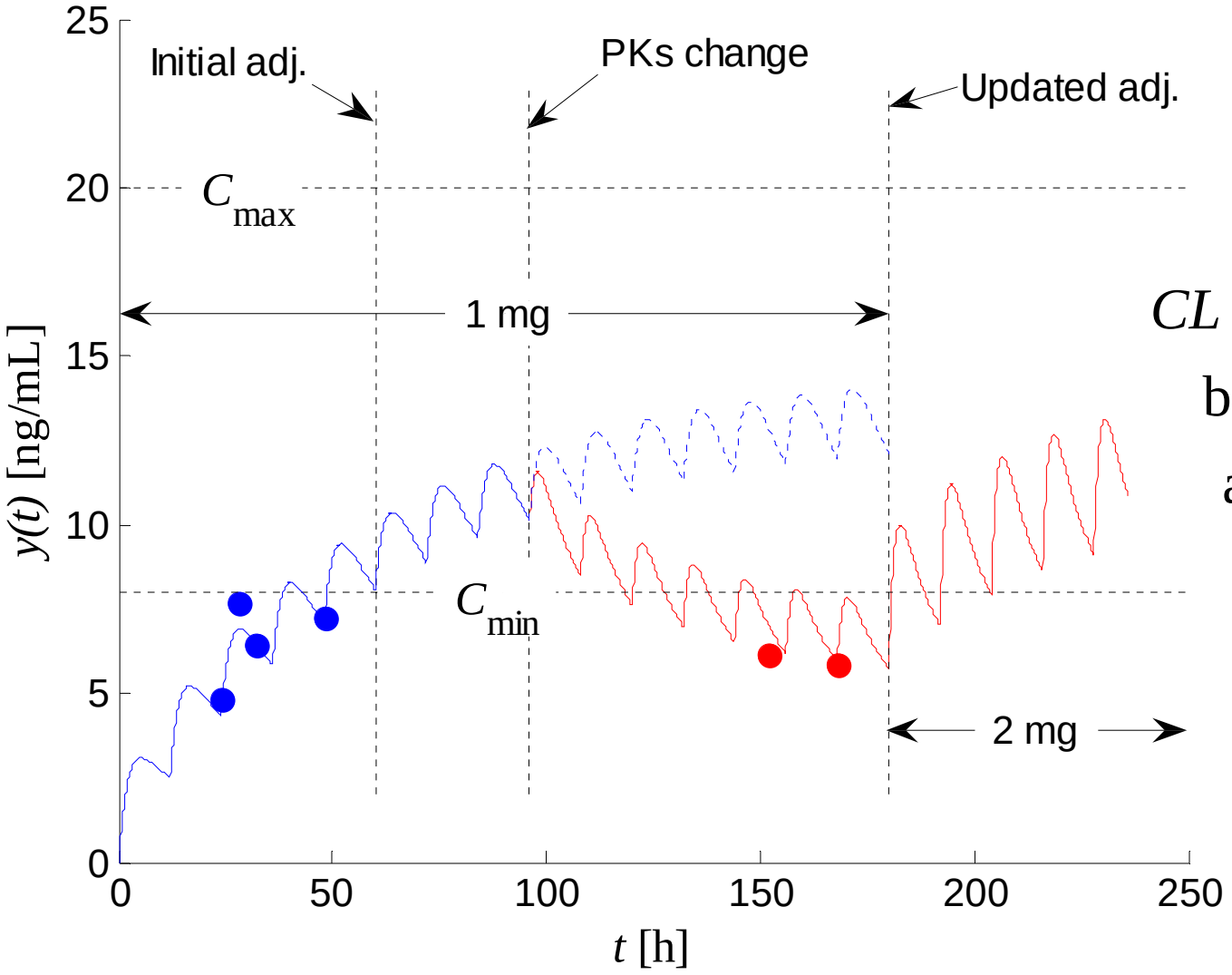


Dosage adjustment / Average CL



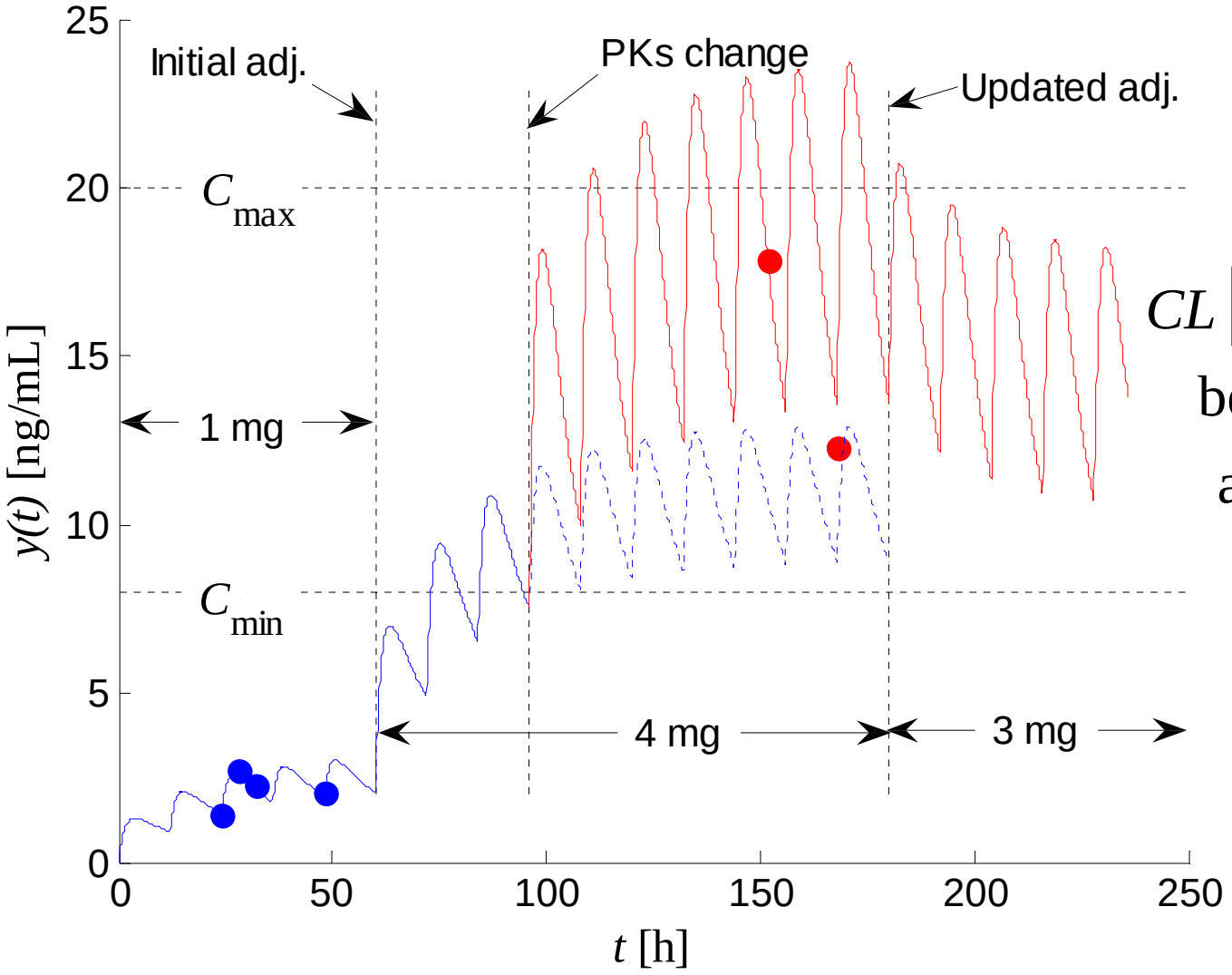
$CL\left[\mathrm{L}\cdot\mathrm{h}^{-1}\right]$	true	estim.
	15.36	16.44

Updated adjustment / Low CL



$CL\left[\mathrm{L}\cdot\mathrm{h}^{-1}\right]$	true	estim.
before	5.94	5.93
after	13.21	12.36

Updated adjustment / High CL



$CL\left[\mathrm{L}\cdot\mathrm{h}^{-1}\right]$	true	estim.
before	29.65	23.98
after	17.14	18.93

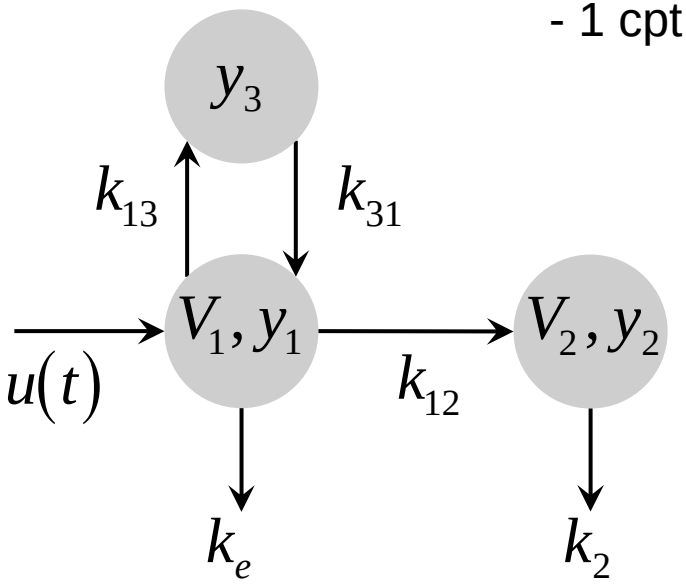
Tracking a reference signal

- Administration protocol :
  - ★ schedule : $0 < t_1 < \ldots < t_k < \ldots < t_N = T$ ⇒ set
  - ★ amounts : $D_1 \quad \ldots \quad D_k \quad \ldots \quad D_N$ ⇒ unknown
  - ★ T is the treatment duration and N the number of administrations.
- Optimality (2) :
  - ☐ Compute $D_k, k = 1,\ldots,N$ such that $y_\bullet(t)$ follows the reference signal $s_R(t)$.
    - ★ solve the NLP problem : $\underline{\hat{D}} = \arg\min\left\{\int_0^T [y_\bullet(t,\underline{D}) - s_R(t)]^2 \cdot dt\right\}$
    - ★ associated with possible constraints on drug levels.

Goal - 2

Multi - output system identification

- Analysis of time-concentration curves of ISDN :
  - administration : 2.5 mg infused during 1.75 h,
  - sampling : 15 blood samples over 8 h,
  - analytical assay : ISDN and 2-ISMN levels obtained by capillary GC,
  - structural cpt model : - 2 cpt for ISDN (y_1 for the central, y_3 for the peripheral cpt),
    - 1 cpt for 2-ISMN (y_2).



$$\frac{dy_1}{dt} = -(k_e + k_{12}) \cdot y_1 - k_{13} \cdot (y_1 - y_3) + \frac{u(t)}{V_1}$$

$$\frac{dy_2}{dt} = k_{12} \cdot \frac{V_1}{V_2} \cdot y_1 - k_2 \cdot y_2$$

$$\frac{dy_3}{dt} = k_{31} \cdot (y_1 - y_3)$$

Estimation of parameters and fitting

- Obtain predicted levels by numerical integration (Runge-Kutta).
- Estimate unknown model parameters by using the multi - output MLE criterion.

$$\frac{1}{V_1} = 0.0134 \text{ L}^{-1}$$

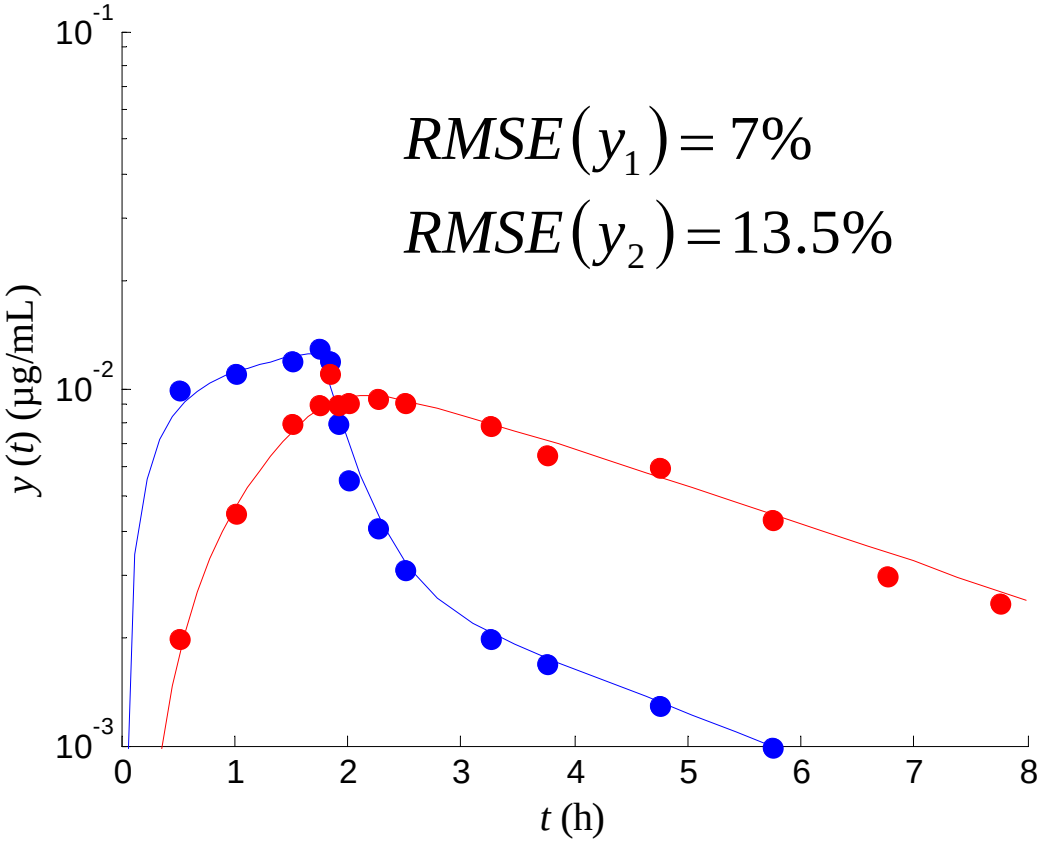
$$k_e + k_{12} = 1.914 \text{ h}^{-1}$$

$$k_{12} \cdot \frac{V_1}{V_2} = 0.692 \text{ h}^{-1}$$

$$k_2 = 0.4 \text{ h}^{-1}$$

$$k_{13} = 1.151 \text{ h}^{-1}$$

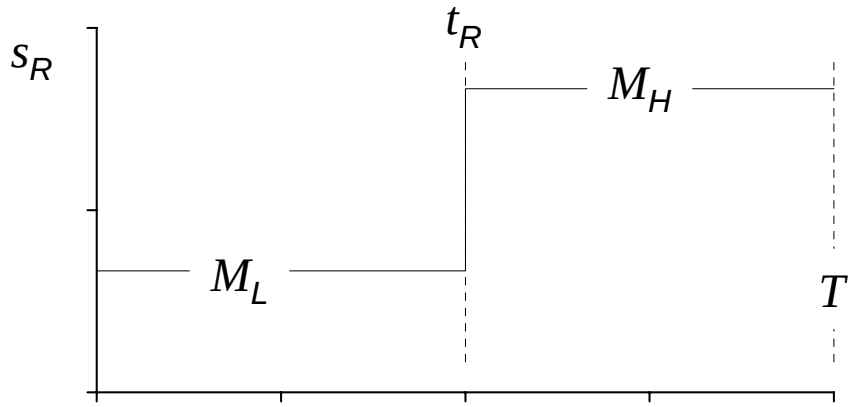
$$k_{31} = 0.473 \text{ h}^{-1}$$



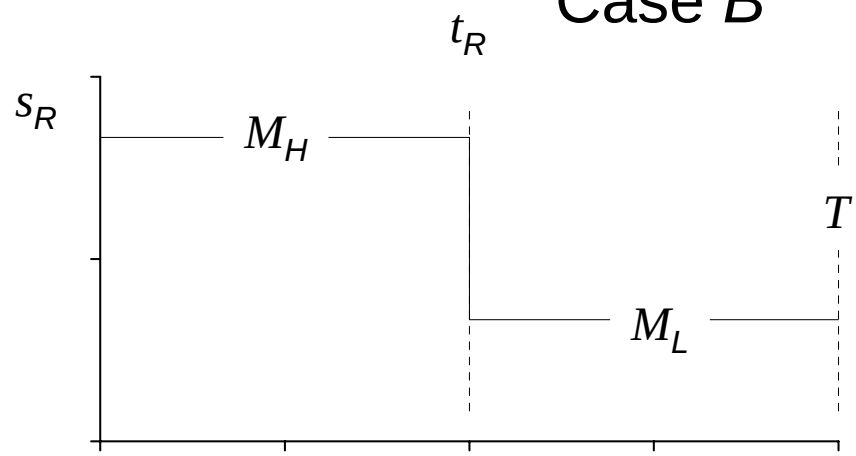
Compute the optimal doses

- Control metabolite levels : $y_\bullet \equiv y_2$
- Schedule characteristics : $T = 24\ \text{h},\ t_k - t_{k-1} = 2\ \text{h},\ k = 1,\ldots,12$
- Reference signal : $\left[M_L, M_H\right] = \left[20,\ 50\ \text{ng}\cdot\text{mL}^{-1}\right]$ $\qquad t_R = T/2$

Case *A*



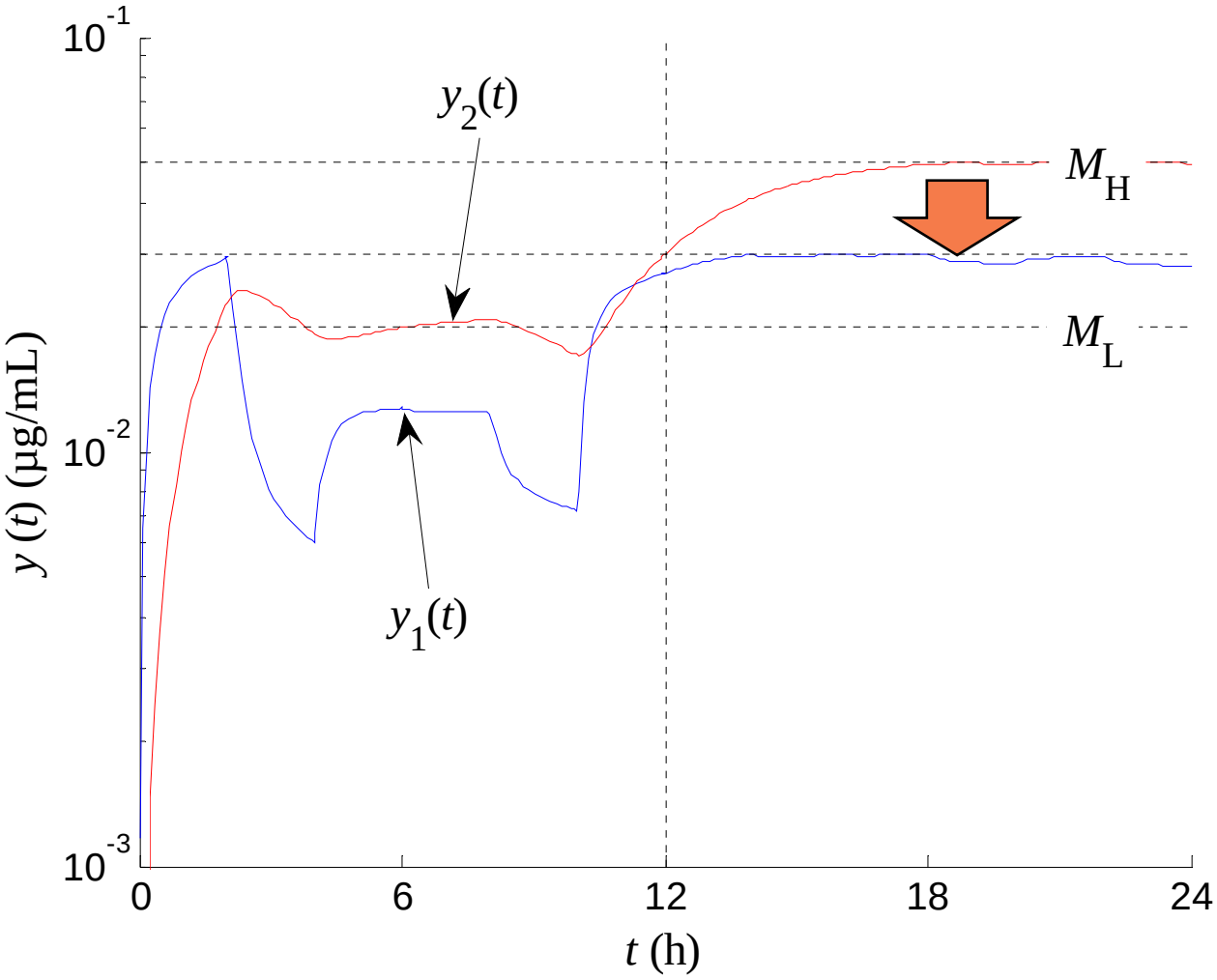
Case *B*



☐ Constraint on y_1 levels : $y_1(t) \le 30\ \text{ng}\cdot\text{mL}^{-1}$

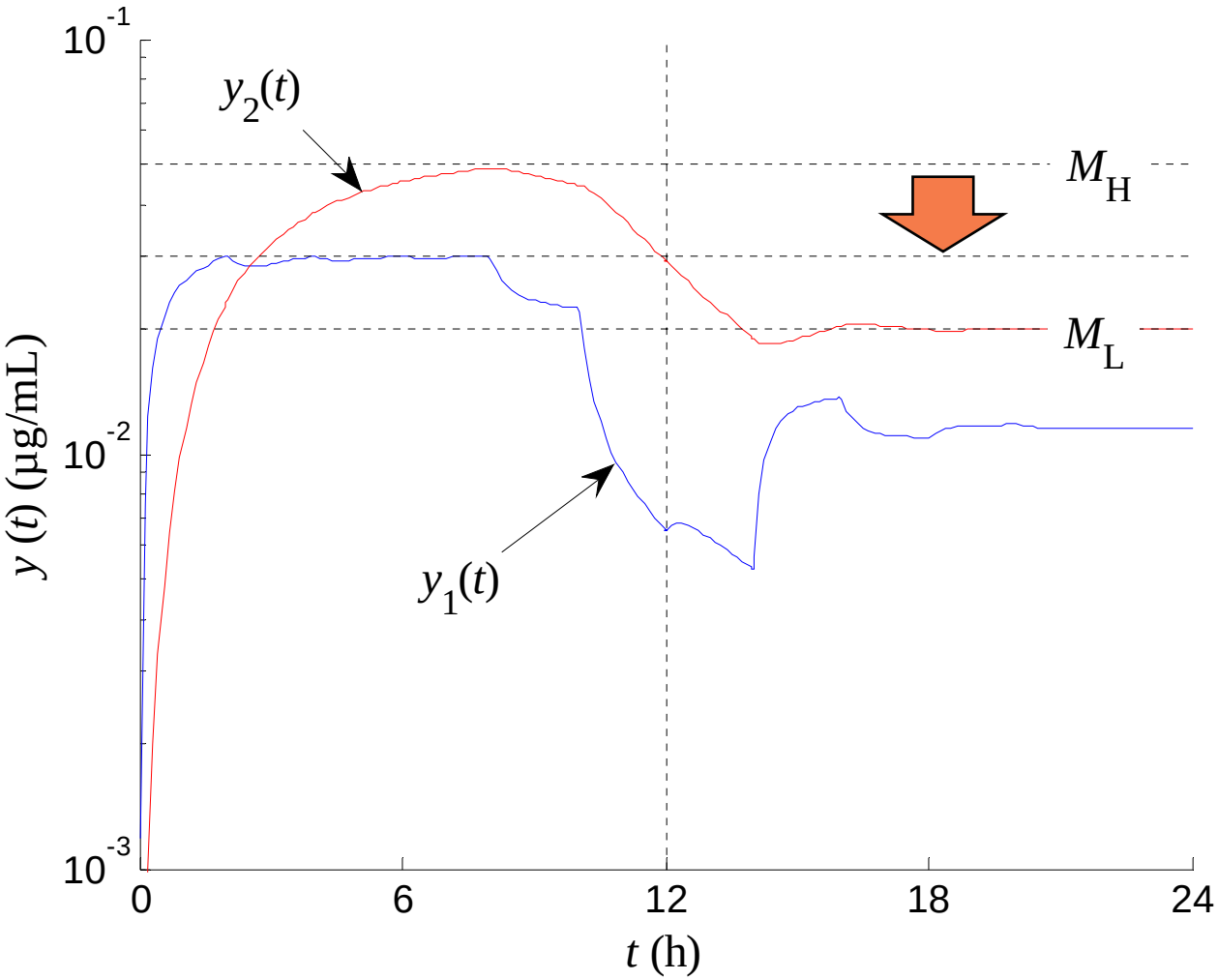
Adjusted levels – Case A

$y_1(t)$ levels are constrained at 2 h and, from 14 to 18 h



Adjusted levels – Case B

$y_1(t)$ levels are constrained from 2 up to 8 h



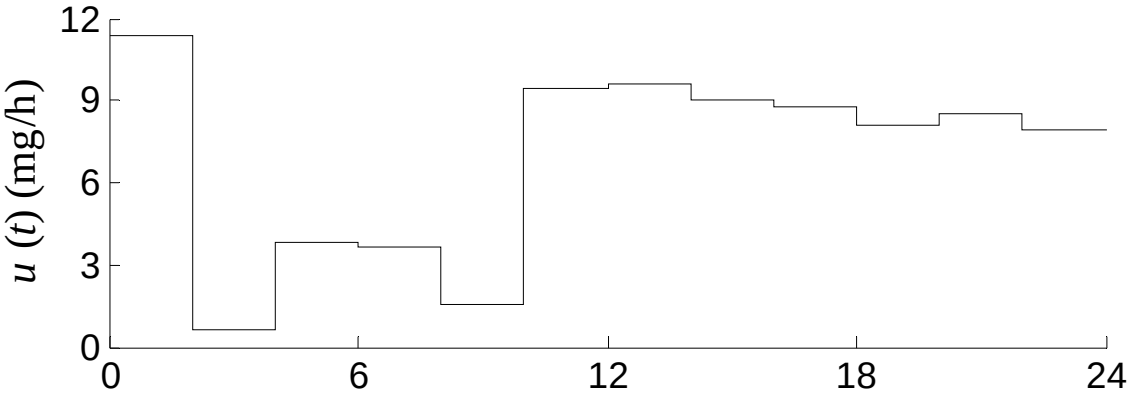
Optimal drug inputs

- Total amount :

❶ Case *A* : 82.37 mg

$$M_L \longrightarrow M_H$$

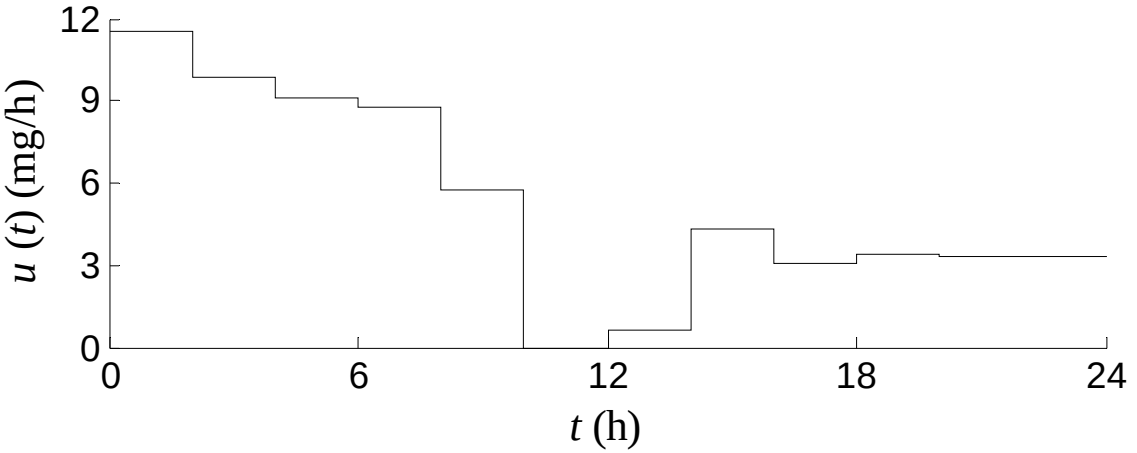
$$\int_0^T [y_\bullet(t, \underline{D}) - s_R(t)]^2 \cdot dt = 1.084$$



❷ Case *B* : 63.04 mg

$$M_H \longrightarrow M_L$$

$$\int_0^T [y_\bullet(t, \underline{D}) - s_R(t)]^2 \cdot dt = 1.890$$



The mathematical model

- PKs described by ordinary differential equations :

$$\dot{\underline{y}}(t) = A(\underline{x}) \cdot \underline{y}(t) + \underline{c}(\underline{x}) \cdot u(t) \qquad \underline{y}(0) = \underline{y}_0$$

  1. L : nbr. of compartments,
  2. $\underline{y}(t)$: the state vector,
  3. $u(t)$: scalar control (dosage regimen),
  4. $\underline{x}$: the PK parameters, assumed known from identification.

- Constraints :
  1. State : $y_j(t) \geq 0, \quad j = 1, \ldots, L$.
  2. Control : $C_{\text{inf}} \leq u(t) \leq C_{\text{sup}}$.

- Controls in PKs :
  1. intra-vascular : $0 \leq u(t) \leq R_{\max}$.
  2. extra-vascular : $0 \leq u(t) \leq D_{\max}$.

The fastest transition

- Controllability and optimality :
  - ☐ PK systems are stable and controllable.
  - ☐ Controllability :
    - ★ define first the reachable area and then, by means of an appropriate $u(t)$,
    - ★ drive the system from $\underline{y}_{\mathrm{i}}$ to $\underline{y}_{\mathrm{f}}$ in a finite time : $t_0 = t_{\mathrm{f}} - t_{\mathrm{i}}$.
- Optimality (3) : From $\underline{y}_{\mathrm{i}}$ reach $\underline{y}_{\mathrm{f}}$ in minimal time, i.e. :

  Optimize the functional $u(t)$: $\hat{u}(t) = fcn \min\{t_0\}$

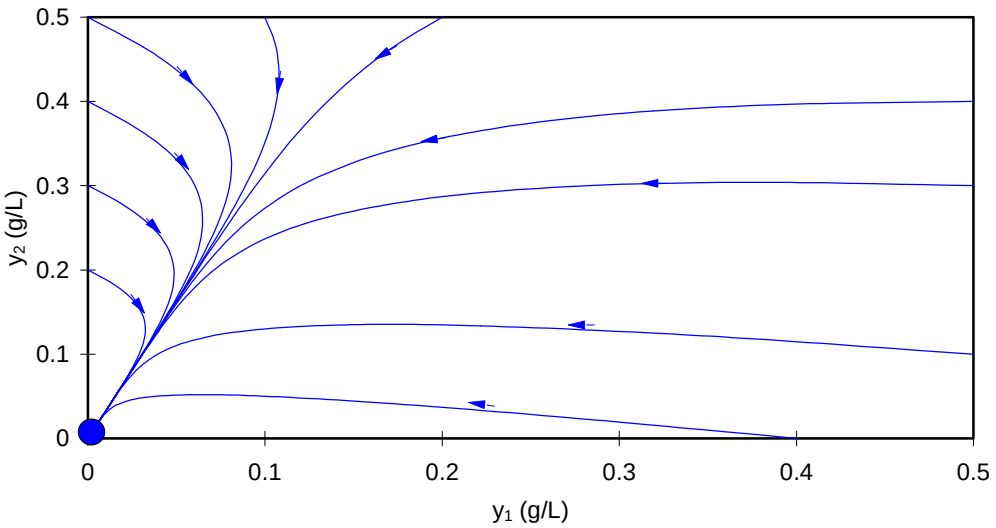
  Goal - 3
- Optimal control :
  - ★ It is a bang-bang process : $\hat{u}(t)$ lies either on C_{inf} , or on C_{sup} .
  - ★ The number of switches between C_{inf} and C_{sup} is equal to $L-1$.

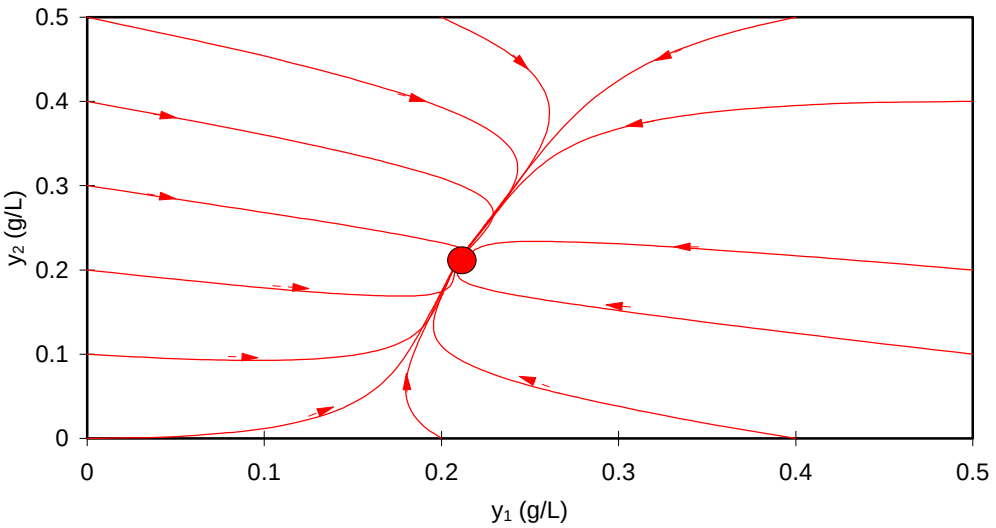
The state space

- Pairs of states define graphically : *state space*.
- $\underline{y}(t)$ are coordinates in the state space : *describing point*.
- Motion of $\underline{y}(t)$: *state trajectory*.

$u(t) = 0$: the origin

$u(t) = R_{max}$: the steady-state





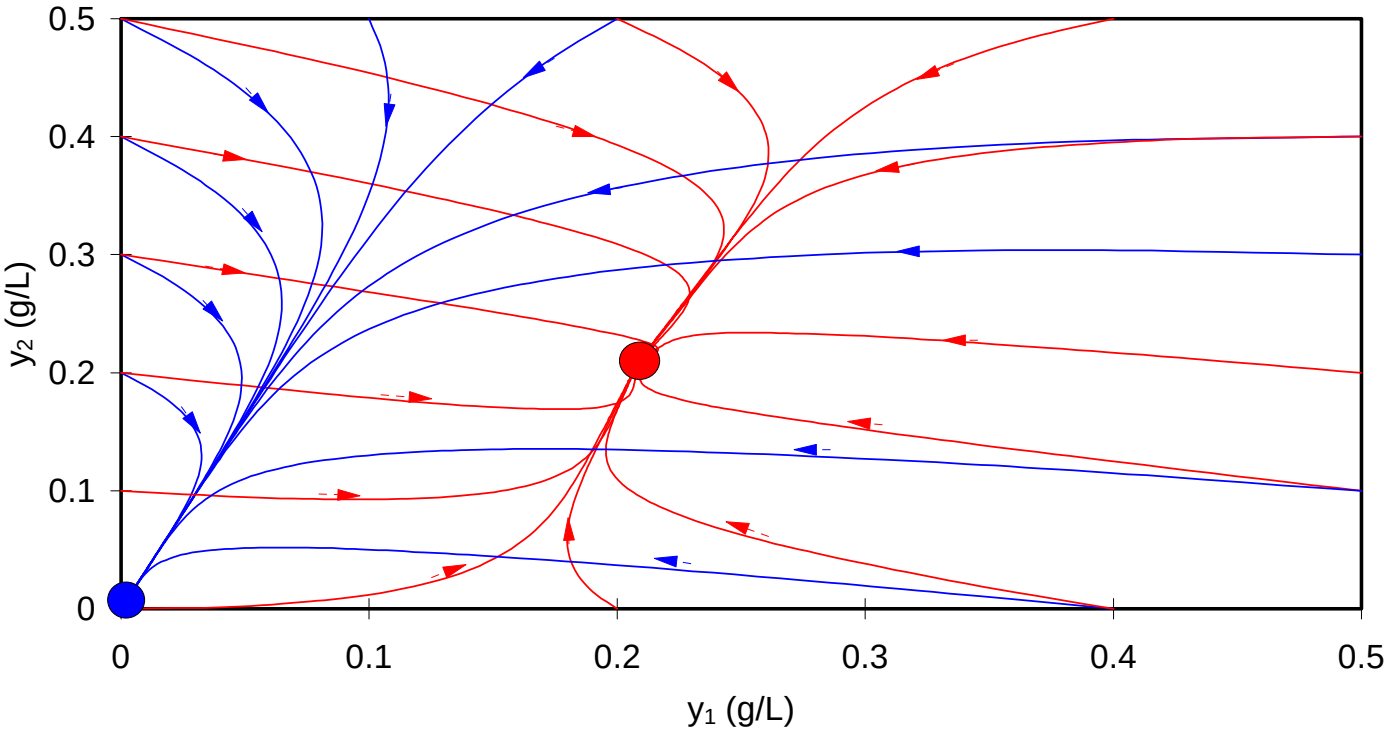
The system trajectories

- The trajectories are parametric forms which depends on the time : the elapsed time between two points of the trajectory is known.
- Read the transient time in order to reach prescribed levels in a minimal time.

☐ Combination of :

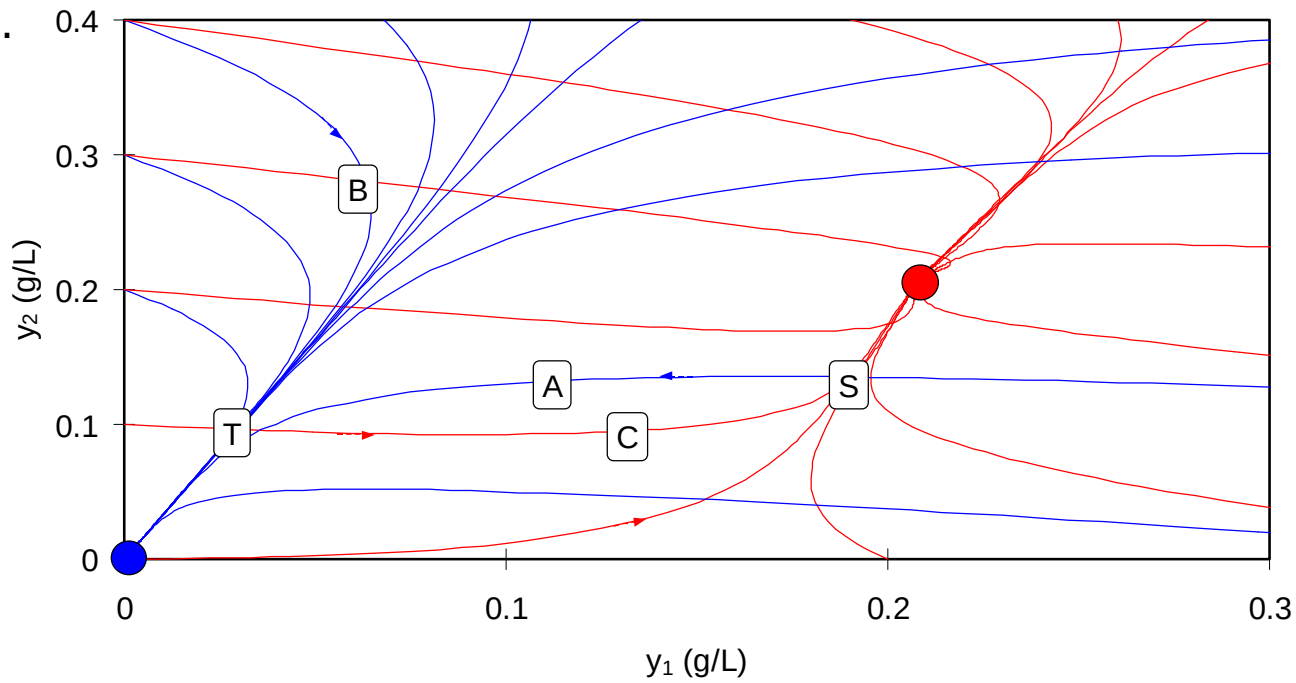
$$u(t) = 0$$

$$u(t) = R_{max}$$



Performing the fastest transition

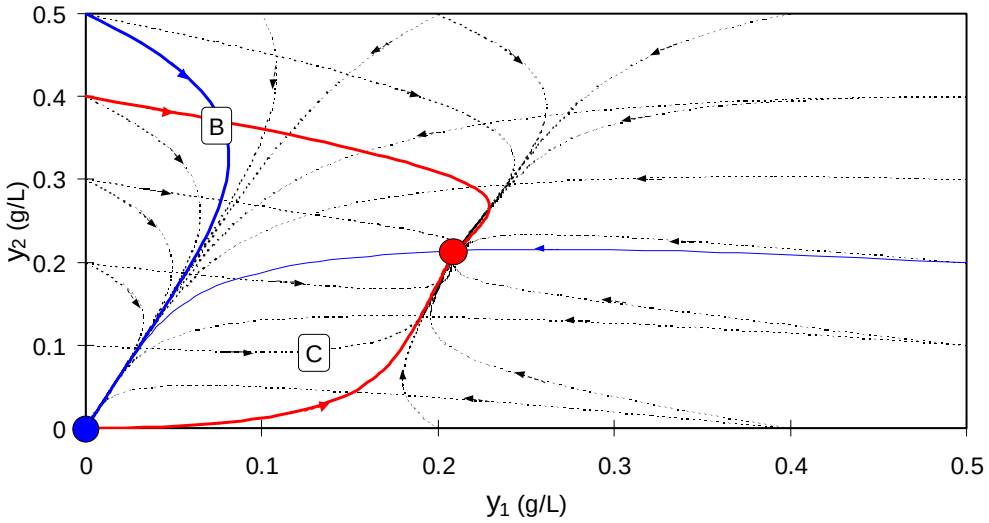
- Reach A from the origin :
  - ☐ Mark the trajectories : ❶ from the origin to ● ; and ❷ from A to ●.
  - ☐ Find intersection S and read the t_S.
  - ☐ Infuse at R_{max}, until t_S.
- Reach C from B :
  - ☐ Mark the trajectories :
    - ❶ from B to ● ; and
    - ❷ from C to ●.
  - ☐ Find T and read t_T.
  - ☐ Infuse at R_{max}, from t_T until C is reached.



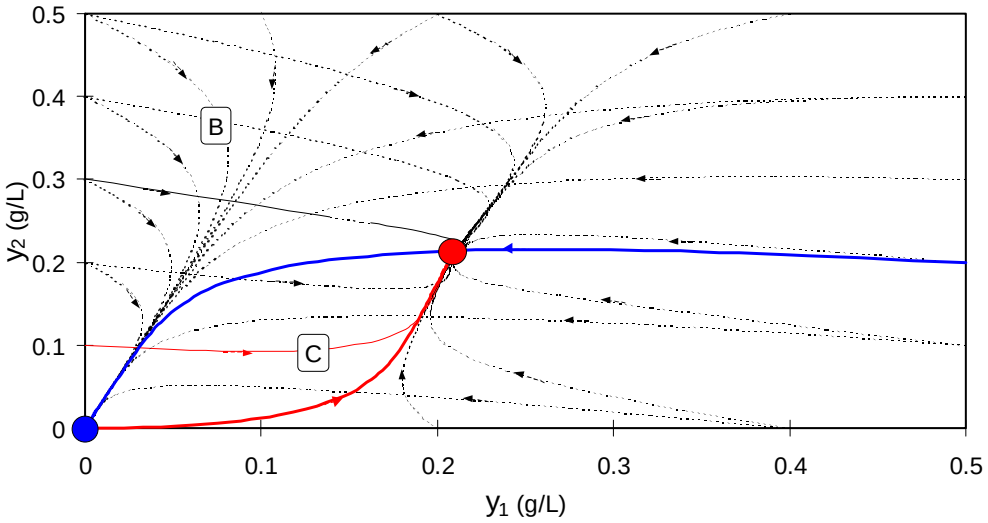
The reachable area

- **Definition :** The largest closed domain in the state plane bounded by the trajectories going through :
  1°) $\underline{y}_i$, and obtained by the minimal and maximal infusion rates ;
  2°) the origin, and obtained by the maximal infusion rate ;
  3°) the steady state, and obtained by the minimal infusion rate.

C is reachable from *B*



B is not reachable from *C*



Optimal control - example

- Two compartment linear model :

  → 1 switching time t_S

  $R_{\max} = 2\ \mathrm{g \cdot h^{-1}}$

$$\frac{d}{dt}\begin{Bmatrix} y_1 \\ y_2 \end{Bmatrix} = \begin{bmatrix} -(k_e + k_{12}) & k_{12} \\ k_{21} & -k_{21} \end{bmatrix}\begin{Bmatrix} y_1 \\ y_2 \end{Bmatrix} + \begin{Bmatrix} \frac{1}{V_1} \\ 0 \end{Bmatrix} u(t)$$

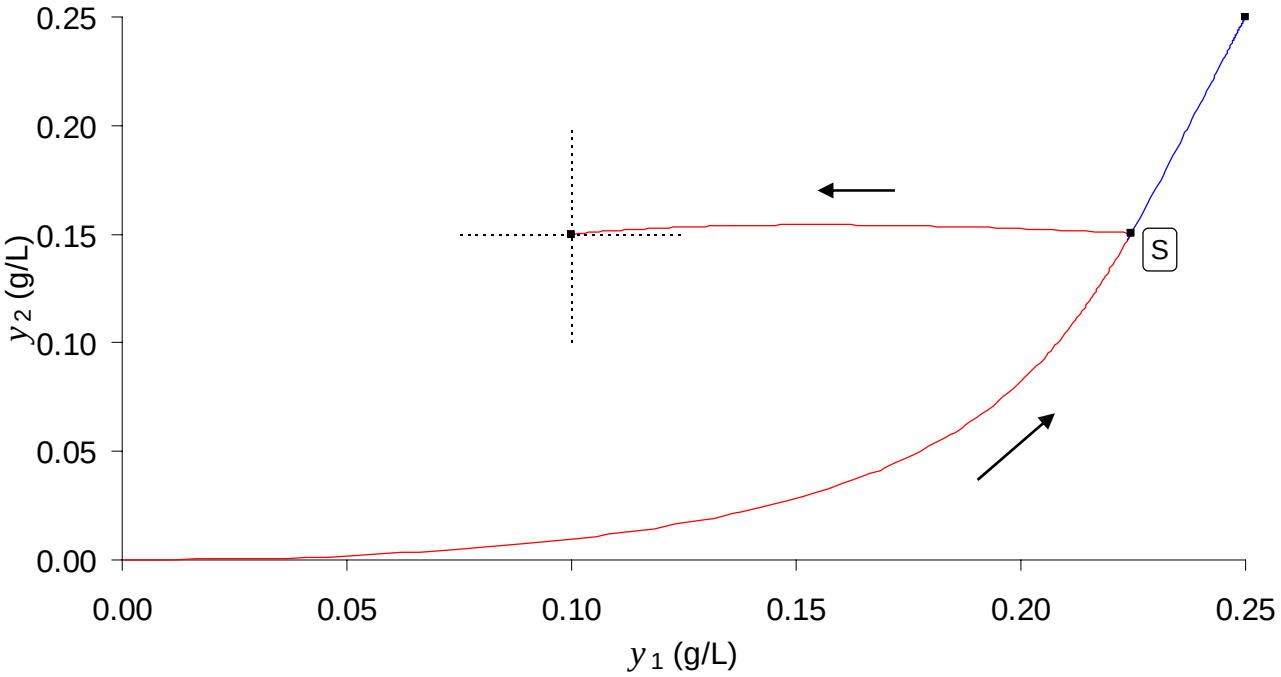
- Estimated PK parameters :

$$V_1 = 11.51\ \mathrm{L}$$
$$k_e = 0.695\ \mathrm{h^{-1}}$$
$$k_{12} = 0.175\ \mathrm{h^{-1}}$$
$$k_{21} = 0.230\ \mathrm{h^{-1}}$$

- Goal :

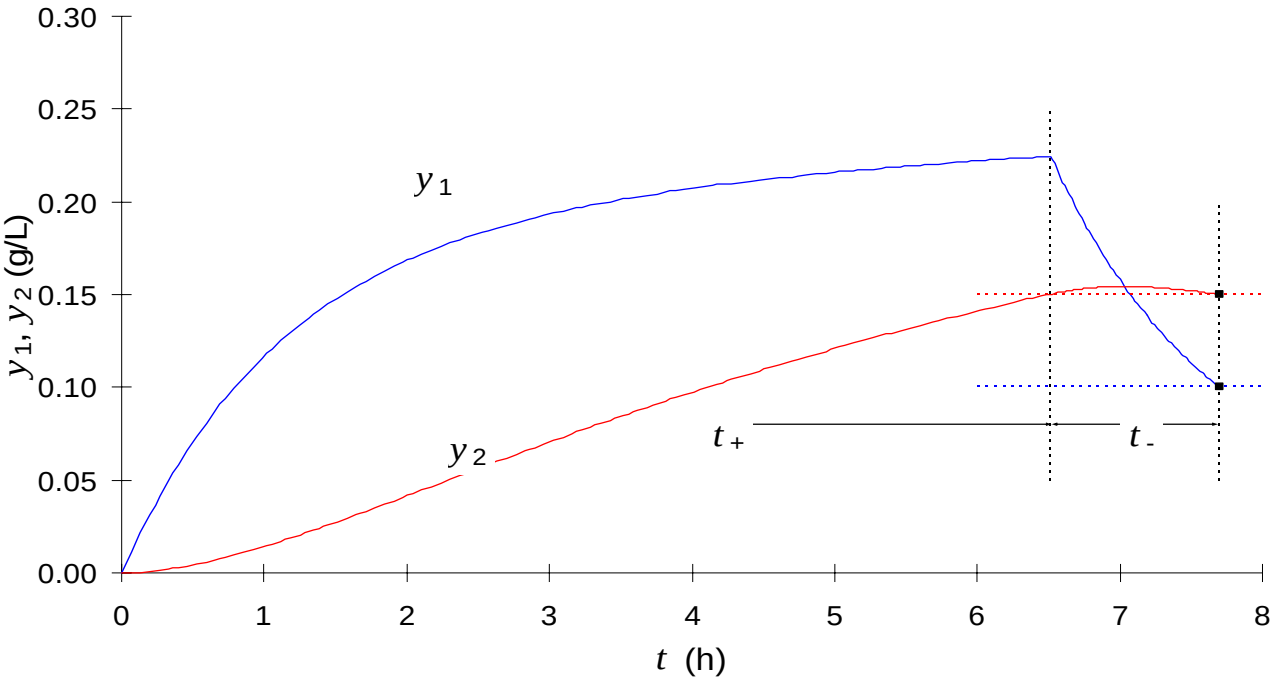
  From the origin reach :

$$(0.10, 0.15)\ \mathrm{g \cdot L^{-1}}$$



The optimal time-courses

- The optimal control :
  - Intravenous infusion at $R_{\max} = 2\ \mathrm{g \cdot h^{-1}}$ with : $t_S = t_+ = 6.6\,\mathrm{h} \quad t_- = 1.1\,\mathrm{h}$
  - $t_0 = t_+ + t_- = 7.7\,\mathrm{h}$ is the fastest transition from $(0,0) \rightarrow (0.10,0.15)\ \mathrm{g \cdot L^{-1}}$

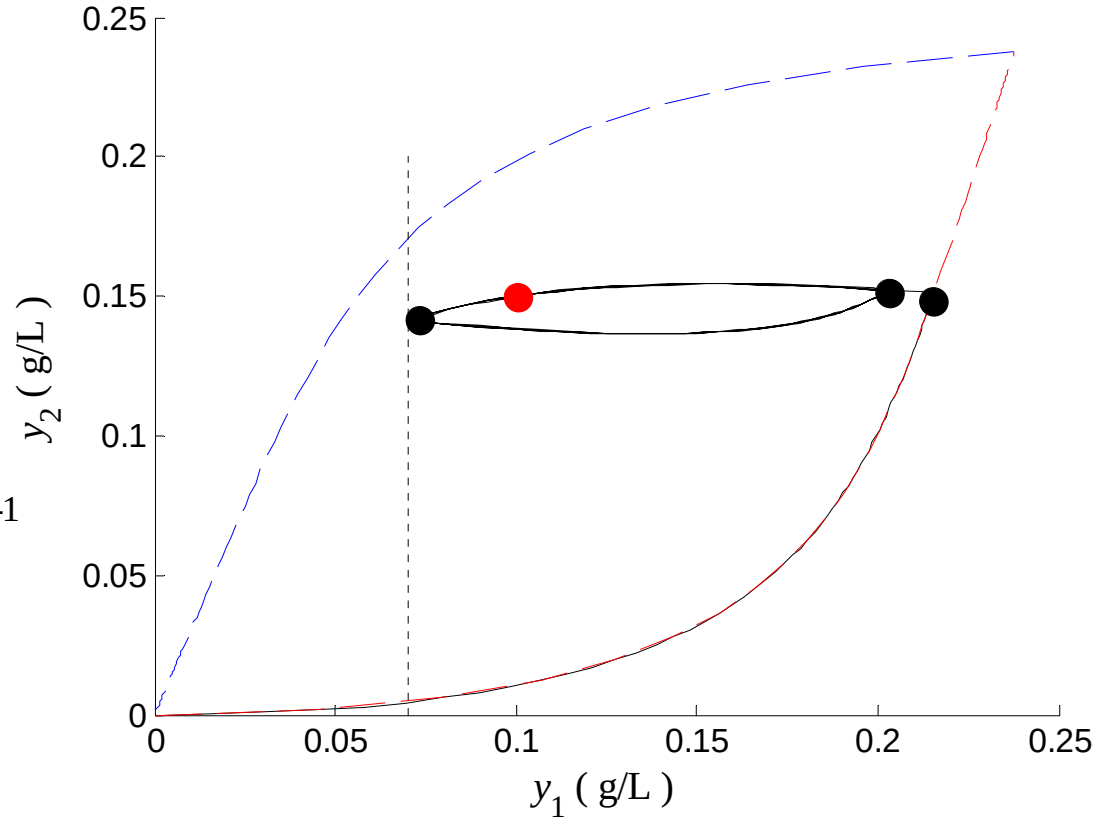


Repeated optimal control

- IV infusion : $R_{\max} = 2\ \mathrm{g}\cdot\mathrm{h}^{-1}$

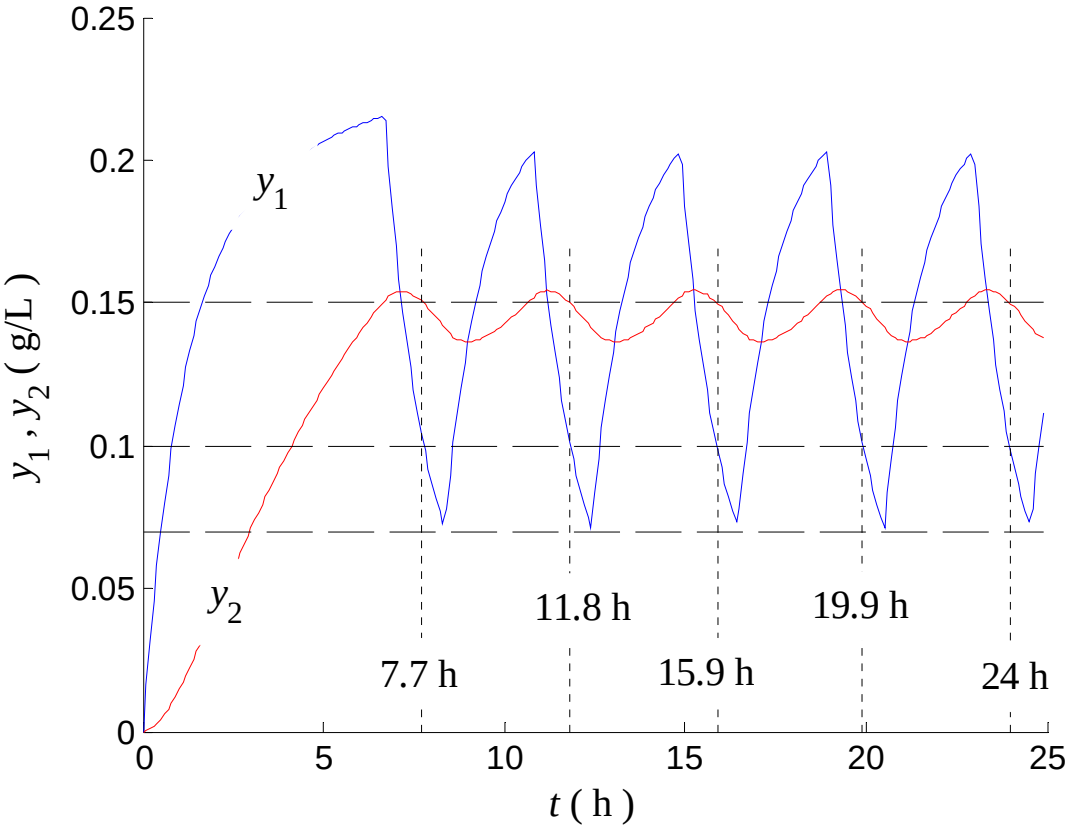
  $t_S = 6.6\ \mathrm{h} \quad t_0 = 7.7\ \mathrm{h}$

  and then in RD : $y_1(t) \geq 0.07\ \mathrm{g}\cdot\mathrm{L}^{-1}$



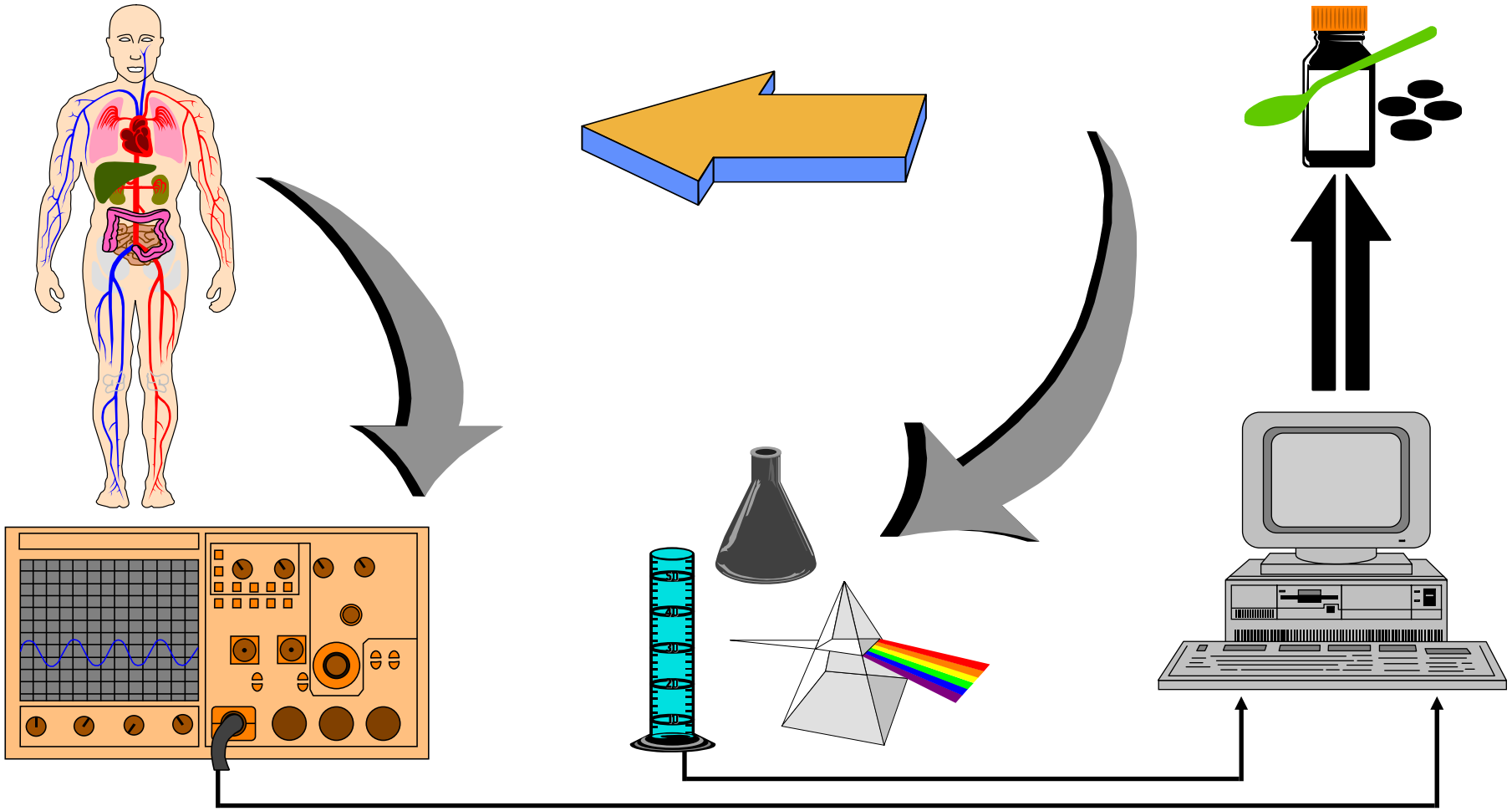
The optimal time-courses

- Administer $R_{\max}$ every $4\ \mathrm{h}$, with infusions of $T = 2.5\ \mathrm{h}$.

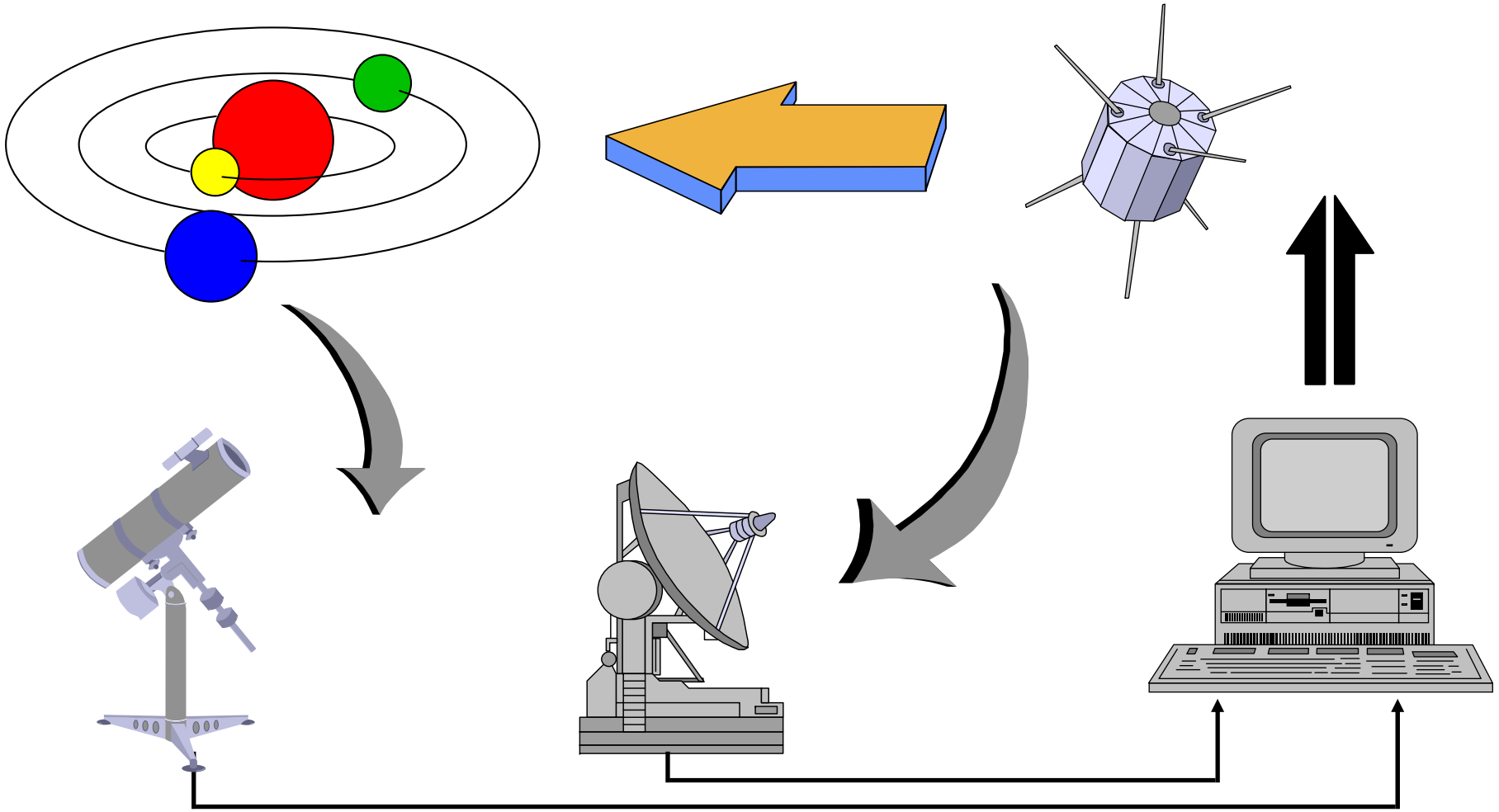


- Optimal drug combination :
  when a drug is the principal agent (it has the pharmacological action) and another is a controller, use a model involving independent additive and multiplicative control terms to design optimal bilinear inputs.

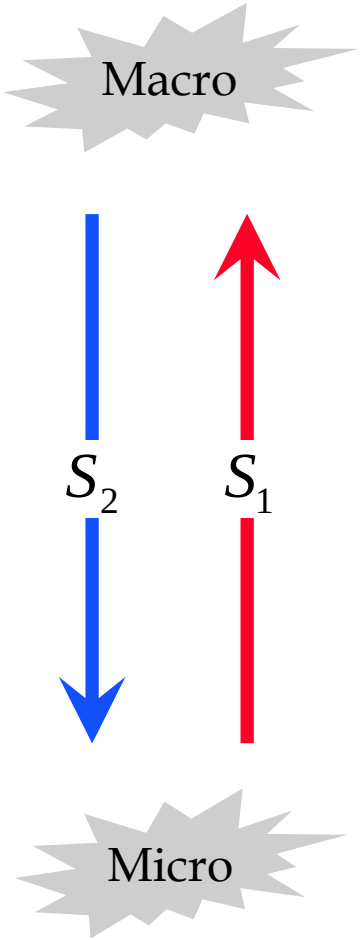
Clinical PKs



Space voyager



Strategies in modeling architecture



S_1 « Bottom-up » approach:
Details of the component parts and connectivity of them.
Incorporate in a complex model all the available biologic information.
Observations from non in-vivo experiments.
DRAWBACK : Difficulties to apply in clinical practice.

S_2 « Top-down » approach:
Functional representation of the entire process.
Start with a simple model. If it lacks to fit with in-vivo observations, integrate progressively available biological information.
AVANTAGE : Direct clinical applications.

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