Automatic control and biological systems : some results, difficulties, challenges and opportunities

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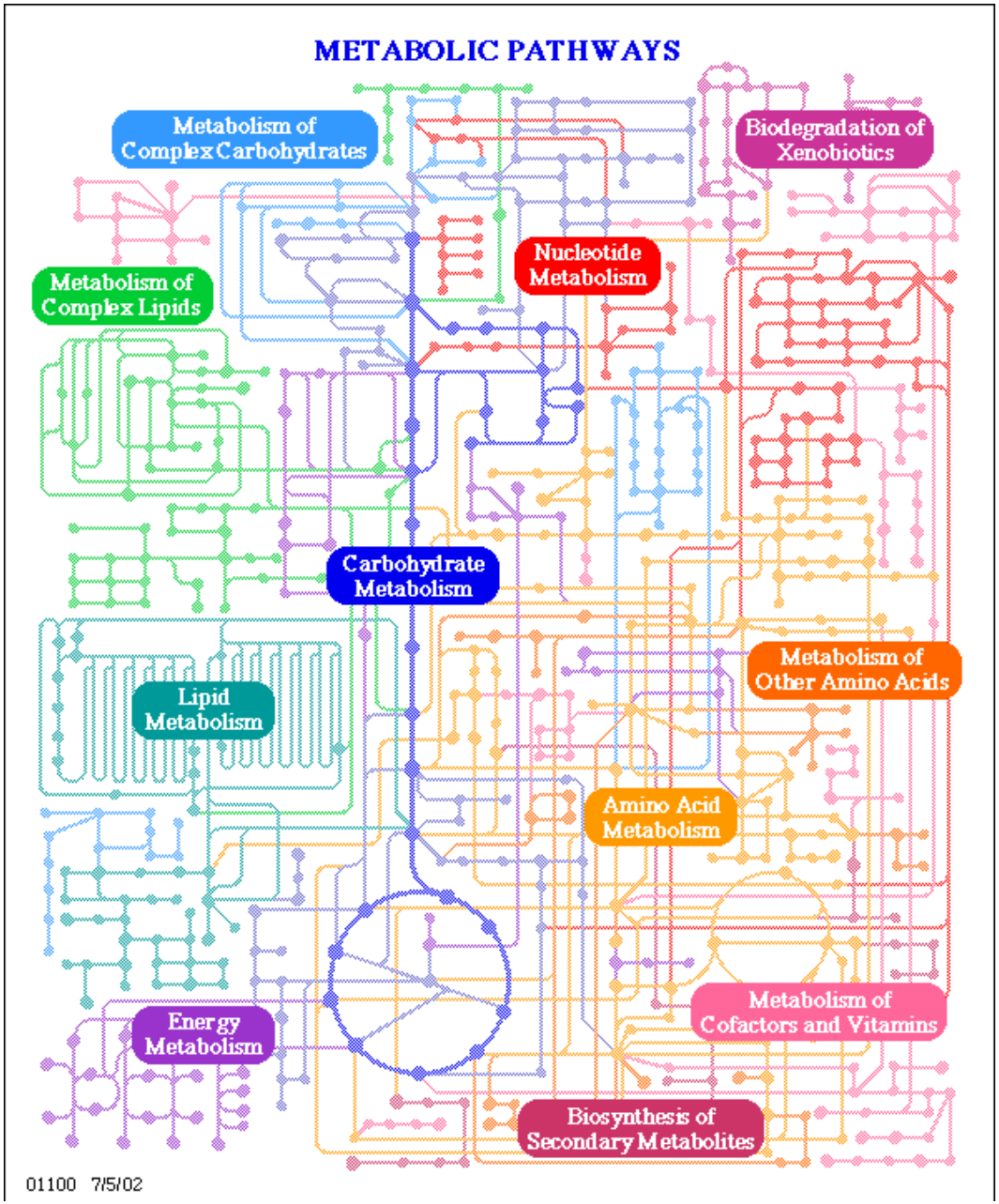
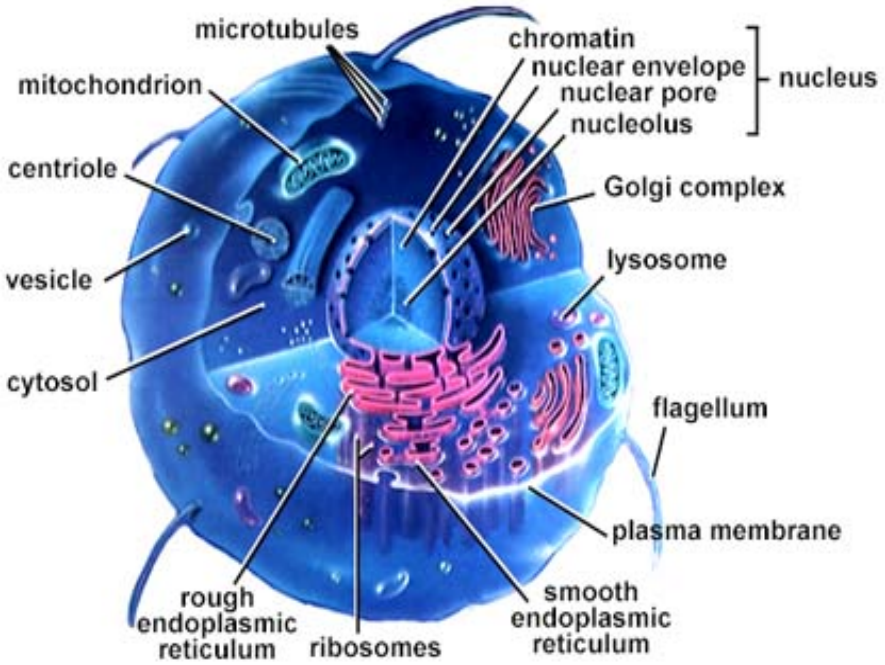
My options in this plenary lecture:

- a few technical results
- a diversity of examples

Biology looks complex...





In simple words...

A biosystem :

- growth of micro-organisms (« biomass »)
  by the consumption of nutrient (substrate)
  (C, O, N, H, P,...)

- under favourable enviromental conditions
  (temperature, pH,...)

(Early) challenges

- Complex reaction network
- Living organisms : their behaviour changes with time
- Badly known kinetics (mixture of complex biochemical kinetics and (auto-)catalytic reactions (multi-phase)

-> Complex high-order nonlinear models

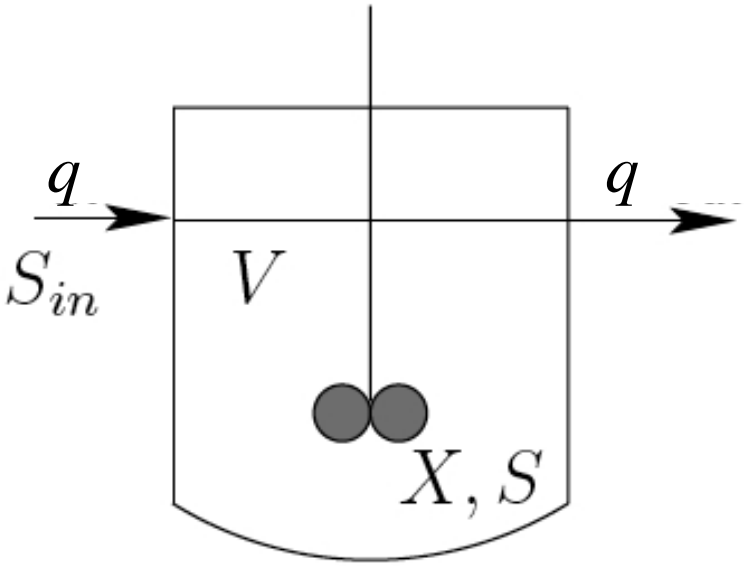
- Few available (on-line and off-line) measurements

-> Difficult to obtain reliable models

Automatic control and biological systems

- Dynamical Modelling
  - Basic & General Dynamical Model
    (+ structural properties)
  - Metabolic engineering & microbial ecology
  - Model identification
- Monitoring - Software sensors
- Control
  - Link between control theory and biological regulatory mechanisms
  - Adaptive extremum seeking & real-time optimization

Dynamical modelling : basic model



- Simple microbial growth reaction :

$$S \dashrightarrow X$$

- Mass balance equations :

$$\frac{dX}{dt} = r - \frac{q}{V}X$$

$$\frac{dS}{dt} = -k_1 r + \frac{q}{V}(S_{in} - S)$$

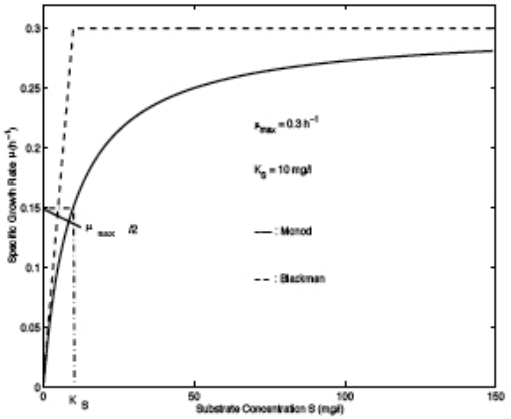
- valid for continuous (V constant), batch (q = 0) et fedbatch ($\frac{dV}{dt} = q$)

- $r = \mu X$ with μ : specific growth rate

μ depends on S, X, T, pH, …

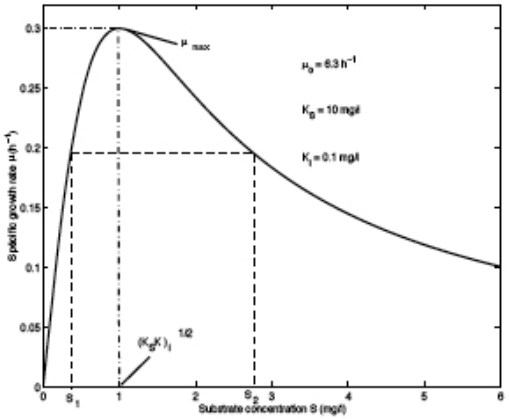
μ depends on S

Monod

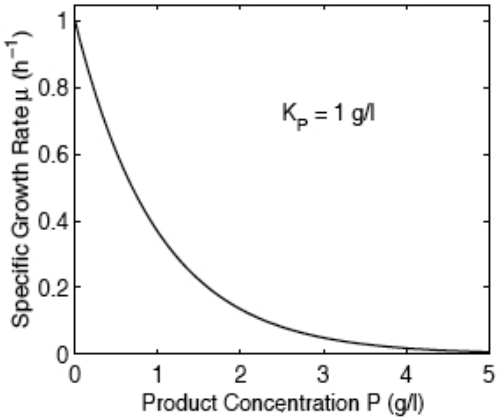


μ depends on S

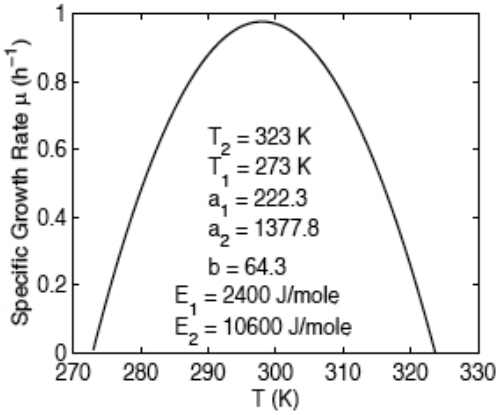
Haldane



μ depends on P



μ depends on T



Multiple reactions

Example : anaerobic digestion

- Wastewater treatment with CH_4 production

- Complex process → simplified reaction scheme

1) acidogenesis : $S_1 \rightarrow X_1 + S_2 + P_1$

S_1: organic matter

X_1: acidogenic bacteria

P_1: CO_2

2) methanisation : $S_2 \rightarrow X_2 + P_1 + P_2$

S_2: fatty volatile acids

X_2: methanogenic bacteria

P_2: CH_4

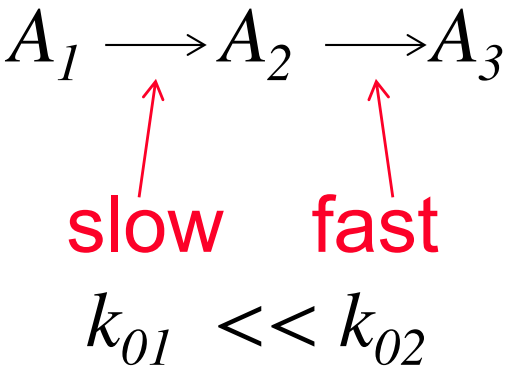
General Dynamical Model

$$\frac{dx}{dt} = Kr(x) + F - Q - \frac{q}{V}x$$

conversion transport dynamics

x : component concentration vector
K : yield coefficient matrix
$r(x)$: reaction rate vector
F : feeding rate vector
Q : gas outflow rate vector

Model reduction (slow-fast dynamics)



$$r_1 = k_{01} C_{A1} \phi_1(C_{A1}, C_{A2})$$
$$r_2 = k_{02} C_{A2} \phi_2(C_{A2}, C_{A3})$$

Let us define $\varepsilon = 1/k_{02}$ $(<< 1)$

Mass balance equation of C_{A2} (multiplied by ε) :

$$\varepsilon \frac{dC_{A2}}{dt} = -\varepsilon \frac{q}{V} C_{A2} + \varepsilon k_{01} C_{A1} \phi_1(C_{A1}, C_{A2}) - C_{A2} \phi_2(C_{A2}, C_{A3})$$

$$\varepsilon \to 0 \quad \Rightarrow \quad 0 = -C_{A2}\, \phi_2(C_{A2}, C_{A3})$$

Since $\phi_2(C_{A2}, C_{A3}) > 0$, we have : $C_{A2} = 0$

In other words: the balance equation of $C = C_{A2} + C_{A3}$

$$\frac{dC}{dt} = -\frac{q}{V} C + r_1$$

becomes the balance equation of C_{A3}

- Quasi Steady State (QSS) approximation
- General rule for model reduction :

$$\frac{dx}{dt} = 0 \text{ et } x = 0$$

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How to better account of the complexity of the cell and of its interactions with the environment?

- Metabolic engineering (and “system biology”)

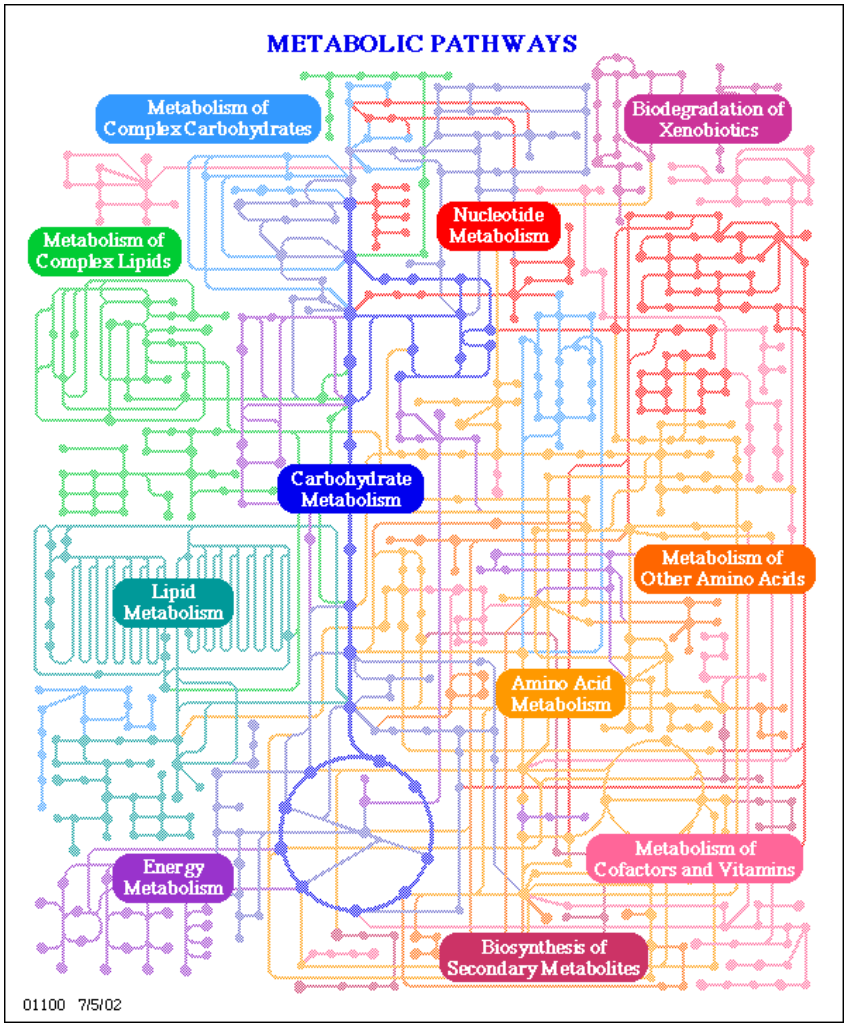
- Microbial ecology → study of the interactions between different species

Metabolic engineering

- Metabolic engineering : complex reaction networks involving cell metabolism

- Challenge : can we validate metabolic pathways with a limited number of measured components while preserving the orientation of the reactions?

- Solution : convex basis

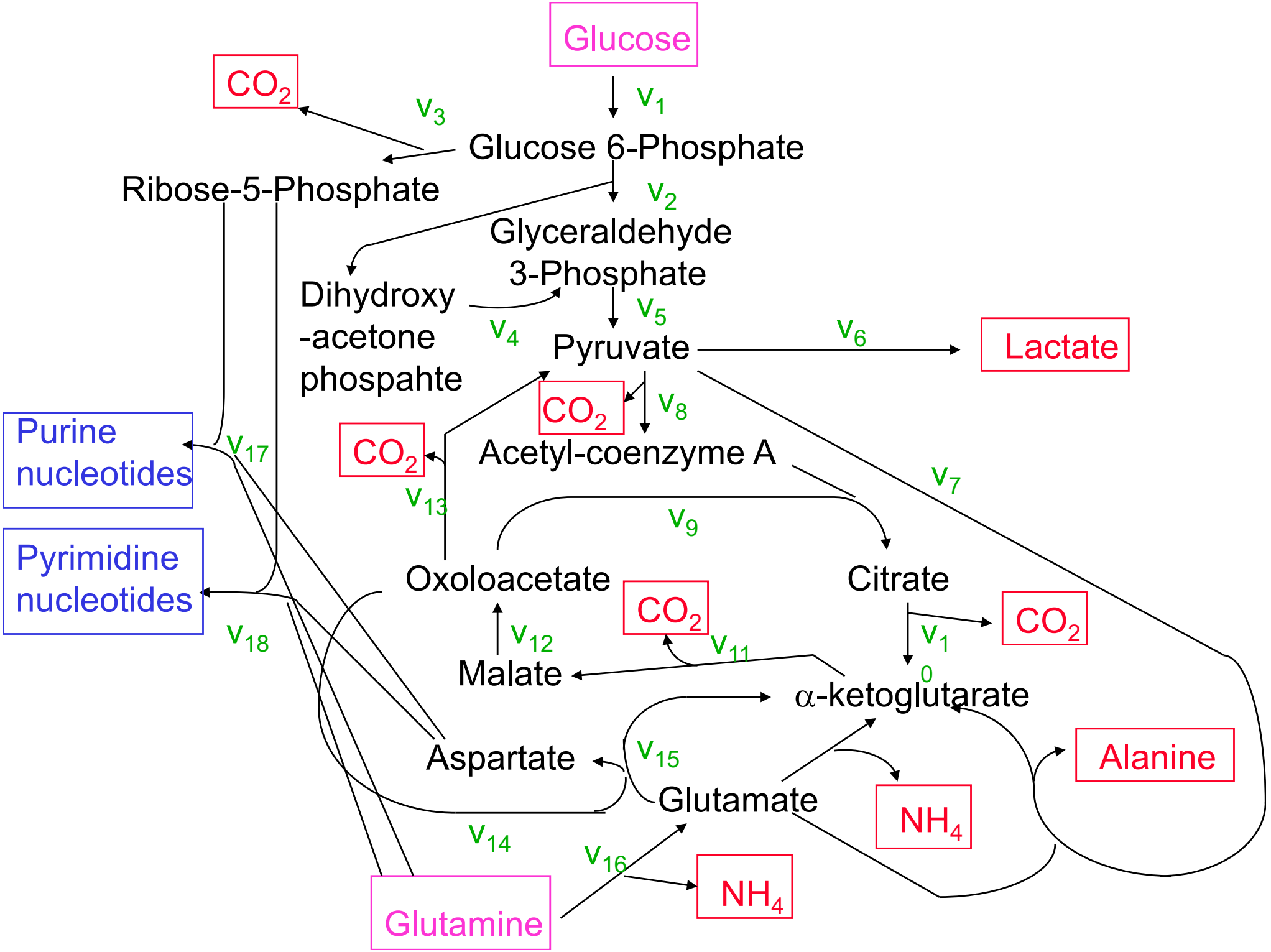


A simple example: CHO cells (animal cells)

- Metabolism : utilisation of only two main energetic nutrients

- 2 initial substrates : glucose and glutamine
- 4 terminal extracellular products : lactate, alanine, NH_4, CO_2
- 2 terminal intracellular metabolites :
  purine and pyrimidine nucleotides
- 12 internal metabolites

- 4 fundamental pathways : glycolysis, glutaminolysis, TCA cycle,
  nucleotides synthesis


Glucose
CO_2
v_3
v_1
Glucose 6-Phosphate
Ribose-5-Phosphate
v_2
Glyceraldehyde
3-Phosphate
Dihydroxy
-acetone
phospahte
v_4
v_5
Pyruvate
v_6
Lactate
CO_2
v_8
CO_2
Acetyl-coenzyme A
Purine
nucleotides
v_{17}
v_7
v_{13}
v_9
Pyrimidine
nucleotides
Oxoloacetate
Citrate
CO_2
CO_2
v_{18}
v_{12}
v_{11}
v_1
0
Malate
α-ketoglutarate
Alanine
Aspartate
v_{15}
Glutamate
NH_4
v_{14}
v_{16}
Glutamine
NH_4

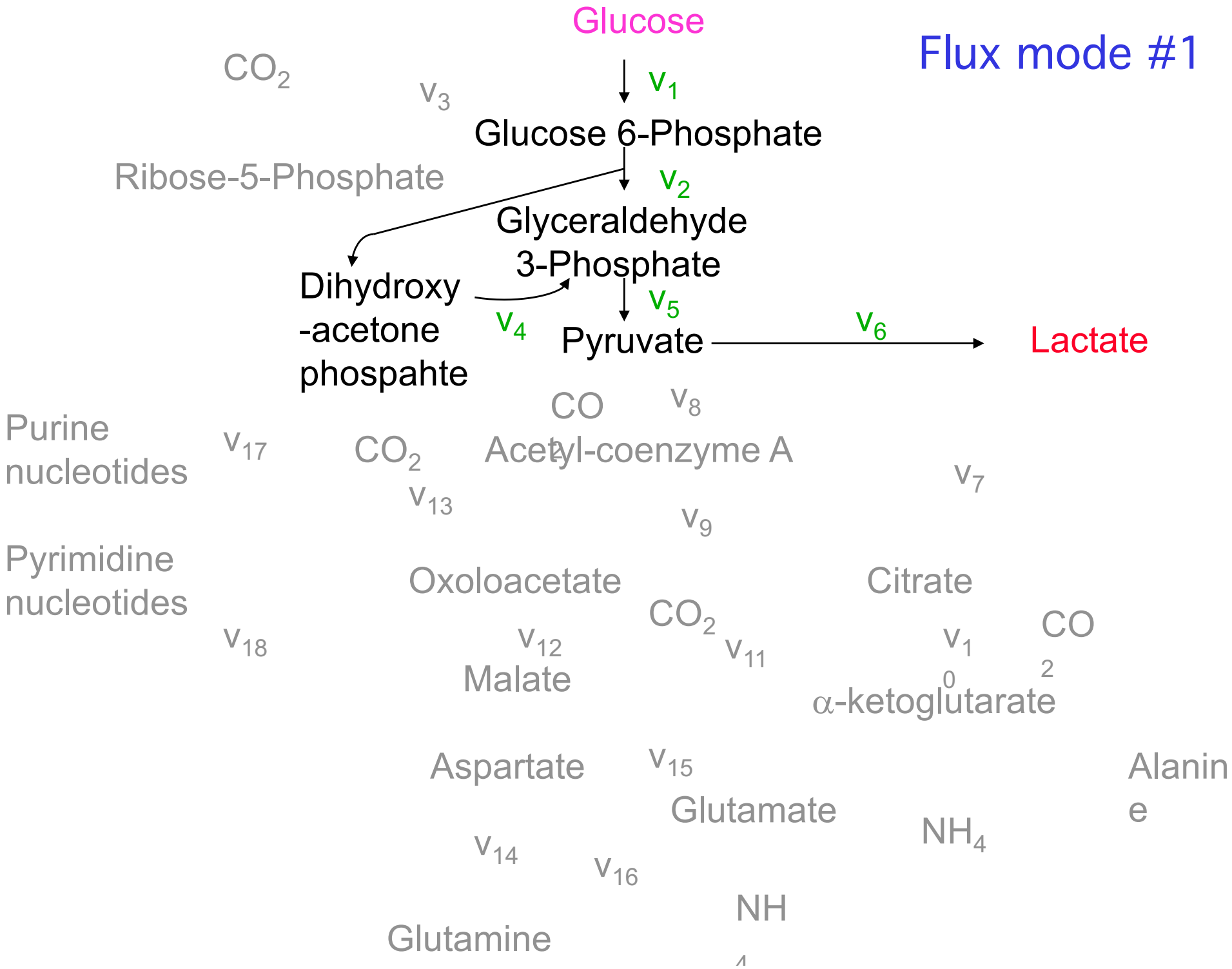
Metabolic flux analysis

- QSS approximation : Kr = 0 (dim(r) = 18)
- Rates of (measured) extracellular species : Pr = r_m

- Convex bases (in order to provide positive flux values) :
  here : 7

---> 7 macroscopic reactions :

1) Glucose ---> 2 Lactate
2) Glucose ---> 6 CO_2
3) Glutamine ---> Alanine + 2 CO_2 + NH_4
4) Glutamine ---> Lactate + 2 CO_2 + NH_4
5) Glutamine ---> 5 CO_2 + 2 NH_4
6) Glucose + 3 Glutamine ---> Purine + 2 CO_2 + NH_4
7) Glucose + 2 Glutamine ---> Pyrimidine + 2 CO_2 + NH_4


Glucose
Flux mode #1
CO_2
v_3
v_1
Glucose 6-Phosphate
Ribose-5-Phosphate
v_2
Glyceraldehyde
3-Phosphate
Dihydroxy
-acetone
phospahte
v_4
v_5
Pyruvate
v_6
Lactate
CO
v_8
Purine
nucleotides
v_{17}
CO_2
Acetyl-coenzyme A
v_7
v_{13}
v_9
Pyrimidine
nucleotides
Oxoloacetate
Citrate
CO_2
CO
v_{18}
v_{12}
v_{11}
v_{10}
2
Malate
α-ketoglutarate
Aspartate
v_{15}
Alanin
e
Glutamate
NH_4
v_{14}
v_{16}
NH
Glutamine
4

Flux mode #1

- First vector of the convex basis : $e_1 = [1\ 1\ 0\ 1\ 2\ 2\ 0\ \ldots.\ 0]^T$

- In other « words » :

v_1 : Glucose ---> Glucose6P

v_2 : Glucose6P ---> DihydroxyacetoneP + Glyceraldehyde3P

v_4 : DihydroxyacetoneP ---> Glyceraldehyde3P

v_5 : Glyceraldehyde3P ---> 2 Pyruvate

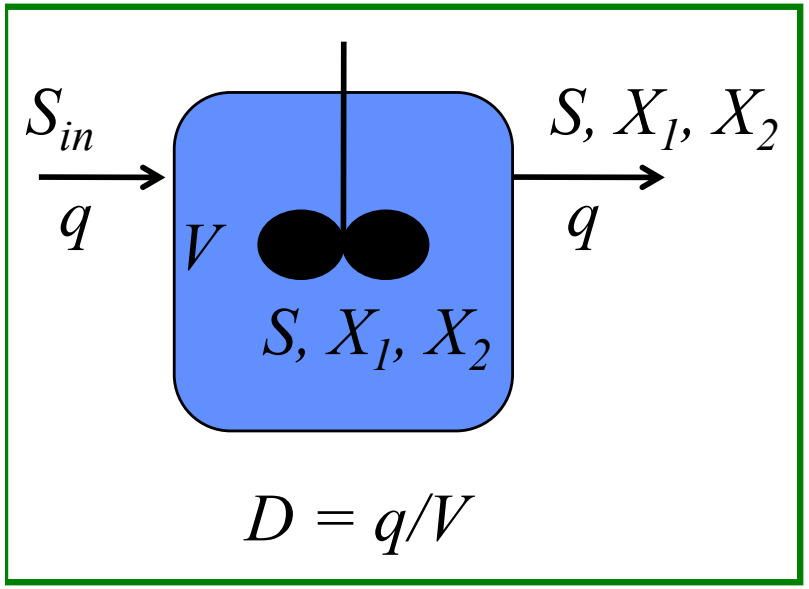
v_6 : 2 Pyruvate ---> 2 Lactate

- Associated macroscopic reaction :

Glucose ---> 2 Lactate

Microbial ecology

Basic concept : competitive exclusion principle



Basic dynamical model
with two biomasses X_1 and X_2
growing on one limiting substrate S :

$$\frac{dX_1}{dt} = \mu_1(S)X_1 - DX_1$$

$$\frac{dX_2}{dt} = \mu_2(S)X_2 - DX_2$$

$$\frac{dS}{dt} = -\frac{1}{Y_1}\mu_1(S)X_1 - \frac{1}{Y_2}\mu_2(S)X_2 + D(S_{in} - S)$$

- At steady state : $\overline{\mu}_1(S) = \overline{\mu}_2(S) = \overline{D}$

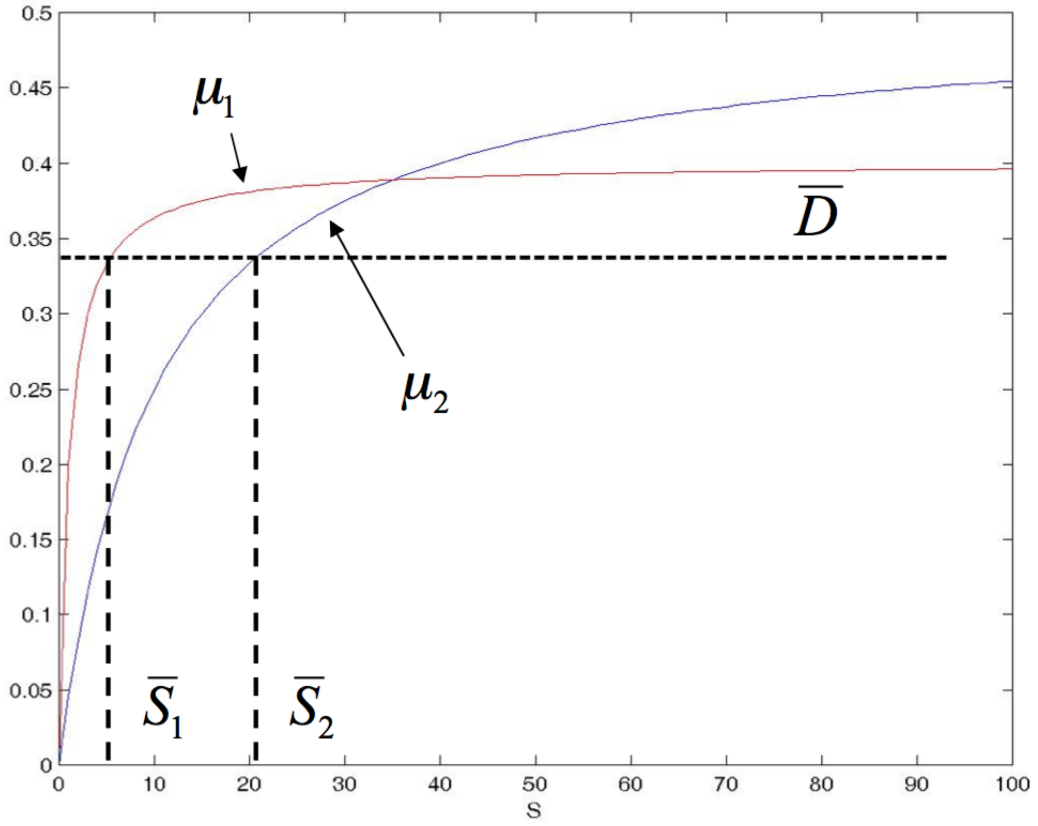
  (only valid for specific values of D)

- In general, only one species will «win the competition and survive» : --> growth curve that crosses D the first («best affinity» or «smallest break-even concentration»)

- Here :

$$\overline{X}_1 = Y_1(S_{in} - \overline{S}), \overline{X}_2 = 0$$

(*Hardin, 1960; Butler & Wolkowicz, 1985*)



(Extension to n species and other growth curves)

Competitive exclusion principle : experimental validation

X_{A1} : E. coli (1)
X_{A2} : E. coli (2)
X_B : P. aeroginosa

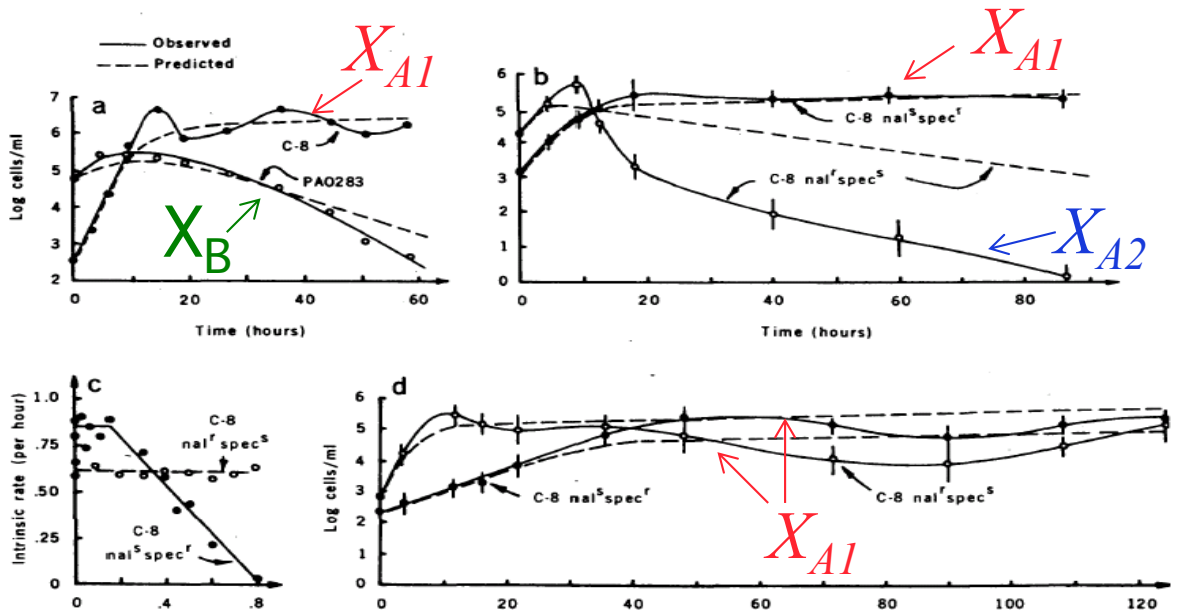
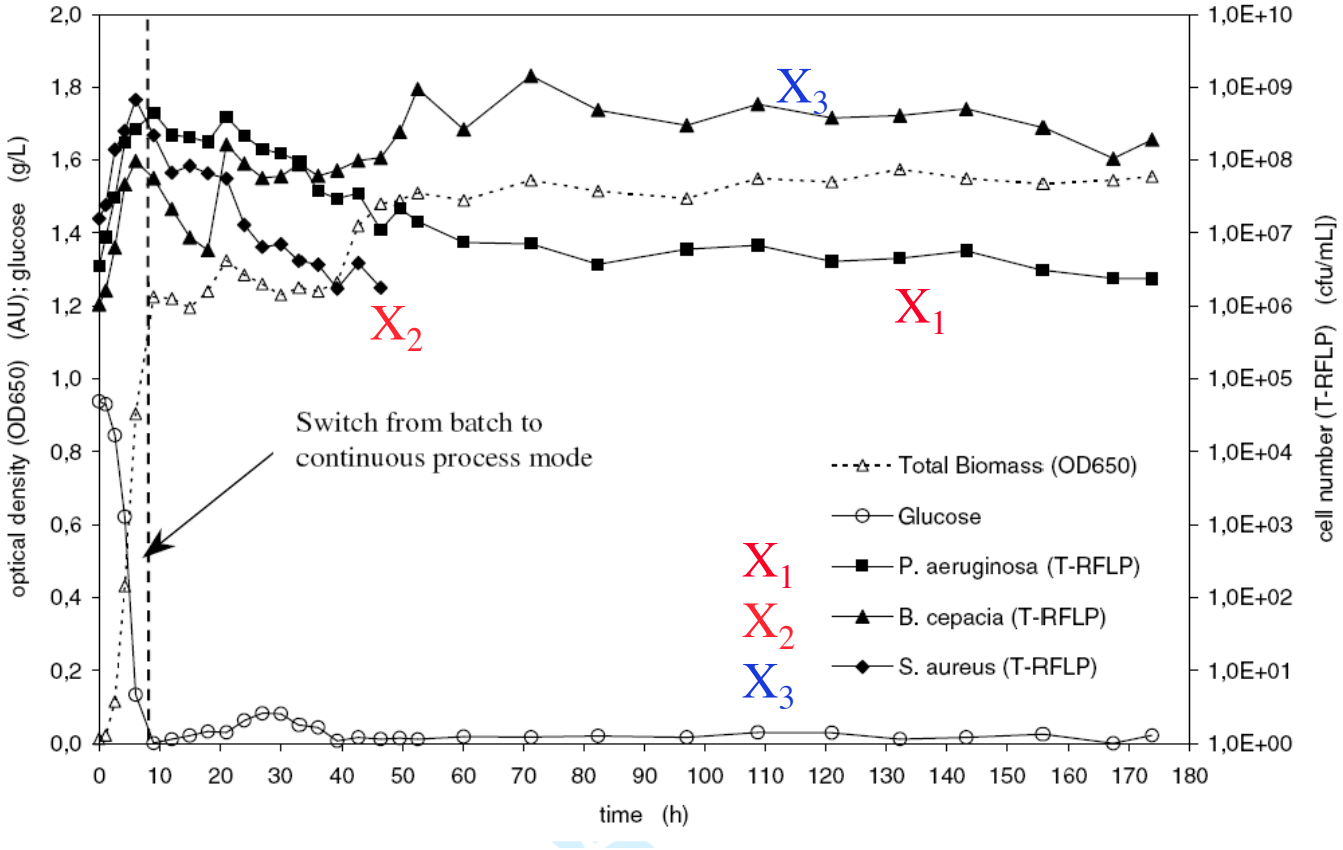


FIG. 5.2 – Validation qualitative expérimentale du comportement du modèle. Les prédictions qualitatives du modèle sont vérifiées pour : a) 2 espèces (*Escherichia coli*, souche C-8 et *Pseudomonas aeruginosa*, souche PA0283) qui diffèrent par leur constante de demi-saturation. b) 2 souches de *Escherichia coli* qui diffèrent par leur taux de croissance maximal. d) Coexistence obtenue avec 2 souches de *Escherichia coli* qui ont le même paramètre J_i. La figure c) représente l'effet de l'acide nalidixique sur le taux de croissance maximal pour les souches considérées C-8. D'après Hansen et Hubbell (1980).

S. R. Hansen S. P. Hubell, Single nutrient microbial competition, Science, 207(28), 1980, pp. 1491-1493

The coexistence of different species is often encountered

experimental evidence :



Schmidt, J. K., B. König et U.Reichl Characterization of a three bacteria mixed culture in a chemostat: Evaluation andapplication of a quant

Dynamical persistence

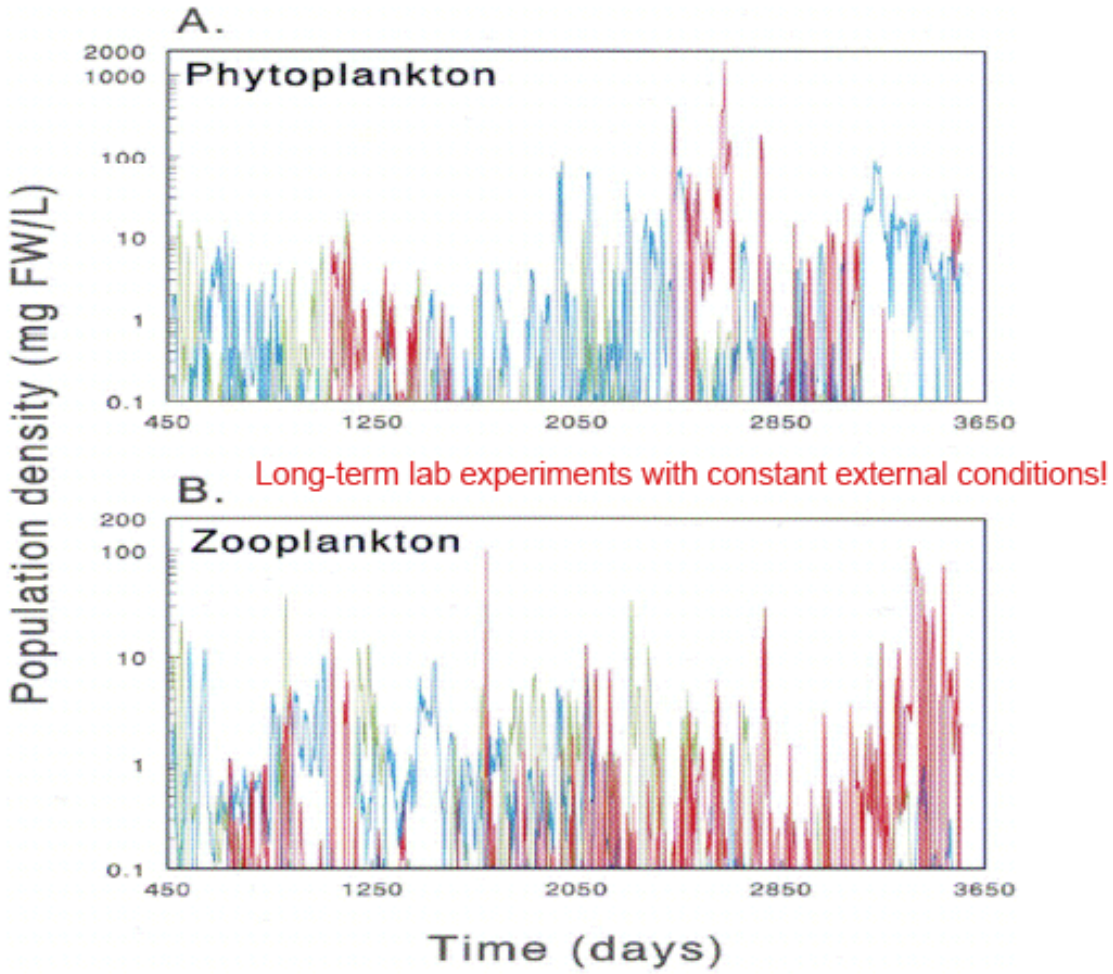


Figure 5. Non-equilibrium dynamics observed in an experimental multispecies community. The community developed in a long-term laboratory experiment under constant external conditions, and consisted of more than 20 different species. Data show the observed time course of (A) the dominant phytoplankton groups (green = green flagellates, blue = prokaryotic pico-phytoplankton, red = the diatom *Melosira*), and (B) the dominant zooplankton groups (green = the rotifer *Brachionus*, blue = the copepod *Eurytemora*, red = protozoans). Data were kindly provided by Heerkloss (unpublished), and by Heerkloss & Klinkenberg (1998), with permission from Schweizerbartsche Verlagsbuchhandlung.

One possible « solution » to have coexistence : density dependence

e.g. Contois model

$$\mu = \frac{\mu_{max} S}{K_C X + S}$$

One possible « solution » to have coexistence : density dependence

e.g. Contois model

$$\mu = \frac{\mu_{max} S}{K_C X + S}$$

which can be rewritten as : $$\mu = \frac{\mu_{max} \frac{S}{X}}{K_C + \frac{S}{X}}$$

Issues and challenges

The knowledge of the dynamical mechanisms of coexistence/competition of microbial species can be helpful for improving the running of biological systems, e.g. :

- Invasion of a culture by a contaminant
  (Can we avoid systematic re-inoculation?)(e.g. yeast)

- Mixed cultures, e.g. :
  - Lactic fermentation (*L. bulgaricus* vs *S. thermophilus* in yoghurt)
  - Anaerobic digestion (*thermophilic* vs *mesophilic* bacteria (*Tatarovsky et al*))

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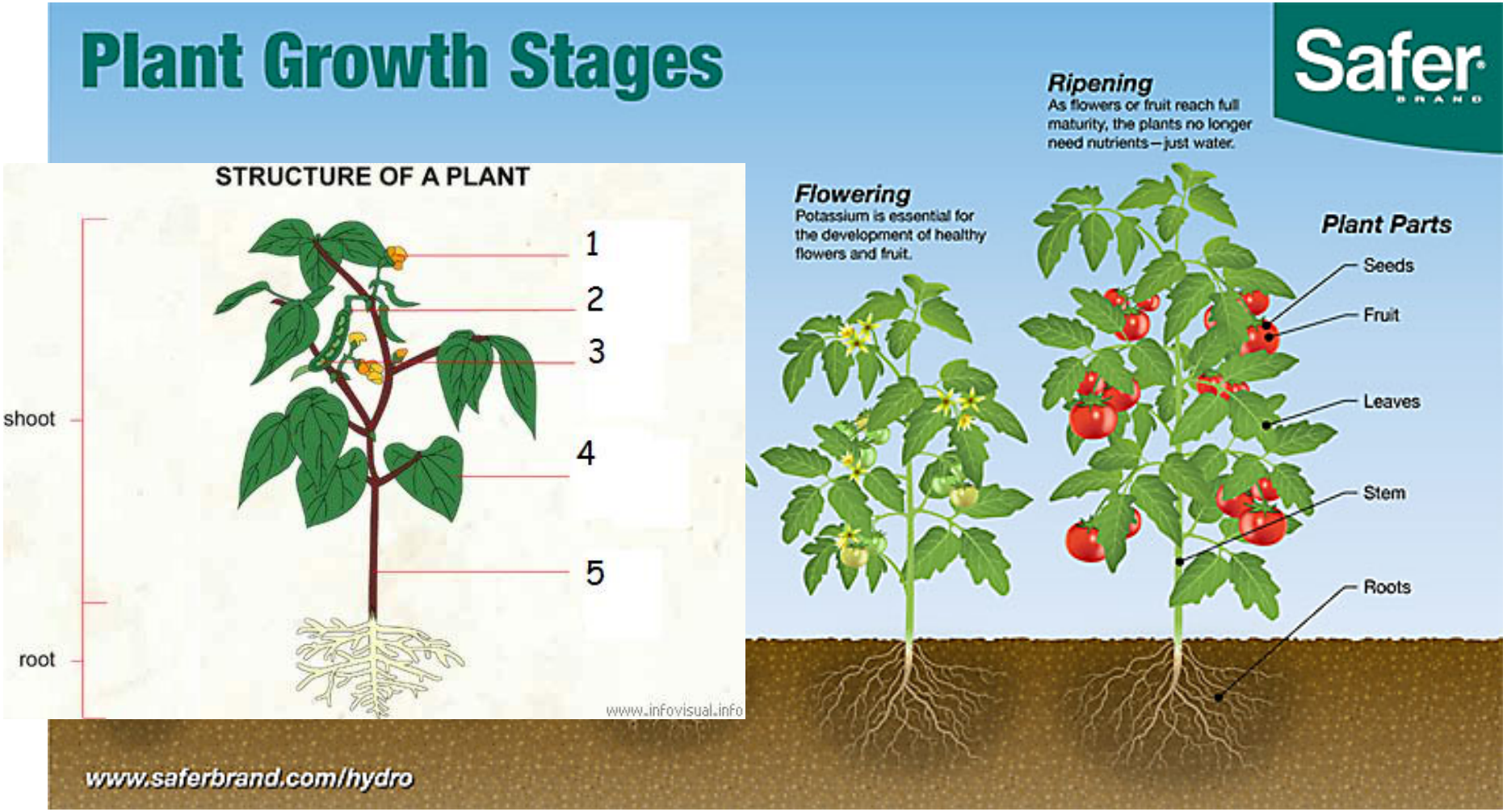
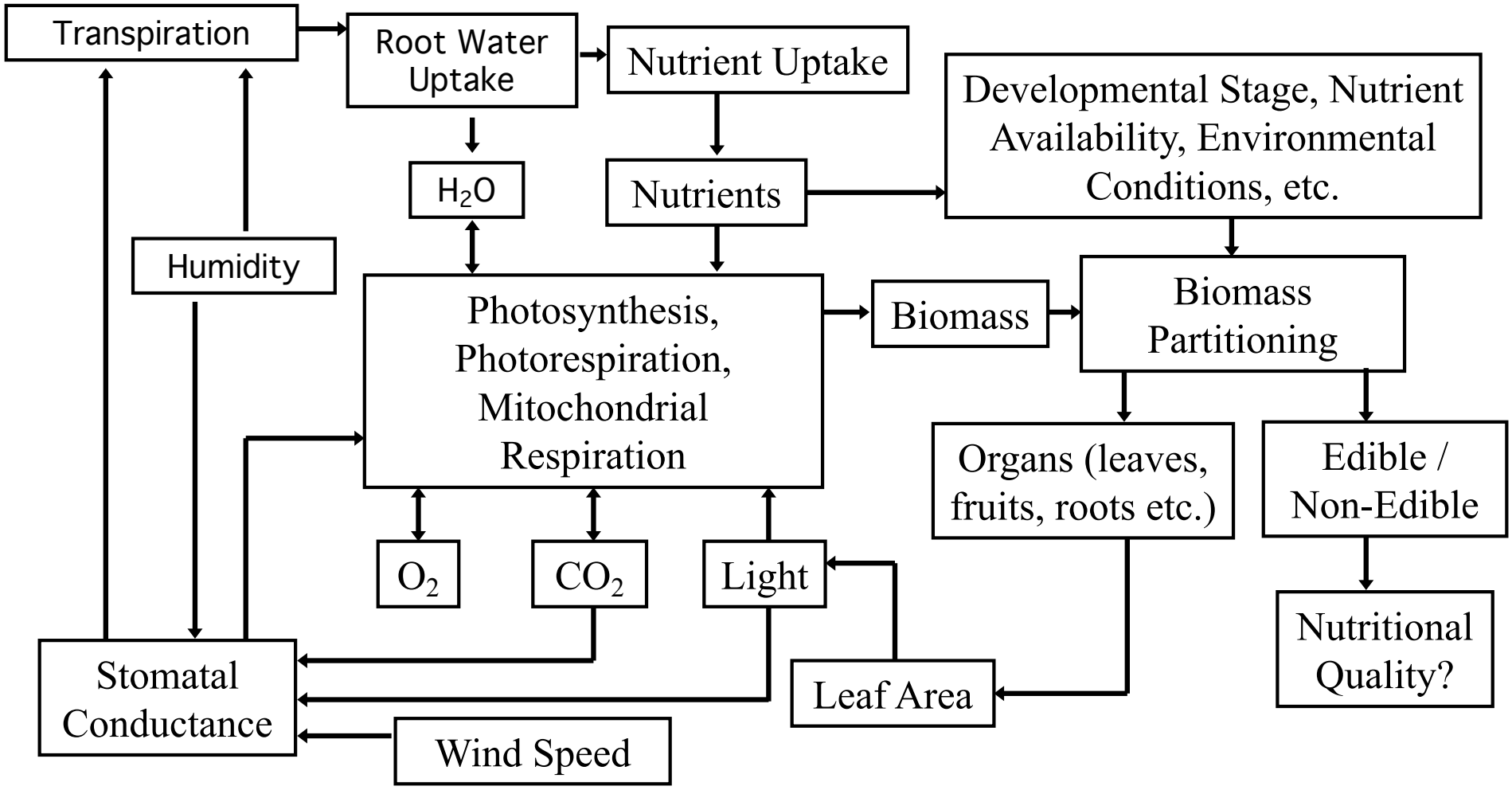
Example : plant growth



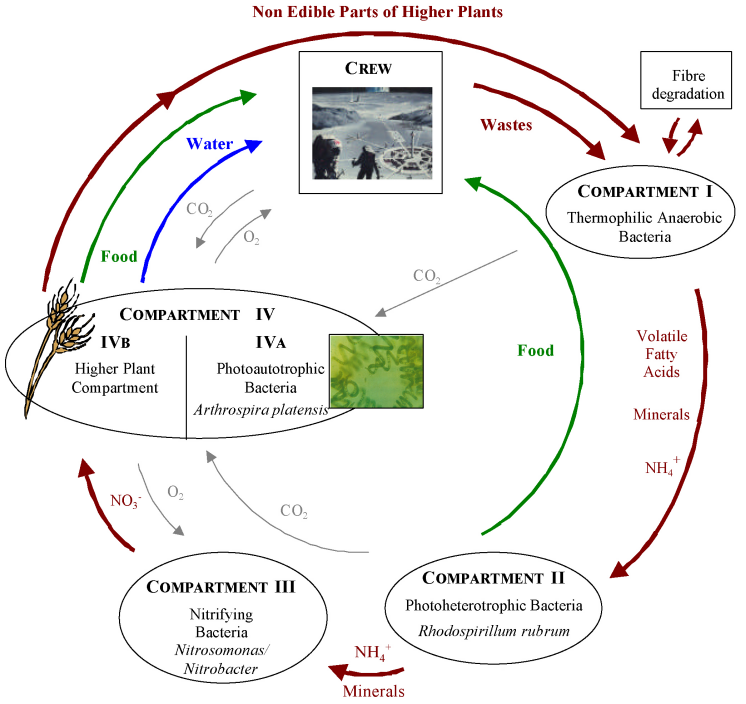
A plant is a particularly complex biosystem

A plant is a particularly complex biosystem (continued)



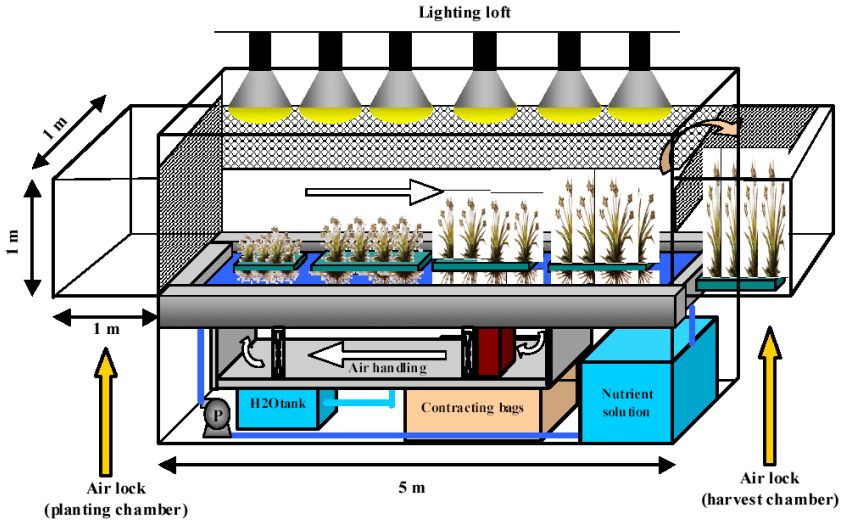
- Context : MELISSA (**M**icro **E**cological **L**ife **S**upport **S**ystem **A**lternative) project (ESA)

  Objective : to have autonomous space stations, also in terms of food production



- Objective of the plant growth :

  to guarantee a sufficient constant production by using at best the available resources (nitrogen, carbon) while minimizing the energy consumption and the waste production

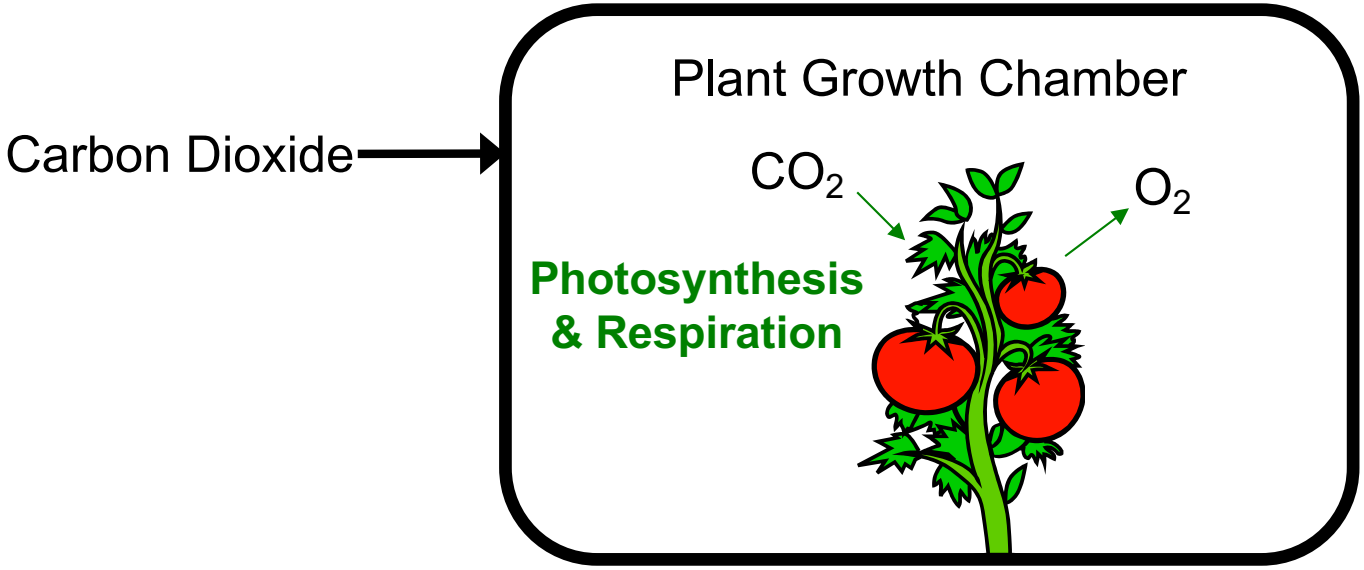


Modelling may not be a long quiet river...

- Constraints :
  - duration of the experiments
  - variability of the growth
  - diversity of elements (roots, shoot, leaves, flowers, fruits)
  - measurements (e.g., how to measure the biomass?)

- Choice of the model : simple or complex?

Model Development (starting point)



Consider photosynthesis and respiration reactions to be most important

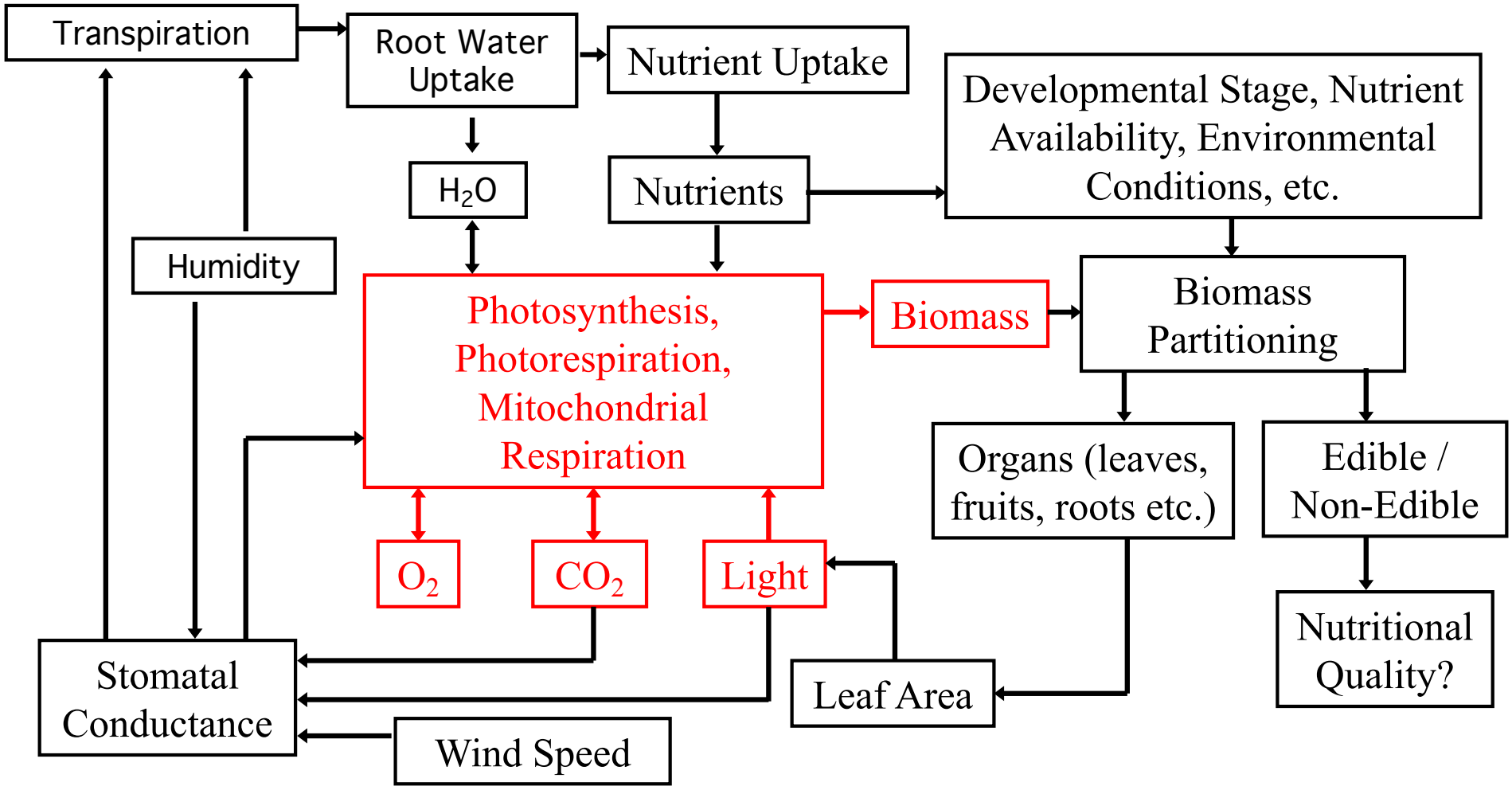
Photosynthesis: $CO_2 + H_2O \xrightarrow{Light} Biomass + O_2$

Photorespiration: $Biomass + O_2 \xrightarrow{Light} CO_2 + H_2O$

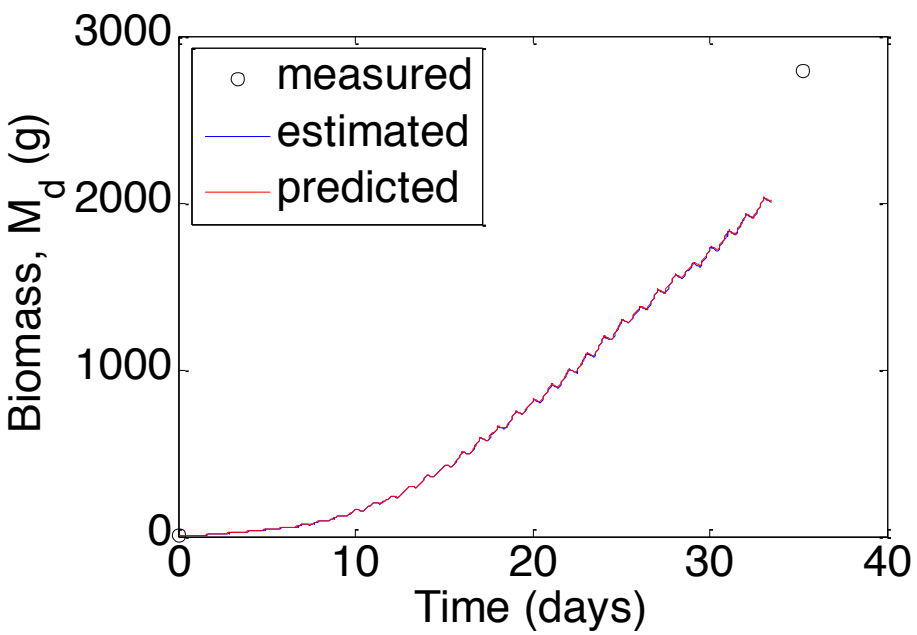
Mitochondrial respiration: $Biomass + O_2 \longrightarrow CO_2 + H_2O$

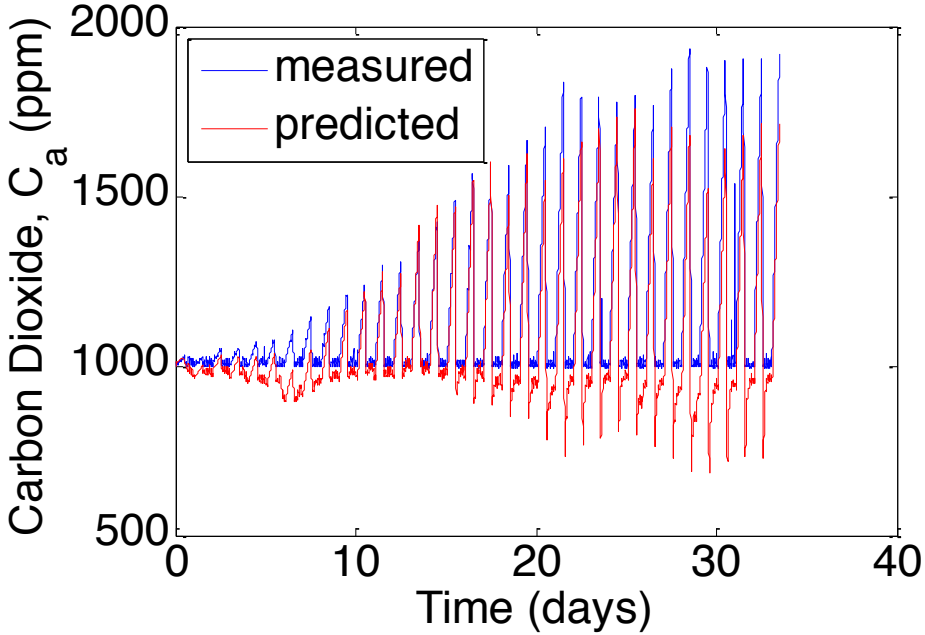
$$CO_2 + H_2O \xleftarrow{Light^*} Biomass + O_2$$

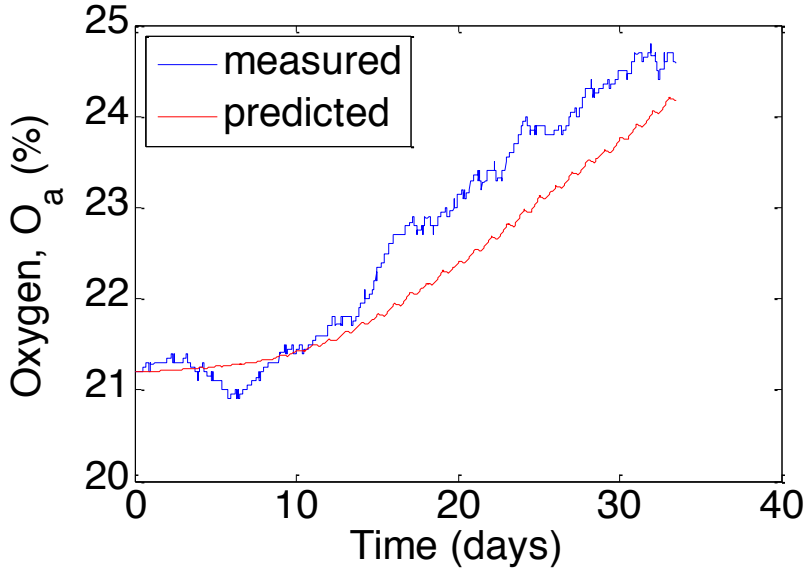
Treat as stoichiometrically reversible


Transpiration
Root Water Uptake
Nutrient Uptake
Developmental Stage, Nutrient Availability, Environmental Conditions, etc.
H_2O
Nutrients
Humidity
Photosynthesis, Photorespiration, Mitochondrial Respiration
Biomass
Biomass Partitioning
Organs (leaves, fruits, roots etc.)
Edible / Non-Edible
O_2
CO_2
Light
Nutritional Quality?
Stomatal Conductance
Leaf Area
Wind Speed

Experimental results (lettuce)







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Reaction invariants : a tool for the synthesis of state observers

Consider the state partition : $x = \begin{bmatrix} x_a \\ x_b \end{bmatrix}$

such that K_a is full rank

Then there exists $z = A_0 x_a + x_b$ with $A_0 K_a + K_b = 0$ such that:

$$\begin{cases} \dfrac{dx_a}{dt} = K_a r(x) + F_a - Q_a - \dfrac{q}{V} x_a \\ \dfrac{dz}{dt} = A_0(F_a - Q_a) + F_b - Q_b - \dfrac{q}{V} z \end{cases}$$

does not depend on the kinetics

Equivalent dynamical model

Application : state observer independent of the kinetics

Let $x = \begin{bmatrix} x_1 \\ x_2 \end{bmatrix}$ $\begin{matrix} \rightarrow \text{measured variables (dim}[x_1] \geq \text{rang}[K]) \\ \rightarrow \text{unmeasured variables} \end{matrix}$

We can then write: $z = A_1 x_1 + A_2 x_2$

$$\rightarrow \begin{cases} \dfrac{d\hat{z}}{dt} &= A_0(F_a - Q_a) + F_b - Q_b - \dfrac{q}{V}\hat{z} \\ \hat{x}_2 &= A_2^{+}(\hat{z} - A_1 x_1) \end{cases}$$

A_2^{+} → left inverse

« Asymptotic » observer :

$$\lim_{t\to\infty}(x_2 - \hat{x}_2) = 0 \quad \text{si} \quad \int_t^{t+\delta} \frac{q}{V}(\tau)d\tau \geq \beta > 0$$

Example : Intracellular production of PHB

PHB = Poly-β-hydroxybutyric acid (biodegradable polymer)

Aerobic culture of *Alcaligenes eutrophus* in fedbatch reactor

- 2 limiting substrates :
  Carbon source (fructose, glucose, ...)
  Nitrogen source (NH^+_4)

- Intracellular production : 2 metabolic pathways :
  1) associated to the growth (low yield)
  2) X catalyzed by an enzyme (fully inhibited by the nitrogen)

- Bioreactor operation : 2 steps :
  1) growth “without” production → fed with both substrates
  2) production without growth → fed only with carbon

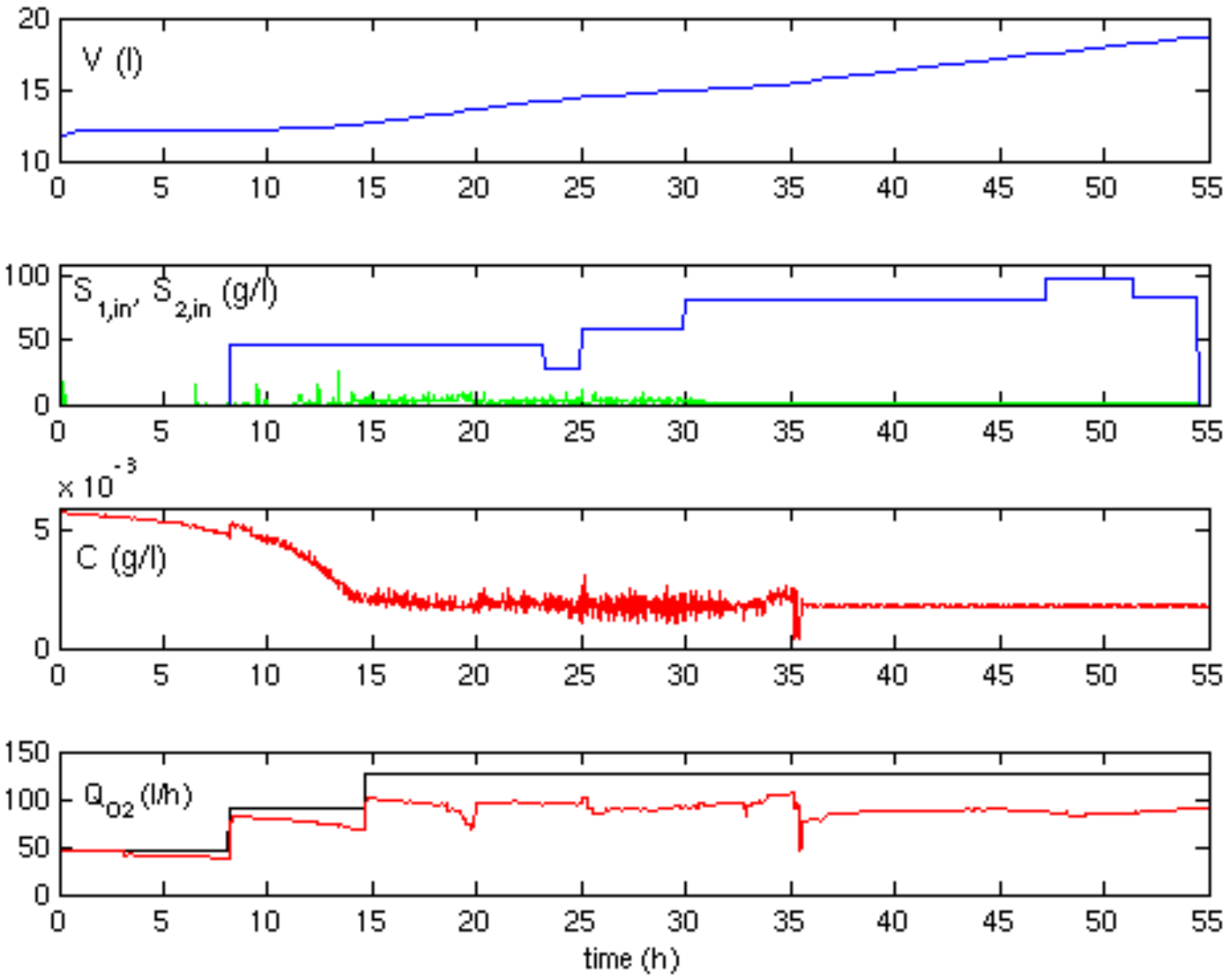
Data

Volume

Inlet feed (glucose, nitrogen)

Dissolved oxygen

O_2 flow rates (inlet, outlet

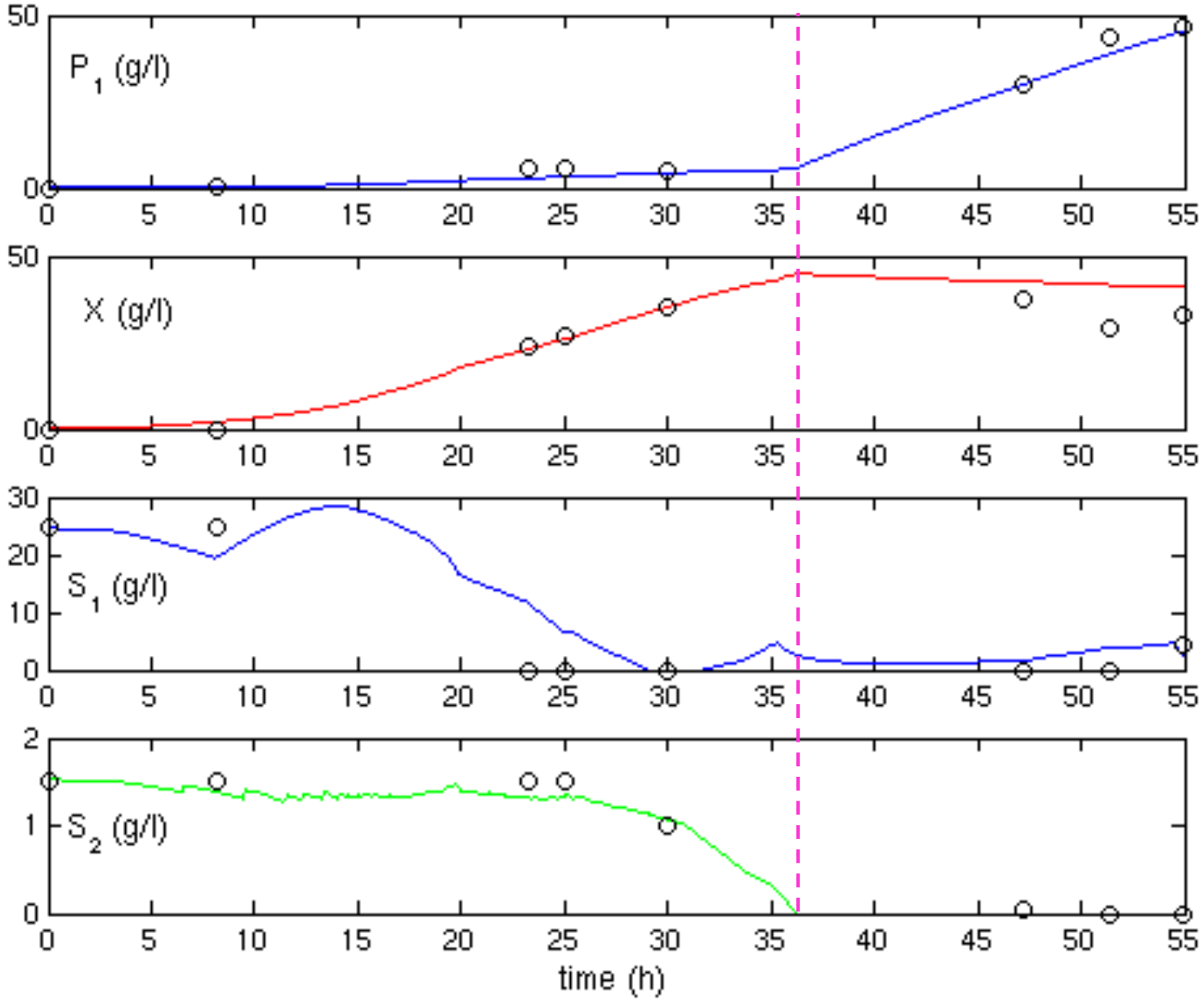


PHB

Biomass

Glucose

Nitrogen



o : off-line analyses

Automatic control and biological systems

- Dynamical Modelling
  - Basic & General Dynamical Model
    (+ structural properties)
  - Metabolic engineering & microbial ecology
  - Model identification
- Monitoring - Software sensors
- Control
  - Link between control theory and biological regulatory mechanisms
  - Adaptive extremum seeking & real-time optimization

Link between control theory and biological regulatory mechanisms

- Homeostasis (*definition)* :
  - Property of a system within the body of an organism in which a variable, such as the concentration of a substance in solution, is actively regulated to remain very nearly constant
  - Characteristics of an ecosystem that resists to changes (disturbances) and preserves an equilibrium state.

- Can we make the link e.g. with a PI controller?

(F. Mairet, « A biomolecular proportional integral controller based on feedback regulation of protein level and activity »)

Rationale

- Protein X with active state (x*) and inactive state (x) : $X = x^* + x$
- Product y : represses the production of the protein (gene regulation) and its activity (e.g. phosphorylation)

- Variation around the reference equilibrium: $e = y_{ref} - y$
- Dynamics of X : production $f(y)$ – degradation k_d

  where $f(y) \simeq f(y_{ref}) + f'(y_{ref})e$ with $f'(y_{ref}) < 0$ (repression by y) :

$$\dot{X} = f(y) - k_d = f'(y_{ref})e$$

- Solution : $X(t) = X_{ref} + f'(y_{ref}) \int_0^t e(s)ds$

- Dynamics of the active protein: $\dot{x}^* = k_a x - k_i(y)x^*$

- Slow-fast assumption: $k_a x >> k_i(y)x^*$ → quasi steady-state (QSS) approximation:

$$x^*(t) = \frac{k_a}{k_a + k_i(y)} X(t)$$

- Case #1 : no regulation of the activity (k_i constant)

$$x^*(t) = \frac{k_a}{k_a + k_i} X_{ref} + \frac{k_a}{k_a + k_i} f'(y_{ref}) \int_0^t e(s)ds$$

integral action

- Case #2 : regulation of the activity

Let $k_i(y) \simeq k_i(y_{ref}) + k_i^{'}(y_{ref})e$

$$\frac{1}{a+\epsilon} \simeq \frac{1}{a}\left(1 - \frac{\epsilon}{a}\right),\ \epsilon << 1$$

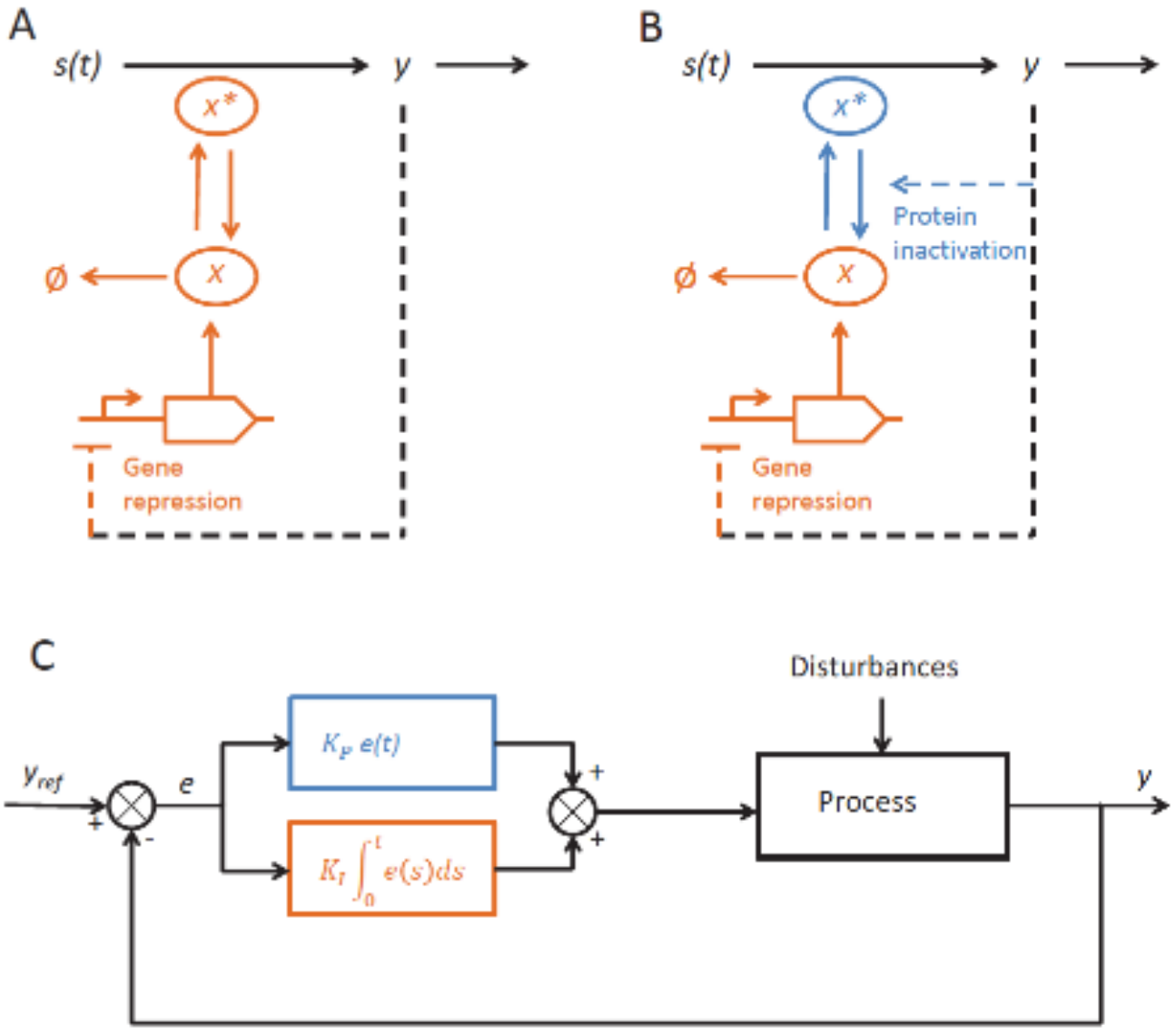
--> $$\boxed{x^*(t) \simeq x^*_{ref} - K_P e(t) - K_I(y)\int_0^t e(s)ds}$$

with

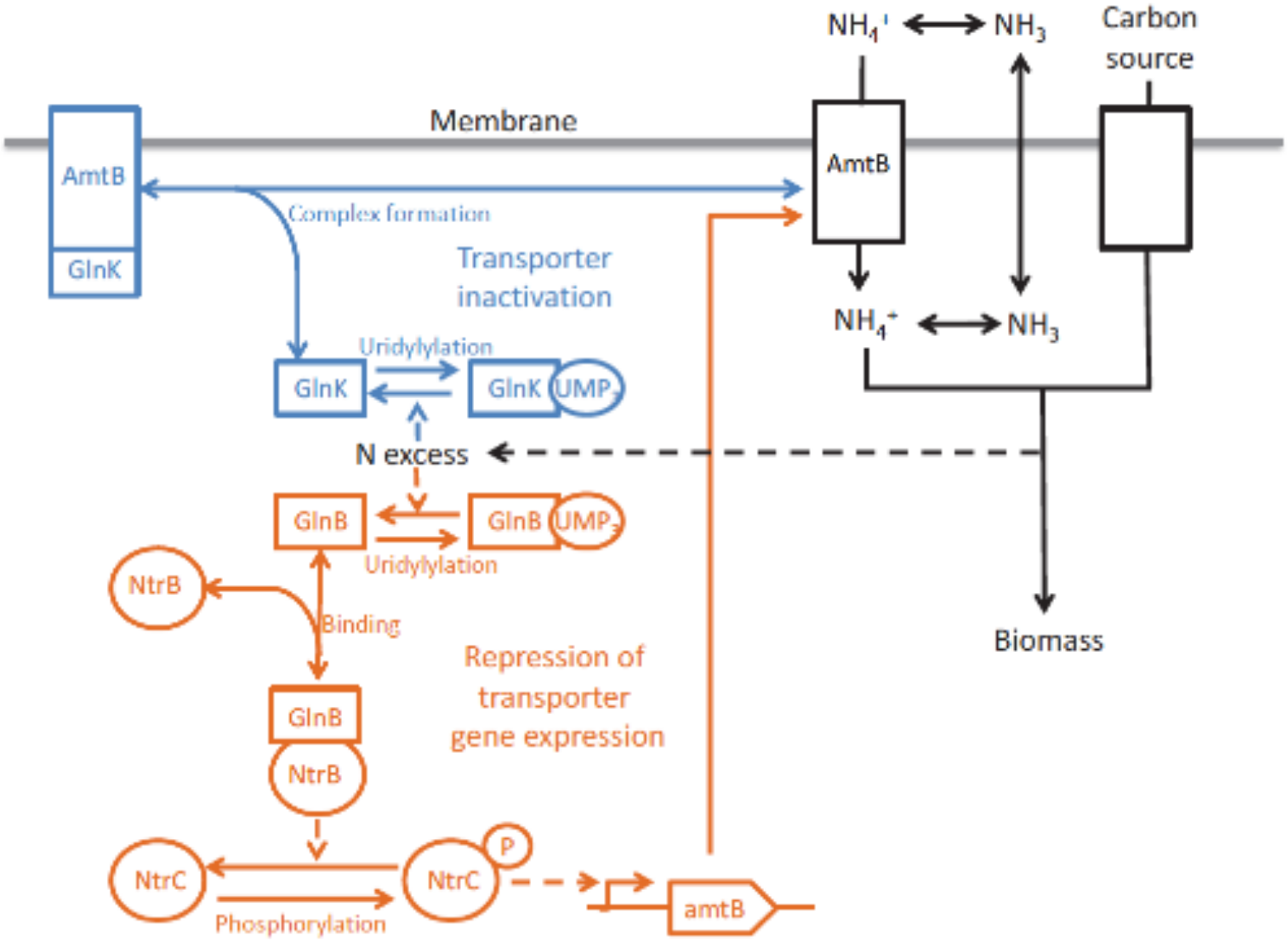
$$x_{ref} = \frac{k_a X_{ref}}{k_a + k_i(y_{ref})}$$

$$K_P = \frac{k_i^{'}(y_{ref})k_a X_{ref}}{(k_a + k_i(y_{ref}))^2},\ K_I(y) = -\frac{k_a f'(y_{ref})}{k_a + k_i(y)}$$

Basic schemes



Example : regulation of the ammonia consumption by *E. Coli* via AmtB transporters



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Control of biological systems : which issues ?

- Stabilisation

  A key feature of reaction systems : multiple steady states

- Real-time optimisation

  ... in the absence of the precise knowledge of the optimum

Real-time optimisation

- Example : biomedical
- Context : drug delivery
- Tolerance to the cardio-accelerating effect of nicotine :
  --> attributed to the buildup of a drug metabolite
  --> antagonist to the drug
  --> reduces drug effect over time
- Dynamical model :

$$\begin{cases} \dot{c} &= -c + u \\ \dot{a} &= k_a(c - a) \end{cases}$$

drug concentration

drug infusion rate

antagonist concentration

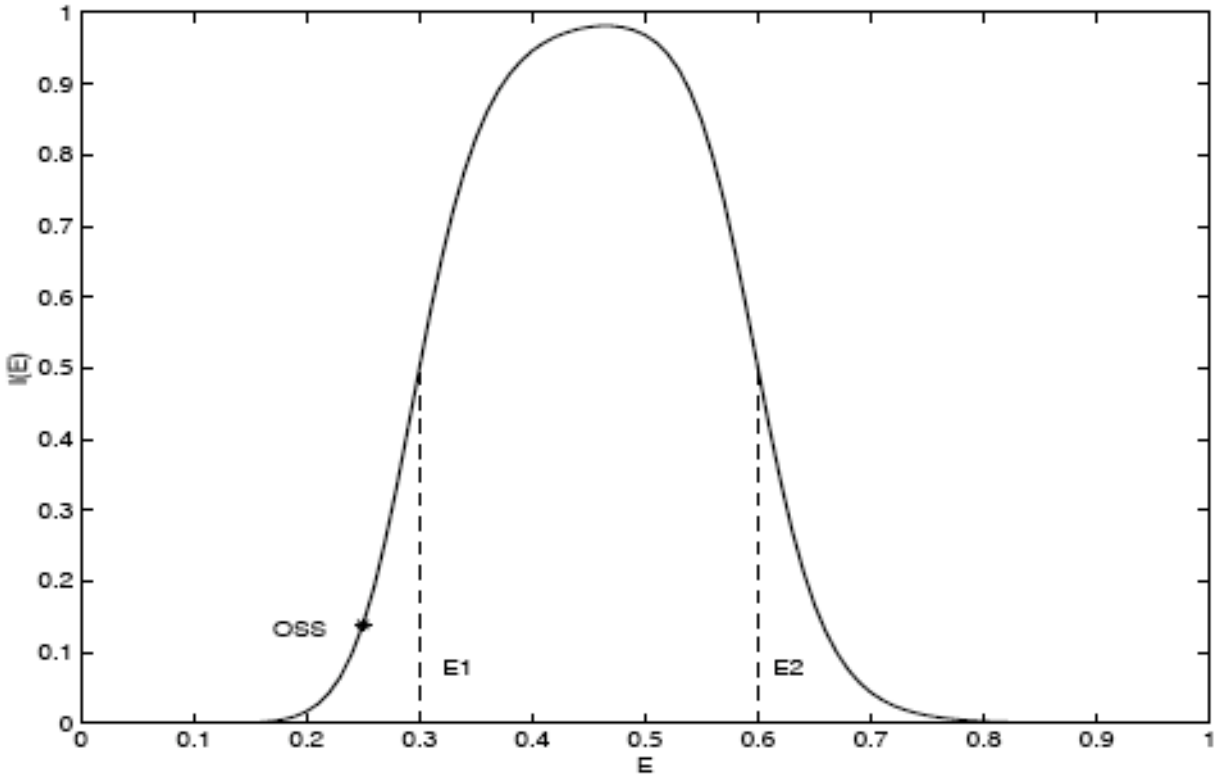
- Drug effect E on the patient :

$$E(c, a) = \frac{c}{(1 + c)(1 + a/a^*)}$$

relative potency of the antagonist wrt drug

- Optimal Steady State (OSS) : $\bar{E}_{max} = \dfrac{\sqrt{a^*}}{(1+\sqrt{a^*})^2}$
- A simple objective : to keep *E* in a prescribed interval [E_1, E_2] (desired interval for the heart rate)

--> Indicator *I(E)*



- What if $\bar{E}_{max} < E_1$?

Bittanti et al (1973) :

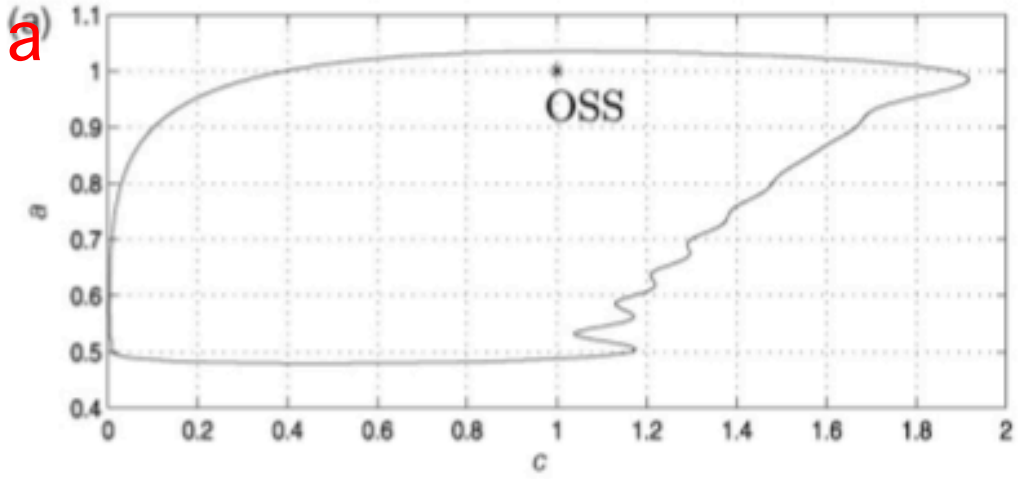
possible improvement with periodic operation

(« Π-test »)

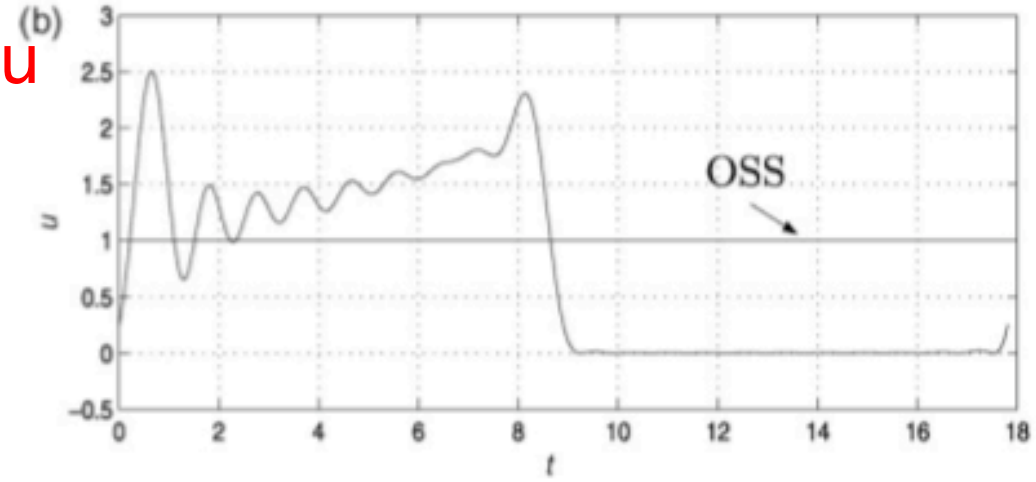
--> periodic drug delivery that maximizes the time average of *I(E)* :

$$J = \frac{1}{T} \int_0^T I(E(c,a))dt$$

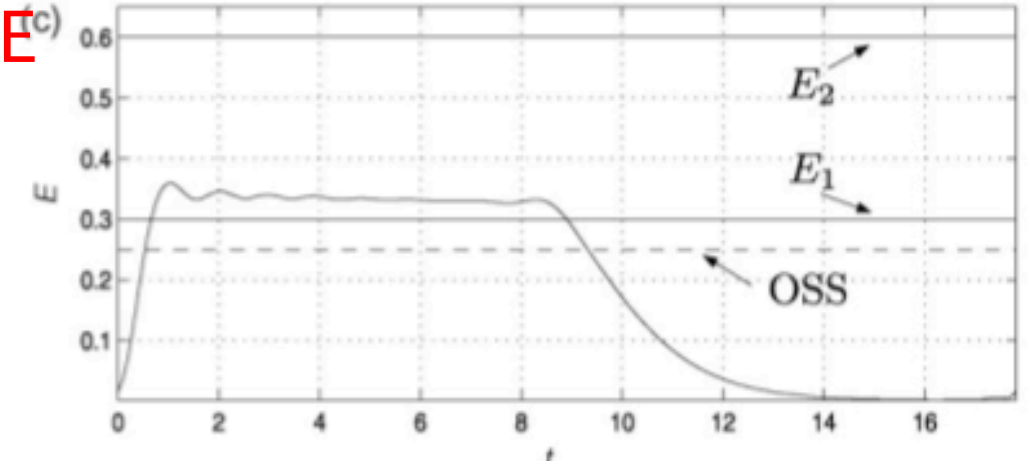
a



u



E



$J(u_{periodic}) = 0.35$

$> J(u_{constant}) =$

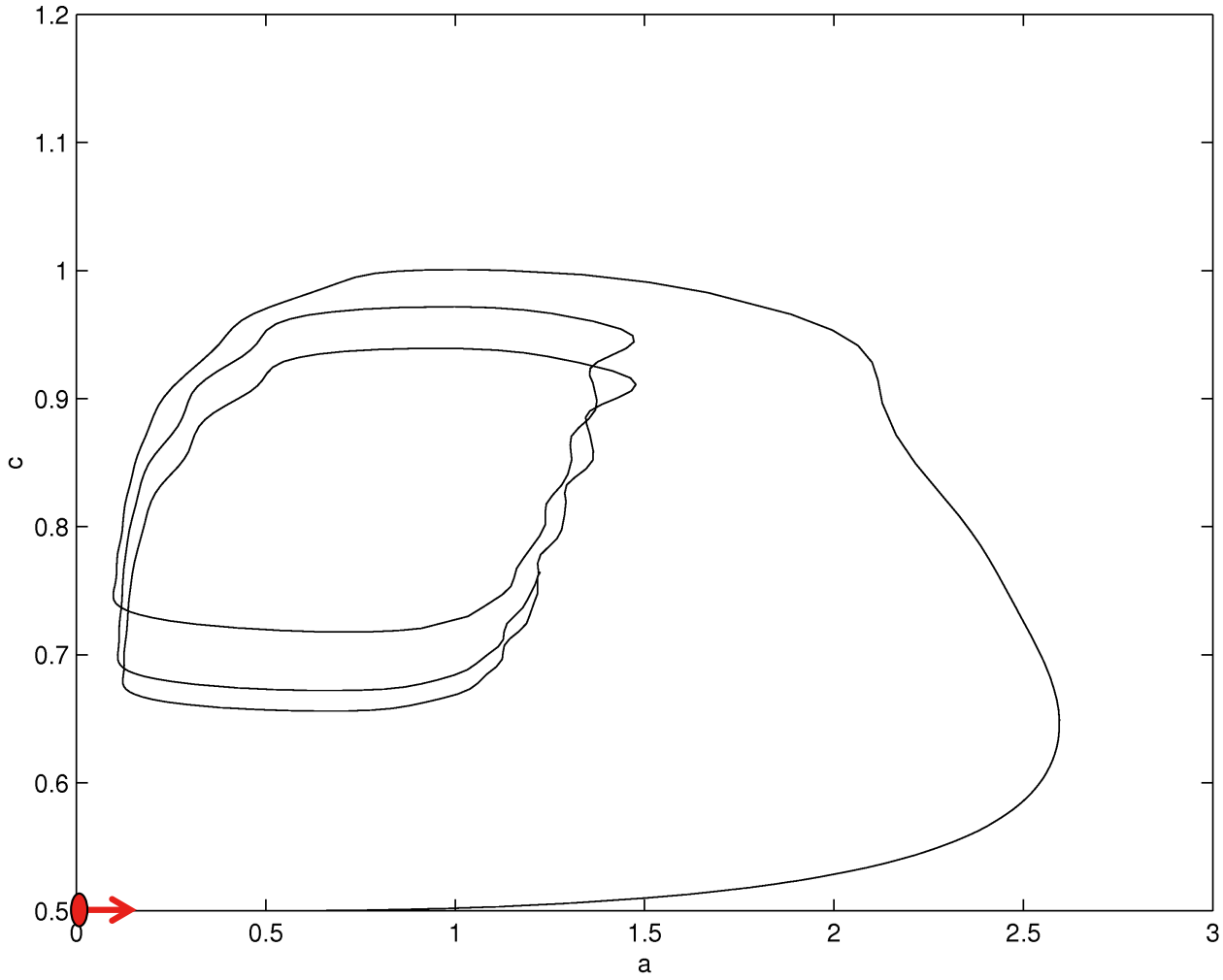
0.14

It is here that the adaptive extremum seeking controller comes into play

- The model parameters vary depending on the patients
  --> the periodic optimum is unknown

- The adaptive extremum seeking controller will find the optimum while controlling the system

Remark : the optimum can also be a static point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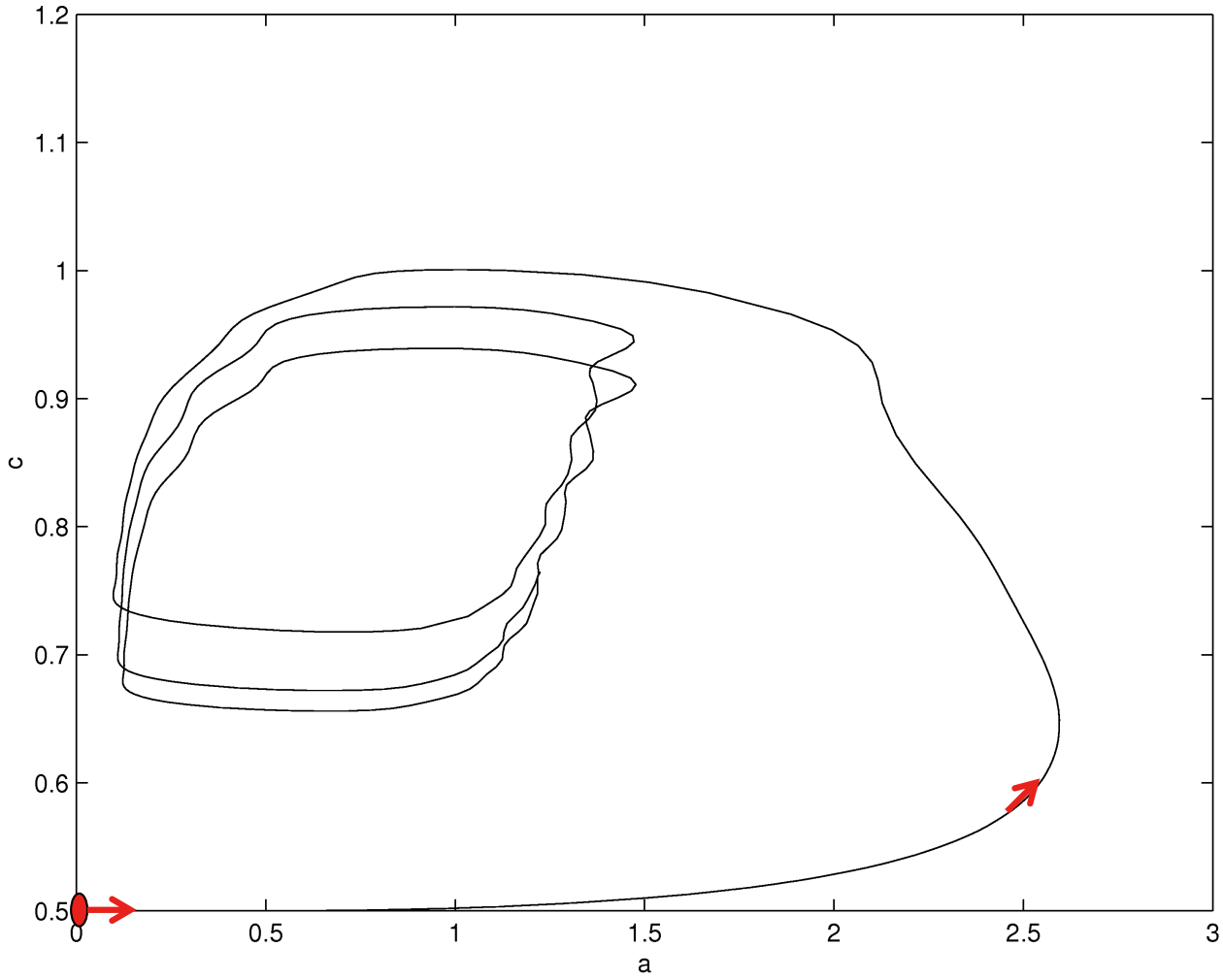
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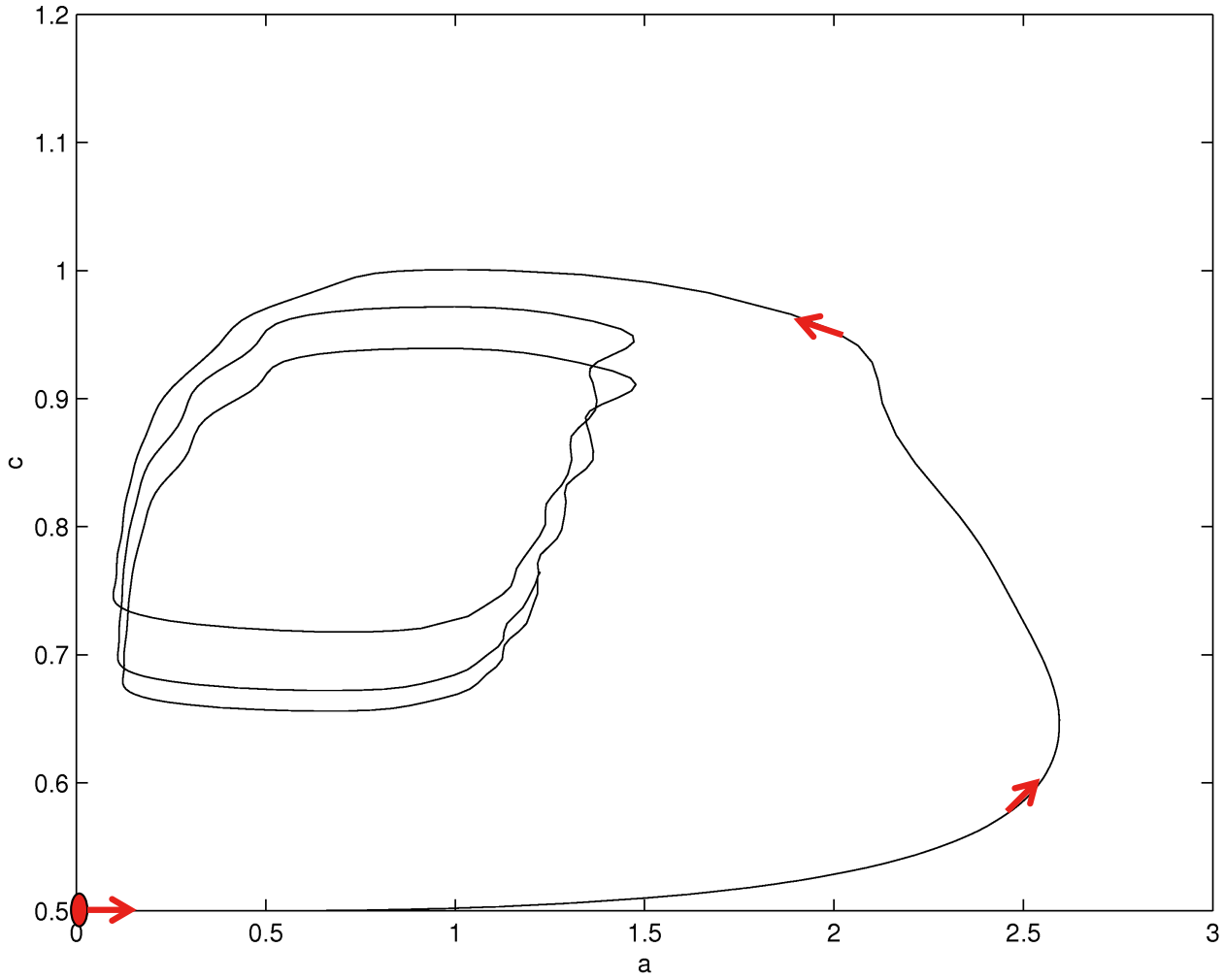
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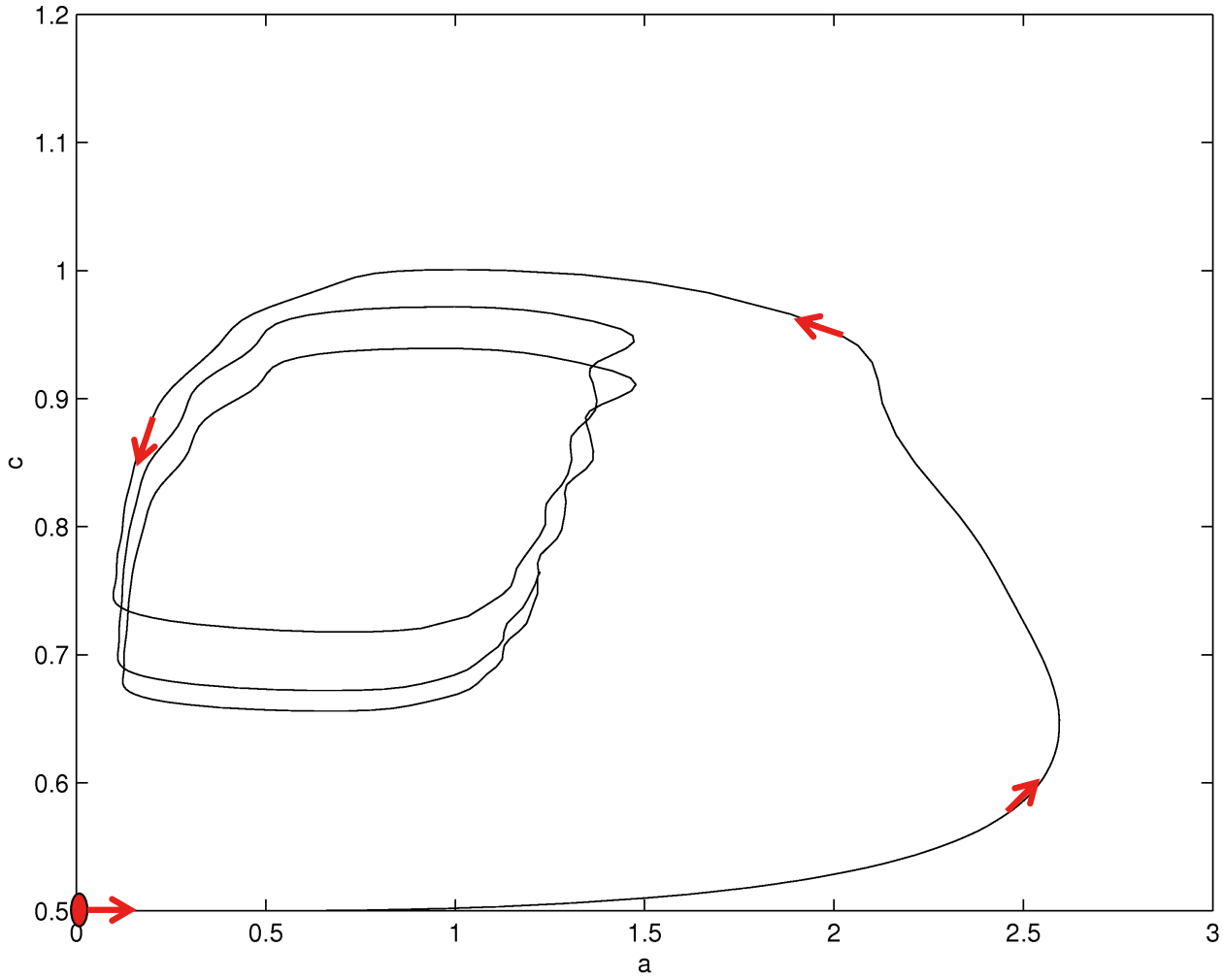
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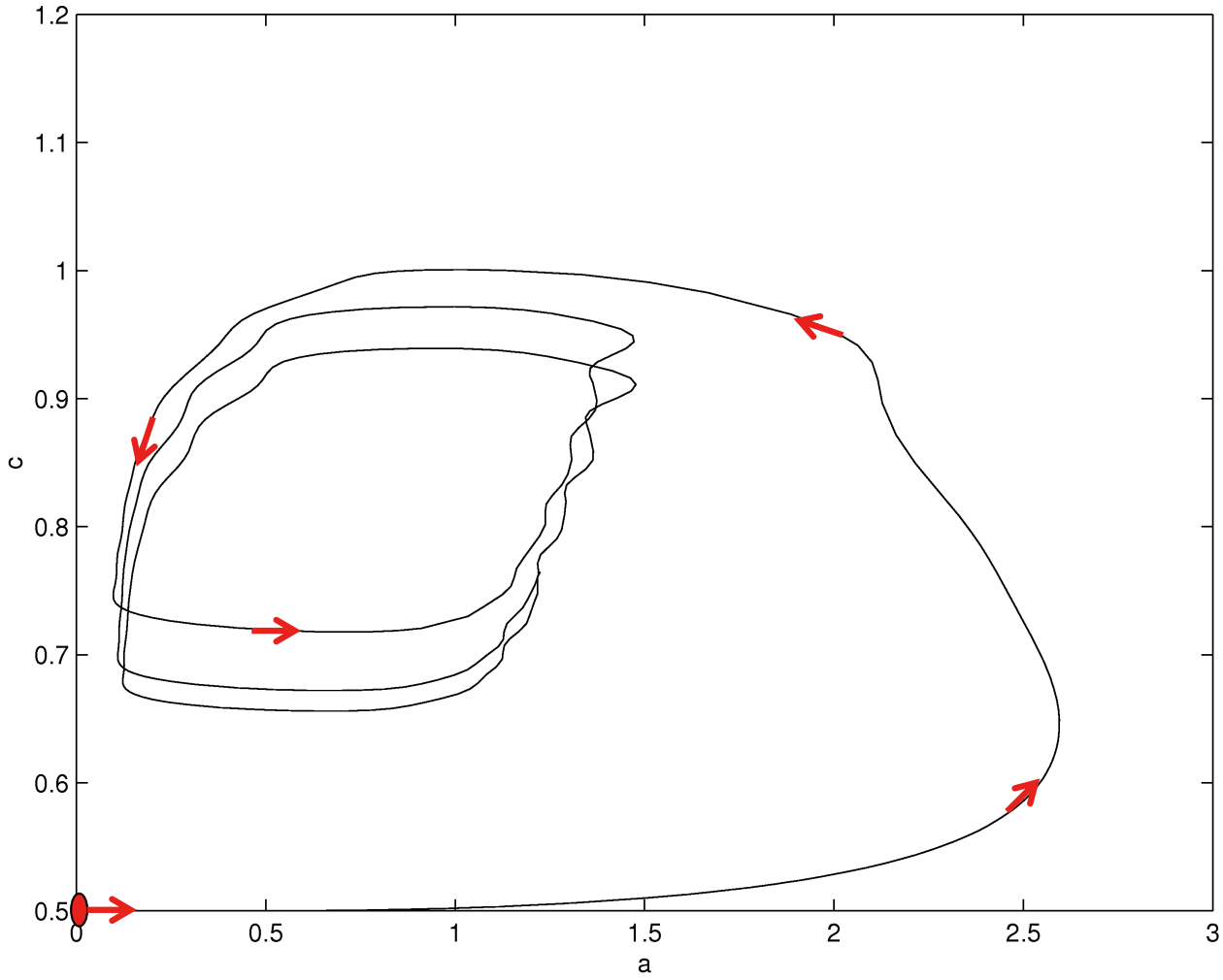
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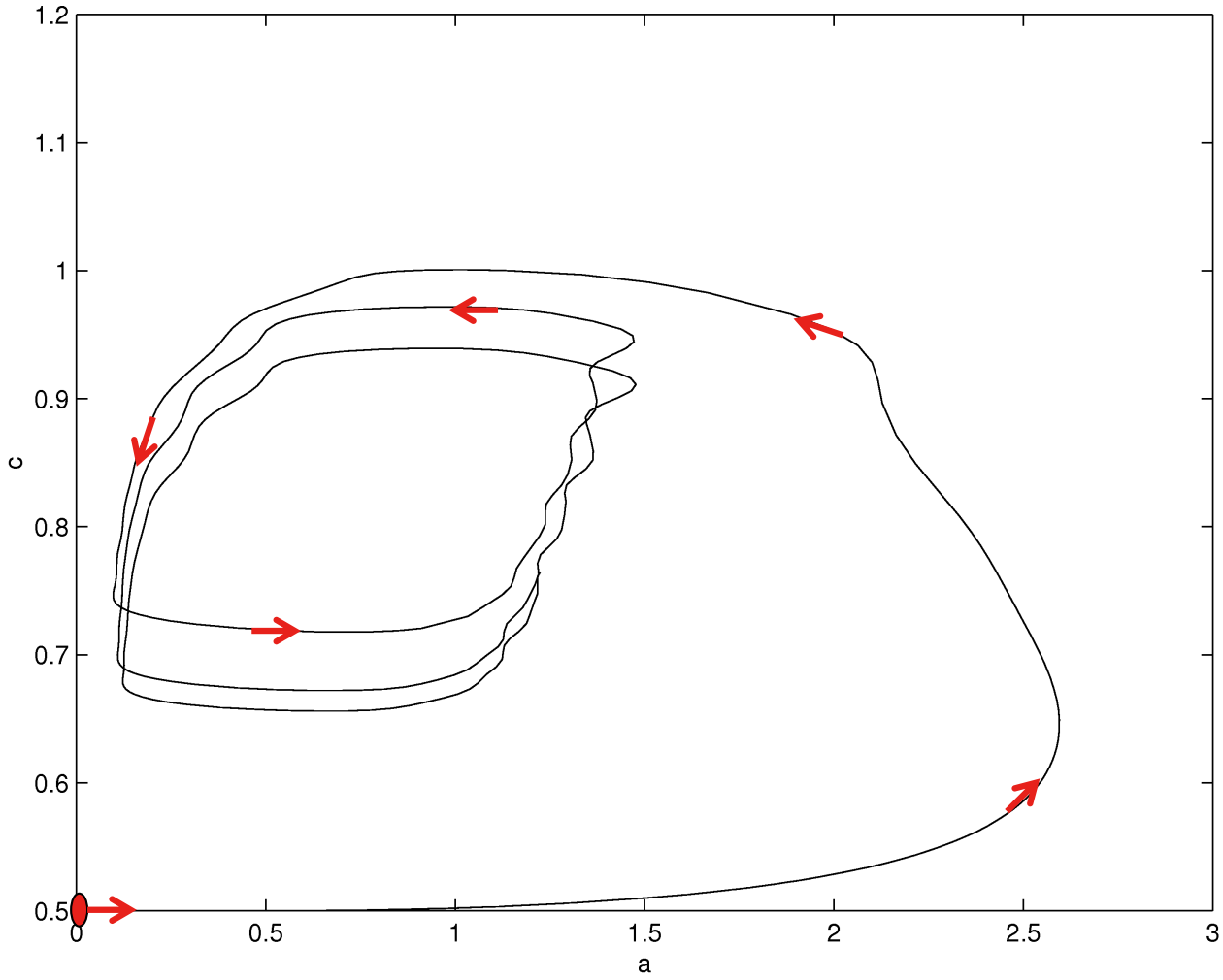
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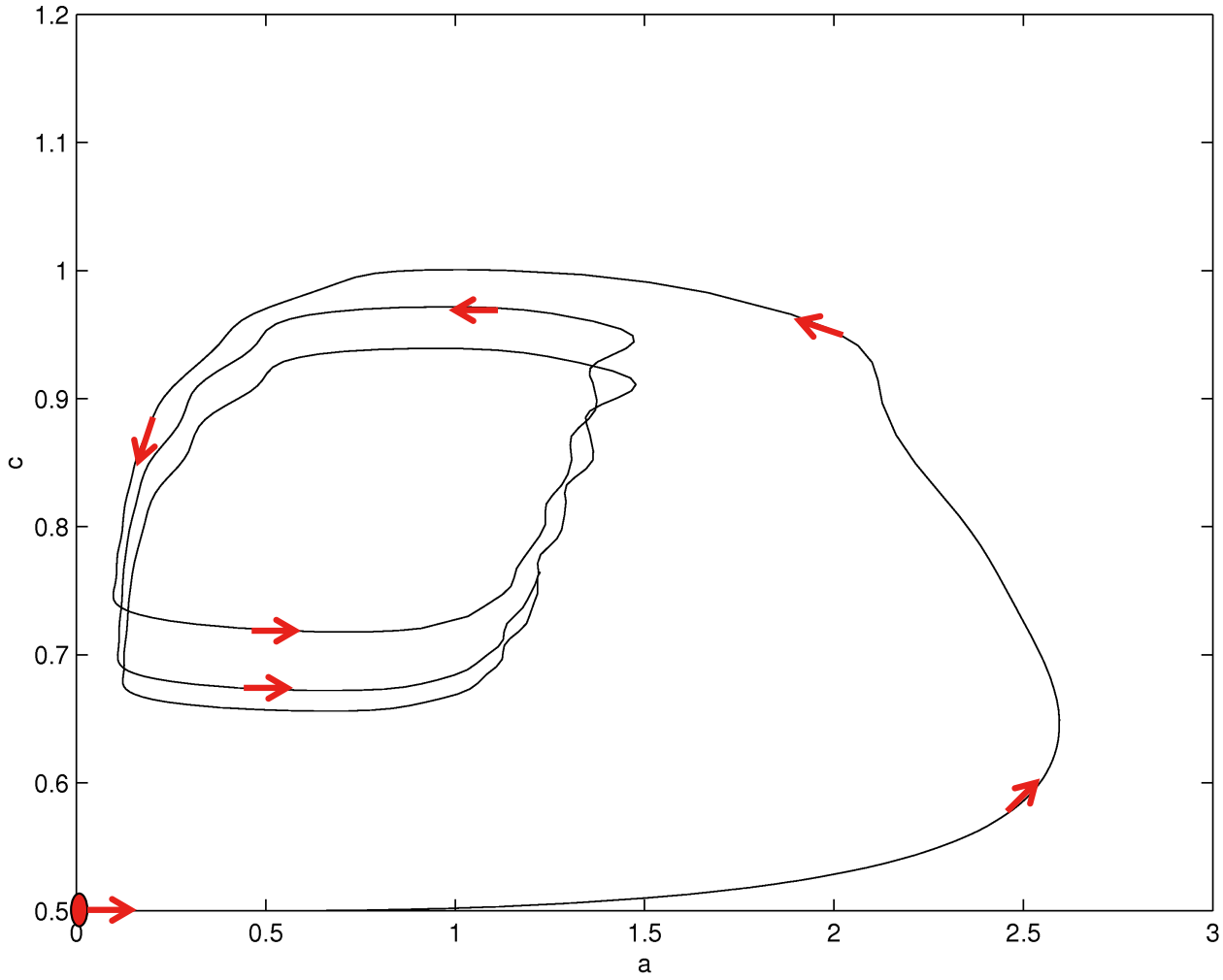
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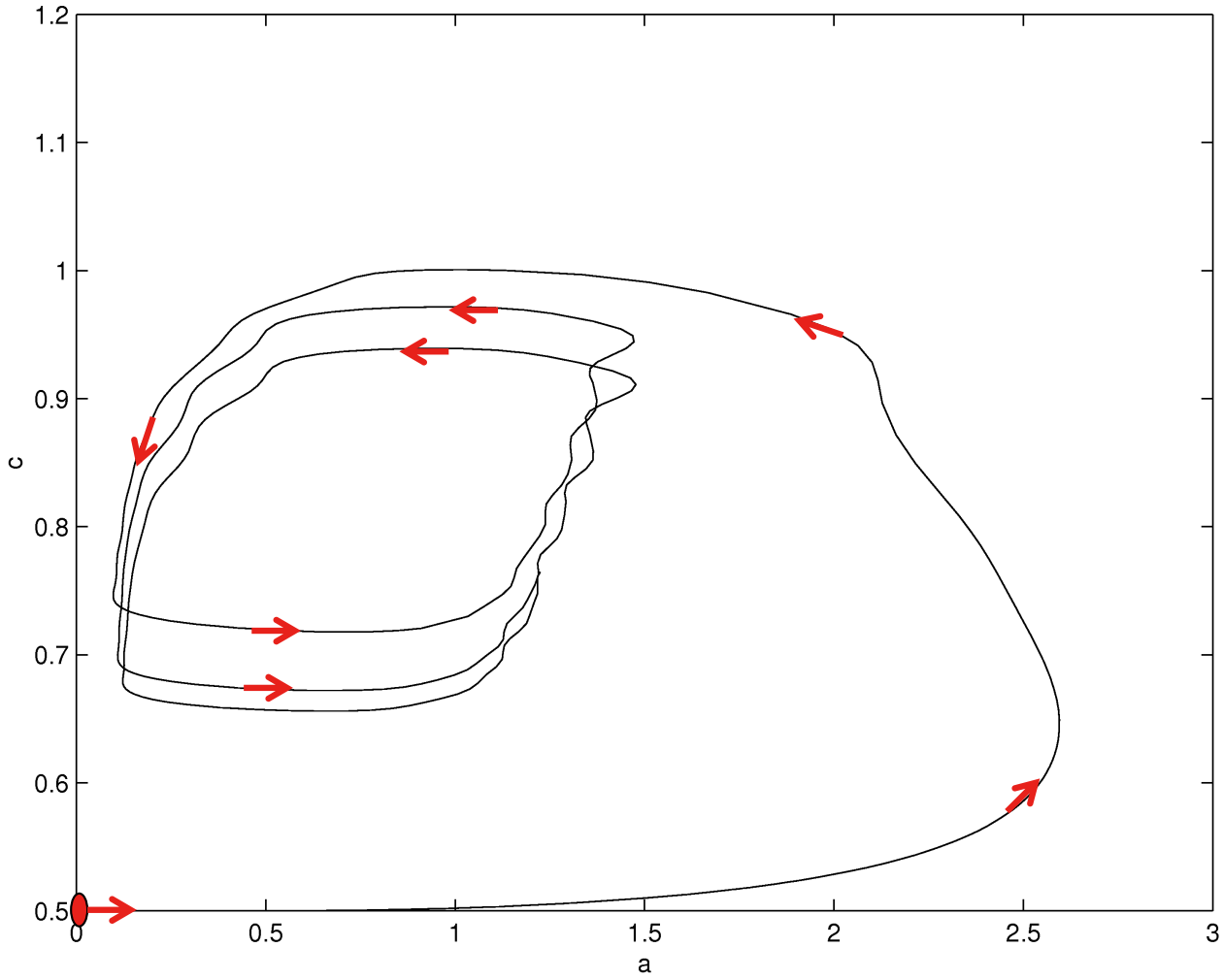
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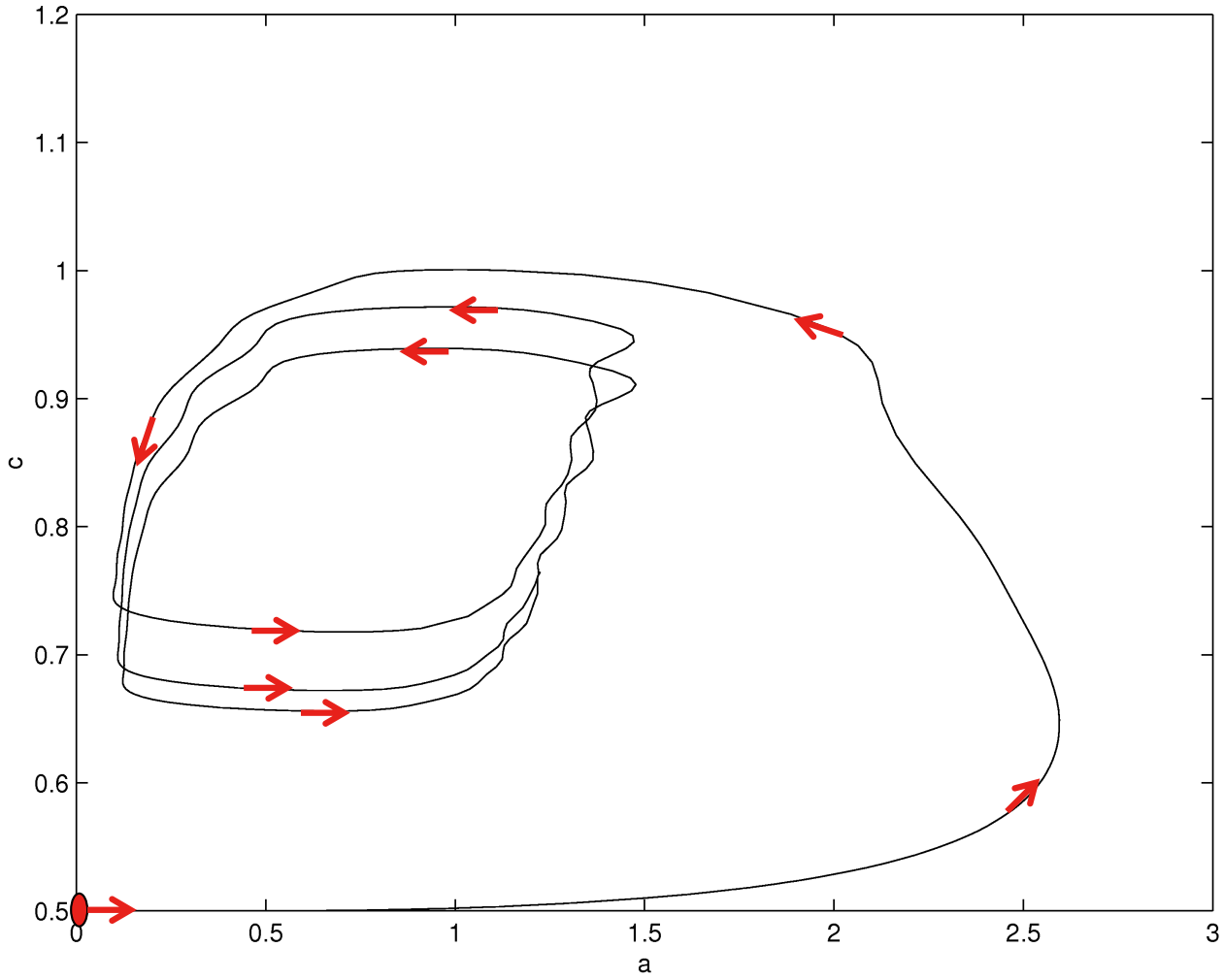
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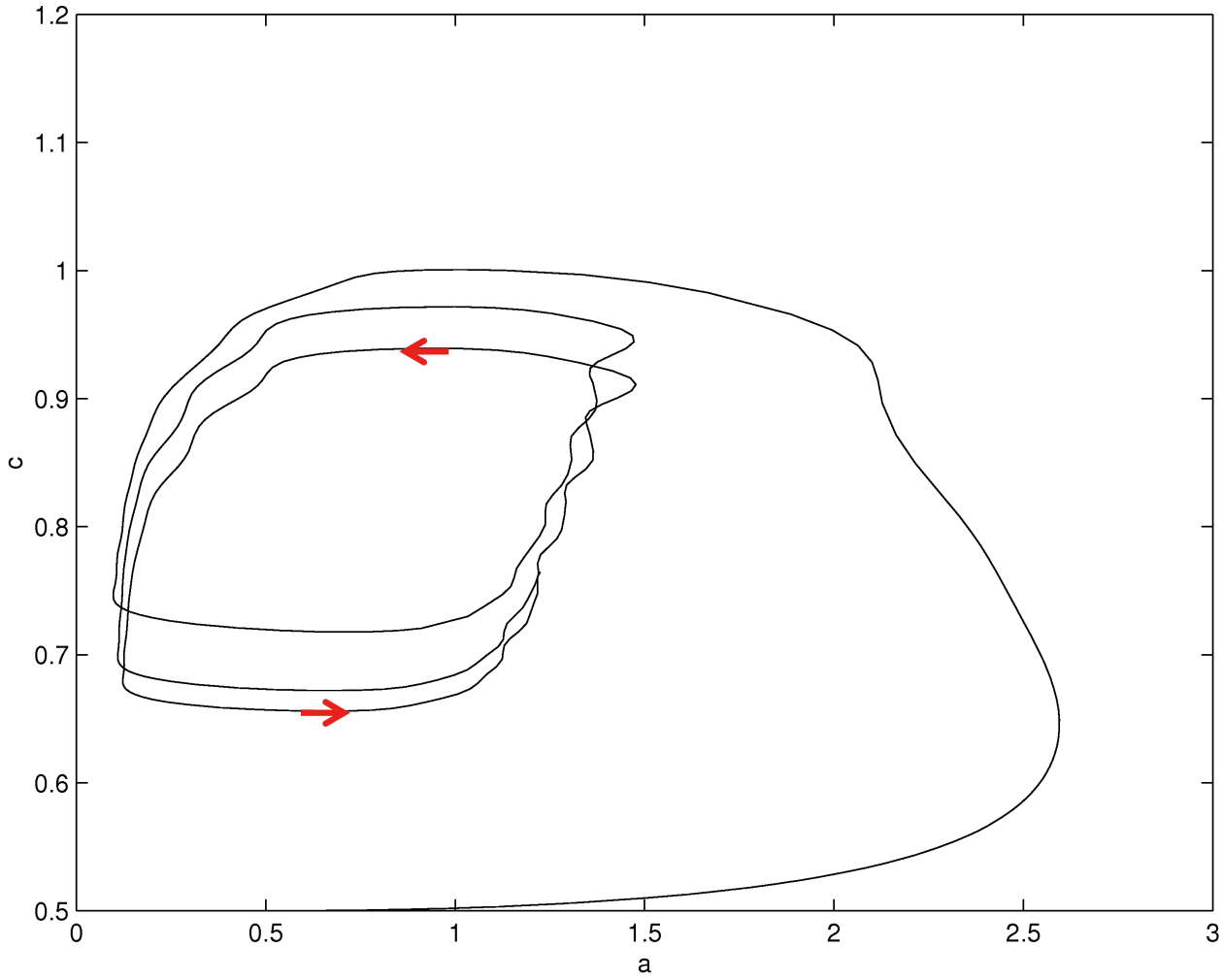
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Thank you for your attention