

About dynamical system modelling

Illustration in micro-biology

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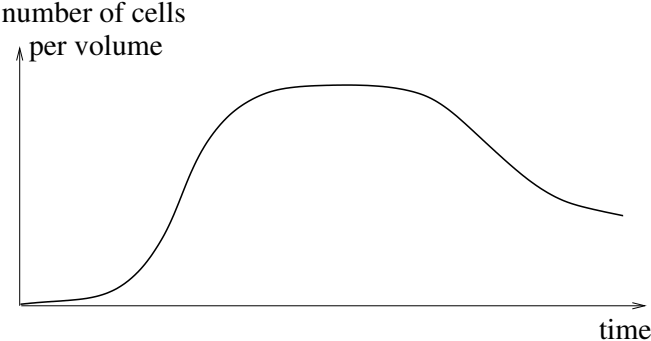
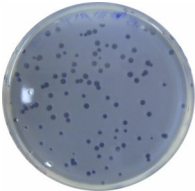
Research School AgreenSkills

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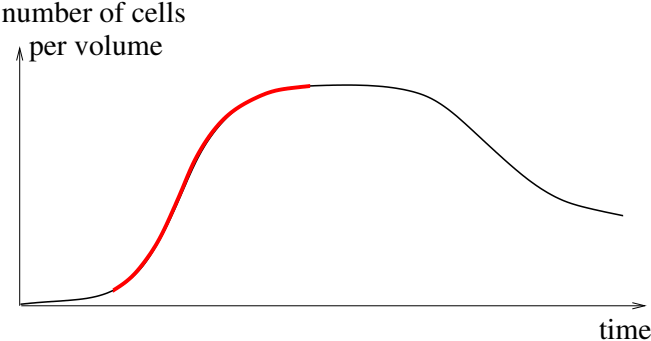
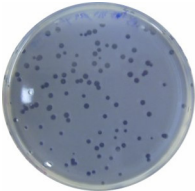
Contents

- ▶ Modeling **bacterial growth** in batch and continuous cultures
- ▶ Simple representations of **space**
- ▶ Questions related to **biodiversity**
- ▶ Modeling and analysis of **growth inhibition**
- ▶ Facing models with **experimental data**

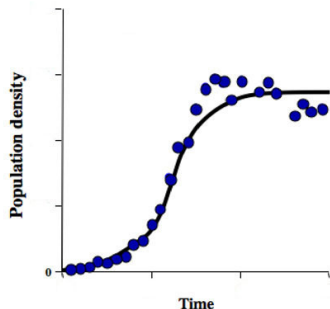
Bacterial growth in batch



Bacterial growth in batch



The logistic growth (Verhulst, 1838)

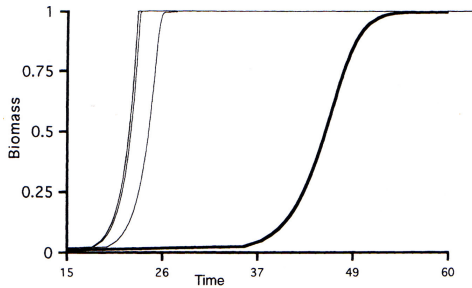


$$\rightarrow x(t) = \frac{x_{\max}}{1 + e^{-rt} \left(\frac{x_{\max}}{x_0} - 1 \right)}$$

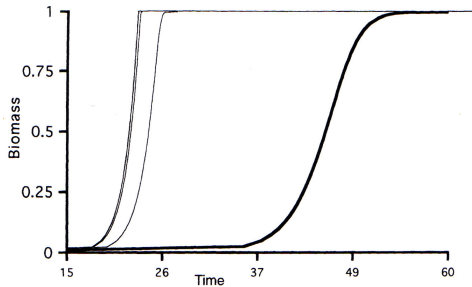
Equivalent formulation: $x(\cdot)$ is solution of the differential equation

$$\frac{dx}{dt} = rx \left(1 - \frac{x}{x_{\max}} \right)$$

Jacques Monod's experiments (1930)



Jacques Monod's experiments (1930)



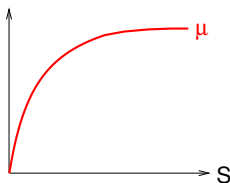
does not fit the logistic curves...

Mathematical modeling

Hypothesis H0. There exists y s.t. $x + ys = m = cste$

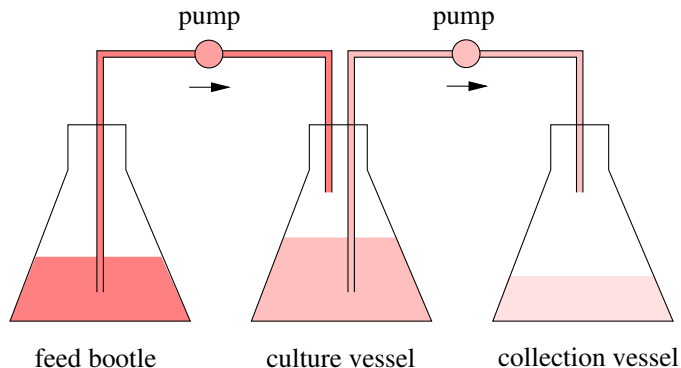
Hypothesis H1a. $\frac{dx}{dt} = \mu s x \Rightarrow \frac{dx}{dt} = \underbrace{\mu \frac{m}{y}}_r x \left(1 - \frac{x}{m}\right)$

Hypothesis H1b. $\frac{dx}{dt} = \mu(s)x$ where $\mu(\cdot)$ is not necessarily linear:



► How to identify with accuracy this specific growth curve?

The chemostat device



Monod 1950 – Novick & Szilard 1950

Dynamical modelling

- ▶ Mechanics: 2nd motion law:

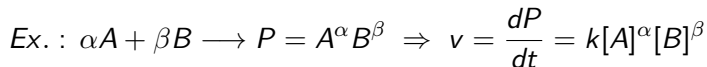
$$mass \times acceleration = \sum forces$$

- ▶ Bio-reaction kinetics: mass balance (for biotic and abiotic):

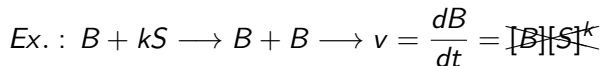
$$mass\ variation = \sum inputs - \sum outputs + \underbrace{growth - death}_{\text{for biotic only}}$$

Dynamical modelling

- ▶ chemical kinetics:



- ▶ microbial kinetics:




*growth is not simply a matter of matching
bacteria with molecules of substrate...*

The mathematical model (in concentrations)

$$\begin{bmatrix} \frac{dx}{dt} \\ \frac{ds}{dt} \end{bmatrix} = \underbrace{\begin{bmatrix} \mu(s)x \\ -\frac{\mu(s)}{y}x \end{bmatrix}}_{\text{growth}} + \underbrace{\begin{bmatrix} -\frac{Q}{V}x \\ \frac{Q}{V}(s_{in} - s) \end{bmatrix}}_{\text{dilution}}$$

Remark. $Q = 0 \Rightarrow x + ys = \text{constant}$

Simplification and notations. $y = 1 \quad \dot{\quad} = \frac{d}{dt} \quad D = \frac{Q}{V}$


$$\begin{cases} \dot{s} = -\mu(s)x + D(s_{in} - s) \\ \dot{x} = \mu(s)x - Dx \end{cases}$$

Determination of equilibria

$$\dot{s} = -\mu(s)x + D(s_{in} - s)$$

$$\dot{x} = \mu(s)x - Dx$$

\Rightarrow

$$x^* = 0$$

$$s^* = s_{in}$$

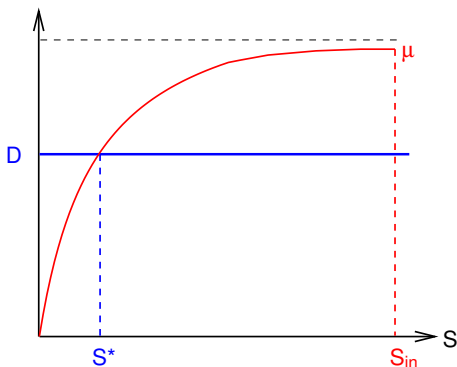
wash-out

or

$$\mu(s^*) = D$$

$$x^* = s_{in} - s^*$$

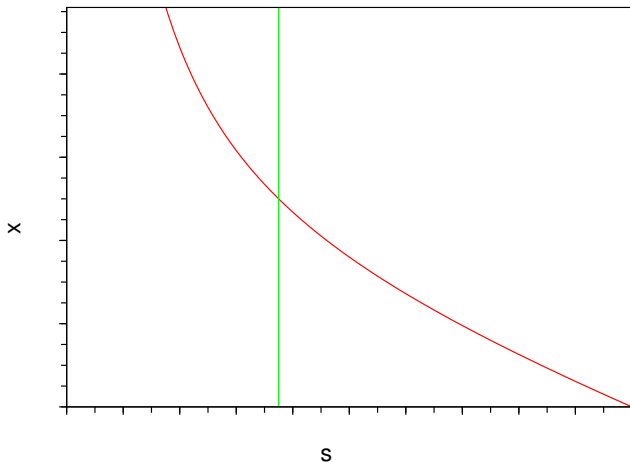
positive equilibrium



Null-clines

$$\dot{s} = -\mu(s)x + D(s_{in} - s)$$

$$\dot{x} = \mu(s)x - Dx$$



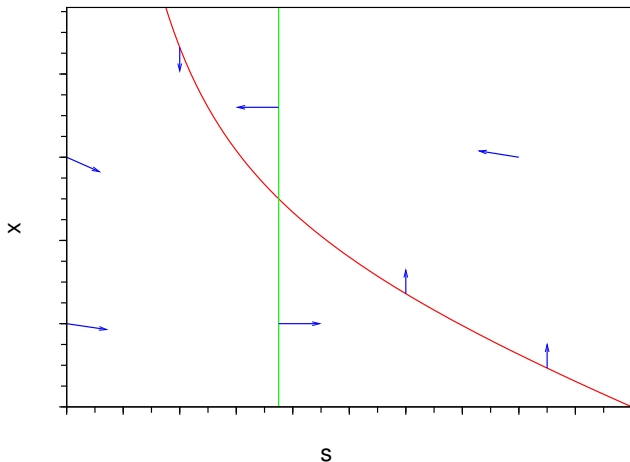
$$\dot{x} = 0$$

$$\dot{s} = 0$$

Vector field

$$\dot{s} = -\mu(s)x + D(s_{in} - s)$$

$$\dot{x} = \mu(s)x - Dx$$



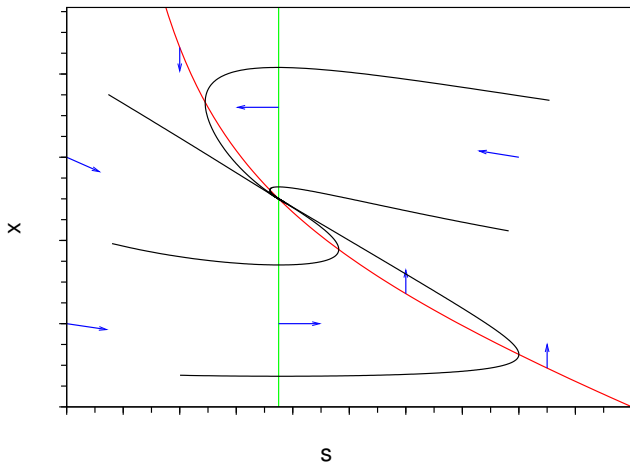
$$\dot{x} = 0$$

$$\dot{s} = 0$$

Phase portrait

$$\dot{s} = -\mu(s)x + D(s_{in} - s)$$

$$\dot{x} = \mu(s)x - Dx$$

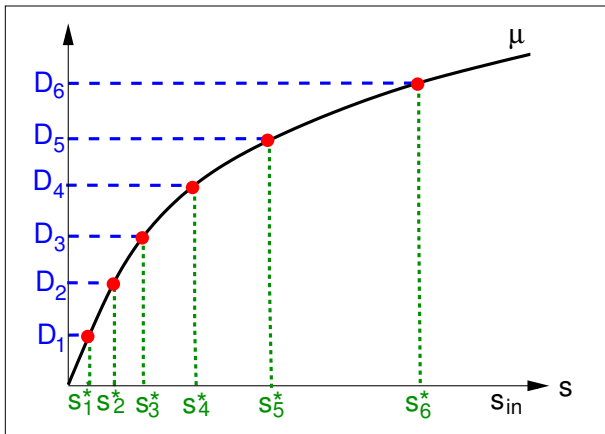


$$\dot{x} = 0$$

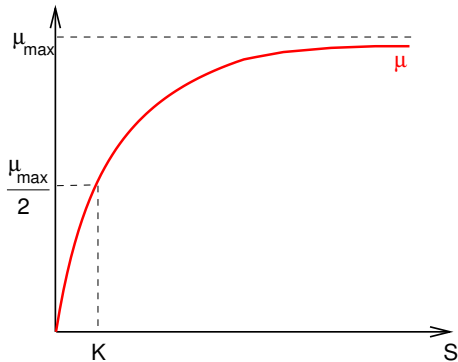
$$\dot{s} = 0$$

Back to experiments

For each dilution rate D , one obtains a steady state s^* with
$$\mu(s^*) = D:$$



The Monod's law



$$\mu(s) = \frac{\mu_{\max} S}{K + s}$$

The chemostat model

$$\begin{aligned}\dot{s} &= -\mu(s)x + D(s_{in} - s) \\ \dot{x} &= \mu(s)x - Dx\end{aligned}$$

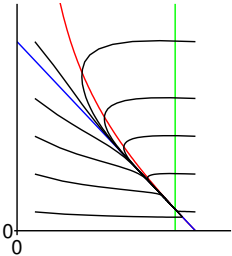
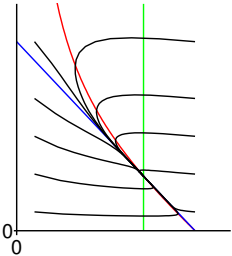
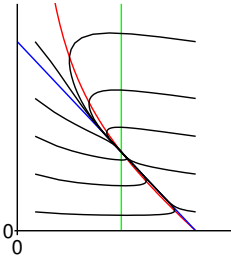
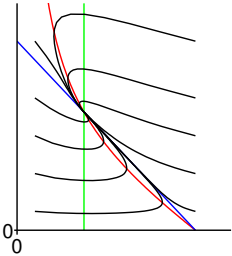
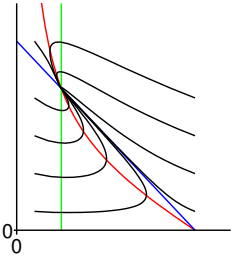
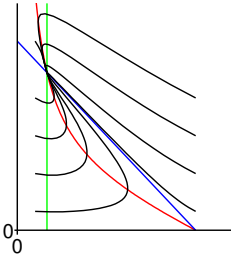


Ecology of mountain lakes

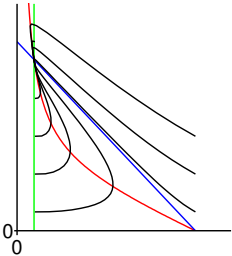
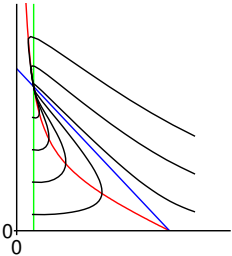
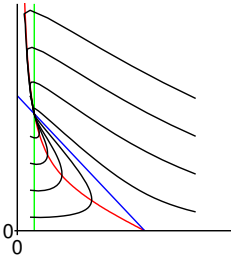
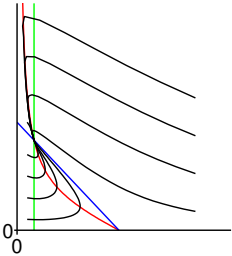
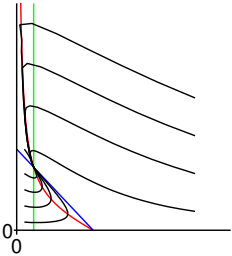
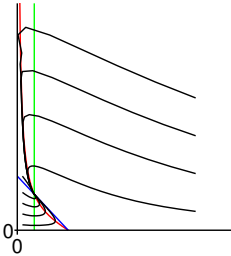


Industrial bioreactors

For various increasing dilution rates



For various increasing input concentrations

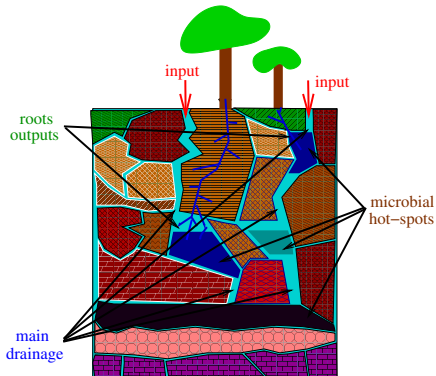


About conversion yield at equilibrium

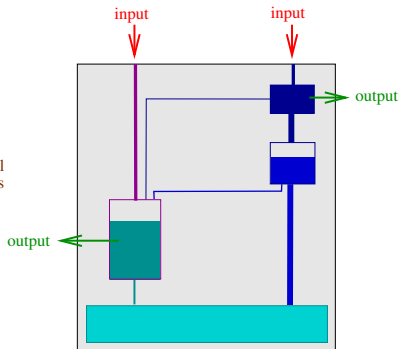
- ▶ The mathematical model of the chemostat predicts that the **substrate concentration** at equilibrium is **independant** of the input concentration s_{in} (provided that $\mu(s_{in}) > D$).
- ▶ Micro-biologists report that this property is not verified when the tank is not homogeneous or in natural ecosystems such as soil ecosystems.

Question: What is the influence of a spatial repartition on output substrate concentration at steady state?

The paradigm of simple representations of space

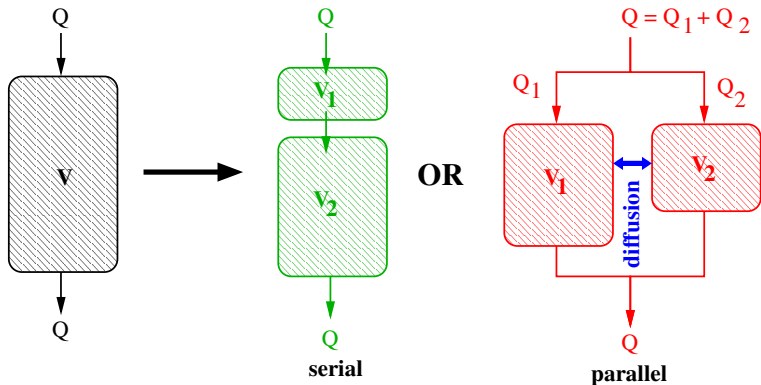


real soil



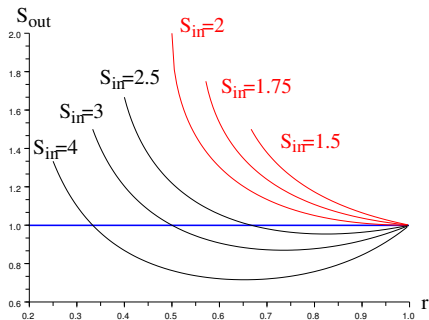
interconnected chemostats

Study of some simple spatial configurations

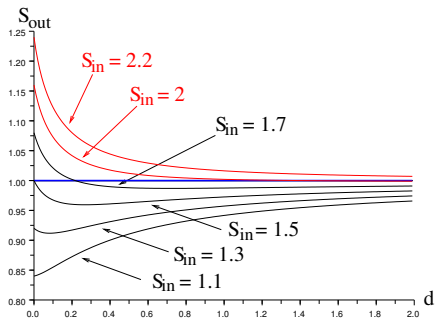


with $V = V_1 + V_2$

Comparison of performances at steady-state



serial



parallel

Roles of spatial structure and diffusion

Message 1. For any monotonic $\mu(\cdot)$, there exists a threshold \bar{s}_{in} such that

- ▶ for $s_{in} > \bar{s}_{in}$, the **serial** configuration is more efficient,
- ▶ for $s_{in} < \bar{s}_{in}$, the **parallel** configuration is more efficient,

Message 2. For the parallel configurations,

- ▶ for $s_{in} > \bar{s}_{in}$, the map $d \mapsto s_{out}^*(d)$ is **decreasing**,
- ▶ for $s_{in} < \bar{s}_{in}$, the map $d \mapsto s_{out}^*(d)$ admits a **unique minimum** for $d^* < +\infty$

Furthermore, there exists another threshold $\underline{s}_{in} < \bar{s}_{in}$ s.t. $d^* = 0$ for $s_{in} < \underline{s}_{in}$.

Questions related to microbial biodiversity

- ▶ How to model microbial **competition**?
- ▶ Can a **biodiversity** be maintained?
- ▶ Does **spatial structures** impact biodiversity?
- ▶ Is biodiversity is in favor of bioconversion **yielding**?

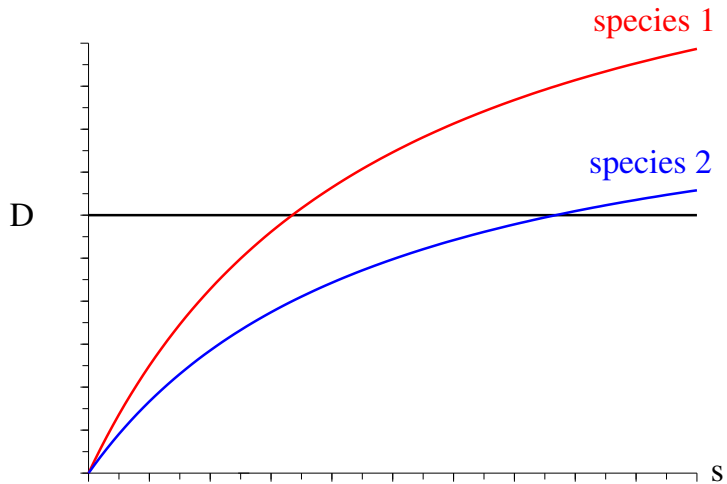
Having two species in the chemostat

$$\begin{aligned}\dot{s} &= -\mu_1(s)x_1 - \mu_2(s)x_2 + D(s_{in} - s) \\ \dot{x}_1 &= \mu_1(s)x_1 - Dx_1 \\ \dot{x}_2 &= \mu_2(s)x_2 - Dx_2\end{aligned}$$

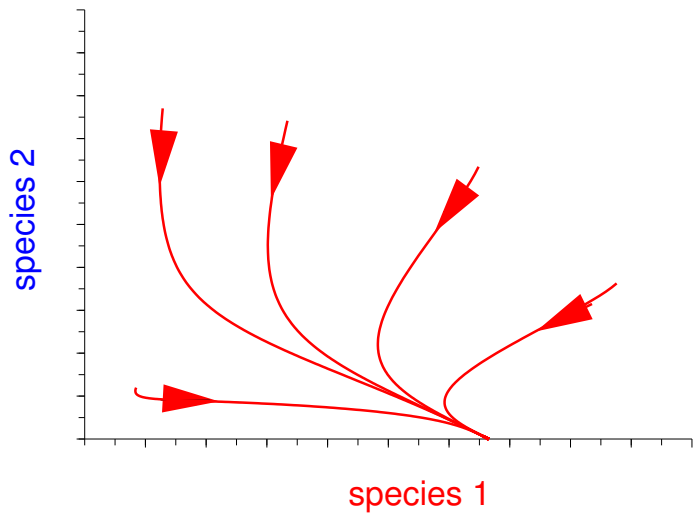
Equilibria:

wash-out	species 1 only	species 2 only	species coexistence
$\begin{bmatrix} s_{in} \\ 0 \\ 0 \end{bmatrix}$	$\begin{bmatrix} s_1^* \\ s_{in} - s_1^* \\ 0 \end{bmatrix}$	$\begin{bmatrix} s_2^* \\ 0 \\ s_{in} - s_2^* \end{bmatrix}$	would require $\mu_1(s^*) = \mu_2(s^*) = D$ non generic condition!

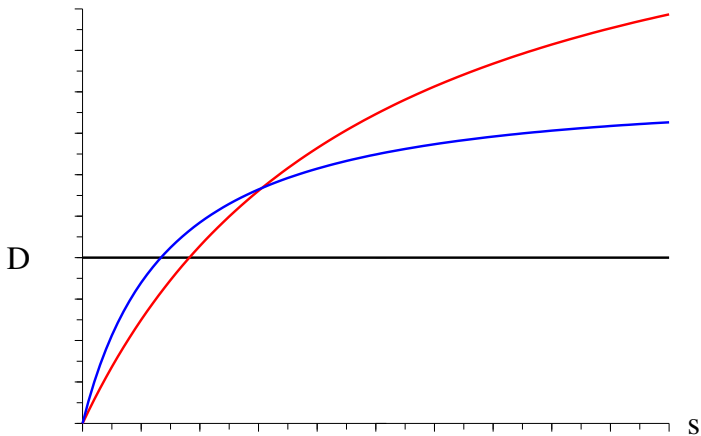
Species competition



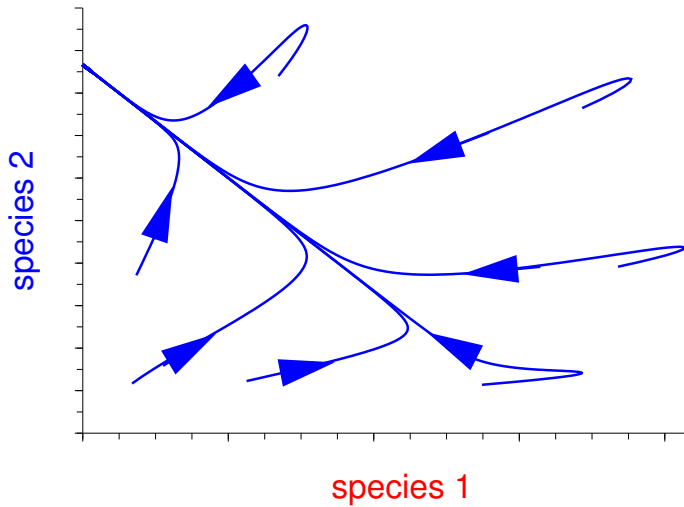
Species competition



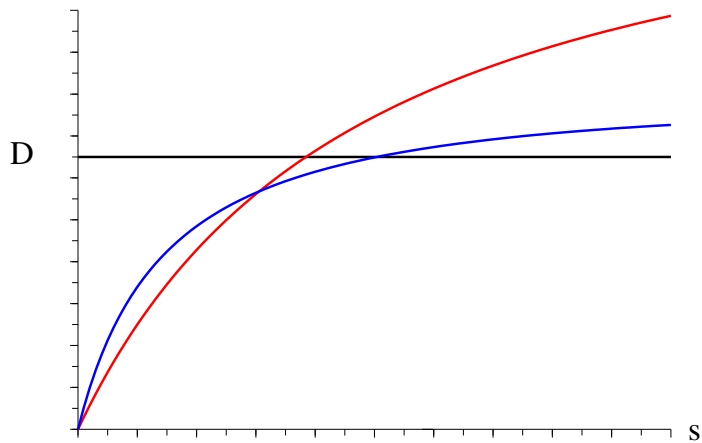
Species competition



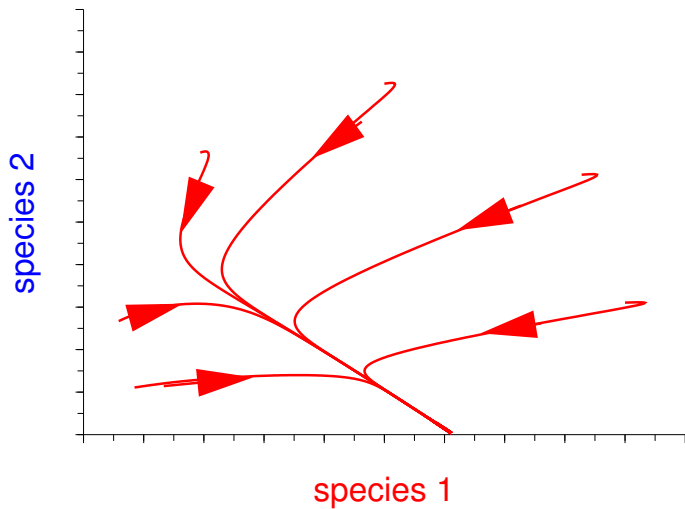
Species competition



Species competition



Species competition

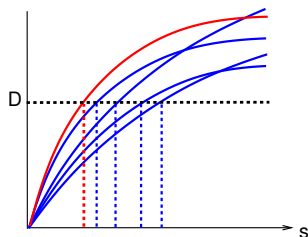


The Competitive Exclusion Principle

Assume that all $\mu_i(\cdot)$ are increasing

Let $\Lambda_i(D) = \{s \geq 0 \mid \mu_i(s) > D\}$ and define the **break-even concentrations**

$$\lambda_i(D) = \inf \Lambda_i(D)$$

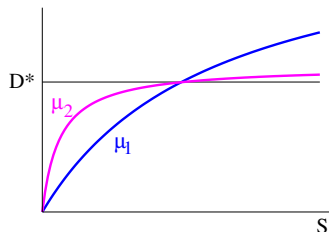


Principle.

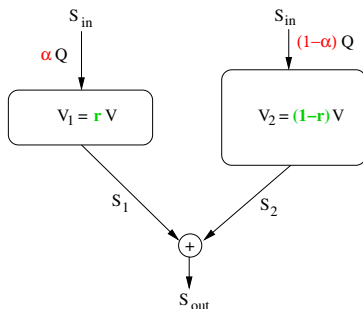
- ▶ Generically, there is at *most one* species at equilibrium.
- ▶ The equilibrium (if it exists) with the species that possesses the **smallest** break-even concentration is the only *attractive* equilibrium.

About niches and over-yielding

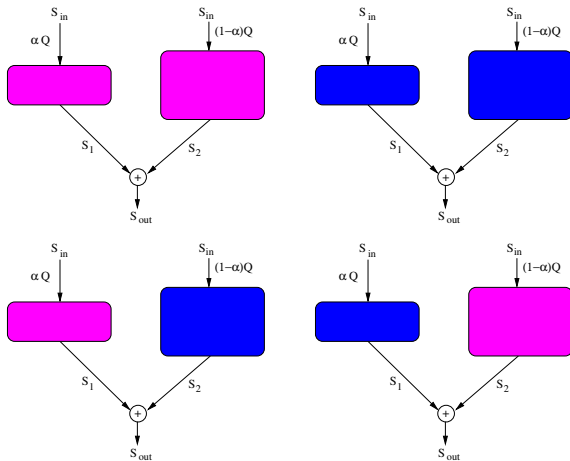
Consider two strains:



and the spatial structure:



Bioconversion and over-yielding



What is the most efficient configuration?

Overyielding at equilibrium

For increasing $\mu(\cdot)$, define the **conditional break-even conc.**

$$\bar{\lambda}(D) = \begin{cases} \mu^{-1}(D) & \text{if } D \leq \mu(s_{in}) \\ s_{in} & \text{if } D > \mu(s_{in}) \end{cases}$$

and consider $F(\alpha, r) := \alpha \bar{\lambda}\left(\frac{\alpha}{r}D\right) + (1-\alpha)\bar{\lambda}\left(\frac{1-\alpha}{1-r}D\right)$

Definition : There is **over-yielding** when

$$G(\alpha, r) := \alpha \bar{\lambda}_1\left(\frac{\alpha}{r}D\right) + (1-\alpha)\bar{\lambda}_2\left(\frac{1-\alpha}{1-r}D\right) < \min(F_1(\alpha, r), F_2(\alpha, r))$$

Overyielding at equilibrium

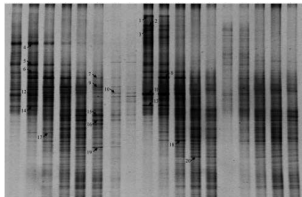
Assume there exists D^* such that $\bar{\lambda}_1(D^*) = \bar{\lambda}_2(D^*)$.

Proposition. If $\mu(\cdot)$ is **concave**, then there exist configurations (α, r) such that

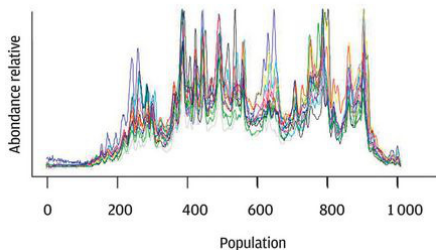
$$\frac{\alpha}{r}D < D^* < \frac{1-\alpha}{1-r}D < \min(\mu_1(s_{in}), \mu_2(s_{in}))$$

that exhibit **over-yielding**.

The high diversity case



DGGE



With tools of molecular biology (fingerprints), biologists observe bioreactors with substrate and biomass concentrations at **quasi steady state**, while the **diversity** of the biomass is **high** and its composition is **constantly evolving**...

The chemostat model with “many” species

$$\dot{s} = - \sum_{j=1}^n \mu_j(s)x_j + D(s_{in} - s)$$

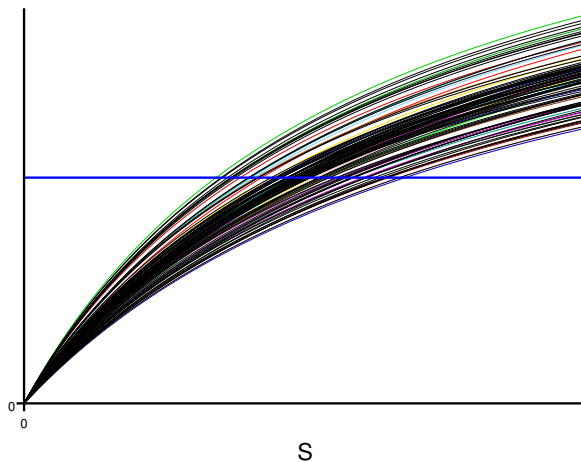
$$\dot{x}_i = \mu_i(s)x_i - Dx_i \quad (i = 1 \cdots n)$$

Numerical simulations with n large (over hundred):

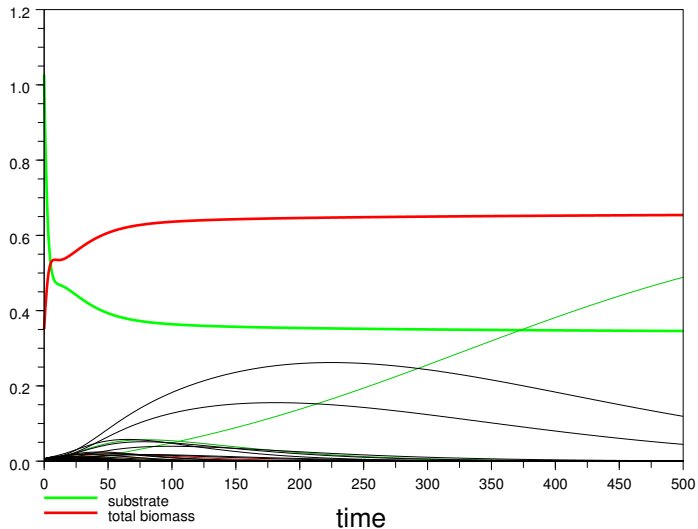
- ▶ random drawing of functions $\mu_i(\cdot)$ among a family of Monod functions
- ▶ random drawing of the initial composition of the biomass

The chemostat model with “many” species

Growth curves



The chemostat model with “many” species

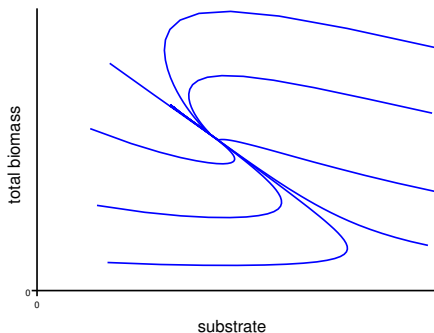


The chemostat model with “many” species

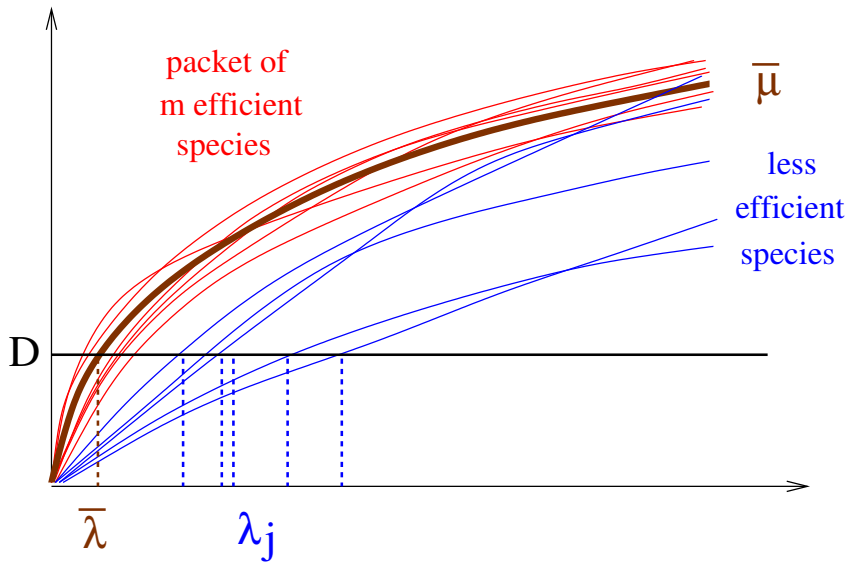
$$\text{Let } b = \sum_{i=1}^n x_i \text{ et } p_i = \frac{x_i}{b}$$

$$\Rightarrow \begin{cases} \dot{s} &= -\tilde{\mu}(s, p)b + D(s_{in} - s) \\ \dot{b} &= \tilde{\mu}(s, p)b - Db \end{cases} \quad \text{with} \quad \tilde{\mu}(s, p) = \sum_{i=1}^n p_i \mu_i(s)$$

$$\text{and } \dot{p}_i = (\mu_i(s) - \tilde{\mu}(s, p)) p_i$$



Splitting species in two groups



The fast dynamics

$$\begin{cases} \dot{s} &= -\bar{\mu}(s)\bar{x} - \sum_{j=m+1}^n \mu_j(s)x_j + D(s_{in} - s) \\ \dot{\bar{x}} &= \bar{\mu}(s)\bar{x} - D\bar{x} \\ \dot{x}_j &= \mu_j(s)x_j - Dx_j \quad (j = m+1 \dots n) \end{cases}$$

Competitive Exclusion Principle:

$$\begin{cases} \lim_{t \rightarrow +\infty} s(t) = s^* \\ \lim_{t \rightarrow +\infty} \bar{x}(t) = x^* = s_{in} - s^* \\ \lim_{t \rightarrow +\infty} x_j(t) = 0 \quad (j = m+1 \dots n) \end{cases}$$

The slow dynamics

for $i = 1 \cdots m$ let write $\mu_i(s) = \bar{\mu}(s) + \varepsilon \nu_i(s)$

$$\Rightarrow \dot{p}_i = \varepsilon \left(\nu_i(s^*) - \sum_{j=1}^m p_j \nu_j(s^*) \right) p_i$$

Explicit solution:

$$p_i(t) = \frac{p_i(0) e^{A_i \varepsilon t}}{\sum_{j=1}^m p_j(0) e^{A_j \varepsilon t}} \quad \text{with} \quad A_j = \nu_j(s^*)$$

Properties of the slow dynamics

- ▶ Each proportion $t \mapsto p_i(t)$ is
 - either increasing up to a time T_i and then decreasing,
 - either increasing for any t ,
 - either decreasing for any t .
- ▶ When $\varepsilon \rightarrow 0$ then $T_i \rightarrow +\infty$ for all species excepted one.
- ▶ The “reactional entropy”

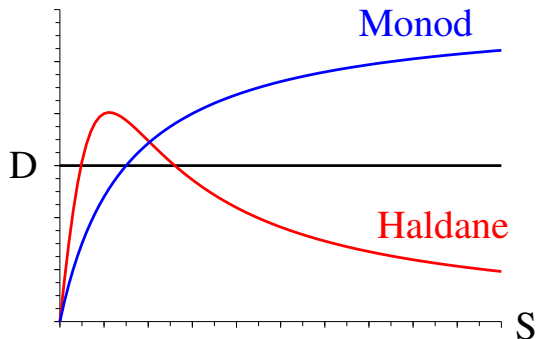
$$E(t) := \sum_j \mu_j(\bar{s}) p_j(t)$$

is increasing toward D .

Concluding remark

The Competitive Exclusion Principle provides only an **asymptotic** result.

Substrate inhibition



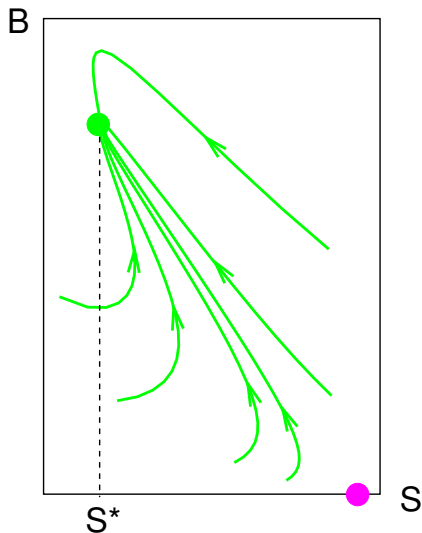
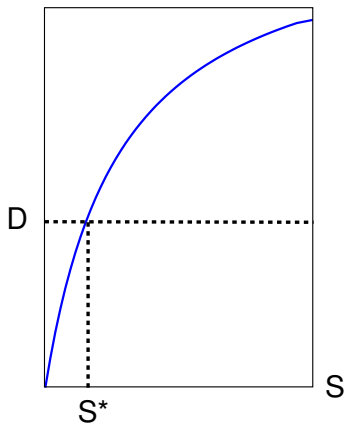
$$\mu(S) = \frac{\mu_{max} S}{K + S}$$

$$\mu(S) = \frac{\bar{\mu} S}{K + S + S^2/K_i}$$

e.g. J. F. Andrews, *A mathematical model for the continuous culture of microorganisms utilizing inhibitory substrates*, *Biotech. Bioengr.*, 10 (1968), pp. 707-723.

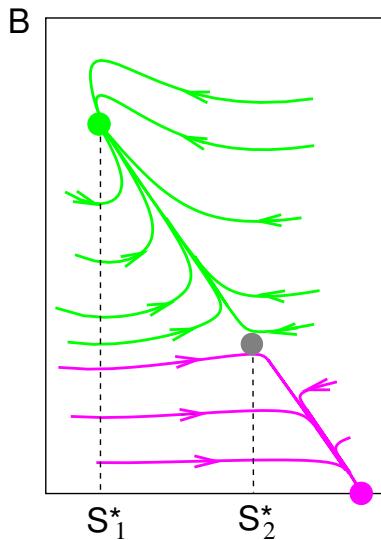
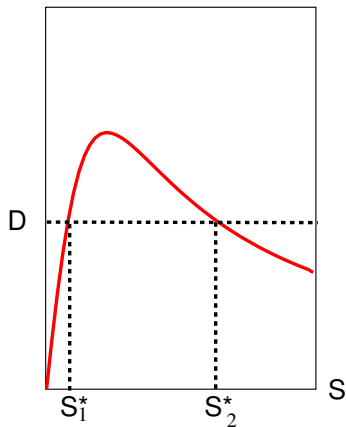
The chemostat model with the Monod law

$$\mu(S) = \frac{\mu_{max} S}{K + S}$$

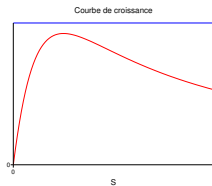


The chemostat model with the Haldane law

$$\mu(S) = \frac{\bar{\mu}S}{K + S + S^2/K_i}$$

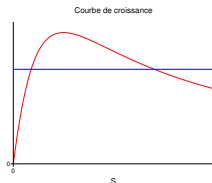


Possible behaviors



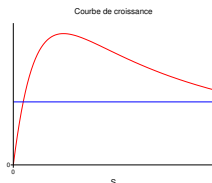
$$D > \max_{s \in [0, S_{in}]} \mu(s)$$

1 equilibrium: wash-out



$$\mu(S_{in}) < D < \max_{s \in [0, S_{in}]} \mu(s)$$

3 equilibria : bi-stability



$$D < \mu(S_{in})$$

2 equilibria : stability

Operating real bioreactors



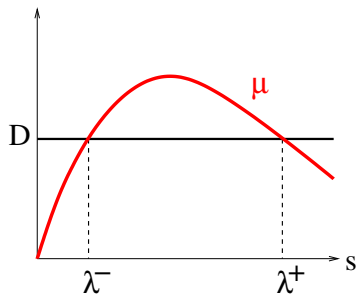
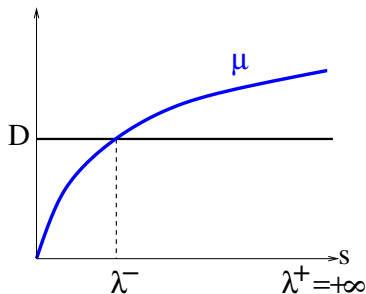
INRA LBE (Narbonne)

“It happens that *some* **additional species** need to be added for the bioprocess to **start**, but these additional species are **no longer present at steady state.**”

Generalization of the Exclusion Principle

Hypothesis: $E_i(D) = \{s > 0 \mid \mu_i(s) > D\}$ is an interval

$$(\lambda_i^-(D), \lambda_i^+(D))$$



Generalization of the Exclusion Principle

Proposition.

$$\text{Let } Q(D) = \bigcup_i E_i(D) = \bigcup_i (\lambda_i^-(D), \lambda_i^+(D))$$

- ▶ There is **generically** competitive exclusion.
- ▶ There are as many species that could win the competition as the number of **connected components** of the set $Q(D)$.

Adding another species

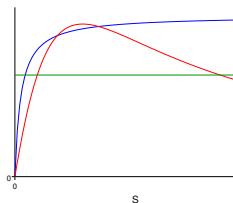
$$\dot{s} = -\mu_1(s)x_1 - \mu_2(s)x_2 + D(s_{in} - s)$$

$$\dot{x}_1 = \mu_1(s)x_1 - Dx_1$$

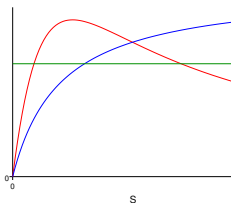
of Haldane type

$$\dot{x}_2 = \mu_2(s)x_2 - Dx_2$$

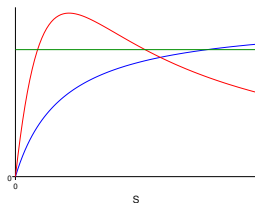
of Monod type



case 1

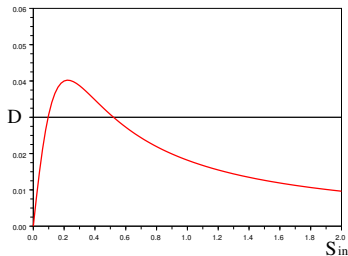


case 2



case 3

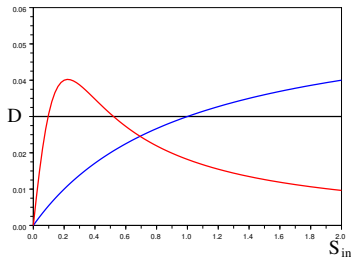
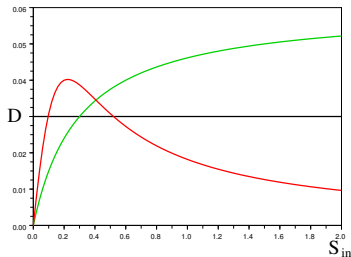
About the bio-augmentation



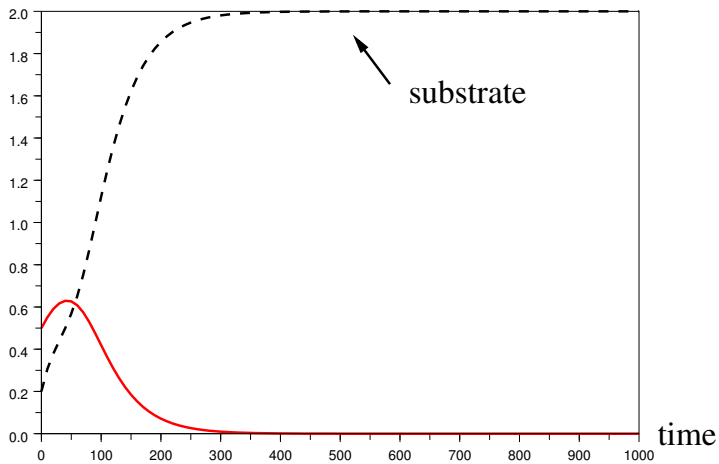
$$\max_{[0, S_{in}]} \mu < \mu(S_{in}) < D$$

\Rightarrow the wash-out is attractive...

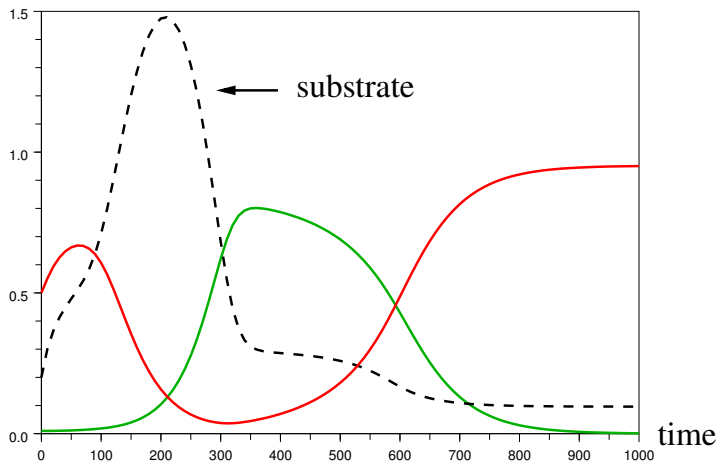
What is the effect of adding strain “blue” or “green” (in small quantity)?



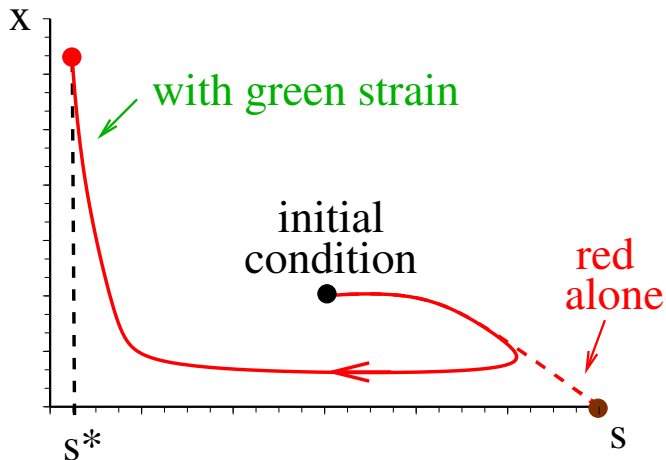
Red species alone



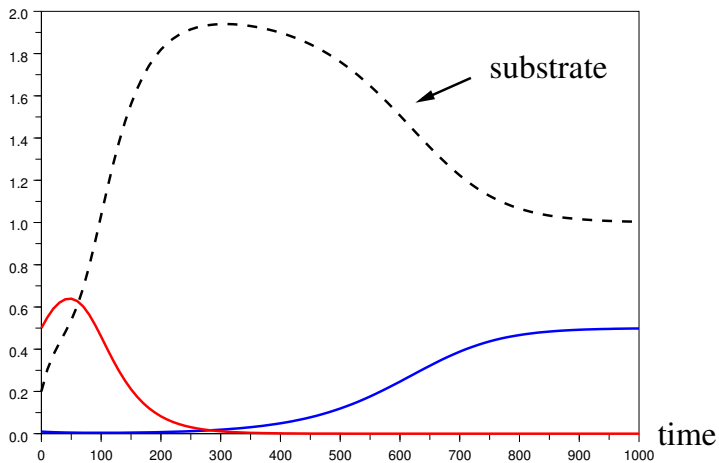
Adding green strain



Phase portrait



Adding blue strain



Toward the “biological control”

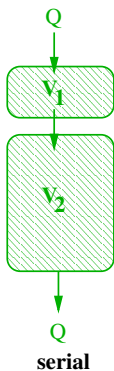
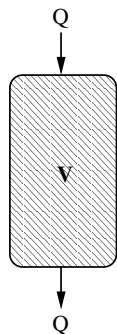
Let $E = (\lambda^-, \lambda^+)$ for the red species.

Let λ be the break-even conc. for the additional species.

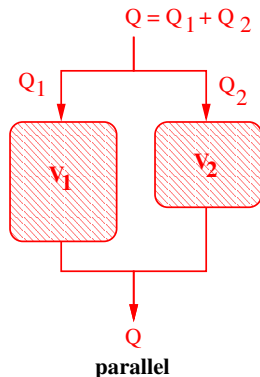
- ▶ $\lambda \in E$: stabilization of the red species
- ▶ $\lambda \notin E$: possibility of invasion

Playing with interconnections

Consider $D = \frac{Q}{V}$ s.t. $\mu(s_{in}) < D < \max_{s \in [0, S_{in}]} \mu(s)$.

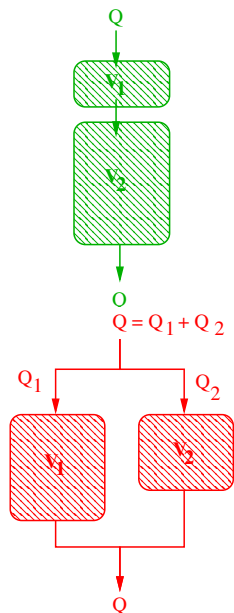


OR



with $V = V_1 + V_2$

Serial and parallel patterns



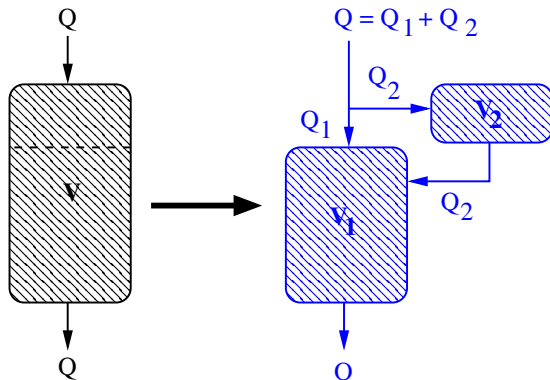
$$V_1 < V \Rightarrow \frac{Q}{V_1} > D, \quad V_2 < V \Rightarrow \frac{Q}{V_2} > D$$

*The wash-out equilibrium is attractive
in both tanks.*

$$\frac{Q_1}{V_1} < \mu(s_{in}) \Rightarrow \frac{Q_2}{V_2} > \mu(s_{in}) \text{ (and vice-versa)}$$

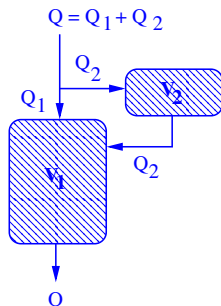
*The wash-out equilibrium is attractive
in at least one tank.*

The buffered pattern



with $V = V_1 + V_2$

The buffered chemostat



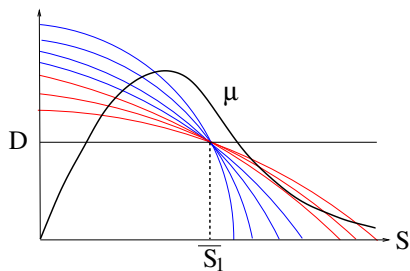
Two parameters: (α, r) with

$$\frac{Q_2}{V_2} = \alpha D \text{ et } V_1 = rV$$

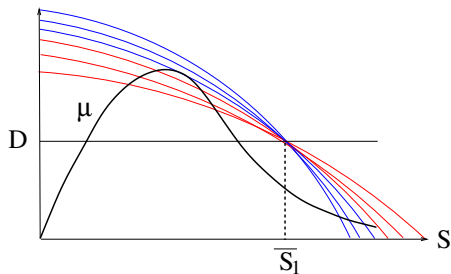
- ▶ *buffer tank*: classical chemostat
 \Rightarrow unique positive equ. if $\alpha D < \mu(s_{in})$
- ▶ *main tank*: chemostat with double inputs:

$$\mu(s_1^*) = \frac{D}{r} - \alpha D \left(1 - \frac{1}{r}\right) \frac{s_{in} - s_2^*}{s_{in} - s_1^*}$$

A graphical characterization



or

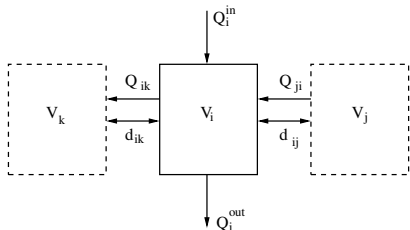


A matricial generalization

$$\dot{S} = -\frac{1}{y}R(S, X) + MS + DS^{in}$$
$$\dot{X} = R(S, X) + MX + DX^{in}$$

where D is a diagonal matrix, and M is a *compartmental* matrix:

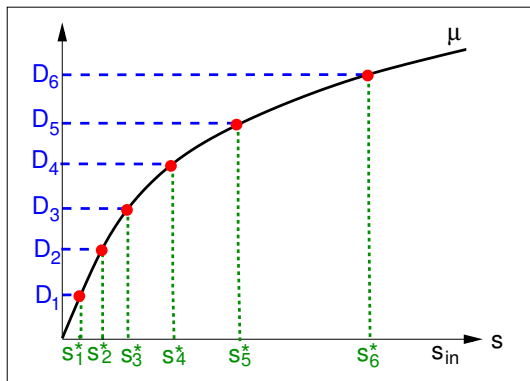
- i. $M_{ii} \leq 0$ for any indice i ,
- ii. $M_{ij} \geq 0$ for any indices $i \neq j$,
- iii. for any indice i , one has $\sum_j M_{ij} \leq 0$



that fulfills the **Kirchoff law** of mass conservation.

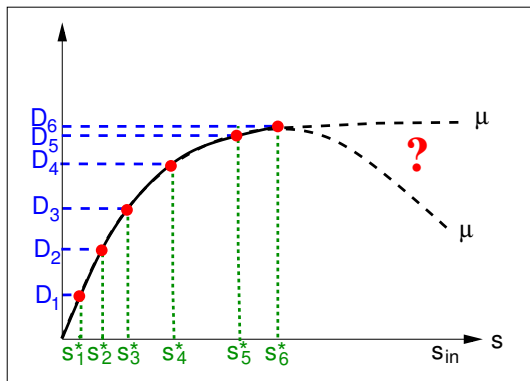
About experimental identification

Principle: one fixes a dilution rate D_i and “wait” for the corresponding equilibrium s_i^* .



About experimental identification

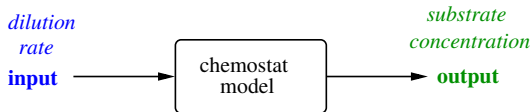
Principle: one fixes a dilution rate D_i and “wait” for the corresponding equilibrium s_i^* .



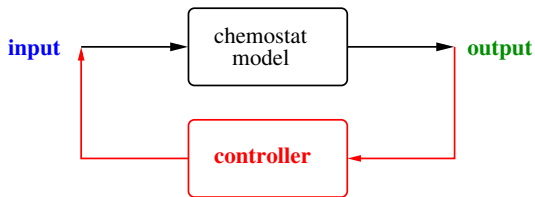
Change of view point

One fixes a reference value s^* and look for **stabilizing** the chemostat at $s = s^*$ **adjusting the dilution rate D** .

open loop:



closed loop:



Adaptive controller

Fix \bar{D} as a value of the dilution rate.

- ▶ **Step 1:** With the **feedback law**

$$D(\bar{D}, s) = \bar{D} + G_1(s^* - s)$$

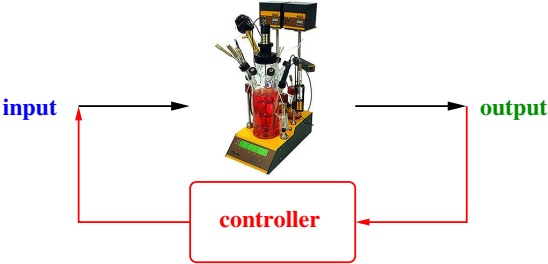
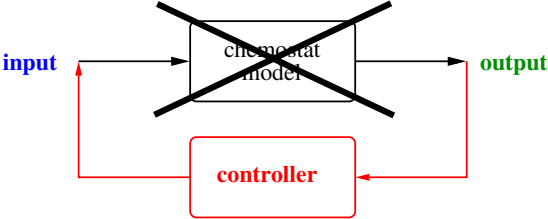
the closed-loop chemostat admits an equilibrium with $s = \bar{s}$ such that $\mu(\bar{s}) = D(\bar{D}, \bar{s})$.

- ▶ **Step 2:** With the **adaptation law** for \bar{D} :

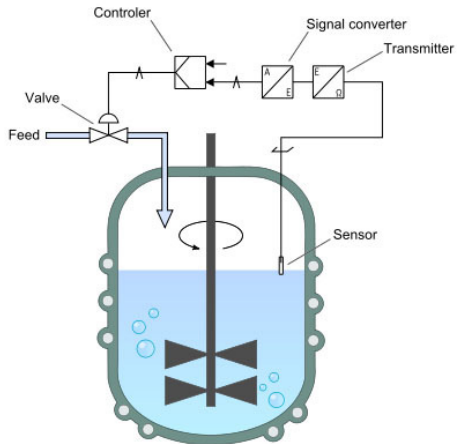
$$\frac{d\bar{D}}{dt} = G_2(s^* - s)$$

the closed-loop chemostat admits the equilibrium with $s = s^*$ and $\bar{D}^* = \mu(s^*)$.

Facing the real life...



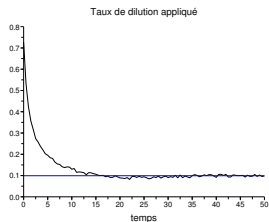
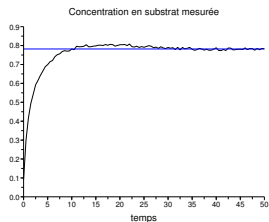
The auxostat



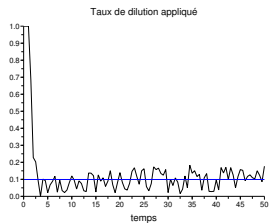
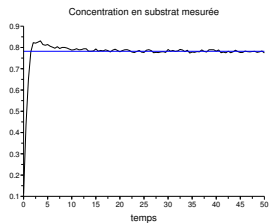
see Gostomski, Muhlemann, Lin, Mormino & Bungay. *Auxostats for continuous culture research*. Journal of Biotechnology, 1994

Simulations with noisy measurements

$$G_1 = 1, \\ G_2 = 1 :$$



$$G_1 = 10, \\ G_2 = 10 :$$

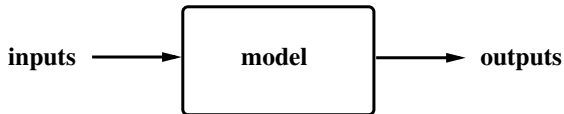


Dilemma accuracy/speed

General comments

- ▶ A model is **ONE** representation of the reality. There exist model**S**.
- ▶ A model is generally built for a question of interest
⇒ *different representations for the same object.*
- ▶ A model is a representation **ALONG WITH HYPOTHESES**
⇒ *a validity domain is associated to a model.*
- ▶ Simple models can represent complex systems, depending on the scale of representation.

Inputs-outputs models



inputs	model	outputs	
known	known	unknown	prediction
known	unknown	known	identification
unknown	known	known	control

Further reading

- ▶ J. HAEFNER. *Modeling Biological Systems*, Springer 2005.
- ▶ C. TAUBES. *Mathematical Differential Equations in Biology*, Cambridge 2008.
- ▶ L. EDELSTEIN-KESHET. *Mathematical Models in Biology*, SIAM 2005.
- ▶ N. BRITTON. *Essential Mathematical Modelling*, Springer 2005.