

**About mathematical modelling  
for microbial ecosystems  
with control and design perspectives**

ALAIN RAPAPORT

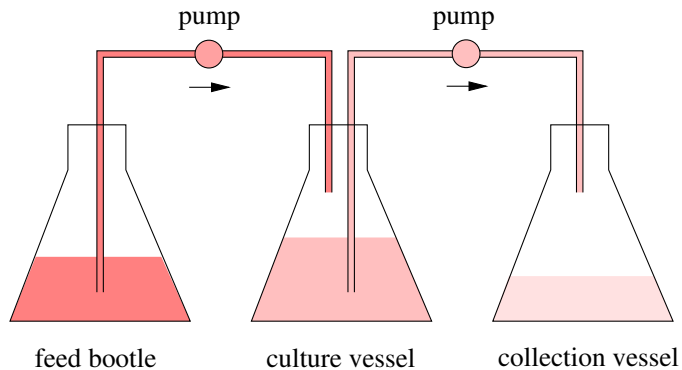
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10th MPDE Conference

5-9 September 2016, Luminy (France)

# Continuous culture

Monod 1950 – Novick & Szilard 1950:



# The mathematical model of the chemostat

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

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

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

# The multi-species chemostat model

$$\begin{aligned}\dot{s} &= -\sum_{i=1}^n \mu_i(s)x_i + D(s_{in} - s) \\ \dot{x}_i &= \mu_i(s)x_i - Dx_i \quad (i = 1 \dots n)\end{aligned}$$

**extensively** studied in the **bio-mathematics** literature, with several extensions such as

- ▶ **spatialization**

e.g. H. Smith, P. Waltman. *The Theory of the chemostat*, 1995

- ▶ **adaptive dynamics**

e.g. O. Diekmann. *A beginner's guide to adaptive dynamics*, 2004

# Resource-consumers models

- ▶ in (theoretical) ecology for understanding, prediction...



- ▶ in biotechnology for control, optimization...



# Common questioning

1. What are the effects of a **spatialization**?
2. What are the effects of a **time-varying** inputs?
3. Is **biodiversity** always favorable?
4. What are the impacts of populations **patterns** (e.g. attachment, flocculation, biofilms...) ?

Many studies about coexistence, persistence... but relatively few about **performances** of microbial ecosystems.

# An input-output approach



**Bioconversion performance:**  $S_{out}/S_{in}$  to be minimized.

# Contents

- ▶ *Preliminaries on the chemostat model*
- ▶ Considerations of simple spatial representations
- ▶ About time-varying inputs
- ▶ Interplay between diversity and patterns
- ▶ Inhibition and spatial patterns
- ▶ About bio-augmentation
- ▶ About modelling flocculation and bacteria attachment



# 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

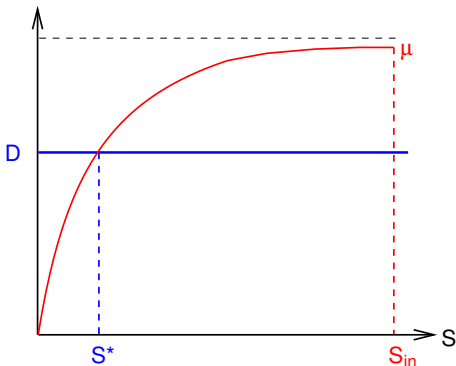
$$\mu(s^*) = D$$

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

positive equilibrium

The Monod function:

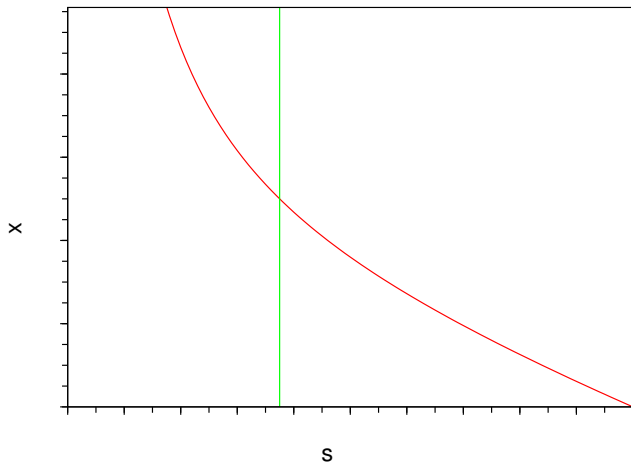
$$\mu(s) = \frac{\mu_{\max} s}{K + s}$$



# Null-clines

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

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



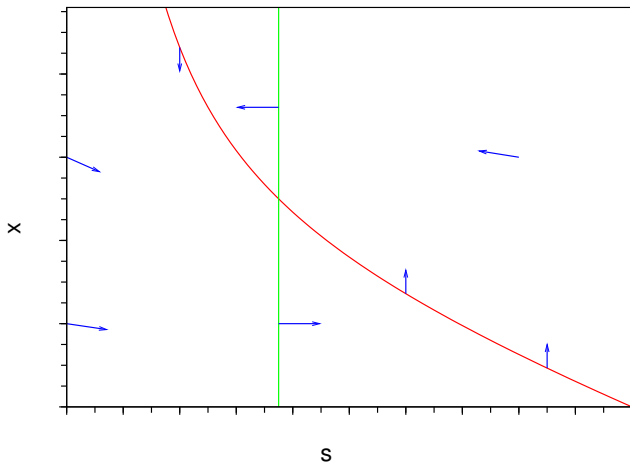
$$\dot{x} = 0$$

$$\dot{s} = 0$$

# Vector field

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

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



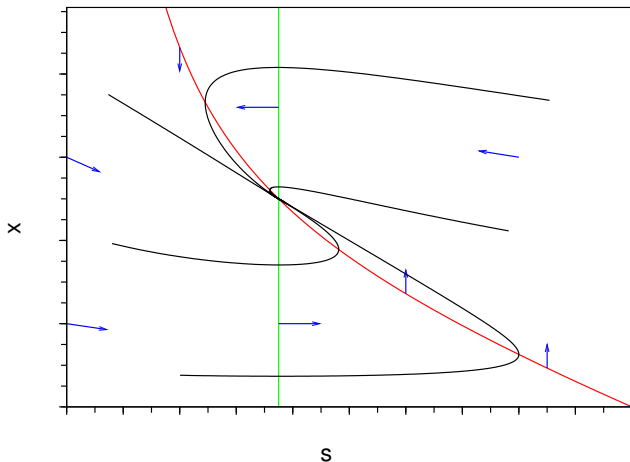
$$\dot{x} = 0$$

$$\dot{s} = 0$$

# Phase portrait

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

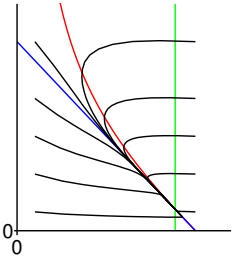
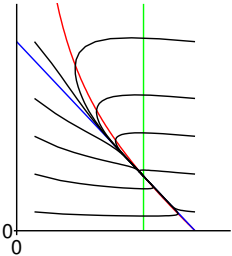
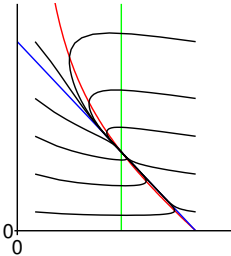
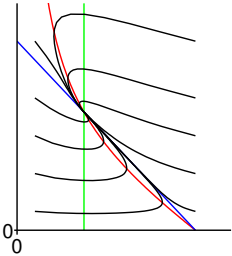
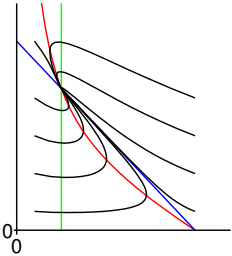
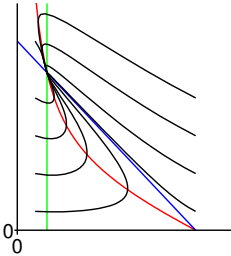
$$\dot{x} = \mu(s)x - Dx$$



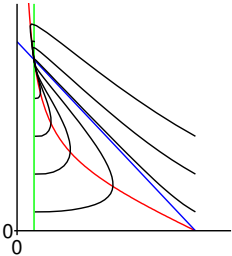
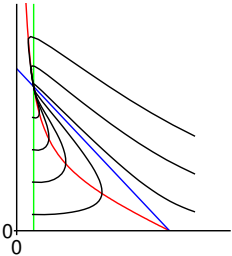
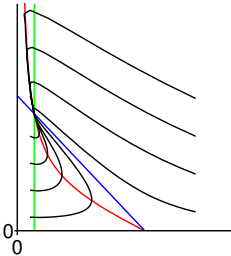
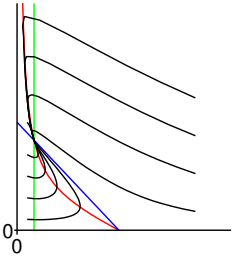
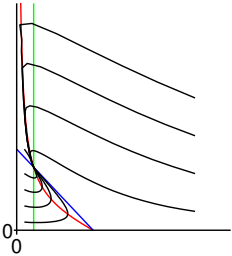
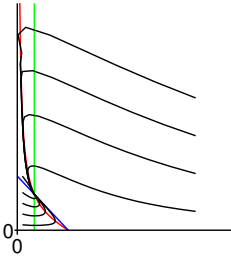
$$\dot{x} = 0$$

$$\dot{s} = 0$$

# For various increasing dilution rates



# For various increasing input concentrations



# About conversion yield at equilibrium

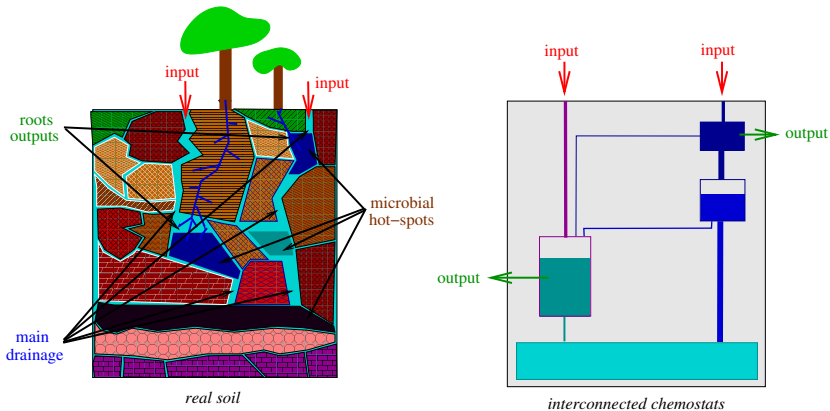
- ▶ The mathematical model of the chemostat predicts that the **substrate concentration** at equilibrium is **independant** of the input concentration  $s_{in}$  (provided that  $\mu(s_{in}) > D$ ).
- ▶ Micro-biologists report that this property is not verified when the tank is not homogeneous or in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

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

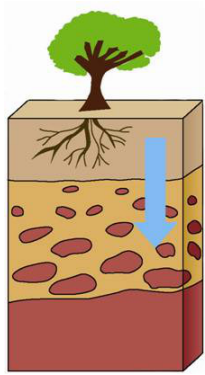
# Considerations of simple spatial representations



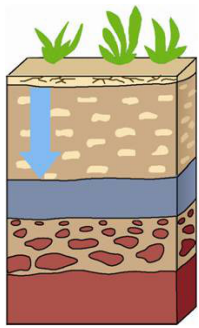
# A motivation: study of soil ecosystems



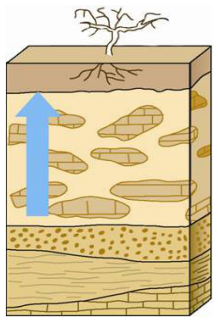
# Different kind of soils



temperate

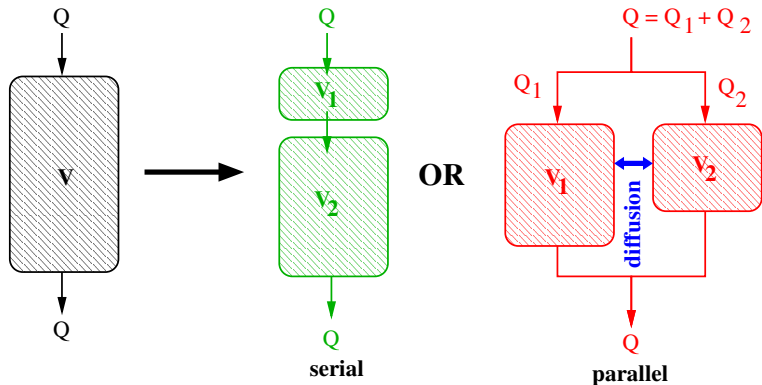


wet



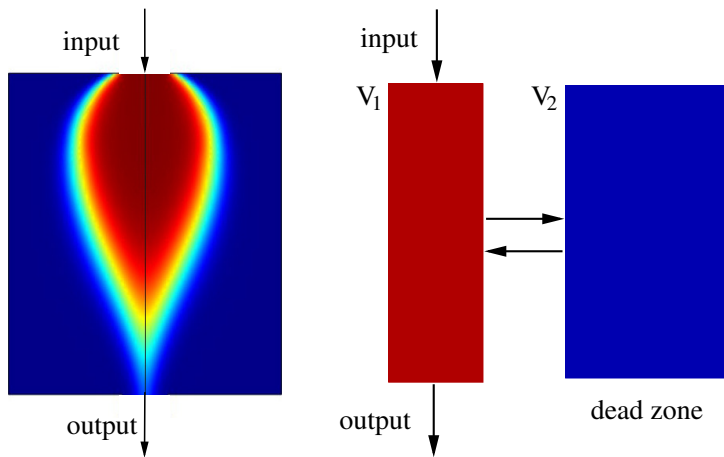
dry

# Study of some simple spatial configurations



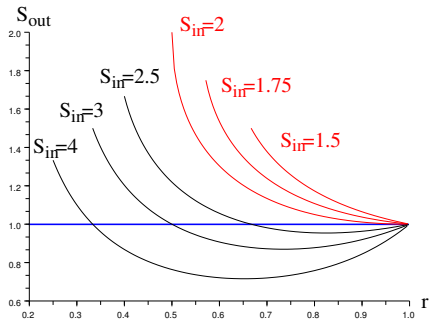
with  $V = V_1 + V_2$

## Another motivation: dead zones in bioreactors

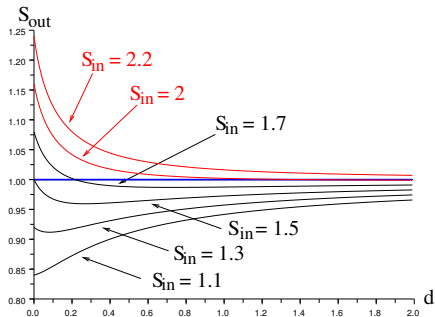


with  $V = V_1 + V_2$

# Simulations of performances at steady state

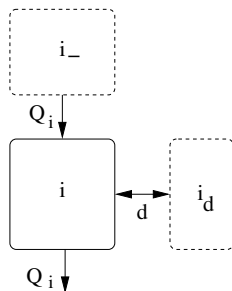


serial



parallel

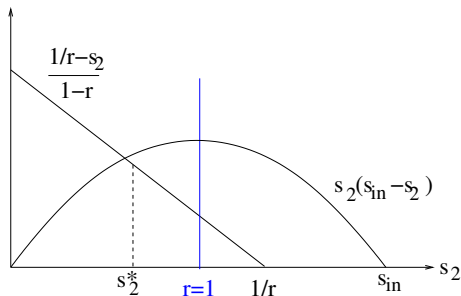
## From the mathematical point of view



$$\begin{aligned}\dot{S}_i &= -\frac{\mu(s_i)}{y}X_i + \frac{Q_i}{V_i}(S_{i-} - S_i) + \frac{d}{V_i}(S_{i_d} - S_i) \\ \dot{X}_i &= \mu(s_i)X_i + \frac{Q_i}{V_i}(X_{i-} - X_i) + \frac{d}{V_i}(X_{i_d} - X_i)\end{aligned}$$

## Serial configuration with linear growth

$$\begin{cases} \dot{s}_1 &= -s_1 x_1 + \frac{1}{r}(s_{in} - s_1) \\ \dot{x}_1 &= s_1 x_1 - \frac{1}{r} x_1 \\ \dot{s}_2 &= -s_2 x_2 + \frac{1}{1-r}(s_1 - s_2) \\ \dot{x}_2 &= s_2 x_2 + \frac{1}{1-r}(x_1 - x_2) \end{cases}$$



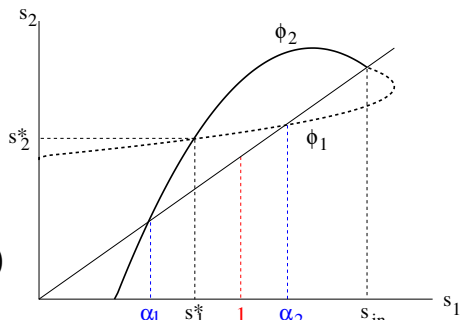
## Parallel configuration with linear growth

$$\left\{ \begin{array}{l} \dot{s}_1 = -s_1 x_1 + \frac{\alpha}{r}(s_{in} - s_1) + \frac{d}{r}(s_2 - s_1) \\ \dot{x}_1 = s_1 x_1 - \frac{\alpha}{r} x_1 + \frac{d}{r}(x_2 - x_1) \\ \dot{s}_2 = -s_2 x_2 + \frac{1-\alpha}{1-r}(s_{in} - s_2) + \frac{d}{1-r}(s_1 - s_2) \\ \dot{x}_2 = s_2 x_2 - \frac{1-\alpha}{1-r} x_2 + \frac{d}{1-r}(x_1 - x_2) \end{array} \right.$$

$$\alpha_1 = \frac{\alpha}{r}, \quad \alpha_2 = \frac{1-\alpha}{1-r}$$

$$\phi_2(s_1) = s_1 + \frac{r}{d}(s_{in} - s_1)(s_1 - \alpha_1)$$

$$\phi_1(s_2) = s_2 + \frac{1-r}{d}(s_{in} - s_2)(s_2 - \alpha_2)$$





# Roles of spatial structure and diffusion

**Proposition 1.** For any monotonic **concave**  $\mu(\cdot)$ , 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,

**Proposition 2.** For the parallel configurations,

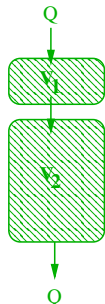
- ▶ for  $s_{in} > \bar{s}_{in}$ , the map  $d \mapsto s_{out}^*(d)$  is **decreasing**,
- ▶ for  $s_{in} < \bar{s}_{in}$ , the map  $d \mapsto s_{out}^*(d)$  admits an **unique minimum** for  $d^* < +\infty$

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

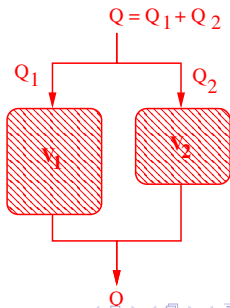
see *Haidar R. Gérard. Effects of spatial structure and diffusion on the performances of the chemostat, Math. Biosciences Eng. 2011*

# Message

In *rich* environments (i.e. for  $s_{in}$  large), the serial pattern is more efficient with moderate diffusion.



In *poor* environments (i.e. for  $s_{in}$  small), the parallel pattern is more efficient (with a moderate diffusion).



## About time-varying inputs

## Time-varying inputs

Consider  $T$ -periodic  $S_{in}(\cdot)$  and/or  $D(\cdot)$  such that

$$\frac{1}{T} \int_t^{t+T} S_{in}(\tau) d\tau = \bar{S}_{in} \quad \frac{1}{T} \int_t^{t+T} D(\tau) d\tau = \bar{D}$$

Then, periodic solutions satisfy

$$0 = \frac{1}{T} \int_t^{t+T} \frac{\dot{x}(\tau)}{x(\tau)} d\tau = \frac{1}{T} \int_t^{t+T} \mu(s(\tau)) d\tau - \bar{D}$$

$$\mu(\cdot) \text{ concave} \Rightarrow \bar{s} = \frac{1}{T} \int_t^{t+T} s(\tau) d\tau > \mu^{-1}(\bar{D})$$

# Interplay between diversity and patterns

# 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 $\mu_1(s^*) = \mu_2(s^*) = D$ <b>non generic condition!</b>

# Having two species in the chemostat

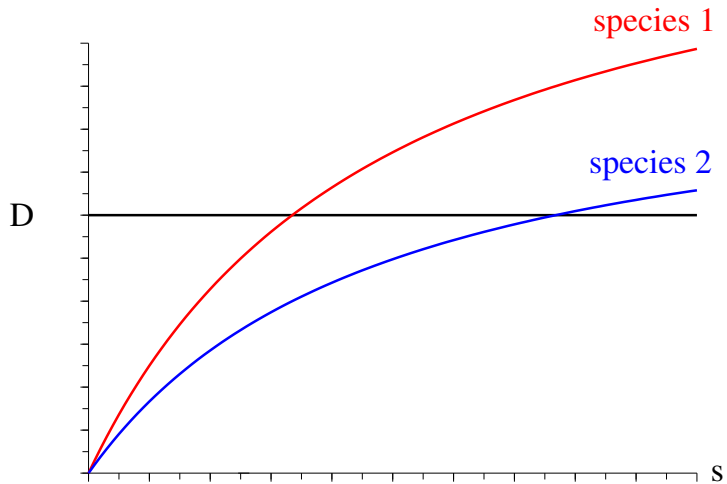
$$\begin{aligned}\dot{s} &= -\mu_1(s)x_1 - \mu_2(s)x_2 + D(s_{in} - s) \\ \dot{x}_1 &= \mu_1(s)x_1 - Dx_1 \\ \dot{x}_2 &= \mu_2(s)x_2 - Dx_2\end{aligned}$$

**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 $\mu_1(s^*) = \mu_2(s^*) = D$ <b>non generic condition!</b>

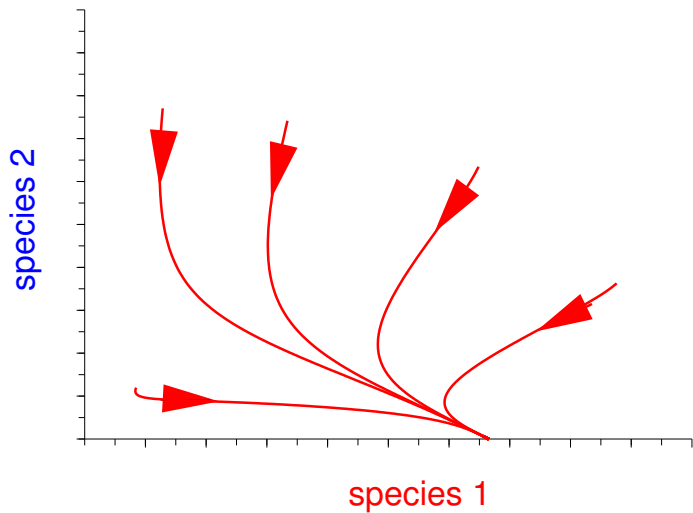
$$p = \frac{x_1}{x_1 + x_2} \quad \Rightarrow \quad \dot{p} = (\mu_1(s) - \mu_2(s))p(1 - p)$$

# Species competition

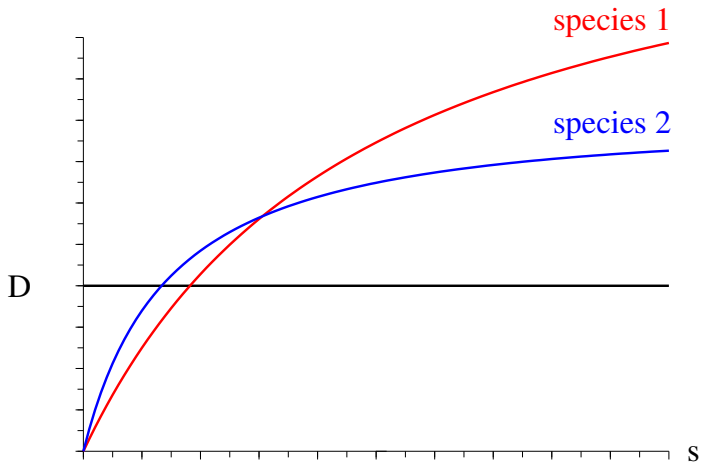




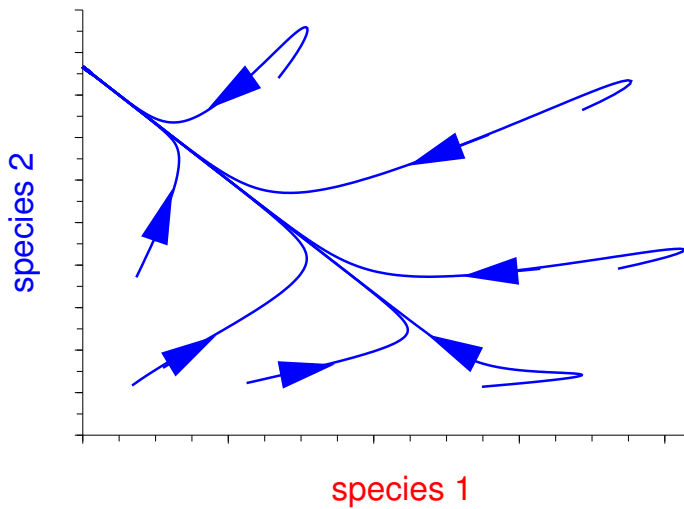
# Species competition



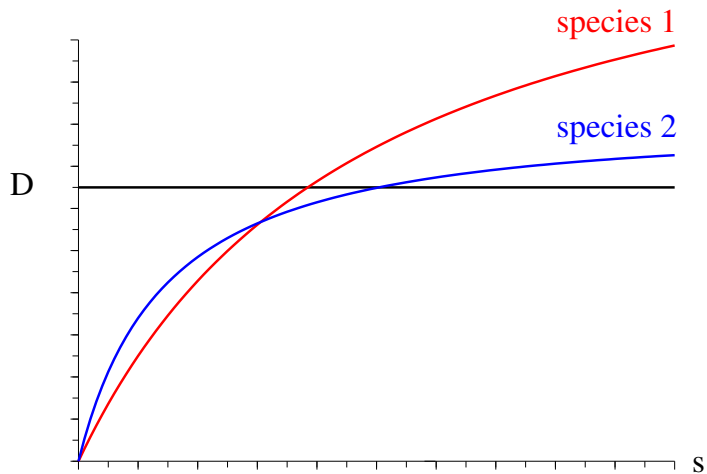
# Species competition



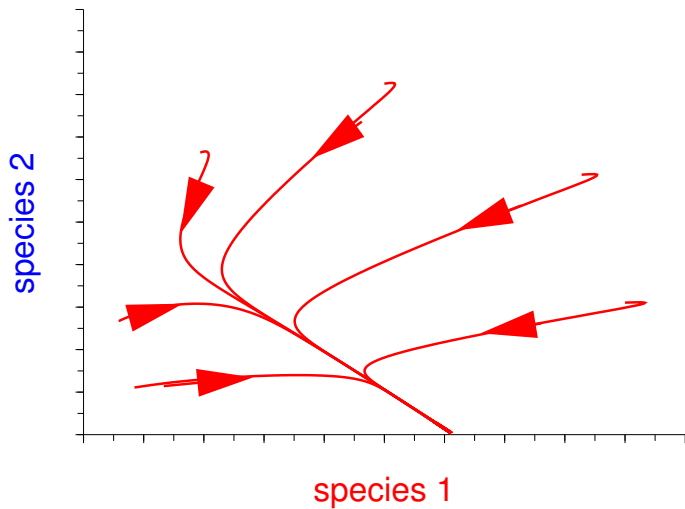
# Species competition



# Species competition

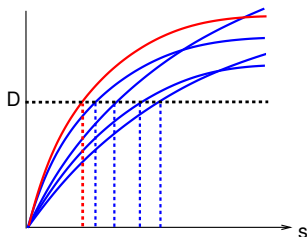


# Species competition



# The Competitive Exclusion Principle

$$\begin{aligned}\dot{s} &= -\sum_{j=1}^n \mu_j(s)x_j + D(s_{in} - s) \\ \dot{x}_i &= \mu_i(s)x_i - Dx_i \quad (i = 1 \cdots n)\end{aligned}$$



**Proposition** (Hsu Hubbell Waltman 77...) Under the conditions

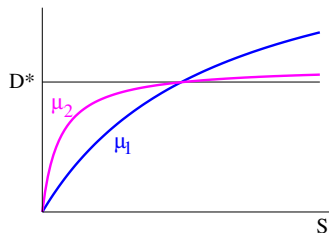
$$\begin{aligned}0 < \mu_1^{-1}(D) < \mu_2^{-1}(D) \leq \cdots \mu_n^{-1}(D) \\ \mu_1^{-1}(D) < s_{in}\end{aligned}$$

any solution with  $x_1(0) > 0$  satisfies

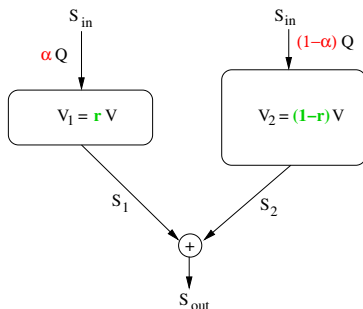
$$\lim_{t \rightarrow +\infty} (s(t), x_1(t), \cdots, x_n(t)) = (\mu_1^{-1}(D), s_{in} - \mu_1^{-1}(D), 0, \cdots, 0)$$

# About niches and over-yielding

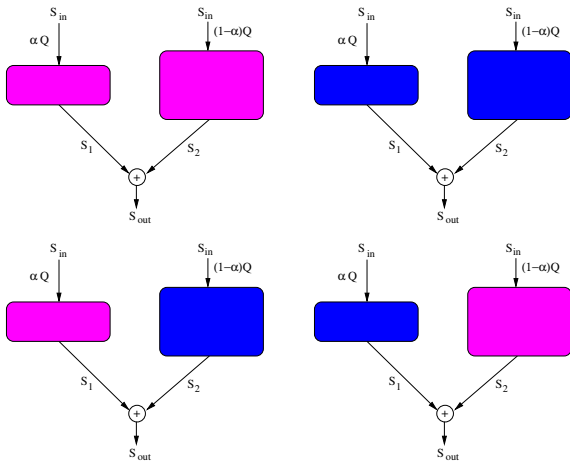
Consider two species:



and the spatial structure:



# Bioconversion and over-yielding



**What is the most efficient configuration?**

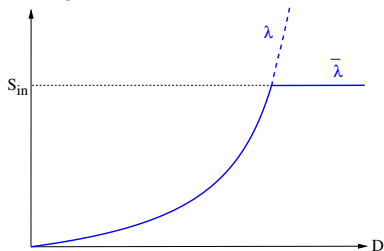


## Same species in both compartments

Define

$$\lambda(D) = \mu^{-1}(D)$$

$$\bar{\lambda}(D) = \min(\lambda(D), S_{in})$$



► Steady-state output:

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

**Proposition.** Assume  $\mu(\cdot)$  is concave, then

$$\min_{[0,1]^2} F = \begin{cases} \lambda(D) = F(\alpha, \alpha), \forall \alpha \in [0, 1] & \text{for } S_{in} \geq T^{in}(D) \\ \min_{\alpha} F(\alpha, 0) < \lambda(D) & \text{for } S_{in} < T^{in}(D) \end{cases}$$

where  $T^{in}(D) = \lambda(D) + D\lambda'(D)$

## Different species in each compartment

Steady-state output:  $G(\alpha, r) := \alpha \bar{\lambda}_1 \left( \frac{\alpha}{r} D \right) + (1 - \alpha) \bar{\lambda}_2 \left( \frac{1 - \alpha}{1 - r} D \right)$

**Proposition.** Assume there exists  $D^*$  such that  $\bar{\lambda}_1(D^*) = \bar{\lambda}_2(D^*)$ .  
Then for any  $D$  and  $(\alpha, r)$  such that

$$\frac{\alpha}{r} D < \bar{D} < \frac{1 - \alpha}{1 - r} D < \min(\mu_1(S_{in}), \mu_2(S_{in}))$$

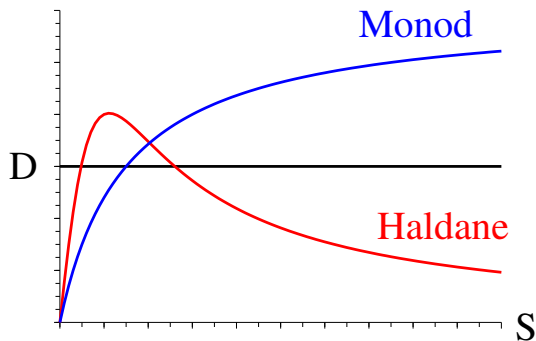
one has *over-yielding*:

$$G(\alpha, r) < \min(F_1(\alpha, r), F_2(\alpha, r))$$

see *Dochain De Leenheer R. About transgressive over-yielding in the chemostat*, Proc. MathMod 2012

# Growth inhibition and spatial patterns

# Growth inhibition by the resource



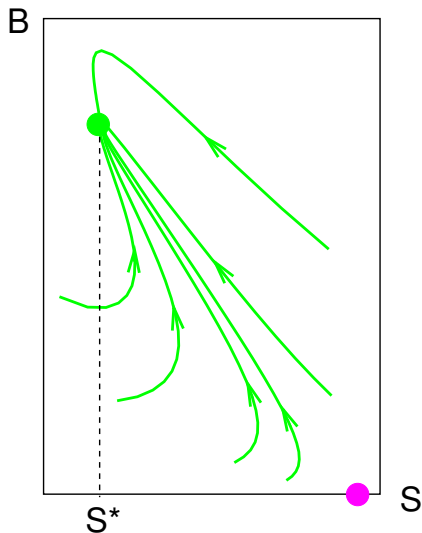
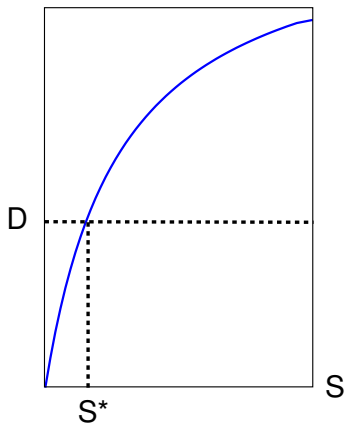
$$\mu(S) = \frac{\mu_{max} S}{K + S}$$

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

e.g. J. F. Andrews, *A mathematical model for the continuous culture of microorganisms utilizing inhibitory substrates*, Biotech. Bioengng. 1968

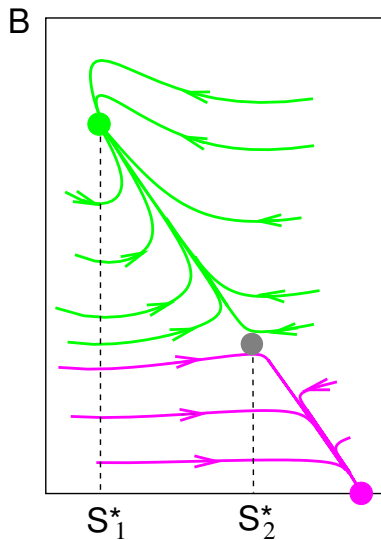
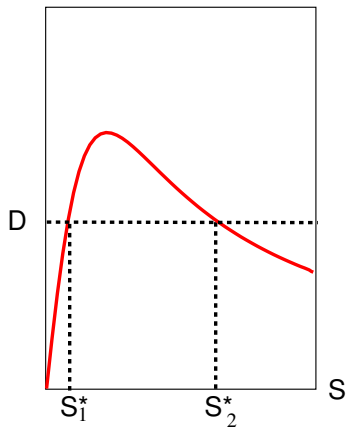
# The chemostat model with the Monod law

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

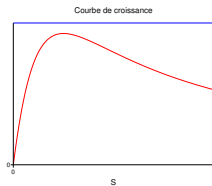


# The chemostat model with the Haldane law

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

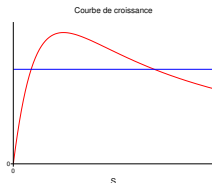


# Possible behaviors



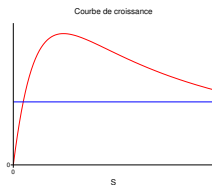
$$D > \max_{s \in [0, S_{in}]} \mu(s)$$

1 equilibrium: wash-out



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

3 equilibria : bi-stability

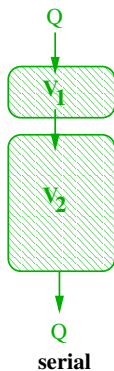
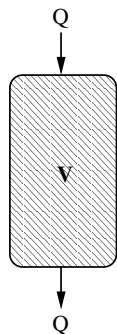


$$D < \mu(s_{in})$$

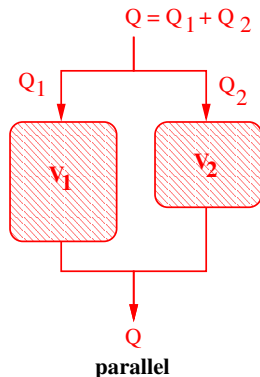
2 equilibria : stability

# Playing with interconnections

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



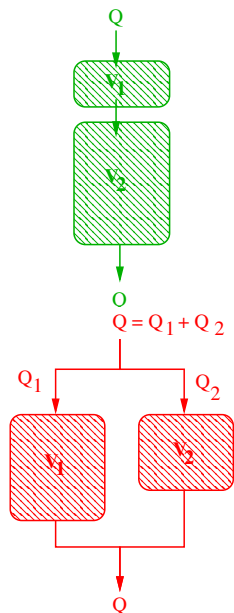
OR



with  $V = V_1 + V_2$



# Serial and parallel patterns



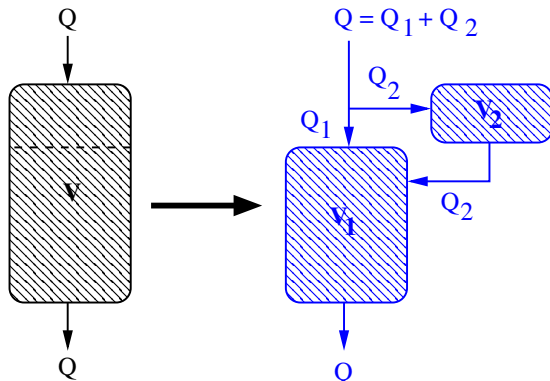
$$V_1 < V \Rightarrow \frac{Q}{V_1} > D, \quad V_2 < V \Rightarrow \frac{Q}{V_2} > D$$

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

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

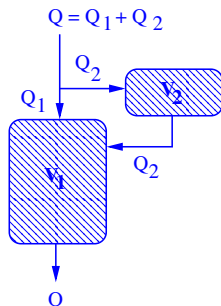
*The wash-out equilibrium is attractive  
in at least one tank.*

# The buffered pattern



with  $V = V_1 + V_2$

# The buffered chemostat



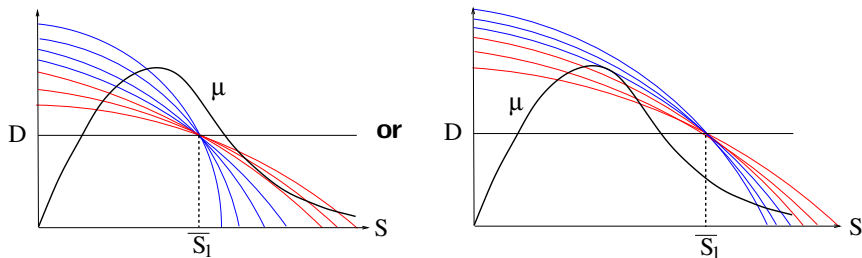
Two parameters:  $(\alpha, r)$  with

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

- ▶ *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

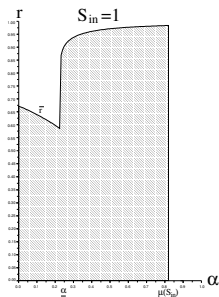
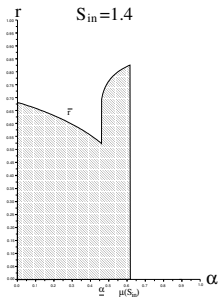
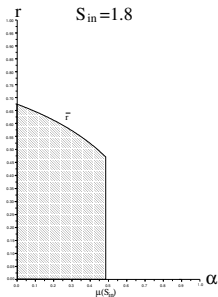


► There **always** configurations that are **globally stable!**

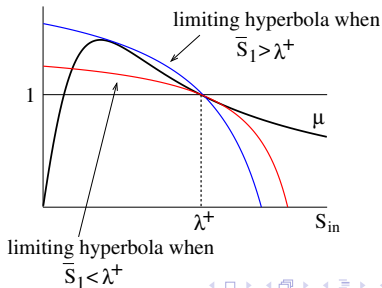
see R. Haidar & Harmand. *Global dynamics of the buffered chemostat for a general class of growth functions*. *J. Math. Bio.* 2014.

# The set of (globally) stable configurations

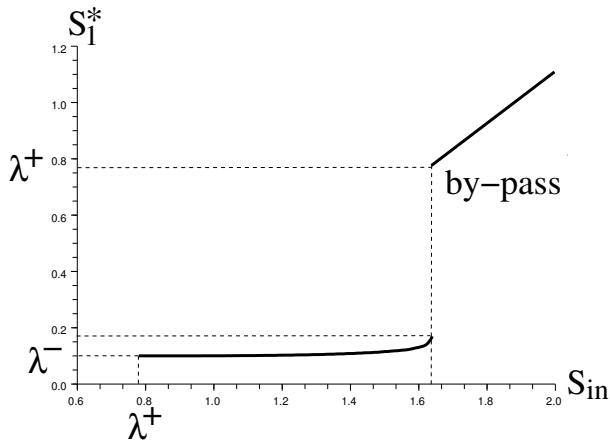
Examples with the Haldane law and  $D = 1$ :



Limiting cases:  $\bar{s}_1 = \lambda^+$



# Performances of the “buffered” chemostat



smallest output concentration at steady state  
as function of  $s_{in}$

# Performances of the buffered chemostat

Consider  $\psi(s) = \mu(s)(S_{in} - s)$

Let  $\psi^* = \max_{s \in [0, \bar{s}]} \psi(s)$  where  $\mu(\bar{s}) = \mu(s_{in})$ .

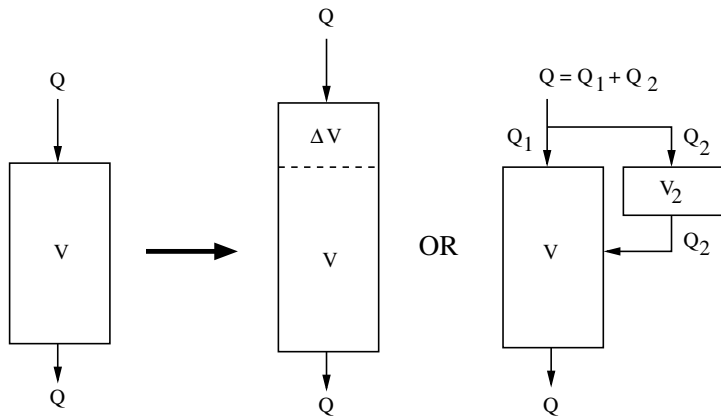
Let  $s^* \in \arg \max \psi^*$  and define  $\alpha^* = \mu(s^*)$ .

## Proposition.

The best stable configuration consists in having  $\alpha = \alpha^*$  and

- ▶ making a **by-pass** of the volume  $V$  with a flow rate equal to  $(1 - \alpha^*)Q$ , when  $\psi^* < S_{in} - \lambda_+$ .
- ▶ choosing any value of  $r \in (0, \bar{r}(\alpha^*))$ , when  $\psi^* = S_{in} - \lambda_+$ .
- ▶ taking  $r$  smaller and arbitrarily close to  $\bar{r}(\alpha^*)$ , when  $\psi^* > S_{in} - \lambda_+$ .

## Adding a “buffer”

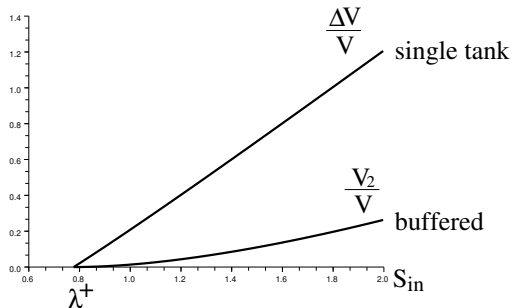


What is the smallest volume to add to obtain global stability?



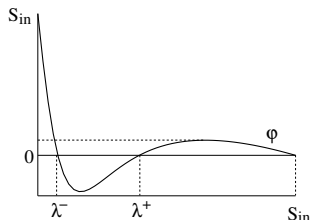
## Comparison with a single tank

For a single tank, one should have  $\Delta V > V \left( \frac{1}{\mu(s_{in})} - 1 \right)$ .



# Comparison with a single tank

Let  $\varphi(s) = (s_{in} - s)(D - \mu(s))$



## Proposition.

The G.A.S. property is fulfilled for an additional volume such that

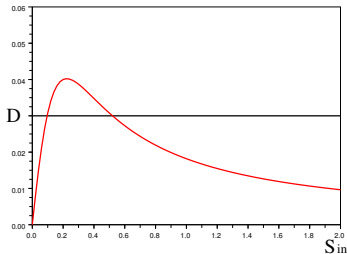
$$V_2 > \frac{V}{\psi^*} \max_{s \in (\lambda^+, s_{in})} \varphi(s)$$

# Main messages

- ▶ A buffered interconnection of two volumes can globally stabilize the chemostat, preserving the total volume and input rate (while this is not possible with serial or parallel interconnections).
- ▶ The input concentration impacts the shape of  $\mathcal{C}$ . There exists a threshold above it a by-pass is more efficient.
- ▶ The minimum volume to add to a given single tank for obtaining the global stability can be significantly reduced using a “buffered” interconnection.

# About bio-augmentation

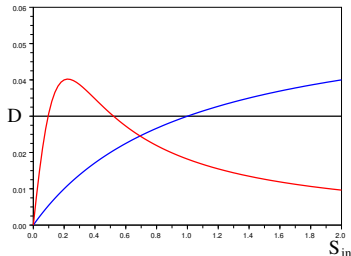
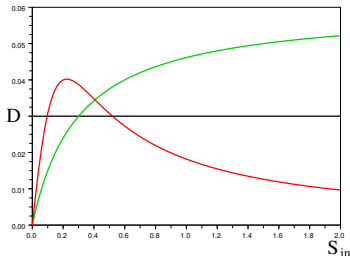
# Bio-augmentation



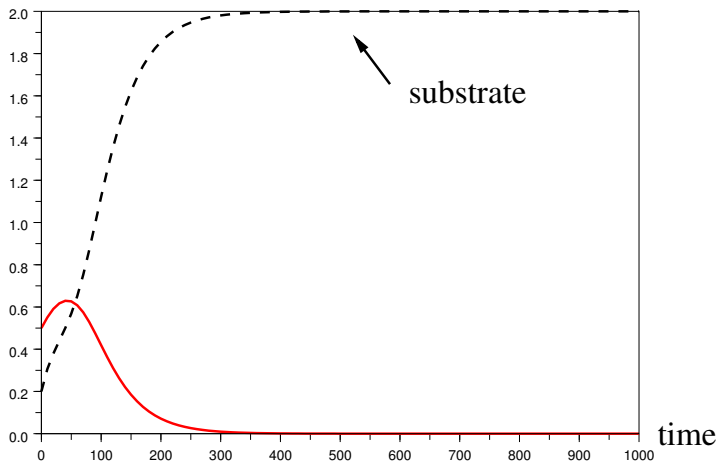
$$\max_{[0, S_{in}]} \mu < \mu(S_{in}) < D$$

$\Rightarrow$  the wash-out eq. is attractive

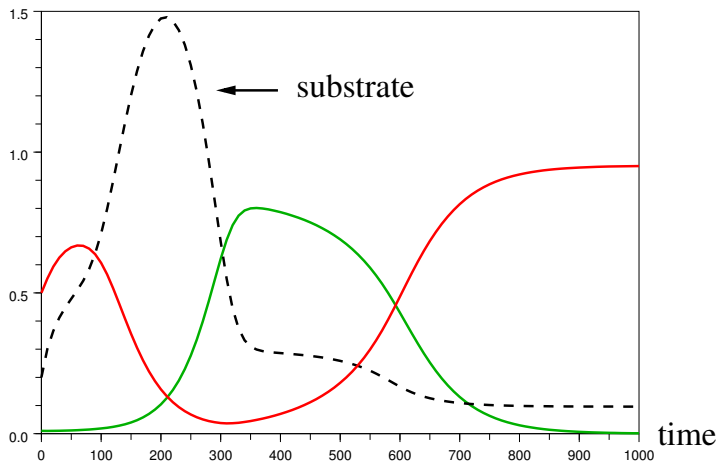
What is the effect of adding a “blue” or a “green” one?



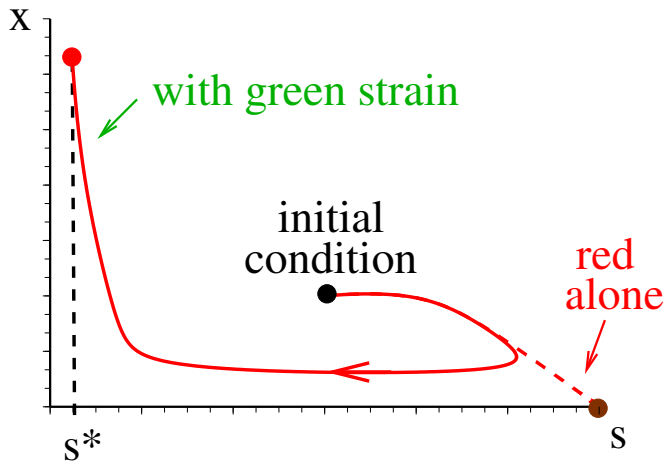
## Species red only



## Adding green species

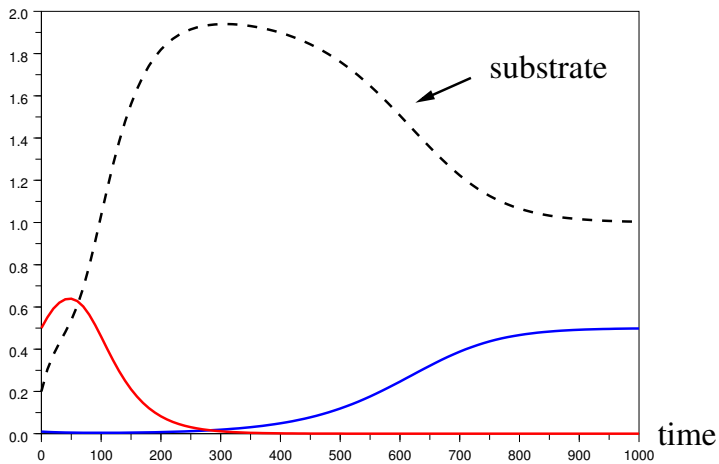


# Phase portrait



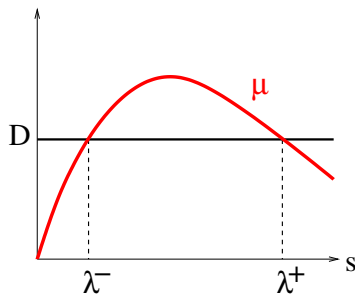
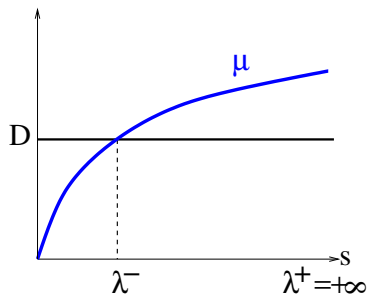


## Adding blue one



# Generalizing the Competitive Exclusion Principle

**Hypothesis:**  $E_i(D) = \{s > 0 \mid \mu_i(s) > D\}$  is an interval  $(\lambda_i^-(D), \lambda_i^+(D))$



# Generalizing the Competitive Exclusion Principle

**Proposition.** Let  $Q(D) = \bigcup_i E_i(D) = \bigcup_i (\lambda_i^-(D), \lambda_i^+(D))$

- ▶ There is **generically** competitive exclusion.
- ▶ There is as many possible winners as **connected components** of the set  $Q(D)$ .

[1] *Butler & Wolkowicz. A mathematical model of the chemostat with a general class of functions describing the nutrient uptake. SIAM J. Appl. Math. 1985.*

[2] *R. & Harmand. Biological control of the chemostat with nonmonotonic response and different removal rates. Math. Bio. Eng. 2008.*

# Main message: the biological control

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

Let  $\lambda$  be the break-even conc. for an additional monotonic species.

- ▶  $\lambda \in E$ : global stabilization of the red species
  - ▶  $\lambda \notin E$ : possibility of invasion
- ▶ *In practice one can add periodically the “right” species the robustify the performances*

*cf R. & Harmand. Biological control of the chemostat with nonmonotonic response and differnt removal rates. Math. Bio. Eng. 2008.*

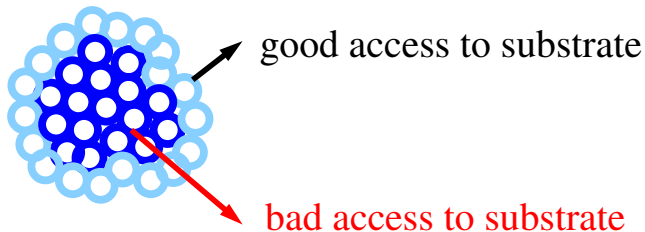
# About modelling flocculation and bacteria attachment (at a macroscopic level)

# Main objective

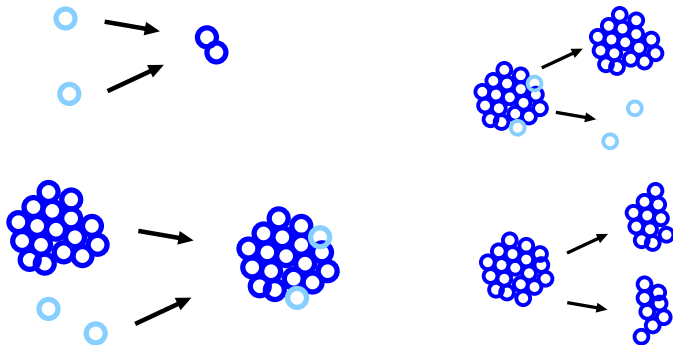
Introduce in the simple chemostat model:

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

a consideration of planktonic bacteria and attached bacteria:



# Attachment and detachment processes



# A simple modelling

An extension with planktonic bacteria (of concentration  $v$ ) and attached bacteria (of concentration  $w$ ) with  $x = v + w$ :

$$\begin{aligned}\dot{s} &= -\mu_v(s)v - \mu_w(s)w + D(s_{in} - s) \\ \dot{v} &= \mu_v(s)v - D_v v - a(\cdot)v + b(\cdot)w \\ \dot{w} &= \mu_w(s)w - D_w w + a(\cdot)v - b(\cdot)w\end{aligned}$$

where  $\left| \begin{array}{l} a(\cdot)v : \text{ specific attachment} \\ b(\cdot)w : \text{ specific detachment} \end{array} \right.$

## Assumptions.

1.  $\mu_v(s) \geq \mu_w(s), \forall s \geq 0$
2.  $D_v \geq D_w$



# Examples

- ▶ **adaptive nutrient uptake.**  $a(\cdot) = a(s)$ ,  $b(\cdot) = b(s)$   
Tang Sitomer Jackson 97
- ▶ **wall attachment.**  $a(\cdot) = a$ ,  $b(\cdot) = b$   
Pilyguin Waltman 99
- ▶ **intestine model.**  
 $a(\cdot) = a \left(1 - \frac{v}{v_{\max}}\right)$ ,  $b(\cdot) = b + \mu_v(s) \left(1 - G\left(\frac{v}{v_{\max}}\right)\right)$  with  $G(\cdot) \searrow$   
Freter 83
- ▶ **flocs.**  $a(\cdot) = av$ ,  $b(\cdot) = b$   
Haegeman R. 08

# Slow-fast dynamics

$$\begin{aligned}\dot{s} &= -\mu_v(s)v - \mu_w(s)w + D(s_{in} - s) \\ \dot{v} &= \mu_v(s)v - D_v v - a(\cdot)v + b(\cdot)w \\ \dot{w} &= \mu_w(s)w - D_w w + a(\cdot)v - b(\cdot)w\end{aligned}$$

**Assumption**  $a(\cdot) = \frac{1}{\varepsilon}\alpha(\cdot)$  and  $b(\cdot) = \frac{1}{\varepsilon}\beta(\cdot)$  with  $\varepsilon$  **small**

$\Rightarrow$  **quasi-stationary approximation:**

$$\begin{aligned}\alpha(s, v, w)v &= \beta(s, v, w)w \\ v + w &= x\end{aligned}$$

# The slow manifold

**Proposition.** Under the assumptions

1.  $\alpha$  depends only on  $v, w$  and  $v > 0 \Rightarrow \alpha(v, 0) > 0$
2.  $\beta$  depends only on  $w$  and  $w > 0 \Rightarrow \beta(w) > 0$
3.  $\alpha(v, w) = \alpha_v(v) + \alpha_w(w)$  with  $\alpha'_v(v) \geq \alpha'_w(w) \geq 0$
4.  $w \mapsto \beta(w)w$  increasing with  $\beta'(w) \leq 0$

there exists a regular **decreasing** function  $x \mapsto p(x)$  such that

$$\begin{cases} \alpha(v, w)v = \beta(w)w \\ v + w = x \end{cases} \iff \begin{cases} v = p(x)x \\ w = (1 - p(x))x \end{cases}$$

# Examples

- ▶ flocs of two individuals:

$$\alpha(\cdot) = av, \quad \beta(\cdot) = b$$

$$\Rightarrow p(x) = \frac{2}{1 + \sqrt{1 + 4a/bx}}$$

- ▶ undifferentiated flocs:

$$\alpha(\cdot) = a(v + w), \quad \beta(\cdot) = b$$

$$\Rightarrow p(x) = \frac{1}{1 + a/bx}$$

# Reduced dynamics

Define  $\mu(s, x) = p(x)\mu_v(s) + (1 - p(x))\mu_w(s)$ .

$$\Rightarrow \text{Model 1: } \begin{cases} \dot{s} = -\mu(s, x)x + D(s_{in} - s) \\ \dot{x} = \mu(s, x)x - Dx \end{cases} \quad \text{if } D_v = D_w = D$$

$$\Rightarrow \text{Model 2: } \begin{cases} \dot{s} = -\mu(s, x)x + d(x)(s_{in} - s) \\ \dot{x} = \mu(s, x)x - d(x)x \end{cases} \quad \text{if } D_v \neq D_w$$

with  $d(x) = p(x)D_v + (1 - p(x))D_w$

*Remark.* The functions  $\mu(\cdot)$  and  $d(\cdot)$  are decreasing w.r.t.  $x$

## Remark about time-varying inputs

Consider model 1 with  $D(\cdot)$  time-varying. Asymptotically, one has

$$\dot{x} = \tilde{\mu}(s)x - D(t)x$$

with  $\tilde{\mu}(s) = \mu_v(s)p(s_{in} - s) + \mu_w(s)(1 - p(s_{in} - s))$ .

$$\Rightarrow \tilde{\mu}'' = \mu_v''p + \mu_w''(1 - p) + 2(\mu_w' - \mu_v')p' + (\mu_1 - \mu_2)p''$$

Ex.:  $\mu_{v,w}$  linear and  $p$  convex  $\Rightarrow f$  **convex**.

► Overyielding with periodic  $D(\cdot)$  is possible !

# Competition with mono-specific flocs

$$\begin{aligned}\dot{s} &= - \sum_{j=1}^n \mu_j(s, x_j) x_j + D(s_{in} - s) \\ \dot{x}_i &= \mu_i(s, x_i) x_i - D x_i \quad i = 1 \cdots n\end{aligned}$$

*Example.* Species 1 makes flocs and not species 2  
(see Haegeman R. 08)

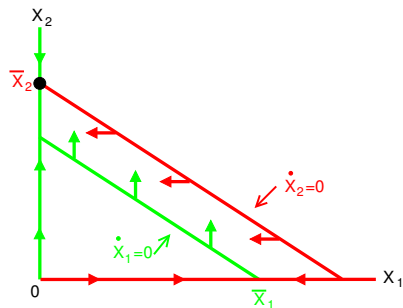
**Proposition** (Lobry Mazenc R. 05, 07) Under the conditions

$$\begin{aligned}\mu_i(\cdot, \cdot) &\text{ increasing w.r.t. } s, \text{ decreasing w.r.t. } x_i \\ \mu_i(s_{in}, 0) &> D \\ \mu_i(s, +\infty) &= 0, \quad \forall s \geq 0\end{aligned}$$

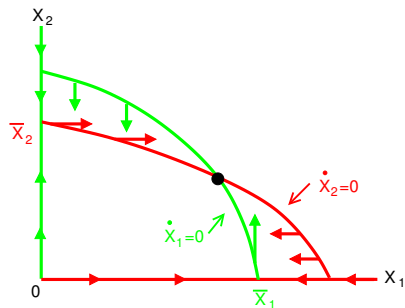
there exists an unique **positive equilibrium**, that is globally exponentially stable.

# Sketch of proof in 2D

Example of two species on the attractive manifold  $x_1 + x_2 = s_{in} - s$



*without density dependency*

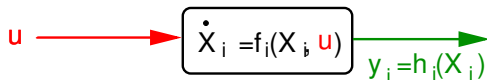


*with density dependency*



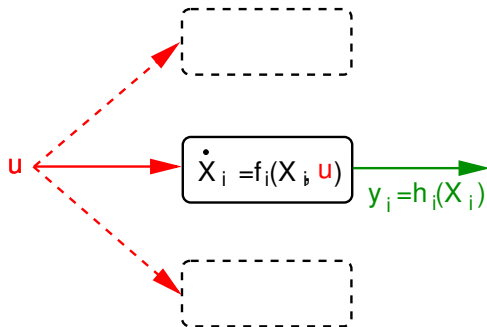
## Sketch of proof in higher dimensions

An *input-output* approach: 
$$\begin{cases} \dot{x}_i &= f_i(x_i, \mathbf{s}) = \mu_i(\mathbf{s}, x_i)x_i - Dx_i \\ y_i &= h_i(x_i) = x_i \end{cases}$$



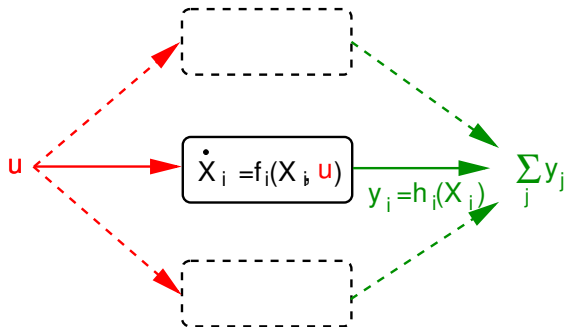
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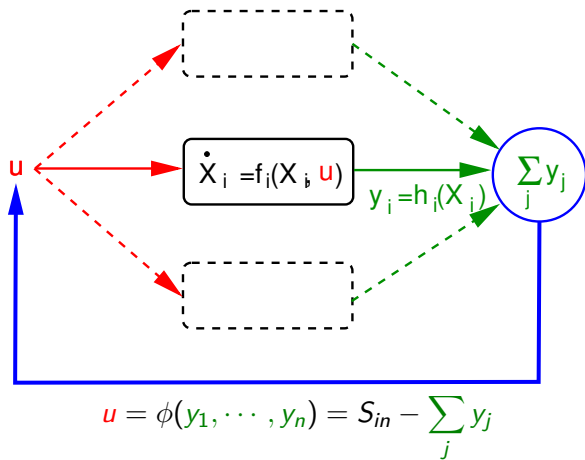
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## Sketch of proof in higher dimensions

An *input-output* approach: 
$$\begin{cases} \dot{x}_i &= f_i(x_i, \mathbf{s}) = \mu_i(\mathbf{s}, x_i)x_i - Dx_i \\ y_i &= h_i(x_i) = x_i \end{cases}$$



see also de Leenheer Angeli Sontag. *Crowding effects promote coexistence in the chemostat*. JMMA 06

# A multi-phase portrait analysis

$$\dot{x}_i = x_i f_i(x_i, u)$$

## Hypotheses.

1.  $\exists \psi_i(\cdot)$  s.t.  $f_i(x_i, \psi_i(x_i)) = 0$  with

$$u \neq \psi_i(x_i) \Rightarrow (u - \psi_i(x_i)) \cdot f_i(x_i, u) > 0$$

2.  $\exists r(\cdot)$  s.t.  $\frac{\partial r}{\partial x_i} \geq a_i > 0$  for any  $i$
3.  $\exists x^*$  s.t.  $f_i(x_i^*, -r(x^*)) = 0$  for any  $i$

**Proposition.** Any bounded positive solution of

$$\dot{x}_i = x_i f_i(x_i, -r(x))$$

converge asymptotically to  $x^*$ .

## Chemostat model with multi-specific flocs

$$\begin{aligned}\dot{s} &= -\sum_{j=1}^n \mu_j(s, x_1, \dots, x_n) x_j + D(s_{in} - s) \\ \dot{x}_i &= \mu_i(s, x_1, \dots, x_n) x_i - D x_i \quad i = 1 \dots n\end{aligned}$$

Typically  $a_i(\cdot) = \frac{1}{\varepsilon} \sum_j \alpha_{ij} x_j$  and  $b_i(\cdot) = \frac{1}{\varepsilon} \beta_i$

$$\Rightarrow p_i(x_1, \dots, x_n) = \frac{\beta_i}{\beta_i + \sum_j \alpha_{ij} x_j}$$

Lobry Harmand 06: Under the conditions

$\mu_i(\cdot)$  increasing in  $s$ , decreasing in each  $x_j$

$x_i = 0 \Rightarrow \mu_i(s_{in}, \dots) > D$

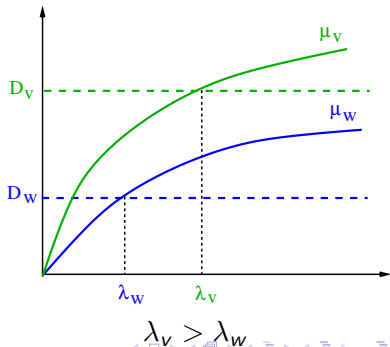
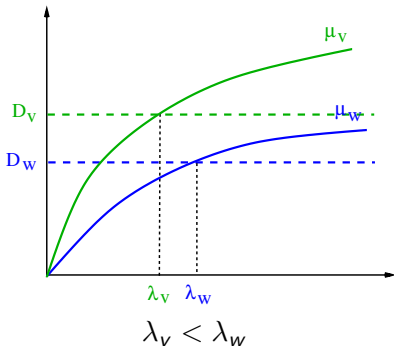
$x_i = +\infty \Rightarrow \mu_i(\cdot) = 0$

simulations show the existence of asymptotically stable **positive equilibrium**, but the *theory* is not ready at the moment...

# The case of density-dependent dilution rate

$$\begin{cases} \mu(s^*, x^*)x^* = D(s_{in} - s^*) \\ \mu(s^*, x^*) = d(x^*) \end{cases} \implies \begin{cases} s^* = g(x^*) := s_{in} - x^* \frac{d(x^*)}{D} \quad \downarrow \\ s^* = f(x^*) \quad \uparrow \text{ or } \downarrow ? \end{cases}$$

$$s^* = f(x^*) : \boxed{p(x^*) \underbrace{[\mu_v(s^*) - D_v]}_{= 0 \text{ for } s^* = \lambda_v} + (1 - p(x^*)) \underbrace{[\mu_w(s^*) - D_w]}_{= 0 \text{ for } s^* = \lambda_w} = 0}$$



# Multiplicity of equilibria

## Proposition

$\lambda_v < \lambda_w$ ( $f \nearrow$ )		$\lambda_v > \lambda_w$ ( $f \searrow$ )	
$\lambda_v < s_{in}$	$\lambda_v > s_{in}$	$\lambda_v < s_{in}$	$\lambda_v > s_{in}$
$\exists!(s^*, x^*)$ G.A.S.	no positive equ.	even nb. of equ. alter. stab. and unstab.	uneven nb. of equ. alter. stab. and unstab.
		wash-out eq. repulsive	wash-out eq. attractive

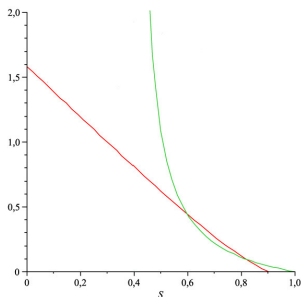
*Fekih-Salem Harmand Lobry R. Sari Extensions of the chemostat model with flocculation JMMA 2013*



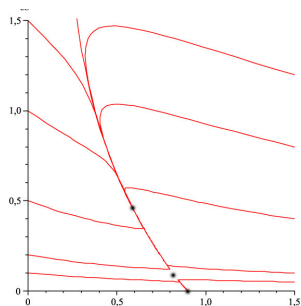
## Example

$$\mu_v(s) = \frac{2s}{1+s}, \quad \mu_w(s) = \frac{1.5s}{0.8+s}$$

$$D_u = D = E, \quad D_1 = 0.5, \quad \alpha = 4, \quad \beta = 1, \quad s_{in} = 0.9$$



*intersection of the null-clines*



*phase portrait*

# The multiple species case

$$\begin{aligned}\dot{s} &= -\sum_{j=1}^n \mu_j(s, x) x_j + D(s_{in} - s) \\ \dot{x}_i &= \mu_i(s, x) x_i - d_i(x) x_i \quad i = 1 \cdots n\end{aligned}$$

Define  $\bar{\lambda}_v = \max_i \lambda_{v,i}$  and  $\underline{\lambda}_w = \min_i \lambda_{w,i}$ .

**Assumptions.**  $\lambda_{v,i} < \lambda_{w,i}$ ,  
 $d'_i(x_i) > \partial_{x_i} \mu_i(s, x_i)$ ,  
 $\bar{\lambda}_v < \min(\underline{\lambda}_w, s_{in})$ .

**Proposition** (Fekih-Salem Harmand Lobry R. Sari 12) Dynamics admits an unique positive equilibrium  $E^*$  if and only if

$$\sum_i \mu_i(\bar{\lambda}_v, g_i^{-1}(\bar{\lambda}_v)) g_i^{-1}(\bar{\lambda}_v) < D(s_{in} - \bar{\lambda}_v)$$

When  $E^*$  exists, it is locally exponentially stable.

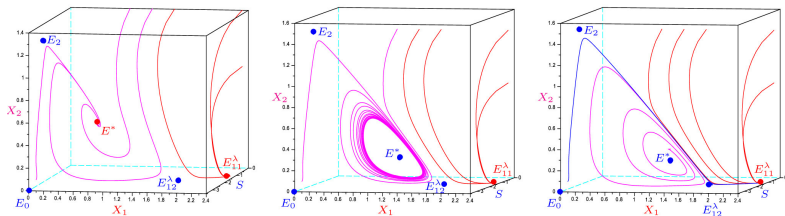
# Ongoing work

Consider a species with  $\left\{ \begin{array}{l} \mu_V(\cdot) \text{ non monotonic (Haldane)} \\ \mu_W(\cdot) \text{ monotonic (Monod)} \end{array} \right.$

- Possible behaviors:
- no positive equilibrium
  - one positive equilibrium (L.A.S)
  - bi-stability

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**Add a species with monotonic growth, that does not aggregate:**



Fekih-Salem R. Sari T Emergence of coexistence and limit cycles in the chemostat model with flocculation for a general class of functional responses

App. Math. Mod. 2016

## Concluding remarks and perspectives

- ▶ Macroscopic models of flocs with same dilution rate lead to **density-dependent growth rate** for the overall biomass.
- ▶ Macroscopic models of flocs with different dilution rate lead in addition to **density-dependent dilution rate** for the overall biomass.
- ▶ Richness of possible behaviors with possibly multiple positive equilibria, bi-stability, limit cycle... **How to infer the right attachment and detachment terms?**

# Conclusion

There are still many works and open problems with systems of (deterministic) **ordinary differential equations** for chemostat-like or resource-consumers models...

**Thank you !**