The chemostat

Some notions of phase plane analysis

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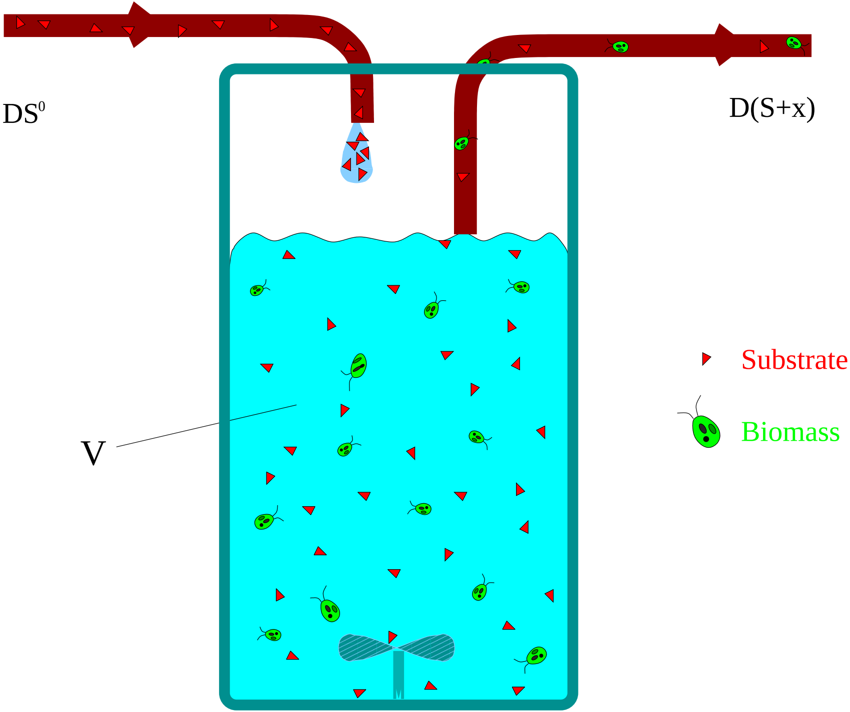
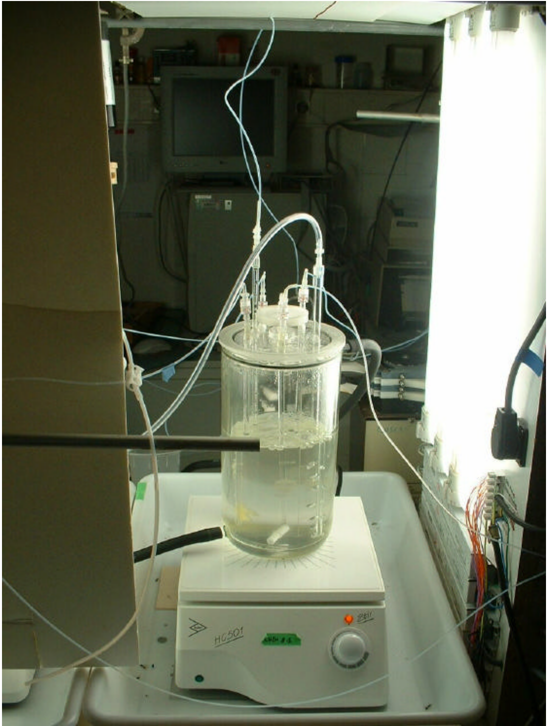
Principle

- One main chamber (vessel), in which some microorganisms (bacteria, plankton), typically unicellular, are put, together with liquid and one or several *limiting nutrients*
- Contents are stirred, so nutrient and organisms are well-mixed
- Organisms consume nutrient, grow, multiply
- Two major modes of operation:
    - *Batch* mode: let the whole thing sit.
    - *Continuous flow* mode: there is an input of fresh water and nutrient, and an outflow the comprises water, nutrient and organisms, to keep the volume constant


DS^0
$D(S+x)$
V
Substrate
Biomass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A popular artificial ecosystem

- Popularised by Jacques Monod (1910-1976, 1965 Nobel Prize in Physiology and Medicine)

- Study of the growth of micro-organisms as a function of nutrient, in a very controlled setting

- Very good reproducibility of experiments

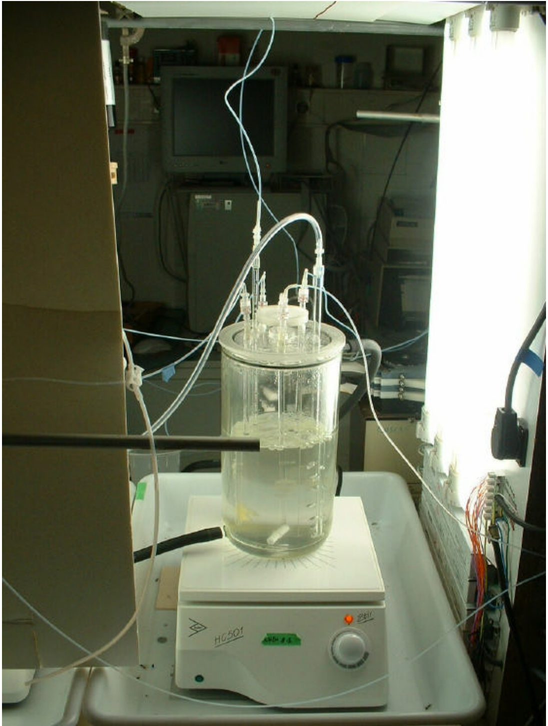
- Used in all sorts of settings: fundamental science, but also, production or degradation of products (simplest example of *bioreactor*)

One remark – Biology is *hard work*

Never forget that producing the data you may be using in your models can be highly nontrivial

- Monod carried out hundreds of experiments during his PhD to obtain the curve that bears his name (see later)
- Not easy *per se*, but add a bit more context: thesis defended in Paris in 1941, while Monod had joined the Résistance in 1940 and had already once narrowly evaded capture by the Gestapo

- Better conditions (remember the pictures earlier ..), but still, remember that chemostat?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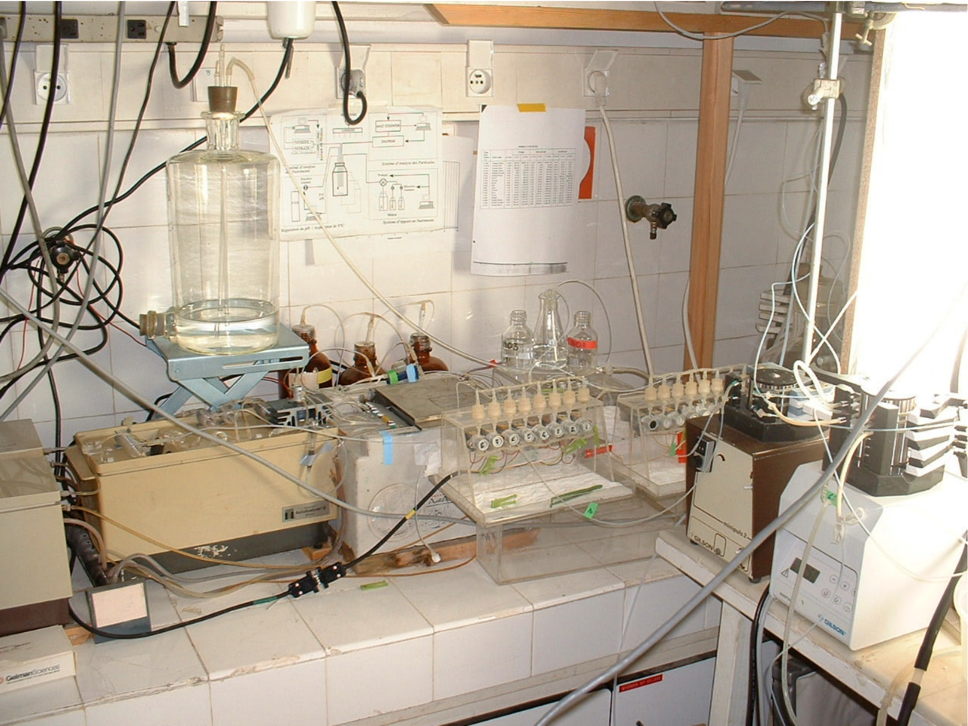
Système d'analyse des Particules
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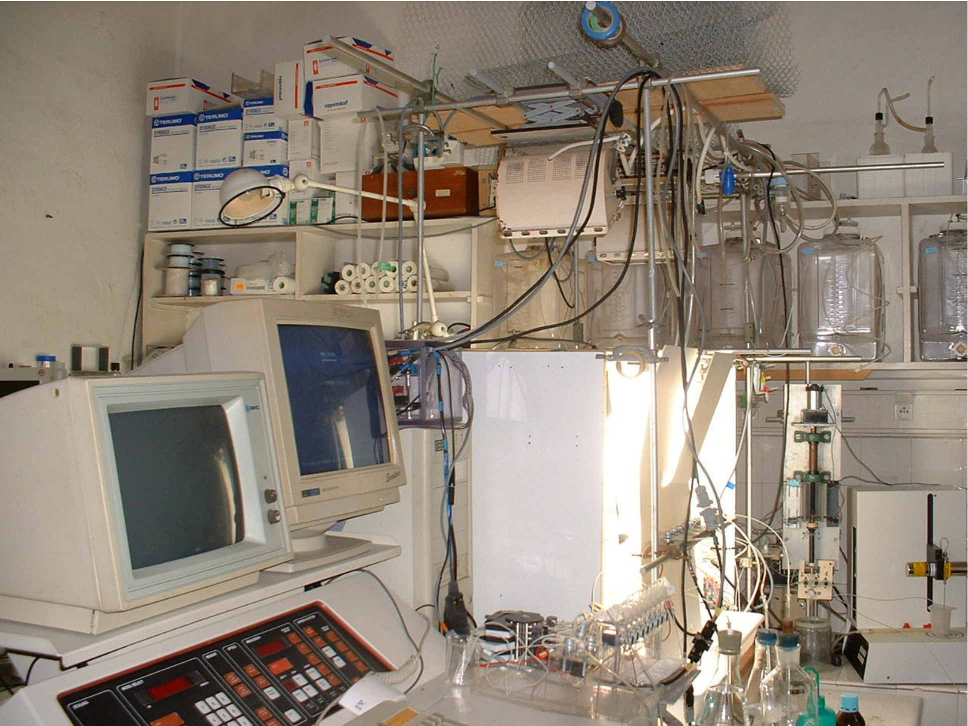
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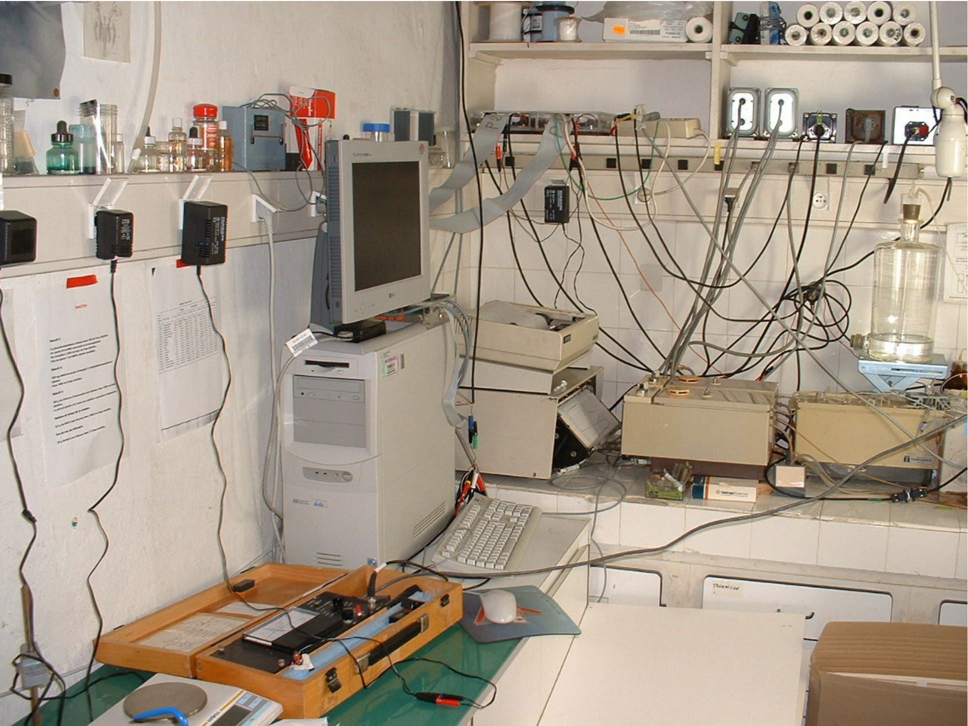


Modelling principles – Batch mode

- Organism biomass x in the vessel
- Limiting substrate has concentration S in the vessel
- No inflow or outflow, just let everything sit in the vessel
- Homogeneous mixing. Remember, there is continuous stirrer, so that's a very reasonable assumption
- Organisms uptake nutrient at the rate $\mu(S)$, a function of the concentration of nutrient around them
- Suppose for simplicity that things are scaled so that uptake=growth

Model for batch mode – No organism death

First, assume no death of organisms. Model is

$$S' = -\mu(S)x \tag{1a}$$

$$x' = \mu(S)x \tag{1b}$$

with initial conditions $S(0) \geq 0$ and $x(0) > 0$, and where $\mu(S)$ is such that

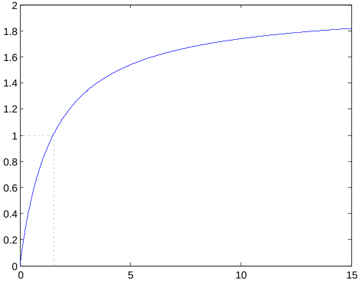
- $\mu(0) = 0$ (no substrate, no growth)
- $\mu(S) \geq 0$ for all $S \geq 0$
- $\mu(S)$ bounded for $S \geq 0$

The Monod curve

Typical form for $\mu(S)$ is the *Monod* curve (called this in the chemostat world instead of Michaelis-Menten or Holling type II)

$$\mu(S) = \mu_{max} \frac{S}{K_S + S} \tag{2}$$

- μ_{max} maximal growth rate
- K_S half-saturation constant ($\mu(K_S) = \mu_{max}/2$)



From now on, assume Monod function

Equilibria

To compute the equilibria, suppose $S' = x' = 0$, giving

$$\mu(S)x = -\mu(S)x = 0$$

This implies $\mu(S) = 0$ or $x = 0$. Note that $\mu(S) = 0 \Leftrightarrow S = 0$, so the system is at equilibrium if $S = 0$ or $x = 0$

This is a complicated situation, as it implies that there are lines of equilibria ($S = 0$ and any x, and $x = 0$ and any S), so that the equilibria are not *isolated*

Non-isolated equilibria

Michael Li has mentioned several times the *epidemic versus endemic* model distinction. One of the issues that arise with *epidemic* models also arises here in the case of batch culture

Remark

In presence of a continuum of equilibria, things (read *LAS*) go bad

In words: arbitrarily small neighborhoods of one equilibrium contain other equilibria, and therefore, LAS is not possible

Consider the IVP

$$x' = f(x), \qquad x(t_0) = x_0 \tag{3}$$

and denote $x(t, x_0)$ the solution to (3) at time $t \geq t_0$ through the initial condition (t_0, x_0)

$x^\star$ is an **equilibrium point** of (3) if $f(x^\star) = 0$

$x^\star$ is **locally asymptotically stable** (LAS) if $\exists \mathcal{S} \ni x^\star$ open in the domain of f s.t. for all $x_0 \in \mathcal{S}$, $x(t, x_0) \in \mathcal{S}$ for all $t \geq 0$ (**stability**) and furthermore, $\lim_{t\to\infty} x(t, x_0) = x^\star$ (**asymptotic convergence**)

If there is a continuum of equilibria, then $x^\star \in \mathcal{C}$, where $\mathcal{C}$ is some curve in the domain of f s.t.

$$f(y^\star) = 0 \text{ for all } y^\star \in \mathcal{C}$$

We say $x^\star$ is **not isolated**

But then any open neighbourhood of $x^\star$ contains elements of $\mathcal{C}$ and taking $x_0 \in \mathcal{C}$, $x_0 \neq x^\star$, implies that $\lim_{t\to\infty} x(t, x_0) = x_0 \neq x^\star$

$x^\star$ is *locally stable* but not *locally asymptotically stable* !

Also, think back about Michael Li's Lecture 2 and the Lyapunov Stability Theorem (here)

Theorems 1 should hold true and Theorem 2 should not

Here, some analysis is however possible (closely mimicking KMK SIR). Consider

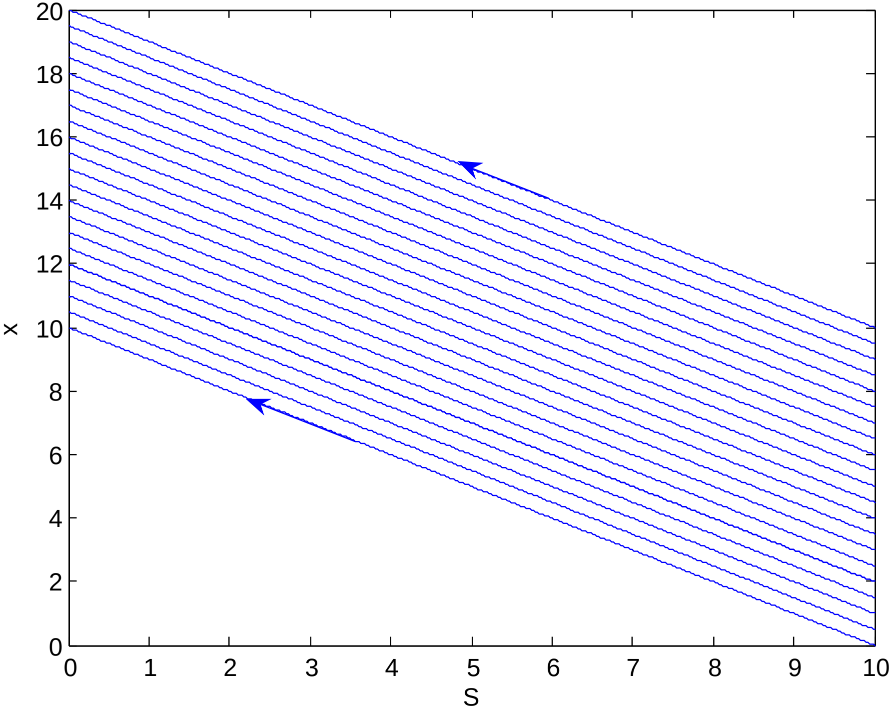
$$\frac{dx}{dS} = \frac{dx}{dt}\frac{dt}{dS} = -\frac{\mu(S)x}{\mu(S)x} = -1$$

This implies that we can find the solution

$$x(S) = C - S$$

or, supposing the initial condition is $(S(0), x(0)) = (S_0, x_0)$, that is, $x(S_0) = x_0$,

$$x(S) = S_0 + x_0 - S$$



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Model for batch mode – Organism death

Assume death of organisms at per capita rate d

Model becomes

$$S' = -\mu(S)x \tag{4a}$$

$$x' = \mu(S)x - dx \tag{4b}$$

Equilibria

$$S' = 0 \Leftrightarrow \mu(S)x = 0$$

$$x' = 0 \Leftrightarrow (\mu(S) - d)x = 0$$

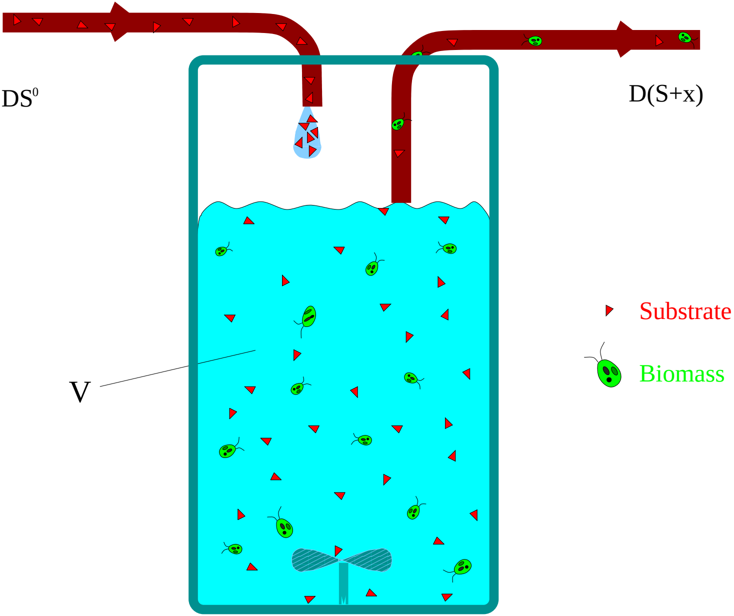
So we have $x = 0$ or $\mu(S) = d$. So $x = 0$ and any value of S, and S such that $\mu(S) = d$ and $x = 0$. One such particular value is $(S, x) = (0, 0)$

This is once again a complicated situation, since there are lines of equilibria. Intuitively, most solutions will go to $(0, 0)$. This is indeed the case (we will not show it)

Modelling principles – Continuous flow mode

- Organism biomass x in the vessel
- Limiting substrate has concentration S in the vessel
- Limiting substrate flows into vessel at rate D and concentration S^0
- There is an outflow of both nutrient and organisms (at same rate D as input)
- Homogeneous mixing
- Residence time in device is assumed small compared to lifetime (or time to division) $\Rightarrow$ no death considered

Schematic representation



Model for continuous flow mode

Model is

$$S' = D(S^0 - S) - \mu_{max} \frac{S}{K_S + S} x \tag{5a}$$

$$x' = \mu_{max} \frac{S}{K_S + S} x - Dx \tag{5b}$$

with initial conditions $S(0) \geq 0$ and $x(0) \geq 0$, and $D, S^0 > 0$

Seeking equilibria

Setting $S' = x' = 0$, we get

$$0 = D(S^0 - S) - \mu_{max} \frac{S}{K_S + S} x \tag{6a}$$

$$0 = \left(\mu_{max} \frac{S}{K_S + S} - D \right) x \tag{6b}$$

Phase plane analysis

- In $\mathbb{R}^2$, nullclines are curves and union of curves
- Nullclines are the level set 0 of the vector field. If we have

  $$x_1' = f_1(x_1, x_2)$$
  $$x_2' = f_2(x_1, x_2)$$

  then the nullcline for x_1 is the curve defined by

  $$\{(x_1, x_2) \in \mathbb{R}^2 : f_1(x_1, x_2) = 0\}$$

  that for x_2 is

  $$\{(x_1, x_2) \in \mathbb{R}^2 : f_2(x_1, x_2) = 0\}$$

- On the nullcline associated to one state variable, this state variable has zero derivative
- Equilibria lie at the intersections of nullclines for both state variables (in $\mathbb{R}^2$)

Nullcline for x

Nullcline is given by (6b) in (6), i.e.,

$$0 = \left(\mu_{max} \frac{S}{K_S + S} - D \right) x \tag{6b}$$

From (6b), nullcline for x is union of $x = 0$ and

$$\mu_{max} \frac{S}{K_S + S} - D = 0$$

Write the latter as

$$\begin{aligned} \mu_{max} \frac{S}{K_S + S} - D = 0 &\Leftrightarrow \mu_{max} S = D(K_S + S) \\ &\Leftrightarrow (\mu_{max} - D) S = D K_S \\ &\Leftrightarrow S = \frac{D K_S}{\mu_{max} - D} \end{aligned}$$

Nullcline for x

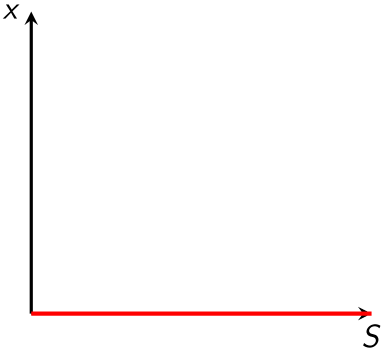
So, for x, there are two parts to the nullcline:

- the line $x = 0$
- the line $S = \dfrac{DK_S}{\mu_{max} - D}$

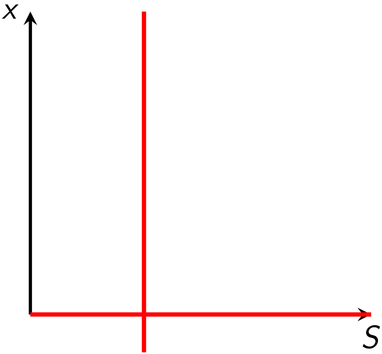
From the line $S = DK_S/(\mu_{max} - D)$, we deduce a condition:

- If $\mu_{max} - D > 0$, that is, if $\mu_{max} > D$, i.e., the maximal growth rate of the cells is larger than the rate at which they leave the chemostat due to *washout*, then the nullcline intersects the first quadrant
- If $\mu_{max} < D$, then the nullcline does not intersect the first quadrant

Summary – Nullcline for x



$\mu_{max} < D$



$\mu_{max} > D$

Nullcline for S

Nullcline is given by (6a) in (6), i.e.,

$$0 = D(S^0 - S) - \mu_{max} \frac{S}{K_S + S} x \tag{6a}$$

Rewrite (6a):

$$\begin{aligned} D(S^0 - S) - \mu_{max} \frac{S}{K_S + S} x = 0 &\Leftrightarrow \mu_{max} S x = D(S^0 - S)(K_S + S) \\ &\Leftrightarrow x = \frac{D(S^0 - S)(K_S + S)}{\mu_{max} S} \end{aligned}$$

Nullcline for S: S intercept

The equation for the nullcline for S is

$$x = \Gamma(S) \triangleq \frac{D}{\mu_{max}} \left(\frac{S^0 K}{S} - S + S^0 - K \right)$$

We look for the intercepts. First, S intercept:

$$\begin{aligned}
\Gamma(S) = 0 &\Leftrightarrow \frac{S^0 K_S}{S} - S + S^0 - K_S = 0 \\
&\Leftrightarrow \frac{S^0 K}{S} = S - S^0 + K \\
&\Leftrightarrow S^0 K_S = S^2 + (K_S - S^0) S \\
&\Leftrightarrow S^2 + (K - S^0) S - S^0 K_S = 0
\end{aligned}$$

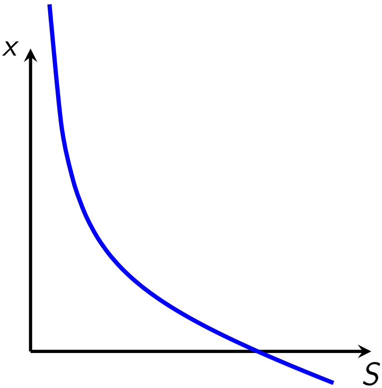
Roots of this degree 2 polynomial are $-K_S$ (< 0) and S^0

Nullcline for S: x intercept

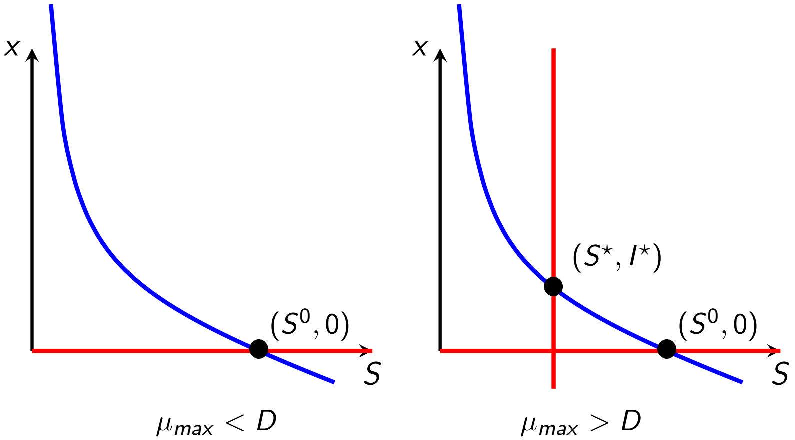
x intercept is found at $\Gamma(0)$. But this is not defined (division by $S = 0$), so consider

$$
\begin{aligned}
\lim_{S \to 0^+} \Gamma(S) &= \lim_{S \to 0^+} \frac{D}{\mu_{max}} \left(\frac{S^0 K}{S} - S + S^0 - K \right) \\
&= \frac{D}{\mu_{max}} \left(\lim_{S \to 0^+} \frac{S^0 K}{S} - S + S^0 - K \right) \\
&= \frac{D}{\mu_{max}} \left(\lim_{S \to 0^+} \left(\frac{S^0 K}{S} \right) + \lim_{S \to 0^+} \left(-S + S^0 - K \right) \right) \\
&= \frac{D}{\mu_{max}} \left(+\infty + S^0 - K \right) \\
&= +\infty
\end{aligned}
$$

The nullcline for S



Putting things together – Equilibria



So depending on $\text{sgn}(\mu_{max} - D)$, we have one or two EP

Conservation of mass

Summing the equations in (5), we get

$$(S+x)' = D\left(S^0 - (S+x)\right)$$

Denote $M = S + x$ the total organic mass in the chemostat. Then

$$M' = D(S^0 - M)$$

This is a linear equation in M. Solving it (e.g., integrating factor), we find

$$M(t) = S^0 - e^{-Dt}\left(S^0 - M(0)\right)$$

and so

$$\lim_{t\to\infty} M(t) = S^0$$

This is called the **mass conservation principle**

Implication of mass conservation

(Bio)mass is *asymptotically* constant

We can use the theory of *asymptotically autonomous* DE

In short: it is often *allowed* to use the limit of a variable rather than the variable itself, provided you know that convergence occurs

So here, e.g., study S with $x = S^0 - S$

$$\begin{aligned} S' &= D(S^0 - S) - \mu_{max}\frac{S}{K_S + S}(S^0 - S) \\ &= \left(D - \mu_{max}\frac{S}{K_S + S}\right)(S^0 - S) \end{aligned}$$

The 1-D system

$$S' = \left(D - \mu_{max}\frac{S}{K_S + S}\right)(S^0 - S) \tag{7}$$

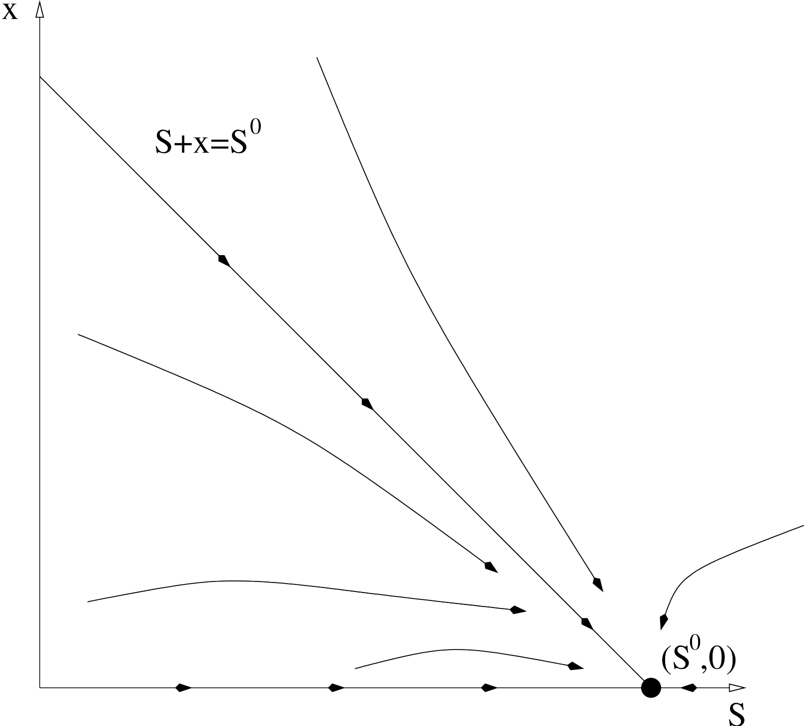
Two easy EPs: $S = S^0$ and λ, solution to

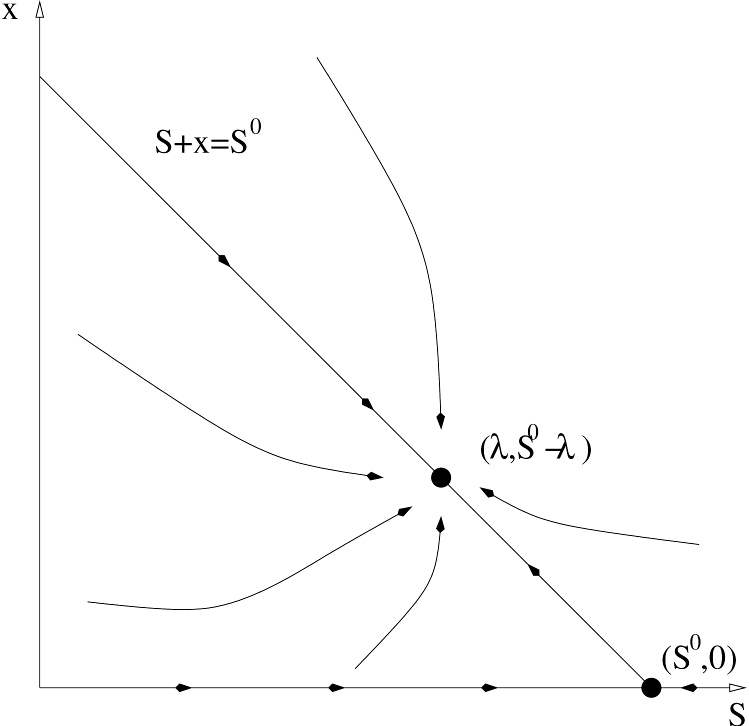
$$D - \mu_{max}\frac{S}{K_S + S} = 0$$

i.e.,

$$\lambda = \frac{DK_S}{\mu_{max} - D} \tag{8}$$

which is only biologically relevant when $\mu_{max} > D$


x
$S+x=S^0$
$(S^0,0)$
S


x
S+x=S^0
(λ,S^0−λ)
(S^0,0)
S

Uptake $\neq$ growth

In the Monod model, we assumed that with some proper renormalisation, uptake and growth can be expressed using the same function

Let us look at a more general version

J. Arino, S.S. Pilyugin & G.S.K. Wolkowicz. Considerations on yield, nutrient uptake, cellular growth, and competition in chemostat models. Canadian Applied Mathematics Quarterly **11**(2), 2003; pdf here

The model

$$S' = D(S^0 - S) - u(S)x \tag{9a}$$
$$x' = (g(S) - D_1)x \tag{9b}$$

Differences from before:

- D_1 in (9b) is $\neq D$ in (9a). D_1 can be sum of D and specific death rate
- uptake $u(S)$ in (9a) is $\neq$ growth $g(S)$ in (9b)
- u, g continuously differentiable, $u(0) = g(0) = 0$, $u(S), g(S) > 0$ for $S > 0$, u, g increasing or unimodal

Local analysis

Washout EP $E_0 \equiv (S^0, 0)$ always exists

Lemma 1

$E^\star \equiv (S^\star, x^\star) = \left(S^\star, \frac{D(S^0 - S^\star)}{u(S^\star)}\right)$, where $S^\star$ is any solution of

$$g(S) = D_1 \tag{10}$$

is a feasible positive equilibrium $\iff S^\star < S^0$

Since u, g increasing or unimodal, define $\lambda, \mu \in \bar{\mathbb{R}}$ with $\lambda < \mu$, with $\mu = \infty$ if (10)has only one solution and $\lambda = \mu = \infty$ if (10) has no solution

When λ or $\mu < \infty$, denote $E_\lambda^\star$ or $E_\mu^\star$, respectively

Jacobian at arbitrary (S, x) is

$$\begin{pmatrix} -D - u'(S)x & -u(S) \\ g'(S)x & g(S) - D_1 \end{pmatrix} \tag{11}$$

Thus, at $E_0 = (S^0, 0)$,

$$\begin{pmatrix} -D & -u(S^0) \\ 0 & g(S^0) - D_1 \end{pmatrix}$$

Lemma 2

The washout equilibrium E_0 is LAS if $g(S^0) - D_1 < 0$

Feasible positive EP $E^\star$

Lemma 3

$E^\star \gg \mathbf{0}$ LAS if, simultaneously,

$$g'(S^\star) > 0 \quad \textit{and} \quad u'(S^\star) > -\frac{u(S^\star)}{S^0 - S^\star} \tag{12}$$

Lemma 4

The linearisation of (9) *about $E^\star \gg \mathbf{0}$ has complex eigenvalues $\iff$*

$$(D + u'(S^\star)x^\star)^2 < 4u(S^\star)g'(S^\star)x^\star$$

($\implies$ if $g'(S^\star) < 0$ there are no oscillations in a neighbourhood of $E^\star$)

Lemma 5

The linearisation of (9) *about* $E^\star \gg \mathbf{0}$ *has purely imaginary eigenvalues* $\iff$

$$g'(S^\star) > 0 \quad \textit{and} \quad u'(S^\star) = -\frac{u(S^\star)}{S^0 - S^\star} \tag{13}$$

($\implies$ *Hopf bifurcation, if any, can only occur at* $E^\star_\lambda$ *since* g *must be increasing at* $S^\star$*)*

You see where we're going..?

Theorem 6

Assume $\exists \alpha = \alpha_C$ *s.t.* $x^\star_{\alpha_C} u'(\lambda_{\alpha_C}) + D = 0$. *System* (9) *undergoes a Hopf bifurcation at* $E^\star_{\lambda_{\alpha_C}}$ *if* $g'(\lambda_{\alpha_C}) > 0$ *and*

$$\frac{d}{d\alpha} \left(-D x^\star(\alpha) u'(S^\star(\alpha))\right)\Big|_{\alpha=\alpha_C} \neq 0 \tag{14}$$

This bifurcation is supercritical if $\mathcal{C}_\mathcal{H} < 0$ *and subcritical if* $\mathcal{C}_\mathcal{H} > 0$, *where*

$$\begin{aligned}\mathcal{C}_\mathcal{H} \equiv & -u(\lambda_{\alpha_C}) g'(\lambda_{\alpha_C}) u'''(\lambda_{\alpha_C}) \\ & + u''(\lambda_{\alpha_C})(u'(\lambda_{\alpha_C}) g'(\lambda_{\alpha_C}) + u(\lambda_{\alpha_C}) g''(\lambda_{\alpha_C}))\end{aligned}$$

Lemma 7

Both the nonnegative cone and the interior of the nonnegative cone are positively invariant under the flow of (9)

Lemma 8

Solutions of (9) *are defined and remain bounded for all* $t \geq 0$

Lemma 9

For any $\varepsilon > 0$, $\exists T_\varepsilon \geq 0$ *s.t.* $S(t) \leq S^0 + \varepsilon$ *for all* $t \geq T_\varepsilon$. *If, in addition,* $\lambda < S^0$, $g(S) > D_1$ *for* $S \in (\lambda, S^0]$ *and* $x(0) > 0$, *then* $\exists T$ *s.t.* $S(t) < S^0$ *for all* $t > T$

Theorem 10

If $S^0 \leq \lambda$, *then the washout equilibrium* E_0 *of* (9) *is GAS*

Theorem 11

If $\lambda < S^0$, $g'(\lambda) > 0$, $g(S^0) > D_1$, $u'(\lambda) > -u(\lambda)/(S^0 - \lambda)$ *and* $1 - u(S)(S^0 - \lambda)/((u(\lambda)(S^0 - \lambda)))$ *has exactly one sign change for* $S \in (0, S^0)$, *then* $E^\star_\lambda$ *is GAS w.r.t. the interior of the positive cone*

Elements of the proof of Theorem 11

Won't show much, just the Lyapunov function used… We define

$$V(S,x) = \int_{\lambda}^{S} \frac{(g(\xi)-D_1)(S^0-\lambda)}{u(\lambda)(S^0-\xi)}\, d\xi + x - x_\lambda^\star \ln\left(\frac{x}{x_\lambda^\star}\right) \tag{15}$$

Let

$$\Psi(S) = \frac{u(S)}{S^0-S} \tag{16}$$

Then

$$V' = x(g(S)-D_1)\left(1-\frac{\Psi(S)}{\Psi(\lambda)}\right)$$

with $V'=0$ iff $S=\lambda$ or $x=0$ or $S=\mu=S^0$. With some work, get a Lyapunov function (of the type requiring LaSalle's extension)

$$S' = D(S^0 - S) - \sum_{i=1}^{n} u_i(S) x_i \tag{17a}$$

$$x_i' = (g_i(S) - D_i) x_i, \quad i = 1, \ldots, n \tag{17b}$$

Define per-species break-even concentrations λ_i, μ_i as before

We obtain a few results related to coexistence (won't detail here)

A simple case – 2 species with yield in the uptake

Rescale x, y, S and time t so that $D = S^0 = 1$. Model becomes

$$S' = 1 - S - \frac{p_1(S)}{\gamma_1(S)}x - \frac{p_2(S)}{\gamma_2}y \tag{18a}$$

$$x' = (p_1(S) - 1)x \tag{18b}$$

$$y' = (p_2(S) - 1)y \tag{18c}$$

where p_i are Monod functions

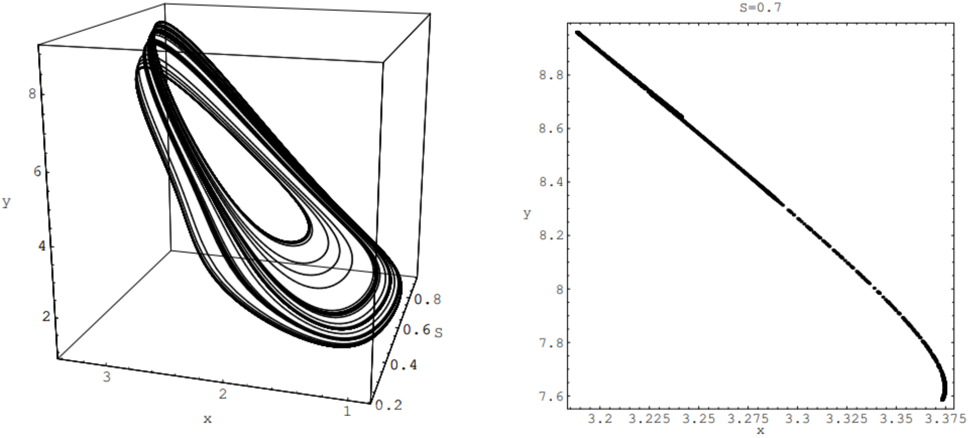
$$p_i(S) = m_i \frac{S}{a_i + S}, \quad i = 1, 2$$

and

$$\gamma_1(S) = b_1 + c_1 S^n$$

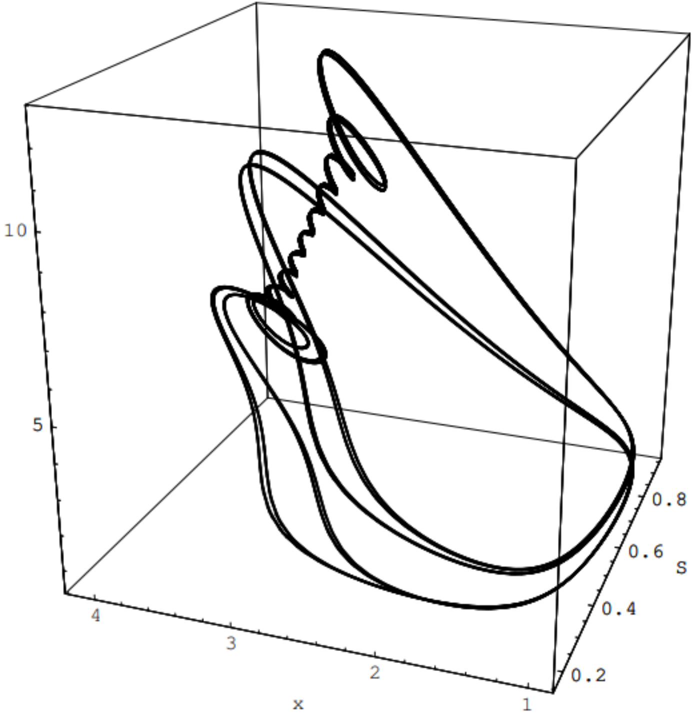
$b_1, c_1 > 0$ and $n \in \mathbb{N}_+ \setminus \{0\}$

We get some pretty complicated dynamics



(a) (b)

FIGURE 4: (a) Chaotic attractor corresponding to $m_2 = 10.0$, $c_1 = 45.0$. (b) The cross-section $S = \lambda_1$ of the attractor.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0.6
0.8
S

A simple case – 3 species with yield in growth

Consider (17) with 3 species and

$$g_i(S) = Y_i(S)u_i(S), \quad i = 1, 2, 3$$

allowing the efficacy of the uptake-to-growth process to depend on substrate concentration

Specifically, take $Y_2(S) \equiv Y_2$ and $Y_3(S) \equiv Y_3$ to be constants and only let $Y_1(S)$ vary

Interesting dynamics again

Without variable yield (i.e., $g_i(S) = k_i g_i(S)$), *competitive exclusion* holds

Here:

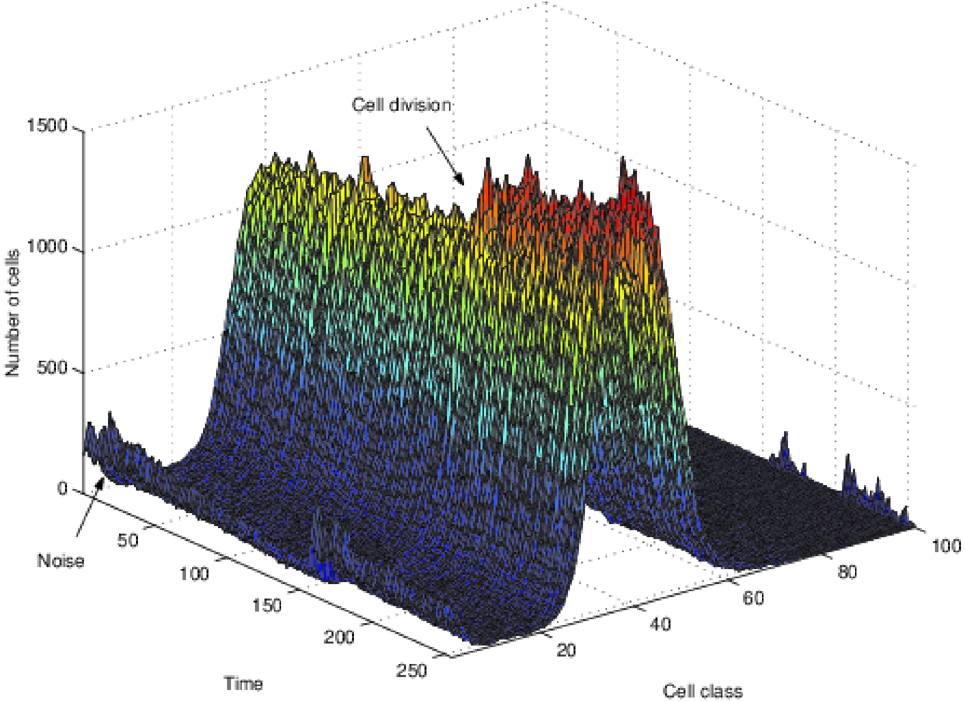
- Under some conditions, *coexistence* of the three species happens
- Under other conditions, removing one species leads to competitive exclusion among the remaining two, showing *competitor mediated coexistence*

Importance of size-structure

Models this far assume x is the total concentration/biomass of the organism

Typically, data is acquired using a particle counter, which has information about the distribution of cell sizes

J. Arino, J.-L. Gouzé, A. Sciandra. A discrete, size-structured model of phytoplankton growth in the chemostat – Introduction of inhomogeneous cell division size. Journal of Mathematical Biology **45** (2002); pdf file


Cell division
Number of cells
1500
1000
500
0
Noise
50
100
150
200
250
Time
20
40
60
80
100
Cell class

Biological hypotheses

Original model (Gage *et al* revisited by H.L. Smith)

- (**H1**) In a constant environment (i.e., if the concentration of limiting nutrient is constant and high), the growth of a cell is exponential
- (**H2**) Cells are born with a biomass b, they grow, then divide when they reach a biomass $2b$
- (**H3**) When a cell divides, it divides into two daughter cells, whose individual biomass is exactly one half of the biomass of the original cell

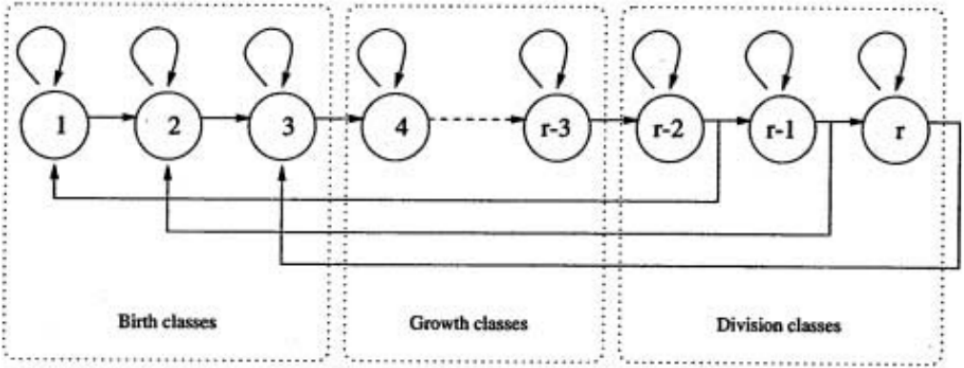
We replace (**H2**) with

- (**H2'**) The division biomass $2b$ (accordingly, the birth biomass b) is not a constant. There exists a distribution of division biomass, describing the individual cellular division biomass

Biomass is in $[b_{min}, b_{max}]$, r biomass classes, $x_t = (x_1(t), \dots, x_r(t))^T$ the total biomass in each biomass class at time t

$U_t = \mathbb{1}^T x_t$ the total biomass in the system at time t, where $\mathbb{1}^T = (1, \dots, 1)$

$r = r_b + r_g + r_d$, with $r_b = r_d$, r_b birth classes, r_g growth classes and r_d division classes


1
2
3
4
r-3
r-2
r-1
r
Birth classes
Growth classes
Division classes

Describing exponential growth

Use a constant M representing the size increment for a cell moving from class i to class $i+1$

To fulfill (**H1**), M must account for exponential growth of cells when nutrient is abundant

Suppose cell growing exponentially from biomass b to biomass $2b$. To track along, say, n classes, then using $M = 2^{1/n}$ works: if $M^{i-1}b$ is biomass of cell in class i, then a cell progressing from one class to the next each time step grows exponentially

To allow more than doubling, we need $M > 2^{1/r}$ so that $M^r b_{min} > 2b_{min}$. But we also want each division class to correspond to a unique birth class

Let d_r be the (division class relative) index of a division class (e.g., 3rd division class). For the correspondance to hold, the division of a cell in class d_r must be two cells in birth class $k = d_r$ (relative to birth classes this time)

Thus there must hold that, for all $d_r = 1, \dots, r_d$

$$MM^{r_b+r_g+d_r-1} b_{min} = 2M^{d_r-1} b_{min}$$

(LHS: we make the hypothesis that division follows growth)

Must be true for $d_r = 1$, so

$$M = 2^{1/(r_b+r_g+1)}$$

and the mean biomass of cells in class i is $M^{i-1} b_{min}$

Describing nutrient limited growth

So far, we have assumed unlimited growth ($S = +\infty$), but the substrate is limiting

The model is discrete $\Rightarrow$ need to determine proportion of cells in one size class which that move to the next size class, given current substrate concentration

Lengthy mechanistic derivation, but for short: proportion of cells in class i moving to class $i+1$ is

$$P_t = \frac{f(S_t)}{M-1} \tag{19}$$

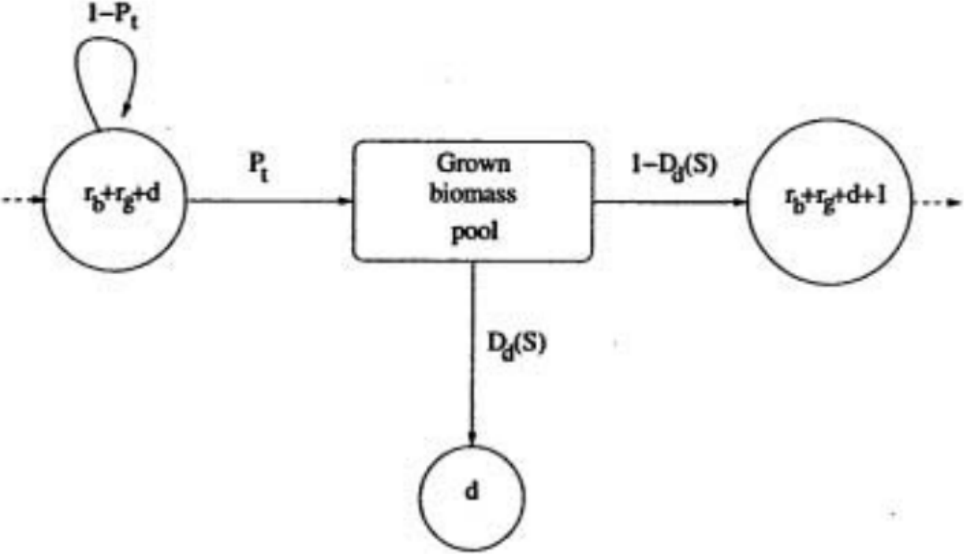
where $f(S)$ uptake and growth function, s.t., $f(0) = 0$, $f'(S) > 0$ and $f''(S) < 0$. (Define $m = \lim_{S\to\infty} f(S)$, maximal growth rate per iteration period)

Describing cell division

Model of Gage *et al.* assumes $r_b = r_d = 1$, we want division (and consequently, birth) to occur for a range of sizes

Let $D_i(S)$ be proportion of cells in division class $i = 1, \ldots, r_d$ which undergo mitosis

For $i = 1, \ldots, r_d - 1$ and all $S \in \mathbb{R}_+$, assume $0 \leq D_i(S) \leq 1$, where both inequalities have to be strict for some S; further assume that all cells in the last division class divide, i.e., $D_{r_d}(S) \equiv 1$


1−P_t
r_b+r_g+d
P_t
Grown biomass pool
1−D_d(S)
r_b+r_g+d+1
D_d(S)
d

The model

Let E be the fraction of cells and substrate washed out at each iteration (equiv. D in the continous time models), then the model takes the form

$$x_{t+1} = (1-E)A(S_t)x_t \tag{20a}$$

$$S_{t+1} = (1-E)[S_t - f(S_t)U_t] + ES^0 \tag{20b}$$

where $x_t \in \mathbb{R}_+^r, S_t \in \mathbb{R}_+$ and $A(S_t)$ is an $r \times r$ transition matrix (next page), in which $P_t = f(S_t)(M-1)^{-1}$ and $D_i = D_i(S_t)$

Note that there are constraints to satisfy on the time step to ensure $P_t \in [0,1]$..

$$\left[\begin{array}{cccc|ccc|ccccc}
1-P_t & 0 & & & & & & MP_tD_1 & & & & \\
MP_t & 1-P_t & & & & & & & MP_tD_2 & & & \\
0 & \ddots & \ddots & & & & & & & \ddots & & \\
 & & & & & & & & & & MP_tD_{r_d-1} & \\
 & & & 1-P_t & & & & & & & & MP_t \\
\hline
 & & & MP_t & 1-P_t & & & & & & & \\
 & & & & \ddots & \ddots & & & & & & \\
 & & & & & MP_t & 1-P_t & & & & & \\
\hline
 & & & & & & MP_t & 1-P_t & & & & \\
 & & & & & & & MP_t(1-D_1) & 1-P_t & & & \\
 & & & & & & & & \ddots & \ddots & & \\
 & & & & & & & & & & 1-P_t & \\
 & & & & & & & & & & MP_t(1-D_{r_d-1}) & 1-P_t
\end{array}\right]$$

Mass conservation principle

We have

$$\mathbb{1}^T A(S) = (1 + (M-1)P_t)\mathbb{1}^T = (1 + f(S_t))\mathbb{1}^T$$

(i.e., $1 + f(S_t)$ eigenvalue of $A(S_t)$ associated to left e-vector $\mathbb{1}^T$)

$\Longrightarrow$

$$U_{t+1} = \mathbb{1}^T x_{t+1} = \mathbb{1}^T A(S_t) x_t = (1-E)(1+f(S_t))U_t$$

$\Longrightarrow$

$$U_{t+1} + S_{t+1} = (1-E)(U_t + S_t) + ES^0$$

So (asymptotic) mass conservation holds

Consequences of mass conservation

- Mass conservation ⇒ total “mass” contained in the chemostat tends to S^0
- ⇒ dynamics studied on the invariant set $U + S = S^0$, where the system reduces to a 1-D system
- On $U + S = S^0$, Smith showed that under certain conditions, there exists a GS equilibrium; this works here as well
- ⇒ global dynamics of the 2-D system in substrate and total biomass can be deduced: it admits, under the same conditions as 1-D system, a GS non trivial equilibrium
- Finally, using the Fundamental Theorem of Demography, the distribution of biomass in each one of the size classes is deduced

A few of the results

From the mass conservation relation

$$U_{t+1} + S_{t+1} = (1 - E)(U_t + S_t) + ES^0$$

it follows that

$$U_{t+1} + S_{t+1} = S^0 - (S^0 - U_0 - S_0)(1 - E)^t, \qquad t \geq 1$$

Define Γ, positive bounded set, as

$$\Gamma = \left\{ (x, S) \in \mathbb{R}_+^{r+1} : \mathbb{1}^T x + S \leq W \right\}$$

where W is a constant derived from constraints time step and system state

Proposition 12

If $(x_0, S_0) \in \Gamma$*, then* $(x_t, S_t) \in \Gamma$ *for* $t \geq 1$*,* $S_t - U_t f(S_t) > 0$ *for* $t \geq 1$ *and*

$$S_t + U_t \to S^0, \qquad t \to \infty$$

So now consider system restricted to positively invariant set

$$\{(U, S) \in \mathbb{R}_+^2 : U + S = S^0\}$$

On this set, (20) reduces to

$$U_{t+1} = (1 - E)(1 + f(S^0 - U_t))U_t \tag{21}$$

Proposition 13

If $(1-E)(1+f(S^0)) \le 1$, *then* $\lim_{t\to\infty} U_t = 0$ *for all solutions of* (21) *with* $U_0 \in [0, S^0]$
If $(1-E)(1+f(S^0)) > 1$, *then* $\lim_{t\to\infty} U_t = \tilde{U}$ *for all solutions of* (21) *with* $U_0 \in [0, S^0]$

The limiting value $\tilde{U}$ is the positive fixed point of

$$F(U) = (1-E)(1+f(S^0-U))U$$

Define $\lambda = f^{-1}((1-E)^{-1}-1)$. Recall that $m = f(\infty)$ is the maximal growth rate, then $\lambda < \infty$ if $(1-E)^{-1}-1 < m$ and $\lambda = \infty$ otherwise. (Classic chemostat behaviour: dilution rate E too high ⇒ washout). If $\lambda < S^0$, then $\tilde{U} = S^0 - \lambda$

Moving to 2-D

Let now

$$\Omega = \{(U,S) \in \mathbb{R}_+^2 : U + S < W\}$$

and consider

$$U_{t+1} = (1-E)(1+f(S^0 - U_t))U_t \tag{22a}$$

$$S_{t+1} = (1-E)(S_t - f(S_t)U_t) + ES^0 \tag{22b}$$

Theorem 14

If $(1-E)(1+f(S^0)) < 1$, *then for all solutions of* (22a) *s.t.* $(U_0, S_0) \in \Omega$

$$(U_t, S_t) \to (0, S^0), \quad t \to \infty$$

If $(1-E)(1+f(S^0)) > 1$, *then there exists a nonzero steady state and for all solutions of* (22a) *s.t.* $(U_0, S_0) \in \Omega$

$$(U_t, S_t) \to (S^0 - \lambda, \lambda), \quad t \to \infty$$

Moving to $(r+1)-D$

To do this, we need the Fundamental Theorem of Demography (recall Jacek Banasiak's course yesterday). This version is by Golubitsky, Keener and Rotschild (JTB 1975)

Theorem 15

Suppose that T_k is a sequence of nonnegative primitive matrices, and that $T_k \to T$ as $k \to \infty$, where T is also nonnegative and primitive. If e is the Perron-Frobenius eigenvector of T satisfying $\mathbb{1}^T e = 1$ and $\xi_{k+1} = T_k \xi_k$ is a sequence starting with $\xi_0 \geq 0$ and $\xi_0 \neq 0$, then

$$\frac{\xi_k}{\mathbb{1}^T \xi_k} \to e, \quad k \to \infty$$

Theorem 16

Let e *be the Perron-Frobenius eigenvector of* $(1-E)A(\lambda)$ *satisfying* $\mathbb{1}^T e = 1$*. If* $(1-E)(1+f(S^0)) > 1$, $x_0 \neq 0$ *and* $\lambda \in S_{int}$*, then* (20) *admits one GAS nontrivial equilibrium* $(\tilde{x}, \tilde{S})$*, where*

$$\frac{\tilde{x}}{\tilde{U}} = e$$

S_{int} is a (potentially disconnected) set defined to ensure that the requirement that $0 \leq D_i(S) \leq 1$ be strict for at least one S (on both sides): $S_{int} \subset \mathbb{R}_+$, $S_{int} \neq \{0\}$, defined by

$$S_{int} = \{\bar{s} \in \mathbb{R}_+ : \forall i < r_d, D_i(\bar{s}) \in (0,1)\}$$

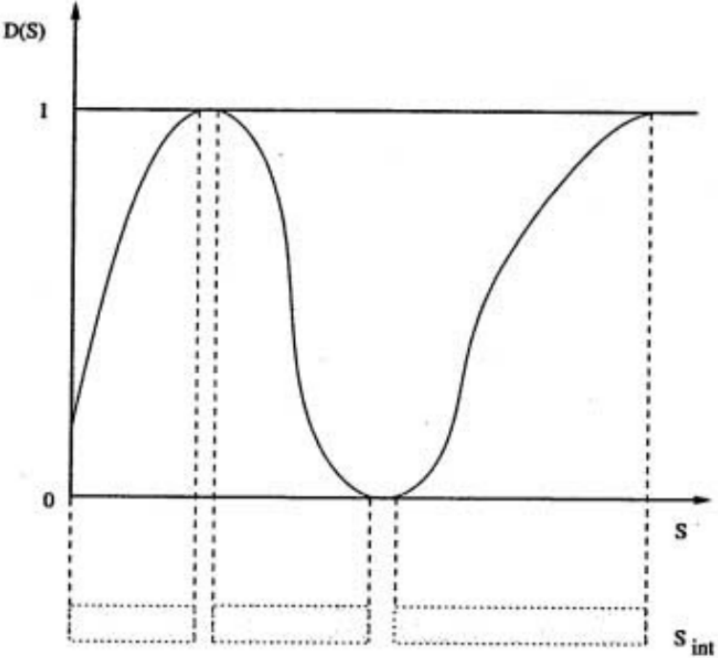


Fig. 1.3. A possible S_{int} set (for a given division class i)

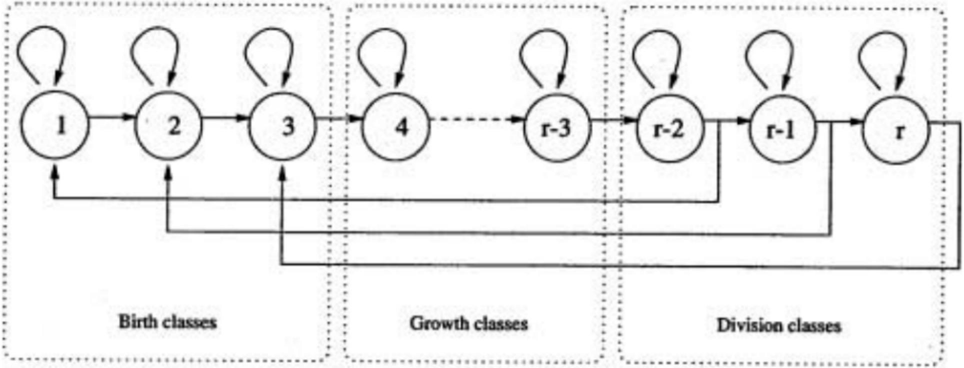
Why do we need S_{int}?

$$\left[\begin{array}{cccc|cccc|ccccc}
1-P_t & 0 & & & & & & & MP_tD_1 & & & & \\
MP_t & 1-P_t & & & & & & & & MP_tD_2 & & & \\
0 & \ddots & \ddots & & & & & & & & \ddots & & \\
 & & & & & & & & & & & MP_tD_{r_d-1} & \\
 & & & 1-P_t & & & & & & & & & MP_t \\
\hline
 & & & MP_t & 1-P_t & & & & & & & & \\
 & & & & & \ddots & \ddots & & & & & & \\
 & & & & & & MP_t & 1-P_t & & & & & \\
\hline
 & & & & & & & MP_t & 1-P_t & & & & \\
 & & & & & & & & MP_t(1-D_1) & 1-P_t & & & \\
 & & & & & & & & & \ddots & \ddots & & \\
 & & & & & & & & & & & 1-P_t & \\
 & & & & & & & & & & & MP_t(1-D_{r_d-1}) & 1-P_t
\end{array}\right]$$

Why we need S_{int}

A sufficient condition for a matrix to be primitive is for it to be irreducible (i.e., with strongly connected associated digraph) with at least one positive diagonal entry

- Positive diagonal ✓
- Irreducible ?


1
2
3
4
r-3
r-2
r-1
r
Birth classes
Growth classes
Division classes

Why we need S_{int}

A sufficient condition for a matrix to be primitive is for it to be irreducible (i.e., with strongly connected associated digraph) with at least one positive diagonal entry

- Positive diagonal ✓
- Irreducible ✓ if $\lambda \in S_{int}$

The Perron-Frobenius eigenvector

The PF eigenvalue is $(1-E)(1-P+MP) = (1-E)(1+f(\tilde{S}))$ and the associated PF eigenvector is

$$e = \frac{1}{r} \begin{pmatrix} D_1(\tilde{S}) \\ \vdots \\ 1 - \prod_{k=1}^{r_b-1}(1-D_k(\tilde{S})) \\ 1 \\ \mathbb{1}_{r_g}^T \\ 1 \\ 1 - D_1(\tilde{S}) \\ \vdots \\ \prod_{k=1}^{r_d-1}(1-D_k(\tilde{S})) \end{pmatrix}$$

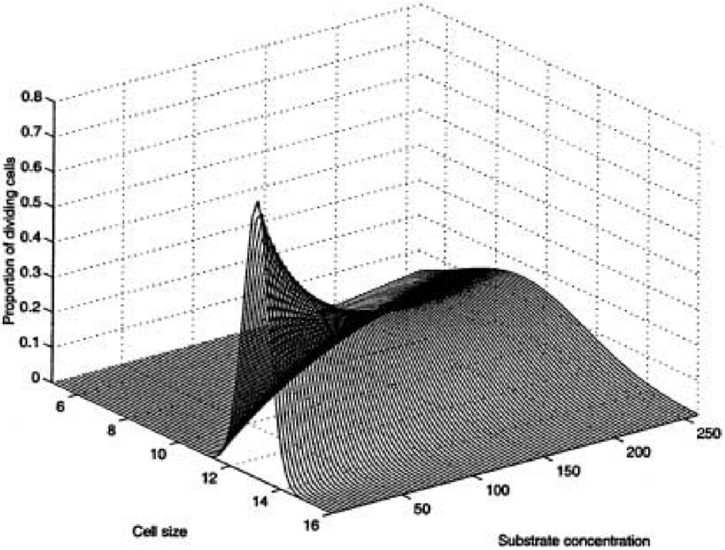


Fig. 3.1. An example of division proportions functions. Cell size is here expressed in diameter

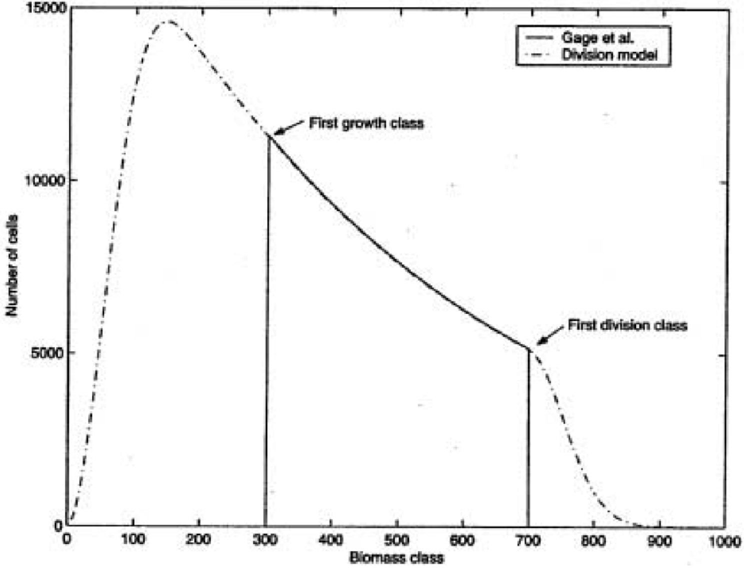


Fig. 3.2. Comparison of the equilibrium distributions (converted to numbers), as given by the two models. This example uses $r_b = r_d = 300$ and $r_g = 400$. The vertical lines show the passage from one type of class to another

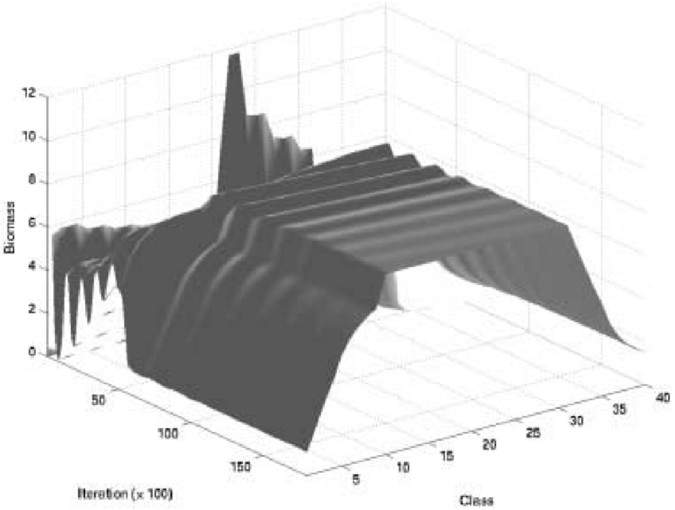


Fig. 3.3. Transient behaviour of the model following an initial condition of Dirac type in class 20 (of a total of 40). The parameters are $T = 0.001$, $r_b = r_d = 10$ and $r_g = 20$. The figure shows a sampling (every 100 iterations) out of a total 18000 iterations (corresponding to 18 days)