The chemostat
Some notions of phase plane analysis

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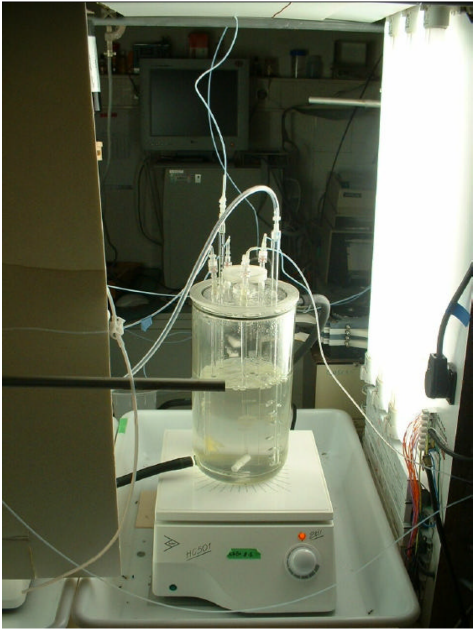
Batch mode

Continous flow mode

Stability

Conservation of mass

A chemostat



Principle

- One main chamber (vessel), in which some microorganisms (bacteria, plankton), typically unicellular, are put, together with liquid and nutrient.
- 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.

A very popular tool

- 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, for production of products.

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Modelling principles – Batch mode

- Organisms (concentration denoted x) are in the main vessel.
- Limiting substrate (concentration in the vessel denoted S).
- Homogeneous mixing.
- Organisms uptake nutrient at the rate $\mu(S)$, a function of the concentration of nutrient around them.

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

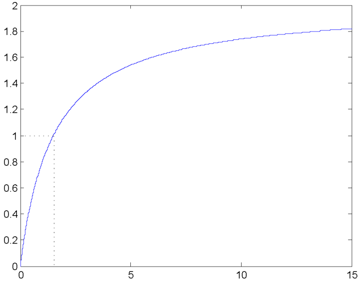
- $\mu(0) = 0$ (no substrate, no growth)
- $\mu(S) \geq 0$ for all $S \geq 0$
- $\mu(S)$ bounded for $S \geq 0$

The Michaelis-Menten curve

Typical form for $\mu(S)$ is the *Monod* curve,

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

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



From now on, assume Michaelis-Menten 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* (arbitrarily small neighborhoods of one equilibrium contain other equilibria), and therefore, studying the linearization is not possible.

Here, some analysis is however possible. Consider

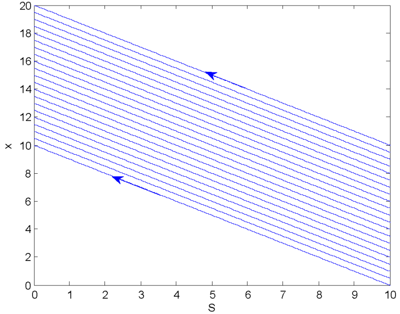
$$\frac{dx}{dS} = \frac{dx}{dt}\frac{dt}{dS} = -\frac{\mu(S)x}{\mu(S)x} = -1$$

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, $x(S_0) = x_0$,

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



Model for batch mode – Organism death

Assume death of organisms at per capita rate d. Model is

$$S' = -\mu(S)x \tag{3a}$$

$$x' = \mu(S)x - dx \tag{3b}$$

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).

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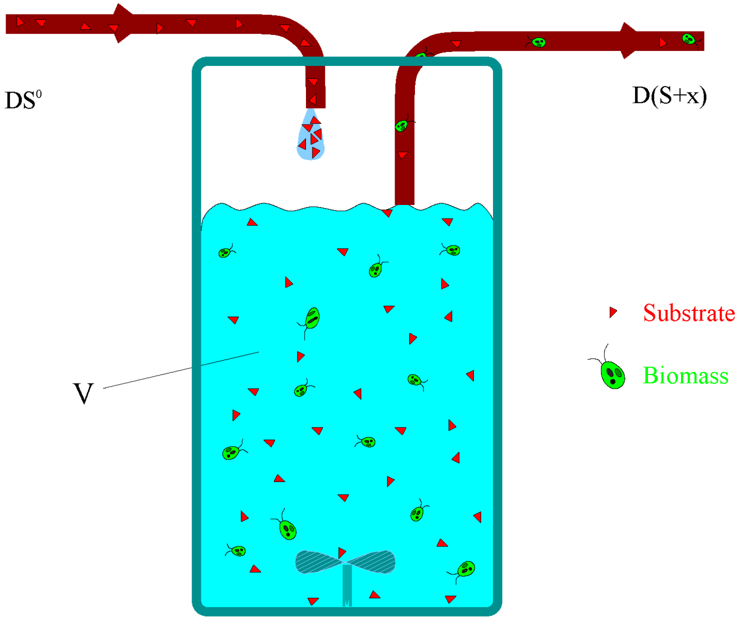
Modelling principles – Continuous flow mode

- Organisms (concentration denoted x) are in the main vessel
- Limiting substrate (concentration in the vessel denoted S) is input (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

$$S' = D(S^0 - S) - \mu(S)x \tag{4a}$$
$$x' = \mu(S)x - Dx \tag{4b}$$

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

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

Phase plane analysis

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

$$
\begin{aligned}
x_1' &= f_1(x_1, x_2) \\
x_2' &= f_2(x_1, x_2)
\end{aligned}
$$

  then the nullclines for x_1 are the curves defined by

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

  those for x_2 are

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

- 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 $\mathbb{R}^2$)

Nullclines for x

Nullclines are given by

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

$$0 = \left(\mu_{max} \frac{S}{K_S + S} - D \right) x \tag{5b}$$

From (5b), nullclines for x are $x = 0$ 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 nullclines:

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

For 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

Nullclines for S

Nullclines are given by

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

$$0 = \left(\mu_{max} \frac{S}{K_S + S} - D \right) x \tag{5b}$$

Rewrite (5a),

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

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

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

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

Maple for help

Maple has a plot function, `implicitplot` (part of the `plots` library), that is very useful for nullclines (d is used instead of D, because maple does not allow to change D without using `unprotect`)

```
> with(plots):
> d := 0.4; S0 := 1; mu := 0.7; K := 2;
> implicitplot(d*(S0-S)-mu*S/(K+S)*x=0,S=0..10,x=0..10)
```

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Stability of the equilibria

In $\mathbb{R}^2$, global stability can be proved more often than in $\mathbb{R}^{\geq 3}$. This is summarized in the well known

Theorem (Poincaré-Bendixson)

If for $t \geq t_0$, a trajectory is bounded and does not approach any equilibrium point, then it is either a closed periodic orbit or approaches a closed periodic orbit as

In other words: a system in $\mathbb{R}^2$ with bounded solutions either approaches an equilibrium point (a constant solution) or approaches a periodic orbit (a periodic solution)

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Summing the equations in (4), 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

Not as strong as what we had in the SIS epidemic model, where the total number of individuals was constant. Here, the mass is *asymptotically* constant

But we can still use it, using the theory of *asymptotically autonomous* differential equations. Too complicated for here, just remember that often, it is *allowed* to use the limit of a variable rather than the variable itself, provided you know that the convergence occurs