

## MATH 3610 – 05

# The chemostat – Some notions of phase plane analysis

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The University of Manitoba campuses are located on original lands of Anishinaabeg, Ininew, Anisininew, Dakota and Dene peoples, and on the National Homeland of the Red River Métis.

We respect the Treaties that were made on these territories, we acknowledge the harms and mistakes of the past, and we dedicate ourselves to move forward in partnership with Indigenous communities in a spirit of Reconciliation and collaboration.

# Outline

The chemostat

Batch mode

Continuous flow mode

Stability

Conservation of mass

## The chemostat

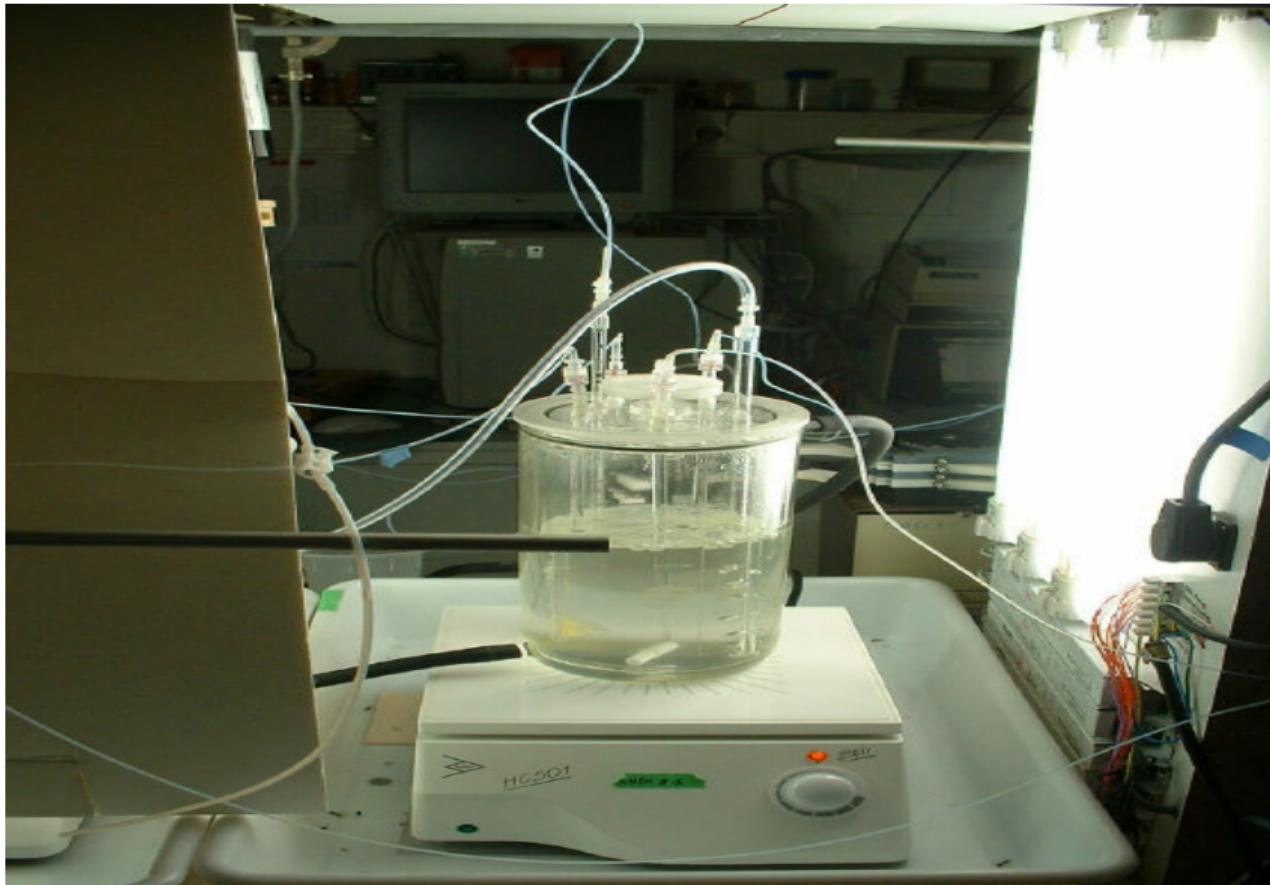
Batch mode

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## 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

$$S' = -\mu(S)x \quad (1a)$$

$$x' = \mu(S)x \quad (1b)$$

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

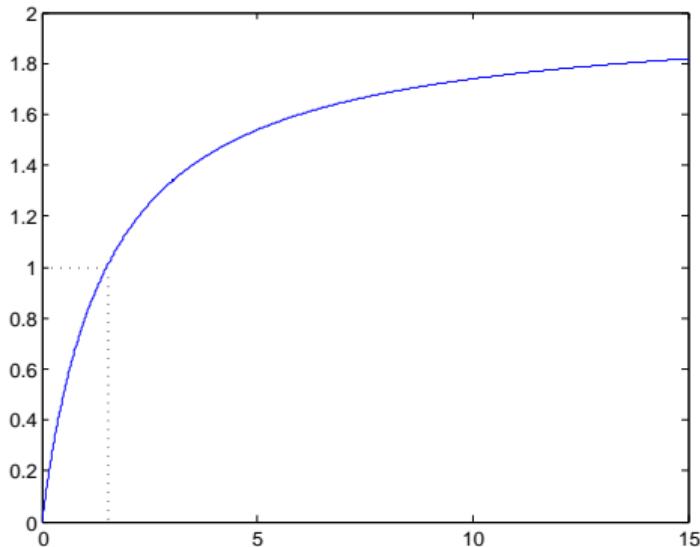
- ▶  $\mu(0) = 0$  (no substrate, no growth)
- ▶  $\mu(S) \geq 0$  for all  $S \geq 0$
- ▶  $\mu(S)$  bounded for  $S \geq 0$

## The Michaelis-Menten curve

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

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

- ▶  $\mu_{max}$  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

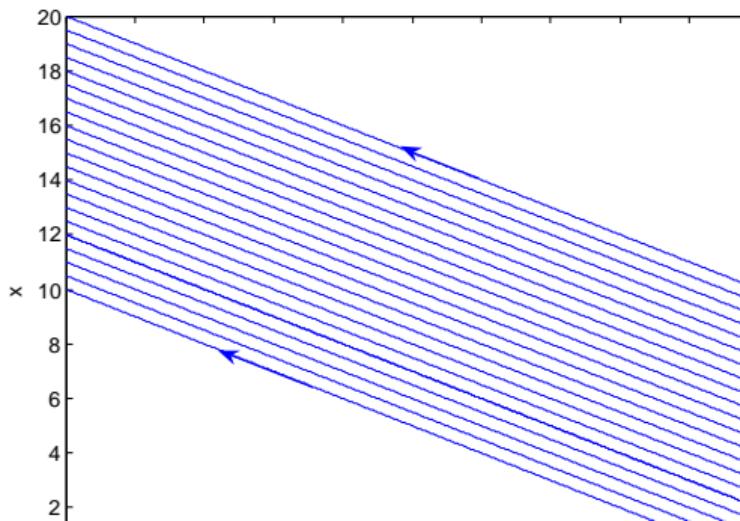
$$\frac{dx}{dS} = \frac{dx}{dt} \frac{dt}{dS} = -\frac{\mu(S)x}{\mu(S)x} = -1$$

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

$$S' = -\mu(S)x \quad (3a)$$

$$x' = \mu(S)x - dx \quad (3b)$$

## 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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Continuous flow mode

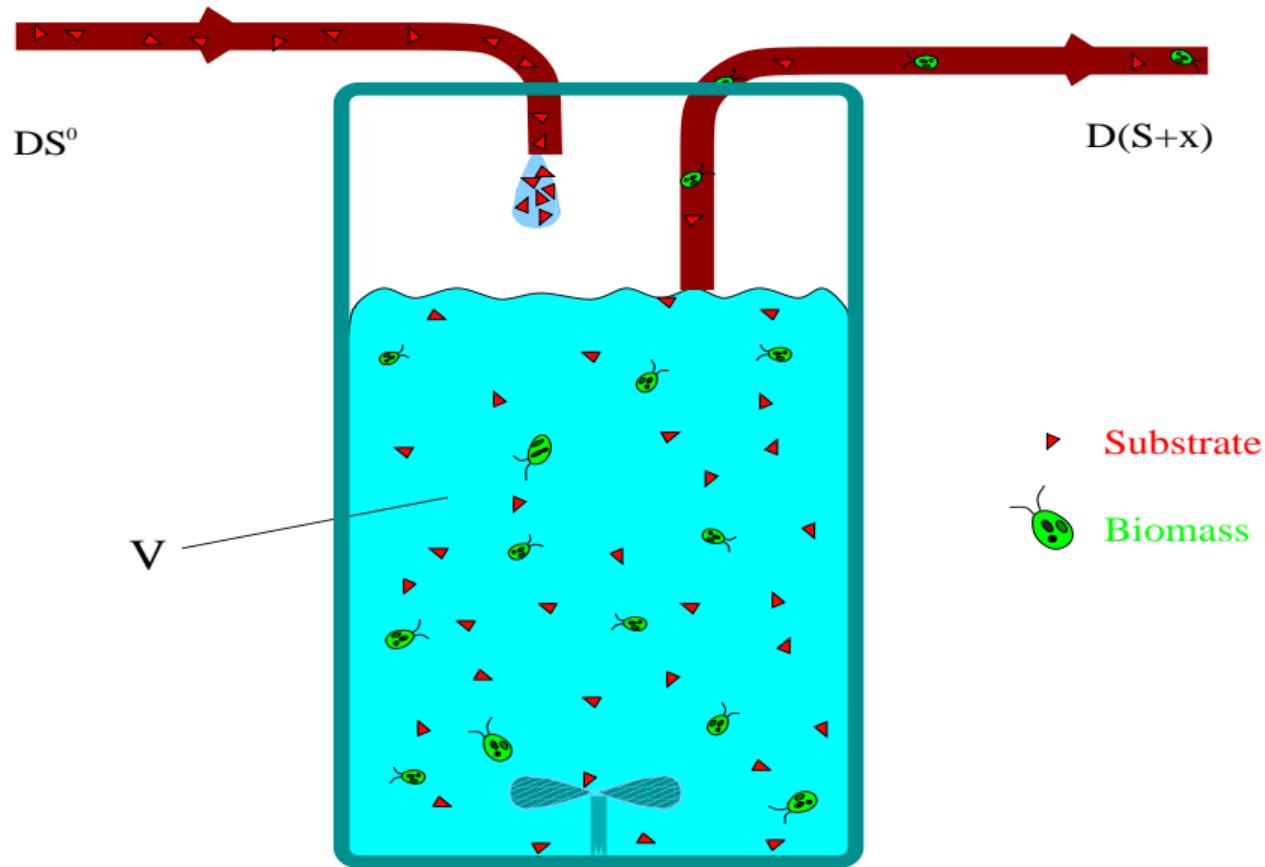
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## Modelling principles – Continuous flow mode

- ▶ 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

$$S' = D(S^0 - S) - \mu(S)x \quad (4a)$$

$$x' = \mu(S)x - Dx \quad (4b)$$

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

$$x'_1 = f_1(x_1, x_2)$$

$$x'_2 = f_2(x_1, x_2)$$

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

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

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

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

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

Write the latter as

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

## Nullcline for $x$

So, for  $x$ , there are two nullclines:

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

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

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

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

Rewrite (5a),

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

## 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

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

## 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  $\mathbb{R}^{>3}$ . This is summarized in the well known

### Theorem 1 (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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## Conservation of mass

Summing the equations in (4), we get

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

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

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

and so

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

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