

M1 BBS - EM8BBSEM

Simulation de Systèmes Biologiques

(#7)

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Equations logistiques

Suppose living cells grow in a nutrient-rich medium. If X is the concentration of the biomass, then dX/dt is the **growth rate**, or change in biomass per unit time.

Usually the change of cellular mass is directly related to the amount of digested nutrients. This, in turn, is proportional to the biomass concentration. The growth rate is then given by the Malthus law (1798):

$$\frac{dX}{dt} = \mu X$$

where the constant of proportionality μ is the **per capita growth rate**:

$$\mu = \frac{1}{X} \frac{dX}{dt}$$

The solution of the above equation is an exponential curve:

$$X(t) = X_0 e^{\mu t}$$

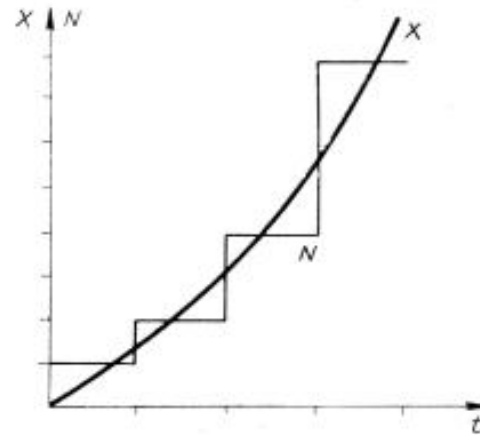
with the initial condition $X=X_0$ at $t=0$.

No living cell grows infinitely. Nutrients are absorbed through the surface of a cell, proportional to r^2 (a square of the cell's radius) while its volume grows as r^3 . At some point the nutrient flow becomes insufficient to sustain the cell's growth. The cell either stops growing or divides.

Mean time between cell divisions τ can be calculated from:

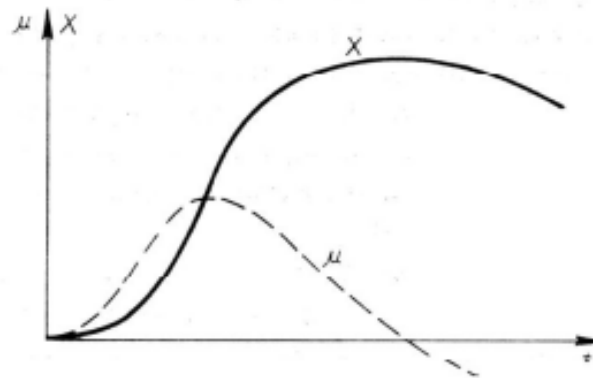
$$2X_0 = X_0 e^{\mu\tau}, \quad \tau = \frac{\ln 2}{\mu}$$

If the cell divisions are independent, the concentration of biomass in a microbial culture is proportional to the number of cells. Under normal conditions the growth of cells is not synchronized (see figure below). Hence, the terms **biomass growth** and **increase of the number of cells** are equivalent.



Bacterial growth: N – number of cells, X – biomass.

The *per capita* growth rate μ is constant only if all components of the growth medium remain constant. Otherwise, it changes as a function of available resources (e.g. nutrients, oxygen, pH, light) and accumulated waste:



In 1845 Verhulst suggested the following model reflecting antagonistic interactions within a population:

$$\frac{dx}{dt} = \mu \cdot x - \beta \cdot x^2$$

Probability of death is proportional to the number of existing organisms. In the long-term limit the population stabilizes at $x_{\infty} = \mu/\beta$.

Real populations do not realize constant *per capita* growth rates. By engineering the growth rate as a function of the population size, finely structures population models can be constructed.

If the growth rate decreases with increasing population size, then a finite limit, the **carrying capacity**, is imposed on the population.

If the growth rate becomes negative for small population sizes, the population is be driven to **extinction**.

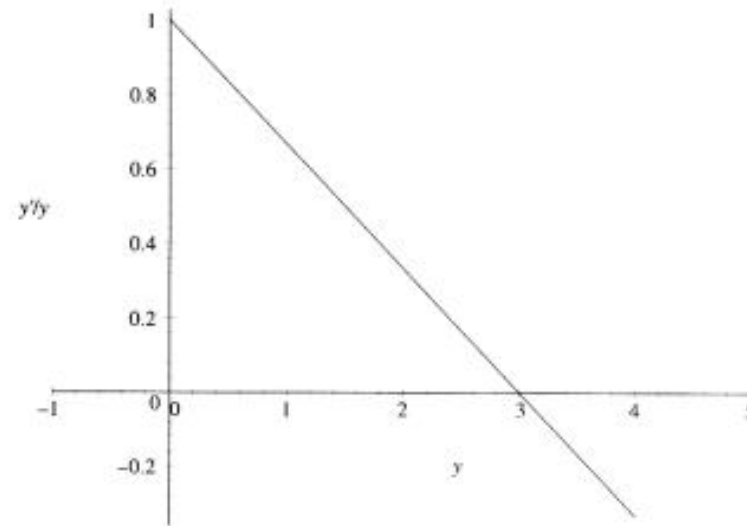
Example: logistic growth

When a biological population becomes too large, the *per capita* growth rate diminishes. This is because individuals interfere with each other and are forced to compete for limited resources. In the Verhulst model the *per capita* growth rate decreases linearly with population size y :

$$\frac{1}{y} \frac{dy}{dt} = r \left(1 - \frac{y}{K} \right)$$

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This equation is known as the **logistic equation**. The linearly decreasing *per capita* growth rate is depicted in the figure below.



The alternative form of this differential equation is:

$$\frac{dy}{dt} = ry \left(1 - \frac{y}{K} \right)$$

We see that the derivative is zero when:

$$y = 0$$

or

$$y = K$$

These are the stationary points of the equation. The stationary point $y = K$, at which the *per capita* growth rate becomes zero, is called the **carrying capacity** (of the environment).

For small population sizes $Y/K \approx 0$ and the population increases exponentially with the *per capita* growth rate r . Hence solutions are repelled from the stationary point $y = 0$.

But as the population size approaches the carrying capacity K , the growth rate decreases to zero and the population ceases to change in size.

Further, if the population size ever exceeds K , the *per capita* growth rate becomes negative and the size decreases to K . Hence, solutions are globally attracted to the stationary point $y = K$.

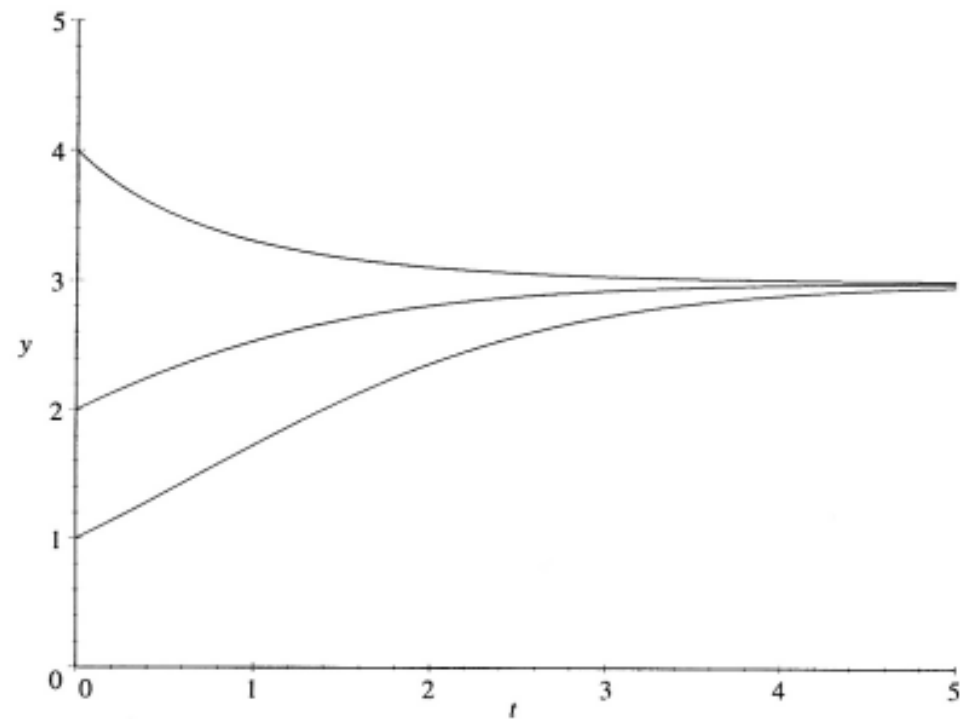
Rewriting the logistic equation as:

$$\frac{dy}{y\left(1-\frac{y}{K}\right)} = \left(\frac{1}{y} + \frac{\frac{1}{K}}{1-\frac{y}{K}}\right) dy = r dt$$

and integrating it directly, we obtain the explicit, analytical solution:

$$y(t) = \frac{y_0 K e^{rt}}{y_0 (e^{rt} - 1) + K}$$

A few of these solutions are shown in the figure below. Here, we take $r=1$, $K=3$ and find solutions with $y_0=1$, or 2 , or 4 .



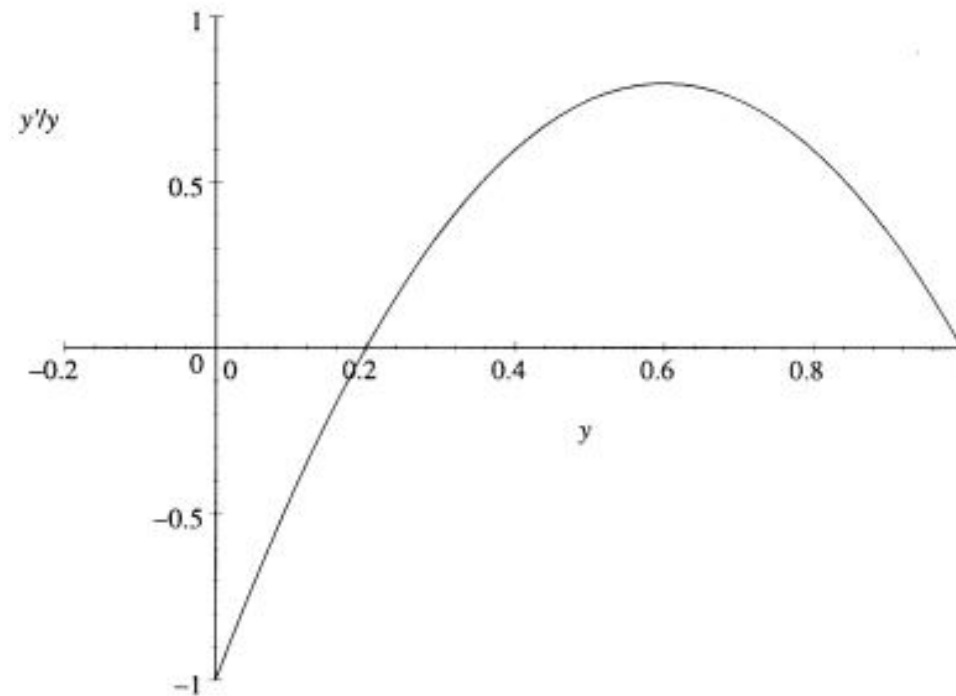
Example: non-linear *per capita* growth rate

Real populations are in danger of extinction if their size falls to a low level. Predation might eliminate the last few members completely, finding mates becomes more difficult, and a lack of genetic diversity renders the population susceptible to epidemics.

By constructing a *per capita* growth rate that is actually negative below some critical value, θ , there results a population model that tends to extinction if the population size falls too low. For example:

$$\frac{1}{y} \frac{dy}{dt} = r \left(1 - \frac{y}{K} \right) \left(\frac{y}{\theta} - 1 \right)$$

Where $0 < \theta < K$. The figure below shows the form of the *per capita* growth rate using the specific parameters: $r=1$, $\theta=1/5$, and $K=1$. This particular form is sometimes referred to as the *predator pit*.



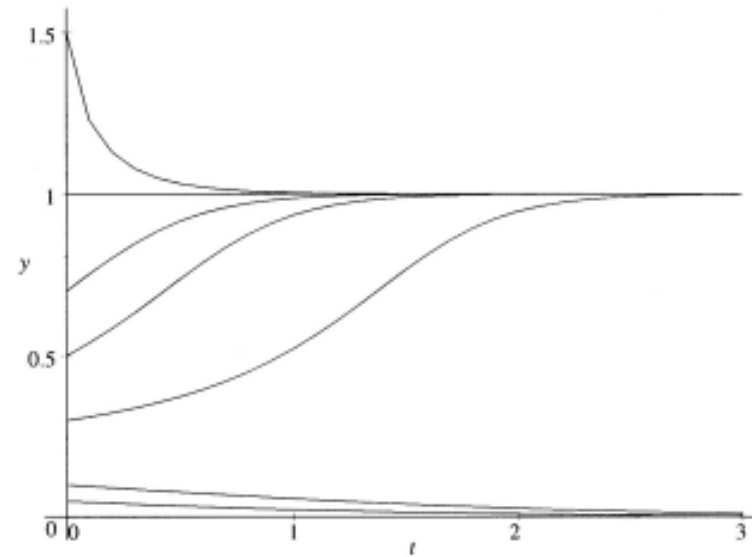
The stationary points of the equation:

$$\frac{1}{y} \frac{dy}{dt} = r \left(1 - \frac{y}{K} \right) \left(\frac{y}{\theta} - 1 \right)$$

are $y = 0$, $y = \theta$ and $y = K$. But now $y = 0$ is asymptotically stable: if the starting value y_0 is near enough to 0 , then the solution tends to 0 as t increases. This follows because the sign of the rhs of the equation is negative for $0 < y < \theta$ causing $dy/dt < 0$. Hence y will decrease.

On the other hand, a solution starting with $y_0 > \theta$ tends to K as t increases. This is because when $\theta < y < K$, the rhs of the equation is positive, so $dy/dt > 0$ also, hence y will increase.

As before, solutions starting with $y_0 > K$ decrease asymptotically to K . Here are some solutions to the predator pit equation:



Here is one more example of complex population modeling. The equation below represents a population model that engenders little growth for small populations, rapid for intermediate ones, and low growth again for large populations. This is achieved by the quadratic per capita growth rate:

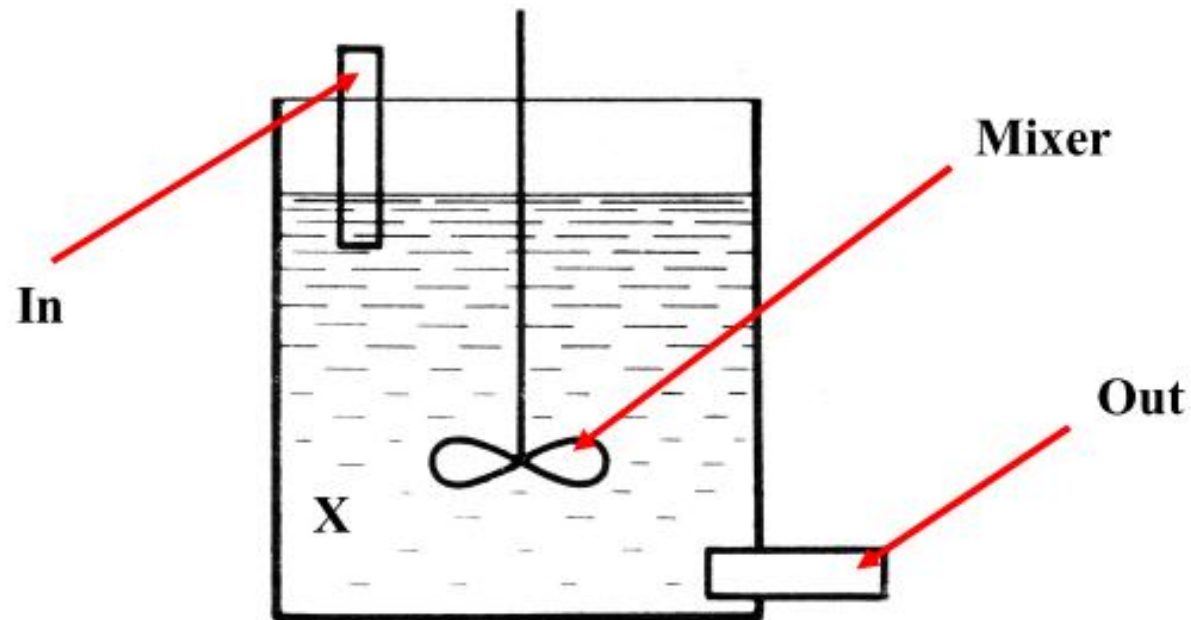
$$\frac{1}{y} \frac{dy}{dt} = ry \left(1 - \frac{y}{K} \right)$$

Croissance de la biomasse : chemostat

Changes in conditions prevalent in growth media cause modifications of the *per capita* growth rate. However, even though the overall number of different factors affecting cellular growth may be high, usually only a ***small number of external parameters are relevant***. The regulation of the growth processes depends mainly on ***bottlenecks*** in the chain of chemical reactions.

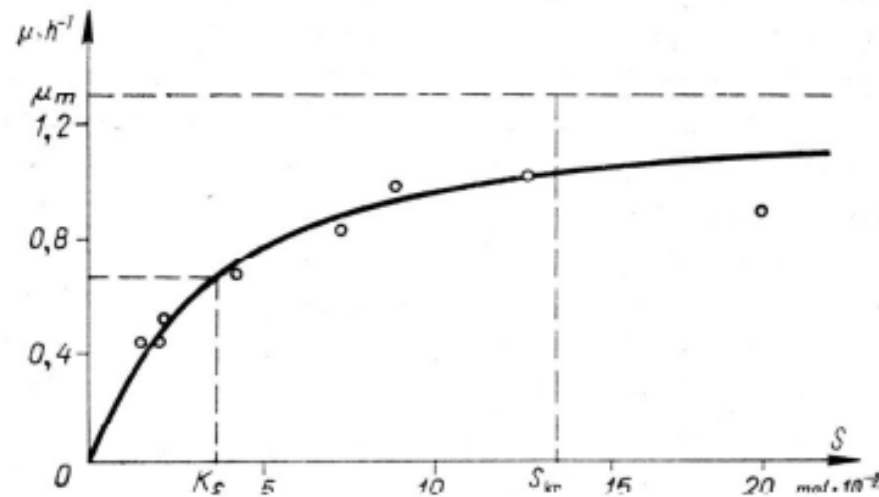
If one of the components is missing from the growth medium, cells grow significantly slower. The growth rate depends then directly on the concentration of the missing component. We talk about growing cells in a ***limiting medium***.

In order to study the characteristics of cellular growth, Monod (1942) proposed a **flow cultivator** (**homeostat**):



The structure's volume V contains substrates S , biomass X and products P . Mixing assures homogeneity of the components. After a suitable time, a stable equilibrium is established.

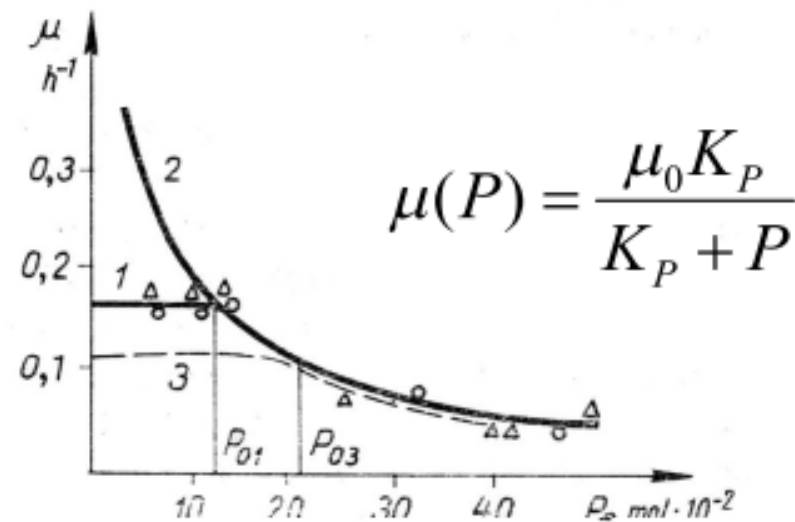
In homeostat, a stable equilibrium is established for given values of the flow rate and nutrient (i.e. substrate) concentration. The dependence of the *per capita* growth rate on the substrate **S** can be measured experimentally and has the following form:



$$\mu(S) = \frac{\mu_m S}{K_s + S}$$

Note the similarity of the functional form of μ with the enzymatic reaction rates given by the Michaelis law.

Influence of reaction products **P** (inhibitors) on cells can become a source of bottlenecks, significantly limiting cellular growth:



The total effect (**S,P**) can be described by the following curve:

$$\mu(S, P) = \frac{\mu_m S K_P}{(K_S + S)(K_P + P)}$$

Examples of homeostatic systems in living organisms:

- **blood vessel system**

Bone marrow continuously produces erythrocytes (ca. $15 \cdot 10^6/s$), carried away by blood. Their concentration is constant (ca. $5 \cdot 10^6/mm^3$), hence they must continuously perish in liver and spleen.

- **renewal of fat tissue**

Studies based on isotopic markers have shown that the composition of fat tissue is continuously changing, while its total amount remains constant.

***Multicellular organisms function in the state of
dynamic equilibrium.***

Important for qualitative analysis of dynamic phenomena:

To reduce the number of independent variables (i.e. the number of differential equations) to the absolute minimum (e.g. two, or three).

The smaller the equation set the better the model!

In the case of homeostat we have the following options:

# of variables (and equations)	Cellular growth	Inhibition by product	Biological inertia
2	yes	no	no
3	yes	yes	no
4	yes	yes	yes

Variables:

- 1) Biomass concentration
- 2) Substrate concentration
- 3) Product concentration
- 4) Ribosome concentration

In the simplest case of two variables (substrate, biomass), the equation describing the variation of **biomass** concentration **x** is composed of two terms:

$$\frac{dx}{dt} = \mu x - Dx$$

The first term describes the exponential growth of cells, while the second refers to the loss of biomass **x** due to steady flow of culture out of homeostat. The flow rate determines the **dilution constant D**.

There are three components in the equation for the **substrate y** . The nutrient is used by cells, hence its concentration decreases proportionally to the growth rate of the biomass, with the proportionality constant α corresponding to the efficiency of this process. It also flows out with the rate given by D . However, its concentration increases because of the continuous supply with the initial concentration y_0 . The balance is:

$$\frac{dy}{dt} = -\alpha\mu x + D(y_0 - y)$$

Taking into account the hyperbolic dependence of the *per capita* growth rate μ on the substrate concentration y we get:

$$\left\{ \begin{array}{l} \frac{dx}{dt} = \frac{\mu_m y}{K_y + y} x - Dx \\ \frac{dy}{dt} = -\alpha \frac{\mu_m y}{K_y + y} x + D(y_0 - y) \end{array} \right.$$

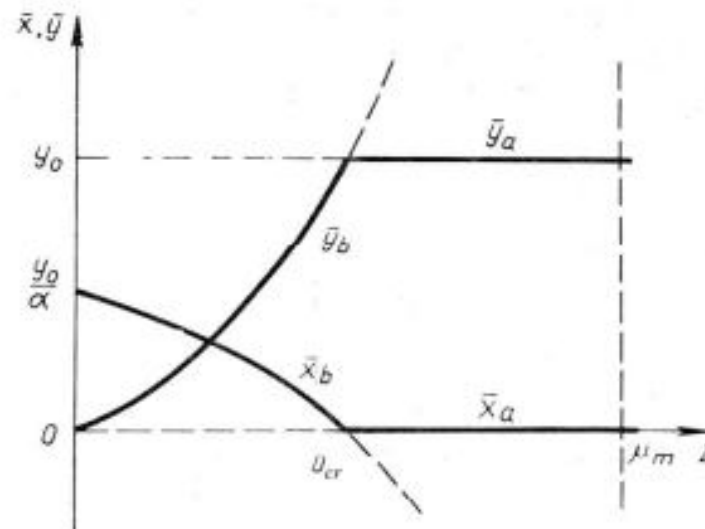
In the **first stage of analysis** we will search for the stationary points of the system. By equating the derivatives to zero, we get two algebraic equations:

$$\left. \begin{aligned} \frac{d\bar{x}}{dt} = 0 &= \frac{\mu_m \bar{y}}{K_y + \bar{y}} \bar{x} - D\bar{x} \\ \frac{d\bar{y}}{dt} = 0 &= -\alpha \frac{\mu_m \bar{y}}{K_y + \bar{y}} \bar{x} + D(y_0 - \bar{y}) \end{aligned} \right\} \Rightarrow \left\{ \begin{aligned} \bar{x} \left(\frac{\mu_m \bar{y}}{K_y + \bar{y}} - D \right) &= 0 \\ \alpha \bar{x} + \bar{y} &= y_0 \end{aligned} \right.$$

The second equation reflects a linear dependence of the two concentrations in the stationary state. From the first equation it follows that there are two solutions:

$$\begin{aligned} \bar{x} = \bar{x}_a = 0, & \quad \Rightarrow \quad \bar{y} = \bar{y}_a = y_0 \\ \bar{y} = \bar{y}_b = \frac{K_y D}{\mu_m - D}, & \quad \Rightarrow \quad \bar{x} = \bar{x}_b = \frac{y_0 - \bar{y}_b}{\alpha} = \frac{\mu_m y_0 - D(K_y + y_0)}{\alpha(\mu_m - D)} \end{aligned}$$

The two solutions (as functions of D) are depicted in the figure below:



Note that $D < \mu_m$. For $D > D_{cr} = \mu_m y_0 / (K_y + y_0)$ the biomass concentration becomes negative, which has no physical sense! In reality, it will remain zero (because of fast flow of biomass out of homeostat; growth no longer compensates the dilution). For $D < D_{cr}$ both solutions are acceptable.

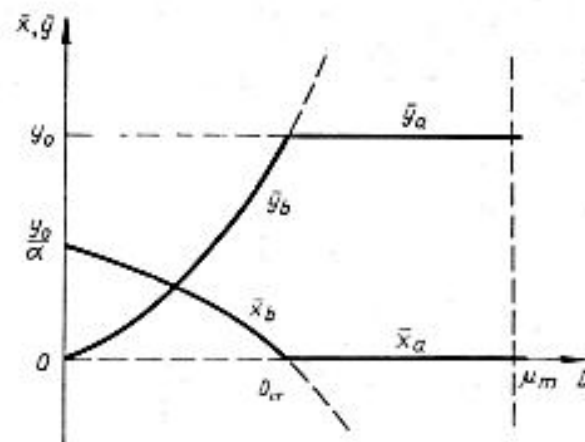
In the **second stage of analysis** we apply the perturbation theory to determine the stability of the two stationary points of the system. The analysis concerns the two following possibilities:

1. $D < D_{cr}$

Following the outline presented previously, we learn that for $D < D_{cr}$ the **trivial (zero) solution is unstable**. In other words, if $x(0) = 0$, no biomass can be grown. However, even a minimal number of cells can initiate the growth, which will continue until the **stable equilibrium (the second stationary point)** is reached. Subsequent small fluctuations will be compensated for, and the system can remain arbitrarily long in this stable state.

2. $D \geq D_{cr}$

For large flow rates, when $D \geq D_{cr}$, the situation is different. Placing cells in the homeostat has no consequences; the biomass will not develop. The flow directed to the outside of homeostat is so fast that dilution of biomass is instantaneous (before the cells multiply, they are carried out of the homeostat). In this case we can see that the stationary point corresponding to **zero concentration of biomass is stable**.



Q: *Under what conditions does a homeostat work optimally?*

A: *Define efficiency and optimize it!*

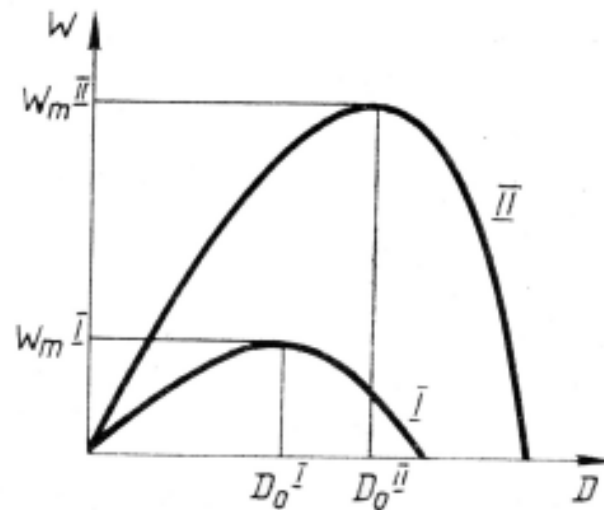
We define **efficiency** of a homeostat as the quantity of biomass it can produce per unit time per unit volume:

$$w = \frac{1}{V} \frac{\Delta m}{\Delta t} = \frac{1}{V} \frac{\Delta(xV)}{\Delta t} = \frac{\Delta x}{\Delta t} = \mu x$$

Hence, efficiency is defined as that part of the equation describing concentration of biomass, which corresponds to its growth. Moreover, in the state of stable equilibrium, this is equal to:

$$w = \mu x = Dx$$

As can be seen from the above, the efficiency tends to zero as $D \rightarrow 0$. Also, no biomass is produced when $D \geq D_{cr}$. Between the two limiting values there must occur a maximum of the efficiency, e.g. for $D = D_0$:



Efficiency of a flow cultivator as a function of D
I: $y_0 = K_y$; II: $y_0 = 2K_y$

The maximum of the efficiency:

$$w = D\bar{x} = D \frac{\mu_m y_0 - D(K_y + y_0)}{\alpha(\mu_m - D)}$$

can be found by equating its derivative $\partial w / \partial D$ to zero. Using the basic relationship:

$$\frac{d}{dx} \left(\frac{f(x)}{g(x)} \right) = \frac{f'(x) \cdot g(x) - f(x) \cdot g'(x)}{g^2(x)}$$

we arrive at the following expression:

$$\frac{\partial w}{\partial D} = \frac{[(\mu_m - D)(D_{cr} - 2D) + D(D_{cr} - D)](K_y + y_0)}{\alpha(\mu_m - D)^2} = 0$$

Since $(K_y + y_0) > 0$ and $(\mu_m - D) > 0$, we can write:

$$(\mu_m - D)(D_{cr} - 2D) + D(D_{cr} - D) = 0, \quad D_{cr} = \frac{\mu_m y_0}{K_y + y_0}$$

$$D^2 - 2\mu_m D + \mu_m D_{cr} = 0$$

Of the two solutions available we keep the one for which $D < \mu_m$:

$$D_0 = \mu_m \left(1 - \sqrt{\frac{K_y}{K_y + y_0}} \right)$$

$$w_m = \frac{\mu_m}{\alpha} \left(\sqrt{K_y + y_0} - \sqrt{K_y} \right)$$

The second equation is the maximal efficiency, obtained for $D = D_0$.

The analysis accomplished so far has neglected the influence of inhibitors on the overall biomass production. Adding the third variable z (inhibitor concentration, usually waste product) and using the following form of the per capita growth rate:

$$\mu(y,z) = \frac{\mu_m y K_z}{(K_y + y)(K_z + z)}$$

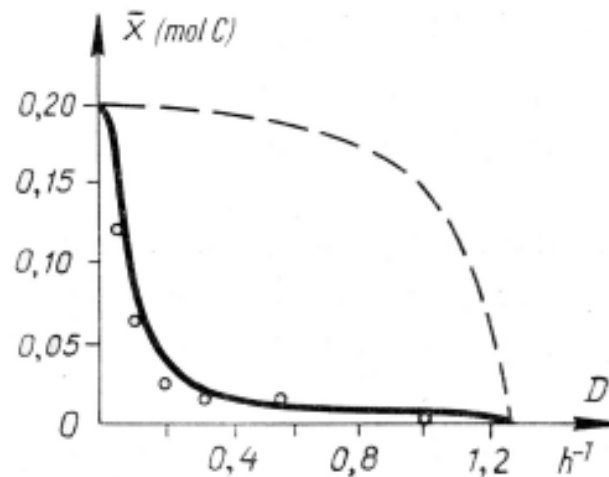
leads to the following equations for the stationary states of the system:

$$\bar{x} + \bar{y} + \bar{z} = y_0$$

$$\alpha \bar{x} + \bar{y} = y_0$$

$$\bar{x} \left[\frac{K_z \mu_m \bar{y}}{(K_y + \bar{y})(K_z + \bar{z})} - D \right] = 0$$

It can easily be found that D_{cr} (corresponding to the critical mass dilution) has the same value as before, but this time the curve describing the growth of biomass (stationary non-zero solution of $x(D)$) has a different form:



***Solid curve and experimental points: effect of inhibition on biomass growth.
Dashed curve: case with no inhibitor.***

It follows that in this case serious errors can result from predictions of biomass concentration based on the simplified model.