An introduction to modeling of bioreactors

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Abstract

This material is made for the course "Modelling of Dynamic Systems".

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1 Background

Mathematical models is an important tool in bio-reactor applications including wastewater treatment. Typical general applications include

- Design of a treatment process. A model is then helpful in evaluating the impact of changing system parameters etc. It is, however, fair to mention that often empirical rules or thumb rules are used in design of wastewater treatment plants.
- Process control. Efficient control strategies are often model based.
- Forecasting. Models can be used to predict future plant performance.
- Education. Models used in simulators can be used for education and training.
- Research. Development and testing of hypotheses.

We will derive a simple model for a bioreactor. Such a model can help explain some fundamentals properties of bioreactors and also give suitable background for understanding more advanced models.

Bioreactors are used in many applications including industries concerned with food, beverages and pharmaceuticals. Biotechnology, which deals with the use of living organisms to manufacture valuable products, has had a long period of traditional fermentations

(production of beer, wine, cheese etc.). The development of microbiology, around hundred years ago, expanded the use of bioreactors to produce primary metabolic products. In 1940's the large scale production of penicillin was a major breakthrough in biotechnology. Some 20 years ago, the computer technology started to make advanced process control possible. The development of genetic engineering have played a major role in creating the current progress in the field of biotechnology.

Until recently, the biotechnical industry has been lagged behind other industries in implementing control and optimization strategies. A main bottleneck in biotechnological process control is the problem to measure key physical and biochemical parameters.

2 The specific growth rate

Many biochemical processes involves (batch) growth of microorganisms. After adding living cells to a reactor containing substrate[1], one may distinguish four phases, see also Figure 1:

- A lag phase when no increase in cell numbers is observed.
- An exponential growth phase. This phase can not go on forever since at some stage the amount of substrate will be limiting for the growth.
- A stationary phase.
- A death phase. The number of cells decreases due to food shortage.

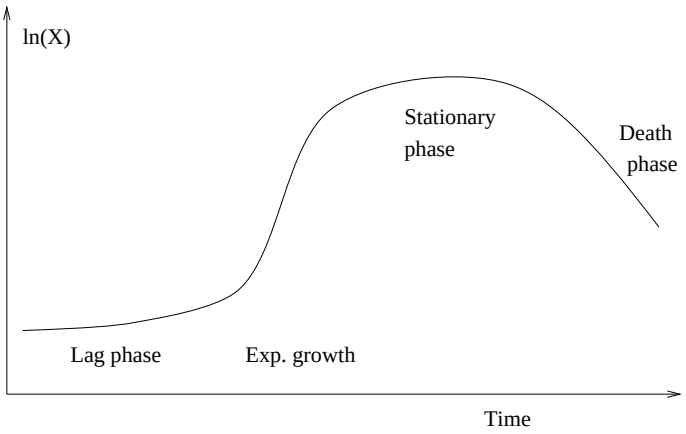

Figure 1: Typical bacterial growth curve in a reactor after adding substrate. X denotes the biomass concentration.

Next we will consider the exponential growth phase. Let $X(t)$ denote the concentration of biomass population (mass/unit volume). An exponential growth can be expressed as

$$\frac{dX(t)}{dt} = \mu X(t) \tag{1}$$

The parameter μ is denoted the *specific growth rate*, "rate of increase in cell concentrations per unit cell concentrations" ([1/time unit]).

[1]Substrate is defined as the source of energy, it can be organic (for heterotrophic bacteria), inorganic (e.g. ammonia), or even light (for phototrophs).

2.1 Derivation

For completeness we give a derivation of (1) commonly used in microbiology literature.

An exponential growth means that the concentration (or number of cells) is doubled during each fixed time interval. Hence, $X(t)$ can be expressed as

$$X(t) = X_o 2^{(t-t_o)/t_d} \tag{2}$$

where t_d is the doubling time and X_o is the initial concentration at time $t = t_o$. Logarithming both sides gives

$$\frac{\ln X(t) - \ln X_o}{t - t_o} = \frac{1}{t_d} \ln 2 \tag{3}$$

Let, $t \to t_o$, the use of the definition of the derivative then gives

$$\frac{d}{dt} \ln X(t) = \frac{1}{t_d} \ln 2 \tag{4}$$

Now, since

$$\frac{d}{dt} \ln X(t) = \frac{1}{X(t)} \frac{dX(t)}{dt} \tag{5}$$

we have

$$\frac{1}{X(t)} \frac{dX(t)}{dt} = \frac{1}{t_d} \ln 2 = \mu \tag{6}$$

which can be written in the standard form (1).

3 The Monod function

Often the specific growth rate μ depends on the substrate concentration S. It is natural to assume that a low amount of substrate gives a low growth rate and if the substrate concentration increases the growth rate increases. For sufficiently high substrate levels though, the growth rate becomes saturated. The following empirical relation is often used and is commonly named the *Monod function*[2]

$$\mu(S) = \mu_{max} \frac{S}{K_S + S} \tag{7}$$

where

μ_{max} is the maximum specific growth rate
S is the concentration of growth limiting substrate
K_S is the half saturation constant

The impact of the substrate concentration on the specific growth rate is shown in Figure 2.
As the microorganisms increase, substrate is used. This is commonly expressed as:

$$\frac{dX}{dt} = -Y \frac{dS}{dt} \tag{8}$$

[2]It was initially proposed by Michaelis-Menton in 1913 (the relation is therefore also often called Michaelis-Menton law) and extended by Monod in 1942 to describe growth of microorganisms.

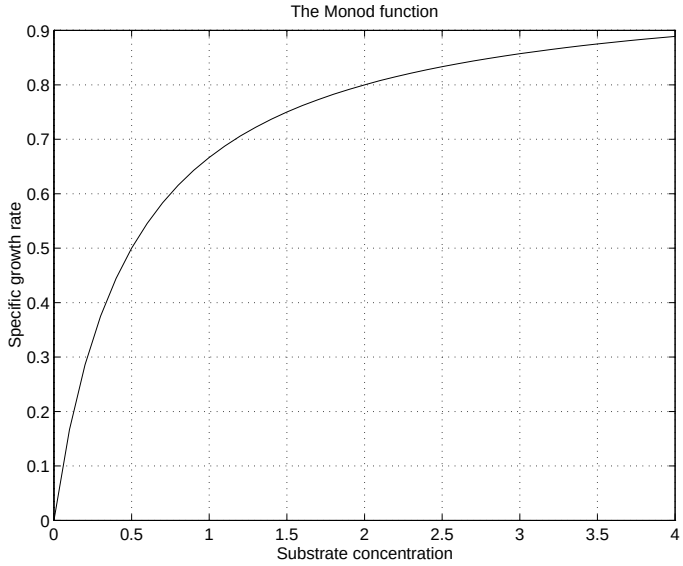

Figure 2: Illustration of the Monod function. The following parameters are used $K_S = 0.5$ and $\mu_{max} = 1$. Note that $S = K_S$ gives $\mu = 0.5\mu_{max}$.

where Y is the *yield coefficient*, "the ratio of the mass of cells formed to the mass of substrate consumed". In (8) and in the following the time argument t is omitted, that is $X = X(t)$ and $S = S(t)$.
The yield coefficient can be expressed as

$$Y = -\frac{dX}{dS} \tag{9}$$

In the literature, it is common to "neglect" the minus sign in the definition of Y and/or to consider the inverse of the yield coefficient.

4 Microbial growth in a stirred tank reactor

We will consider the dynamics of a completely mixed tank reactor shown in Figure 3. The influent flow rate is equal to the effluent (output) flow rate Q [volume/time]. Hence, the volume V is constant. The influent has a substrate concentration S_{in} [mass/volume] and substrate concentration X_{in} [mass/volume].

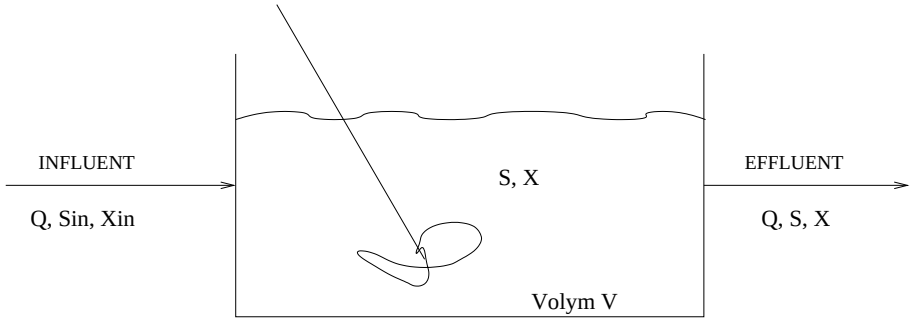

Figure 3: A completely mixed bioreactor.

The rate of accumulation of biomass is obtained from a mass balance. Assume that the biomass has a specific growth rate μ (which for example may be given by (7)). The total amount of produced biomass per time unit in a reactor with volume V is μVX, compare with (1). Since the reactor is completely mixed, the outflow concentration of biomass is equal to the concentration in the tank. The rate of change of biomass is then given as[3]

$$V\frac{dX}{dt} = \mu VX + QX_{in} - QX \tag{10}$$

Now, define the *dilution rate*

$$D = \frac{Q}{V} \tag{11}$$

The model (10) can now be written as

$$\frac{dX}{dt} = \mu X + D(X_{in} - X) \tag{12}$$

For the substrate consumption we assume that the yield coefficient is Y, see (8). Paralleling, the procedure above for the substrate mass balance gives

$$V\frac{dS}{dt} = QS_{in} - \frac{\mu}{Y}VX - QS \tag{13}$$

Introducing the dilution rate (11) gives

$$\frac{dS}{dt} = -\frac{\mu}{Y}X + D(S_{in} - S) \tag{14}$$

The model consisting of (12) and (14) form the basis for most bioreactors models.

[3]For physical reasons it always hold that $X \geq 0$. Hence (10) only holds for non negative X.

Typical extensions of the model are:

- The use of a specific grow rate which depends on several variables S_1, S_2, ... S_N (for example various substrates and nutrients). That is

$$\mu = \mu_{max} \prod_{n=1}^{N} \frac{S_n}{K_{S,n} + S_n} \tag{15}$$

  Note that other environmental factors like pH and temperature also affect the growth rate. This may be modeled in a similar way. It is also common that a substance, say S_i, has an inhibitory effect at high concentrations. This may be modelled by having the following factor in the growth rate:

$$\mu_i = \frac{K_i}{K_i + S_i} \tag{16}$$

  If $S_i >> K_i$ then μ_i is close to zero. A typical example is the modelling of anoxic growth of heterotrophs. Then S_i corresponds to the concentration of dissolved oxygen in the water.

- The Monod function (7) does not account for any inhibitory effects at high substrate concentrations (overloading). Substrate inhibition may be modeled by the *Haldane* law

$$\mu = \frac{\mu_o S}{K_M + S + K_I S^2} \tag{17}$$

  It is clearly seen in (16) that $\mu \to 0$ as $S \to \infty$.

- Very often the dissolved oxygen consumption is included in the model.

- The use of different substrate and biomass compounds. For example, different types of microrganisms may be included in the model.

- Conversion relations between different compounds, i.e. hydrolysis[4].

- A decay term for biomass can be added to account for the death of microorganisms. The specific biomass decay rate b is defined similarly as the specific growth rate μ:

$$b = -\frac{dX(t)}{X\,dt} \tag{18}$$

  The net growth rate is then $\mu - b$ and (12) becomes

$$\frac{dX}{dt} = (\mu - b - D)X \tag{19}$$

4.1 Stationary points and wash-out

We will here consider the basic bioreactor model (12) and (14) for the case that the influent biomass concentration is neglectable, that is $X_{in} = 0$. The model then becomes:

$$\frac{dX}{dt} = (\mu - D)X \tag{20}$$

$$\frac{dS}{dt} = -\frac{\mu}{Y}X + D(S_{in} - S) \tag{21}$$

[4]In the hydrolysis process, larger molecules are converted into small degradable molecules.

In the following we assume that D is constant and we will derive the *stationary points* (also called equilibrium state or fixed point) of the model. The stationary points are found by solving $\frac{dX}{dt} = \frac{dS}{dt} = 0$. The stationary points are denoted $\bar{X}$ and $\bar{S}$.

It is directly seen from (20) that a necessary condition for $\dot{X} = 0$ is

$$\bar{X} = 0 \tag{22}$$

or

$$\mu = D \tag{23}$$

The first condition (22) is known as *wash-out*. All biomass will (as $t \to \infty$) disappear! In most cases the wash-out condition is undesirable and should be avoided. Wash out is typically obtained if D is too high (too much biomass is then taken out from the reactor and the reactor becomes "overloaded") and below we will derive an expression for the maximum dilution rate. Note that, the corresponding $\bar{S}$ for the condition (22) is $\bar{S} = S_{in}$ which is very natural.

Next we will consider the condition (23) when μ is a Monod function:

$$\mu(S) = \mu_{max} \frac{S}{K_S + S} \tag{24}$$

We then obtain from (23)

$$\mu_{max} \frac{\bar{S}}{K_S + \bar{S}} = D \tag{25}$$

Solving for $\bar{S}$ yields

$$\bar{S} = \frac{DK_S}{\mu_{max} - D} \tag{26}$$

Note that $\bar{S}$ does not depend on S_{in}! That means that during steady state the effluent substrate concentration from the reactor does not depend on the influent concentration of substrate. Note that we have assumed that the specific growth rate can be modelled as a Monod function and that the influent biomass concentration is zero).

The steady state value of the biomass is obtained by solving (21) which gives

$$\bar{X} = Y(S_{in} - \bar{S}) \tag{27}$$

Finally, we will in this section derive a condition for the dilution rate D to avoid wash-out. In order to not get a wash-out, we must have $\bar{X} > 0$. From (27) this gives $S_{in} > \bar{S}$. By using (26) we get

$$S_{in} > \frac{DK_S}{\mu_{max} - D} \tag{28}$$

Solving for D gives:

$$D < \frac{S_{in}\mu_{max}}{S_{in} + K_S} = D_c \tag{29}$$

Hence, if we select $D < D_c$ wash-out is avoided.

4.2 State space description

The model consisting of (12) and (14) can easily be written in a state space form. Define the state space vector as

$$z(t) = \begin{pmatrix} X(t) \\ S(t) \end{pmatrix}$$

Let X be the output (denoted $y(t)$) and S_{in} be the input signal. The model (12)–(14) can now be written as

$$\begin{aligned} \dot{z}(t) &= \begin{pmatrix} \mu - D & 0 \\ -\frac{\mu}{Y} & -D \end{pmatrix} z(t) + \begin{pmatrix} 0 \\ D \end{pmatrix} S_{in} \\ y(t) &= \begin{pmatrix} 1 & 0 \end{pmatrix} x(t) \end{aligned} \tag{30}$$

The model (30) is linear and time invariant if μ, Y, and D are constant. This is rarely the case! The model can be linearized around a *stationary point*, compare with the basic control course.

4.3 Different flow rates*

In the case the influent flow rate is different from the effluent flow rate, the volume variation in the reactor needs to be taken into account:

$$\frac{dV}{dt} = Q_{in} - Q_{out} \tag{31}$$

where Q_{in} is the influent flow rate and Q_{out} the effluent flow rate.
A mass balance for the biomass yields

$$\frac{d}{dt}(VX) = \mu VX - Q_{out}X \tag{32}$$

By applying the chain rule, we have

$$\frac{d}{dt}(VX) = X(\frac{d}{dt}V) + V(\frac{d}{dt}X) = X(Q_{in} - Q_{out}) + V(\frac{d}{dt}X)$$

In the last equality, (31) has been used. Rearranging the terms gives

$$V(\frac{dX}{dt}) = \frac{d}{dt}(VX) + (Q_{out} - Q_{in})X \tag{33}$$

Inserting (32) in (33) gives

$$V(\frac{dX}{dt}) = \mu VX - Q_{in}X \tag{34}$$

For this case, it is feasible to define the dilution rate as

$$D = \frac{Q_{in}}{V} \tag{35}$$

The model (34) can now be written in the simple form

$$\frac{dX}{dt} = (\mu - D)X \tag{36}$$

which is the same as (12), given the (more careful) definition of the dilution rate in (35).

For the substrate concentration, a similar modeling exercise can be done. The results is the same as (14).