Notes
Ma12 Mathematics of Enzyme Kinetics
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Lecture 1

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0.1 *The terms*

Enzyme: Catalyst; one aiding (or initiating) the action without being changed by it
(like Mercutio in *Romeo and Juliet*)
from the German word *Enzym*, derived from the Greek word
Enzumos, meaning "leavened":
En: Within, *zumē*: leaven

Kinetics: Relating to motion
(eg., of a particle in Physics, of a product in a Chemical reaction)
from the Greek word(s)
Kinētikos, meaning "moving"
kinein: , to move *kinetos*: moved
(*kinema*: cinema, moving pictures)
In Chemistry: signifies *rate of change in a reaction*

Mathematics: Science of formal systems (modern definition)
from the Greek word(s)
Mathema, meaning science, knowledge;
a lesson that is learnt (modern Gr); what one learns (ancient Gr)
mathematike, mathematikos: fond of learning
Aristotle: *Ta Mathematika*: All things mathematical (384-322 BC)

In North America, Mathematics is abbreviated as *Math*, though it is in the plural. In England and other Commonwealth countries, the abbreviation is "Maths."

0.2 Mathematical modeling

Given a real world problem, perform the following steps:

(i) Look for patterns, and a possible structure

(ii) Isolate the mathematical aspect, or part, of the problem

(iii) What are the variables (dependent and independent) ?

(iv) Determine the type of math which may be useful
- differential equations, statistics, discrete math, . . .

(v) Understand the basic laws (or principles) governing the situation

(vi) Make a toy model, under very simplified assumptions:
Come up with a mathematical equation expressing the dependent variables in terms of independent ones

(vii) If successful, expand and incorporate further subtleties

(viii) Use approximations which lead to a solution

(ix) Check the validity of results/predicitons obtained with data
- experimental or numerical

(x) Make corrections in the model, which may lead to further complexity

(xi) Determine when exact solutions may be obtained, equilibria, and stability

(xii) Estimate those quantities which cannot be calculated explicitly or measured in an experiment.

0.3 An Example from Population Dynamics

Consider the following problem:

Suppose the population of a region is P_0 *at the start of a measurement, say at* $t = t_0$*, and it increases at a constant rate of* k *per unit time. What is the population* $P(t)$ *at time* $t = T$*?*

Since it involves the rate of change, it is natural to consider the derivative. We are given that $P'(t) = k$. The *simplest model* we could have is to integrate this and obtain

$$P(t) \;=\; kt + P_0,$$

which shows $P(t)$ changes linearly. Plugging in $t = T$ gives the answer searched for.

But this is too simple, since it does not count the number of deaths in that period. A *reasonable assumption* is that the number of dead is a fixed fraction of the population per unit time So the differential equation providing a better model for the problem is

$$P'(t) \;=\; k - rP(t),$$

for a fixed (non-zero) "rate" r. This ODE can also be solved, though not so simply. Experience tells one to look for a solution of the form

$$P(t) \;=\; Ae^{-rt} + B,$$

which reduces t the simple case when $r = 0$. Then

$$P'(t) \;=\; -rAe^{-rt} \;=\; -r(P(t) - B),$$

which implies

$$B \;=\; k/r.$$

Moreover,

$$P_0 \;=\; P(0) \;=\; A + B \;=\; A + k/r,$$

yielding the solution

$$P(t) \;=\; \left(P_0 - \frac{k}{r}\right) e^{-rt} + \frac{k}{r}.$$

Note that as $t \to \infty$, $e^{-rt} \to 0$ since r is positive (by hypothesis), implying that the solution $P(t)$ for very large time t approaches k/r.

Of course even this refined model gives only an approximate solution, since the rate r is usually time dependent as well, as is k, but there are no simple formulas for them as a function of time.

0.4 The Law of Mass Action

In many instances, for example in enzyme kinetics, we will rely, for the mathematical model, the following “law,” or principle:

The rate of a single step reaction is proportional to the product of the concentrations of the reactants.

In other words if we have a reaction in which $A_1, a_2, \dots, A_r m$ combine to produce a product P, denoted symbolically as

$$A_1 + A_2 + \cdots + A_m \longrightarrow P,$$

then for a constant k, called the *rate constant*, one should have the differential equation

$$p'(t) = k a_1 a_2 \dots a_m,$$

where the lower case letters such as p, a_j, denote the concentrations of the (corresponding upper case terms) P, A_j, for $j = 1, 2, \dots, m$. This can be extended to the case where there are several products.

One often denotes $p'(t)$ $(= \frac{dp}{dt})$ by v, the “velocity.”

Here is the *heuristic reasoning* to justify assuming this principle:

At any time t, the number of possible reactions is measured by the probability of collisions of molecules. Suppose (i) there are large numbers of molecules, and (ii) all collisions are equally probable. Then the probability of a collision should be proportional to the product of the concentrations of the reactants, when they are measured in molarity.

0.5 DiffEQs for Reversible Reactions

A single step reaction

$$A_1 + A_2 \xrightarrow{k_1} B$$

(with rate constant k_1) is often reversible to obtain

$$A_1 + A_2 \xleftarrow{k_2} B,$$

for a rate constant k_2. Sometimes we will combine the two and write

$$A_1 + A_2 \leftrightarrow B.$$

Applying the Law of Mass Action, we get the differential equations

$$a_j'(t)\, k_2 b - k_1 a_1 a_2, \;\text{ for }\; j = 1, 2,$$

and

$$b'(t) \;=\; -k_2 b + k_1 a_1 a_2.$$

These equations are called *ordinary* since they do not involve any partial derivatives, which is because they all depend on just one independent variable, namely t. They are of *first order* because the highest order of the derivatives which occur is 1. They are non-linear because of the degree 2 term $a_1 a_2$. (A monomial $x_1^{n_1} x_2^{n_2} \dots x_m^{n_m}$ is said to be of degree $n = n_1 + n_2 + \dots n_m$, which is linear if, and only if, $n = 1$.)

Some prefer to write k_{-1} for k_2 to indicate that it is the constant for the reaction in the reverse direction.

We will write ODE to signify *Ordinary Differential Equation.*

Note that by adding the differential equations above, we obtain, for each $j \leq 2$,

$$a_j'(t) + b'(t) \;=\; 0.$$

In other words, $a_j + b$ is independent of time, and so must equal the initial value at $t = t_0$, i.e., at any time t,

$$a_j(t) + b(t) \;=\; a_{j,0} + b_0.$$

0.6 A simplistic model of enzyme kinetics

The presence of *enzymes* speed up biochemical reactions, and lead to *product(s)* from *substrate(s).* Substrates are molecules on which an enzyme acts.) There are many examples of enzymes, and a simple one is *amylase*, an enzyme found in human saliva, which turns the substrate *maltose* into the product *glucose syrup.* Another one is *caralase* which breaks down the substrate *hydrogen peroxide* (= H_2O_2), which is a harmful chemical found in cells. Enzymes are usually *proteins*, but not always, since there are *rybozymes*, which are RNA-based. Conversely, there are (many) proteins which are not catalytic, and so not enzymes, such as *hormones* and *transporters.*

The single step reaction expressing the action of an enzyme E acting on a substrate S to produce a product P, with E unaffected, is

$$S + E \;\longrightarrow\; P + E,$$

which, by the Law of Mass Action, leads to the ODE:

$$v(t) = p'(t) \;=\; k_1 se,$$

where (again) the lower case letters denote the concentrations of the upper case quantities. This *simple minded model* leads to the *formal solution* (with $p_0 = p(t_0)$):

$$p(t) \;=\; p_0 + k_1 \int_{t_0}^{t} s(t)e(t)dt,$$

which can be integrated if se is a simple function of t.

This model does not lead to a satisfactory result, for the equation for the rate v of the product implies that if e is fixed constant, v is proportional to s, which implies that we can in particular make v_0 as large as we want by increasing s_0. This does not agree with experiments, as saturating the reaction with substrate does not result in a higher v_0.

0.7 A better model

To take care of the problem above, one introduces an *intermediate compound* (or complex) C, which first reaches an equilibrium with $S + E$, and then slowly decomposes, producing the desired product P and E back again like the Phoenix in Greek mythology. Taking also into account that the first reaction is to a degree reversible, one is led to the schematic

$$S + E \leftrightarrow C \rightarrow P + E,$$

with rate constants k_1 for $S + E \rightarrow C$, k_2 for $C \rightarrow S + E$, and k_3 for $C \rightarrow P + E$.

Applying the Law of Mass Action, we are led to the following system of coupled, first order, non-linear ODEs:

$$\frac{ds}{dt} \;=\; -k_1 se + k_2 c \tag{1}$$

$$\frac{dc}{dt} \;=\; k_1 se - (k_2 + k_3)c \tag{2}$$

$$\frac{de}{dt} \;=\; -k_1 se + (k_2 + k_3)c \tag{3}$$

$$v = \frac{dp}{dt} = k_3 c \tag{4}$$

It is not easy to just write down a solution analytically, due to the non-linearity. Numerical solutions are possible, and also possible are recursive solutions. We will investigate them in more detail in this course.

Adding equations (3) and (4), we see that the derivative of $e + c$ is zero, leading to the result (for all t)

$$c(t) + e(t) = e_0;$$

$c_0 = 0$ as there was no intermediate complex C initially. As $e(t)$ goes to e_0 as $t \to \infty$, $c(t)$ starts off at 0 but then increases, taking the value $e_0 - e(t)$ at time t, the slowly falling to 0 as t goes to ∞.

When we combine this observation on c with equation (4), we see that the rate v of production of the product P starts at 0, steadily increases, and then falls to 0 at very large time. Since the onject is to produce as much P as possible, it is of great interest to know $v_{\max}$, the maximum value taken by v in the time interval $[0, \infty)$. Equally, we want to know the "peak time(s)" $t_{\max}$ when $v = v_{\max}$. The best situation is $t_{\max}$ is close enough to the starting point.

Finally, note that if we add equations (1), (2) and (4) together, we get

$$s'(t) + c'(t) + p'(t) = 0,$$

implying that at any time t,

$$s(t) + c(t) + p(t) = s_0.$$