TOPIC 4
Simulation of medico-biological process
by means of the differential equation

Many problems in biophysics are described by differential equations. This is due in part to the basic laws of nature.

In Newtonian mechanics one considers the position x of a particle of mass m as a function of time t: $x = x(t)$. If the force $F(x, t)$ acting on the particle is known, then one can write down a second order differential equation to find $x(t)$.

$$F(x,t) = m\frac{d^2x(t)}{dt^2}$$

which is Newton's second law of mechanics.

Construction of differential equations is the first step of mathematical simulation of some process.

In applying differential equation to any of the numerous fields in which they are useful, it is necessary first to formulate the appropriate differential equation that describes, or models, the problem being investigated. In constructing future mathematical models your-self, you shod recognize that each problem is different, and that successful modeling is not a skill that can be reduced to the observance of a set of prescribed rules. Indeed, constructing a satisfactory model is sometimes the most difficult part of the problem.

4.1. Pharmacokinetic Modeling

It has been observed that, after the administration of a drug, the concentration of the drug in the body appears to be able to be described by exponential equations. Thus, it appears that, even though the processes by which the drug is absorbed, distributed, metabolized and excreted may be very complex, the kinetics which mimics these processes is made up of relatively simple first order processes and is called **first order pharmacokinetics**. A second observation is that the resulting concentration is proportional to dose. When this is true, the kinetics is called **linear**. When this math is applied to the safe and effective therapeutic management of an individual patient, it is called **clinical pharmacokinetics**. Thus, in clinical pharmacokinetics, we monitor plasma concentrations of drugs and suggest dosage regimens which will keep the concentration of drug within the desired therapeutic range. **Pharmacodynamics** refers to the relationship between the drug concentration at the receptor and the intensity of pharmacological (or toxicological) response. It is important to realize that we want to control the pharmacological response. We do that indirectly by controlling the plasma concentration. In order which is that there is a predict for this to work, we assume kinetic homogeneity, able relationship between drug concentration in the plasma (which we can measure) and drug concentration at the receptor site (which we cannot measure). This assumption is the basis for all clinical therapeutics.

Models are simply mathematical constructs (pictures) which seem to explain the relationship of concentration with time (equations) when drugs are given to a person (or an animal). These models are useful to predict the time course of drugs in the body and to allow us to maintain drug concentration in the therapeutic range (optimize therapy).

We model to summarize data, to predict what would happen to the patient given a dosage regimen, to conceptualize what might be happening in disease states and to compare products. In every case, the observations come first and the explanation next. Given that a data set fits a model, the model can be used to answer several different types of questions about the drug and how the patient handles the drug (its disposition), for example: if the drug were to be given by an oral dose, how much is absorbed and how fast? Are there things which might affect the absorption, such as food or excipients in the dosage form itself? What would happen if the drug were to be given on a multiple dose regimen? What if we increased the dose? etc.

4.2. Pharmacokinetic models

I. One Compartment Open Model

After administration, a drug may distribute into all of the accessible regions instantly. In such a case the body is considered to be a homogenous container for the drug and, the disposition kinetics of the drug can be described as a one compartment open model. It is called 'one compartment' because all of the accessible sites have the same distribution kinetics as if the drug is dissolved in a beaker containing a single solvent. It is 'open' because unlike the beaker model the drug **is eliminated** from the container.

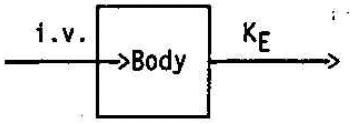

Fig. 4.1. Schematic presentation of a one compartment open model.

The drug introduced into the body as an instant (bolus) intravenous dose and eliminated with an overall elimination rate constant of K_u.

Routes of drug administration: enteral (orally, rectally), parenteral (intravenous, intra-arterial, intramuscular) topical (inhalational, subcutaneous, intradermal, sublingual, transdermal).

Elimination. Drugs are cleared primarily by the liver and kidneys. Excretion into the urine is a major route of elimination for metabolites and unchanged drug. Most drugs are eliminated by a first-order process. With first-order elimination, the amount of drug eliminated is directly proportional to the serum drug concentration (SDC). With first order elimination, at a certain point in therapy, the ***amount of drug administered during a dosing interval exactly replaces the amount of drug excreted. When this equilibrium occurs (rate in = rate out), steady-state is reached.***

1. ***Model with a bolus dose***

Following an intravenous injection of a drug (bolus dose), dissolution of medicinal drug its excretion may be represented by the following pharmacokinetic scheme*:*

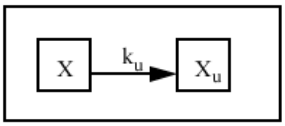

Fig. 4.2. Schematic presentation of an intravenous injection of a drug

where X is the mass of unchanged drug in the body at any time; X_u is the cumulative mass of unchanged drug in the urine up to any time; k_u is the apparent first-order rate constant for excretion of unchanged drug.

We want to find out how the mass of drug, X, changes with time in that compartment, the rate, and how the rates change with time, the differential equations. Consider how the body excretes a drug. The building block is the arrow and what it touches. This first box (compartment) of interest is X. The arrow (k_u) is going out, therefore, the rate is going out and is negative, thus

$$\frac{dX}{dt} = -k_u X,$$

The negative sign indicates loss from the body.

Solution is $X = X_0 e^{-k_u t}$.

The **elimination rate constant** (k_u) represents the fraction of drug eliminated per unit of time.

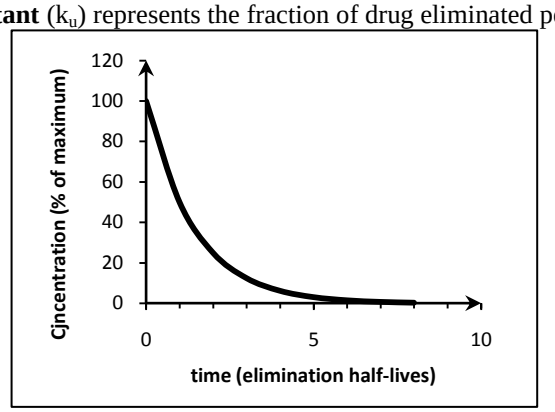

Fig. 4.3. Drug concentration vs. time after a single intravenous bolus, using a linear concentration scale

Another important parameter that relates to the rate of drug elimination is half-life ($t_{½}$). **The half-life** is the time necessary for the concentration of drug in the plasma to decrease by half. Both $t_{½}$ and k_u attempt to express the same idea, how quickly a drug is removed, and therefore, how often a dose has to be administered. An important relationship between $t_{½}$ and k_u can be shown by mathematical manipulation:

$$\frac{X}{X_0} = \frac{1}{2} \text{ (from definition about half-life)}$$

$$\text{put in solution of differential equation } \frac{1}{2} = e^{-k_u t_{1/2}}$$

$$\text{taking the logarithm and get } k_u t_{1/2} = \ln 2$$

$$t_{1/2} = 0.693/k_u.$$

These relationships illustrate that drugs, themselves, do not have half-lives. For example, gentamycin, which is cleared by renal excretion, has a half-life of two to three hours in a yang adult with normal renal function but as much as 24 hours, or more, in a patient with severe renal impairment.

2. Model with a dropper

During the intravenous infusion of a drug, its excretion may be represented by the following pharmacokinetic scheme*:*

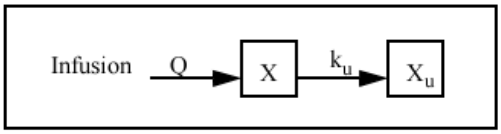

Fig. 4.4 Schematic presentation of model with a dropper

Where *Q* is the zero-order infusion rate constant (the drug is entering the body at a constant rate and the rate of change of the mass of drug in the body is governed by the drug entering the body by infusion and the drug leaving the body by excretion).

The drug entering the body does so at a constant (zero-order) rate.

$$\frac{dX}{dt} = Q - k_u X \ .$$

Solving

$$\int \frac{dX}{Q - k_u X} = \int dt$$

$$-\frac{1}{k_u}\int \frac{d(Q - k_u X)}{Q - k_u X} = \int dt$$

$$\int \frac{d(Q - k_u X)}{Q - k_u X} = -k_u \int dt$$

$$\ln\left|Q - k_u X\right| = -k_u t + \ln C$$

$$Q - k_u X = Ce^{-k_u t}$$

$$k_u X = Q - Ce^{-k_u t}$$

$$X = \frac{Q}{k_u} - \frac{Ce^{-k_u t}}{k_u}.$$

If at time *t=0* all the drug is still in bag, therefore there no drug in the body. $X_0 = 0$, $C = Q$

$$X(t) = \frac{Q}{k_u} - \frac{Q}{k_u}e^{-k_u t} = \frac{Q}{k_u}(1 - e^{-k_u t}).$$

If at the moment *t=0*, initial mace $X(t=0) = X_0$,

$$X_0 = \frac{Q}{k_u} - \frac{C}{k_u}.$$

Thus $C = Q - X_0 k_u$.

Partial solution of initial differential equation:

$$X(t) = \frac{Q}{k_u} + \left(X_0 - \frac{Q}{k_u}\right)e^{-k_u t}.$$

3. *Model with a linear suction*

During the intramuscular infusion of a drug, its excretion may be represented by the following pharmacokinetic scheme ***(linear suction pharmacokinetic model):***

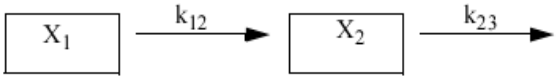

Fig. 4.5 Schematic presentation of intramuscular infusion of a drug

The building blocks are $k_{12}\,X_1$ and $k_{23}\,X_2$. Every arrow that touches the compartment of interest becomes part of the differential equation. If the arrow goes to the box, it's positive; if it goes away from the box, it's negative.

To find $\frac{dX_1}{dt}$ (the rate of change of X_1 with time), we simply add up all of the rates which affect X_1 (all of the arrows that touch X_1)

$$\begin{cases} \frac{dX_1}{dt} = -k_{12}X_1, \\ \frac{dX_2}{dt} = k_{12}X_1 - k_{23}X_2, \end{cases}$$

In the initial moment of time ($t=0$): $X_1 = X_{01}, X_2 = 0$.

After integration

$X_1 = X_{01}e^{-k_{12}t}$.

Insert this solution in 2-nd equation

$$\frac{dX_2}{dt} + k_{23}X_2 = k_{12}X_{01}e^{-k_{21}t}.$$

This is ***non-homogeneous*** first order linear differential equation

Partial solution of this equation is

$$X_2(t) = \frac{X_{01} \cdot k_{12}}{k_{12} - k_{23}}(e^{-k_{23}t} - e^{-k_{12}t}).$$

Example (linear pharmacokinetic model)

The quantity of medical drugs decreases in time by law $m(t) = m_0e^{-kt}$. The constant of speed of dissolution of some kind of medicines in weight 0,25 g is 0,02 min^{-1}.

Calculate how much medical products are dissolved in 30 minutes.

Solution

Quantity of drugs which are not dissolved we calculate using formula $m(t) = m_0e^{-kt}$.

$$m(t)=0.25\cdot e^{-0.02\cdot 30} \approx 0.14(g).$$

Quantity of drugs which are dissolved is

$$m=0.25-0.14=0.11\ (g).$$

II. Multi Compartment Models

Very seldom a drug may follow a true one compartment open model. Upon administration drugs usually distribute into the vascular space and some readily accessible peripheral spaces in a much faster rate than into deeper tissues. In such cases the drug is being taken out of the vascular system not only via elimination but also through distribution to other tissues:

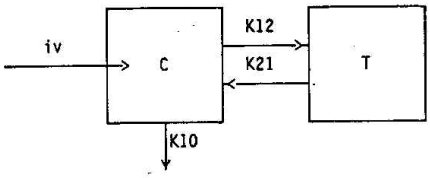

Fig. 4.6. A two compartment open model. *C* and *T* are the central and tissue compartments, respectively.

In a one compartment open model the rate of decline of the drug concentration (*-dC/dt*) is governed only by one single first-order process (i.e., elimination). In a multi compartmental model, on the other hand, beside elimination, there are distribution processes that are also involved in removing the drug out of the vascular space. Consequently *-dC/dt* depends upon more than one first order processes.

4.2. Chemical kinetics

Separable differential equations often appear in chemical kinetics, which is the study of rates of chemical reactions.

As an introduction to using differential equations to model chemical kinetics, consider the following situation. A stirred vessel contains a solution of a chemical substance **W**, which decays spontaneously to form products. If we let *w(t)* represent the concentration of species **W** in the vessel as a function of time, then it has been found experimentally that the rate at which **W** decays is proportional to its concentration. In mathematical terms, this means that w(t) satisfies a differential equation of the form

$$\frac{d}{dt}w(t) = -kw(t),$$

which can be solved by the method of separation of variables to yield the solution

$$w(t) = Ce^{-kt}.$$

As a more interesting example, suppose that two substances, **Y** and **Z**, combine in a chemical reaction to form a substance **X**. We will assume that the rate at which the molecules of **X** are formed is proportional to the product of the concentrations of **Y** and **Z** at time **t**. Let *x(t), y(t),* and *z(t)* be, respectively, the concentrations of chemicals **X**, **Y**, and **Z** present at time **t**. Then we have the rate law

$$\frac{d}{dt}x(t) = ky(t)z(t).$$

The next step is to express *y(t)* and *z(t)* in terms of *x(t)* and then substitute the resulting expressions into the rate law to get a differential equation involving only *x(t)*. This is done as follows.

We are assuming that one molecule of **Y** and one molecule of **Z** combine to form one molecule of **X** and that there is no **X** present initially. That is, for every molecule of **X** formed, one molecule of **Y** and one molecule of **Z** must be consumed. This means that *y(t)=y(0)-x(t)* and *z(t)=z(0)-x(t)*, where *y(0)* and *z(0)* are the initial concentrations of **Y** and **Z**. Thus we have

$$\frac{d}{dt}x(t) = k(y(0) - x(t))(z(0) - x(t)).$$

This is a separable differential equation that can be solved using the technique described above. An example is given below.

Example

Suppose that a solution initially containing 2 moles/liter of **Y** and 1 mole/liter of Z is allowed to react. Find an expression for the amount of **X** at time **t**.

Solution

We have to solve the initial value problem

$$\frac{dx}{dt} = k(2-x)(1-x), \quad x(0) = 0.$$

(The constants 2 and 1 come from the initial concentrations.) Separating variable we get

$$\frac{\frac{dx}{dt}}{(2-x)(1-x)} = k$$

Using the technique described above, we integrate both sides with respect to **t**.

$$\int \frac{dx}{(2-x)(1-x)} = \int k dt + C$$

We know:

$$\frac{1}{(2-x)(1-x)} = \frac{A}{2-x} + \frac{B}{1-x}$$

Multiply both parts to $(2-x)(1-x)$

Obtain $1=A(1-x)+B(2-x) \Rightarrow 1=A-Ax+2B-Bx \Rightarrow 1=x(-A-B)+(A+2B)$

Equate coefficients at identical degrees

x^1: $-A-B=0$

x^0: $A+2B=1$

Solving: $A=-B$;

$-B+2B=1$; $B=1$;$A=-1$

Thus $\frac{1}{(2-x)(1-x)} = \frac{-1}{2-x} + \frac{1}{1-x}$.

$$\int \frac{dx}{(2-x)(1-x)} = \int \left(\frac{-1}{2-x} + \frac{1}{1-x} \right) dx = \int \left(\frac{1}{x-2} - \frac{1}{x-1} \right) dx = \int k dt + C$$

Thus the general solution, in implicit form, is

$$\ln|x-2| - \ln|x-1| = kt + C$$

We now obtain an explicit solution for *x(t)* and use the initial condition to determine **C**.

$$x(t) = \frac{2 - e^{kt+C}}{1 - e^{kt+C}}$$

if $t=0$; $x(t)=0$

Thus $C=ln2$.

4.3. Microbiology

Law of reproduction of bacteria in time

Speed of reproduction of some bacteria is proportional to the quantity of bacteria presently.

Denote the quantity of bacteria present presently *X*. Thus

$$\frac{dX}{dt} = kX,$$

k – coefficient of proportionality.

After integration obtain

$$X = Ce^{kt}.$$

When $t=0$, $X=X_0$, thus $C= X_0$.
Consequently

$$X = X_0 e^{kt}.$$

At favorable condition the increase of quantity of bacteria in time takes place on an exponential law.

Exercises

Independent work in the class

1. Find the law of drug decrease in the human organism, if 1 hour after infusion of 10 mg of the drug its mass decreases twice. How much drug remains in human organism in 2 hours?
2. Initial mass of enzyme is 1 g, in 1 hour it is 1.2g. Find its mass in 5 hours after the beginning of fermentation. The speed of increase of enzyme is considered to be proportional to its available quantity.
3. Dissolving rate of salt is proportional to difference of concentration of saturated y_0 and real x solutions. Find the law of variation of salt concentration, if for $t = 0 \quad x = x_0$.
4. A bacterial population grows at a rate proportional to the population size at time *t*. Let *y(t)* be the population size at time t. By experiment it is determined that the population at $t = 10$ min is15 000 and at $t = 30$ min it is 20 000.
a) What was the initial population?
b) What will the population be at time t = 60 min?
5. Chemicals **Y** and **Z** combine to form **X** at a rate that is proportional to the product of the concentrations of **Y** and **Z**. If the initial concentrations of species **Y** and **Z** are 3 and 5, respectively, find an expression for the number of moles of X at any time. Use the value of **k** from the first exercise and plot your result.

Homework

Exercises
1. The rate of disintegration of a drug is proportional to its available quantity. In 1 hour 31.4 g of the drug remained in human organism, in 3 hours – 9.7 g. Find
a) initial mass of the drug;
b) time, when remained 1% of the initial mass remains in the organism.
2. A colony of bacteria is treated with a mild antibiotic agent so that the bacteria start to die. It is observed that the density of bacteria as a function of time follows the approximate relationship $b(t) = 85e^{-0.5t}$ where t is time in hours. Determine the time it takes for half of the bacteria to disappear (This is called the half life.) Find how long it takes for 99% of the bacteria to die.

3. Rate of enzymatic reactions sometimes is given by formula $\frac{dx}{dt} = \frac{k_1(\alpha - x)}{1 + k_2(\alpha - x)}$, where x is the concentration of a product at the moment t, a is the initial concentration of reagent. Find concentration dependence on time.

4. Distribution of potential along a passive fiber is set by the differential equation $\lambda \frac{d^2V}{dx^2} = V$, where λ is the constant, which equals to the ratio of resistance of protoplasm and membrane per unit of length of a fiber, x - length of a fiber. Find dependence of change of potential on length of a fiber taking into account, that the potential cannot increase along a fiber till infinity at $x=0$, $V=0$.
5. The half-life of a radioactive material is 1620 years. What percentage of the radioactivity will remain after 500 years?
6. Cobalt 60 is a radioactive substance with half life 5.3 years. It is used in medical application (radiology). How long does it take for 80% of a sample of this substance to decay?
7. A population of animals has a per-capita birth rate of $b = 0.08$ per year and a per-capita death rate of $m = 0.01$ per year. The population density, *P(t)* is found to satisfy the differential equation $\frac{dP(t)}{dt} = bP(t) - mP(t)$
a) If the population is initially $P(0) = 1000$, find the population in 5 years.
b) When will the population double?
8. The per capita birthrate of one species of rodent is 0.05 newborns per day. (This means that, on average, each member of the population will result in 5 newborn rodents every 100 days.) Suppose that over the period of 1000 days there are no deaths, and that the initial population of rodents is 250. Write a differential equation for the population size *N(t)* at time t (in days). Write down the initial condition that N satisfies. Find the solution, i.e. express N as some function of time t that satisfies your differential equation and initial condition. How many rodents will there be after 1 year?
9. The population *y(t)* of a certain microorganism grows continuously and follows an exponential behavior over time. Its doubling time is found to be 0.27 hours. What differential equation would you use to describe its growth? (Note: you will have to find the value of the rate constant, k, using the doubling time.)

10. With exposure to ultra-violet radiation, the population ceases to grow, and the microorganisms continuously die off. It is found that the half-life is then 0.1 hours. What differential equation would now describe the population?

11. Two populations are studied. Population 1 is found to obey the differential equation

$dy_1/dt = 0.2y_1$

and population 2 obeys

$dy_2/dt = -0.3y_2$

where t is time in years.

a) Which population is growing and which is declining?

b) Find the doubling time (respectively half-life) associated with the given population.

c) If the initial levels of the two populations were $y_1(0) = 100$ and $y_2(0) = 10\,000$, how big would each population be at time t ?

d) At what time would the two populations be exactly equal?

12. The human population on Earth doubles roughly every 50 years. In October 2000 there were 6.1 billion humans on earth. Determine what the human population would be 500 years later under the uncontrolled growth scenario. How many people would have to inhabit each square kilometer of the planet for this population to fit on earth? (Take the circumference of the earth to be 40,000 km for the purpose of computing its surface area.)

13. When chemists say that a chemical reaction follows "first order kinetics", they mean that the concentration of the reactant at time t, i.e. c(t), satisfies an equation of the form $dc/dt = -rc$, where r is a rate constant, here assumed to be positive. Suppose the reaction mixture initially has concentration 1M ("1 molar") and that after 1 hour there is half this amount.

a) Find the "half life" of the reactant.

b) Find the value of the rate constant r.

c) Determine how much will be left after 2 hours.

d) When will only 10% of the initial amount be left?

14. Reaction of the first order is entered by 1000 molecules and for 1 second 400 from them breaks up. How many molecules break up for 2 seconds?

15. Carbon 14 has a half-life of 5730 years. This means that after 5730 years, a sample of Carbon 14, which is a radioactive isotope of carbon will have lost one half of its original radioactivity.

a) Estimate how long does it take for the sample to fall to roughly 0.001 of its original level of radioactivity.

b) Each gram of C^{14} has an activity given here in units of 12 decays per minute. After some time, the amount of radioactivity decreases. For example, a sample 5730 years old has only one half the original activity level, i.e. 6 decays per minute. If a 1 gm sample of material is found to have 45 decays per hour, approximately how old is it? (Note: C^{14} is used in radiocarbon dating, a process by which the age of materials containing carbon can be estimated. W. Libby received the Nobel prize in chemistry in 1960 for developing this technique.)