Project 1 : One Compartment Model

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Abstract

The most common and preferred route of drug administration is the use of pharmaceuticals such as capsules or oral infusions. However, we cannot directly determine how the administered drug affects our body. So, we implement a pharmacokinetics model to find out what effect the drug has. Pharmacokinetics describe the process by which drugs move in and out of the body (the time course of absorption, distribution, metabolism, and excretion). In order to implement a pharmacokinetics model that dynamically explains and predicts the effect of a drug, both the route of administration and the movement of the drug in the body need to be known.

Therefore, in this project, we modeling a change in the drug concentration of the body over time from when the drug enters the body, considering our body as one compartment. In the given Exercise 1. 2., find out the concentration according to k(the rate of changing in decrease) and find out by inverse estimation of k using SSQ(Residual Sum-of-Squares) in Exercise 3. 4. 5..

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1. Introduction

The biggest issue in modern society is by far the COVID-19(Corona virus). Because of this, many people have been vaccinated, and now the fourth vaccine has been distributed. As the times go by, various diseases and new drugs are being developed accordingly. This project was conducte d to solve the question of how these new drugs affect our human body.

In this project, our body was regarded as one compartment or kinetically homogeneous unit, and the change in the drug concentration of the body was observed over time after the drug was injected into the body. Through various exercises, the formula for one compartment modeling and the method of estimating the k(reduction rate of change of the drug in the body) in linear and non-linear models were described.

2. Experimental Details

1 Intravenous Injection (drug concentration in the plasma)

- By the Laplace transform

$$s\overline{X} - X_0 = -k\overline{X}$$

$$\overline{X} = X_0/(s+k)$$

$$x = x_0 e^{-kt}$$

- Taking the natural logarithm of both sides gives

$$\ln x = \ln x_0 - kt$$

Since $2.303\log a = \ln a$

$$\log x = \log x_0 - \frac{kt}{2.303}$$

If the volume of compartment is know

$$X = VC \text{ or } C = X/V$$

where $C =$ drug concentration

$$\log C = \log C_0 - \frac{kt}{2.303}$$

$C_0 =$ the drug concentration in plasma immediately after injection

2 Simulation

$$y = 75e^{-kt}$$

3 Least Squares Method

$$Residual = Y_i - \widehat{Y}_i$$

$$SSQ = \sum_{i=1}^{n} (Y_i - \widehat{Y}_i)^2$$

4 Linear Least Squares

- Fitting a line

Given $y = a+bx$

$$\frac{dq}{da} = -2\sum(y_i - a - bx_i) = 0$$

$$\frac{dq}{db} = -2\sum x_i(y_i - a - bx_i) = 0$$

Rewrite

$$an + b\sum x_i = \sum y_i$$

In matrix form

$$\begin{pmatrix} n & \sum x_i \\ \sum x_i & \sum x_i^2 \end{pmatrix}\begin{pmatrix} a \\ b \end{pmatrix} = \begin{pmatrix} \sum y_i \\ \sum x_i y_i \end{pmatrix}$$

- Fitting a function (generalized form)

$$y = f(x) = a_1\Phi_1(x) + a_2\Phi_2(x) + \cdots + a_n\Phi_n(x)$$

$$q_k = y_k - a_1\Phi_1(x_k) - a_2\Phi_2(x_k) - \cdots - a_n\Phi_n(x_k)$$

$$S = \sum_{i=1}^{m}[y_i - a_1\Phi_1(x_i) - a_2\Phi_2(x_i) - \cdots - a_n\Phi_n(x_i)]^2$$

$$\frac{dS}{da_k} = 0, k = 1, 2, \ldots, n$$

$$\frac{dS}{da_k} = \sum_{i=1}^{m} 2[y_i - a_1\Phi_1(x_i) - a_2\Phi_2(x_i) - \cdots - a_n\Phi_n(x_i)]\Phi_k(x_i) = 0$$

$$\sum_{i=1}^{m} y_i\Phi_k(x_i) - a_1\sum_{i=1}^{m}\Phi_1(x_i)\Phi_k(x_i) + a_2\sum_{i=1}^{m}\Phi_2(x_i)\Phi_k(x_i) + \cdots + a_n\sum_{i=1}^{m}\Phi_n(x_i)\Phi_k(x_i) = 0$$

$$k = 1, 2, \ldots, n$$

$$\begin{bmatrix} \sum_{i=1}^{m}\Phi_1(x_i)^2 & \sum_{i=1}^{m}\Phi_2(x_i)\Phi_1(x_i) & \cdots & \sum_{i=1}^{m}\Phi_n(x_i)\Phi_1(x_i) \\ \sum_{i=1}^{m}\Phi_1(x_i)\Phi_2(x_i) & \sum_{i=1}^{m}[\Phi_2(x_i)]^2 & \cdots & \sum_{i=1}^{m}\Phi_n(x_i)\Phi_2(x_i) \\ \cdots & \cdots & & \cdots \\ \sum_{i=1}^{m}\Phi_1(x_i)\Phi_n(x_i) & \sum_{i=1}^{m}\Phi_2(x_i)\Phi_n(x_i) & & \sum_{i=1}^{m}[\Phi_n(x_i)]^2 \end{bmatrix}\begin{bmatrix} a_1 \\ a_2 \\ \cdots \\ a_n \end{bmatrix} = \begin{bmatrix} \sum_{i=1}^{m} y_i\Phi_1(x_i) \\ \sum_{i=1}^{m} y_i\Phi_2(x_i) \\ \cdots \\ \sum_{i=1}^{m} y_i\Phi_n(x_i) \end{bmatrix}$$

$$Pa = b \qquad [*]$$

$$P_{ki} = \sum_{i=1}^{m}\Phi_k(x_i)\Phi_i(x_i) \text{ and } b_k = \sum_{i=1}^{m} y_i\Phi_k(x_i)$$

3. Results

Exercise 1.

Plot y(t) for t is from 0 to 120 minutes at every 0.5min. Label x and y-axis.

The given k at the simulation has a value of 0.05, the value of t ranges from 0 to 120 minutes in 0.5 minute. Substitute this into the followi ng equation to obtain y.

$$y = 75e^{-kt} \quad [1]$$

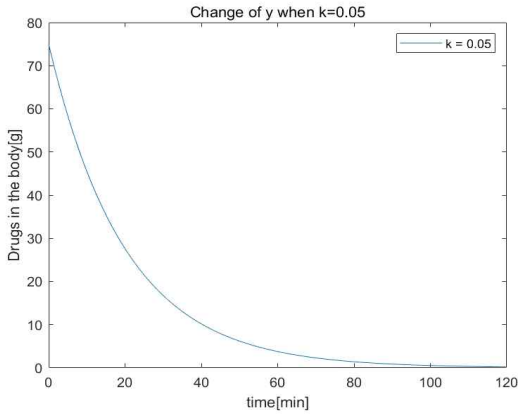

Fig.1 Change of drug concentration in the body with time when k=0.05

Exercise 2.

Plot t vs. y(t) for k=0.05, 0.025, and 0.10. Use different line formats.

Observer the change in drug concentration based on the k and t values given on Eq[1] of Exercise 1.. In Exercise 1., only the change in dru g concentration with time was measured when k was fixed, whereas in Exercise 2., the effect of k was observed when k was changed.

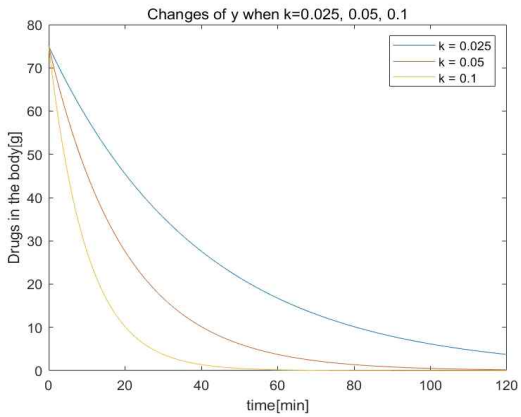

Fig.2 Change of drug concentration in the body with time according to change of k

Referring to Fig.1, it can be seen that the drug concentration decreases with time when k is fixed. This can be seen as the same as the absorption pattern of the drug over time. In the beginning, the drug is rapidly absorbe d, but the rate of absorption decreases as time goes on. Also, Fig.2 shows the situation according to k, and it can be seen that the absorption rate decreases more rapidly as k increases.

Exercise 3.

Find k from the data computed in Exercise 1.. Discuss.

In the previous procedures, the change in drug concentration over time was measured through a given k, but in Exercise 3., k is inversely est imated through the change in the body concentration over time. Since Eq[1] is expressed as an exponential function and has non-linear characteri stics, in order to inversely estimate k, it must be converted into a linear form and the ln function is taken on both sides. The inversely estimated k is expressed in the form.

$$k = \frac{\ln 75}{t} - \frac{\ln y}{t} \qquad [2]$$

As can be seen in Tab.1, if we take k,t in Exercise 1. and find the value of y, we get about 0.1859. By substituting this into Eq[2], k can be inversely estimated with the result shown in Fig.3.

Tab.1 Value of y when k=0.05, t=0~120

y (1*241 double)					
···	237	238	239	240	241
···	0.2107	0.2055	0.2004	0.1954	0.1859

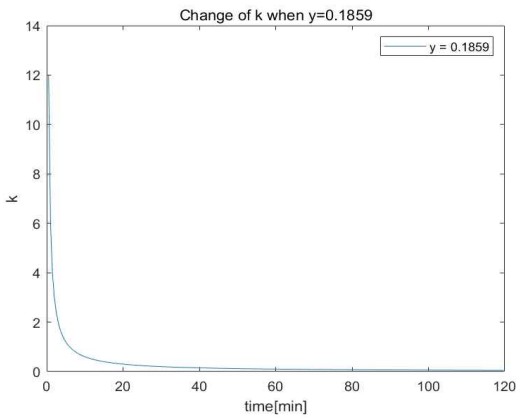

Fig.3 Change of k with time when y=0.1859

Exercise 4.

Derive P by hands, a and b for $y(t) = b_0 + b_1 x + b_2 x^2$ according to procedures in 2 and 3.

In Fig.4,

$$y(t) = b_0 + b_1 x + b_2 x^2 \quad [3]$$

$$q = \sum (y_i - b_0 - b_1 x_i - b_2 x_i^2)^2 \quad [4]$$

In order to minimize the expression for q, the partial derivatives of b_0, b_1, and b_2 are expressed as (1), (2), (3) in Fig.4. After expressing the result as a matrix, b_0, b_1, and b_2 were obtained using the inverse matrix.

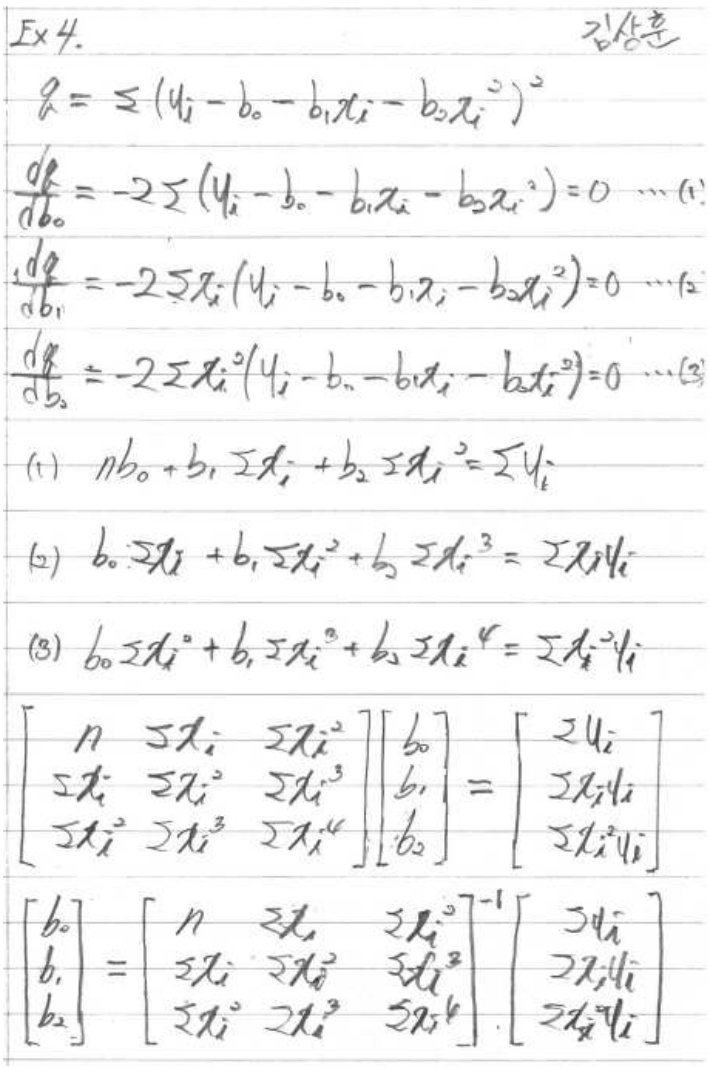

Fig.4 The procedure for deriving P

Exercise 5.

Find k in Exercise 1. by writing a Matlab program for linear fitting (i.e., use Eq[*] and inv function of Matlab)

Like Exercise 4.,

$$\frac{dq}{da} = -2\sum(y_i - a - bx_i) = 0 \quad [5]$$

$$\frac{dq}{db} = -2\sum x_i(y_i - a - bx_i) = 0 \quad [6]$$

The expressions of Eq[5] and Eq[6] were converted to Eq[7] using a matrix.

$$\begin{pmatrix} n & \sum x_i \\ \sum x_i & \sum x_i^2 \end{pmatrix}\begin{pmatrix} a \\ b \end{pmatrix} = \begin{pmatrix} \sum y_i \\ \sum x_i y_i \end{pmatrix} \quad [7]$$

Eq[8] was obtained by taking the lnfunction on both sides of Eq[1].(Assume x_0 is 75)

$$\ln y = \ln x_0 - kt \quad [8]$$

Substituting Eq[8] into Eq[7] gives Eq[9].

$$\begin{pmatrix} 241 & \sum t_i \\ \sum t_i & \sum t_i^2 \end{pmatrix}\begin{pmatrix} \ln x_0 \\ -k \end{pmatrix} = \begin{pmatrix} \sum \ln y_i \\ \sum t_i \ln y_i \end{pmatrix} \quad [9]$$

(P) (Q) (Y)

Eq[9] was found by using Matlab's inv function to find x_0 and k. Invert the P matrix of Tab.2, can get the Q of Tab.3 by $Q = P^{-1}Y$.

Tab.2 Value of P with t

P	
241	14460
14460	1159210

Tab.3 Value of Q using inv(P)

Q
4.3175
-0.0500

Therefore, it can be seen that $x_0 = e^{4.3175} = 75,\ k = 0.05$.

Exercise 6.

Find k in Exercise 1. by writing a Matlab program for non-linear least squares fitting. Plot SSQ vs. iteration. Plot k_estimated vs. iteration. Plot fitting curve at every iteration.

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4. Discussions

Through a series of processes, the most important part was to inves tigate the relationship between the concentration and absorption of the drug remaining in the body as the k value changed over time. In addition, using SSQ, we studied how to inversely estimate k with given data and mad e a matrix. Finally, we found that it is important to increase the drug's persistence by creating linear and non-linear models.

In the case of Coronavirus, for example, it is conceivable that it could be possible to increase the durability by replacing the vaccine with a pill rather than a vaccination.

5. Conclusions

Through this project, we considered our body as one compartment and confirmed the change in the drug concentration of the body over time from the time the drug entered the body by establishing a simple formula. At this time, since the concentration of the drug in progress varies from person to person, the human body was regarded as a kinetically homogeneous unit and changes were observed.

Even if all people develop the same disease, each person's physical characteristics are different, so the amount of medication that needs to be administered is different. Therefore, I think that a lot of research should be done so that the treatment can be further improved by collecting the data and modeling it in advance.

References

1 Jennifer Le, *Overview of Pharmacokinetics*, www.msdmanuals.com/professional/clinical-pharmacology/pharmacokinetics/overview-of-pharmacokinetics

2 Jennifer Le, *Drug Absorption*, www.msdmanuals.com/professional/clinical-pharmacology/pharmacokinetics/drug-absorption

3 Lon, H. K., Liu, D., DuBois, D. C., Almon, R. R., and Jusko,W.J.,*Modeling pharmacokinetics*, Journal of Pharmacokinetics andPharmacodynamics, Volume 40, Section 6, pp241-252.

4 Zurlinden, Todd J, *Computational modeling of the pharmacokinetic and pharmacodynamics of selected xenobiotics*, Colorado State University, 2016, pp 119-148.

5 Glassman, P. M., Balthasar, J. P.,*Physiologically-based pharmacokinetic modeling to predict the clinical pharmacokinetics of monoclonal antibodies*, Journal of Pharmacokinetics and Pharmacodynamics, Volume 43, Section4, pp492-498.

Appendices

Exercise 1.

```
t = 0:0.5:120;
k = 0.05;
y = 75*exp(-k.*t);
figure(1);
plot(t,y);
title('Change of y when k=0.05');
xlabel('time[min]');
ylabel('Drugs in the body[g]');
legend('k = 0.05');
```

Exercise 2.

```
t = 0:0.5:120;
k = 0.025;
y= 75*exp(-k.*t);
figure(1);
for i = 1:1:3;
        plot(t,y);
        hold on;
        k = 2*k;
        y = 75*exp(-k.*t);
end;
title('Changes of y when k=0.025, 0.05, 0.1');
xlabel('time[min]');
ylabel('Drugs in the body[g]');
legend('k = 0.025', 'k = 0.05', 'k = 0.1');
```

Exercise 3.

```
t = 0:0.5:120;
y = 0.1859;
k = (log(75) - log(y))./t;
figure(1);
plot(t,k);
title('Change of k when y=0.1859');
xlabel('time[min]');
ylabel('k');
legend('y = 0.1859');
```

Appendices

Exercise 5.

```
t = 0:0.5:120;
k = 0.05;
y = 75*exp(-k.*t);
n = size(t);
N = n(1,2);
P = [N sum(t); sum(t) sum(t.*t)];
Y = [sum(log(y)); sum(t.*log(y))];
Q = inv(P)*Y;
```

Exercise 6.

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