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STUDENT VERSION
LIPOPROTEIN METABOLISM

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STATEMENT

The background for this modeling scenario comes from [1, pp. 208-217] and appears in a section entitled The Basic Estimation Problem in which the author describes a number of parameter estimation techniques using "... the data which is based on baboon low-density-lipoprotein (LDL) data taken over a 10-day period in laboratory animal studies relating to the material in [2]." The data (see Table 1) is in time, days, with amount of a tracer compound in Compartment 1 - Blood Plasma while "... the experiment consists of a bolus injection of a unit amount of tracer into Compartment 1 - Blood Plasma at time $t = 0$, and then subsequent sampling of Compartment 1 at times t in days. Compartment 2 is the extravascular or non-blood plasma space of the body. The single model exit ($a_{02} = 0$) is used." The tracer (^{125}I radioactive labeled LDL) is a normalized dose of size 1 unit to begin at time $t = 0$.

> The kinetic parameters for LDL turnover were calculated using methods originally described by Matthews [4] and by Nosslin [5] and recently adapted to LDL turnover studies by Langer [3]. Curve fitting was performed using the SAAM 25 Computer Program to derive the two exponential components of the plasma die-away curve."[2, p. 1422]

In Table 1 we see data on a tracer for low-density-lipoprotein (LDL) after an initial intravenous injection. Again, this is "... based on baboon low-density-lipoprotein data taken over a 10-day period in laboratory animal studies relating to the material in [2]." We will attempt to model this using the two compartment model pictured in Figure 1.

Activity 1

Using the notion of "simple change in something," in this case concentration of LDL in each compartment, we can produce the system of differential equations in (1).

Time (days)	Tracer in Units in A
0.0	1.0000
0.5	0.4610
1.0	0.2590
1.5	0.1700
2.0	0.1210
3.0	0.0722
4.0	0.0451
5.0	0.0319
6.0	0.0240
7.0	0.0182
8.0	0.0141
9.0	0.0100
10.0	0.0094

Table 1. Data on amount of low-density-lipoprotein (LDL) tracer over time in days found in plasma compartment of baboon after initial intravenous injection. [1, p. 211])

a) Explain how we can develop the differential equations (1) from the diagram in Figure 1which shows the flow of LDL between the plasma compartment and the non-plasma compartment of the body.

If we are going to model this phenomenon as offered in Figure 1 then we need to identify variables and relationships between variables.

$x(t)$ - amount (unknown units) of LDL in the body plasma.
$y(t)$ - amount (unknown units) of LDL in the extravascular space.
V_x - volume of the body plasma.
V_y - volume of the extravascular space.

a_{21} - rate constant (1/day) for the flow of LDL from plasma to the extravascular space.
a_{12} - rate constant (1/day) for the flow of LDL from the extravascular space to plasma.
a_{01} - rate constant (1/day) for the metabolism and excretion of LDL in plasma.
a_{02} - rate constant (1/day) for the metabolism and excretion of LDL in extravascular.

Here is the resulting differential equations model we ask you to defend.

$$\begin{aligned} x'(t) &= -a_{21}x(t) - a_{01}x(t) + a_{12}y(t) \\ y'(t) &= a_{21}x(t) - a_{12}y(t) - a_{02}y(t\,. \end{aligned} \tag{1}$$

Notice that the volumes of parts of our model, V_x and V_y are not given to us. However, we do know the initial concentration of LDL in the plasma compartment, i.e. $x(0) = 1$, an unknown unit, but we presume there is no LDL in the rest of the extravascular space, so $y(0) = 0$ is used. Furthermore, recall that "single exit" ($a_{02} = 0$) model is assumed [1, p.210].

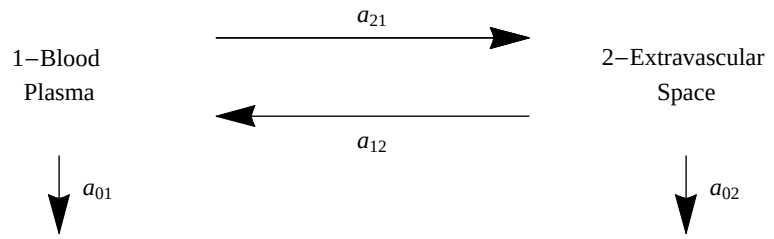

Figure 1. Diagram (from [1, p. 103]) of two compartment model for the study of low-density-lipoprotein (LDL) kinetics in a baboon.

Activity 2

We seek to estimate the parameters a_{21}, a_{12}, and a_{01}, each with units 1/day if we are to fully understand this process.

a) Perform the necessary analysis to determine the parameters a_{21}, a_{12}, and a_{01}, using the data in Table 1.

So how do we estimate these parameters? We use Mathematica to get closed form solutions for $x(t)$ and $y(t)$, each of which is about 5 lines of complex algebraic expressions in the familiar format of solutions to such systems, i.e. sums of exponentials with messy terms involving a_{21}, a_{12}, and a_{01}. If we place the values of the amount of LDL tracer in the plasma at each time t into an array, calling it X, with time as the first coordinate and the amount of LDL tracer in the plasma at the corresponding time as the second coordinate we have 13 (from observations) time-units data pairs. From these we form the sum of square errors (2) between the model $x(t)$ values and the observed values for amount (units) of LDL tracer in the plasma. Call the latter $O_i, i = 1, 2, \ldots, 13$.

$$\text{SSE}(a_{21}, a_{12}, a_{01}) = \sum_{i=1}^{7} (x(t_i) - O_i)^2 \tag{2}$$

Now with Mathematica's powerful `FindMinimum` command we can determine the values of the parameters a_{21}, a_{12}, and a_{01}, which minimize this $\text{SSE}(a_{21}, a_{12}, a_{01})$ function,

`FindMinimum[SSE[`a_{21}`, `a_{12}`, `a_{01}`], {`a_{21}`, 1}, {`a_{12}`, 1}, {`a_{01}`, 1}]` .

b) Use the resulting parameters in the model (1) and determine a function for $x(t)$, the amount of LDL in the body plasma or bloodstream at time t minutes.

b) Plot the model function, $x(t)$, with the data on observed levels of LDL found in Table 1 and compare them.

c) How much time will it take to get the LDL levels down to 5% in the blood plasma compartment of the original amount injected according to this two compartment model?

d) Use your parameters in the model (1) and determine a function for $y(t)$, the amount of LDL in the extravascular space, i.e. the extravascular space at time t minutes.

e) Determine the time at which the amount of LDL in the extravascular space, i.e. $y(t)$, peaks and the time at which the concentration of LDL in the extravascular space will fall to 5% of that maximum value.

Activity 3

Vary one of the parameters, say a_{21} the rate at which the tracer goes from the bloodstream to the extravascular region of the body and see how sensitive the mode is to slight or large changes in the parameter. Discuss what you see and how it makes sense in your understanding of the physiology involved.

REFERENCES

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