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STUDENT VERSION
MODELING IBUPROFEN

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Abstract: We consider several modeling opportunities for data from a clinical experiment in which subjects were administered oral doses of 400 mg ibuprofen, an analgesic pain reliever. Concentrations of ibuprofen in the serum/plasma of the subjects were recorded after the initial ingestion of the drug. We offer three different models and ask students to model, determine parameters, and compare models using the Akaike Information Criterion to determine which model is best.

In each case we ask students to determine the time at which individual models predict ibuprofen concentration is greatest in the plasma and compare that to the time of peak amount of ibuprofen from the data.

SCENARIO DESCRIPTION

Ibuprofen, an analgesic pain reliever, is ingested into the gastrointestinal tract by swallowing a pill of the substance or drinking a solution. The drug then moves to the serum or plasma (blood) where it travels to sites to do its work of pain relief.

The following data (see Table 1) comes from an experiment in which "Following oral dosing with 400 mg ibuprofen, serial blood samples were taken from five healthy male volunteers and four patients."[1, p.528] This is the data from one of the healthy subjects. This data was read off an enlargement of the plot in Figure 1 of [1, p.529]. We used Figure 1a data for one of the healthy subjects. It is worth noting that a standard dose in each pill of Advil Liqui-Gels is 200 mg of ibuprofen, but often patients take two pills for relief, resulting in a dose of 400 mg ibuprofen.

Model 1

This is an example of a two compartment model. We show a diagram of the situation in Figure 1. For our data we do not know the volume of the gastrointestinal tract nor the volume of the plasma for our patients, so we shall call these v_1 and v_2 respectively.

Define variables to be:

Time	Ibuprofen
(hr)	Conc. μg/ml
0	0
0.65	25.81
1.03	34.22
1.26	33.47
1.63	32.91
1.73	28.42
2.10	27.16
3.00	16.64
3.97	9.91
5.08	7.48
6.02	5.24
7.00	4.86

Table 1. serum/plasma concentration of Ibuprofen at time intervals after an initial oral dose of 400 mg of ibuprofen was administered to a healthy patient.

$x_1(t)$ = concentration of ibuprofen in the gastrointestinal (tract) compartment in μg/ml or mg/l;
$x_2(t)$ = concentration of ibuprofen in the serum/plasma compartment in μg/ml or mg/l.

1. Construct a system of linear differential equations to model the absorption of ibuprofen as depicted in Figure 1. You might consider modeling the change in the *amount* of ibuprofen in the two compartments:

$$\begin{aligned} v_1 x_1'(t) &= \\ v_2 x_2'(t) &= \end{aligned} \tag{1}$$

2. Then offer a revised system of differential equations model in which we combine rate constants and volumes of regions of the body, i.e. gastrointestinal tract, $x_1(t)$, and serum/plasma $x_2(t)$. Since we do not know these respective compartment volumes, but have a value of v_2 for a typical human being of 5 l from the literature [3] let us assume this data comes from a typical human with $v_2 = 5$ l serum/plasma. We then solve the system of differential equations and identify the functions from solution.

   Now $v_1 x_1(t) = X_1(t)$ is the actual amount of ibuprofen in mg in the gastrointestinal tract at time t and $v_2 x_2(t) = X_2(t)$, using $v_2 = 5$, is the actual amount of ibuprofen in mg in the serum/plasma in the body at time t.

   Let us rewrite the system of differential equations (1) in terms of the functions $X_1(t)$ and

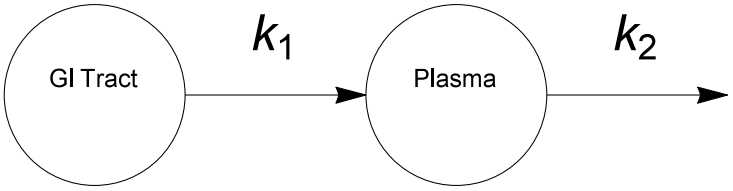

Figure 1. Diagram for two compartment model of ibuprofen absorption. k_1 is called the *absorption rate* from gastrointestinal tract to serum/plasma while k_2 is called the *elimination rate* constant. Both have units 1/hr.

$X_2(t)$, the respective amounts in mg of ibuprofen in the respective compartments, gastrointestinal tract - $X_1(t)$ and serum/plasma - $X_2(t)$.

$$\begin{aligned} X_1'(t) &= \\ X_2'(t) &= \end{aligned} \tag{2}$$

3. Solve the differential equations (2) assuming $v_2 = 5$ for the respective amounts of ibuprofen. Worried about v_1? Be patient and watch and see as your work progresses.
4. Here are three sets of estimates of the parameters for this model. Which one is best (of the three presented) for predicting the data?
   (a) $k_1 = 0.91$, $k_2 = 0.15$,
   (b) $k_1 = 0.65$, $k_2 = 0.41$,
   (c) $k_1 = 0.85$, $k_2 = 0.92$.
5. Develop a strategy and execute it for determining a truly best estimate of the rate parameters k_1 and k_2.
6. Compute the sum of square errors between the data and your best model for the concentration of ibuprofen in the serum/plasma.
7. Plot the resulting model over your data and comment on its ability to predict the drug behavior.

Model 3

This model is essentially the same as Model 1 except that we do introduce a delay time period τ between when the ibuprofen enters the serum/plasma and when it become effective in relieving pain. See Figure 2. Presumably the rate at which it enters the serum/plasma remains the same, but there is a time delay, τ, between when it enters the serum/plasma compartment and it becomes effective.

Here, as in Model 1, we assume $v_2 = 5$ l, thus keeping this model in two parameters k_1 and k_2 as well as τ. Still worried about v_1? Be patient and watch and see as your work progresses.

13. Construct a system of linear differential equations to model the absorption of ibuprofen as

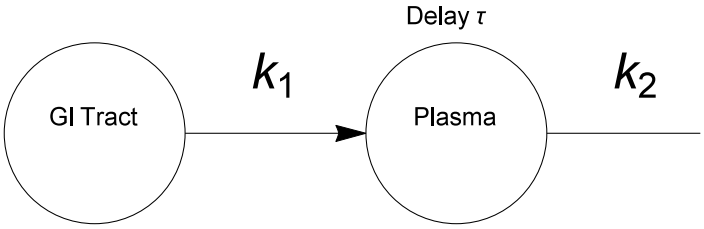

Figure 2. Diagram for two compartment model of ibuprofen absorption with a delay of τ hours before it becomes effective as a pain killer. k_1 is called the *absorption rate* from gastrointestinal tract to serum/plasma while k_2 is called the *elimination rate* constant. Both have units 1/hr.

depicted in Figure 2. Hint: Model the delay τ ONLY after solving for $X_2(t)$ in the modified system of differential equations (2) by using the delay τ to produce $X_2(t-\tau)$ in place of $X_2(t)$ when computing sum of square errors and then determining the best rate parameters k_1 and k_2, and the time delay τ.

14. Solve this modified set of differential equations for the respective amounts of ibuprofen.
15. Develop a strategy and execute it for determining a best estimate of the rate parameters k_1 and k_2, as well as the time delay τ. Remember, when computing sum of square errors and then determining the best rate parameters k_1 and k_2, and the time delay τ use $X_2(t-\tau)$ in place of $X_2(t)$ ONLY after solving for $X_2(t)$.
16. Give a best estimate of the rate parameters k_1 and k_2, and the time delay τ.
17. Compute the sum of square errors between the data and your best model for the concentration of ibuprofen in the serum/plasma.
18. Plot the resulting model over your data and comment on its ability to predict the drug behavior.

Model 4

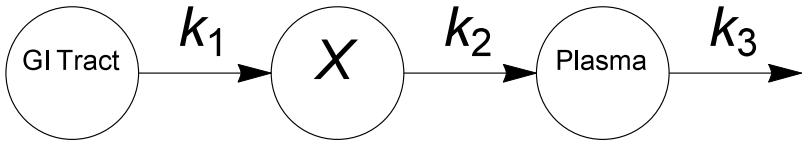

Figure 3. Diagram for three compartment model of ibuprofen absorption with an introduced intermediate compartment X between when the ibuprofen clears the gastrointestinal compartment and enters the serum/plasma compartment. k_1 is the *absorption rate* from gastrointestinal tract to the X compartment, k_2 is the *absorption rate* from the X compartment to serum/plasma, while k_3 is called the *elimination rate* constant. All have units 1/hr.

20. Construct a system of linear differential equations to model the absorption of ibuprofen as depicted in Figure 3. Here, as in Model 1, we assume $v_2 = 5$ l. Worried about v_1? Be patient and watch and see as your work progresses.
21. Solve the differential equation for the respective amounts of ibuprofen.
22. Develop a strategy and execute it for determining a best estimate of the rate parameters k_1, k_2, and k_3.
23. Give a best estimate of the rate parameters k_1, k_2, and k_3.
24. Compute the sum of square errors between the data and your model for the concentration of ibuprofen in the serum/plasma.
25. Plot the resulting model over your data and comment on its ability to predict the drug behavior.

Which model is best? AIC to the rescue.

We will offer a way of determining which model, Model 1, Model 3, or Model 4, is best. It is called the Akaike Information Criterion (AIC). A readable reference for AIC can be found in [2, p.138 ff].

The Akaike Information Criterion (3), where k is the number of parameters to fit, n is the number of observations, and RSS is the minimum residual sum of square errors (or just sum of square errors) is an attempt to balance the number of parameters with the minimum sum of square errors.

$$\text{AIC} = 2(1+k) + n\log\left(\frac{RSS}{n}\right). \tag{3}$$

The AIC can help a modeler decide which of two reasoned models is best. For, one can get a perfect fitting model with n observations by running an $n-1$ degree polynomial exactly through all the data, but if n is large this makes the AIC large. Moreover, such a polynomial model is really not good at explaining anything with respect to the phenomenon being studied. So we are not surprised that while such a model is absolutely best (with RSS being zero the AIC is effectively $-\infty$) we should not rely on it for any true information about the process being modeled.

Smaller (even negative) values of AIC represent higher level of statistical support for the corresponding model. A difference of 2 in the AIC's is needed to suggest a significant difference between two adjacent (ordered by AIC) models, if its AIC is at least 2 less than the next model.

The smallest AIC means best model - in terms of balancing ACCURACY (RSS) and COMPLEXITY (k).

Again, to compute the AIC for each of the four models you will need (1) the minimum sum of square errors, (2) the number of parameters in the model, (3) the number of observations or data points.

27. Compute AIC for all three model analyses (Model 1, Model 3, and Model 4) and report which model is best, if possible.

REFERENCES

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[3] Wikipedia contributors. 2016. Blood volume. *Wikipedia, The Free Encyclopedia*. https://en.wikipedia.org/w/index.php?title=Blood_volume&oldid=701110431. Accessed 20 May 2016.