Mathematical Journeys I

Lab 9
Faculty Notes

Hemodialysis

The following web site contains a dictionary of measurement units. Your students may find it helpful, especially for defining International Units.
www.unc.edu/~rowlett/units/dictI.html

Information regarding the anticoagulant heparin and common dosage strengths is available from the web site, www.mediresource.net/canoe/health/DrugInfo.asp?drugName-heparin.

One approach to implementing this laboratory is to break it up into three stages:

Stage One
Bring yourself and your students up to speed on the process of dialysis.

Stage Two
Visit or bring in a dialysis technician. See how the process of dialysis is practiced. Get a complete understanding of how the blood is thinned to keep it from clotting. You may also want to obtain anonymous patient data to use in conjunction with the heparin model.

Stage Three
Work through the heparin-clearance model with your students. Obtain anonymous dialysis data from your dialysis technician and analyze it with your heparin-clearance model.

Extensions

Note: In the following, line numbers refer to in equations in the lab, not in the Faculty Notes.

The area of heparin dosing for dialysis patients is an unresolved issue in medical research. Currently there are studies with unfractioned heparin, low-weight heparin, and even some studies in which dialysis is done without an anticoagulant. In your search you should come across several different proposed models. Investigating any one of these models would provide a rich mathematical journey.

The following articles provide a good foundation for further investigation of heparin modeling.

Khazine, F. & Simons, O. (1985, February). Pharmacokinetic monitoring of heparin therapy for regular hemodialysis. Artificial Organs, 9 (1), 59-61.

Low, C. L., Bailie, G., Morgan, S., Eisele, G. (1996, February). Effect of a sliding scale protocol for heparin on the ability to maintain whole blood activated partial thromboplastin times within a desired range in hemodialysis patients. Clinical Nephrology, 45 (2), 120-124.

Mitsuoka, J. C. (1983). A calculator program to determine heparin requirements during hemodialysis. Computer Biological Medicine 13, (3), 239-243.

Ouseph, R., Brier, M. E., Ward, R. A. (2000, January). Improved dialyzer reuse after use of a population pharmacodynamic model to determine heparin doses. American Journal Kidney Disease, 35 (1), 89-94.

Smith, B. P., Ward, R. A., Brier, M. E. (1998, September). Prediction of anticoagulation during hemodialysis by population kinetics and an artificial neural network. Artificial Organs, 22 (9), 731-739.

Ward, R. A. (1995, October). Heparinization for routine Hemodialysis. Advanced Renal Replacement Therapy, 2 (4), 362-370.

In this laboratory, the students will develop formulas to determine the loading dose. In practice, when a patient is started on a hemodialysis treatment, the physician will decide upon a loading dose of heparin. There are different criteria for deciding on the loading dose. A weight-based protocol will determine a dose based on the patient's weight. A rough guideline would be to administer 50 units of heparin per kilogram of body weight. Thus, a man weighing 70 kg might be given a loading dose of 3,500 units. These values may vary from one dialysis center to another and from patient to patient.

Answers to Exercises

Exercise 1

Determine the sensitivity of a patient with a baseline of 70 seconds who has a WBPTT of 160 seconds after a dose of 2000 IU of heparin.

Baseline WBPTT = 70 seconds
WBPTT after dose of 2000 IU = 160 seconds
Then $S = R/D = (160 - 70)/2000 = 0.045$ s/IU.

Exercise 2

Write a first-order differential equation to describe the reaction and solve.

$$\frac{dC}{dt} = -k \cdot C(t) \quad \text{where } k > 0$$

$$\frac{dC}{C(t)} = -k\,dt$$

$$\int \frac{dC}{C(t)} = -k \int dt$$

$$\ln\left|C(t)\right| = -k \cdot t + A$$

where A is any real number.

$$\left|C(t)\right| = e^{-kt+A} = e^{A} \cdot e^{-kt}$$

$$C(t) = \pm Be^{-kt} \quad \text{where B is any positive real number}$$

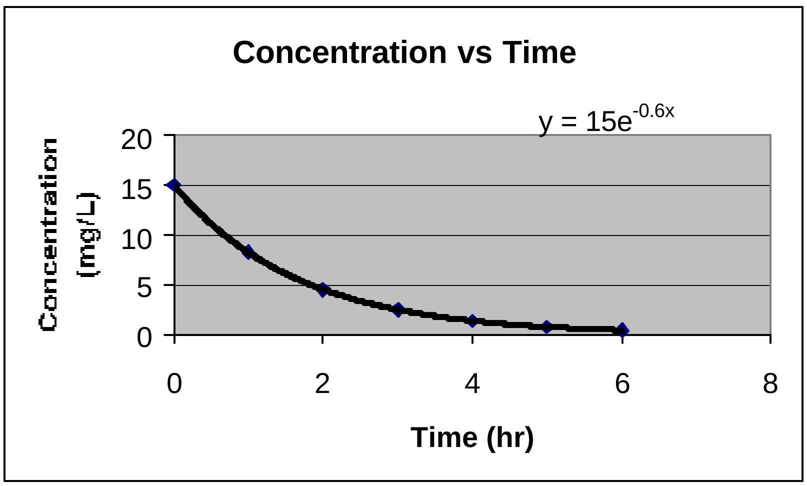
However, notice that if B = 0, then C(t) is identically equal to zero, and this function satisfies the original differential equation. Hence, the general solution of the differential equation is

$$C(t) = C_0 e^{-kt} \quad \text{where } C_0 \text{ is any real number.}$$

Exercise 3

Construct a table of values for the concentration of a drug every hour for 6 hours following administration of a dose that achieves an initial drug-plasma concentration of 15 mg/liter. Assume that the elimination rate constant is 0.6. Plot the graph of drug-plasma concentration over time.

Time (hrs)	Concentration (mg/L)
0	15
1	8.23
2	4.52
3	2.48
4	1.36
5	0.75
6	0.41



Note: The half-life of a drug is defined as the amount of time that elapses for the drug concentration to reach one half of its initial value. It is denoted by $t_{1/2}$. Thus

$$\frac{1}{2}C_0 = C_0 e^{(-kt_{1/2})}$$

so that

$$k = \frac{-\ln(0.5)}{t_{1/2}} \approx \frac{0.693}{t_{1/2}}$$

Thus, if a drug's half-life is known it is easy to determine its elimination rate constant.

Exercise 4

Verify that Equation (5) is the general solution to Equation (4).

$$\frac{dR}{dt} = I_R S - KR$$

$$\int \frac{dR}{I_R S - KR} = \int dt$$

$$\frac{-1}{K} \int \frac{-K dR}{I_R S - KR} = \int dt$$

$$-\frac{1}{K} \ln \left| I_R S - KR \right| = t + A$$

$$\left| I_R S - KR \right| = e^{-Kt + B} = De^{-Kt} \quad \text{where D is any positive real number}$$

$$I_R S - KR = \pm De^{-Kt} = Ee^{-Kt} \quad \text{where E is any real number}$$

(Note: It may be of interest to have students prove that E can be equal to zero. By setting the left-hand side of the equation to zero, the students can solve for R. The resulting equation represents a constant function that is a solution to the differential equation.)

Thus,

$$R = -\frac{E}{K} e^{-Kt} + \frac{I_R S}{K} \quad \text{where E is any real number} \qquad **$$

Now define a number R_0 so that

$$R_0 = \frac{I_R S}{K} - \frac{E}{K}$$

which gives

$$-\frac{E}{K} = R_0 - \frac{I_R S}{K}$$

Substitute this result into the equation ** to obtain

$$R = \left(R_0 - \frac{I_R S}{K} \right) e^{-Kt} + \frac{I_R S}{K}$$

which implies that

$$R = R_0 e^{-Kt} + \frac{I_R S}{K}\left(1 - e^{-Kt}\right)$$

Notice that R_0 is the initial response. To emphasize that R is a function of time, write

$$R_t = R_0 e^{-Kt} + \frac{I_R S}{K}\left(1 - e^{-Kt}\right)$$

Exercise 5

Substitute $R_t = R_D = R_0$ in Equation (6) and solve for I_R, the constant infusion rate.

That is, R_t is to be maintained at a constant value, R_D. Substitute in Equation (6) and solve for I_R.

$$R_D = R_D e^{-Kt} + \frac{I_R S}{K}\left(1 - e^{-Kt}\right)$$

$$R_D\left(1 - e^{-Kt}\right) = \frac{I_R S}{K}\left(1 - e^{-Kt}\right)$$

$$R_D = \frac{I_R S}{K}$$

$$I_R = \frac{K R_D}{S}$$

Exercise 6

Verify that Equation (6) can be solved algebraically to obtain Equation (7).

$$R_t = R_0 e^{-Kt} + \frac{I_R S}{K}\left(1 - e^{-Kt}\right)$$

$$KR_t = KR_0 e^{-Kt} + I_R S\left(1 - e^{-Kt}\right)$$

$$K\left(R_t - R_0 e^{-Kt}\right) = I_R S\left(1 - e^{-Kt}\right)$$

$$K = \frac{I_R S\left(1 - e^{-Kt}\right)}{\left(R_t - R_0 e^{-Kt}\right)}$$

$$K = \frac{I_R S\left(1 - e^{-Kt}\right)}{R_0\left(\frac{R_t}{R_0} - e^{-Kt}\right)}$$

Substituting R_{t-1} for R_0 gives Equation (7).

Exercise 7

Solve this equation for K. This will give you the formula to determine the elimination rate constant K when infusion has been discontinued.

Substituting $R_0 = R_{t-1}$ and $I_R = 0$ into Equation (5) gives

$$R_t = R_{t-1} e^{-Kt}$$

$$\frac{R_t}{R_{t-1}} = e^{-Kt}$$

$$-Kt = \ln\left(\frac{R_t}{R_{t-1}}\right)$$

$$K = -\frac{1}{t}\ln\left(\frac{R_t}{R_{t-1}}\right)$$

Exercise 8

Complete Table 1 on the next page by calculating values of the response and elimination rate constant. The response values at each time t can be determined from Equation (1) written as R = WBPTT – BL, where BL = 70. Note that for t = 1, 2, 3, and 4 you will need to use Equation (7) to calculate values for K. This equation can be solved intrinsically using technology such as the TI-86™ or TI-92™ graphing calculators or a symbolic algebra system such as Derive™ or Maple™. For t = 4.5, you will need to use the formula for K when infusion has been discontinued.

Elimination rate constant K for t = 1, 2, 3, 4

t = 1:
$$K = \left[\frac{(1500)(0.045)}{85}\right]\left[\frac{1-e^{-Kt}}{\frac{70}{85}-e^{-Kt}}\right] \Rightarrow K = 1.08$$

t = 2:
$$K = \left[\frac{(1500)(0.045)}{70}\right]\left[\frac{1-e^{-Kt}}{\frac{60}{70}-e^{-Kt}}\right] \Rightarrow K = 1.21$$

t = 3:
$$K = \left[\frac{(1500)(0.045)}{60}\right]\left[\frac{1-e^{-Kt}}{\frac{55}{60}-e^{-Kt}}\right] \Rightarrow K = 1.27$$

t = 4:
$$K = \left[\frac{(1500)(0.045)}{55}\right]\left[\frac{1-e^{-Kt}}{\frac{55}{55}-e^{-Kt}}\right] \Rightarrow K = 1.23$$

t = 4.5:
$$K_{4.5} = \frac{1}{t}\ln\left[\frac{R_{t-1}}{R_t}\right] = \frac{1}{0.5}\ln\left[\frac{55}{30}\right] = 1.21$$

Table 1
Measured Values of WBPTT

Time from Start of Dialysis (hours)	WBPTT (seconds)	Response (seconds)	Heparin Infusion (IU/hour)	Elimination Rate Constant (per hour)
0	155	85	1500	—
1	140	70	1500	1.08
2	130	60	1500	1.21
3	125	55	1500	1.27
4 (Infusion discontinued)	125	55	1500	1.23
4.5	100	30	—	1.21

Exercise 9

Calculate the mean value and the standard deviation for K from the values in Table 1.

The mean value for K in Table 1 is 1.20 h^{-1} with a standard deviation of 0.07 h^{-1}.

Exercise 10

Use the mathematical model that you have developed to determine the loading dose and the constant infusion rate.

Loading dose:
From Equation (2), the loading dose is D = R/S = 55/0.045 = 1222 IU. Round this to the nearest hundred to get

$$D = 1200 \text{ IU}$$

Constant infusion rate:
From your solution of Exercise (5), the infusion rate is given by

$$I_R = \frac{R_D K}{S} = \frac{(55)(1.20)}{0.045} = 1467 \text{IU/h}$$

Again, rounding to the nearest hundred gives the value

$$I_R = 1500 \text{ IU/h}$$

In the next dialysis treatment, you will recommend a loading dose of 1200 IU and a continuous infusion rate of 1500 IU/h.