UMAP

Modules in Undergraduate Mathematics and its Applications

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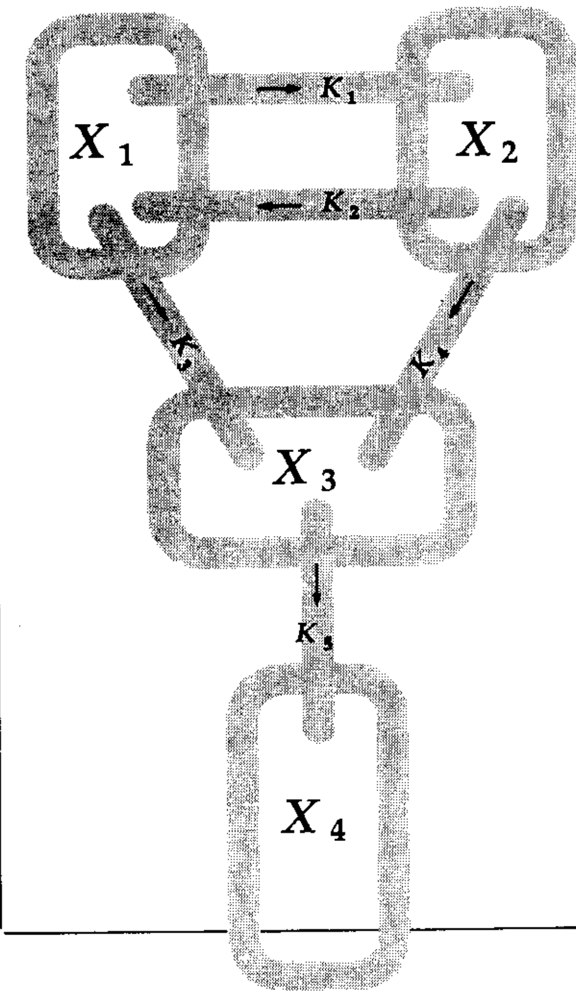
COMAP

Module 686

Biokinetics of a Radioactive Tracer

Merzik Kamel
Joanne Harris



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TITLE:	Biokinetics of a Radioactive Tracer
AUTHOR:	Merzik Kamel and Joanne Harris Division of Mathematics, Engineering and Computer Science University of New Brunswick Saint John, New Brunswick, Canada, E2L 4L5
MATH FIELD:	Calculus, differential equations
APPLICATIONS FIELD:	Biology, chemistry, medicine
TARGET AUDIENCE:	Students in a sophomore-level course in multivariable calculus or differential equations
ABSTRACT:	A system of differential equations is used to describe the transfer and breakdown of I_{131} albumin in rabbits. The original research was by E. B. Reeve and J. E. Roberts.
PREREQUISITES:	Familiarity with linear systems of differential equations and methods of solution of such. No background is assumed in biology, chemistry, or medicine.

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Merzik Kamel
and
Joanne Harris
Division of Mathematics, Engineering and Computer Science
University of New Brunswick
Saint John, N. B. Canada E2L 4L5

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MODULES AND MONOGRAPHS IN UNDERGRADUATE MATHEMATICS AND ITS APPLICATIONS (*UMAP*) PROJECT

The goal of UMAP is to develop, through a community of users and developers, a system of instructional modules in undergraduate mathematics and its applications to be sued to supplement existing courses and from which complete courses may eventually be built.

The Project was guided by a National Advisory Board of mathematicians, scientists, and educators. UMAP was funded by a grant from the National Science Foundation and is now supported by the Consortium for Mathematics and Its Applications (COMAP), Inc., a non-profit corporation engaged in research and development in mathematics education.

1. Introduction

One of the peaceful uses of nuclear energy is the use of radioactive isotopes in scientific research. Employed as tracers in biological work they have become very important tools in many areas of study [Chapman and Ayrey 1981; Comar 1955]. The fate of a given compound in an organism or biological process can be traced by following the pathway taken by an applied radioactive isotope. In the early 1950s biochemists began to use radioactive amino acids to study the processes involved in protein synthesis.

Albumin is a protein substance found in many animal tissues and fluids. It is assumed to be present in animals in constant amounts, some in the vascular system (the plasma) and some in the extravascular system (lymph and tissue fluids). To study the synthesis, transfer and breakdown of albumin, researchers have intravenously injected a certain amount of radioactive albumin into rabbits and then made measurements of the radioactivity in plasma, urine, and feces over many days.

In the presentation that follows, we will look at the mathematical modeling used by Reeve and Roberts for the distribution, transfer, and excretion of radioactivity following an injection of I_{131} albumin in rabbits [Reeve and Roberts 1959a].

2. The Model

Figure 1 shows the four-compartment model. Initially I_{131} albumin is injected into the vascular compartment. From there, its behavior is assumed to follow that of unlabelled albumin. That is, there is a transfer of albumin between the vascular and extravascular compartments; since albumin is continually being broken down, there is a breakdown products compartment. It is not certain where the breakdown actually occurs, whether it is in the vascular system or the extravascular system or in both, thus "the complete model" shows the transfer of breakdown products from both. Finally, there is an excretion compartment in which the radioactivity accumulates.

At any time t after the injection of I_{131} albumin into the animal's vascular system, let x_1, x_2, x_3 and x_4 be the fractions

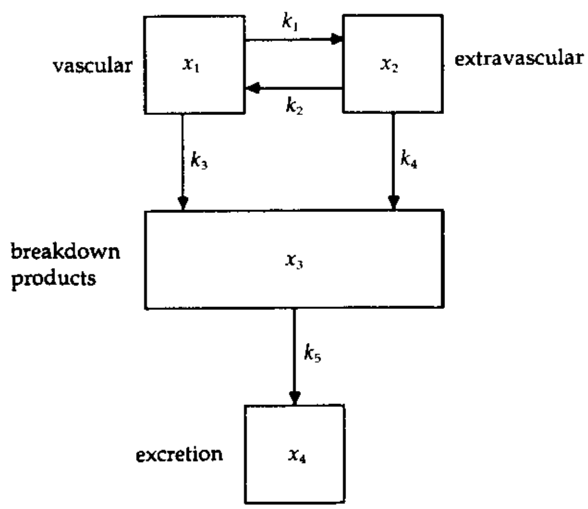

Figure 1. Model C.

of the total administered radioactivity attached to the albumin in the vascular, extravascular, breakdown products, and excretion compartments.

The rate of transfer from one compartment to another is assumed to be proportional to the amount present in the former compartment at time t. The constants of proportionality k_i are shown in **Figure 1** and are called the rate constants. The change in the amount in a compartment equals the difference between the input and the output in that compartment. For example, in the vascular compartment, x_1 is changing by gaining k_2x_2 and losing k_1x_1 and k_3x_1, so that $dx_1/dt = k_2x_2 - k_1x_1 - k_3x_1$. In the extravascular compartment, x_2 is changing by gaining k_1x_1 and losing k_2x_2 and k_4x_2, thus $dx_2/dt = k_1x_1 - k_2x_2 - k_4x_2$.

In this way, the following system of differential equations is obtained:

$$\frac{dx_1}{dt} = -(k_1 + k_3)x_1 + k_2x_2$$

$$\frac{dx_2}{dt} = k_1x_1 - (k_2 + k_4)x_2$$

$$\frac{dx_3}{dt} = k_3x_1 + k_4x_2 - k_5x_3$$

$$\frac{dx_4}{dt} = k_5 x_3.$$

The initial values when $t = 0$ are $x_1 = 1$, $x_2 = x_3 = x_4 = 0$, since the I_{131} albumin is initially injected into the vascular system.

3. Solution of the System

The solution of the system of differential equations depends on the rate constants k. These constants were determined by Reeve and Roberts using experimental measurements made from blood samples taken at one or more day intervals after the I_{131} albumin was injected and from measurements taken from the urine and feces [Reeve and Roberts 1959a].

Reeve and Roberts used plasma data and excretory data from eleven different rabbits and determined the k_i's in each case. In the following we will use the mean experimental values for these constants, truncated to two decimal places and solve the system of differential equations obtained above. Thus, using $k_1 = 1.06$, $k_2 = 0.69$, $k_3 = 0.19$, $k_4 = 0.03$, $k_5 = 2.50$ [Reeve and Roberts 1959a, 433], the system of differential equations becomes

$$\frac{dx_1}{dt} = -1.25x_1 + 0.69x_2 \tag{1}$$

$$\frac{dx_2}{dt} = 1.06x_1 - 0.72x_2 \tag{2}$$

$$\frac{dx_3}{dt} = 0.19x_1 + 0.03x_2 - 2.50x_3 \tag{3}$$

$$\frac{dx_4}{dt} = 2.50x_3 \tag{4}$$

This homogeneous linear system can be solved using the matrix method [Zill 1986], i.e., by finding the eigenvalues and the corresponding eigenvectors of the matrix

$$\begin{pmatrix} -1.25 & 0.69 & 0 & 0 \\ 1.06 & -0.72 & 0 & 0 \\ 0.19 & 0.03 & -2.50 & 0 \\ 0 & 0 & 2.50 & 0 \end{pmatrix}$$

(Alternatively, since **(1)** and **(2)** of the system are independent of x_3 and x_4, these can be solved by elimination for x_1 and x_2; then using these solutions, see **Exercise 1**.) **(3)** can be solved for x_3 and then equation **(4)** for x_4.

To find the eigenvalues, consider the equation

$$\begin{vmatrix} -1.25-\lambda & 0.69 & 0 & 0 \\ 1.06 & -0.72-\lambda & 0 & 0 \\ 0.19 & 0.03 & -2.50-\lambda & 0 \\ 0 & 0 & 2.5 & -\lambda \end{vmatrix} = 0,$$

from which $\lambda = 0, -2.50, -1.88, -0.09$ can be obtained.

The corresponding eigenvectors are (0,0,0,1), (0,0,1,−1), (1,−0.91,0.26,−0.35), and (1,1.68,0.10,−2.78) respectively. (Details are left to the reader as **Exercise 2**.) The general solution of the system of differential equations is then

$$\begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix} = C_1\begin{pmatrix} 0 \\ 0 \\ 0 \\ 1 \end{pmatrix} + C_2\begin{pmatrix} 0 \\ 0 \\ 1 \\ -1 \end{pmatrix}e^{-2.50t} + C_3\begin{pmatrix} 1 \\ -0.91 \\ 0.26 \\ -0.35 \end{pmatrix}e^{-1.88t}$$
$$+ C_4\begin{pmatrix} 1 \\ 1.68 \\ 0.10 \\ -2.78 \end{pmatrix}e^{-0.09t}.$$

Using the initial conditions (at $t = 0$, $x_1 = 1$, $x_2 = x_3 = x_4 = 0$) yields the following values for the C's: $C_1 = 1.00$, $C_2 = -0.21$, $C_3 = 0.65$, $C_4 = 0.35$ and hence

$$x_1 = 0.65e^{-1.88t} + 0.35e^{-0.09t}$$

$$x_2 = -0.59e^{-1.88t} + 0.59e^{-0.09t}$$

$$x_3 = -0.21e^{-2.50t} + 0.17e^{-1.88t} + 0.04e^{-0.09t}$$

$$x_4 = 1 + 0.21e^{-2.50t} - 0.23e^{-1.88t} - 0.98e^{-0.09t}.$$

Graphs of these four functions are shown in **Figures 2–5**.

Note that the sum of the fractions of the total administered radioactivity is equal to 1; that, as expected, after a long period of time, all this radioactivity accumulates in the excretion compartment. Moreover, from the graphs in

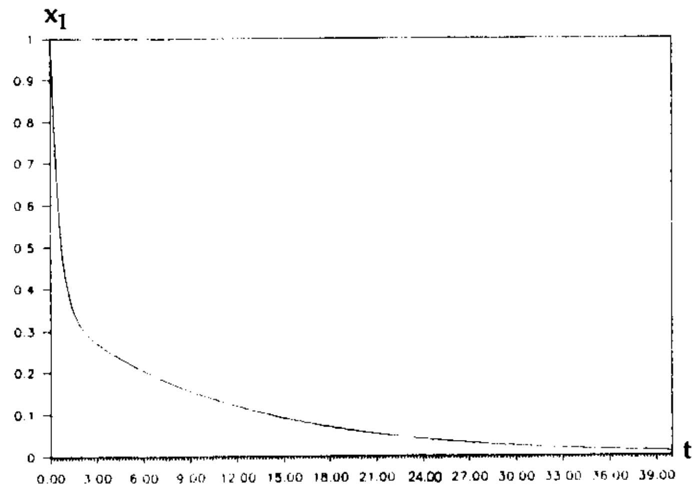

Figure 2. Radioactivity in vascular compartment over time.

Figures 2–5 we see that the amount of radioactivity in the vascular system steadily decreases from 1 to 0, whereas in the extravascular and breakdown products compartments it first increases from 0 to a certain maximum and then decreases towards 0 (see **Exercise 3.**). In the excretion compartment, the radioactivity increases steadily from its initial value of 0 towards the value 1.

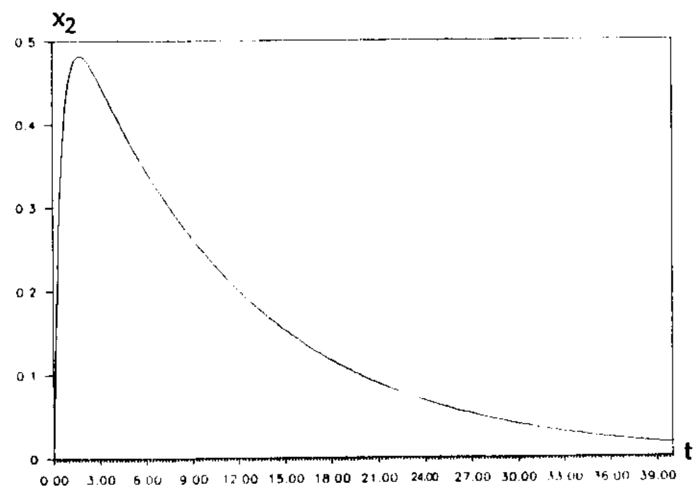

Figure 3. Radioactivity in extravascular compartment over time.

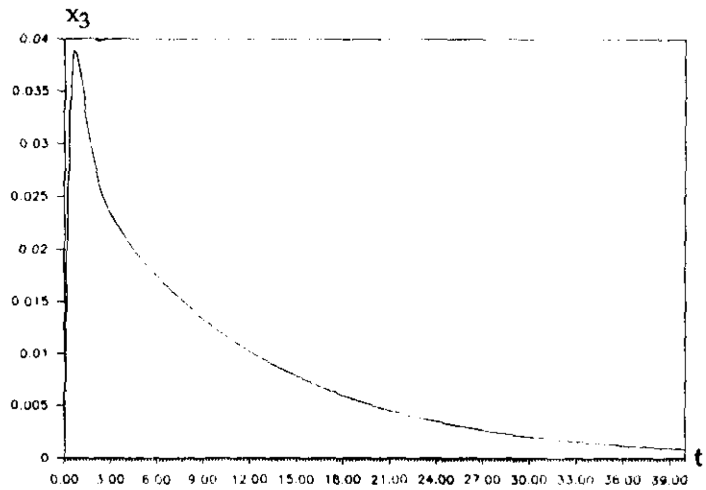

Figure 4. Radioactivity in breakdown compartment over time.

4. Reality of the Model

Does the model predict quantitatively the experimental measures that can be made in such experiments: Is the model physiologically reasonable?

To discuss these questions, first note that our "complete model," called model C by Reeve and Roberts, can be reduced to two other simpler models, A and B, which were also discussed by Reeve and Roberts [1959a].

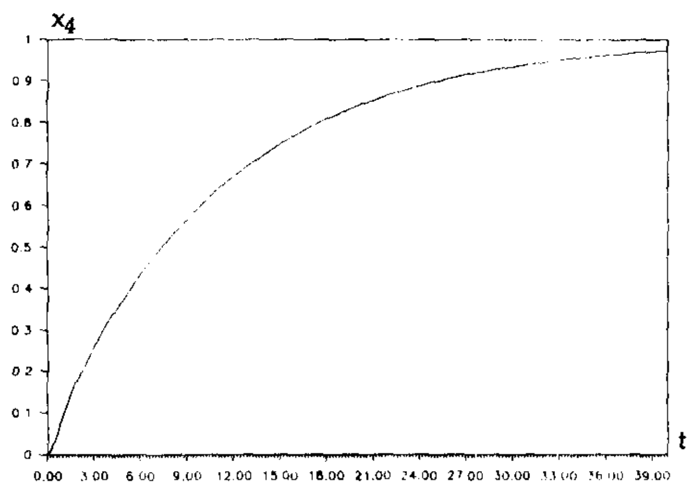

Figure 5. *Radioactivity in excretion compartment over time.*

Models A and B are shown in **Figure 6.**

In model A it is assumed that breakdown occurs only in the vascular compartment. Setting up the resulting system of differential equations constitutes **Exercise 4** and solving it is **Exercise 5.** Model B, on the other hand, assumes that breakdown occurs only in the extravascular compartment. (See **Exercise 6.**)

Reeve and Roberts show that their experimental data were reasonably well predicted by models A and C but that model B was not capable of describing the data obtained from the experiments. This means that most of the breakdown occurs in the vascular compartment. Also note, since model A was found to predict measured values reasonably well, the value of k_4 in model C could be expected to be small.

Further, Reeve and Roberts state that picturing the vascular albumin as a single compartment is reasonable physiologically but that it would be better to consider the extravascular albumin as a group of different compartments between which there is not much transfer. Thus, even models A and C, which do give satisfactory predictions of the radioactivity involved, certainly oversimplify the extravascular behavior of albumin.

Because of this, Reeve and Roberts considered an ex-

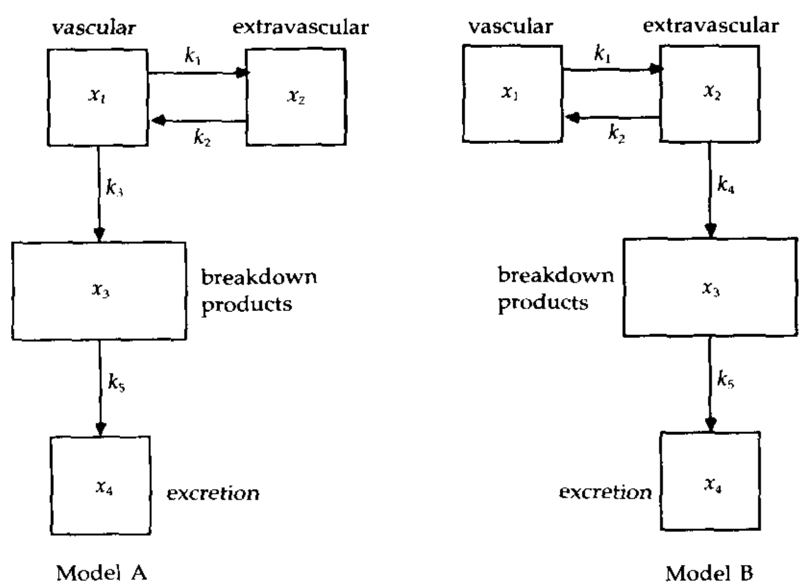

Figure 6. Models A and B.

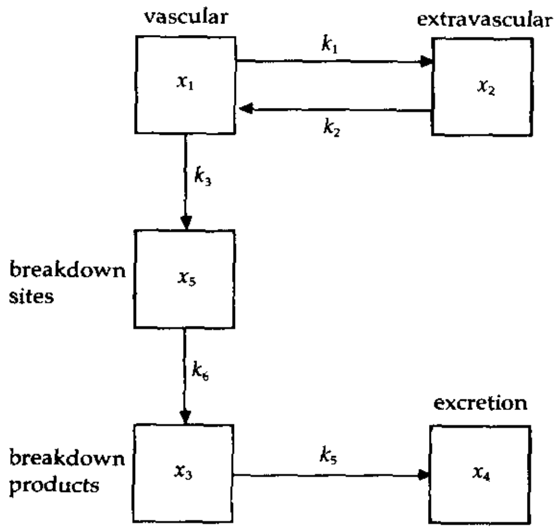

Figure 7. Model D.

tended model in which an additional compartment, called *breakdown sites*, has been added (see **Figure 7**).

However, Reeve and Roberts only had sufficient experimental data from one rabbit to test model D and stated that more experimentation would be required to conclude whether model D predicts results closer to the observed results than do models A or C (see **Exercise 7**).

While we have considered solutions of equations with specific numerical parameters, Reeve and Roberts solve models C and D in full generality with literal parameters and they also show how to identify the values of k_i's from observable quantities.

Exercises

1. Solve the system of differential equations consisting of **(1)**–**(4)** by the method of elimination.

2. Carry out the details of the solution of system **(1)**–**(4)** using the matrix method as suggested in **Section 3.**

3. Use calculus and the expressions for x_2 and x_3 to determine the time for the radioactive material to reach its

maximum value in each of the extravascular and breakdown compartments.

4. Set up a system of differential equations for model A.

5. Solve the system **Exercise 4,** for the values of the constants are taken to be $k_1 = 1.03$, $k_2 = 0.72$, $k_3 = 0.24$, $k_5 = 2.50$.

6. Set up a system of differential equations for model B.

7. Write the system of differential equations which describes model D. Solve this system for $k_1 = 1.01$, $k_2 = 0.69$, $k_3 = 0.19$, $k_5 = 2.5$, $k_6 = 2.1$ (values truncated from Reeve and Roberts [1959a, 433, 441]).

5. Solutions to the Exercises

1. Differentiating **(1)** and substituting from **(2)** for dx_2/dt, we have

$$\frac{d^2x_1}{dt^2} = -1.25\frac{dx_1}{dt} + 0.69(1.06x_1 - 0.72x_2). \qquad \textbf{(5)}$$

Solving **(1)** for x_2 and substituting that expression in **(5)**, we obtain

$$\frac{d^2x_1}{dt^2} + 1.97\frac{dx_1}{dt} + 0.1686x_1 = 0.$$

Thus $x_1 = C_4e^{\ 0.09t} + C_3e^{-1.88t}$. **(6)**

Then, from **(1)**, $x_2 = 1/0.69(dx_1/dt + 1.25x_1)$, and using **(6)**, we find that

$$x_2 = 1.68C_4e^{-0.09t} - 0.91C_3e^{-1.88t}. \qquad \textbf{(7)}$$

Then using **(6)** and **(7)**, **(3)** becomes

$$\frac{dx_3}{dt} + 2.50x_3 = 0.24C_4e^{-0.09t} + 0.16C_3e^{-1.88t}$$

Thus $x_3 = C_2e^{-2.50t} + 0.10C_4e^{-0.09t} + 0.26C_3e^{\ 1.88t}$. **(8)**

Finally, from **(4)** and **(8)**, we obtain

$$x_4 = C_1 - C_2e^{-2.50t} - 0.35C_3e^{-1.88t} - 2.78C_4e^{-0.09t}.$$

2. We solve the determinant equation

$$\begin{vmatrix} -1.25-\lambda & 0.69 & 0 & 0 \\ 1.06 & -0.72-\lambda & 0 & 0 \\ 0.19 & 0.03 & -2.50-\lambda & 0 \\ 0 & 0 & 2.50 & -\lambda \end{vmatrix} = 0,$$

to get the eigenvalues of the matrix. Expanding the determinant by cofactors about the last column yields

$$\lambda(\lambda + 2.50)(\lambda^2 + 1.97\lambda + 0.1686) = 0,$$

from which we obtain the eigenvalues $\lambda = 0, -2.50, -1.88, -0.09$.

To find an eigenvector corresponding to, for example, $\lambda = -2.50$, we solve the homogeneous system, whose augmented matrix is

$$\left(\begin{array}{cccc|c} -1.25+2.50 & 0.69 & 0 & 0 & 0 \\ 1.06 & -0.72+2.50 & 0 & 0 & 0 \\ 0.19 & 0.03 & -2.50+2.50 & 0 & 0 \\ 0 & 0 & 2.50 & 2.50 & 0 \end{array}\right)$$

obtaining the eigenvector $(0,0,1,-1)$. Similarly, the eigenvectors corresponding to $\lambda = 0, -1.88, -0.09$ are found to be $(0,0,0,1)$, $(1,-0.91,0.26,-0.35)$ and $(1,1.68,0.10,-2.78)$, respectively.

3. From the expression for x_2,

$$\frac{dx_2}{dt} = 1.11e^{-1.88t} - 0.05e^{-0.09t}.$$

Setting this equal to zero and solving for t yields $t = 1.73$ (the time for the radioactive material to reach its maximum value in the extravascular compartment).

Similarly, setting $\frac{dx_3}{dt} = 0$ yields $t = 0.73$.

4. $$\frac{dx_1}{dt} = -(k_1 + k_3)x_1 + k_2x_2$$

$$\frac{dx_2}{dt} = k_1x_1 - k_2x_2$$

$$\frac{dx_3}{dt} = k_3x_1 - k_5x_3$$

$$\frac{dx_4}{dt} = k_5x_3$$

5. The system is

$$\frac{dx_1}{dt} = -1.27\,x_1 + 0.72x_2$$

$$\frac{dx_2}{dt} = 1.03\,x_1 - 0.72x_2$$

$$\frac{dx_3}{dt} = 0.24x_1 - 2.50x_3$$

$$\frac{dx_4}{dt} = 2.50x_3.$$

Solving this system by the matrix method, as in the solution to **Exercise 2,** we find that the eigenvalues are 0, −2.50, −0.09, −1.90 with corresponding eigenvectors are (0,0,0,1), (0,0,1,−1), (1,1.64,0.10,−2.74), and (1,−0.87,0.40,−0.53). Thus, the solution to the system is

$$\begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix} = C_1\begin{pmatrix} 0 \\ 0 \\ 0 \\ 1 \end{pmatrix} + C_2\begin{pmatrix} 0 \\ 0 \\ 1 \\ -1 \end{pmatrix}e^{-2.50t} + C_3\begin{pmatrix} 1 \\ 1.64 \\ 0.10 \\ -2.74 \end{pmatrix}e^{-0.09t}$$

$$+ C_4\begin{pmatrix} 1 \\ -0.87 \\ 0.40 \\ -0.53 \end{pmatrix}e^{-1.90t}.$$

7. $$\frac{dx_1}{dt} = -(k_1 + k_3)x_1 + k_2x_2$$

$$\frac{dx_2}{dt} = k_1x_1 - k_2x_2$$

$$\frac{dx_3}{dt} = -k_5x_3 + k_6x_5$$

$$\frac{dx_4}{dt} = k_5x_3$$

$$\frac{dx_5}{dt} = k_3x_1 - k_6x_5.$$

With the given values of the rate constants the system becomes

$$\frac{dx_1}{dt} = -1.20x_1 + 0.69x_2$$

$$\frac{dx_2}{dt} = 1.01x_1 - 0.69x_2$$

$$\frac{dx_3}{dt} = -2.5x_3 + 2.1x_5$$

$$\frac{dx_4}{dt} = 2.5x_3$$

$$\frac{dx_5}{dt} = 0.19x_1 - 2.1x_5.$$

Solving this system we find that the eigenvalues are 0, −2.5, −2.1, −0.07, − 1.82 with corresponding eigenvectors (0,0,0,1,0), (0,0,1,−1,0), (0,0,1,−1.19,0.19), (1,1.63,0.08,−2.81,0.09), and (1,−0.90,2.07,−2.85,0.67).

Thus the solution to the system is

$$\begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ x_5 \end{pmatrix} = C_1 \begin{pmatrix} 0 \\ 0 \\ 0 \\ 1 \\ 0 \end{pmatrix} + C_2 \begin{pmatrix} 0 \\ 0 \\ 1 \\ -1 \\ 0 \end{pmatrix} e^{-2.5t} + C_3 \begin{pmatrix} 0 \\ 0 \\ 1 \\ -1.19 \\ 0.19 \end{pmatrix} e^{-2.1t}$$

$$+ C_4 \begin{pmatrix} 1 \\ 1.63 \\ 0.08 \\ -2.81 \\ 0.09 \end{pmatrix} e^{-0.07t} + C_5 \begin{pmatrix} 1 \\ -0.90 \\ 2.07 \\ -2.85 \\ 0.67 \end{pmatrix} e^{-1.82t}.$$

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