To the Graduate Council:

I am submitting herewith a thesis written by Brenda L. Bleavins entitled, "Some Mathematical Models of Cold Pill Concentration in the Body." I have examined the final copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree Master's of Science, with a major in Mathematics.

Don Hinton

Don Hinton, Major Professor

We have read this thesis
and recommend its acceptance.

Clark C

W R Wade

Accepted for the Council:

Associate Vice Chancellor and
Dean of The Graduate School

SOME MATHEMATICAL MODELS OF COLD PILL CONCENTRATION IN THE BODY

A Thesis
Presented for the
Master of Science
Degree
The University of Tennessee, Knoxville

Brenda Bleavins
August 2000

ACKNOWLEDGEMENTS

My gratitude for support and encouragement during my time at the University of Tennessee, Knoxville extends to many wonderful people First, I am deeply indebted to my graduate committee Don Hinton, Charles Collins and William Wade for the never-ending supply of patience, generosity, and correction

Second, great thanks goes to my fellow graduate students simply for sharing their lives with me Always willing to bestow wise counsel, they have given me a more profound understanding into others and myself The last two years have been filled with laughter and joy because of them

ABSTRACT

The motivation for this discussion comes from a set of exercises in Borelli and Coleman's *Ordinary Differential Equations: A Modeling Approach.* In this particular set of exercises the focus is to model the amount of cold medication (antihistamines and decongestants) in the body We will consider a two-compartment model with the two components being the GI tract and the bloodstream, producing a two-dimensional system of ordinary differential equations. Initially we assume a simple linear model, then we increase the complexity by including a saturation effect in the amount of the drug clearing the bloodstream We also examine three ways of dosing the medication. administering just one dose, continuous dosing, and periodic dosing Closed-form solutions are determined for the one dose, continuous dosing and non-saturation periodic cases, but only numerical solutions are given for the nonlinear, periodic cases While we do not find closed-form solutions for the nonlinear, periodic cases we do explore their existence and stability. A software package called *ODE Architect* is used to generate the numerical solutions to all the models in this thesis

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CHAPTER I: INTRODUCTION

[Pharmacokinetics]

First formalized in 1937 by Torsten Teorell, pharmacokinetics is the study of the rate of change of drug concentrations in the body One major approach is compartmental modeling in which the body is assumed to be made up of one or more divisions or compartments. For example, if the drug is administered orally, the GI tract may be considered one compartment and the bloodstream might be considered another. [3]

The administration of drugs falls into two major categories· parenteral and enteral If a drug is given in a manner other than by means of the GI tract, it is *parenterally* administered For example, drugs given intravenously, intramuscularly, subcutaneously (just beneath the skin), intradermally (within the dermis), percutaneously (through the skin), intra-arterially, intrathecally (within the spinal column), vaginally or are inhaled are administered parenterally If a drug is administered by means of the GI tract, then it is *enterally* administered For example, drugs given buccally (in the buccal cavity of the mouth), sublingually, gastricly, intestinally or rectally are given enterally. This is by far the most common means of administration of drugs Figure 1 1 is a diagram of the GI tract [3]

A major factor affecting the absorption rate of the drug is the form it takes Because a tablet is more tightly packed, it may take longer for it to go into solution Different from a tablet, the capsule is less tightly packed allowing for greater ease in dissolving. Since some have negative reaction to certain drugs, aspirin for example, a

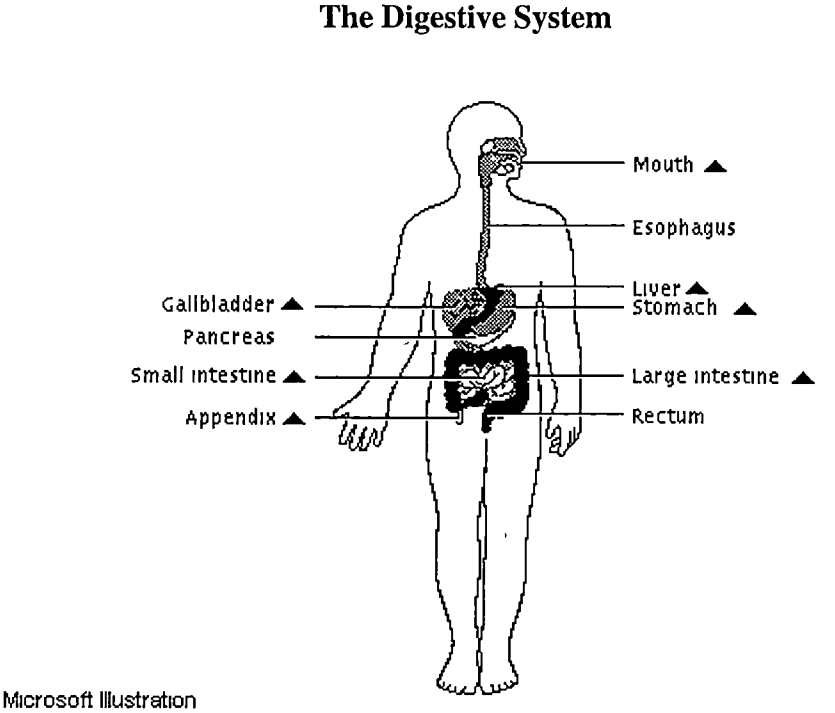

Figure 1.1. Diagram of the digestive system. The GI tract consists of the mouth, stomach, duodenum (the beginning portion of the small intestine) and the small and large intestines

coated tablet alleviates discomfort by delaying the dissolution. The coating is designed to remain intact in the acidic environment of the stomach, but upon reaching the small intestine which is more neutral or even alkaline, the drug dissolves Elixirs, syrups, and emulsions have no problem going into solution, producing faster and more undiminished absorption Further, solutions are easier to swallow making it ideal for children and the elderly [3]

The body can remove the drug through renal, biliary, pulmonary or salivary

excretion However, the kidneys are the are the primary means of clearance [3]

[Model]

Figure 1.2 is a diagram showing the flow of the medication in the body. The drug enters the first compartment which is the GI tract (consisting of the mouth, stomach and the intestines) containing an initial amount A. We will assume that the rate at which the drug leaves the GI tract and enters the second compartment, the bloodstream, is proportional to the amount of medication in the GI tract, $x(t)$. Let the proportionality constant be k_1 with units of hour^{-1}. The drug is cleared or eliminated from the blood (through the kidneys) with rate proportional to the amount present in the blood, $y(t)$ Let the proportionality constant be k_2 Although three possibilities exist concerning the rate constants, namely (1) $k_1 > k_2$, (2) $k_1 < k_2$ or (3) $k_1 = k_2$, case (1) is the most common Borrelli [1] gives typical values for antihistamines and decongestants in young and healthy individuals as well as older and sick individuals.

[Discussion of Chapters]

First, we examine the results of giving one dose of antihistamine determining the time of maximum dosage We also explore the effects of varying the rate at which the drug leaves the GI tract and enters the bloodstream. Second, we study what happens when one dose of decongestant is administered investigating the effects of changing

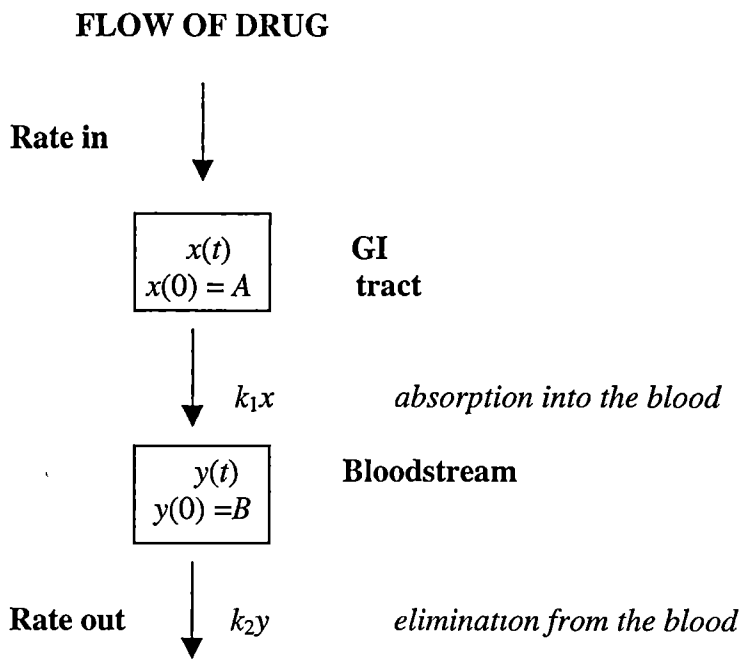

Figure 1.2. Two-compartment model of drug flow

the clearance coefficient. Typically dosing is periodic in that one takes one dose every 4-6 hours In Chapter IV we consider a system in which decongestant is given with periodic dosing Next we, look at the case in which dosing occurs continuously For example, time-released capsules would try to ensure a steady dosing rate. In an attempt to make the models more realistic, we investigate two different saturation models, determining when or if the system reaches some sort of equilibrium and if a periodic solution exists

CHAPTER II: ONE DOSE OF ANTIHISTAMINE

[Model]

In our first model we shall suppose that A units of antihistamine are already present in the GI tract and B units are present in the blood at time $t = 0$. Figure 2.1 is the boxes-and-arrows diagram. Thus, we have the following Initial Value Problem to solve

$$(1) \qquad \begin{cases} \dfrac{dx}{dt} = -k_1 x, \quad x(0) = A \\ \dfrac{dy}{dt} = k_1 x - k_2 y, \quad y(0) = B \end{cases}$$

Since the differential equation for the concentration of antihistamine in the GI tract is first-order linear, it has the solution

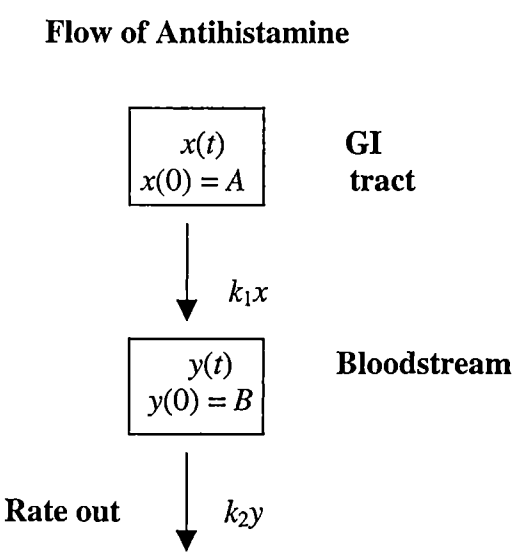

Figure 2.1. Diagram for the flow of antihistamine in the body

(2) $$x(t) = Ae^{-k_1 t}$$

Using the integrating factor $e^{k_2 t}$ and substituting the solution for $x(t)$ above in the second equation of (1) we obtain

$$y(t) = \frac{k_1 A}{k_2 - k_1} e^{-k_1 t} + ce^{-k_2 t}$$

as the solution for $y(t)$ Applying the initial condition $y(0) = B$, we can solve for c, i e.,

$$y(0) = B = \frac{k_1 A}{k_2 - k_1} + c \Rightarrow c = B - \frac{k_1 A}{k_2 - k_1},$$

which gives,

$$y(t) = \frac{k_1 A}{k_2 - k_1} e^{-k_1 t} + \left(B - \frac{k_1 A}{k_2 - k_1} \right) e^{-k_2 t},$$

or simplifying,

(3) $$y(t) = \frac{k_1 A}{k_2 - k_1} \left(e^{-k_1 t} - e^{-k_2 t} \right) + Be^{-k_2 t}.$$

Figure 2 2 displays the results from the numerical solver *ODE Architect* used to solve and graph the levels of antihistamine in the GI tract and in the blood over a time period of six hours Notice that the antihistamine concentration in the blood rises, peaks at about 4 hours, and then appears to decline within the six-hour period.

A point of concern would be the maximum concentration the antihistamine reaches in the blood If the concentration remains too low, the drug is ineffective However, if the concentration becomes to high, overdose occurs From Figure 2.2, it appears that the maximum antihistamine level is about 1 8 units at 4 hours However, we can determine more precisely the maximum level of antihistamine in the blood stream by finding the critical values of $y(t)$

$$k_1 = 0.6931;\ k_2 = 0\ 0231$$
$$x' = -k_1 x, \qquad x(0) = 1$$
$$y' = k_1 x - k_2 y, \quad y(0) = 1$$

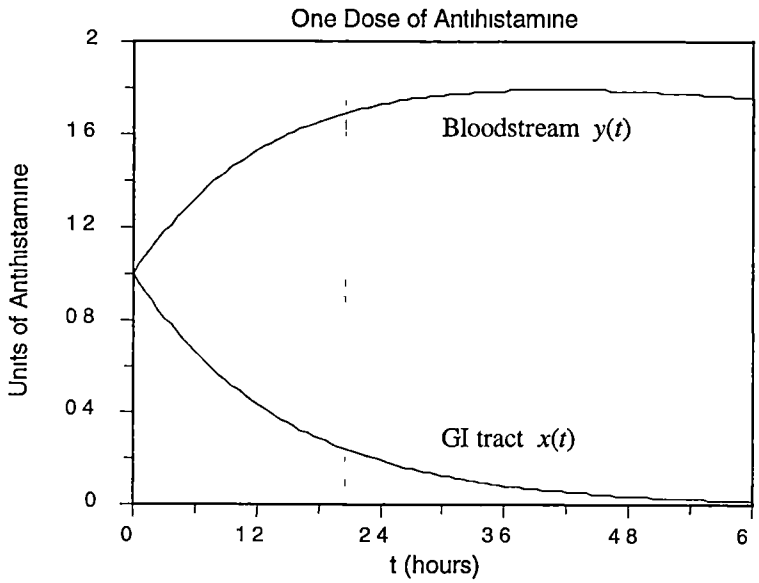

Figure 2.2. Effect of one dose of antihistamine Notice that the antihistamine level in the blood rises, peaks and then declines during the 6 hour period The peak value in the bloodstream is about 1 79 units at $t = 4.1$ hours

$$y'(t) = \frac{0\ 6931}{0\ 0231 - 0\ 6931}(-0\ 6931e^{-0\ 6931t} + 0.0231e^{-0\ 0231t}) - 0\ 0231e^{-0\ 0231t}.$$

Setting the first derivative equal to zero and solving for t^* gives the critical value of $t^* =$ 4 067 hours Now to verify that $y(t^*) = 1.7903$ units is indeed a maximum, let's use the second derivative test to show that at t^*, $y(t^*)$ is concave down.

$$y''(t) = \frac{0\ 6931}{0\ 0231 - 0\ 6931}(0\ 6931^2 e^{-0\ 6931t} - 0\ 0231^2 e^{-0\ 0231t}) + 0\ 0231^2 e^{-0\ 0231t}.$$

Note that $y''(t^*) = -0\ 0064 < 0$ which implies that $y(t)$ is concave down at t^* and t^* is a maximum Hence, the maximum level of antihistamine is 1.7903 units at 4.067 hours

[Time of Maximum Dosage]

Now we shall determine more generally when the maximum concentration of the antihistamine in the bloodstream is attained assuming that initially antihistamine is absent in the blood stream Here is the IVP that models the concentration in the bloodstream

$$\text{(4)} \qquad \begin{cases} \dfrac{dx}{dt} = -k_1 x, \quad x(0) = A \\ \dfrac{dy}{dt} = k_1 x - k_2 y, \quad y(0) = 0 \end{cases}$$

Again, we have a linear system of ODEs. The solution to the first differential equation is given by

$$\text{(5)} \qquad x(t) = Ae^{-k_1 t},$$

similar to what we found earlier Substituting this solution into the second equation and using an integrating factor of $e^{k_2 t}$ we get

$$\text{(6)} \qquad y(t) = \frac{k_1 A}{k_2 - k_1}\left(e^{-k_1 t} - e^{-k_2 t}\right),$$

for $y(t)$.

We will use the Second Derivative Test to determine the maximum concentration of antihistamine in the bloodstream where we will need to find the critical value t^* where the first derivative is zero and verify that the second derivative is negative there.

$$y'(t) = \frac{k_1 A}{k_2 - k_1}\left(-k_1 e^{-k_1 t} + k_2 e^{-k_2 t}\right),$$

$$\frac{k_1 A}{k_2 - k_1}\left(-k_1 e^{-k_1 t} + k_2 e^{-k_2 t}\right) = 0 \Rightarrow k_1 e^{-k_1 t} = k_2 e^{-k_2 t},$$

$$\frac{k_1}{k_2} = e^{(k_1 - k_2)t} \Rightarrow t^* = \frac{\ln k_1 - \ln k_2}{k_1 - k_2}.$$

Notice that if $k_1 > k_2$ or if $k_1 < k_2$, t^* is still positive

$$y''(t) = \frac{k_1 A}{k_2 - k_1}\left(k_1^2 e^{-k_1 t} - k_2^2 e^{-k_2 t}\right).$$

In the case that $k_1 > k_2$, the factor $\frac{k_1 A}{k_2 - k_1}$ is negative and the second factor

$k_1^2 e^{-k_1 t} - k_2^2 e^{-k_2 t}$ is positive so that at $t = t^*$ $y''(t^*) < 0$ In the case that $k_1 < k_2$, $\frac{k_1 A}{k_2 - k_1}$ is

clearly positive and the second factor $k_1^2 e^{-k_1 t} - k_2^2 e^{-k_2 t}$ is negative, again making

$y''(t^*) < 0$.

[Sensitivity to k_1]

In this section we will explore the effects of varying the rate at which the drug exits the GI tract and enters the bloodstream. Figure 2 3 shows the results of having one unit of antihistamine already present in the GI tract and the blood initially free of the drug. The clearance coefficient k_2 is fixed at 0 0231, but k_1 varies. Notice that the graphs for larger values of k_1 cross the graphs for the smaller values. If k_1 is small, the

k_1 = as shown

$k_2 = 0\ 0231$

$x' = -k_1 x, \quad x(0) = 1$

$y' = k_1 x - k_2 y, \quad y(0) = 0$

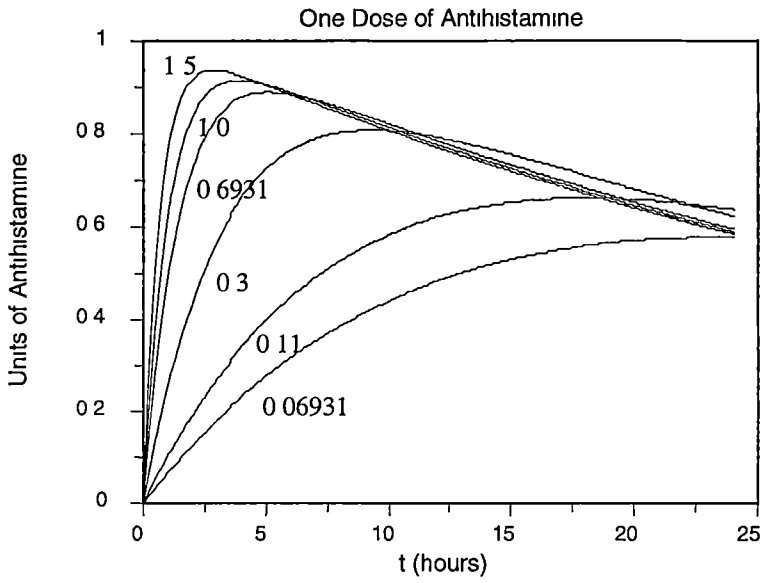

Figure 2.3. Sensitivity to the rate constant k_1 As k_1 increases, the time at which the maximum concentration is reached is sooner and sooner.

antihistamine level takes longer to peak indicating that clearance from the bloodstream occurs only after the antihistamine level has peaked Observe in Figure 2 4 that as k_1 increases, the time at which the maximum concentration occurs decreases

[Safe and Effective Zone]

As alluded to earlier, medication levels must remain within a fixed range in order to be both therapeutic and safe. Suppose that the desired range for antihistamine levels in the blood is from 0 2 to 0 8 for a unit dose taken once. With $k_2 = 0.0231$, we shall

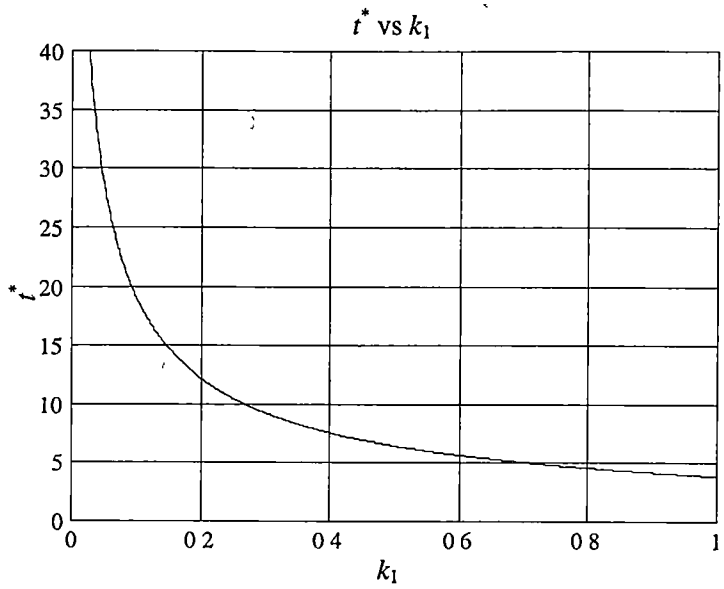

Figure 2.4. Graph of t^* vs k_1 Notice that as k_1 increases, the time t^* at which the maximum concentration occurs decreases

establish the upper and lower bounds on k_1 so that the antihistamine levels in the blood reach 0 2 within 2 hours and stay below 0.8 units for 24 hours. First, we will determine the lower bound We want

$$f(k_1) = y(2) = \frac{k_1}{0\ 0231 - k_1}\left(e^{-2k_1} - e^{-2(0\ 0231)}\right) \geq 0\ 2.$$

Using the root finding capabilities of the TI calculator, with an initial guess of 0.11, the root obtained was 0.1146 Hence, when $k_1 > 0.1146$, the antihistamine level will reach 0 2 units within two hours. Looking at Figure 2.5, we see a graphical representation that the zero indeed occurs when k_1 equals 0.1146.

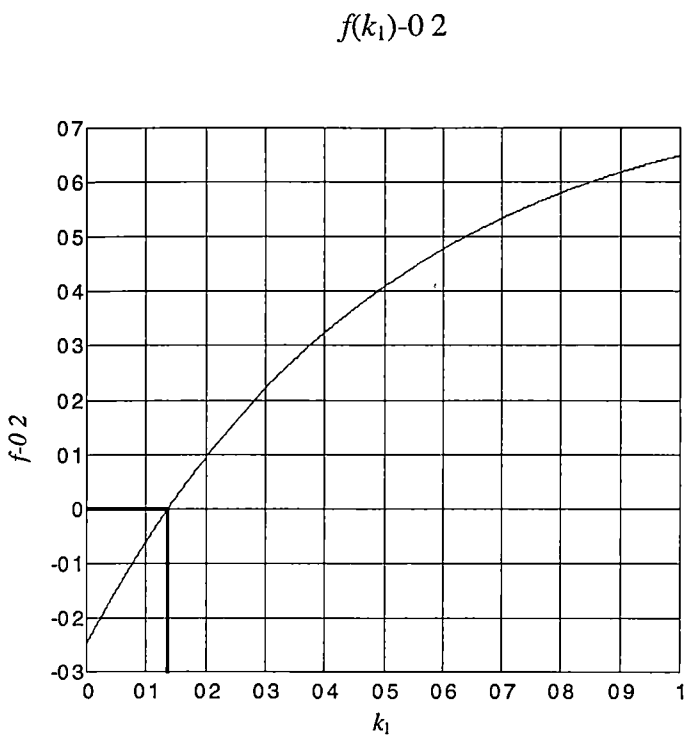

Figure 2.5. Graph of $f(k_1)$-0 2 When $k_1 > 0.1146$, the amount of antihistamine in the blood reaches 0 2 units within 2 hours

Since the concentration of the antihistamine in the bloodstream rises, peaks, and falls, determining the upper bound for k_1 requires examination of not only the antihistamine concentration at $t = 24$ hours but also at $t = t^*$ where $t^* \in (0, 24)$ is the maximum concentration of antihistamine in the bloodstream In the first case, we want

$$g(k_1) = y(24) = \frac{k_1}{0\ 0231 - k_1}\left(e^{-24k_1} - e^{-24(0\ 0231)}\right) \leq 0.8\,.$$

From the graph in Figure 2.6 we notice that for $k_2 = 0\ 0231$, the concentration of antihistamine remaining in the blood at 24 hours is less than 0 8 units for all values of k_1. Now we simply need to determine the k_1 values that guarantee that the maximum

$$g(k_1) = y(24) = \frac{k_1}{0\,0231 - k_1}\left(e^{-24k_1} - e^{-24(0\,0231)}\right) \leq 0\,8$$

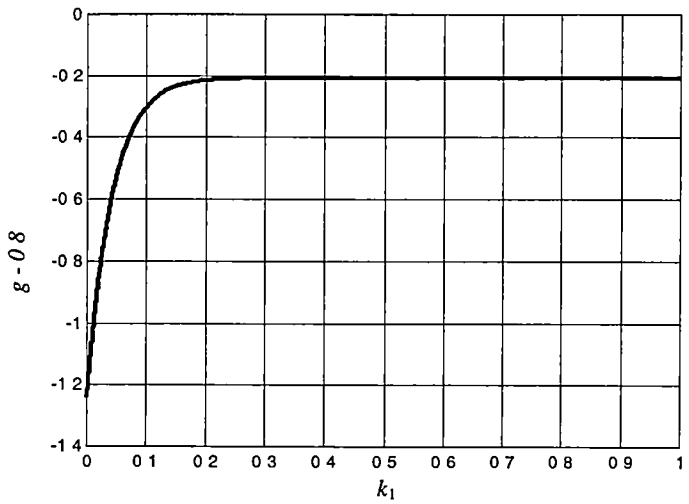

Figure 2.6. Graph of $g(k_1)$-0.8 When $k_2 = 0.0231$ the concentration of antihistamine remaining in the blood at 24 hours is less than 0 8 units for all values of k_1.

concentration does not exceed 0 8 units for $t \in (0, 24)$ Figure 2 7 shows the graph of the rate constant as a function of the maximum concentration. We see that when $k_1 = 0.2821$ the maximum concentration begins to exceed the limit. Thus, it follows that for $k_1 \in$ (0 1146, 0 2821), the level of antihistamine will reach 0 2 units within 2 hours and not surpass 0 8 units in 24 hours

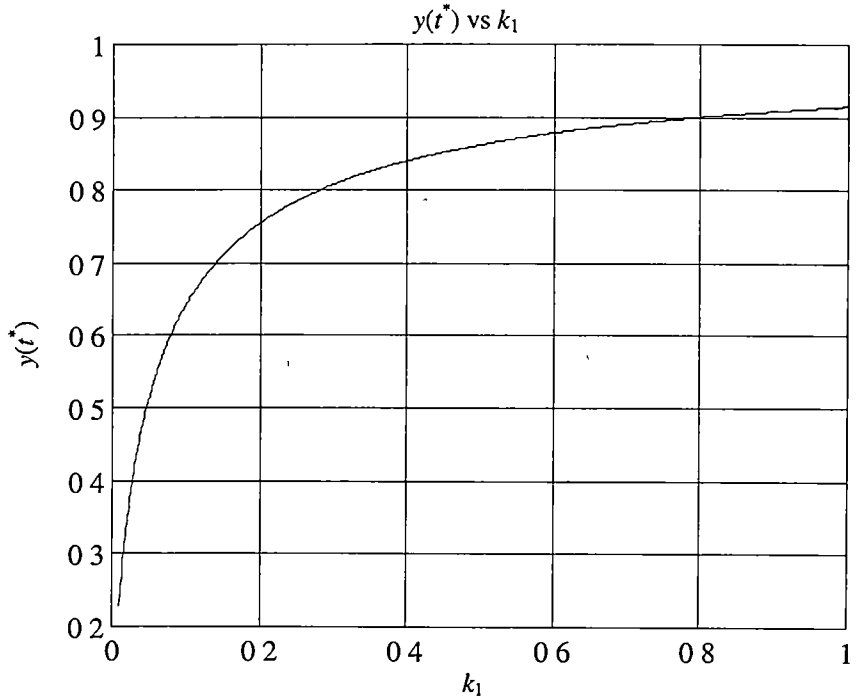

Figure 2.7. Graph of $y(t^*)$ vs k_1 When $k_1 < 0\ 2821$, the maximum concentration of antihistamine in the blood is less than 0.8 units.

CHAPTER III: ONE DOSE OF DECONGESTANT

In addition to an antihistamine, cold pills usually contain a decongestant The rate equations for the flow of decongestant are the same as that for antihistamines, but the rate constants are different Again, we will use $x(t)$ for the amount of decongestant in the GI tract and $y(t)$ for the amount of decongestant in the blood as with the antihistamine

[Model]

Suppose that A units of decongestant are in the GI tract at time $t = 0$, while the blood is free of decongestant Figure 3.1 shows a labeled boxes-and arrows diagram for the flow of decongestant

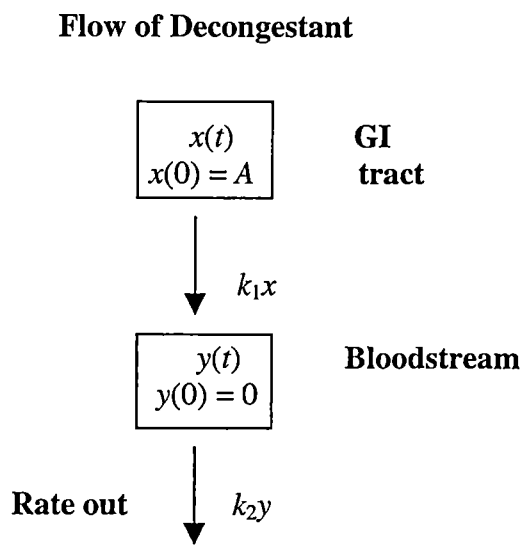

Figure 3.1. Diagram for the flow of decongestant in the body

Thus the corresponding system of ODEs is

$$(1) \qquad \begin{cases} \dfrac{dx}{dt} = -k_1 x, & x(0) = A \\ \dfrac{dy}{dt} = k_1 x - k_2 y, & y(0) = 0 \end{cases}.$$

The first differential equation is first-order linear; therefore,

$$(2) \qquad x(t) = Ae^{-k_1 t}.$$

Substituting for $x(t)$ and using an integrating factor of $e^{k_2 t}$ in the second differential equation we have

$$(3) \qquad y(t) = \frac{k_1 A}{k_2 - k_1}\left(e^{-k_1 t} - e^{-k_2 t}\right)$$

Looking at Figure 3 2, we can see that the decongestant level peaks quickly at about 1.9 hours and begins to clear the blood, more quickly than the antihistamine.

[Sensitivity to Clearance Coefficient]

A person's health and age may drastically effect the rate at which his or her body is able to remove the decongestant The older and less healthy a person is the smaller the clearance coefficient becomes. Figure 3 3 is plots of decongestant levels in the blood when initially one unit of antihistamine is present in the GI tract and k_1 is fixed at 1.386, but k_2 takes on the values 0 01386, 0 06836, 0.1386, 0.6836 and 1.386 From the graph we notice that the greater the clearance coefficient k_2, the sooner the decongestant level peaks and begins to clear the bloodstream. The decongestant level for a young and healthy individual peaks at about 0 72 hours at 0 4 units. For an old and sick person,

$$k_1 = 1\ 386;\ k_2 = 0\ 1386$$
$$x' = -k_1 x, \qquad x(0) = 1$$
$$y' = k_1 x - k_2 y,\ y(0) = 0$$

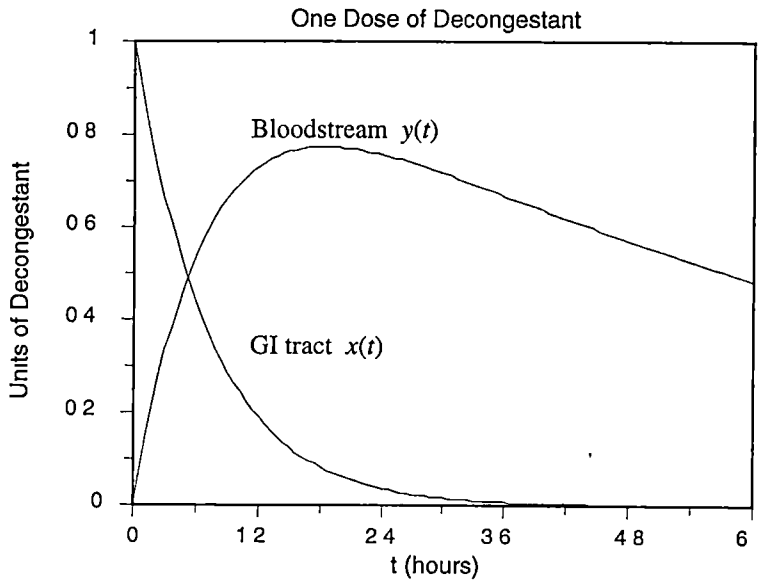

Figure 3.2. Effect of one dose of decongestant As with the antihistamine, the decongestant level in the blood stream rises, peaks at about 0 77 units when $t = 1\ 9$ hours and then diminishes within the 6 hour period.

$k_1 = 1\ 386,\ k_2 =$ as shown

$x' = -k_1 x, \qquad x(0) = 1$

$y' = k_1 x - k_2 y,\ y(0) = 0$

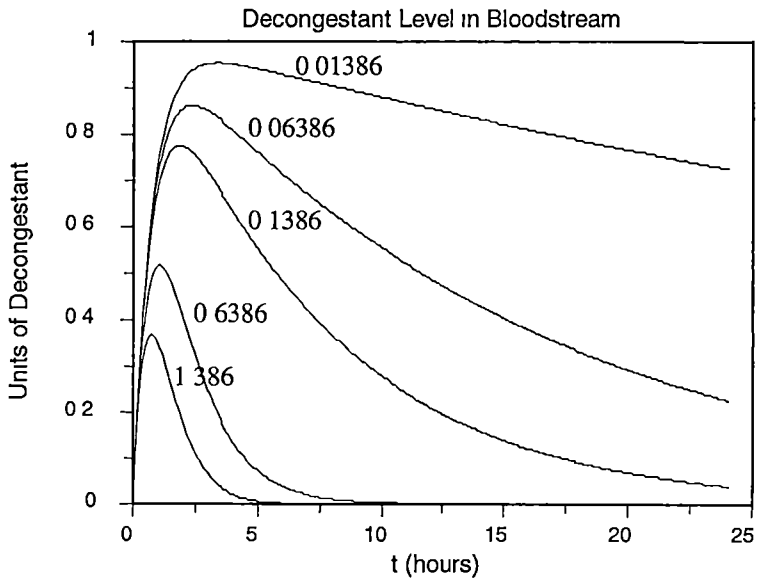

Figure 3.3. Sensitivity to clearance coefficient k_2 As the clearance coefficient increases, the level of decongestant in the blood peaks sooner and sooner Decongestant levels in a young and healthy person peak at about 0 72 hours at 0.4 units For an old and sick individual, the decongestant level peaks at about 3 hours at 0 95 units

The decongestant level peaks at about 3 hours at 0 95 units

CHAPTER IV: DECONGESTANT WITH PERIODIC DOSING

[Model]

Instead of just receiving one dose, suppose decongestant is released in the GI tract at the constant rate of 12 units/hour for one-half hour and then repeated every six hours. The plot of this type of dosing would look like the square wave $I(t)$ in Figure 4 1. *ODE Architect* has the square wave as a built-in function, SqWave(t, t_p, t_i), where t_p is the period and t_i is the on-time for the cycle. Figure 4 2 illustrates the boxes-and-arrows diagram to model the flow of the medication Given the presence of the nonlinearity of dosing input, we will present here the numerical solutions in graphical form and discuss the existence and stability of periodic solutions later in Chapter VII.

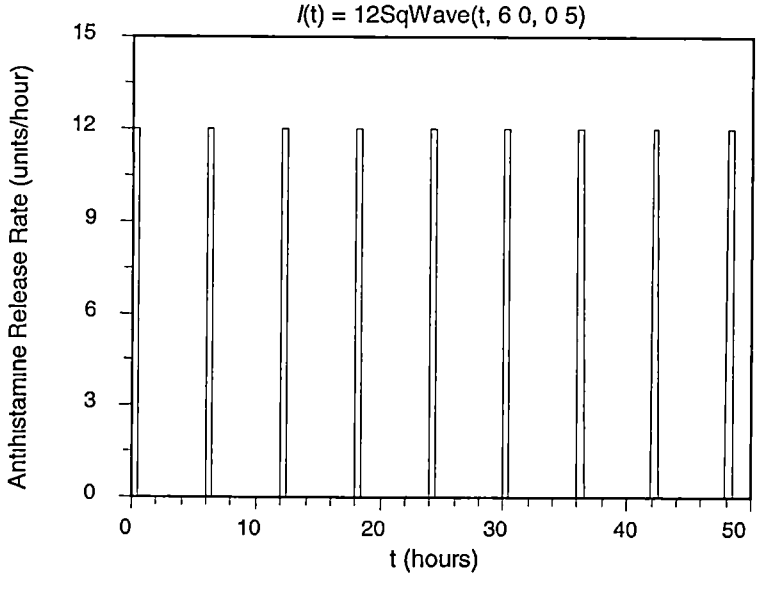

Figure 4.1. Periodic dosing into the GI tract at the constant rate of 12 units/hour for one-half hour and then repeated every six hours

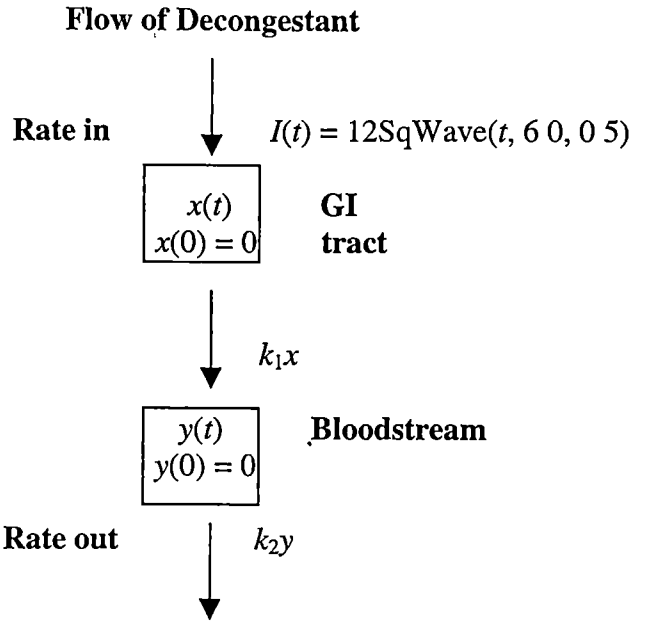

Figure 4.2. Diagram for the flow of decongestant with periodic dosing.

Thus the corresponding system of ODEs is given by

$$(1) \qquad \begin{cases} \dfrac{dx}{dt} = I - k_1 x, \quad x(0) = 0 \\ \dfrac{dy}{dt} = k_1 x - k_2 y, \quad y(0) = 0 \end{cases}$$

[Sensitivity to Clearance Coefficient]

Figure 4 3 shows that the amount of decongestant in the GI tract rises quickly as the pill dissolves, but then drops to almost zero before the next dose is taken. The graph

$$k_1 = 1\ 386,\ k_2 = 0\ 1386$$

$$x' = 12*\mathrm{SqWave}(t, 6\ 0, 0\ 5) - k_1 x, \qquad x(0) = 0$$

$$y' = k_1 x - k_2 y, \qquad y(0) = 0$$

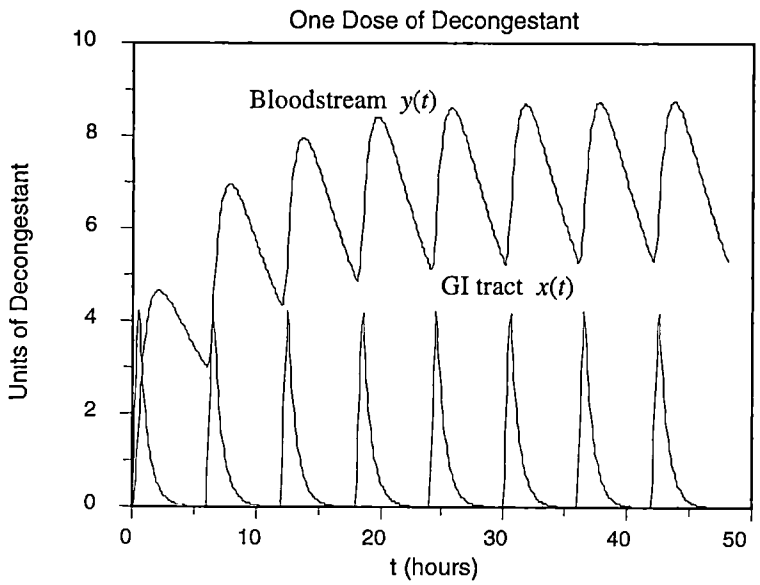

Figure 4.3. Decongestant levels in a young and healthy individual with periodic dosing over 48 hours

for the blood decongestant level reveals that a type of equilibrium possibly has been established within 48 hours The maximum concentration in the blood appears to be around 8 7 units

Using the same periodic dosing as above, Figure 4.4 are plots of decongestant levels in the GI tract and in the blood of a young and healthy person over a five-day period Older and less-healthy individuals clear the decongestant from their bodies less efficiently than a younger and healthier person, therefore, the clearance rate k_2 is smaller Figures 4 5, 4.6 and 4 7 illustrate clearly that there will be excessive decongestant

$$k_1 = 1\ 386,\ k_2 = 0\ 1386$$

$$x' = 12*\mathrm{SqWave}(t, 6\ 0, 0\ 5) - k_1 x, \qquad x(0) = 0$$

$$y' = k_1 x - k_2 y, \qquad y(0) = 0$$

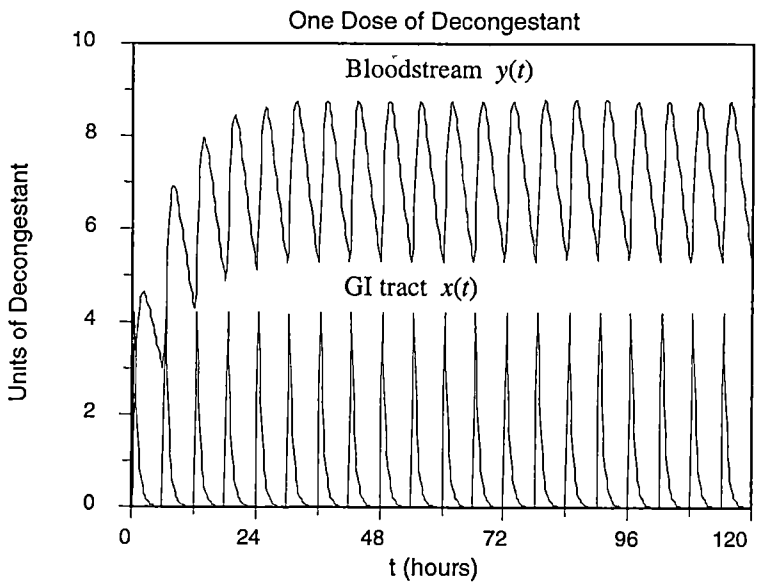

Figure 4.4. Decongestant levels in a young and healthy individual with periodic dosing over a 5 day period.

$$k_1 = 1.386,\ k_2 = 0\ 06386$$

$$x' = 12*\mathrm{SqWave}(t, 6\ 0, 0.5) - k_1 x, \qquad x(0) = 0$$

$$y' = k_1 x - k_2 y, \qquad y(0) = 0$$

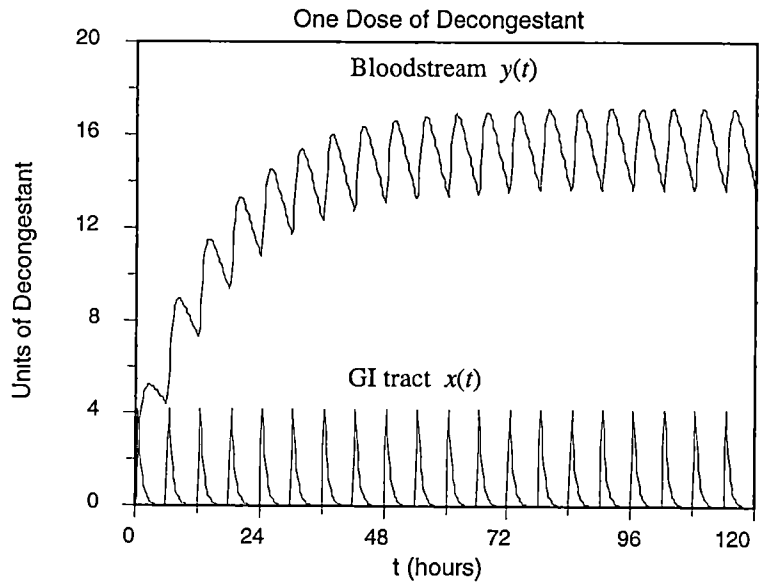

Figure 4.5. Decongestant levels in an older and less healthy individual with periodic dosing over a 5 day period

$$k_1 = 1\ 386,\ k_2 = 0\ 01386$$
$$x' = 12*\mathrm{SqWave}(t, 6.0, 0\ 5) - k_1 x, \qquad x(0) = 0$$
$$y' = k_1 x - k_2 y, \qquad y(0) = 0$$

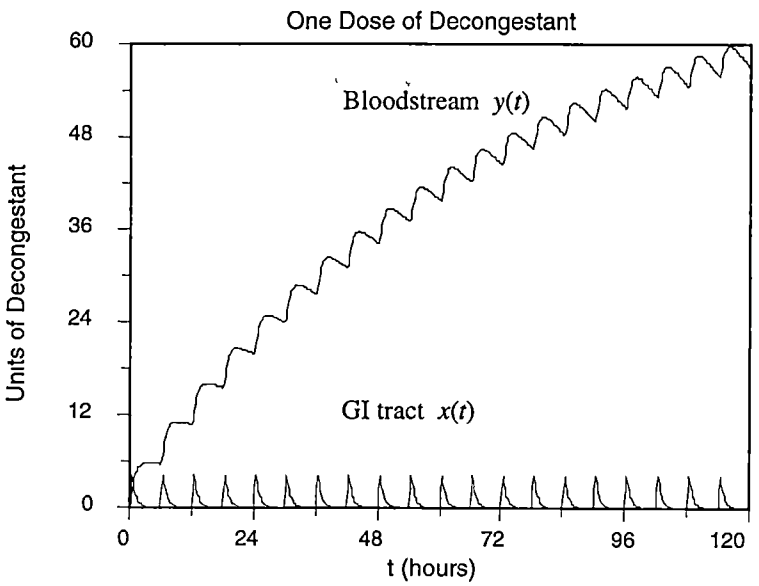

Figure 4.6. Decongestant levels in an old and sick individual with periodic dosing over a 5 day period.

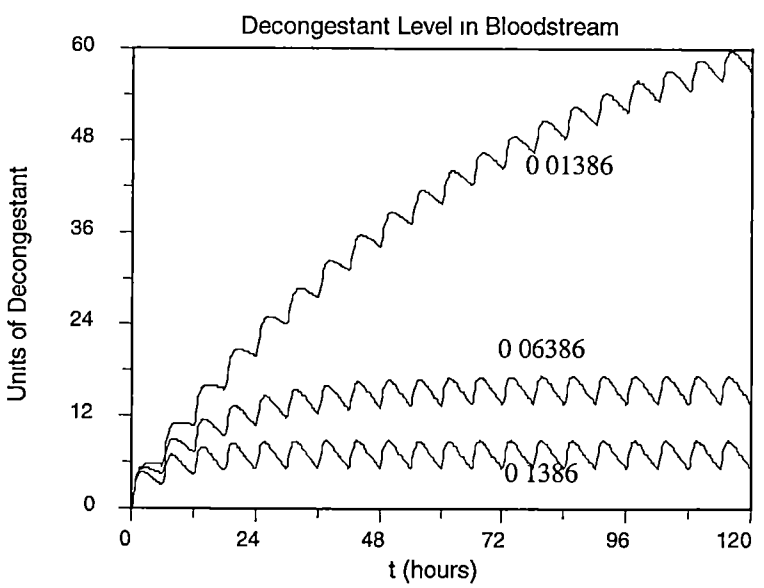

Figure 4.7. Sensitivity to clearance coefficient with periodic dosing As k_2 decreases, the amount of decongestant in the blood climbs.

accumulation in the blood of the old and sick Note that it appears in the first two cases that a type of equilibrium has been established within five days, but not in the third

CHAPTER V: CONTINUOUS DOSING

[Model]

If a medication is embedded in beads of resins that dissolve at varying rates, a constant flow rate I can be assured Figure 5 1 shows the box-and-arrows diagram for this model. Thus the corresponding system of ODEs is given by

$$(1) \qquad \begin{cases} \dfrac{dx}{dt} = I - k_1 x, & x(0) = 0 \\ \dfrac{dy}{dt} = k_1 x - k_2 y, & y(0) = 0 \end{cases}$$

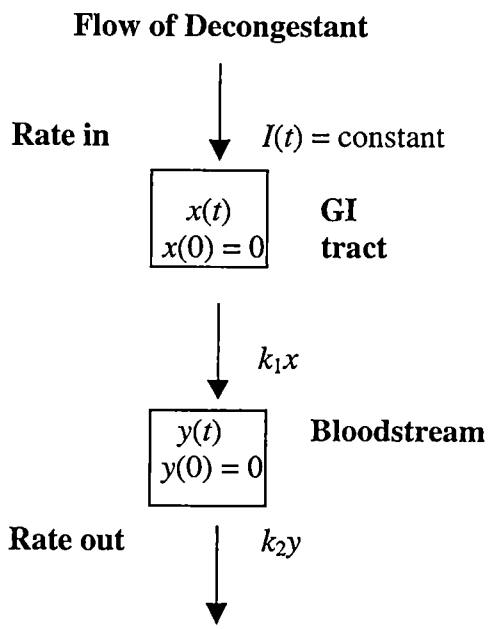

Figure 5.1. Diagram for the flow of decongestant with continuous dosing

Now let's solve this system from the top down, assuming $k_1 \neq k_2$. The first differential equation is first-order linear. Let's solve the differential equation by using the integrating factor $e^{k_1 t}$,

$$e^{k_1 t}\frac{dx}{dt} + e^{k_1 t}k_1 x - e^{k_1 t}I = 0,$$

$$\left(e^{k_1 t}x\right)' = e^{k_1 t}I,$$

$$e^{k_1 t}x = \frac{I}{k_1}e^{k_1 t} + c,$$

$$x(t) = \frac{I}{k_1} + ce^{-k_1 t}$$

Applying the initial condition, we get

$$x(0) = 0 = \frac{I}{k_1} + c \Rightarrow c = -\frac{I}{k_1},$$

so that

(2) $$x(t) = \frac{I}{k_1}\left(1 - e^{-k_1 t}\right)$$

Using an integrating factor of $e^{k_2 t}$ and substituting $x(t)$ above, we get that

$$\frac{dy}{dt} = k_1\left[\frac{I}{k_1}\left(1 - e^{-k_1 t}\right)\right] - k_2 y,$$

$$\frac{dy}{dt} + k_2 y = I - Ie^{-k_1 t},$$

$$e^{k_2 t}\frac{dy}{dt} + k_2 y e^{k_2 t} = Ie^{k_2 t} - Ie^{(k_2 - k_1)t},$$

$$\left(e^{k_2 t}y\right)' = Ie^{k_2 t} - Ie^{(k_2 - k_1)t},$$

$$e^{k_2 t} y = \frac{I e^{k_2 t}}{k_2} - \frac{I e^{(k_2 - k_1)t}}{k_2 - k_1},$$

$$y(t) = \frac{I}{k_2} - \frac{I e^{-k_1 t}}{k_2 - k_1} + c e^{-k_2 t}.$$

Now, applying the initial condition,

$$y(0) = 0 = \frac{I}{k_2} - \frac{I}{k_2 - k_1} + c \Rightarrow c = \frac{I}{k_2 - k_1} - \frac{I}{k_2}$$

$$= \frac{I k_1}{k_2 (k_2 - k_1)},$$

so that

$$y(t) = \frac{I}{k_2} - \frac{I e^{-k_1 t}}{k_2 - k_1} + \frac{I k_1}{k_2 (k_2 - k_1)} e^{-k_2 t},$$

(3) $$y(t) = \frac{I}{k_2 - k_1} \left[\left(e^{-k_2 t} - 1 \right) k_1 + \left(1 - e^{-k_2 t} \right) k_2 \right]$$

[Approach to Equilibrium]

Another vital issue to consider is what happens to the levels of medication in the GI tract and blood long term, i.e , as t approaches infinity Taking the limit as t goes to infinity of our solutions for $x(t)$ and $y(t)$ in equations (2) and (3), respectively, or

(4) $$\lim_{t \to \infty} x(t) = \lim_{t \to \infty} \frac{I}{k_1} (1 - e^{-k_1 t}) = \frac{I}{k_1}$$

and

(5) $$\lim_{t \to \infty} y(t) = \lim_{t \to \infty} \frac{I}{k_2 (k_2 - k_1)} \left[\left(e^{-k_2 t} - 1 \right) k_1 + \left(1 - e^{-k_1 t} \right) k_2 \right] = \frac{I}{k_2},$$

we find that $x(t)$ approaches $\frac{I}{k_1}$ and $y(t)$ approaches $\frac{I}{k_2}$ as $t \to \infty$.

Graphs of $x(t)$ and $y(t)$ for 200 hours are plotted in Figure 5 2 A young and healthy person was given $I = 1$ unit of antihistamine per hour. From (4), the equilibrium value in the blood is 1/ 0 0231 = 43.29 units The graph shows that the antihistamine level is at 42 85 units at $t = 200$ hours, suggesting that equilibrium has not quite been established This is not the case with the decongestant. Figure 5 3 shows plots of $x(t)$ and $y(t)$ for 100 hours for a young and healthy individual given 1 unit of decongestant per hour We discovered from above that the equilibrium value is 1/0 1386 = 7.215 units The graph shows that the decongestant level is at 7 215 units at $t = 100$ hours indicating that indeed the level of medication in the blood reaches an equilibrium within 100 hours

[The Old and Sick]

In this section we will continue to investigate what happens to medication levels when the dosage is continuous More specifically, we will want to see, as in the other dosing models, if medication levels in the old and sick become much larger than in the young and healthy. For the old and sick, we will take for our rate constants one-third of the rate constants of the young and healthy. Comparing Figure 5.4 to Figure 5 2, we notice that at 200 hours the amount of antihistamine present in the bloodstream is 101.01 units, much greater than 42.85 units for a young and healthy person. Further, the antihistamine level has not peaked within the 200-hour period. The same situation arises

$$k_1 = 0\ 6931,\ k_2 = 0.0231$$
$$I = 1\ 0$$
$$x' = I - k_1 x, \qquad x(0) = 0$$
$$y' = k_1 x - k_2 y, \qquad y(0) = 0$$

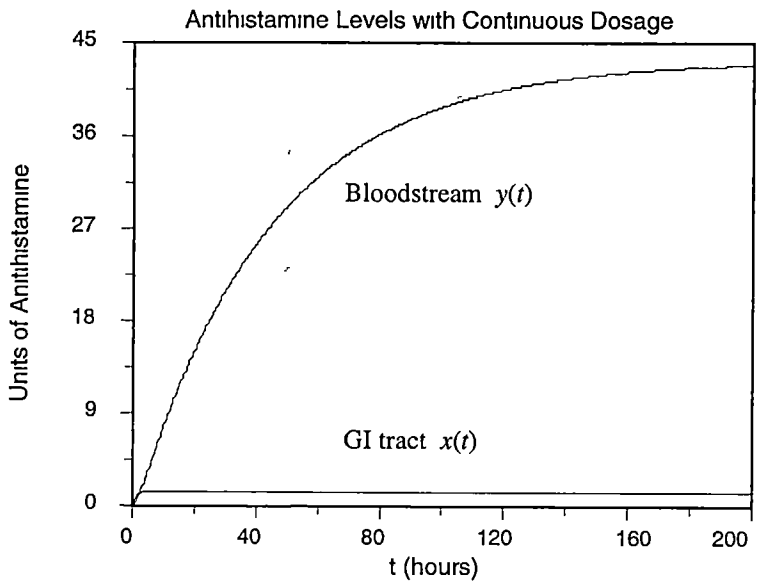

Figure 5.2. Antihistamine levels in a young and healthy individual with continuous dosage of one unit per hour over a 200 hour time interval The equilibrium value for $y(t)$ is 43 29 units, but the graph indicates that at $t = 200$ hours, the antihistamine level in the blood is 42 85 units

$$k_1 = 1.386,\ k_2 = 0\ 1386$$
$$I = 1\ 0$$
$$x' = I - k_1 x, \qquad x(0) = 0$$
$$y' = k_1 x - k_2 y, \qquad y(0) = 0$$

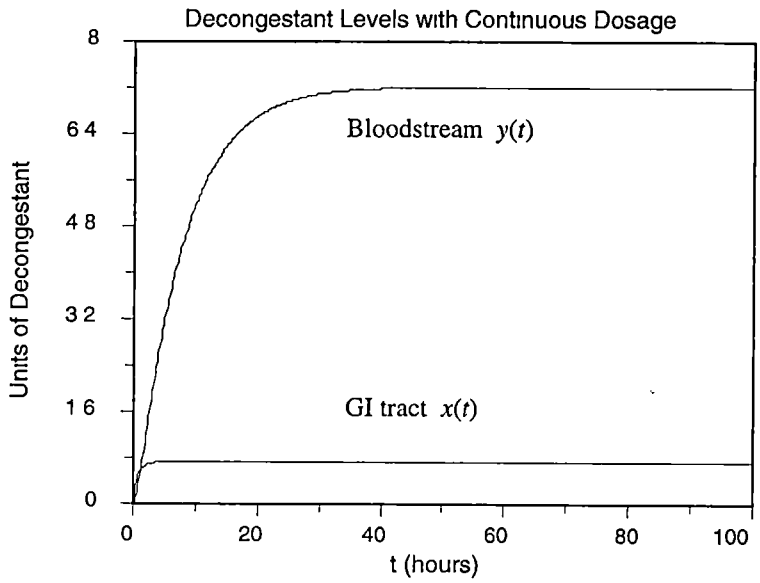

Figure 5.3. Decongestant levels in a young and healthy individual with continuous dosage of one unit per hour over a 100 hour time interval. The system has reached its equilibrium value of 7 215 units in the bloodstream by $t = 100$ hours

$$k_1 = 0\ 6931/3,\ k_2 = 0\ 0231/3$$
$$I = 1.0$$
$$x' = I - k_1 x, \qquad x(0) = 0$$
$$y' = k_1 x - k_2 y, \qquad y(0) = 0$$

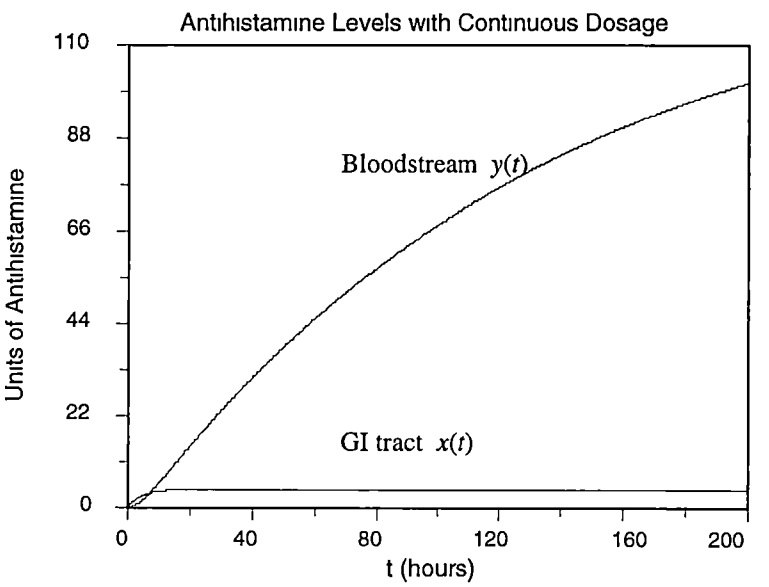

Figure 5.4. Antihistamine levels in an old and sick individual with continuous dosage of one unit per hour over a 200 hour time interval The equilibrium value for $y(t)$ is 129 87 units, but at $t = 200$ hours, the antihistamine level is only 101 units.

in the decongestant. Comparing Figure 5.5 to Figure 5 3, observe that after 100 hours, the decongestant level in the old and sick has reached 21 41 units whereas in the young and healthy the level has reached only 7.22 units

[Safe and Effective Zone]

Suppose that the levels of antihistamine in the blood are designed to reach and remain between 25 and 50 units for a dose taken continuously at the rate of 1 unit per hour We

$$k_1 = 1.386\text{-}3;\ k_2 = 0.1386/3$$
$$I = 1.0$$
$$x' = I - k_1 x, \qquad x(0) = 0$$
$$y' = k_1 x - k_2 y, \qquad y(0) = 0$$

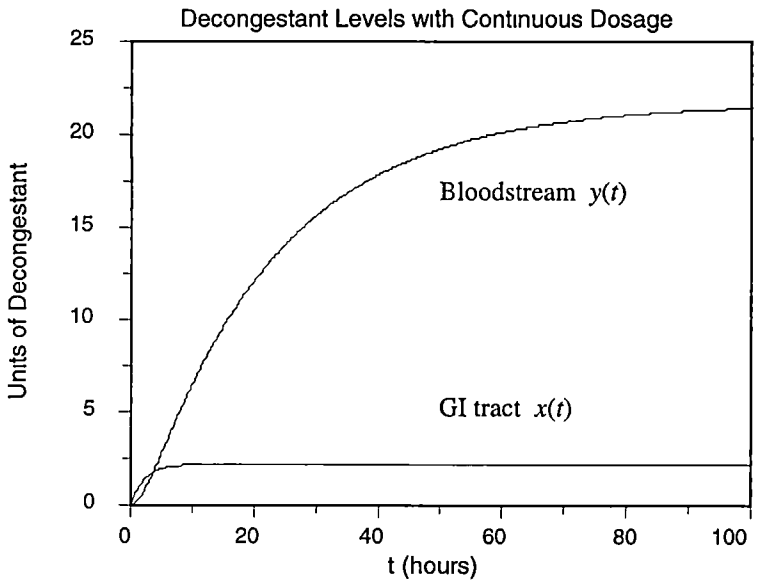

Figure 5.5. Decongestant levels in an old and sick individual with continuous dosage of one unit per hour over a 100 hour time interval The equilibrium value for the bloodstream is 21 64 units At $t = 100$ hours, 21 4 units are in the blood

would like to examine the possibility of this scenario for the second through the fifth days The second day through the fifth day means hours 48–120 Figure 5 6 clearly indicates that it is not possible for the antihistamine level to remain between 25 and 50 units during the second through the fifth days

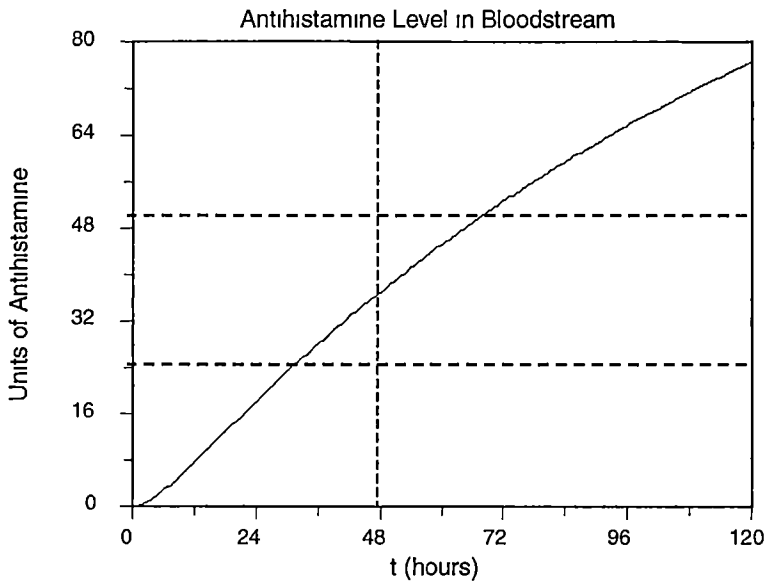

Figure 5.6. Safe and Effective Zone. It is not possible for the antihistamine level to stay between 25 and 50 units between 48 and 120 hours

CHAPTER VI: SATURATION MODELS

Rather than the rate function for clearance in the bloodstream being linear in y as in our previous models, suppose that the clearance is nonlinear and proportional to $\frac{y}{1+cy}$. This introduces one type of saturation effect where clearance is not always increasing, but begins to level off at some point. A second type of saturation model to which we will give attention to is if the clearance is proportional to $\frac{y^{3/2}}{1+cy}$ Note that increasing the constant c also produces further saturation. We proceed in this section by graphically comparing the saturation models to the previous non-saturation models. In Chapter VII we will discuss the existence and stability of periodic solutions of all three types of models in the case of periodic dosing

[Type I Saturation]

Periodic Dosing (c = 0.1)

In this section we shall explore the saturation effect with periodic dosing, that is, when the decongestant or antihistamine is released in the GI tract at the constant rate of 12 units/hour for 1/2 hour, and then repeated every six hours In particular, we would like to determine if excessive buildup of decongestant occurs in the blood of the old and sick We introduce a saturation effect in removal from the bloodstream like that in the

compartmental diagram shown in Figure 6.1 Thus the corresponding system of ODEs is given by

$$(1) \qquad \begin{cases} \dfrac{dx}{dt} = I - k_1 x, \quad x(0) = 0 \\ \dfrac{dy}{dt} = k_1 x - k_2 \left(\dfrac{y}{1+cy} \right), \quad y(0) = 0 \end{cases}$$

Using the data $k_1 = 1\ 386$ and $k_2 = 0.1386$, Figure 6.2 shows plots of decongestant levels in the GI tract and in the blood over a 5-day period Compare this plot to Figure 4 4, the corresponding non-saturation model The peak value for the decongestant in the bloodstream in the Type I Saturation model is roughly 23 5 units compared to the 8 7

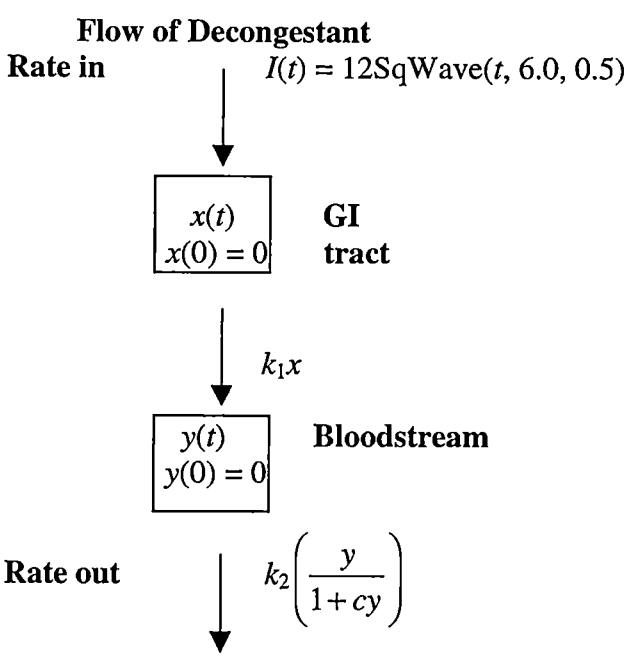

Figure 6.1. Diagram for the Type I Saturation Model with periodic dosing

$$k_1 = 1\ 386,\ k_2 = 0\ 1386$$
$$c = 0\ 1$$
$$x' = 12*\mathrm{SqWave}(t, 6\ 0, 0\ 5) - k_1 x, \qquad x(0) = 0$$
$$y' = k_1 x - k_2(y/(1 + cy)), \qquad y(0) = 0$$

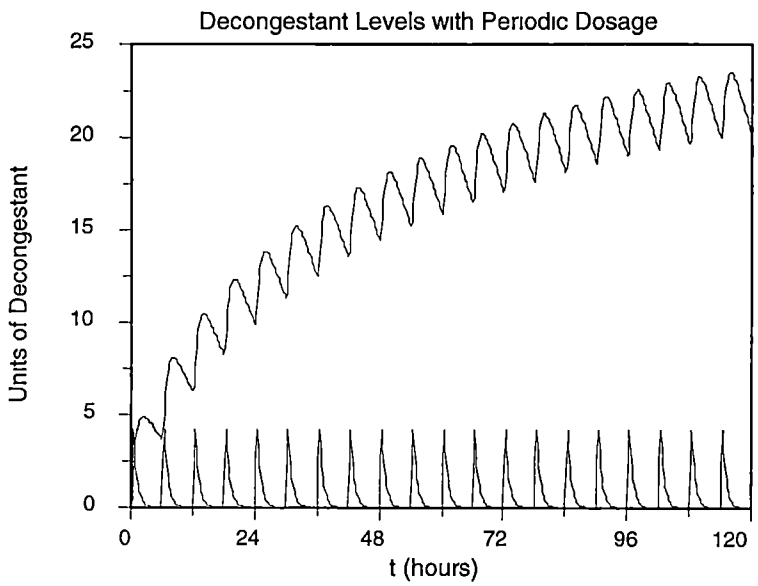

Figure 6.2. Decongestant level in a young and healthy individual in the Type I Saturation Model with periodic dosing over a 5 day period Compare to Figure 4 4

units in the non-saturation model. Repeating with $k_2 = 0\ 06386, 0.01386$ in Figures 6 3 (compare to Figure 4.5) and 6 4 (compare to Figure 4 6), respectively, we see that there will be excessive decongestant accumulation in the blood of the old and sick just as in the previous model, but the medication levels become more dangerously high Summarizing the solutions for the decongestant levels in the bloodstream, Figure 6 5 again clearly emphasizes that there will be excessive buildup of decongestant in the bloodstream of the old and sick.

$$k_1 = 1\ 386,\ k_2 = 0\ 06386$$
$$c = 0.1$$
$$x' = 12*\mathrm{SqWave}(t, 6\ 0, 0\ 5) - k_1 x, \qquad x(0) = 0$$
$$y' = k_1 x - k_2(y/(1 + cy)), \qquad y(0) = 0$$

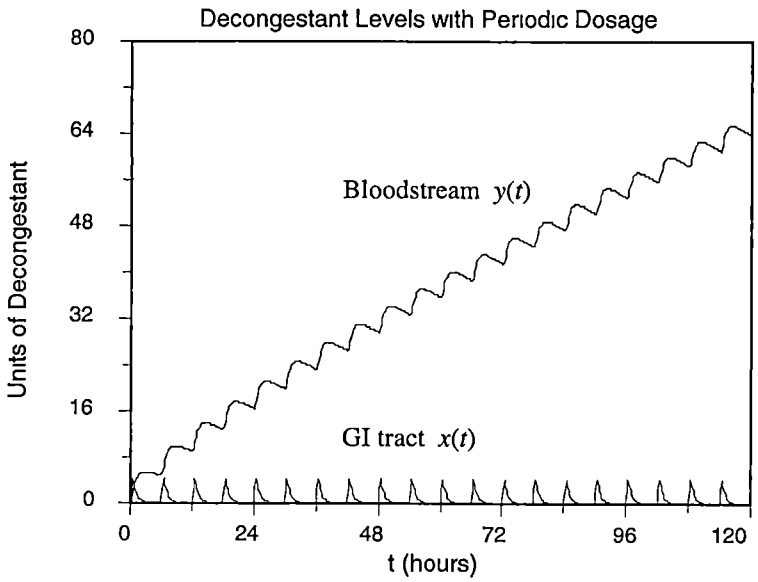

Figure 6.3. Decongestant levels in an older and less healthy individual in the Type I Saturation Model with periodic dosing over a 5 day period Compare to Figure 4 5

$$k_1 = 1\ 386,\ k_2 = 0\ 01386$$
$$c = 0\ 1$$
$$x' = 12*\text{SqWave}(t, 6\ 0, 0.5) - k_1 x, \qquad x(0) = 0$$
$$y' = k_1 x - k_2(y/(1 + cy)), \qquad y(0) = 0$$

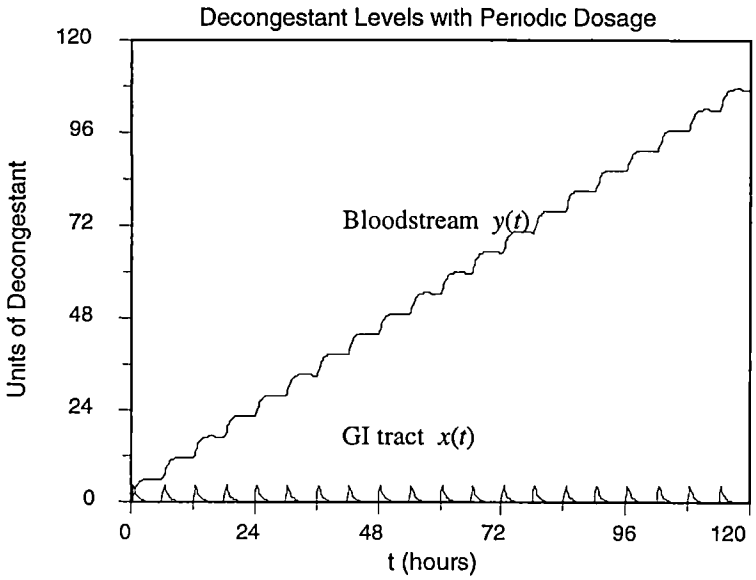

Figure 6.4. Decongestant levels in an old and sick individual in the Type I Saturation Model with periodic dosing over a 5 day period Compare to Figure 4 6.

$k_1 = 1\ 386,\ k_2 =$ as shown

$c = 0\ 1$

$x' = 12*\text{SqWave}(t, 6\ 0, 0\ 5) - k_1 x, \qquad x(0) = 0$

$y' = k_1 x - k_2(y/(1 + cy)), \qquad y(0) = 0$

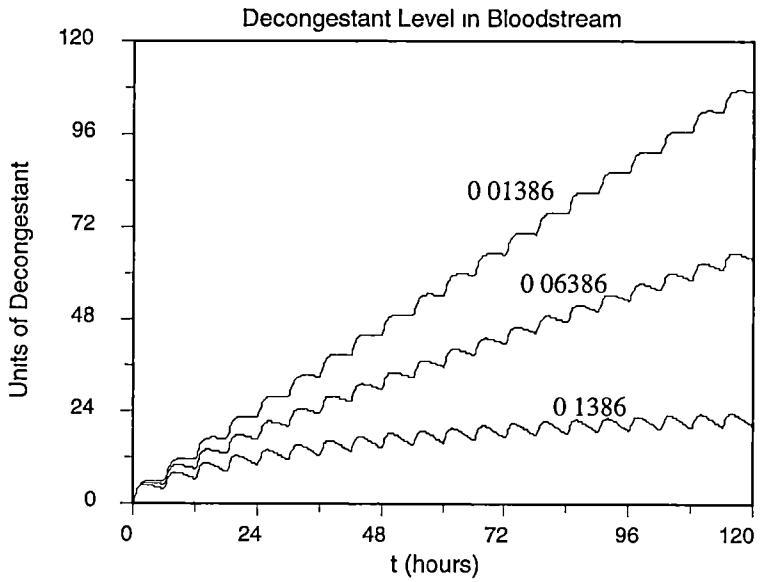

Figure 6.5. Sensitivity to clearance coefficient in the Type I Saturation Model Compare to Figure 4 7 The medication levels become dangerously high.

Periodic Dosing (c = 1.0)

In this section we continue our investigation of the Type I Saturation model, but increase the saturation effect slightly by changing the constant c from 0 1 to 1 0 We shall examine what happens with periodic dosing as in the previous section

Suppose decongestant is released in the GI tract at the constant rate of 12 units/hour for 1/2 hour, and then repeated every six hours. This system of ODEs is same as that in (1) Using the same data $k_1 = 1.386$ and $k_2 = 01386$, but increasing c to 1 0,

Figure 6 6 shows plots decongestant levels in the GI tract and in the blood over a 48-hour period In the non-saturation model, after 48 hours the decongestant level has peaked at around 8.7 units, but in the Type I Model, the level reaches around 42 units, without yet establishing equilibrium Figures 6 7, 6 8, and 6 9 show the solutions for $x(t)$ and $y(t)$ with $k_2 = 0\ 1386$, 0.06386 and 0.01386, respectively, but over a five-day period In Figure 6 10, the plots of Figures 6 7, 6 8, and 6 9 are combined to emphasize the sensitivity to k_2

$$k_1 = 1\ 386;\ k_2 = 0\ 1386$$
$$c = 1\ 0$$
$$x' = 12\text{SqWave}(t, 6\ 0, 0\ 5) - k_1 x, \qquad x(0) = 0$$
$$y' = k_1 x - k_2(y/(1+cy)), \qquad y(0) = 0$$

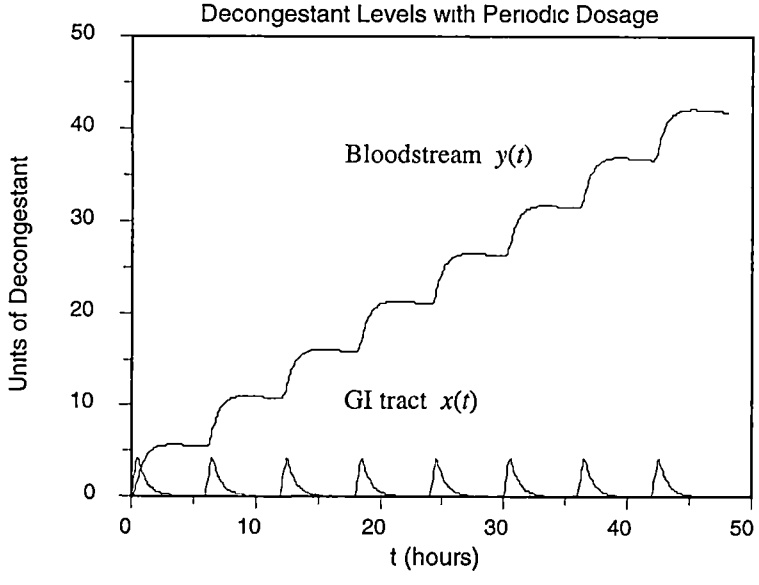

Figure 6.6. Decongestant levels in a young and healthy individual in the Type I Saturation Model with periodic dosing over 48 hours Compare to Figure 4.3.

$$k_1 = 1\ 386,\ k_2 = 0\ 1386$$
$$c = 1\ 0$$
$$x' = 12\text{SqWave}(t, 6.0, 0.5) - k_1 x, \qquad x(0) = 0$$
$$y' = k_1 x - k_2(y/(1+cy)), \qquad y(0) = 0$$

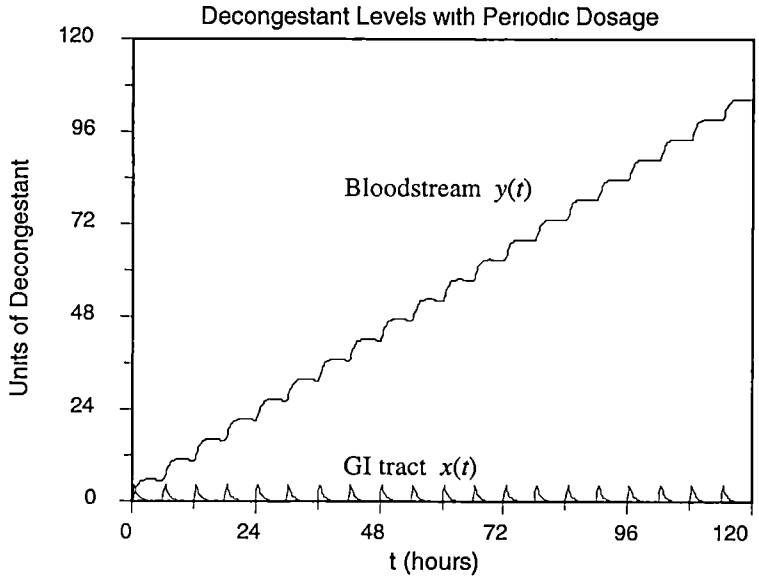

Figure 6.7. Decongestant levels in a young and healthy individual in the Type I Saturation Model with periodic dosing over a 5 day period. Compare to Figures 4 4 and 6 2

$$k_1 = 1.386,\ k_2 = 0\ 06386$$
$$c = 1\ 0$$
$$x' = 12\text{SqWave}(t, 6\ 0, 0\ 5) - k_1 x, \qquad x(0) = 0$$
$$y' = k_1 x - k_2(y/(1+cy)), \qquad y(0) = 0$$

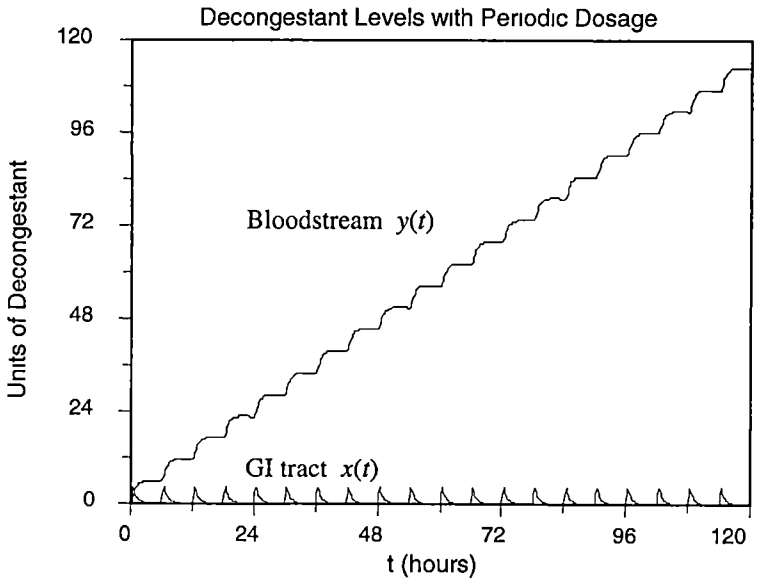

Figure 6.8. Decongestant levels in an older and less healthy individual in the Type I Saturation Model with periodic dosing over a 5 day period Compare to Figures 4 5 and 6 3

$$k_1 = 1\ 386,\ k_2 = 0\ 01386$$
$$c = 1\ 0$$
$$x' = 12\text{SqWave}(t, 6\ 0, 0\ 5) - k_1 x, \qquad x(0) = 0$$
$$y' = k_1 x - k_2(y/(1+cy)), \qquad y(0) = 0$$

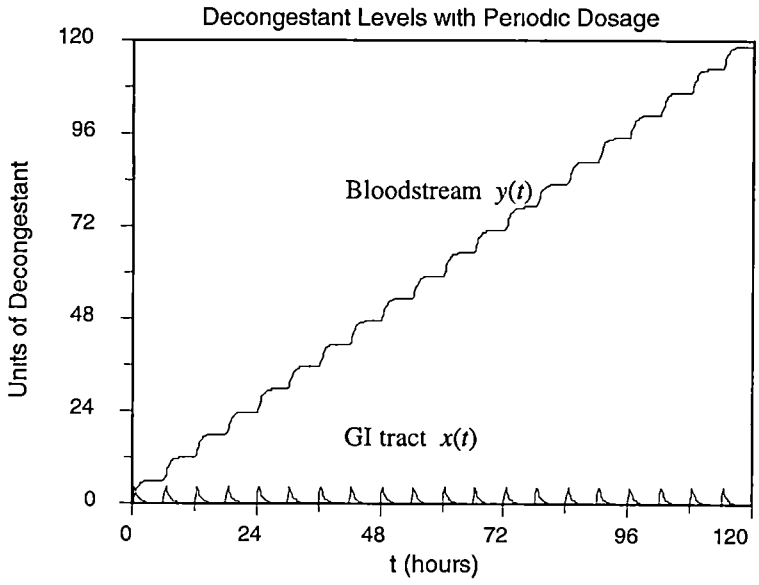

Figure 6.9. Decongestant levels in and old and sick individual in the Type I Saturation Model with periodic dosing over a 5 day period. Compare to Figures 4 6 and 6 4

$$k_1 = 1\ 386;\ k_2 = \text{as shown}$$
$$c = 1\ 0$$
$$x' = 12\text{SqWave}(t, 6\ 0, 0\ 5) - k_1 x, \qquad x(0) = 0$$
$$y' = k_1 x - k_2(y/(1+cy)), \qquad y(0) = 0$$

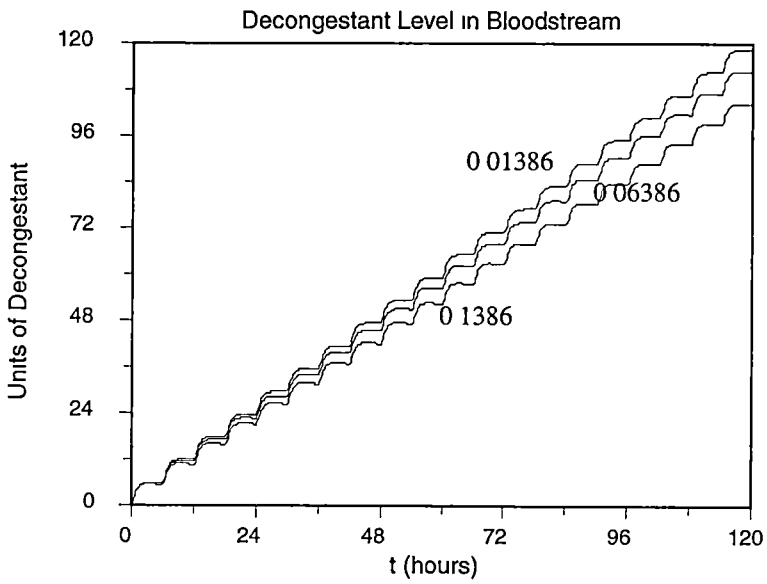

Figure 6.10. Sensitivity to clearance coefficient. Compare to Figures 4 7 and 6.5.

Continuous Dosing

Suppose that the medication is administered continuously at the rate of I unit per hour This model is depicted in Figure 6.11 Thus, for the Type I Saturation Model with continuous dosing, the corresponding system of ODEs is given by

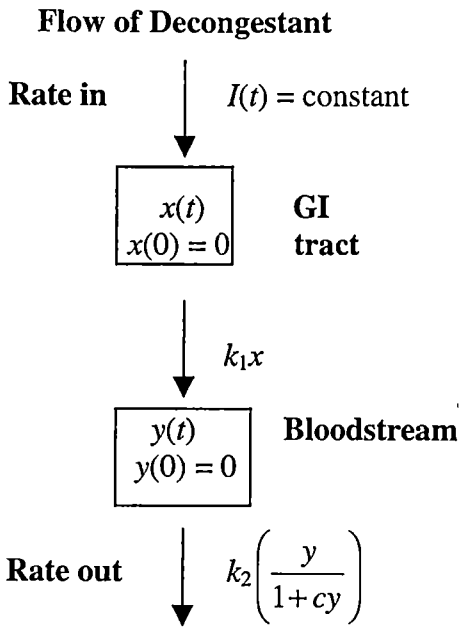

Figure 6.11. Diagram of Type I Saturation Model with continuous dosing.

(2)
$$\begin{cases} \dfrac{dx}{dt} = I - k_1 x, \quad x(0) = 0 \\ \dfrac{dy}{dt} = k_1 x - k_2\left(\dfrac{y}{1+cy}\right), \quad y(0) = 0 \end{cases}$$

Approach to Equilibrium

Once the system arrives at equilibrium, the medication level in the GI tract and bloodstream remain constant Therefore, $\frac{dx}{dt} = 0$ and $\frac{dy}{dt} = 0$, which gives as the closed-form solutions for the medication levels at equilibrium the expressions in (3) and (4).

(3) $$\lim_{t\to\infty} x(t) \Rightarrow \frac{dx}{dt} = 0 \Rightarrow x^*(t) = \frac{I}{k_1}$$

and

(4) $$\lim_{t\to\infty} y(t) \Rightarrow \frac{dy}{dt} = 0 \Rightarrow y^*(t) = \frac{I}{k_2 - Ic}.$$

ODE Architect was used to plot $x(t)$ and $y(t)$ over a 200 hour interval Figure 6 12 shows the results for the antihistamine if the dosage is $I = 1$ unit/hour, $k_1 = 0.6931$ hour^{-1} and $k_2 = 0\ 0231$ hour^{-1} According to (4) the equilibrium value for the antihistamine level in the blood is $\frac{I}{k_2 - Ic} = \frac{1}{0\ 0231 - (1)(0\ 1)} = -13\ 003$ units This negative value indicates that for this set of data, no equilibrium is established in the blood The expression for $\frac{dy}{dt}$ in (4) is positive leading to the conclusion that the antihistamine level is unbounded as $t \to \infty$. The graph in Figure 6 12 shows that at $t =$ 200 hours there are about 160 457 units of antihistamine in the bloodstream Compare this to Figure 5 2

Repeating for the decongestant case with the data $k_1 = 1\ 386$ hour^{-1} and $k_2 =$ $0\ 1386$ hour^{-1}, it appears that in Figure 6 13 even after 200 hours the system has not quite stabilized The equilibrium value is $\frac{I}{k_2 - Ic} = \frac{1}{0\ 1386 - (1)(0.1)} = 25\ 91$ units . The graph shows that at $t = 200$ hours there are 24.64 units of decongestant in the bloodstream Compare this example to Figure 5 3

$$k_1 = 0\ 6931,\ k_2 = 0\ 0231$$
$$I = 1\ 0$$
$$c = 0\ 1$$
$$x' = I - k_1 x, \qquad x(0) = 0$$
$$y' = k_1 x - k_2(y/(1+cy)), \qquad y(0) = 0$$

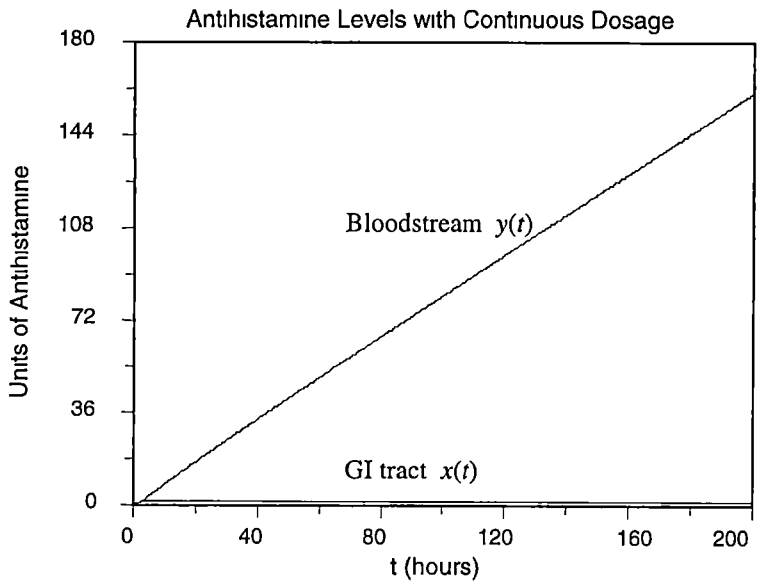

Figure 6.12. Antihistamine levels in a young and healthy individual in the Type I Saturation Model with continuous dosing over a 200 hour interval The medication level in the blood continues to increase as t becomes large Compare to Figure 5.2.

$$k_1 = 1\ 386;\ k_2 = 0\ 1386$$
$$I = 1.0$$
$$c = 0\ 1$$
$$x' = I - k_1 x, \qquad x(0) = 0$$
$$y' = k_1 x - k_2(y/(1+cy)), \qquad y(0) = 0$$

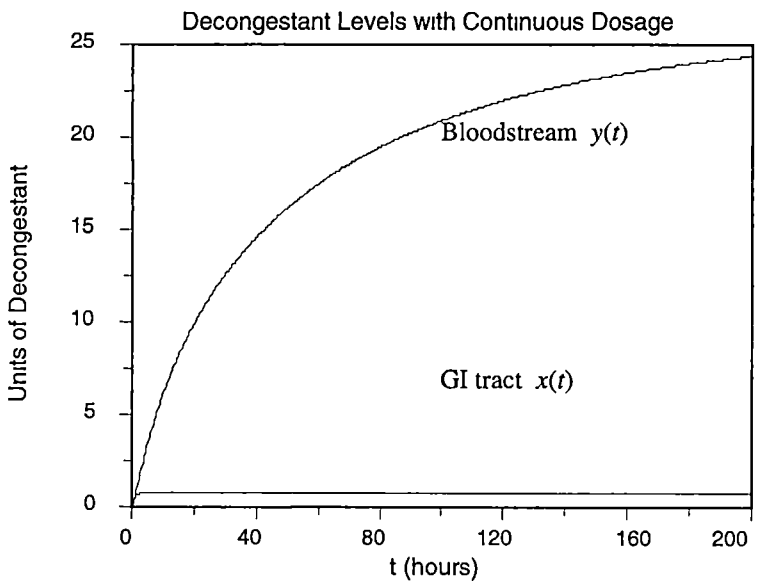

Figure 6.13. Decongestant levels in a young and healthy individual in the Type I Saturation Model with continuous dosing over a 200 hour interval. At $t = 200$ hours, the decongestant level in the blood is 24 64 units The equilibrium value is 25 91units Compare to Figure 5.3

The Old and Sick

As in the non-saturation models, we would like to determine if antihistamine and decongestant levels in the saturation models show excessive build-up in the bloodstream of the old and sick Recall that the rate constants are much smaller in older and less healthy individuals Suppose, in fact, that they are one-third of those of a young and

healthy person Figure 6 14 shows the results for the antihistamine case and Figure 6 15 that of the decongestant case. For the antihistamine case, the equilibrium value is

$\frac{I}{k_2 - Ic} = \frac{1\,0}{0\,023\frac{1}{3} - 0.1} = -10\,8342$ units, indicating that $\frac{dy}{dt}$ is positive for t large and that $y(t)$ grows without bound as $t \to \infty$ Compare this to the non-saturation situation in Figure 5 4 Similarly for the decongestant, the equilibrium value is

$k_1 = 0\,6931/3;\ k_2 = 0\,0231/3$
$I = 1.0$
$c = 0\,1$
$x' = I - k_1 x, \qquad x(0) = 0$
$y' = k_1 x - k_2(y/(1+cy)), \qquad y(0) = 0$

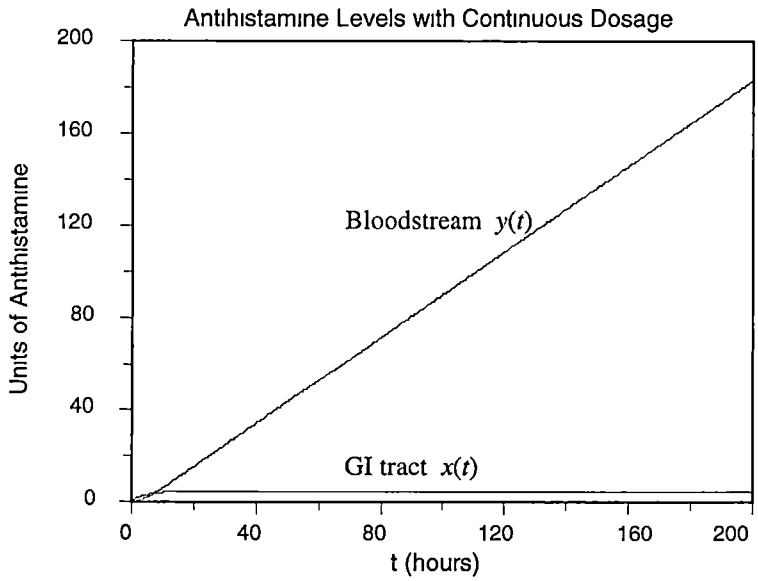

Figure 6.14. Antihistamine levels in an old and sick individual in the Type I Saturation Model with continuous dosing over a 200 hour interval. The antihistamine level in the blood is unbounded for t large. Compare to Figure 5 4

$$k_1 = 1.386/3;\ k_2 = 0\ 1386/3$$
$$I = 1\ 0$$
$$c = 0.1$$
$$x' = I - k_1 x, \qquad x(0) = 0$$
$$y' = k_1 x - k_2(y/(1+cy)), \qquad y(0) = 0$$

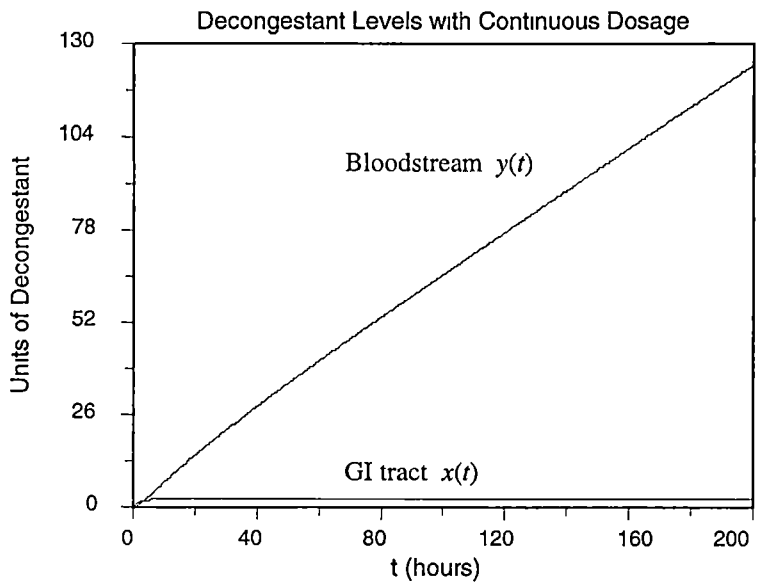

Figure 6.15. Decongestant levels in an old and sick individual in the Type I Saturation Model with continuous dosing over a 200 hour interval The decongestant level in the blood is unbounded for t large Compare to Figure 5 5.

$\frac{I}{k_2 - Ic} = \frac{1\ 0}{0\ 1386/3 - 0\ 1} = -18\ 5874$ units. Again, we conclude that the decongestant in the bloodstream will continue to increase. Compare this to Figure 5 5

One Dose: Sensitivity to k_1 and k_2

Consider again the case when only one dose of antihistamine is administered to

the patient, but now in the context of the Type I Saturation Model This model is given by the system of ODEs in (5)

$$\text{(5)} \qquad \begin{cases} \dfrac{dx}{dt} = -k_1 x, & x(0) = A \\ \dfrac{dy}{dt} = k_1 x - k_2 \left(\dfrac{y}{1+cy} \right), & y(0) = 0 \end{cases}$$

Let $A = 1$, $k_2 = 0\ 0231$ hours $^{-1}$, but let k_1 vary We saw in Figure 2 3 with the non-saturation model that as k_1 increased the time of maximum dosage decreased and the maximum dosage increased In Figure 6 16, when $k_1 = 1\ 5$ hours $^{-1}$, the peak time occurs

k_1 = as shown, $k_2 = 0\ 0231$
c = 1 0
$x' = - k_1 x$, $x(0) = 1$
$y' = k_1 x - k_2(y/(1 + cy))$, $y(0) = 0$

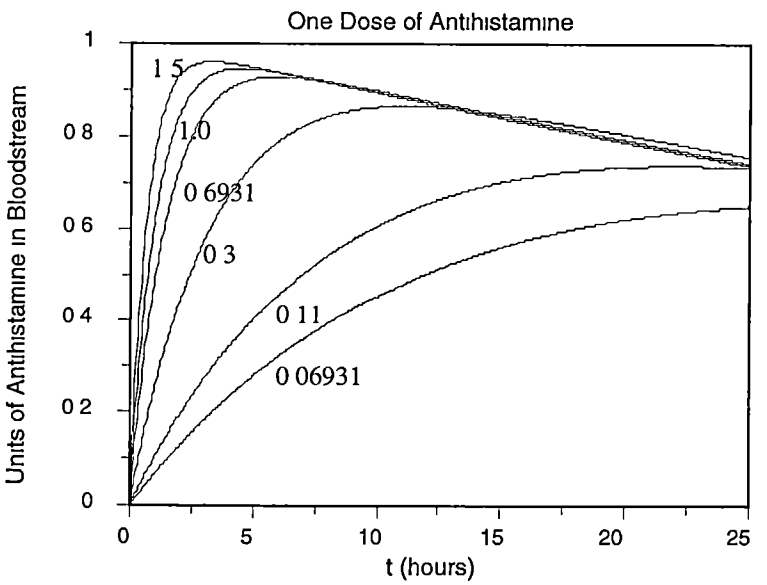

Figure 6.16. Sensitivity to k_1 in the Type I Saturation Model Compare to Figure 2 3

at about 3 3 hours with the peak antihistamine level reaching about 0 96 units However, when $k_1 = 0\ 11$ hours $^{-1}$, the maximum concentration is 0 74 units at 21 98 hours In the non-saturation model, for $k_1 = 1\ 5$ hours $^{-1}$, the maximum level occurs at (2 88 hours, 0.94 units) and for $k_1 = 0\ 11$ hours $^{-1}$ at (18 hours, 0.66 units)

Consider again the case when one dose of decongestant is administered, but now in the context of the Type I Saturation Model Figure 6 17 displays the results of varying

$$k_1 = 1\ 386,\ k_2 = \text{as shown}$$
$$c = 1\ 0$$
$$x' = -k_1 x, \qquad x(0) = 1$$
$$y' = k_1 x - k_2(y/(1+cy)),\ y(0) = 0$$

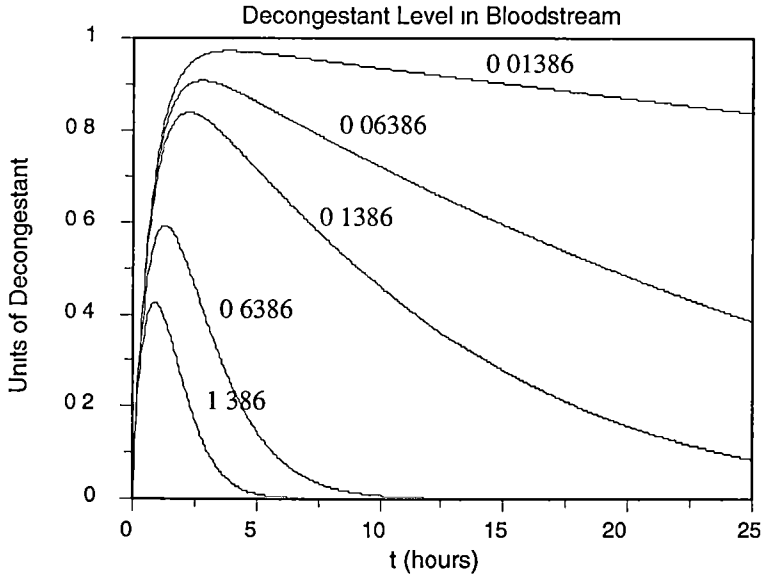

Figure 6.17. Sensitivity to clearance coefficient in Type I Saturation Model Compare to Figure 3 3

the clearance coefficient which is analogous to the situation in Figure 3 3 in which we accounted for the health and age of the one to whom the medication is administered. In the non-saturation model we found that as k_2 increased the sooner the decongestant peaked and began to clear the blood When k_2 = 1 386 hours $^{-1}$, the decongestant level in the blood peaked at 0.72 hours at 0 37 units. When k_2 = 0 01386 hours $^{-1}$, the maximum concentration was 0 95 units at 3 36 hours. However, in the Type I Saturation Model, when k_2 = 1 386 hours $^{-1}$, the peak occurs at (0.86 hours, 0 42 units) and when k_2 = 0 01386 hours $^{-1}$ at (3 84 hours, 0 97 units)

[Type II Saturation]

Let's turn our discussion to an alternative way of incorporating a saturation effect, $\frac{y^{3/2}}{1+cy}$ We shall investigate the cold pill model with periodic dosing, continuous dosing and just one dose noting any differences from the non-saturation model and Type I model.

Figure 6 18 is a periodic dosing case for this Type II model The medication level appears to reach a maximum value of about 11 44 units. In the non-saturation model, the level of decongestant in the bloodstream reaches about 17 15 units (Figure 4 5) The decongestant level in the Type I model has yet to reach equilibrium and is still on the rise (Figure 6 3).

$k_1 = 1\ 386,\ k_2 = 0\ 06386$

$c = 0\ 1$

$x' = 12\text{SqWave}(t, 6\ 0, 0\ 5) - k_1 x, \qquad x(0) = 0$

$y' = k_1 x - k_2((y\text{^}1.5)/(1 + cy)), \qquad y(0) = 0$

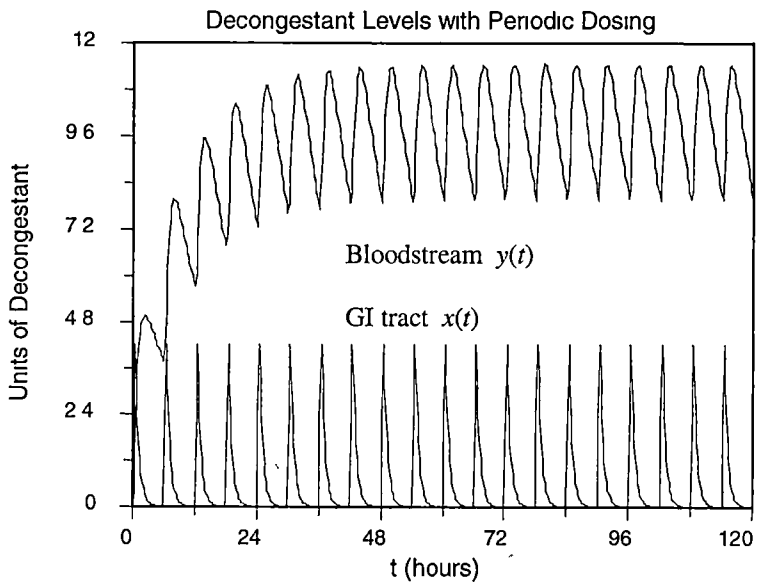

Figure 6.18. Decongestant levels in an older and less healthy individual in the Type II Saturation Model with periodic dosing over a 5 day period Compare to Figure 6 3

The equilibrium levels can be determined in the continuous dosing case Since at equilibrium there is no change in $x(t)$ or $y(t)$, $\frac{dx}{dt} = 0$ and $\frac{dy}{dt} = 0$. The equilibrium value for the antihistamine or decongestant in the GI tract remains the same, but the equilibrium for $y(t)$ is different in the Type II model. From (6), page 55, the level in the GI tract reaches $\frac{I}{k_1}$ units Equation (7) requires that we solve for a root in a nonlinear equation

(6) $$\lim_{t\to\infty} x(t) \Rightarrow \frac{dx}{dt} = 0 = I - k_1 x \Rightarrow x^*(t) = \frac{I}{k_1}$$

and

(7) $$\lim_{t\to\infty} y(t) \Rightarrow \frac{dy}{dt} = 0 = I - k_2 \frac{y^{3/2}}{1+cy} \Rightarrow k_2 y^{3/2} - cIy - I = 0.$$

The example in Figure 6 19 shows that at $t = 200$ hours, $y = 31$ 93 units. However, the

$k_1 = 0\ 6931,\ k_2 = 0\ 0231$
$I = 1.0$
$c = 0\ 1$

$x' = I - k_1 x,$ $\quad x(0) = 0$
$y' = k_1 x - k_2((y\text{^}1\ 5)/(1 + cy)),$ $\quad y(0) = 0$

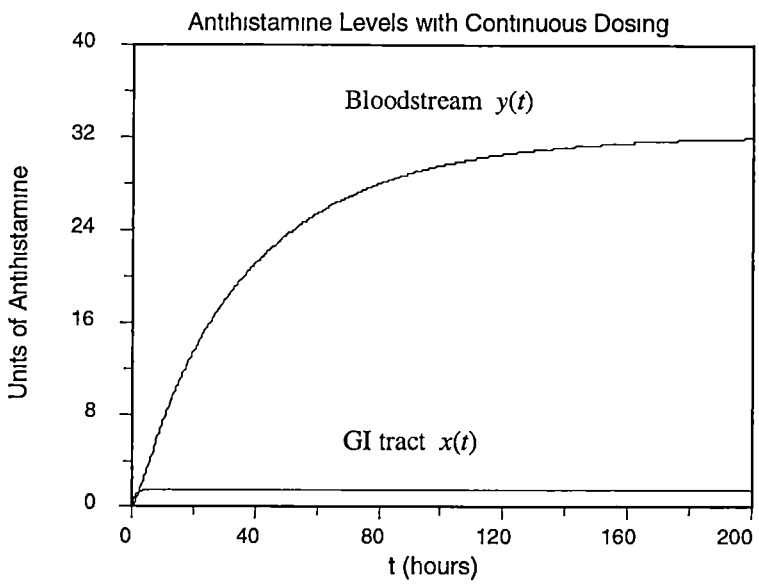

Figure 6.19. Antihistamine levels in a young and healthy individual in the Type II Saturation Model with continuous dosing over a 200 hour interval The equilibrium value in the blood is 32 19 units, but at $t = 200$ hours, $y = 31$ 93 units Compare to Figure 6 12

$k_1 = 1.386$; k_2 = as shown

c = 1 0

$x' = - k_1 x,$ $x(0) = 1$

$y' = k_1 x - k_2((y\text{^}1\ 5)/(1 + cy)),$ $y(0) = 0$

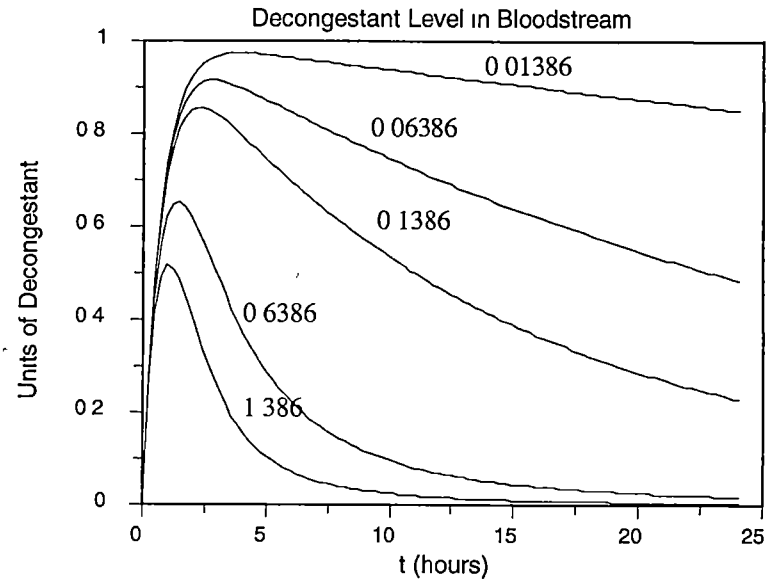

Figure 6.20. Sensitivity to clearance coefficient in Type II Saturation Model Compare to Figure 6 17

equilibrium value found from solving $0\ 0231y^{3/2} - 0\ 1y - 1\ 0 = 0$, gives 32 19 units as the equilibrium value. Contrast this to 43 29 units in the non-saturation model (Figure 5 2) and the Type I model (Figure 6.12) in which the antihistamine level is unbounded Compare to 6 17.

Figure 6 20 shows the sensitivity to the clearance coefficient in the Type II Saturation Model When $k_2 = 1\ 386$ hours^{-1}, the maximum level of decongestant is about 0 52 units at $t = 0\ 96$ hours When $k_2 = 0\ 01386$ hours^{-1}, the decongestant level in the

blood reaches its max of 0 97 units at $t = 3\ 84$ hours. Contrasting these results with the non-saturation and the Type I models, the Type II model has a later peak time and larger peak concentration

CHAPTER VII: STABILITY OF PERIODIC MODELS

[Existence of Periodic Solution of Non-Saturation Model]

Recall that in Chapter IV, we desired a closed-form solution for

$$(1) \qquad \begin{cases} \dfrac{dx}{dt} = I(t) - k_1 x, \ I(t) \text{ periodic} \\ \dfrac{dy}{dt} = k_1 x - k_2 y \end{cases},$$

i e., we want to show that there is a unique $x_p(t)$, $y_p(t)$, periodic, such that

$\begin{bmatrix} x(t) \\ y(t) \end{bmatrix} - \begin{bmatrix} x_p(t) \\ y_p(t) \end{bmatrix} \to 0 \ as \ t \to \infty$ The following two theorems from [1] establish that a periodic solution does indeed exist (Theorem 1) and that that solution is stable (Theorem 2)

Theorem 1 [*Periodic Forced Oscillations*]. Suppose that A is a constant matrix in the system $\boldsymbol{x}' = A\boldsymbol{x} + \boldsymbol{F}(t)$, and that the driving term $\boldsymbol{F}(t)$ is continuous (or piecewise continuous) and periodic with period T If $\dfrac{2\pi i}{T}$ is not an eigenvalue of A, then the system has a unique periodic forced oscillation of period T

Proof. All solutions of $\boldsymbol{x}' = A\boldsymbol{x} + \boldsymbol{F}(t)$ can be written

$$\boldsymbol{x}(t) = e^{tA}\left\{\boldsymbol{x}(0) + \int_0^t e^{-sA}\boldsymbol{F}(s)ds\right\}$$

by the variation of constants formula.

$x(t)$ is periodic of period T when and only when $x(T) = x(0)$

$$x(0) = x(T) = e^{TA}\left\{x(0) + \int_0^T e^{-sA}F(s)ds\right\}$$

$$\Leftrightarrow e^{TA}\int_0^T e^{-sA}F(s)ds = \left[\mathrm{I} - e^{TA}\right]x(0)$$

which is uniquely solvable since $\mathrm{I} - e^{TA}$ is nonsingular as $\frac{2\pi\iota}{T}$ is not an eigenvalue of

A ($\mathrm{I} - e^{TA}$ singular implies $x' = Ax$ has a nontrivial periodic solution which implies $\frac{2\pi\iota}{T}$

is an eigenvalue of A by the structure of the solutions of $x' = Ax$). ■

Theorem 2. [*Periodic Steady State*] Suppose all eigenvalues of the constant matrix A have negative real parts and that $F(t)$ is periodic with period T Then the system $x' = Ax + F(t)$, has a unique steady state, which is periodic of period T

Proof If the eigenvalues of A have negative real parts, then $\frac{2\pi\iota}{T}$ is not an eigenvalue of

A Theorem 1 holds, and $x' = Ax + F(t)$ has a periodic forced oscillation of period T

which we will call $x_p(t)$ Since all solutions of the system have the form

$$x(t) = e^{tA}c + x_p(t)$$

it follows that all solutions tend to $x_p(t)$ as $t \to +\infty$, because $e^{tA}c$ tends to $\mathbf{0}$ as $t \to +\infty$. ■

[1]

We can rewrite the system (1) in matrix form as follows

$$\begin{bmatrix} x' \\ y' \end{bmatrix} = \begin{bmatrix} -k_1 & 0 \\ k_1 & -k_2 \end{bmatrix} \begin{bmatrix} x \\ y \end{bmatrix} + \begin{bmatrix} I(t) \\ 0 \end{bmatrix}.$$

The eigenvalues of A can be found from the characteristic equation

$\lambda^2 + (k_1 + k_2)\lambda + k_1 k_2 = 0$, which has solutions $\lambda_1 = -k_1$ and $\lambda_2 = -k_2$ both with negative real parts The corresponding eigenvectors are $v_1 = \begin{bmatrix} 1 \\ \frac{k_1}{k_2 - k_1} \end{bmatrix}$ and $v_2 = \begin{bmatrix} 0 \\ 1 \end{bmatrix}$ Also note that, the forcing function $F(t) = \begin{bmatrix} I(t) \\ 0 \end{bmatrix}$ is periodic By the above theorems, a unique periodic, steady state solution of period T exists for this system

[Closed-Form Solution of Non-Saturation Model]

This system has as its general solution

$$x(t) = e^{tA}x(0) + e^{tA}\int_0^t e^{-sA}F(s)ds,\ t \in I\,.$$

The matrix exponential is

$$e^{tA} = \begin{bmatrix} e^{-k_1 t} & 0 \\ \frac{k_1}{k_2 - k_1}e^{-k_1 t} & e^{-k_2 t} \end{bmatrix} \begin{bmatrix} 1 & 0 \\ \frac{k_1}{k_2 - k_1} & 1 \end{bmatrix}^{-1}$$
$$= \begin{bmatrix} e^{-k_1 t} & 0 \\ \frac{k_1}{k_2 - k_1}\left(e^{-k_1 t} - e^{-k_2 t}\right) & e^{-k_2 t} \end{bmatrix}$$

Now,

$$x(t)=\begin{bmatrix} x(0)e^{-k_1t} \\ x(0)\dfrac{k_1}{k_2-k_1}\left(e^{-k_1t}-e^{-k_2t}\right)+y(0)e^{-k_2t} \end{bmatrix}$$

$$+\begin{bmatrix} e^{-k_1t} & 0 \\ \dfrac{k_1}{k_2-k_1}\left(e^{-k_1t}-e^{-k_2t}\right) & e^{-k_2t} \end{bmatrix}\int_0^t\left\{\begin{bmatrix} e^{k_1s} & 0 \\ \dfrac{k_1}{k_2-k_1}\left(e^{k_1s}-e^{k_2s}\right) & e^{k_2s} \end{bmatrix}\begin{bmatrix} I(s) \\ 0 \end{bmatrix}\right\}ds$$

$$=\begin{bmatrix} x(0)e^{-k_1t} \\ x(0)\dfrac{k_1}{k_2-k_1}\left(e^{-k_1t}-e^{-k_2t}\right)+y(0)e^{-k_2t} \end{bmatrix}+$$

$$\begin{bmatrix} e^{-k_1t} & 0 \\ \dfrac{k_1}{k_2-k_1}\left(e^{-k_1t}-e^{-k_2t}\right) & e^{-k_2t} \end{bmatrix}\begin{bmatrix} \displaystyle\int_0^t I(s)e^{k_1s}ds \\ \displaystyle\int_0^t I(s)\frac{k_1}{k_2-k_1}\left(e^{k_1s}-e^{k_2s}\right)ds \end{bmatrix}$$

$$=\begin{bmatrix} x(0)e^{-k_1t} \\ x(0)\dfrac{k_1}{k_2-k_1}\left(e^{-k_1t}-e^{-k_2t}\right)+y(0)e^{-k_2t} \end{bmatrix}+$$

$$\begin{bmatrix} e^{-k_1t}\displaystyle\int_0^t I(s)e^{k_1s}ds \\ \dfrac{k_1}{k_2-k_1}\left(e^{-k_1t}-e^{-k_2t}\right)\displaystyle\int_0^t I(s)e^{k_1s}ds+\frac{k_1}{k_2-k_1}e^{-k_2t}\int_0^t I(s)\left(e^{k_1s}-e^{k_2s}\right)ds \end{bmatrix}$$

which finally yields our desired solution,

(2) $$x(t)=\begin{bmatrix} x(0)e^{-k_1t}+e^{-k_1t}\displaystyle\int_0^t I(s)e^{k_1s}ds \\ x(0)\dfrac{k_1}{k_2-k_1}\left(e^{-k_1t}-e^{-k_2t}\right)+y(0)e^{-k_2t}+ \\ \dfrac{k_1}{k_2-k_1}\left[\left(e^{-k_1t}-e^{-k_2t}\right)\displaystyle\int_0^t I(s)e^{k_1s}ds+e^{-k_2t}\int_0^t I(s)\left(e^{k_1s}-e^{k_2s}\right)ds\right] \end{bmatrix}.$$

[Existence of Periodic Solutions of Type I Saturation Model]

In this section we will determine under what conditions there is a unique $x_p(t)$, $y_p(t)$, periodic, such that $\begin{bmatrix} x(t) \\ y(t) \end{bmatrix} - \begin{bmatrix} x_p(t) \\ y_p(t) \end{bmatrix} \to 0$ as $t \to \infty$ for the following system:

$$(3) \qquad \begin{cases} \dfrac{dx}{dt} = I(t) - k_1 x, \ I(t) \text{ periodic} \\ \dfrac{dy}{dt} = k_1 x - k_2 \dfrac{y}{1+cy} \end{cases}$$

We will first tackle the solutions for $x(t)$ and then deal with the solutions to $y(t)$.

Suppose that the patient is given Λ units of medication for half an hour and repeated every six hours, that is, the input dosage is given by $I(t) = \Lambda \text{SqWave}(t, t_p, t_1)$. Our conjecture is that if $|I(t)|$ is sufficiently small (that is, when the dose administered is small enough), there is a unique periodic solution $y(t)$ and if $|I(t)|$ is large enough, $y(t)$ always tends to infinity We will prove the first part of the conjecture but only have the numerical evidence in Chapter VI for the second part Theorem 3 below from [2] will aid in the quest

> **Theorem 3** Let $f: \mathfrak{R} \times \mathfrak{R} \to \mathfrak{R}$, assume that $f(t+T, x) = f(t, x)$ for all $t \in \mathfrak{R}$, $x \in \mathfrak{R}$, and for some $T > 0$, and assume that $f \in C^1(\mathfrak{R} \times \mathfrak{R})$ If $x' = f(t, x)$ has a solution ϕ bounded on $\mathfrak{R}^+$, then it has a T-periodic solution

The periodic solution $x(t)$ of (2) (first component) is formed by solving

$$(4) \qquad x(T) = x(0) = x(0)e^{-k_1 T} + e^{-k_1 T} \int_0^T I(s) e^{k_1 s} ds$$

for $x(0)$ which gives

$$\left[1-e^{-k_1 T}\right]x(0) = e^{-k_1 T}\int_0^{t_1} \Lambda e^{k_1 s}\,ds$$

$$x(0) = \frac{e^{k_1 t_1}-1}{e^{k_1 T}-1}\left(\frac{\Lambda}{k_1}\right)$$

(Recall that t_1 is the "on-time" for the dosing. The maximum value for $x(t)$ will occur at $t = t_1$). Note that $x(0) < \frac{\Lambda}{k_1}$ since $t_1 < T$. From the first component of (2) it is clear that $x(t)$ decays on $[t_1, T]$, and on $[0, t_1]$ we have

$$x(t) = x(0)e^{-k_1 t} + e^{-k_1 t}\Lambda\frac{\left(e^{k_1 t}-1\right)}{k_1}$$

$$= \frac{\Lambda}{k_1} + e^{-k_1 t}\left[x(0) - \frac{\Lambda}{k_1}\right]$$

so that $x(t) < \frac{\Lambda}{k_1}$ on $[0, t_1]$ Thus, $k_1 x(t) < \Lambda$ on [0, T].

Applying Theorem 3 to the differential equation for $y(t)$ (assuming $y(0) \geq 0$), finding the conditions under which its solution is bounded would show the existence of a periodic solution for the system The solution for $x(t)$ remains the same as that of the linear case in (2). Recall that $I(t)$ takes on only two values, 0 or Λ which is some positive real number. Therefore, we conclude that $x(t)$ is positive for all t since both terms in (2) are positive When $x(t)$ is at its maximum value $x^* = x(t_1)$ we have $k_1 x^* < \Lambda$ from above. At $x = x^*$, $\frac{dy}{dt} < \Lambda - k_2\frac{y}{1+cy}$. When $y = 0$, $\frac{dy}{dx} = k_1 x > 0$ So, the solution is increasing at $y = 0$. Thus, y is bounded below by zero Suppose that y is bounded above such that $y(t) \leq M$, $M > 0$, some maximum value. (It is likely that the doctor or pharmacist would know the maximum allowable level of medication) We would like for the solution to be

bounded so that we would have $0 \le y(t) \le M$ This would happen when $\frac{dy}{dt} < 0$ for $y = M$ implying that $\Lambda < k_2 \frac{M}{1+cM}$. Notice that for large M, $\Lambda < \frac{k_2}{c}$ This is our condition to ensure that $y(t)$ is bounded Thus it follows from Theorem 3 that (3) under this condition does have a periodic solution of period T.

[Stability of Periodic Solutions of Type I Saturation Model]

Let $p(t)$ be a periodic solution of the second equation of (3) with $x(t)$ periodic in the first equation Let $y(t)$ be any solution with $y(t) > 0$. Set $z(t) = y(t) - p(t)$ Then

$$\begin{aligned} z'(t) &= y'(t) - p'(t) \\ &= k_1 x(t) - k_2 \frac{y(t)}{1+cy(t)} - k_1 x(t) + k_2 \frac{p(t)}{1+cp(t)} \\ &= \frac{-k_2}{[1+cy(t)][1+cp(t)]}\left[y(t)[1+cp(t)] - p(t)[1+cy(t)]\right] \\ &= \frac{-k_2 z(t)}{[1+cy(t)][1+cp(t)]} \end{aligned}$$

Let $Q = \frac{-k_2}{[1+cy(t)][1+cp(t)]}$ Since $0 \le y(t), p(t) \le M$, it follows that

$-k_2 \le Q \le \frac{-k_2}{(1+cM)^2}$ Let $k = \frac{k_2}{(1+cM)^2}$. If $y(0) > p(0)$, then $y(t) > p(t)$ for all $t \ge 0$ by uniqueness of initial value problems Then $z' \le -kz$ with $z(t) > 0$ which implies $z(t) \le z(0)e^{-kt}$. Thus $y(t) - p(t) \to 0$ as $t \to \infty$. If $y(0) < p(0)$, then $z(t) < 0$ for all t and $z' \ge -kz$ which implies $-z(t) \le -z(0)e^{-kt}$ and again $y(t) - p(t) \to 0$ as $t \to \infty$

[Existence of Periodic Solutions of Type II Saturation Model]

As with the Type I Saturation Model, we want to determine under what conditions there is a unique $x_p(t)$, $y_p(t)$, periodic, such that $\begin{bmatrix} x(t) \\ y(t) \end{bmatrix} - \begin{bmatrix} x_p(t) \\ y_p(t) \end{bmatrix} \to 0$ as $t \to \infty$ for the following system:

$$(5) \qquad \begin{cases} \dfrac{dx}{dt} = I(t) - k_1 x, \ I(t) \text{ periodic} \\ \dfrac{dy}{dt} = k_1 x - k_2 \dfrac{y^{3/2}}{1+cy} \end{cases}$$

Our conjecture is that this system always has a periodic solution

The discussion for the periodic solution of $x(t)$ is analogous to that of the Type I model Therefore the remainder of this section will focus on the conditions that will guarantee existence of a periodic solution of $y(t)$

Suppose $x(t)$ is at its maximum value $x^* = x(t_1)$ which implies that $x^* < \dfrac{\Lambda}{k_1}$ At $x = x^*$, $\dfrac{dy}{dt} < \Lambda - k_2 \dfrac{y^{3/2}}{1+cy}$ When $y = 0$, $\dfrac{dy}{dx} = k_1 x > 0$ So, the solution is increasing at $y = 0$

Thus, y is bounded below by zero Suppose that y is bounded above such that $y(t) \leq M$, $M > 0$, some maximum value We would like for the solution to be bounded so that we would have $0 \leq y(t) \leq M$ This would happen when $\dfrac{dy}{dt} < 0$ for $y = M$ implying that $\Lambda < k_2 \dfrac{M^{3/2}}{1+cM}$ Notice that for large M, $\Lambda < \infty$. This is our condition to ensure that

$y(t)$ is bounded. Since both $x(t)$ and $y(t)$ are bounded under the condition $\Lambda < k_2 \frac{M^{3/2}}{1+cM}$, by Theorem 3, (5) does have a periodic solution of period T for all Λ

[Stability of Type II Saturation Model]

Let $p(t)$ be a periodic solution Let $y(t)$ be any solution with $y(t) > 0$ Set $z(t) = y(t) - p(t)$ Further, set $h(w) = \frac{w^{3/2}}{1+cw}$, then

$$\begin{aligned} z'(t) &= y'(t) - p'(t) \\ &= k_1 x(t) - k_2 h(y) - k_1 x(t) + k_2 h(p) \\ &= -k_2 [h(y) - h(p)]. \end{aligned}$$

If $y(0) > p(0)$, then $y(t) > p(t)$ for all $t \geq 0$ by uniqueness of initial value problems By the Mean Value Theorem, there is an $\alpha = \alpha(t)$ such that $p(t) \leq \alpha \leq y(t)$ for all $t \geq 0$ and $h'(\alpha)(y - p) = h(y) - h(p)$ Let $p(t)$ be bounded by below by α^* and $y(t)$ be bounded above by β^* so that $\alpha^* \leq \alpha(t) \leq \beta^*$ for all $t \geq 0$. Since $h \in C^1$, then there is a $\gamma = \min\{h'(\alpha(t))\}$ for $\alpha^* \leq \alpha(t) \leq \beta^*$ It follows that

$$\begin{aligned} z'(t) &\leq -k_2 \gamma (y - p) \\ &= -k_2 \gamma z. \end{aligned}$$

Let $k = k_2\gamma$, then $z' \leq -kz$ with $z(t) > 0$ implies that $z(t) \leq z(0)e^{-kt}$ Thus $y(t) - p(t) \to 0$ as $t \to \infty$. Likewise, if $y(0) < p(0)$, then $z(t) < 0$ for all t and $z' \geq -kz$ which implies that $-z(t) \leq -z(0)e^{-kt}$ and again $y(t) - p(t) \to 0$ as $t \to \infty$.

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REFERENCES

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VITA

Brenda Bleavins was born in New Orleans, Louisiana, on May 11, 1973, but she and her family soon moved to Norfolk, Virginia. It was there that she received her elementary education in the public school system. After the death of her mother, she and her family relocated to Chattanooga, Tennessee, where her father's family resides. There she continued in the public school system graduating as valedictorian of Red Bank High School in May 1991. She entered Carson-Newman College in August of 1991 where in May 1995, she received the Bachelor of Arts in both mathematics and physics. In the fall of 1995 she had the opportunity to participate in the Science and Engineering Research Semester (SERS) at Oak Ridge National Lab with the Department of Energy. Her project was to write a code in *IDL* to identify and determine the concentrations of gases in the atmosphere given data from a satellite. The next two years of her life were spent in Florianópolis, Santa Catarina, Brazil, where she home-schooled the children of missionaries, volunteered at the Friendship House, and gave informal English lessons to Brazilian adolescents. After returning to the states, she pursued the Master's of Science in Mathematics with a concentration in Applied Mathematics at the University of Tennessee, Knoxville. The degree was received in August 2000.

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