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BIO-MATHEMATICS: INTRODUCTION TO THE MATHEMATICAL MODEL OF THE HEPATITIS C VIRUS

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Bio-Mathematics: Introduction to the Mathematical Model of the Hepatitis C Virus

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A Thesis

Presented to the

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Master of Arts

in

Mathematics

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by

Lucille Jennifer Durfee

December 2016

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Abstract

In this thesis, we will study bio-mathematics. We will introduce differential equations, biological applications, and simulations with emphasis in molecular events. One of the first courses of action is to introduce and construct a mathematical model of our biological element. The biological element of study is the Hepatitis C virus. The idea in creating a mathematical model is to approach the biological element in small steps. We will first introduce a block (schematic) diagram of the element, create differential equations that define the diagram, convert the dimensional equations to non-dimensional equations, reduce the number of parameters, identify the important parameters, and analyze the results. These results will tell us which variables must be adjusted to prevent the Hepatitis C virus from becoming chronic.

Acknowledgements

I would like to acknowledge the personal commitment, invaluable help, and direction of Dr.Giovanna Llosent. Thank you, Dr.Llosent for that commitment, help, and direction. I would also like to thank the other members of my committee for taking the time to read and improve my analysis. Thank you Dr.Aiken and Dr.Chavez. I must also thank Svetlana Borissova for her intelligence and kindness throughout this process. She has given me help in unexpected ways. Lastly, I must recognize the support and sometimes sacrifice of my family and friends: Allison Mackenzie, Alex Chrystal, Fiona Chrystal, Alex Brummel, Angelica Prieto, Damian Palafox, Kevin Bacarra, and Larry Chrystal. Thank you all for the love and support. The pain is almost over...I think!

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Introduction

Mathematical models are useful when there is reason to believe that emergent properties constitute the system. These qualitative features are earmarked when policy changes must be reached. The decision to change policy may involve both qualitative and quantitative analysis that are used to predict behavior under certain conditions or decide which parameters enhance the spread of disease, and hence, which public actions should be taken to counter the effect of that disease. These qualitative features may also be used to calculate the number of vaccines required to eradicate the disease or, at least, get it under control. An example of this type of mathematical model is presented in the article by Marco Arieli Herrera-Valdez, Maytee Cruz-Aponte and Carlos Castillo-Chavez entitled, "Multiple Outbreaks for the Same Pandemic: Local Transportation and Social Distancing Explain the Different "Waves" of A-H1N1PDM Cases Observed in Mexico during 2009". As we look closely at the steps to formulate a mathematical model, based on the material from the book, "A Primer on Mathematical Models in Biology" written by Lee A. Segel and Leah Edelstein-Keshet, we may reference this article.

Chapter 1

Background of a Mathematical Model in Biology

1.1 Introduction of a Model

As Segal and Edelstein-Keshet (2013) states, "A model can be described as a caricature of a real system". A good caricature captures the essence of the system and neglects the detail of the system. Establishing this essence from the complexity of the system is the key to forming an informative mathematical model. A descriptive mathematical model is the simplest type, such as experimental observations that can be approximated to a straight line or a sum of exponential functions. A computer simulation is another type of model that increases the level of detail and brings faithfulness to the underlying model. There are three distinct reasons for using simulations. Firstly, simulations help the investigator get an initial "feel" for the behavior of a model before spending valuable time in the details of the analysis. Secondly, simulations help the investigator make accurate quantitative predictions. Thirdly, simulations help the investigator explore advanced versions of models that are not very easy to analytically track. The ability to pick a model type is an important step. A model can be viewed as a lie since details can be neglected and possible important features distorted to give rise to the essential aspects of the model. We must keep in mind that an initially wrong model should not be rejected, and an initially right model should not be accepted. As Picasso says of art, we must think of in a model, "a lie that helps us see the truth".

[SEK13]

1.1.1 Schematic Diagram

In model building, a crucial first step is conception of a verbal model or a schematic diagram. The thoughts describing the underlying mechanism and/or the words used to describe the relationship between parts of a system maintain a focus on the choice of experiments to be used. From this step, formulating a mathematical model is easier. The best process for this step is to amass an accurate depiction of the relevant background. We need to ask ourselves what the essential ingredients in the embodiment of the phenomenon under investigation are. We need to list the "unknowns" or dependent variables and their relationship to one another. The main independent variable in almost all biological investigations is time. The next step is to determine if the phenomenon is regarded as probabilisitic or deterministic. If deterministic, we use differential equations and regard continuous changes as discrete. The hardest step in formulating a mathematical model is to produce a proper set of equations. The most important aid for this step is bookkeeping. The process of bookkeeping keeps track of some quantity while others remain invariant. In biological problems, this process is difficult and often requires more difficult steps to be taken. [SEK13]

1.1.2 Solving Formulated Equations

After equations are formulated, we must solve them. Most often a combination of numeric, geometric, and analytic approaches are utilized for this task. Software programs such as MAPLE, MATLAB, Mathematica, and XPP are used to approximate numerical solutions for a number of representative parameter values. These numerical solutions can be used in preliminary simulations to show that a developed theory can explain appropriate sets of data. Analytical results are often required when trying to determine if the represented parameter sets agree with the desired result or if they are made to agree with the desired result. [SEK13]

1.1.3 Qualitative Results

Quantitative and qualitative results are two types of conclusions found when the model equations are manipulated. The qualitative conclusions are useful in the identification of solutions after a long period of time, called attractors. The attractor solutions are typically a steady state or periodic oscillation over time. These types of solutions often lead to a "rule of thumb" such as the time affiliated with a chemical reaction, $t \approx 1/k$, where k is the rate constant at which a substance A breaks down to substance B. [SEK13]

It is possible to find qualitative conclusions without prior knowledge of the magnitude of present parameters. However, when models start to become complex it is useful to obtain rough magnitude estimates for those various parameters. Such estimates can be researched from prior literature or developed from general intuition. The most desirable way to obtain these estimates is when the values of all parameters can be determined from experiments other than the current experiment in question. Then the current experiment can be used to verify or disprove the validity of our model. Altering a large number of parameters to fit a variety of different experimental results is difficult. This is true because models are, typically, nonlinear and changing one parameter to "fix-up" a deficiency can make the previously obtained results inconclusive. [SEK13]

1.1.4 Robustness and Analysis

Although the development of specific experimental predictions is important, the concepts that the conclusions produce are advantageous in designing new experiments for further analysis. Therefore, the robustness of the model can be even more important than the agreement with the specific experiment. The principal conclusions of the model must be maintained whether details of the model are amended or not.

Once a model is constructed, one must analyze the results and find the key features hidden that yield the major conclusions. These conclusions may not be receptive to experimental tests, but are still valuable in developing concepts. Models should be considered guides to acquiring experimental information. For a complex system, no

single model is appropriate and different questions require different models. [SEK13]

1.2 Biochemical Kinetics

In this next section, we will write the governing differential equations of biochemical kinetics by considering several examples of chemical dynamics and presenting several principles that can be used to simplify these equations. After these principles are applied, we will see the utility of these simplifications and show how simulations can complement the analysis of a mathematical model.

1.2.1 Kinetic Scheme

Before we begin, let us take a look at the meaning of a kinetic scheme. A kinetic scheme is the conventional description of a molecule shifting between two states, A and B, where A and B represent the concentrations (number per unit volume) of two molecular configurations. Shown as

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B \qquad (2.1)$$

where k_1 and k_{-1} are the rate coefficients. The rate constant, k_1, times a small time interval, Δt, is defined as the probability that a molecule in state A shifts to state B and stays in state B. Similarly, if Δt is sufficiently small, then $k_{-1}\Delta t$ is a good approximation to the probability that a molecule initially in state B changes to state A and remains in state A. We observe that our definitions imply that k_1, k_{-1} have units of 1/time and thus, their reciprocals are characteristic time scales. The time step should be smaller than the characteristic time for the transition between states. Then $\Delta t \ll 1/k_1$ and $\Delta t \ll 1/k_{-1}$. We will follow the Markov properties for the shift of a molecule between two configurations. They are:
(M1) Transitions between states are random.
(M2) The probability that a transition occurs during some time interval does not depend on the history of events preceding the time in question.

(M3) If environmental conditions are fixed then the overall characteristics of the transitions that occur in some time interval, do not depend on the time at which the observations are made. [SEK13]

1.2.2 Differential Equations

Now, let us derive differential equations for the change in time of concentrations A and B. If there are A molecules per unit volume, the expected decrease in the number of these molecules during Δt is:
decrease in A molecules = total number of A molecules $\times$ fraction that becomes B
$= A \times (k_1 \Delta t)$

Thus the following equation describes the expected change in the number of A molecules during the time interval $(t, t + \Delta t)$:

$$A(t + \Delta t) - A(t) = -A(t) \cdot k_1 \Delta t + B(t) \cdot (k_{-1}) \Delta t.$$

Dividing by Δt, taking the limit as $\Delta t \to 0$, and using the definition of derivatives leads to:

$$(2.2a) \quad \frac{dA}{dt} = -k_1 A + k_{-1} B \quad \text{and} \quad \frac{dB}{dt} = k_1 A - k_{-1} B. \quad (2.2b)$$

This gives us two differential equations describing the kinetic scheme of A and B. However, before we move forward, we need to complete the mathematical translation by prescribing the initial state of the system at time $t = 0$. Let $A(0) = A_0$ and $B(0) = B_0$, then the differential equations and the initial conditions make up the model. We can simplify this model by using the conservation law, $A(t) + B(t) = M$, noting that M is a constant since the molecules only shift between conformations and do not degrade over such a short period of time. Thus, $M = A_0 + B_0$, the total number of molecules at $t = 0$. Using this conservation law at time t we can solve for $B(t)$ and substitute into (2.2a). In doing so, we get

$$\frac{dA}{dt} = -k_1 A + k_1 (M - A),$$

which leads to

$$\frac{dA}{dt} = -(k_1 + k_{-1})A + k_{-1}M.$$

Now, solving for A requires a review of first order differential equations. Consider a more general version of $\frac{dA}{dt} = -k_1 A$, such as

$$\frac{dx}{dt} = k(t)x,$$

with initial condition $x(0) = x_0$. This equation is called a First-Order Differential Equation, ODE, since the highest derivative in the equation is the first derivative. The general solution is

$$x(t) = Cexp(K(t))t, \qquad \text{where C is a constant and } K(t) = \int_0^t k(s)ds.$$

This solution is derived as follows:

$$\frac{dx}{dt} = k(t)x \Rightarrow \frac{dx}{x} = k(t)dt.$$

Upon integrating over the interval $0 \leq x \leq t$, $x_0 \leq x(s) \leq x(t)$, we obtain:

$$\ln(u)|_{x(0)}^{x(t)} = \ln(x(t)) - \ln(x(0)) = \ln(x) - \ln(x_0) = \ln(\frac{x}{x_0}) = \int_0^t k(s)ds.$$

Exponentiation of both sides yields the solution

$$x(t) = x_0 exp\left[\int_0^t k(s)ds\right].$$

In the case that $k(t)$ is constant, say $k(t) = r$, we evaluate the integral and obtain

$$x(t) = x_0 exp\left[\int_0^t r\right] = x_0 exp(rt).$$

Therefore, it can be shown that all solutions of $\frac{dx}{dt} = k(t)x$ are special cases of $x(t) = x_0 expK(t)t$ for certain values of x_0. Thus, the solution for $\frac{dA}{dt} = -(k_1 + k_{-1})A + k_{-1}M$ with initial condition A_0 is

$$A(t) = Cexp\Big[-(k_1 + k_{-1})t\Big] + \frac{k_{-1}M}{k_1 + k_{-1}}.$$

In the above, $C = A_0 - A_\infty$ and $A_\infty = \frac{k_{-1}M}{k_1+k_{-1}}$.

Substituting, we have

$$A(t) = A_\infty - (A_\infty - A_0)e^{-(k_1+k_{-1})t}.$$

Similarly,

$$B(t) = M - A(t) = (M - A_\infty) + (A_\infty - A_0)e^{-(k_1+k_{-1})t}.$$

Notice as $t \to \infty, A(t)$ approaches $\frac{k_{-1}M}{(k_1+k_{-1})}$ and $B(t)$ approaches $\frac{k_1M}{(k_1+k_{-1})}$.

At steady state,

$$\frac{dA}{dt} = -k_1A + k_{-1}B = 0 \quad \text{and} \quad \frac{dB}{dt} = k_1A - k_{-1}B = 0,$$

which occurs when the concentrations of A and B are constant. Here the rate of conversion of A to B should exactly balance the rate of conversion of B to A. Thus, $k_1A = k_{-1}B$. The time it takes for A and B to reach their steady states is the time scale $(k_1 + k_{-1})^{-1}$. [SEK13]

1.2.3 Deterministic versus Stochastic Approaches to Solving Problems

Now, we will consider deterministic versus stochastic approaches to solving problems related to biochemical kinetics. A basic assumption of our model is a probabilistic transition between the two states. Using Newton's laws one can derive a deterministic problem, in which, its solution describes the gross motion of molecules. Models of this kind have already been developed and form a basis for numerical simulations that give information about large molecule dynamics. [SEK13]

Our equation (2.1) describing the expected change in the number of A molecules

during time interval $(t + \Delta t)$ is:

$$A(t + \Delta t) - A(t) = -A(t) \cdot (k_1 \Delta t) + B(t) \cdot (k_{-1} \Delta t), \qquad (2.3)$$

which describes probabilistic assumptions for the change in the expected or average number of A molecules. Monte Carlo simulations can be used to depict the stochastic shift between A and B states. Suppose that at time, t, a molecule is in state A. We know that there is a probability, $k_1 \Delta t$, that during the time interval $(t, t + \Delta t)$ it will shift to the B state. If we select a random number between 0 and 1 and that number is between 0 and $k_1 \Delta t$ then the simulation shifts the configuration to B; otherwise the configuration remains A. Repeating this calculation, one can develop a simulated history of the states, A and B, of a single molecule during some time interval. This history can be used to compare simulated data with experiments. There are, also, analytical methods that will allow conclusions to be drawn if one retains the stochastic character of (2.1). [SEK13]

We have considered a type of phenomena where an average number of molecules shift from one state to another. Let's consider a phenomena where we consider a shift in a single channel molecule from an open state to a closed state. These channel molecules are responsible for the electrical conductance through cell membranes. Model (2.3) remains relevant for such situations if A and B are interpreted as the probability that a single channel is, respectively, open and closed. Single channel recordings yield information not only on mean values of $A(t)$ and $B(t)$, but also on standard deviations and other statistical measures. The following graph, Figure 1.1, shows observation of a single channel shifting from its open to closed states. [SEK13]

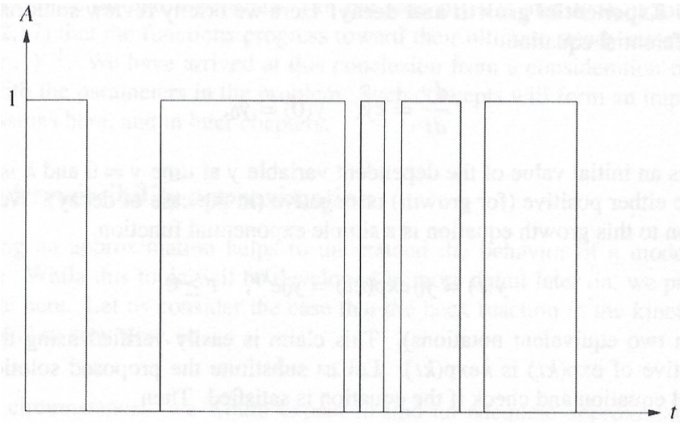

Figure 1.1: Channel Shifting from Open to Closed States. [SEK13]

The derivative of $A(t)$ in this case is either zero or infinite. This characterization of the derivative remains true no matter how many channels are observed. However, if many channels are monitored the jumps between states become less noticeable, as shown in the following graph, Figure 1.2, then a true jumpy curve can be well approximated by a smooth curve. This smooth curve will have a well-behaved derivative, and it is this curve that we seek when we solve for $A(t)$ in our differential equation formulation of kinetics. [SEK13]

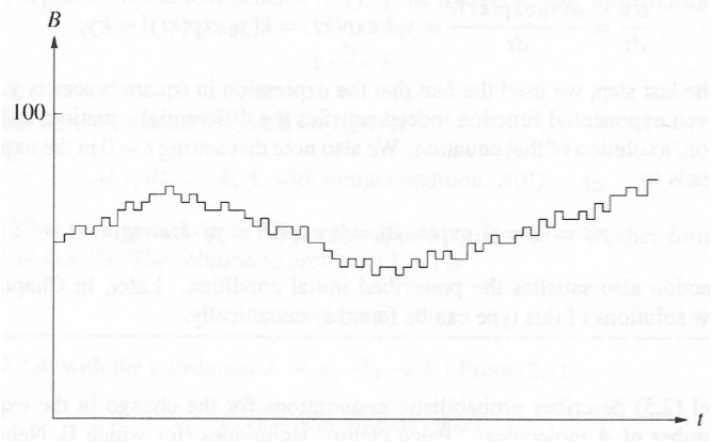

Figure 1.2: Channel Shifting Approximated by a Smooth Curve. [SEK13]

Now, let's consider reactions where two molecules have to collide in order to form some product. These reactions are based on the Law of Mass Action which states: *In a reaction involving the interaction of two types of molecules, the rate of reaction is proportional to the concentrations of the two reactants.* [SEK13]

The reaction $A + B \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} P$ is such a reaction where the rate of the forward reaction would be $k_1[A] \cdot [B]$ (square braces denote concentrations). To obtain this law, it is assumed that the molecules are far enough apart to assume they move independently and, thus, their concentrations are low. [SEK13]

Let us look at a "dimerization" reaction in which two A molecules reversibly combine to form a complex C. The kinetic scheme looks like this:

$$A + A \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C \ .$$

The reaction equations are:

$$\frac{dA}{dt} = -2k_1A^2 + 2k_{-1}C \quad \text{and} \quad \frac{dC}{dt} = k_1A^2 - k_{-1}C. \quad (2.4)$$

Initial conditions at $t = 0$, are $A = A_0$ and $C = 0$ where A_0 represents the concentrations of A at $t = 0$. Combining the differential equations in (2.4) we have

$$\frac{dA}{dt} + 2\frac{dC}{dt} = 0 \ \text{ or } \ \frac{d}{dt}(A + 2C).$$

In this case $A + 2C$ is equal to a constant and, thus, equal to A_0. Again, we consider the molecules to be in free form. Therefore, the molecules are either of form A (per unit volume) or form $2C$ (per unit volume). The recording of complex values of C and given parameters k_{-1}, k_1, and A_0 leads to a great number of possible graphs to evaluate. Thus, a reformulation called "non-dimensionalizing" is required to reduce the number of parameters. This will be discussed later. [SEK13]

The following biochemical model is used as a component of many models in molecular and cellular biology. It is central to the study of enzyme-mediated reactions

in biochemistry. The kinetic scheme of this model is:

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C \xrightarrow[k_2]{} E + P. \quad (2.5)$$

Here E is the concentration of an enzyme that catalyzes the transformation of the substrate, S (concentration), of the reaction into the product, P. This is accomplished by means of an intermediate enzyme substrate complex (concentration C) where the enzyme and complex are bound together. Based on the Law of Mass Action and pervious examples, the differential equations for this kinetic scheme are:

$$\frac{dE}{dt} = -k_1 ES + k_{-1} C + k_2 C, \quad (2.6a)$$

$$\frac{dS}{dt} = -k_1 ES + k_{-1} C, \quad (2.6b)$$

$$\frac{dC}{dt} = k_1 ES - k_{-1} C - k_2 C, \quad (2.6c)$$

$$\frac{dP}{dt} = k_2 C. \quad (2.6d)$$

The initial conditions at $t = 0$ are: $E(0) = E_0, S(0) = S_0, C(0) = C_0 = 0, P(0) = P_0 = 0$. There are two conservation statements produced from these differential equations and initial conditions. They are:

$$E(t) + C(t) = E_0 \quad \text{and} \quad S(t) + C(t) + P(t) = S_0.$$

These statements indicate that, in both free and bound forms, the total amount of enzyme, and the total amount of reactant in the substrate, complex, and product forms is constant. Substituting $E = E_0 - C$ into the differential equations gives us two differential equations with two unknowns:

$$\frac{dS}{dt} = -k_1 (E_0 - C) S + k_{-1} C, \quad \text{and}$$

$$\frac{dC}{dt} = k_1 (E_0 - C) S - (k_{-1} + k_2) C.$$

It is often the case that the enzyme-substrate complexes form rapidly, and,

thus, the number of complexes are roughly constant. Therefore, $\frac{dC}{dt} \approx 0$. This assumption is called a quasi-steady state approximation. We can then solve for C in terms of S and E_0 to obtain:

$$C \approx \frac{E_0 S}{k_m + S}, \quad \text{where } k_m = \frac{k_{-1} + k_2}{k_1}.$$

Substituting C and k_m into the differential equation of the product we get:

$$\frac{dP}{dt} = \frac{V_{max} S}{k_m + S} \text{ where } V_{max} = k_2 E_0. \quad (2.7)$$

This equation is defined as the reaction velocity approximating the rate at which substrate is used up and product is formed. It is known as Michaelis-Menten kinetics. [SEK13]

1.2.4 Polymerization Reactions

Now, let us consider polymerization reactions, in which identical subunits (monomers) form polymers that can grow in size. The Law of Mass Action will still apply for these reactions. The first polymerization reaction we will look at involves simple aggregation. When monomers grow anywhere on the polymer it is described as a simple aggregation polymerization reaction. The following Figure 1.3, shows a simple aggregation with k_f the rate of binding and δ the rate of disassembly and turnover of the polymer.

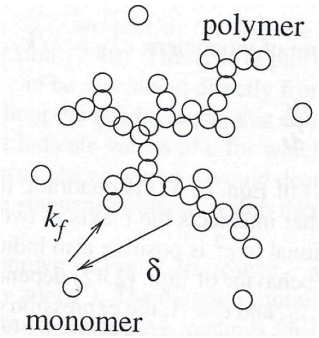

Figure 1.3: Simple Aggregation.[SEK13]

We define the following variables:

$c(t)$ denotes the number of monomer subunits in the volume at time t.
$F(t)$ denotes the amount of polymer (in number of monomer equivalents) at time t.
$A(t)$ denotes the total amount of material (in number of monomer equivalents) at time t.

We assume the rate of growth is a product of c and F, with rate constant $k_f > 0$ and the rate of disassembly or turnover is linearly proportional to the amount of polymer, with rate constant δ. The differential equations are then consistent with the other models we have looked at thus far and are:

$$\frac{dc}{dt} = -k_f cF + \delta F, \quad (2.8a)$$

$$\frac{dF}{dt} = k_f cF - \delta F. \quad (2.8b)$$

Notice the first terms in these equations describe the association of a monomer and a polymer based on mass action. The last terms are the polymer turnover at rate δ. The total amount A is conserved and for physical relevance, we must have $c \leq A$ and

$F \leq A$. Substituting $F = A - c$ into (2.8a) we get:

$$\frac{dc}{dt} = k_f(A - c)(\frac{\delta}{k_f} - c) \quad (2.8c),$$

where $\frac{\delta}{k_f}$ is defined as the critical concentration of monomers, c_{crit}. The right-hand side of this equation forms a quadratic equation and its graph is shown in Figure 1.4 below.

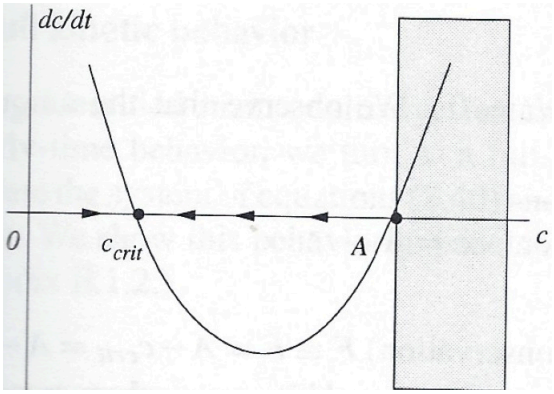

Figure 1.4: Quadratic Equation dC/dt. [SEK13]

The arrows on this plot indicate values of c for which c would increase ($\frac{dC}{dt} > 0$: arrows point to the right) versus places where c would decrease ($\frac{dC}{dt} < 0$: arrows point to the left). We, also, observe stagnate points at which there is no flow. These stagnate points are steady states. The case $A < c_{crit}$ is shown in Figure 1.5 (below).

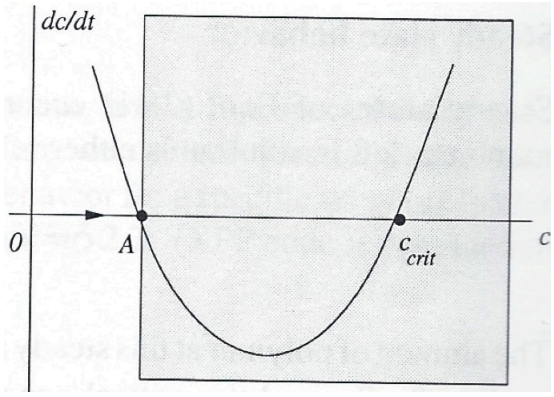

Figure 1.5: Steady State of Equation dc/dt. [SEK13]

Since $c \leq A$, part of the state space is blocked and is represented by the "gray zones". The diagram summarizes the qualitative behavior of the model. Notice, also, that a nontrivial level of polymer occurs only if $A > c_{crit}$ and that steady state occurs when $\frac{dc}{dt} = 0$. Thus, the amount of monomer left in solution is either $c_{crit} = \frac{\delta}{k_f}$ or A. Therefore, the amount of polymer, F, at steady state is equal to zero. [SEK13]

Now, we will look at polymers with growth only at their tips (end of their filaments) as shown in Figure 1.6.

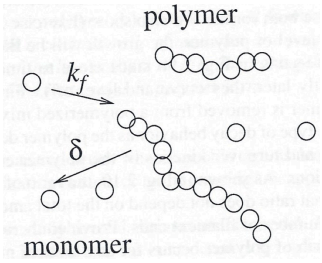

Figure 1.6: Polymer Growth at Their Tips. [SEK13]

In this case, we define n as the number of filament tips at which polymerization can occur. We consider this number to be constant, and that breakage and branching do not occur. Thus, the model is:

$$\frac{dc}{dt} = -k_f cn + \delta F, \quad (2.9a)$$

$$\frac{dF}{dt} = k_f cn - \delta F. \quad (2.9b)$$

Here, monomer addition occurs at a rate proportional to n. As before, conservation holds and replacing F with $(A - c)$ into (2.9a) leads to:

$$\frac{dc}{dt} = \delta A - c(k_f n + \delta).$$

In this case, there is only one steady state with monomer level

$$c = \frac{\delta A}{k_f n + \delta} \equiv \beta A \text{ where } \beta = \frac{\delta}{k_f n + \delta}.$$

In addition, the factor β satisfies $\beta < 1$ since $n, k_f > 0$. That means that this steady state exists in all cases, unlike the previous situation where up to two steady states were possible. Since the number of tips, n, is constant, the steady state levels of monomer and polymer are proportional to each other, so that adding monomer to the solution will increase both forms. We also see that the growth of the polymer is linear. Thus $\frac{dF}{dt} \equiv$ constant. Figure 1.7 distinguishes the differences of (a) the case of a simple aggregation for monomer concentration $C_{crit} \leq A$, where no polymerization occurs and (b) the case of growth only at filament tips. [SEK13]

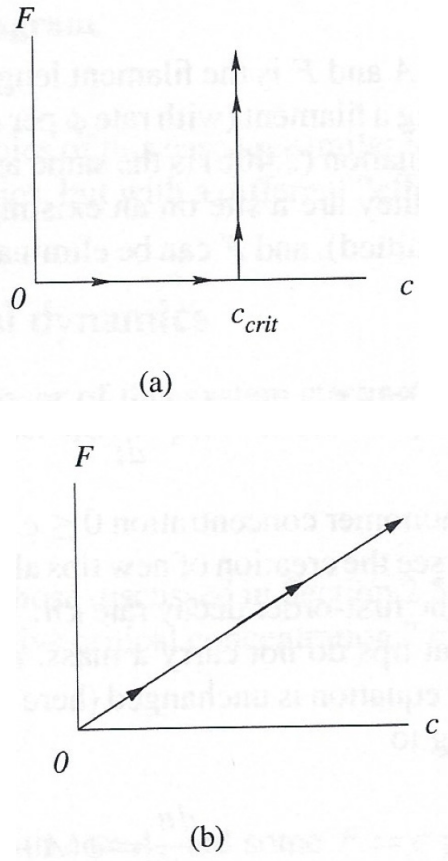

Figure 1.7: Differences of Polymerization Growth. [SEK13]

All the modeling techniques discussed above have illustrated ways of describing rates of simple chemical reactions. These modeling techniques provide a means for reaching reasonable approximations and for providing estimates for behavior under various situations. At this point, we can see and appreciate the usefulness of mathematical modeling in a biological environment. [SEK13]

1.3 Non-Dimensionalization and Scaling

Now, we will look at non-dimensionalization and scaling. We can check the consistency of model equations by reformulating a model in terms of dimensionless quantities. This reformulation will ensure that all terms have the same set of units in an algebraic or differential equation. Non-dimensionalizing a model reduces the number of free parameters and reveals a smaller set of qualities that govern the dynamics. Determining larger or smaller magnitudes helps approximate solutions when using asymptotic analysis techniques. We will show that dimensionless variables can be selected in a variety of ways using the concept of scaling. We will use several of the kinetics problems previously discussed to show this procedure. [SEK13]

1.3.1 Kinetic Scheme

Let us consider the kinetic scheme $A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B$ and the derived equation

$$\frac{dA}{dt} = -(k_1 + k_{-1})A + k_{-1}M, \quad A(0) = A_0 \text{ and } M = A_0 + B_0. \quad (2.10)$$

Remembering rate constants k_1 and k_{-1} have dimensions of 1/time, both $\frac{dA}{dt}$ and $(k_1 + k_{-1})A$ must have the same dimensions, concentration/time. For definiteness, let us define a dimensionless time, t^*, by

$$t^* = \frac{t}{1/k_{-1}}, \text{ i.e. } t^* = k_{-1}t. \quad (2.11)$$

Note: *'s will denote variables carrying no dimensions. The natural way to non-

dimensionalize A is via its initial concentration. Thus, we define a dimensionalized concentration

$$a^* \equiv \frac{A}{A_0}. \qquad (2.12)$$

Using the chain rule and adopting (2.11) and (2.12) we obtain

$$\frac{dA}{dt} = \frac{d(A_0 a^*)}{dt} = A_0 \frac{da^*}{dt} = A_0 \frac{da^*}{dt^*} \cdot \frac{dt^*}{dt} = A_0 \frac{da^*}{dt^*} k_{-1}. \quad (2.13a)$$

or by direct substitution

$$\frac{dA}{dt} = \frac{d(A_0 a^*)}{d(t^*/k_{-1})} = k_{-1} A_0 \frac{da^*}{dt^*}. \quad (2.13b)$$

Therefore,

$$k_{-1} A_0 \frac{da^*}{dt^*} = -((k_1 + k_{-1})A_0)a^* + k_{-1}M.$$

Now dividing both sides of the equation by $A_0 k_{-1}$ we arrive at

$$\frac{da^*}{dt^*} = -[(k_1 + k_{-1})(\frac{A_0}{A_0 k_{-1}})]a^* + \frac{k_{-1}M}{A_0 k_{-1}},$$

which simplifies to

$$\frac{da^*}{dt^*} = -[\frac{(k_1 + k_{-1})}{k_{-1}}]a^* + \frac{M}{A_0} = -[\frac{k_1}{k_{-1}} + 1]a^* + \frac{M}{A_0}.$$

We can define two dimensionless parameters,

$$\varepsilon \equiv \frac{k_{-1}}{k_1}, \quad \theta \equiv \frac{M}{A_0} = \frac{A_0 + B_0}{A_0}.$$

Then the resulting dimensionless equation is

$$\frac{da^*}{dt^*} = -\frac{1}{\varepsilon}a^* + \theta - a^*. \qquad (2.14)$$

Furthermore, the initial condition $A(0) = A_0$ leads to $a^*(0) = A(0)/A_0 = 1$.

Thus dropping the *'s, the new version of the model is

$$\frac{da}{dt} = -\frac{1}{\varepsilon}a + \theta - a, \quad a(0) = 1.$$

where ε and θ are dimensionless parameters. Clearly, non-dimensionalizing and scaling the original problem decreased the four dimensional parameter model to a two non-dimensional parameter model. [SEK13]

1.3.2 Dimerization Model

Now, recall the dimerization model,

$$\frac{dA}{dt} = -2k_1A^2 + 2k_{-1}C, \quad (2.15a)$$

$$\frac{dC}{dt} = k_1A^2 - k_{-1}C. \quad (2.15b)$$

at $t = 0, A = A_0$, and $C = 0$ with kinetic scheme $A + A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C$.

Similar to the previous example, we define the dimensionless time and concentration variables as follows:

$$t^* = \frac{t}{1/k_{-1}} = k_{-1}t \qquad a^* = \frac{A}{A_0}, \qquad c^* = \frac{C}{A_0}.$$

Therefore,

$$t = \frac{t^*}{k_{-1}}, \qquad A = A_0a^*, \qquad C = A_0c^*, \quad (2.16)$$

and the initial conditions can be written as $t^* = 0$, $a^* = 1$, and $c^* = 0$.

Substituting (2.16) into (2.15a) and simplifying, we get

$$\frac{dA}{dt} = \frac{d(A_0a^*)}{d(t^*/k_{-1})} = -2k_1(A_0a^*)^2 + 2k_{-1}(A_0c^*).$$

This leads to

$$k_{-1}A_0\frac{da^*}{dt^*} = -2k_1A_0^2(a^*)^2 + 2k_{-1}A_0c^*.$$

Then simplifying, we get

$$\frac{da^*}{dt^*} = -2\theta(a^*)^2 + 2c^* \quad \text{with} \quad \theta \equiv \frac{k_1A_0}{k_{-1}}.$$

Similarly, substitution of (2.16) into (2.15b) yields

$$\frac{dc^*}{dt^*} = \theta(a^*)^2 - c^*.$$

Dropping the *'s, the new dimerization model becomes

$$\frac{da}{dt} = -2\theta a^2 + 2c, \qquad a(0) = 1 \qquad (2.17a)$$

$$\frac{dc}{dt} = \theta a^2 - c, \qquad c(0) = 0. \qquad (2.17b)$$

Note $\theta = \frac{k_1A_0}{k_{-1}}$ is dimensionless since the concentrations, denoted [ ], of A_0, k_1, and k_{-1} are $[A_0] = L^{-3}, [k_{-1}] = T^{-1}$, and $[k_1] = L^3T^{-1}$. The dimensions of $[k_1]$ are L^3T^{-1} because the dimensions of k_1A^2 and $k_{-1}C$ in equation (2.15) must be the same. Therefore, $[k_1] = L^3T^{-1}$ and θ is dimensionless.[SEK13]

We observe from the new model that the dimensionless complex concentration c depends only on the single dimensionless parameter θ. Therefore, the variable combination C/A_0 is not a general function of the parameters k_{-1}, k_1, A_0 and time t but rather a function only of the combinations $(k_1A_0)/k_{-1}$ and $k_{-1}t$. Thus, all the data concerning dimerization can, in principle, be presented on a single graph of $c \equiv C/A_0$ as a function of $t^* \equiv k_{-1}t$ for a number of different values of $\theta \equiv (k_1A_0)/k_{-1}$. See Figure 1.8 below. [SEK13]

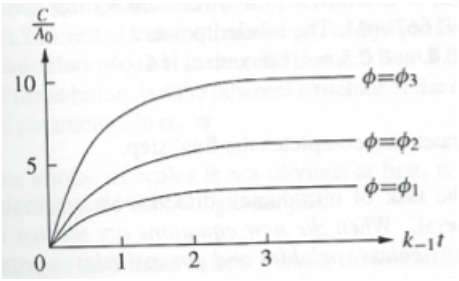

Figure 1.8: Dimerization Data ($C \equiv C/A_o$). [SEK13]

1.3.3 Polymerization by Monomer Aggregation

Lastly, let us create a dimensionless model for polymerization by monomer aggregation. Recall equation (2.8c) in the form

$$\frac{dc}{dt} = (-k_f c + \delta)F = (-k_f c + \delta)(A - c). \qquad (2.18)$$

Rescale time by $(1/\delta)$ and rescale concentration by the total amount A (both of which are constant). This means substitute $t = t^*/\delta$ and $c = c^*A$ into equation (2.18), then using substitution as before,

$$\frac{d(c^*A)}{dt^*/\delta} = A\delta\frac{dc^*}{dt^*} = (-k_f c^* A + \delta)(A - c^* A).$$

Simplifying and multiplying both sides by the constant $(1/A\delta)$ leads to

$$\frac{dc^*}{dt^*} = \frac{1}{A\delta}(-k_f c^* A + \delta)(A - c^* A) = (-\frac{k_f A}{\delta}c^* + 1)(1 - c^*).$$

Dropping the *'s we arrive at

$$\frac{dc}{dt} = (1 - \alpha c)(1 - c) \quad \text{where} \quad \alpha = \frac{A}{(\delta/k_f)},$$

which is the ratio of total amount A to critical concentration $c_{crit} = \delta/k_f$ and dimensionless. Thus, the inherent structure of the model depends only on the grouping of parameters in α. [SEK13]

The new equations developed in these examples are written in their simplest form, containing only dimensionless variables and parameters, and were obtained without solving any equations. The number of dimensionless parameters is generally smaller than the original number of parameters which makes theoretical manipulations easier. Thus, conclusions developed from the reduction in parameters can be of great importance for experimental or numerical work. This minimizes the amount of experimentation that is necessary to describe the possible variation of the results for different parameters values. [SEK13]

1.4 Geometric and Qualitative Methods to First-order Differential Equations

Now, we will apply qualitative and geometric methods to first-order differential equations, where the goal is to construct sketches of the solutions that do not require as much technical work. We will introduce the role of parameter sensitivity and illustrate some transitions, called bifurcations, that take place as a parameter is varied.

1.4.1 Stability of Steady States

To begin, let us first understand the stability of steady states of a first-order differential equation. Consider the general differential equation

$$\frac{dx}{dt} = f(x), \qquad (2.19)$$

with a steady state value $x = x_{ss}$. It follows that

$$\frac{dx_{ss}}{dt} = 0, \quad f(x_{ss}) = 0. \qquad (2.20)$$

Let $x(t) = x_{ss} + x_p$, where $x_p = x_p(t)$ is a small-time dependent quantity, called a perturbation, of the steady state. When $x_p(t)$ decreases with time, we see that $x(t)$ returns to the steady state value and we say that the steady state, x_{ss}, is locally

stable. When $x_p(t)$ increases with time, we see that $x(t)$ moves away from the steady state value and we say the steady state, x_{ss}, is locally unstable. [SEK13]

To see what truly happens, let us substitute $x(t) = x_{ss} + x_p$ into the differential equation (2.19) as follows,

$$\frac{d[x_{ss} + x_p]}{dt} = f(x_{ss} + x_p).$$

When we simplify the LHS using the additive property of derivatives and the RHS by using the Taylor series approximation since x_p is small, we get

$$\frac{d[x_{ss} + x_p]}{dt} = \frac{dx_{ss}}{dt} + \frac{dx_p}{dt} \approx f(x_{ss}) + x_p f^{'}(x_{ss}) + \frac{x_p^2}{2} f^{''}(x_{ss}) + \text{h.o.t.},$$

where h.o.t stands for "higher-order terms". Using the steady state equations of (2.20), we can eliminate some of the terms from each side of the equation to obtain

$$\frac{dx_p}{dt} \approx x_p f^{'}(x_{ss}) + \frac{x_p^2}{2} f^{''}(x_{ss}) + \text{h.o.t.}.$$

In addition, the magnitude of terms that are quadratic or of higher power in small perturbations are very small since, as the powers increase, the magnitude of the quantities decrease. Thus, $x_p^2 \approx 0$ and $x_p^3 \approx 0$. Therefore, we obtain the following linear equation governing the perturbations:

$$\frac{dx_p}{dt} \approx f^{'}(x_{ss}) x_p,$$

where $f^{'}(x_{ss})$ is a constant of negative, positive, or zero value. Denoting $f^{'}(x_{ss})$ by λ, we have

$$\frac{dx_p}{dt} \approx \lambda x_p,$$

which has the general solution

$$x(t) = Cexp(\lambda t).$$

Thus, the linear stability condition is:

$\lambda = f'(x_{ss}) > 0 \Rightarrow$ exponentially growing perturbations, then x_{ss} is unstable.
$\lambda = f'(x_{ss}) < 0 \Rightarrow$ exponentially decaying perturbations, then x_{ss} is stable.
$\lambda = f'(x_{ss}) = 0 \Rightarrow$ no conclusion, since higher-order terms are needed to determine local behavior near the steady state. [SEK13]

For reasons of analogy to higher-order systems of differential equations, the quantity $\lambda = f'(x_{ss})$ is called an eigenvalue of the ODE at the given steady state. It is seen that there is only one eigenvalue, whose value is a real number, at any steady state of a single first-order ODE. In such cases, the eigenvalue can be interpreted as a rate of growth (if positive) or rate of decay (if negative) of small deviations from the steady state. We can restate the stability results verbally by saying that for a single ODE, stability (or instability) of a steady state is equivalent to finding the eigenvalue is negative (positive). A zero eigenvalue is neutral and is usually a sign that some transition in stability is at hand. [SEK13]

Now, let us consider an example where there are three steady states

$$\frac{dx}{dt} = c(x - \frac{1}{3}x^3) \equiv f(x), \quad c > 0 \quad \text{constant.} \qquad (2.21)$$

Solving for the steady states ($\frac{dx}{dt} = f(x) = 0$), we find that there are three such points, one at $x = 0$ and the others at $x = +\sqrt{3}$ and $x = -\sqrt{3}$. These are the intersections of the cubic curve with the x-axis in Figure 1.9a below.

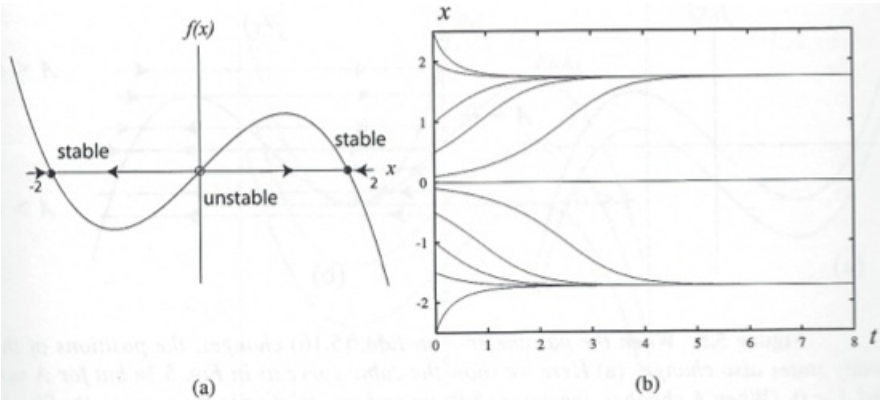

Figure 1.9: (a) Steady-State Points. (b) Steady-State Flow. [SEK13]

We surmise the direction of flow from the sign of f(x), and use that sketch to conclude that $x = 0$ is unstable while both $x = -\sqrt{3}$ and $x = +\sqrt{3}$ are stable. In Figure 1.9b, we show numerically computed solutions to this equation with a variety of initial conditions. We see that all positive initial conditions converge to the steady state at $x = +\sqrt{3} \approx 1.73$, whereas those with negative initial conditions converge to $x = -\sqrt{3} \approx -1.73$. Thus, as seen, the outcome depends on the initial conditions and is an example of bistable kinetics. Figure 1.10 is an abbreviated way of representing the solutions to our equation and is a sketch of the flow along the x-axis called a "phase line". [SEK13]

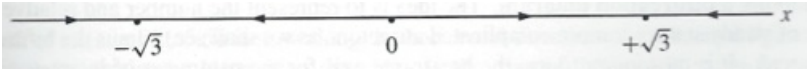

Figure 1.10: Phase-Line. [SEK13]

1.4.2 Bifurcations

Now, let us look at the same differential equation, but introduce a new parameter and explore some of the behavioral transitions (bifurcations) as that parameter is varied.

$$\frac{dx}{dt} = c(x - \frac{1}{3}x^3 + A) \equiv f(x), \qquad (2.22)$$

where A is some additive positive or negative constant. We can set $c = 1$, without loss of generality since time can be rescaled.

Now, look at Figure 1.11a below.

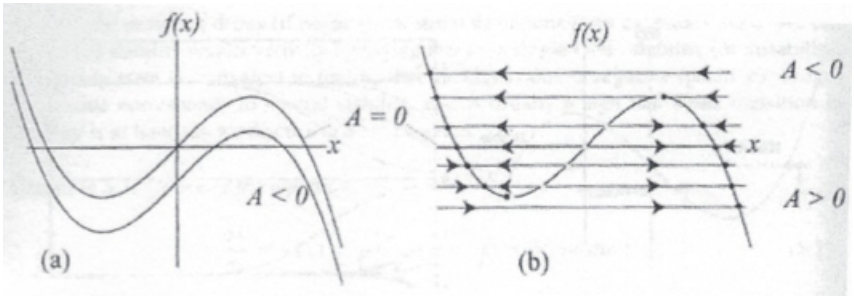

Figure 1.11: (a) Curve Shift. (b) Flow of Shift Curve. [SEK13]

As we know, A shifts the curve up when $A > 0$ and down when $A < 0$. As seen on Figure 1.11b, when A changes, so do the positions and number of intersection points of the cubic and x-axis. The black dots indicate stability while the white dots indicate instability. [SEK13]

There are large values of A in both the positive and negative directions beyond which two steady states coalesce and disappear. At each of these values the graph of $f(x)$ is tangent to the x-axis and is shown below in Figure 1.12. This type of change in qualitative behavior is called a bifurcation and A is called a bifurcation parameter. [SEK13]

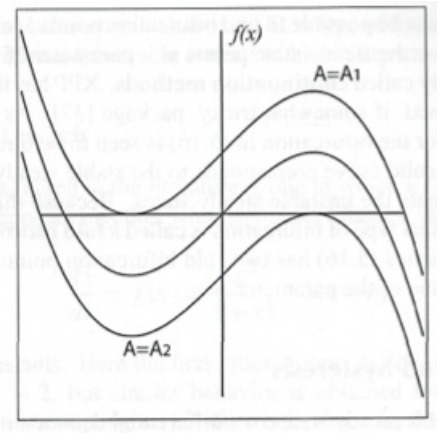

Figure 1.12: Change in Quality Behavior of Bifurcation Parameter. [SEK13]

The behavior of an entire system can be summarized by assembling a bifurcation diagram with the number and relative position of its steady states (or more complicated attractors) along the y-axis and the variation of the bifurcation parameter along the x-axis. Figure 1.13 represents the bifurcation diagram of equation (2.20). [SEK13]

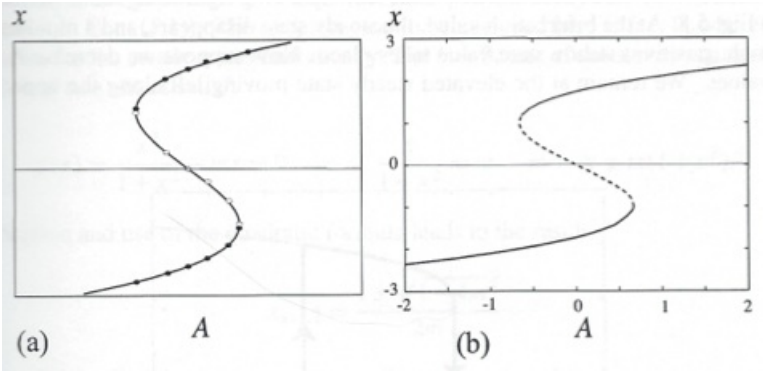

Figure 1.13: Bifurcation of Equation 2.20. [SEK13]

Figure 1.13a simply rotates Figure 1.11b and removes the arrows giving a clear view of the steady states along the y-axis while Figure 1.13b is the true bifurcation diagram where the dotted line represents the unstable state (white dots). Because the bifurcation curve appears to fold over itself, it is known as a fold bifurcation and has

two bifurcation points: one at a positive point and one at a negative point. [SEK13]

The existence of two stable states in a differential equation model is often described by the term bistability. This behavior occurs in many biological situations. Bistability is accompanied by the following hysteresis. [SEK13]

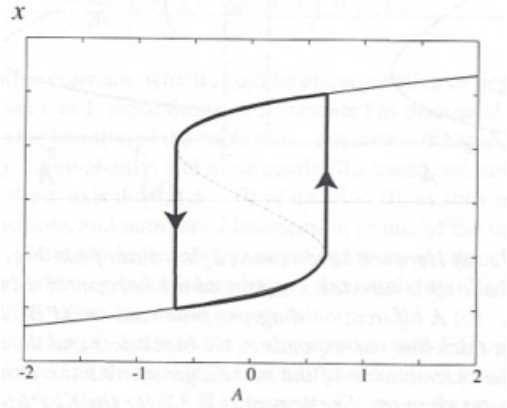

Figure 1.14: Hysteresis of Two Stable States. [SEK13]

Let the parameter A start as the negative steady state value. As A gradually increases we remain at steady state, but the value of that steady state disappears and a rapid transition to the positive steady state value takes place. Now, if we let the value A decrease back to lower values, the elevated state moves left along the upper branch until the negative bifurcation value of A is reached. This type of hysteresis is often used as an experimental hallmark of multiple stable states and bistability in a biological system. [SEK13]

To generalize, let us consider the single differential equation

$$\frac{dx}{dt} = f_r(x),$$

where f depends on one parameter "r' that takes the role of the "bifurcation parameter". First consider the condition $f_r(x) = 0$. This simply restricts our attention to steady states of the ODE.

As r varies, the relation $f_r(x) = 0$ corresponds to a set of curves in the rx plane (the bifurcation plot) that are smooth functions of r except at special points where $f_r^{'}(x) = 0$. A mathematical result states that these special points are the only places where branches of steady states can come together (bifurcate). A point in the rx plane satisfying both $f_r(x) = 0$ and $f_r^{'}(x) = 0$ is a bifurcation point, and the value of the parameter r at such a point is the bifurcation value. The conditions for bifurcation are hence

$$f_r(x) = 0, \quad f_r^{'}(x) = 0, \quad \text{at} \quad x = x_{ss}, \quad r = r_0.$$

Geometrically, these conditions indicate that the function $f_r(x)$ intersects the x-axis and is tangent at that point. Analytically, these conditions imply that at the steady state $x = x_{ss}$ there is a zero eigenvalue. [SEK13]

1.5 Mathematical Model of a Notable Biological Problem

Now, we will use the tools we have developed to construct, analyze, and interpret a mathematical model of a notable biological problem. As a case study, we take the spread of an infection in a population of initially healthy individuals. Using dimensional analysis, qualitative methods, and ideas of bifurcations, we will consider how parameters affect the behavior of the model and what this implies biologically. [SEK13]

1.5.1 Derivation of Model

First, we will derive a model for the spread of infection. Assume any individual is equally likely to come into contact with any other individual and subdivide the population into two classes: those that are healthy, but susceptible to the disease, and those that are infected and able to spread the disease through contact. Figure 1.15 illustrates a view of the process that is closed (the population neither increases nor decreases). [SEK13]

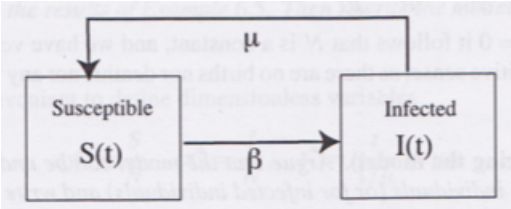

Figure 1.15: "Closed" Process for Speed of Infection. [SEK13]

The "reaction scheme" for this illustrated view is:

$$S + I \longrightarrow 2I, \qquad I \longrightarrow S. \qquad (2.23)$$

To simplify, we will also assume that infected individuals recover at a constant rate and become susceptible again with no immune period. Let us define $S(t)$ = the number of susceptible people and $I(t)$ = the number of infected people in the population. The spread of infection requires contact between healthy and sick individuals, as indicated in the reaction scheme (2.23), the rate at which this type of contact occurs can be approximately represented by the Law of Mass Action. Thus, the rate of increase of infected individuals would be proportional to the product SI. Let us call the proportionality constant β. Since the rate of recovery of a sick individual is assumed to be constant, the overall rate of "flow" out of class I and into class S is proportional to I. Let us denote the rate by μ. [SEK13] Then the equations are:

$$\frac{dS}{dt} = \mu I - \beta SI, \qquad (2.24a)$$

$$\frac{dI}{dt} = \beta SI - \mu I. \qquad (2.24b)$$

Note the flow into one class is identical with flow out of the other class. Therefore, the total population, $N(t) = S(t) + I(t)$, is conserved as shown:

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dI}{dt} = \mu I - \beta SI + \beta SI - \mu I = 0.$$

Therefore, N is a constant. By conservation, we can eliminate $I(t)$ from the equations and substitute $I(t) = N - S(t)$. Since N is constant, if we find $S(t)$, then this relationship

provides $I(t)$. Thus, it suffices to keep only one equation. We will keep equation (2.24a), rewritten as

$$\frac{dS}{dt} = \mu(N - S) - \beta S(N - S), \qquad (2.25)$$

together with $I(t) = N - S(t)$. The model is thus reduced to a single ODE in $S(t)$. Equivalently, we could choose to eliminate S rather than I. This would lead to

$$\frac{dI}{dt} = \beta(N - I)I - \mu I. \qquad (2.26)$$

1.5.2 Dimensional Analysis and Scaling

Next, we will apply dimensional analysis to the model to reduce the number of parameters and make the model dimensionless. Let us measure time in units of days, then the left-hand sides of Equations (2.24a) and (2.24b) have dimensions of [number of people] / [time]. Therefore, μ must have units of $1/time$ and β should have units of per person per unit time. Since μ has units of $1/time$, it follows that $1/\mu$ carries units of time. This *time* unit is a typical time associated with recovery from infection. Let $x^*(t)$ be defined as the fraction of the population in the infected class and $y^*(t)$ be defined as the fraction of the total population in the susceptible class. [SEK13]

It is convenient to define dimensionless variables:

$$y^* = \frac{S}{N}, \;\; x^* = \frac{I}{N}, \;\; t^* = \frac{t}{1/\mu} = \mu t.$$

Since $S(t) + I(t) = N = \text{constant}$, it follows that

$$\frac{S}{N} + \frac{I}{N} = y^* + x^* = \frac{N}{N} = 1.$$

Rewriting the relationships obtained in a form that can be used to substitute directly into the model equations of (2.24), namely, $S = y^*N, \; I = x^*N, \; t = t^*/\mu$ yields

$$\frac{d(y^*N)}{d(t^*/\mu)} = \mu x^* N - \beta(y^*N)(x^*N), \qquad (2.27a)$$

$$\frac{d(x^*N)}{d(t^*/\mu)} = \beta(y^*N)(x^*N) - \mu x^* N. \qquad (2.27b)$$

Canceling the constant common factors of N and μ from both sides we arrive at

$$\frac{dy^*}{dt^*} = x^* - (\frac{\beta N}{\mu})x^*y^*, \qquad (2.28a)$$

$$\frac{dx^*}{dt^*} = (\frac{\beta N}{\mu})x^*y^* - x^*. \qquad (2.28b)$$

Note $(\frac{\beta N}{\mu})$ is the single remaining ratio of parameters that we will denote as R_o. R_o is an important quantity since its parameter combination governs qualitative behavior. Rewriting the equations in terms of R_o and dropping the stars leads to

$$\frac{dy}{dt} = x - R_o\, xy, \qquad (2.29a)$$

$$\frac{dx}{dt} = R_o\, xy - x. \qquad (2.29b)$$

Let us illustrate the process of scaling from the perspective of the reduced model (2.26) where conservation, $y^* + x^* = 1$, was used. Substitutions of $I = x^*N$ and $t = t^*/\mu$ into this model leads to

$$\frac{d(x^*N)}{d(t^*/\mu)} = \beta(N - x^*N)x^*N - \mu x^*N. \qquad (2.30)$$

Canceling factors N and μ from both sides and dropping the stars leads to

$$\frac{dx}{dt} = (\frac{\beta N}{\mu})(1-x)x - x, \qquad (2.31)$$

which together with $y = 1-x$, completely specifies the problem. The same dimensionless parameter ratio $R_o = \frac{\beta N}{\mu}$ is seen here. We can rewrite (2.31) as

$$\frac{dx}{dt} = R_o(1-x)x - x.$$

Considering the fact that $1/\mu$ is a typical recovery time, when there is a single infected person, $I \approx 1$, and the population of susceptibles is $S \approx N$, then the number of new infections per unit time is $\beta N \times 1 = \beta N$. Now, $1/\mu$ is the typical time that the infected person is ill and can spread the disease. Thus, the total number of new infections stemming from this single infected individual is $\frac{\beta N}{\mu} \equiv R_o$. The development of

the model is complete. Our next task is to analyze and understand its behavior. [SEK13]

Let us write a single ODE for the infected fraction of the population in several suggestive forms, namely

$$\frac{dx}{dt} = R_o(1-x)x - x = x(R_o y - 1) = x[(R_o - 1) - R_o x]. \quad (2.32)$$

1.5.3 Steady State

Then the steady states of the model are

$$0 = x[(R_o - 1) - R_o x], \quad (2.33)$$

either $x = 0$ and then (by conservation) $y = 1$. This corresponds to a population that has no infected individuals, $I(t) = 0$, $S(t) = N$. We will refer to this as the disease-free equilibrium. A second possibility is that $x[(R_o - 1) - R_o x] = 0$ so $x = (R_o - 1)/R_o = 1 - (1/R_o)$. Using conservation once more, we find that in this case $y = 1/R_o$. This steady state has some proportion of the population in the infected class, and is denoted the disease endemic state. However, we observe that this steady state is biologically feasible only if $x > 0$, which means that $R_o > 1$. When this steady state exists (which implies that it is positive), we say that the disease can become endemic, which means that it can take hold of some constant fraction of the population. [SEK13]

To summarize,

$$\text{Disease free: } x_o = 0,\ y_o = 1, \quad \text{Disease endemic: } x_1 = 1 - \frac{1}{R_o},\ y_1 = \frac{1}{R_o}. \quad (2.34)$$

To convert these findings to results for the unit-carrying variables, we multiply each quantity by N, so that $S = yN$, $I = xN$, and thus

$$\text{Disease free: } I_o = Nx_o = 0,\ S_o = N,\ y_o = N, \quad (2.35a)$$

$$\text{Disease endemic: } I_1 = Nx,\ = N(1 - \frac{1}{R_o}),\ S_1 = Ny_1 = N\frac{1}{R_o}. \quad (2.35b)$$

This result is summarized in the following Threshold Theorem:

Theorem 2. In a simple SI disease-dynamics model, the disease can become endemic only if $R_o > 1$, where R_o is the reproductive number of the disease, and $R_o = \frac{\beta N}{\mu}$. [SEK13]

1.5.4 Qualitative Techniques - Behavior of the Model

We now apply qualitative techniques to understanding the behavior of the model. We will use the ODE for the infected fraction of the population (2.32) but written in a more convenient form

$$\frac{dx}{dt} = R_o x[(1 - \frac{1}{R_o}) - x] \equiv f(x) \qquad (2.36)$$

Note that the expression $(1 - \frac{1}{R_o})$ is one of the steady state values obtained in (2.34), a constant. Figure 1.16 shows the flow diagram for the RHS of $f(x)$ in (2.36).

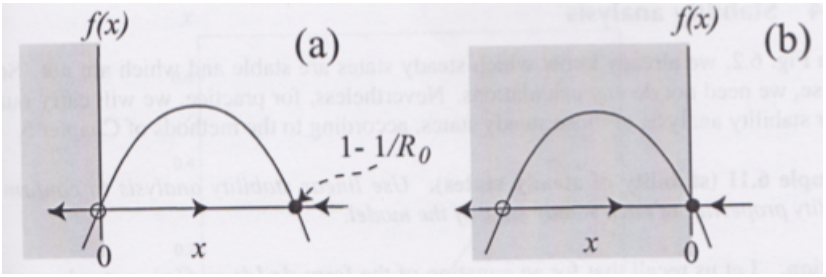

Figure 1.16: Flow Diagram for Equation 2.36. [SEK13]

We see that in the case $R_o > 1$, the disease will progress towards the endemic steady state, $x = 1 - (\frac{1}{R_o})$, and in the case $R_o < 1$, the only steady state is at $x_o = 0$, so the disease is eradicated. Stable steady states (black dots) have arrows directed towards them, and unstable steady states (open dots) have arrows directed away from them. The simulation of this model is shown below in Figure 1.15. It confirms our results that all initial conditions with $x > 0$ eventually approach the endemic steady state.

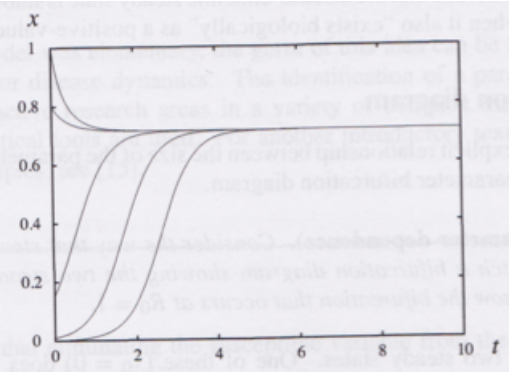

Figure 1.17: Simulation of Model for Equation 2.36. [SEK13]

Now, we will confirm the linear stability of those steady states. Let us recall that for an equation of the form $\frac{dx}{dt} = f(x)$, a steady state x_{ss} (satisfying $f(x) = 0$) is stable whenever $f^{'}(x_{ss}) < 0$, and unstable when $f^{'}(x_{ss}) > 0$.
For the problem at hand, we have

$$f(x) = xR_o[(1 - \frac{1}{R_o}) - x] = R_o[x(1 - \frac{1}{R_o}) - x^2].$$

Hence,

$$f^{'}(x) = R_o[(1 - \frac{1}{R_o}) - 2x].$$

Thus, for the disease-free steady state, $x_o = 0$, we have

$$f^{'}(x) = f^{'}(0) = R_o[(1 - \frac{1}{R_o})] = R_o - 1 > 0 \text{ when } R_o > 1.$$

This means that the disease-free state is unstable when $R_o > 1$ (and stable otherwise). Similarly, for the disease-endemic steady state, $x_{ss} = x_1 = 1 - \frac{1}{R_o}$, so

$$f^{'}(x_1) = R_o[(1 - \frac{1}{R_o}) - 2(1 - \frac{1}{R_o})] = -R_o(1 - \frac{1}{R_o}) = 1 - R_o.$$

Thus, the disease-endemic steady state is stable only when $R_o > 1$. [SEK13]

We now develop an explicit relationship between the size of the parameter, R_o, and the steady state level in a one-parameter bifurcation diagram.

We have two steady states. One of these, $x_o = 0$, does not depend on R_o. The second appears when $R_o = 1$ and is then $x_1 = 1 - (\frac{1}{R_o})$. As $R_o \to \infty$, this second steady state will approach 1 as shown in the following Figure 1.18.

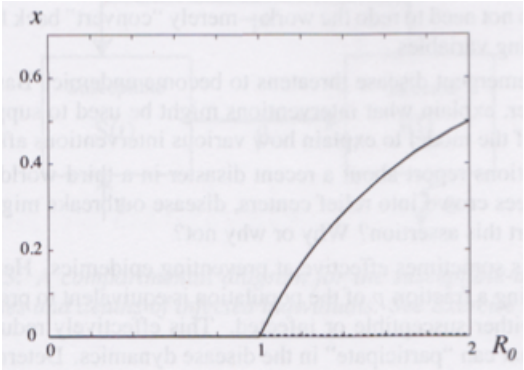

Figure 1.18: Bifurcation of Model for Equation 2.36. [SEK13]

The solid line corresponds to the stable steady state and the dotted line to the unstable steady state. This type of bifurcation is a transcritical bifurcation, in that, for most values of R_o there are two steady states, but for $R_o = 1$ these steady states merge and exchange stability, whereas with the "fold" bifurcation they merged and disappeared. [SEK13]

The analysis, simulation, and bifurcation plot show that the outcome of the infection depends on a single parameter $R_o = \frac{\beta N}{\mu}$, and that there is a transition in the qualitative behavior at $R_o = 1$. Below $R_o = 1$, the disease cannot "reproduce" itself fast enough to be sustained and consequently disappears after some transient. Above $R_o = 1$, this "reproductive number" implies that each infected person infects more than one uninfected person, on average, and the disease becomes endemic. [SEK13]

Chapter 2

Practical Applications

The following applications are to test our understanding of everything we have learned thus far. We have taken these applications directly from the book, "A Primer on Mathematical Models in Biology" by Lee A. Segel and Leah Edelstein-Keshet pages 111-114.

2.1 Application 1 - Total Population

a) Show that eliminating the susceptible variable from the system of equations gives rise to equation 2.26.
b) Simplify that equation and find its dimensionless version using the same procedure as shown in the examples.
ANSWER:
a) Total population is $N(t) = S(t) - I(t)$. Therefore, $S(t) = N - I(t)$ (N is constant) and substituting this equation into $\frac{dI}{dt} = \beta SI - \mu I$ gives $\frac{dI}{dt} = \beta(N - I)I - \mu I$.
b) Time will be measured in units of days with $\frac{dS}{dt}$ and $\frac{dI}{dt}$ having dimensions of the number of people/time, then μ has units of $\frac{1}{time}$ and β has units per person per unit time. Defining $x^*(t)$ as the fraction of the population in the infected class and defining $y^*(t)$ as the fraction of the population in the susceptible class, we define dimensionless variables

$$y^* = \frac{S}{N}, x^* = \frac{I}{N}, t^* = \mu t.$$

Since $S(t) + I(t) = N =$ constant, it follows

$$\frac{S}{N} + \frac{I}{N} = y^* + x^* = \frac{N}{N} = 1.$$

Now, substituting, $S = y^*N, I = x^*N, t = \frac{t^*}{\mu}$ into (2.24a) and (2.24b) we get

$$\frac{d(y^*N)}{d(t^*/\mu)} = \mu x^*N - \beta(y^*N)(x^*N),$$

$$\frac{d(x^*N)}{d(t^*/\mu)} = \beta(y^*N)(x^*N) - \mu x^*N.$$

Dividing both sides by N and μ leads to

$$\frac{dy^*}{dt^*} = x^* - (\frac{\beta N}{\mu})x^*y^*,$$

$$\frac{dx^*}{dt^*} = (\frac{\beta N}{\mu})x^*y^* - x^*.$$

Rewriting the equations with $R_o \equiv (\frac{\beta N}{\mu})$ and dropping the stars, we get

$$\frac{dy}{dt} = x - R_o xy,$$

$$\frac{dx}{dt} = R_o xy - x.$$

Using $y^* + x^* = 1$ and substituting $I = x^*N$ and $t = t^*/\mu$ into

$$\frac{dI}{dt} = \beta(N - I)I - \mu I,$$

gives

$$\frac{d(x^*N)}{d(t^*/\mu)} = \beta(N - x^*N)x^*N - \mu x^*N,$$

leading to

$$\frac{dx}{dt} = (\frac{\beta N}{\mu})(1 - x)x - x.$$

Then, we divide by μ and N with $R_o \equiv (\frac{\beta N}{\mu})$ to get

$$\frac{dx}{dt} = R_o(1-x)x - x.$$

Using $y^* + x^* = 1$ and substituting $S = y^*N$ and $t = t^*/\mu$ into

$$\frac{dS}{dt} = \mu(N-S) - \beta S(N-S),$$

gives

$$\frac{d(y^*N)}{d(t^*/\mu)} = \mu(N - y^*N) - \beta(y^*N)(N - y^*N),$$

leading to

$$\frac{dy}{dt} = (1-y) - \frac{\beta N}{\mu}y(1-y).$$

Then, we divide by μ and N with $R_o \equiv (\frac{\beta N}{\mu})$ to get

$$\frac{dy}{dt} = (1-y) - R_o y(1-y).$$

2.2 Application 2 - Find Steady-State

Find steady states corresponding to the endemic disease in the SI model in terms of the original, dimension - carrying variables (rather than the dimensionless variables x, y). [SEK13]

ANSWER:

We do not have to redo the work - merely "convert" back from dimensionless to unit-carrying variables. The disease endemic non-dimensioned steady state is:

$$x_1 = 1 - \frac{1}{R_o}, \quad y_1 = \frac{1}{R_o}.$$

To convert to dimension-carrying variables, we multiply each quantity by N:

$$Nx_1 = N - \frac{N}{R_o}, \quad Ny_1 = \frac{N}{R_o}.$$

substituting $\beta N/\mu$ for R_o

$$Nx_1 = I_1 = N - \frac{\mu N}{\beta N}, \quad Ny_1 = S_1 = \frac{\mu N}{\beta N}.$$

Thus, the steady state of the original, dimension-carrying variables is

$$I_1 = N - \frac{\mu}{\beta}, \quad S_1 = \frac{\mu}{\beta}.$$

2.3 Application 3 - Endemic Intervention

Suppose an emergent disease threatens to become endemic. Based on the analysis in this chapter, explain what interventions might be used to suppress it. Use R_o or parameters of the model to explain how various interventions affect the dynamics. [SEK13]

ANSWER:

$R_o = \frac{\beta N}{\mu}$, where βN is the number of new infections per unit time and $\frac{1}{\mu}$ is the typical time that the infected person is ill and can spread the disease.

From the stability analysis, we know that the steady states are at $R_o = 0$ and $R_o = 1$. If we maintain the value of R_o between 0 and 1, then the disease cannot sustain itself and, thus, will not spread. To keep R_o between 0 and 1, the value of βN must remain less than μ. Therefore, we want $1/\mu$ to decrease by using a variety of medical care or a pattern of medical care that can decrease the time an infected person is ill and can spread the disease.

Also, we want the number of new infections per unit time to decrease. Thus, isolating the infected patients, decreasing the amount of time an infected person is in contact with an uninfected person (by awareness of symptoms and fast action), and communicating with the public to learn the facts of the disease and avoid infection are critical.

2.4 Application 4 - Disease Outbreak Prediction

A United Nations report about a recent disaster in a third-world country predicted that as refugees crowd into relief centers, disease outbreaks might occur. Does the model support this assertion? Why or why not? [SEK13]

ANSWER:
Yes, the model does support this assertion. As discussed in Application 3, $R_o = \frac{\beta N}{\mu}$, and, therefore, to keep disease from becoming endemic βN must remain small. Since βN is the number of new infections per unit time, increasing the potential of exposure by bringing a large number of people to relief centers increases the rate of possible infection by mass action. Since the rate of mass action is proportional to the product SI and,thus, β, this would increase βN.

2.5 Application 5 - Vaccination

Vaccination is sometimes effective at preventing epidemics. Here we will suppose that vaccinating a fraction p of the population is equivalent to protecting pN people from being either susceptible or infected. This effectively reduces the size of the population that can "participate" in the disease dynamics. Determine the fraction p that would have to be vaccinated in each case to prevent an endemic disease. [SEK13]
a) Smallpox, for which $R_o \approx 5$.
b) Polio, for which $R_o \approx 6$.
c) Measles, for which $R_o \approx 12$.
ANSWER:
a) $R_o = \frac{\beta N}{\mu}$ is the total number of new infections from a single infected person. The steady state Disease Endemic is

$$x_1 = 1 - \frac{1}{R_o}, \quad y_1 = \frac{1}{R_o},$$

with x representing the fraction of the population in the infected class. Thus, with $R_o \approx 5$ we get

$$x_1 = 1 - \frac{1}{5} = 1 - .2 = .8, \quad y_1 = \frac{1}{5} = .2.$$

Therefore, to prevent a smallpox endemic, we need to prevent the population from getting to the steady state of $x_1 = .8$, so the fraction of the population that needs to be vaccinated is $p = .2$ or at least 20 percent.

b) With $R_o \approx 6$ the steady state Disease Endemic is

$$x_1 = 1 - \frac{1}{6} = 1 - .16667 = .83334, \qquad y_1 = \frac{1}{6} = .16667.$$

Therefore, to prevent a Polio endemic, we need to prevent the population from getting to the steady state of $x_1 = .83334$, so the fraction of the population that needs to be vaccinated is $p = .16667$ or at least 16.67 percent.
c) With $R_o \approx 12$ the steady state Disease Endemic is

$$x_1 = 1 - \frac{1}{12} = 1 - .08334 = .91667, \qquad y_1 = \frac{1}{5} = .08334.$$

Therefore, to prevent a Measles endemic, we need to prevent the population from getting to the steady state of $x_1 = .91667$, so the fraction of the population that needs to be vaccinated is $p = .08334$ or at least 8.34 percent.

2.6 Application 6 - Separation of Variables

Use separation of variables to find an analytical solution to Equation 2.36 with initial condition $x(0) = x_o$, where $0 < x < 1 - \frac{1}{R_o}$. It is advisable to first recast the equation by defining the constant

$$\beta = (1 - \frac{1}{R_o}),$$

to obtain

$$\frac{dx}{dt} = R_o x[\beta - x], \qquad 0 < x < \beta.$$

Compare your solution to the results described in this chapter. [SEK13]

ANSWER: Equation 2.36 is

$$\frac{dx}{dt} = R_o x[(1 - \frac{1}{R_o}) - x] \equiv f(x).$$

Substituting $\beta = (1 - \frac{1}{R_o})$, we get

$$\frac{dx}{dt} = R_o x(\beta - x).$$

To integrate, we will use partial fraction decomposition. Thus, we have the partial fraction equation as

$$\frac{1}{R_o x(\beta - x)} = \frac{A}{R_o x} + \frac{B}{\beta - x}.$$

Dividing both sides by $R_o x(\beta - x)$ leads to

$$1 = A(\beta - x) + BR_o x.$$

Letting $x = 0$, we can solve for A as follows

$$1 = A\beta,$$

$$A = \frac{1}{\beta}.$$

Therefore, our equation becomes

$$1 = \frac{\beta - x}{\beta} + BR_o x.$$

Letting $x = 1$, we can solve for B as follows

$$1 = \frac{\beta - 1}{\beta} + BR_o,$$

$$B = \frac{1 - \frac{\beta - 1}{\beta}}{R_o} = \frac{\frac{\beta - \beta + 1}{\beta}}{R_o} = \frac{1}{\beta R_o}.$$

Therefore, our original equation becomes

$$\frac{1}{R_o x(\beta - x)} = \frac{1}{\beta R_o x} + \frac{1}{\beta R_o(\beta - x)}.$$

Our integration will then be

$$\int \frac{1}{R_o x(\beta - x)} dx = \int \frac{1}{\beta R_o x} dx + \int \frac{1}{\beta R_o (\beta - x)} dx = \int dt,$$

which is

$$\frac{1}{\beta R_o} \ln x - \frac{1}{\beta R_o} \ln(\beta - x) + C = t, \text{where C is a constant.}$$

Since x and $(\beta - x)$ represent numbers of people, they are positive and can be written without absolute value bars. Multiplying this equation by βR_o we get

$$\ln x - \ln(\beta - x) + \beta R_o C = \beta R_o t.$$

Now, using the properties of logarithms and raising each term to the value of e, we get

$$\frac{x e^{\beta R_o C}}{(\beta - x)} = e^{\beta R_o t}.$$

Solving for x gives us

$$x = x(t) = \frac{\beta e^{\beta R_o t}}{e^{\beta R_o C} + e^{\beta R_o t}},$$

with $x(0) = x_o$, we can find x_o as

$$x_o = \frac{\beta e^0}{e^{\beta R_o C} + e^0} = \frac{\beta}{e^{\beta R_o C} + 1}.$$

Thus,

$$e^{\beta R_o C} = \frac{\beta - x_o}{x_o},$$

and finally, we obtain the analytical solution to equation 2.36 as

$$x(t) = \frac{\beta x_o e^{\beta R_o t}}{\beta - x_o + x_o e^{\beta R_o t}}.$$

2.7 Application 7 - Susceptible/Infected Pool Model

Suppose that the population has births at rate b to the susceptible pool and mortality at rate δ from the infected pool as shown in the schematic diagram of Figure 2.1. [SEK13]

a) Write down the modified equations of the model.

b) Determine if conservation holds in this case.

c) Determine a dimensionless form of the model using the same kind of method as employed for the example in this chapter.

d) Write an XPP file to simulate this model and plot some of its solutions.

ANSWER:

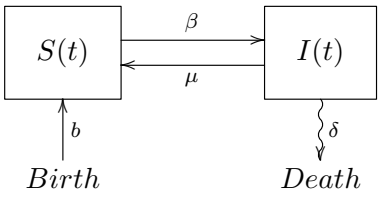

Figure 2.1: Schematic Diagram of the Population with Births and Mortality Rates

a) Modified equations of the model are:

$$\frac{dS}{dt} = \mu I - \beta SI + bS,$$

$$\frac{dI}{dt} = \beta SI - \mu I - \delta I.$$

b) Conservation: Total population is $N(t) = S(t) + I(t)$.

Thus

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dI}{dt} = \mu I - \beta SI + bS + \beta SI - \mu I - \delta I = bS - \delta I,$$

which is not equal to zero. Therefore, N is not constant and conservation does not hold.

c) The dimension of $\frac{dI}{dt}$ and $\frac{dS}{dt}$ is still [number of people] / [time], μ still has units of $1/time$, and β, b, δ have units of per person per time. Defining $x^*(t)$ and $y^*(t)$ as before, the dimensionless variables are

$$y^* = \frac{S}{N},\ x^* = \frac{I}{N},\ t^* = \mu t.$$

Thus,

$$S = Ny^*,\ I = Nx^*,\ t = \frac{t^*}{\mu}.$$

Substituting these into a) we get

$$\frac{d(y^*N)}{d(t^*/\mu)} = \mu x^* N - \beta(y^*N)(x^*N) + b(y^*N),$$

$$\frac{d(x^*N)}{d(t^*/\mu)} = \beta(y^*N)(x^*N) - \mu x^* N - \delta(x^*N).$$

Multiplying each term by $\frac{1}{N\mu}$ we get

$$\frac{dy^*}{dt^*} = x^* - (\frac{\beta N}{\mu})x^*y^* + \frac{b}{\mu}y^*,$$

$$\frac{dx^*}{dt^*} = (\frac{\beta N}{\mu})x^*y^* - x^* - \frac{\delta}{\mu}x^*.$$

Removing the stars, we have the dimensionless form of the equations. They are

$$\frac{dy}{dt} = x - (\frac{\beta N}{\mu})xy + \frac{b}{\mu}y,$$

$$\frac{dx}{dt} = (\frac{\beta N}{\mu})xy - x - \frac{\delta}{\mu}x.$$

d) XPP File, "disease.ode':

$S' = \text{mu} * I - \text{beta} * S * I + b * S$

$I' = -\text{mu} * I + \text{beta} * S * I - \text{delta} * I$

par mu $= 0.1, \text{beta} = 0.2, b = 0.05, \text{delta} = 0.05$

init $S = 1, I = 0$

@ xp $= S$, yp $= I$, xlo $= 0$, xhi $= 2$, ylo $= -0.2$, yhi $= 1.2$

done

A simulation of this model with some of its solutions is:

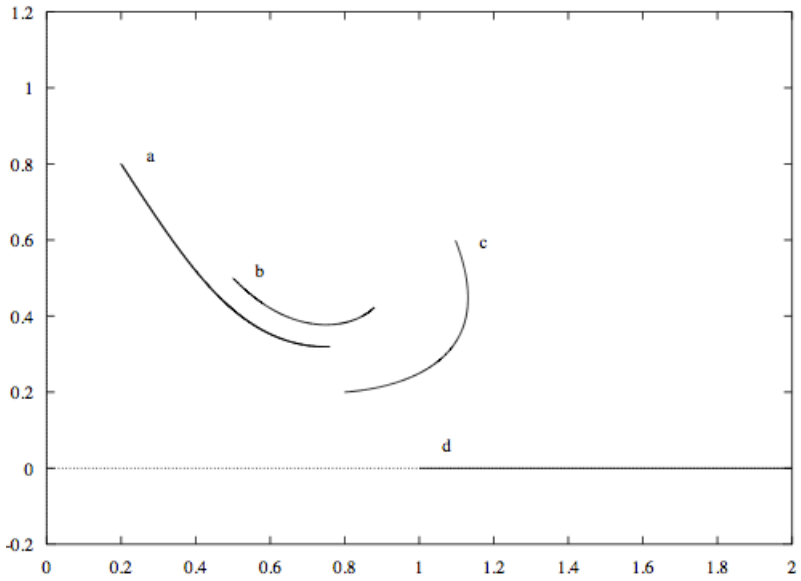

Figure 2.2: XPP Simulation with Curve a) S=0.2,I=0.8 Curve b) S=0.5,I=0.5 Curve c) S=0.8,I=0.2 Curve d) S=1,I=0

2.8 Application 8 - Kermack and Mckendrick Epidemic

Consider the simple model for an epidemic due to Kermack and Mckendrick [76] discussed in Brauer and Castillo-Chavez [15]:

$$\frac{dS}{dt} = -\beta SI, \quad \frac{dI}{dt} = \beta SI - \mu I, \quad \frac{dR}{dt} = \mu I.$$

Here $R(t)$ denotes a removed (either immune or dead) class of individuals. [SEK13]

a) Interpret the equations and sketch a schematic diagram for this model.

b) Explain why the model can be studied as a 2-variable model; which variable is not coupled to the other two.

c) Consider the "trick" of dividing $\frac{dI}{dt}$ by $\frac{dS}{dt}$. Then

$$\frac{dI/dt}{dS/dt} \equiv \frac{dI}{dS} = \frac{\beta SI - \mu I}{-\beta SI}.$$

Simplify this equation to obtain an ODE for I as a function of S. Show that you can integrate this to obtain the solution curve

$$I(S) = -S + \frac{\mu}{\beta}\ln(S) + K_1, \quad \text{where } K \text{ is constant.}$$

ANSWER:

a)

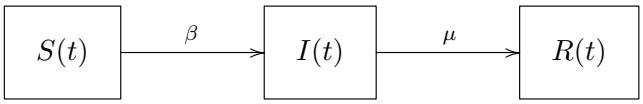

Figure 2.3: Schematic Diagram of Simple Model for an Epidemic due to Kermack and Mckendrick

Flows inward to the block contribute positively to the rate of change, whereas flows outward contribute negatively.

The equation $dS/dt = -\beta SI$ is the rate of change when a susceptible individual becomes infected.

The equation $dR/dt = -\mu I$ is the rate of change when an infected individual becomes immune or dies.

The equation $dI/dt = \beta SI - \mu I$ is the rate of change between dS/dt and dR/dt.

b) Since dR/dt is made up of immune or dead individuals, they can no longer be in the susceptible or infected classes, nor move back and forth between the two classes. Thus, dR/dt is not coupled to the other two.

c)

$$\frac{dI/dt}{dS/dt} \equiv \frac{dI}{dS} = \frac{\beta SI}{-\beta SI} + \frac{\mu I}{\beta SI} = -1 + \frac{\mu}{\beta S}.$$

$$=> \frac{dI}{dS} = -1 + \frac{\mu}{\beta S}.$$

Integrating

$$\int dI = \int -1 dS + \int \frac{\mu}{\beta S} dS,$$

we get

$$=> I(S) = -S + \frac{\mu}{\beta}\ln(S) + K \quad \text{where } K \text{ is constant.}$$

2.9 Application 9 - Creutz-Jakob Disease

Creutz-Jakob and similar prion diseases may result from misfolded protein that "infects" native protein by causing it, too, to misfold, such diseases (also known as "mad cow disease") lead to severe brain damage and death. Consider the schematic diagram below. Assume that the misfolding, like an infection, takes place when the native and misfolded protein come into contact. [SEK13]

a) Propose a model for this process based on the schematic diagram.
b) Reduce the model to a dimensionless formulation. What parameter (grouping) would determine whether prions are maintained or cleared from the body?
c) Simulate the model and explore conditions under which the disease is resolved versus grows continually.

ANSWER:
a)

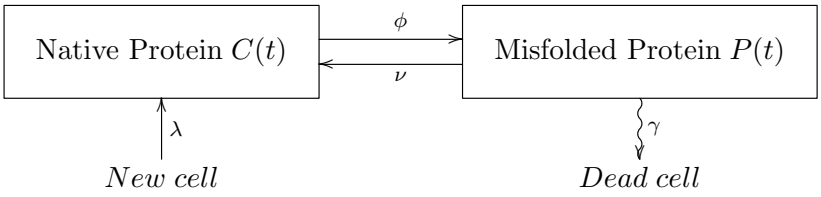

Figure 2.4: Schematic Diagram of the Contact between Native and Misfiled Protein

Again, flow outward is negative and flow inward is positive. We will assume the laws of mass action apply. Thus, we have

$$\frac{dC}{dt} = \nu P - \phi CP + \lambda C,$$

$$\frac{dP}{dt} = \phi CP - \nu P - \gamma P.$$

Let us assume that the protein population consists of only the Native and Misfolded proteins. Then λ is the rate of new Native protein production, γ is the rate of protein death, and ϕ is the rate of mass action between Native protein and Misfolded

protein.

Similar to Application 7, the dimension of dC/dt and dP/dt is still [number of protein cells]/[time]. The dimension of ν is units of $1/time$, and ϕ, λ, γ have units of per protein per time. Defining $x^*(t)$ and $y^*(t)$ as before, the dimensionless variables are

$$y^* = \frac{C}{M},\ x^* = \frac{P}{M},\ t^* = \mu t \quad \text{where} \ \ M = C(t) + P(t).$$

Thus,

$$C = My^*,\ P = Mx^*,\ t = \frac{t^*}{\nu}.$$

Substituting these into a) we get

$$\frac{d(y^*M)}{d(t^*/\nu)} = \nu x^* M - \phi(y^*M)(x^*M) + \lambda(y^*M),$$

$$\frac{d(x^*M)}{d(t^*/\nu)} = \phi(y^*M)(x^*M) - \nu x^* M - \gamma(x^*M).$$

Multiplying each term by $\frac{1}{M\nu}$ we get

$$\frac{dy^*}{dt^*} = x^* - (\frac{\phi M}{\nu})x^*y^* + \frac{I}{\nu}y^*,$$

$$\frac{dx^*}{dt^*} = (\frac{\phi M}{\nu})x^*y^* - x^* - \frac{\gamma}{\nu}x^*.$$

Removing the stars, we have the dimensionless form of the equations. They are

$$\frac{dy}{dt} = x - (\frac{\phi M}{\nu})xy + \frac{\lambda}{\nu}y,$$
$$\frac{dx}{dt} = (\frac{\phi M}{\nu})xy - x - \frac{\gamma}{\nu}x.$$

The parameter (grouping) that would determine whether prion's are maintained or cleared from the body is $R_1 = (\phi M)/\nu$.

c) XPP File, "diseases.ode", to simulate the model:

$C' = \text{nu} * P - \text{phi} * C * P + \text{lambda} * C$

$P' = -\text{nu} * P + \text{phi} * C * P - \text{gamma} * P$

par nu $= 0.1$, phi $= 0.2, b = 0.05$, gamma $= 0.05$

init $C = 1, P = 0$

@ xp $= C$, yp $= P$, xlo $= 0$, xhi $= 2$, ylo $= -0.2$, yhi $= 1.2$

done

The simulation of the model and disease conditions is:

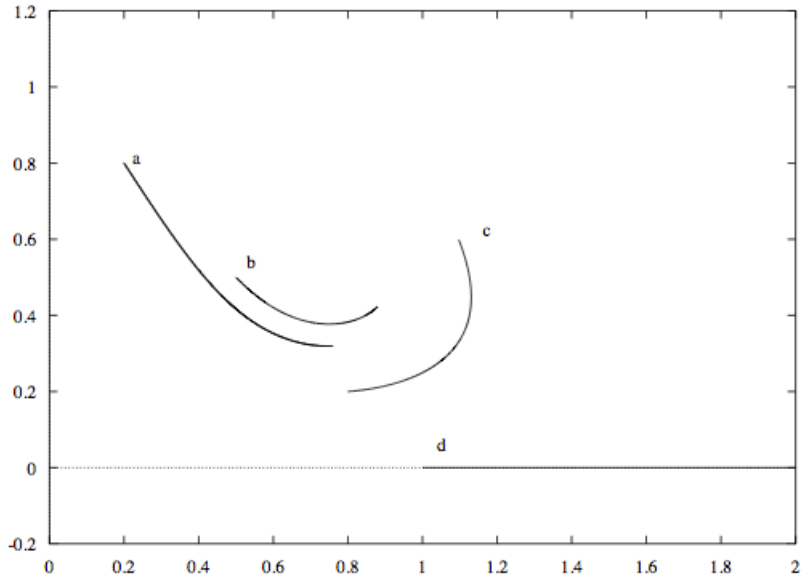

Figure 2.5: XPP Simulation with Curve a) C=0.2,P=0.8 Curve b) C=0.5,P=0.5 Curve c) C=0.8,P=0.2 Curve d) C=1,P=0

As you can see from curves a and b in the graph, when a high number of native protein is infected with the misfolded protein the disease will resolve itself. This occurs because most of the native population will already be infected. However, as seen with curve c, when the number of infected native protein is low the disease will grow continuously to infect as many native proteins as possible.

2.10 Application 10 - Transcritical Bifurcation

a) Redraw $f(x)$ versus x as in Figure 1.16 with $R_0 = 1/2$, and with $R_0 = 2$ on the same set of axes. Show that Equation 2.34 has a transcritical bifurcation at $x_{ss} = x_1$.

b) Use XPP Auto to redraw Figure 1.18 for $-0.2 \leq x \leq 0.7$ to confirm the presence of

a transcritical bifurcation.

c) A student says "since the steady state x_1 ceases to exist, this must be a fold bifurcation". Explain the fallacy. [SEK13]

ANSWER:

a) For a transcritical bifurcation:

1) $f(x)$ undergoes transitions as r varies.

2) There are two steady states.

3) For $r = 0$ these graphs of $f(x)$ merge and exchange stability.

From the graphs seen below, it is clear that Equation 2.34 has a transcritical bifurcation at $x_{ss} = x_1$.

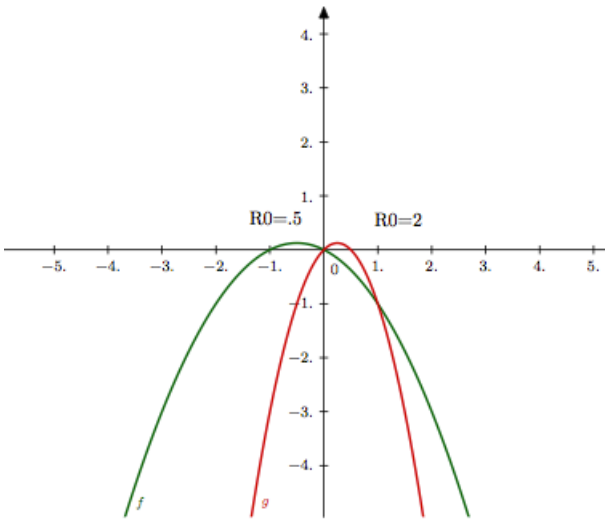

Figure 2.6: f(x) versus x with $R_o = 1/2$ and with $R_o = 2$ on the Same Set of Axes

b)

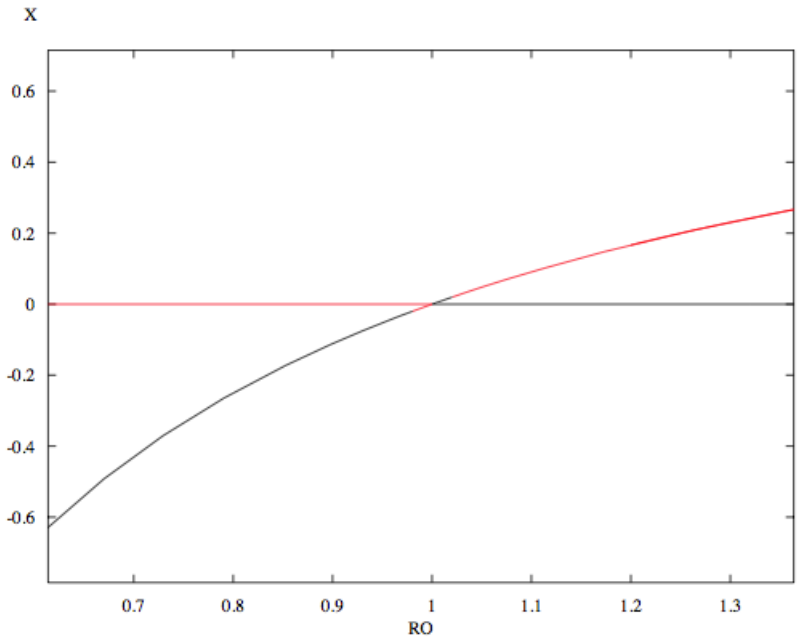

Figure 2.7: Transcritical Bifurcation with $-0.2 \leq x \leq 0.7$

c) The steady state x_1 does not cease to exist it shifts based on the value of R_0.

Chapter 3

Case Study: Hepatitis C Virus

Now that we have completed a number of exercises, we have a good understanding of how a mathematical model can be created and manipulated to interpret a biological event. Let's put this knowledge to use by creating a mathematical model for the well known Hepatitis C virus. Hepatitis C is one of six major recognizable viral types that cause infection of the liver. The three most common of these types are Hepatitis A, Hepatitis B, and Hepatitis C. Hepatitis A virus survives in fecal matter and is primarily transmitted through sexual contact. The Hepatitis A virus causes only a short span of infection and, therefore, does not become chronic. People with Hepatitis A improve without treatment. The Hepatitis B virus is spread similarly to HIV, but is 100 times more infectious because the virus can survive outside the host for many days. Hepatitis B can become chronic in approximately 6 percent of infected individuals and causes extensive damage to the liver. However, Hepatitis B symptoms are more severe and treatment is successful early. Hepatitis C is a bloodborne pathogen and is transmitted primarily by exposure to blood through the skin, such as through Intravenous Drug Use (IDU), by long-term hemodialysis, or by healthcare workers after possible exposure to Hepatitis C positive blood. There is no vaccine for Hepatitis C. However, a combination of harm reduction strategies such as the provision of new needles and syringes, the treatment of substance abuse, and the following of infection control guidelines in healthcare are becoming a successful prevention campaign due to the growth of community planning groups. [AC09]

3.1 Hepatitis C Background

3.1.1 Genotype

Hepatitis C is a small, enveloped, single-stranded, positive-sense RNA virus that enters the cells of the liver and replicates its RNA strand in them. There are seven major genotypes of the Hepatiits C virus. The genotypes are divided into several subtypes. In the US, about 70 percent of the cases are cause by genotype 1 and 20 percent by genotype 2. The incubation period for the Hepatitis C virus ranges from 14-168 days with an average of 28-48 days. A combination of tests is required to diagnose Hepatitis C. The initial test is the Hepatitis antibody enzyme immunoassay test which indicates either past or present infection. If the Hepatitis antibody enzyme test is positive, a Polymerase Chain Reaction (PCR) test is given. This test detects the presence of the Hepatitis C virus in the blood and, thus, is used to diagnose chronic Hepatitis C infection. [HSAH98]

3.1.2 Hepatitis C Virus Progression

The initial symptoms of Hepatitis C are typically misinterpreted and often disappear after a few weeks. This initial stage of the condition is known as Acute Hepatitis C. During the acute infection period, the body's immune system is at work trying to kill the Hepatitis C infected cells. In 15 to 25 percent of the cases, the body is successful and the individuals do not suffer further infections. They are considered "cured" or "dormant" if they remain infection free for 6 months. For the other 75-85 percent, the infections continue and the accumulation of scar tissue resulting from these infections eventually prevents the liver from functioning properly. In approximately 15 percent of these cases, a person develops cirrhosis, necrosis, and, then, cancer. Five percent die. This stage of the Hepatitis C progression is known as Chronic Hepatitis C and is defined as infection with the Hepatitis C virus recurring for more than six months based on the presence of the Hepatitis C single-stranded RNA in the blood. Chronic infections are commonly asymptomatic during the first two decades and, thus, are consistently discovered following the investigation of elevated liver enzyme levels or during a routine screening of high-risk individuals. There is no cure for Hepatitis C, but a proper medication regime can stop the virus from replicating itself. [HSAH98] [AC09]

3.1.3 Treatment

The primary goal of treatment is to achieve a Sustained Viral Response (SVR), which is defined as undetectable Hepatitis C virus in the blood 6 months after the end of treatment. Prior to 2011, treatments consisted of a combination of pegylated interfon alpha and ribavirin for a period of 24-48 weeks depending on the Hepatitis C virus genotype. This combination provided SVR "cure" rates between 70-80 percent for patients with genotype 2 and 3 and 45-70 percent for patients with genotype 1 and 4. After 2011, treatments of a combination of sofosbuvir with ribavirin and interfon have proved to be approximately 90 percent effective in patients with genotype 1,4,5, and 6 and treatments of sofosbuvir with only ribavirin have proved to be approximately 70-95 percent effective in patients with genotype 2 and 3. [HSAH98]

An estimated 4 million Americans (1.8 percent of all Americans) have been infected with the Hepatitis C virus. Based upon national data, in 2012, an estimated 600,000 Californians are currently infected with Hepatitis C and 5,000 Californians are newly infected each year. [HSAH98]

3.2 Hepatitis C Virus Model, Equations, and Analysis

3.2.1 Block Diagram of Hepatitis C Virus Progression

The schematic (Block) diagram for the Hepatitis C virus progression is as follows [HVCACC11]:

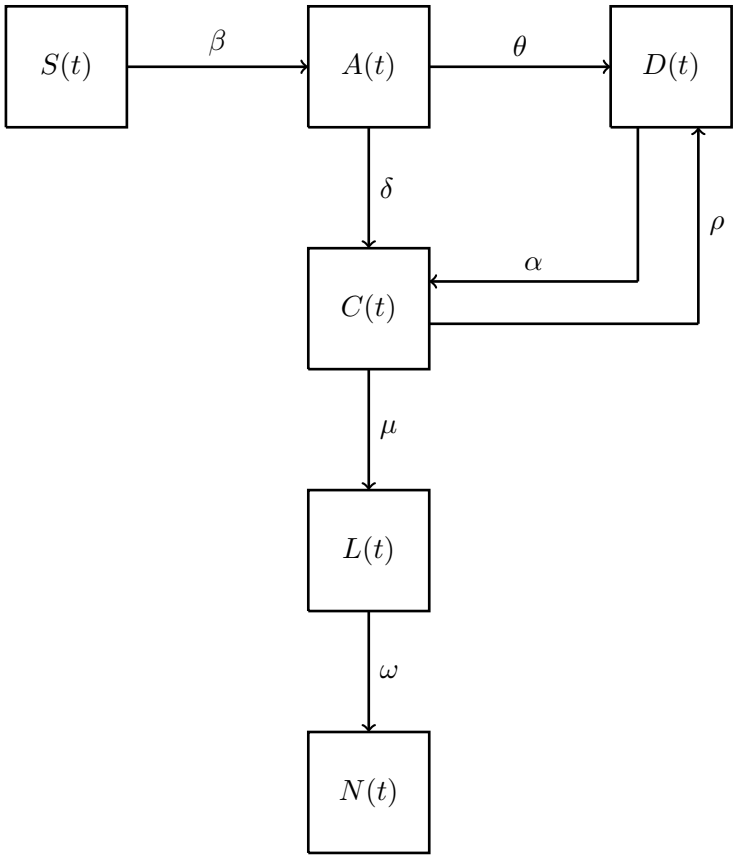

Figure 3.1: Schematic Diagram - Hepatitis C Virus Progression.

We define:

$S(t)$ = the number of Susceptible people

$A(t)$ = the number of Acute infected people

$C(t)$ = the number of Chronic infected people

$D(t)$ = the number of Dormant infected people

$L(t)$ = the number of infected people with Liver disease

$N(t)$ = the number of infected people with Necrosis of the Liver

β = the rate increase of infected people due to IVDA (intravenous drug abuse)

δ = the rate increase of chronic infected people due the bodies inability to kill the active hepatitis C cells

θ = the rate increase of acute infected people with sustained viral response (6months)

ρ = the rate increase of hepatitis C dormant people due to medication, diet, and alcohol

abstinence

α = the rate increase of people with unsustained response (6 months)

μ = the rate increase of extended chronic hepatitis C infected people

ω = the rate increase of people with extended liver disease

Then the equations are:

$$\begin{aligned}
\frac{dS}{dt} &= -\beta SA, \\
\frac{dA}{dt} &= \beta SA - \theta A - \delta A, \\
\frac{dD}{dt} &= \theta A + \rho C - \alpha D, \\
\frac{dC}{dt} &= \delta A + \alpha D - \rho C - \mu C, \\
\frac{dL}{dt} &= \mu C - \omega L, \\
\frac{dN}{dt} &= \omega L.
\end{aligned}$$

In this case, the total conserved population is $\frac{dM}{dt} = \frac{dS}{dt} + \frac{dA}{dt} + \frac{dD}{dt} + \frac{dC}{dt} + \frac{dL}{dt} + \frac{dN}{dt} = -\beta SA + \beta SA - \theta A - \delta A + \theta A + \rho C - \alpha D + \delta A + \alpha D - \rho C - \mu C + \mu C - \omega L + \omega L = 0.$

3.2.2 Simplified Model of Hepatitis C Virus

To simplify the model into a set of ordinary differential equations that we have discussed so far, we will consider only the relationship between the Dormant infected individuals and the Chronic infected individuals. Again, once an individual is infected with the Hepatitis C virus, the virus will always be present. Therefore, the infected population, $I(t)$, will either have chronic Hepatitis C infections, $C(t)$, for the next couple of decades or they will be considered "cured" (virus is dormant) by a Sustained Viral Response (SVR) as described above. Thus, we have the following schematic (block) diagram and differential equations:

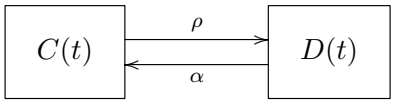

Figure 3.2: Schematic Diagram of Chronic and Dormant Hepititis C Infected Individuals

$$\frac{dC}{dt} = \alpha D - \rho C,$$
$$\frac{dD}{dt} = \rho C - \alpha D,$$

with $I(t) = D(t) + C(t)$ thus,

$$\frac{dI}{dt} = \frac{dD}{dt} + \frac{dC}{dt} = +\rho C - \alpha D + \alpha D - \rho C = 0,$$

so conservation is preserved and I is constant.

Therefore, substituting $I(t) = D(t) + C(t)$ into the equations gives us

$$\frac{dC}{dt} = \alpha(I - C) - \rho C, \qquad (1)$$

$$\frac{dD}{dt} = \rho(I - D) - \alpha D, \qquad (2)$$

$\frac{dC}{dt}$ and $\frac{dD}{dt}$ have dimensions of (number of people) / (time) and ρ and α have units of 1 / (time) ($days^{-1}$).

Defining $x^*(t)$ as the fraction of the number of infected in the Chronic stage and $y^*(t)$ as the fraction of the number of infected in the Dormant stage.

We define dimensionless variables

$$x^* = \frac{C}{I}, \quad y^* = \frac{D}{I}, \quad t^* = \frac{t}{\frac{1}{\rho}} = \rho t.$$

Since, $C(t) + D(t) = I =$ constant, it follows that $C/I + D/I = x^* + y^* = I/I = 1$.

Substituting, $C = x^*I$, $D = y^*I$, $t = t^*/\rho$ into (1) and (2) we have

$$\frac{d(x^*I)}{d(t^*/\rho)} = \alpha(I - x^*I) - \rho x^*I,$$

$$\frac{d(y^*I)}{d(t^*/\rho)} = \rho(I - y^*I) - \alpha y^*I.$$

Dividing both equations by I and ρ, we get

$$\frac{dx^*}{dt^*} = \frac{\alpha}{\rho}(1 - x^*) - x^*,$$

$$\frac{dy^*}{dt^*} = 1 - y^* - \frac{\alpha}{\rho}y^* = 1 - y^*(1 + \frac{\alpha}{\rho}).$$

Dropping the stars, we have

$$\frac{dx}{dt} = \frac{\alpha}{\rho}(1 - x) - x,$$

$$\frac{dy}{dt} = 1 - y(1 + \frac{\alpha}{\rho}).$$

Now, we will find the value of x at steady-state $dx/dt = 0$. Solving for x_{ss}, we obtain

$$\frac{dx}{dt} = \frac{\alpha}{\rho}(1 - x) - x = 0,$$

$$=> \quad \frac{\alpha}{\rho} - \frac{\alpha}{\rho}x - x = 0,$$

$$=> \quad \frac{\alpha}{\rho} - x(\frac{\alpha}{\rho} + 1) = 0,$$

$$=> \quad x = \frac{\frac{\alpha}{\rho}}{\frac{\alpha}{\rho} + 1} = \frac{\alpha}{\alpha + \rho},$$

$$=> \quad x_{ss} = \frac{\alpha}{\alpha + \rho}.$$

To convert back to unit-carrying variables, we multiply by I, so that $C = xI$, then

$$C = \frac{\alpha}{\alpha + \rho}I.$$

Thus, if $x = \alpha/(\alpha + \rho)$ is reached, the virus returns to an active state and the patient becomes chronic. Notice, this steady state is feasible only if $x > 0$ which means

that $\frac{\alpha}{\rho} > 0$. Therefore, $\frac{\alpha}{\rho}$ must be positive for the virus to progress to the chronic state. Figure 3.3 below shows the sketch of $\frac{d(x)}{d(t)} = \frac{\alpha}{\rho} - x(\frac{\alpha}{\rho} + 1) \equiv f(x)$. As seen, $f(x)$ is a straight line with arrows showing the direction of change of $x(t)$ from various initial values.

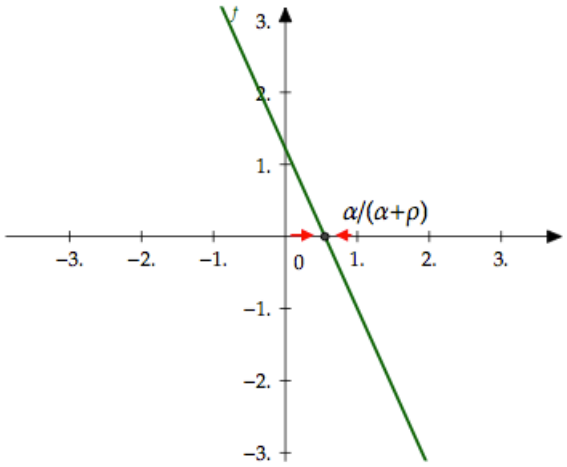

Figure 3.3: Sketch of $f(x)$ vs. x $\quad \alpha = .64, \rho = .36$.

The model simulations shown in Figure 3.4, 3.5, and 3.6 below are plots of $x(t)$ versus t for various initial conditions. The first and second simulations show the fraction of the infected population that are in the chronic stage of Hepatitis C before 2011 with and without the influence of diet and alcohol abstinence. In this case, the available medications consisted of only the combination of Pegylated Interfon Alpha and Ribavirin. As you can see, there is a significant decrease of chronic infected individuals when diet and alcohol abstinence are maintained. The third simulation shows the fraction of the infected population that are in the chronic stage of Hepatitis C currently. In this case, the available medications consist of a combination of Sofosbuvir with Ribavirin and Interfon. The values of α and ρ used in these three simulations were calculated from the percentage of infected individuals that will become chronic, the percentage of chronic infected individuals with Hepatitis C genotype 1 and 2, and the percentage of chronic infected individuals that respond to medication with and without proper diet and abstinence from alcohol. Therefore, Simulation 1, before 2011 and without diet and alcohol abstinence,

$\rho = .70(.80).45 + .20(.80).70 = .36$ and $\alpha = .64$. Simulation 2, before 2011 and with diet and alcohol abstinence, $\rho = .70(.80).50 + .20(.80).80 = .41$ and $\alpha = .59$. Simulation 3 after 2011 and without diet and alcohol abstinence, $\rho = .70(.80).90 + .20(.80).70 = .62$ and $\alpha = .38$. The difference between the first two fractions of infected individuals in Simulation 1 and Simulation 2 can be shown to fluctuate depending on the number of chronic infected individuals who follow the guidelines of diet and alcohol abstinence. Because of this, over the last decade, healthcare professionals and community planning groups are increasing the availability and amount of education programs given to chronic infected individuals on the importance of diet and alcohol abstinence. The difference between the two fractions of infected individuals in Simulation 1 and Simulation 3 is directly proportional to the advancement in medications available to Hepatitis C infected individuals. As you can see, the advanced treatment has greatly decreased the fraction of the population with known chronic Hepatitis C.

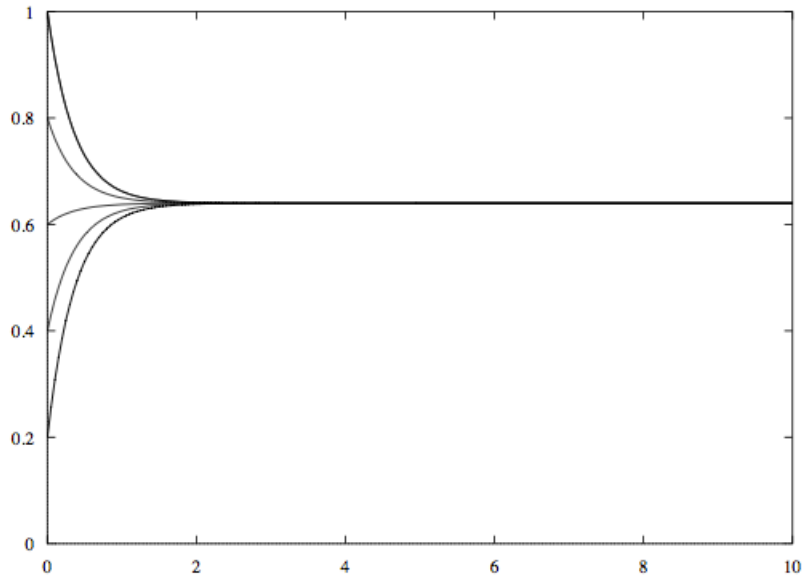

Figure 3.4: Simulation 1 (Infection rates prior to 2011 without Diet and AA) $\alpha = .64, \rho = .36$.

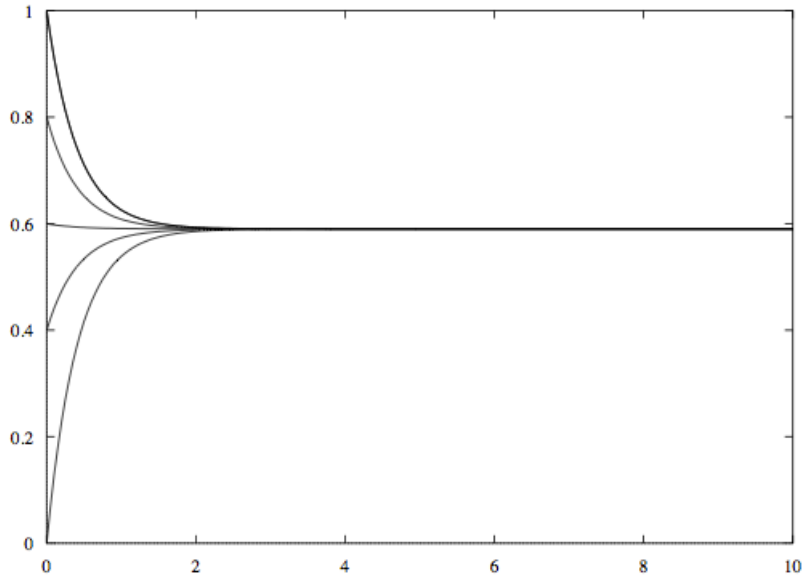

Figure 3.5: Simulation 2 (Infection rates prior to 2011 with Diet and AA) $\alpha = .59, \rho = .41$.

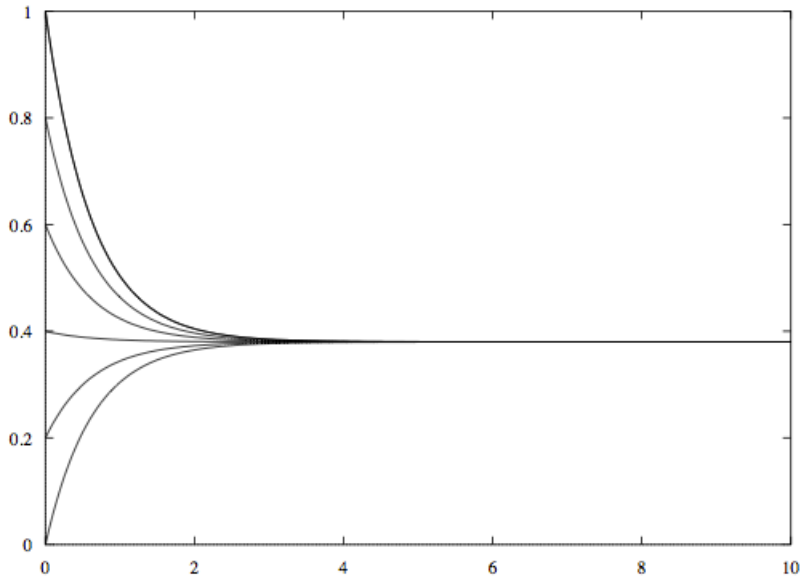

Figure 3.6: Simulation 3 (Infection rates after 2011 without Diet and AA) $\alpha = .38, \rho = .62$.

3.2.3 Future Studies-The Next Step

Remember, we kept the model and equations limited to a simple, single ordinary differential equation for the purpose of remaining within the boundaries of the material reviewed in this paper. The next step would be to apply one more variable to the model and increase the complexity to a system of two first-order differential equations. In doing so, we would use Phase Plan methods to study these systems, generally, written as:

$$\frac{dx}{dt} = f(x, y),$$
$$\frac{dy}{dt} = g(x, y).$$

To show an example of a system of two first-order differential equations, let us add a variable to the simple Hepatitis C schematic (block) diagram:

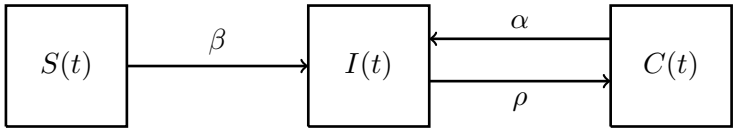

Figure 3.7: Schematic Diagram - Susceptible, Dormant, and Infected Hepitits C Individuals

Let $I(t)$ will represent the combination of $A(t)$ and $D(t)$, the total population of infected individuals that are not chronic. The differential equations for this model are:

$$\frac{dS}{dt} = -\beta SI - \beta SC,$$
$$\frac{dI}{dt} = \beta SI - \alpha I + \rho C + \beta SC,$$
$$\frac{dC}{dt} = \alpha I - \rho C.$$

Total population is conserved:

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dI}{dt} + \frac{dC}{dt} = -\beta SI - \beta SC + \beta SI - \alpha I + \rho C + \beta SC + \alpha I - \rho C = 0.$$

Therefore, N is constant and $S = N - I - C$. Substituting this equation for all S in the differential equations, we get:

$$\frac{dS}{dt} = -\beta(N - I - C)I - \beta(N - I - C)C,$$
$$\frac{dI}{dt} = \beta(N - I - C)I - \alpha I + \rho C + \beta(N - I - C)C,$$
$$\frac{dC}{dt} = \alpha I - \rho C.$$

which is a system of equations with two unknowns, namely, I and C.

From here, solutions to these differential equations are found by graphing an xy plane (phase plane) which shows all trajectories of the solutions through every point. Steady-states are then found by finding the intersection of the x and y nullcline curves of $\frac{dx}{dt} = 0$ and $\frac{dy}{dt} = 0$.

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