THESIS

SENSITIVITY ANALYSIS OF THE BASIC REPRODUCTION NUMBER AND OTHER QUANTITIES FOR INFECTIOUS DISEASE MODELS

Submitted by

Michael A. Mikucki

Department of Mathematics

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Master's Comittee:

Advisor: Simon Tavener

Patrick Shipman
Mike Antolin

ABSTRACT

SENSITIVITY ANALYSIS OF THE BASIC REPRODUCTION NUMBER AND OTHER QUANTITIES FOR INFECTIOUS DISEASE MODELS

Performing forward sensitivity analysis has been an integral component of mathematical modeling, yet its implementation becomes increasingly difficult with a model's complexity. For infectious disease models in particular, the sensitivity analysis of a parameter known as the basic reproduction number, or R_0, has dominated the attention of ecology modelers. While the biological definition of R_0 is well established, its mathematical construction is elusive. An index with a concrete mathematical definition that in many cases matches the biological interpretation of R_0 is presented. A software package called SENSAI that automatically computes this index and its sensitivity analysis is also presented. Other "quantities of interest" that provide similar information to R_0 can also be implemented in SENSAI and their sensitivities computed. Finally, some example models are presented and analyzed using SENSAI.

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Chapter 1

INTRODUCTION

Mathematical modeling has provided researchers with more knowledge about real world systems. Mathematical models are used in many disciplines including physics, chemistry, biology, engineering, economics, and computer science, among many others. Anything that changes can be modeled mathematically. These models provide better understanding to the physical components of the system and allow the researcher to make better predictions about the system's behavior.

Typically, deterministic models are performed in two ways. First, if the data are known at a discrete set of times, the model is structured as a map, or discrete-time dynamical system. Alternatively, if the data can be obtained or interpolated well over any time, the model is given by differential equations, or continuous-time dynamical system. Chapter 2 will develop the notation and provide examples of both discrete and continuous models.

A mathematical model does not provide much information until it is analyzed. Two popular methods of analysis are sensitivity and elasticity. Sensitivity analysis tells the researcher which parameters in the model have the most influence over a quantity of interest. Elasticity analysis is just a scaled version of this information based on the magnitudes of the parameters. Chapter 3 will define sensitivity and elasticity analysis for discrete and continuous systems.

For ecological models, another common analytical tool is the basic reproduction number, or just R_0. If the model concerns the progression of an infectious disease, R_0 is defined such that if the value is above a certain threshold, the disease will persist in a population, but if it is below that threshold, the disease will eventually be removed with no external manipulations. R_0 is defined as the number of secondary infections produced by a single infected

individual introduced in a wholly susceptible population. While this number has a well-defined biological meaning, its mathematical definition is ambiguous. Chapter 4 introduces R_0 and some of its drawbacks.

A consistent method of defining R_0 with a clear mathematical interpretation is presented in Chapter 5 for differential equation models and Chapter 6 for map models. Even still, this construction may not always represent the biological definition of R_0. This primary goal of this dissertation is to explore an alternative to R_0 that is equally informative, but unlike R_0, has a consistent and straightforward mathematical definition. It is hypothesized that this is achieved by using a software package called SENSAI, which computes the sensitivity and elasticity analysis over the entire course of discrete or continuous models. The features of the software are discussed in Chapter 7. Examples will be presented in Chapter 8 illustrating the effectiveness of the new methods as compared to the analysis using R_0 when R_0 is well-defined. Examples when R_0 fails either mathematically or biologically are also presented in Chapter 9. Finally, models with nice block structure will be examined under iterative techniques and evaluated in SENSAI in Chapter 10.

Chapter 2

DYNAMICAL MODELS

2.1 Discrete-time Models

Suppose the system to be modeled is such that the data are collected at a discrete set of times. A discrete-time dynamical model is appropriate for such a system. This is a very common structure for an ecological model. For example, a species may only reproduce a specific time of year, yielding a large growth in one season rather than steady growth through the year. Or, another species may be migratory, making it difficult to collect data when they are away. Yet another example is that a species may have different stages in their growth. While an individual may grow continuously, the only pertinent information may be whether or not that individual is considered a juvenile, young adult, adult, etc... In each of these examples, a discrete-time model is appropriate.

The following notation will be used for discrete models. Let $\mathbf{x}$ be the vector of the variables in consideration, $\mathbf{p}$ be the vector of parameters, and $\mathbf{z}$ be the initial conditions for the model. The basic iterative process considered is the map

$$\left.\begin{aligned} \mathbf{x}(t+1,\mathbf{p}) &= \mathbf{h}\big(\mathbf{x}(t,\mathbf{p}),\ \mathbf{p}\big) \\ \mathbf{x}(0) &= \mathbf{z} \end{aligned}\right\} \tag{2.1}$$

where the vector of variables $\mathbf{x} \in \mathbb{R}^{\mathrm{M}}$, the vector of parameters $\mathbf{p} \in \mathbb{R}^{\mathrm{K}}$, and the vector of initial conditions $\mathbf{z} \in \mathbb{R}^{\mathrm{M}}$.

Many systems converge to an equilibrium solution. Define an equilibrium solution $\mathbf{x}^{\star}(\mathbf{p})$ if the following is satisfied:

$$\mathbf{h}\big(\mathbf{x}^{\star}(\mathbf{p}),\ \mathbf{p}\big) = \mathbf{x}^{\star}(\mathbf{p}). \tag{2.2}$$

That is, if the map $\mathbf{h}$ is applied to a state in equilibrium $\mathbf{x}^\star$, no change occurs. Not all models converge to an equilibrium. A system may grow asymptotically in time, it may oscillate about two or more values, it may exhibit chaotic behavior, etc.

2.1.1 Hantavirus Model

Consider the following discrete model of hantavirus, a disease of wild rodents that is communicable to humans [1]. The model assumes that rodent survival is not affected by the infection, there is no vertical transmission of the infection, and that all rodents are reproductive as there are an equal number of male and female rodents. This model is a type of SI-model, where the S stands for susceptible and the I stands for infective. Both male and female rodents are modeled, resulting in four state variables, S_m, I_m, S_f, and I_f. The model is established by by progressively combining birth, infection, and growth functions. First, the harmonic mean birth function is defined as follows:

$$B(N_m, N_f) = \frac{2bN_mN_f}{N} \tag{2.3}$$

where $N_m = S_m + I_m$ is the total number of males, $N_f = S_f + I_f$ is the total number of females, $N = N_m + N_f$ is the total number of rodents, and $b > 0$ is the average litter size. The birth rate B varies with the population, an example of a common modeling procedure known as density dependence. If a parameter describing a rate is fixed, that parameter is density independent. Density dependence makes this model more realistic. The expected number of births should increase as the ratio of males to females approaches 1:1. Define the probability of infection via a Poisson probability distribution:

$$p(k) = \frac{e^{-\lambda}\lambda^k}{k!} \tag{2.4}$$

where k is the number of contacts that result in an infection and λ is the average number of contacts per susceptible in a time step. The probability that a rodent will become infectious

is $1-p(0)$, as at least one contact must be made for a susceptible rodent to become infective. From chemistry the law of mass action requires that the rate of change of the reaction is proportional to the product of the reactants. If this is applied to the average number of contacts by susceptible males to infected males or females, then $\lambda S_m = (\beta_m I_m + \beta_f I_f)S_m$, where β_m and β_f are the infection rate constants of males and females, respectively. Then, solving for λ and using (2.4) with $k = 0$ yields

$$p(0) = e^{-\beta_m I_m - \beta_f I_f}. \tag{2.5}$$

The probability of remaining noninfectious also exhibits density dependence, as $p(0)$ is a function of I. The infection rate will change based on the density of the population. The model assumes that $\beta_m \gg \beta_f > 0$ due to male aggressiveness. That is, contact from male to male is much greater than contact from female to either male or female. For susceptible females, the value of λ is different, resulting in

$$p(0) = e^{-\beta_f I_m - \beta_f I_f}. \tag{2.6}$$

Now introduce logistic growth to model by

$$D(N) = \frac{K}{K + (b/2)N}. \tag{2.7}$$

Let each term be scaled by this logistic factor. Logistic growth is another form of density dependence on survival. Now the model has density dependent birth, transmission, and

survival rates. The model equations are finally established as

$$\left.\begin{aligned} S_m(t+1) &= \left[\frac{B}{2} + e^{-\beta_m I_m(t) - \beta_f I_f(t)} S_m(t)\right] D(N) \\ I_m(t+1) &= \left[(1 - e^{-\beta_m I_m(t) - \beta_f I_f(t)}) S_m(t) + I_m(t)\right] D(N) \\ S_f(t+1) &= \left[\frac{B}{2} + e^{-\beta_f I_m(t) - \beta_f I_f(t)} S_f(t)\right] D(N) \\ I_f(t+1) &= \left[(1 - e^{-\beta_f I_m(t) - \beta_f I_f(t)}) S_f(t) + I_f(t)\right] D(N) \end{aligned}\right\} \tag{2.8}$$

An example solution, using the initial conditions $(S_m(0), I_m(0), S_f(0), I_f(0)) = (499, 1, 500, 0)$ which correspond to introducing one infected male in the population of susceptible individuals, is given in Figure 2.1. The measure of the time step is approximately the gestation period plus the time to sexual maturity, which is roughly two to three months. The solution is carried out to 10 time steps $\approx$ 2 years. The parameter values are given by Table 2.1. Notice that the equilibrium proportion of infected individuals is $\dfrac{I_m^\star + I_f^\star}{N^\star} = 25\%$.

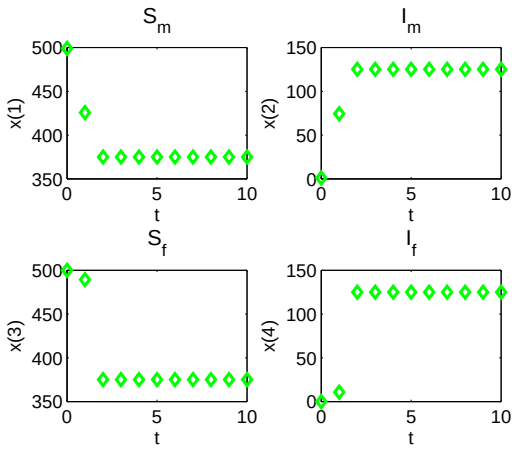


Figure 2.1: Hantavirus Model with Infection Introduced. The plot was created by the software package SENSAI, discussed in Chapter 7.

The model gives some insight to the course of the infection, but on its own, discloses little information of how to counteract the infection. What is the best strategy to reduce the infection in the population? Is there one that will eliminate the infection from the population? The answer to these questions will be pursued in Chapters 3 and 4.

Table 2.1: Parameter Values for Hantavirus Model, units of β_f and β_m are T^{-1}, where T is the time of gestation plus the time until sexual maturity, units of K and b are population.

Parameter	Numerical Value	Interpretation
K	1000	Carrying capacity
β_f	0.09	Infection rate for females
β_m	0.9	Infection rate for males
b	6	Average litter size

2.2 Continuous-time Models

Now consider continuous-time models in the form of ordinary differential equations (ODEs). The notation used for such models is as follows:

$$\left.\begin{aligned} \dot{\mathbf{x}}(t,\mathbf{p}) &= \mathbf{h}\big(\mathbf{x}(t,\mathbf{p}),\ \mathbf{p}\big) \\ \mathbf{x}(0) &= \mathbf{z} \end{aligned}\right\} \tag{2.9}$$

where the dot above the $\mathbf{x}$ represents differentiation with respect to time, $\mathbf{x} \in \mathbb{R}^{\mathrm{M}}, \mathbf{p} \in \mathbb{R}^{\mathrm{K}}$, and the initial conditions $\mathbf{z} \in \mathbb{R}^{\mathrm{M}}$.

Again, define an equilibrium solution $\mathbf{x}^\star(\mathbf{p})$ if

$$\mathbf{h}\big(\mathbf{x}^\star(\mathbf{p}),\ \mathbf{p}\big) = \mathbf{0}. \tag{2.10}$$

That is, the rate of change of a state in equilibrium is 0. This is a different definition than (2.2), but the principle that the solution is unchanging is the same. There are many other possible solutions to continuous time systems besides equilibrium solutions, the forms of which are well studied and can be found in any differential equations text.

2.2.1 Typhoid Model

Consider the following differential equations model of Typhoid fever [2]. This model has nine classes as follows:

$$\begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ x_5 \\ x_6 \\ x_7 \\ x_8 \\ x_9 \end{pmatrix} = \begin{pmatrix} \text{susceptibles} \\ \text{incubating noninfectious} \\ \text{incubating infectious} \\ \text{sick infectious} \\ \text{sick noninfectious} \\ \text{temporary carrier} \\ \text{permanent carrier} \\ \text{short resistance} \\ \text{long resistance} \end{pmatrix}$$

where each x_i is a population density. This model crudely follows the structure of an SIR-model, where S stands for susceptible individuals, I stands for infected individuals, and R stands for recovered individuals. Here, there are several classes that can be deemed "susceptible" and multiple others that are "infectious." Define $y = x_3 + x_4 + x_6 + x_7$ to be the density of all infectious individuals. The dynamics are modeled by the following equations.

$$
\left.
\begin{aligned}
\dot{x_1} &= -(\rho_{12}+\rho_{13})x_1 y + \rho_{41}x_4 + \rho_{51}x_5 + \rho_{61}x_6 + \rho_{81}x_8 + \rho_{91}x_9 - \mu x_1 + \mu \\
\dot{x_2} &= \rho_{12}x_1 y - (\rho_{23}+\rho_{24}+\rho_{25}+\mu)x_2 + \rho_{32}x_3 \\
\dot{x_3} &= \rho_{13}x_1 y - (\rho_{32}+\rho_{34}+\rho_{35}+\mu)x_3 + \rho_{23}x_2 \\
\dot{x_4} &= \rho_{24}x_2 + \rho_{34}x_3 + \rho_{54}x_5 - (\rho_{41}+\rho_{45}+\rho_{46}+\rho_{48}+\mu)x_4 \\
\dot{x_5} &= \rho_{25}x_2 + \rho_{35}x_3 + \rho_{45}x_4 - (\rho_{51}+\rho_{54}+\rho_{58}+\mu)x_5 \\
\dot{x_6} &= \rho_{46}x_4 - (\rho_{61}+\rho_{67}+\rho_{68}+\mu)x_6 \\
\dot{x_7} &= \rho_{67}x_6 - \mu x_7 \\
\dot{x_8} &= \rho_{48}x_4 + \rho_{58}x_5 + \rho_{68}x_6 - (\rho_{81}+\rho_{89}+\mu)x_8 \\
\dot{x_9} &= \rho_{89}x_8 - (\rho_{91}+\mu)x_9
\end{aligned}
\right\} \tag{2.11}
$$

The reader may wish to verify that $\sum_{i=1}^{9} \dot{x_i} = 1$ to see that the total population stays constant. Note that $\sum_{i=1}^{9} x_i = 1$ as the variables are population densities. The parameter values and interpretations are given by Table 2.2. Like most SI-models, the appearance of a new infection occurs in proportion to a contact with an infected individual. In its simplest form, a new infection will appear in the form $+\beta SI$, where β is the infection rate, and the product SI represents contact among a susceptible and an infected individual. In the typhoid model, an example of this is the first term of the second equation: $\rho_{12}x_1 y$. Here, the parameter ρ_{12} is an infection rate, and the product $x_1 y$ is contact between the susceptible individual and any of the infected classes. These new infections will appear in state x_2, and come from the states in x_1. Notice the corresponding term is subtracted from the first equation. Once constructed, the modeler may solve the system and plot the course of the infection in time. An example solution, using the initial conditions $(0.99, 0, 0.01, 0, 0, 0, 0, 0, 0)$ which correspond to introducing 1 incubating infectious individual in the population of total size $P = 100$, is given in Figure 2.2. The measure of the time step is in days; equilibrium is

reached in approximately 100,000 days $\approx$ 274 years. Notice that the equilibrium density of infected individuals is $y^\star = x_3^\star + x_4^\star + x_6^\star + x_7^\star = 14.7\%$.

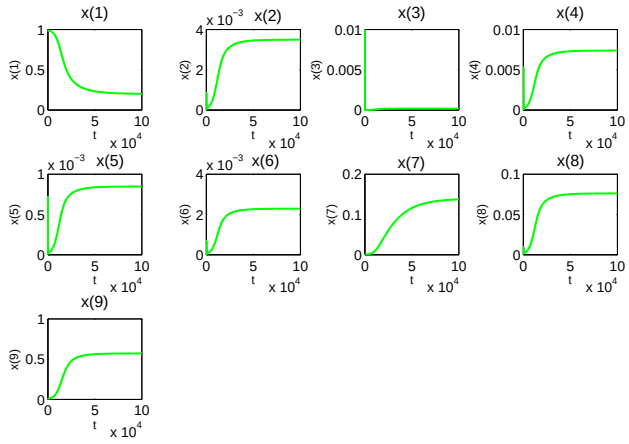


Figure 2.2: Typhoid Model with Infection Introduced. The plot was created by the software package SENSAI, discussed in Chapter 7.

Again, the model gives some insight to the course of the infection, but does not clearly describe how to control the infection.

Table 2.2: Parameter Values for Typhoid Model according to Bailey, all units are $days^{-1}$. Note that each ρ_{ij} is a transfer rate from state i to state j.

Parameter	Numerical Value	Interpretation
ρ_{12}	8.43381×10^{-3}	Infection rate
ρ_{13}	8.51900×10^{-5}	Infection rate
ρ_{23}	2.85720×10^{-3}	Transfer rate from state of incubation
ρ_{24}	6.78585×10^{-2}	Transfer rate from state of incubation
ρ_{25}	7.14300×10^{-4}	Transfer rate from state of incubation
ρ_{32}	7.14300×10^{-4}	Transfer rate from state of incubation
ρ_{34}	6.42870×10^{-2}	Transfer rate from state of incubation
ρ_{35}	6.42870×10^{-3}	Transfer rate from state of incubation
ρ_{41}	3.46000×10^{-3}	Transfer rate from state of sickness
ρ_{45}	3.46000×10^{-3}	Transfer rate from state of sickness
ρ_{46}	3.46000×10^{-3}	Transfer rate from state of sickness
ρ_{48}	2.40124×10^{-2}	Transfer rate from state of sickness
ρ_{51}	3.46000×10^{-3}	Transfer rate from state of sickness
ρ_{54}	6.92000×10^{-3}	Transfer rate from state of sickness
ρ_{58}	2.40124×10^{-2}	Transfer rate from state of sickness
ρ_{61}	1.11100×10^{-3}	Transfer rate from temporary carrier
ρ_{67}	3.33300×10^{-3}	Transfer rate from temporary carrier
ρ_{68}	6.66600×10^{-3}	Transfer rate from temporary carrier
ρ_{81}	2.74000×10^{-4}	Transfer rate from short resistance
ρ_{89}	2.46600×10^{-3}	Transfer rate from short resistance
ρ_{91}	2.74000×10^{-4}	Transfer rate from long resistance
μ	5.48000×10^{-5}	Overall birth and death rate

Chapter 3

SENSITIVITY AND ELASTICITY ANALYSIS

3.1 Sensitivity Analysis

Sensitivity analysis is extremely important for mathematical models. Sensitivity analysis studies the variation of the outputs of a model caused by variations in the inputs. In essence, sensitivity analysis determines which parameters and initial conditions (inputs) affect the quantities of interest (outputs) of the model the most. The first reason why this analysis is important is that it tells the researcher which parameters deserve the most numerical attention. A highly sensitive parameter should be carefully estimated as a small variation in that parameter will lead to large quantitative changes to the quantity of interest and may even produce qualitatively different results. Qualitative changes to a quantity of interest fall under the scope of bifurcation theory and will not be explored in great detail here. An insensitive parameter, on the other hand, does not require as much effort to estimate as a small variation in that parameter will not produce large changes to a quantity of interest. Many times in model analysis, the most sensitive parameters are also the most well established in the sense that the values do not change much from one time period to the next. If this is the case, the second reason for sensitivity analysis becomes more pronounced. That is, sensitivity analysis highlights which parameters should be attacked in management strategies. One goal of mathematical modeling is to determine what the current outcome of a system may be, and if necessary, discover how to change any negative outcomes. Changing the values of the most sensitive parameters will be the most effective strategy in changing the results of the model. The modeler will then implement any applicable real-world scenarios that will change the value of the most sensitive parameter to obtain the most control over the outcome.

The sensitivity is computed by finding the derivatives of each variable with respect to each parameter at any time t.

3.1.1 Sensitivity for Maps

First, write the model equations component-wise. For maps, the equivalent component-wise form of (2.1) is

$$\left.\begin{array}{ll} x_i(t+1,\mathbf{p}) & = h_i(\mathbf{x}(t,\mathbf{p}),\mathbf{p}) \\ x_i(0) & = z_i \end{array}\right\}, \quad i = 1,\ldots,\mathrm{M}. \tag{3.1}$$

Notice that the equation for state x_i may depend on any state from $\mathbf{x}$ and not just x_i. Define the sensitivity of the i^{th} solution variable with respect to the k^{th} parameter $S_{i,k}$ as

$$S_{i,k} = \frac{\partial x_i}{\partial p_k}. \tag{3.2}$$

The sensitivities of all variables with respect to all parameters is given by differentiating (3.1) with respect to the k^{th} parameter p_k,

$$\left.\begin{array}{ll} \dfrac{\partial x_i}{\partial p_k}(t+1) & = \left(\displaystyle\sum_{m=1}^{\mathrm{M}} \frac{\partial h_i}{\partial x_m}\,\frac{\partial x_m}{\partial p_k}(t)\right) + \frac{\partial h_i}{\partial p_k}(t) \\ \dfrac{\partial x_i}{\partial p_k}(0) & = 0 \end{array}\right\} \quad i = 1,\ldots\mathrm{M},\ k = 1,\ldots\mathrm{K}. \tag{3.3}$$

Similarly, the sensitivity of the i^{th} solution variable x_i with respect to the j^{th} initial condition z_j, is given by by differentiating (3.1) with respect to z_j,

$$\left.\begin{array}{ll} \dfrac{\partial x_i}{\partial z_j}(t+1) & = \left(\displaystyle\sum_{m=1}^{\mathrm{M}} \frac{\partial h_i}{\partial x_m}\,\frac{\partial x_m}{\partial z_j}(t)\right) + \frac{\partial h_i}{\partial z_j}(t) \\ \dfrac{\partial x_i}{\partial z_j}(0) & = \delta_{ij} \end{array}\right\} \ i = 1,\ldots,\mathrm{M},\ j = 1,\ldots\mathrm{M}. \tag{3.4}$$

where δ_{ij} is the Kronecker delta: $\delta_{ij} = 1$ if $i = j$ and 0 otherwise.

3.1.2 Sensitivity for ODEs

Sensitivities for ODE models is defined in a similar fashion. The equivalent component-wise form of (2.9) is

$$\left.\begin{aligned} \dot{x_i}(t,\mathbf{p}) &= h_i(\mathbf{x}(t,\mathbf{p}),\mathbf{p}) \\ x_i(0) &= z_i \end{aligned}\right\}, \quad i = 1,\ldots,\mathrm{M}. \tag{3.5}$$

Then the sensitivities for ODEs can be obtained by differentiating (3.5) with respect to the k^{th} parameter p_k, and then reversing the order of differentiation on the left-hand side.

$$\begin{aligned} \frac{\partial}{\partial p_k}(\dot{x_i}(t)) &= \left(\sum_{m=1}^{\mathrm{M}} \frac{\partial h_i}{\partial x_m}\frac{\partial x_m}{\partial p_k}(t)\right) + \frac{\partial h_i}{\partial p_k}(t) \qquad i = 1,\ldots,\mathrm{M},\ j = 1,\ldots\mathrm{M} \\ \frac{d}{dt}\left(\frac{\partial x_i}{\partial p_k}(t)\right) &= \left(\sum_{m=1}^{\mathrm{M}} \frac{\partial h_i}{\partial x_m}\frac{\partial x_m}{\partial p_k}(t)\right) + \frac{\partial h_i}{\partial p_k}(t) \qquad i = 1,\ldots,\mathrm{M},\ j = 1,\ldots\mathrm{M} \end{aligned}.$$

Using the notation in (3.2), the sensitivity equations are then

$$\left.\begin{aligned} \frac{dS_{i,k}}{dt}(t) &= \left(\sum_{m=1}^{\mathrm{M}} \frac{\partial h_i}{\partial x_m}\, S_{m,k}(t)\right) + \frac{\partial h_i}{\partial p_k}(t) \\ S_{i,k}(0) &= 0 \end{aligned}\right\} \quad i = 1,\ldots\mathrm{M},\ k = 1,\ldots\mathrm{K} \tag{3.6}$$

The sensitivity equations for ODE models are ODEs themselves. Once solved, the sensitivities can be known for all times t. Similarly, the sensitivity ODEs for initial conditions is given by by differentiating (3.5) with respect to z_j, and using the notation that $Y_{i,j} = \frac{\partial x_i}{\partial z_j}$,

$$\left.\begin{aligned} \frac{dY_{i,j}}{dt}(t) &= \left(\sum_{m=1}^{\mathrm{M}} \frac{\partial h_i}{\partial x_m}\, Y_{m,j}(t)\right) + \frac{\partial h_i}{\partial z_j}(t) \\ Y_{i,j}(0) &= \delta_{ij} \end{aligned}\right\} \; i = 1,\ldots,\mathrm{M},\ j = 1,\ldots\mathrm{M}. \tag{3.7}$$

where δ_{ij} is the Kronecker delta.

3.2 Elasticity Analysis

Another equally important analytical tool is elasticity analysis. This is just a scaled version of sensitivity analysis. Elasticity analysis is useful when the sensitivity of a certain parameter is extremal only due to the relative magnitude of that parameter to other parameters. For example, suppose a model has three parameters with values $p_1 = 10$, $p_2 = 7$, and $p_3 = 0.001$. Also suppose an equilibrium solution of the model is $x^\star = \frac{p_1 p_2}{p_3} = 70000$. Then, the sensitivity of the equilibrium with respect to p_3 is $\frac{d}{dp_3}(\frac{p_1 p_2}{p_3}) = -\frac{p_1 p_2}{p_3^2} = -7 \times 10^7$. The sensitivity with respect to p_2 is $\frac{d}{dp_2}(\frac{p_1 p_2}{p_3}) = \frac{p_1}{p_3} = 10^4$, a difference of four orders of magnitude. The sensitivity of p_3 is extremely high compared to that of p_1 and p_2 simply because of the scale of p_3. A relative change in parameters will show the sensitivity analysis may be misleading in this example. If p_2 is decreased by ten percent to 6.3, the new equilibrium will be $x^\star = 63000$. But, if the seemingly more sensitive parameter p_3 is increased by ten percent to 0.0011, then the new equilibrium will be $x^\star = 63636$. Notice that the sensitivities of $x^\star$ to p_2 and p_3 are opposite in sign, so a reduction in one parameter should be compared to an increase in the other parameter. While it is true that p_3 proved to be more sensitive, the magnitude of the sensitivity is misleading. Even though p_3 has a sensitivity that is 7000 times greater in magnitude than that of p_2, attacking p_3 instead of p_2 changed the equilibrium similarly. To reduce this effect, consider a scaling of $S_{i,k}$ by the sizes of the parameters. Let

$$\Delta\xi = \frac{\Delta x}{x} \quad \text{and} \quad \Delta\kappa = \frac{\Delta p}{p}$$

be the relative changes of x and p respectively. The relative sensitivity of x with respect to p is defined by the limit of the relative change in x as the relative change in p approaches zero, which is the derivative

$$\frac{\partial \xi}{\partial \kappa} = \lim_{\Delta\kappa \to 0} \frac{\Delta\xi}{\Delta\kappa} = \frac{p}{x} \lim_{\Delta p \to 0} \frac{\Delta x}{\Delta p} = \frac{p}{x} \frac{\partial x}{\partial p}.$$

Define the elasticity of the i^{th} variable with respect to the k^{th} parameter, $E_{i,k}$ as

$$E_{i,k}(t) = \frac{p_k(t)}{x_i(t)} \frac{\partial x_i}{\partial p_k}(t). \tag{3.8}$$

Elasticities with respect to initial conditions are defined in a similar fashion.

Recall the example of the three parameters and compute the elasticities. The elasticity of the equilibrium solution with respect to p_3 is -1, and the elasticity of the equilibrium solution with respect to p_2 is 1. This result is more intuitive as the equilibrium is simply a quotient of the parameters. The negative sign indicates that an increase in this parameter will produce a decrease in the value, as expected.

Chapter 4

THE BASIC REPRODUCTION NUMBER

This chapter discusses another analytical tool for ecological models known as R_0. This number, called the basic reproduction number (or rate, or ratio), has been widely used in infection models and is defined as the average number of secondary cases arising from a single primary case in a very large population of susceptibles [3]. It is primarily used as a threshold parameter: if $R_0 < 1$, the disease will fade out of the population, but if $R_0 > 1$, the disease will persist and become endemic to the population. Furthermore, the larger the magnitude of R_0, the faster the disease will spread, and presumably the more difficult it will be to control. While R_0 is a great concept of biology and has been widely used since its first application in 1952 by George MacDonald [12], the mathematical definition of R_0 is problematic and in some cases ambiguous.

4.1 Methods of Calculating R_0

There are several different methods in which R_0 can be calculated. Some common methods of constructing R_0 are the survival function method, the Next Generation method, existence of an endemic equilibrium, final size equation, constant term of the characteristic polynomial, etc. Many of them yield different values of R_0 for the same model, and many methods produce different values of R_0 based on what the modeler considers to be appropriate. Each method derives its conditions from the threshold nature of R_0, yet many of these methods produce a value that is not consistent with the biological definition.

It is important to understand that employing one of the methods at random does not guarantee the calculation represents the number of secondary infections arising from a single infected individual. Many methods produce different values for R_0 even in the same system.

How can two different values simultaneously represent the number of secondary infections from a single infected individual? If more than the threshold capability of R_0 is of concern, careful consideration should be taken when using a method to calculate R_0.

4.2 The Next Generation Method

Perhaps the most common method of calculating R_0 is the Next Generation method. This approach places appropriate terms from the infected class equations into the vectors $\mathcal{F}$ and $\mathcal{V}$. Terms that describe appearances of new infections belong in $\mathcal{F}$, and terms that describe a transfer of existing infections belong in $\mathcal{V}$ and should be negated. The Jacobian matrices obtained by differentiating $\mathcal{F}$ and $\mathcal{V}$ with respect to the relevant subset of variables are computed and evaluated at a nontrivial disease-free equilibrium (DFE), resulting in the matrices F and V, respectively. The *Next Generation Matrix* for ODEs is defined as FV^{-1}. Finally, $R_0 = \rho(FV^{-1})$, where $\rho(\cdot)$ is the spectral radius operator. The (i, j) entry of this matrix is the expected number of new infections currently in state x_i that originated from state x_j [15]. The *Next Generation Matrix* for maps is defined similarly as $F(I-T)^{-1}$, where $T = -V$. This is quite suitable to the biological definition of R_0 and works in many, but not all, examples.

Because of its mathematical foundation, developed in Chapter 5 for ODEs and Chapter 6 for maps, this method of calculating R_0 will be chosen for implementation into SENSAI (see Chapter 7). While it has its drawbacks, it is perhaps the most common method for R_0, and it has a definitive mathematical interpretation so that the user may know exactly what this index represents.

4.3 R_0 Failures

Most biologists will claim that there is only one value of R_0 for any model. While that may be true, there are many indices that exhibit the same threshold behavior. The Next Generation method only guarantees that R_0 maintains the threshold nature, but does not

guarantee that it accurately describes the number of secondary infections. Suppose the Next Generation $R_0 = 2$. Because $R_0 > 1$, it is guaranteed that infection will persist in the population, but it is not guaranteed that one infected individual will produce two secondary infections; it may be three, or 1000, or $1 + \epsilon$. Similarly, if the index is $R_0 = 0.5$, it is guaranteed that the infection will die out, but it is not necessarily true that one infected individual will produce an average of 0.5 secondary infections. Checking to see if the "R_0" in question exhibits the threshold behavior is not a exhaustive assessment for determining the validity of R_0. It is easy to construct a model with two indices that exhibit the same threshold, one of which has nothing to do with the average number of secondary cases arising from a single primary case. While both indices are endowed with a threshold nature, they can not both simultaneously represent the number of secondary infections from a single infected individual. This point is illustrated in Section 9.1 by two models that have the exact same solution trajectories but different values of R_0. Each model's R_0 is a threshold for the other, though each R_0 is not epidemiologically correct for both models.

Furthering the difficulties of R_0, there is an entire class of models that is not compatible with the Next Generation construction. Some examples of this model type where the Next Generation R_0 is not valid are presented in Section 9.2. The examples are current and relevant research, and the assumptions made which invalidate the Next Generation R_0 are appropriate.

Finally, an example is presented in Section 9.3 where the Next Generation R_0 seems to fail the threshold criterion, even though it passes the conditions to the mathematical theorems. If a finite amplitude disturbance is introduced in the population rather than a single infected individual, R_0 may be less than one with the persistence of the disease in the population. The theorem on R_0 only ensures the persistence of infection under small disturbances of $\epsilon > 0$ and does not provide any information on finite amplitude disturbances, even though an increase of one infected individual is itself a finite amplitude disturbance.

It does not make biological sense to introduce $\epsilon > 0$ infected individuals to the population, though this is actually what is proved for the Next Generation R_0.

Chapter 5

MATHEMATICAL FOUNDATIONS FOR R_0 IN ODES

The goal of this chapter is to provide a mathematical foundation for the quantity R_0. A series of theorems will show that if a vector $\mathbf{x}^\star$ is a disease-free equilibrium, it is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$, where R_0 is the spectral radius of the Next Generation Matrix, $R_0 = \rho(FV^{-1})$ [15].

5.1 Definitions

The following definitions will be used in proving the main theorem for R_0.

Definition. The spectral radius of an $n \times n$ matrix A with eigenvalues $\lambda_i,\ i = 1, \ldots, n$, is the maximum modulus of any eigenvalue λ_i, $\rho(A) = \max_{1 \le i \le n} (|\lambda_i|)$.

Definition. A matrix (or vector) A is nonnegative, written $A \geq 0$, if each element of A is nonnegative. The notation $A > 0$ will be used if every element of A is strictly positive.

Definition. A nonnegative matrix A is irreducible if it is not the 1×1 zero matrix and it can not be expressed as $PAP^{-1} = \begin{pmatrix} A_{11} & A_{12} \\ 0 & A_{22} \end{pmatrix}$, where A_{11} and A_{22} are nontrivial square block matrices and P is a permutation matrix.

Definition. If A is an $n \times n$ matrix such that $a_{ij} \leq 0$ for all $i \neq j$, then A has the Z-sign pattern.

Definition. If A is an $n \times n$ matrix such that $A = sI - B$ where $s > 0$, I is the $n \times n$ identity matrix, $B \geq 0$ entry-wise, and $s \geq \rho(B)$, then A is an M-matrix. Further, if $s > \rho(B)$, then A is a nonsingular M-matrix. If $s = \rho(B)$, then A is a singular M-matrix.

Immediately, one will notice that the representation of $A = sI - B$ with $B \geq 0$ is the Z-sign pattern. The only added stipulations for being an M-matrix are that $s > 0$ and $s \geq \rho(B)$.

5.2 The Perron-Frobenius Theorem

The Perron-Frobenius Theorem will be used in the theorem defining R_0 for both discrete and continuous systems. This theorem is well known and can be found in many texts, such as [4], [8], and [10].

Theorem 5.2.1. *Perron-Frobenius Theorem. Let P be an irreducible, nonnegative matrix. Then*

(a) The spectral radius of P is positive and an algebraically simple eigenvalue of P with corresponding unique left and right positive eigenvectors.

(b) The spectral radius of P is the unique eigenvalue with a (left and right) positive eigenvector. Furthermore, there are no other positive eigenvectors of P except the one associated with the spectral radius.

(c) If any entry of P increases, the spectral radius also strictly increases. If any entry of P decreases, the spectral radius also strictly decreases.

Proof of the theorem may be found in [8], Theorem 8.4.4.

5.3 Equivalent Conditions for an M-matrix

There are several (over 50) equivalent definitions for an M-matrix. The following will be useful for proving the stability condition of R_0. The first lemma is not an equivalent condition, but will be used to prove Lemma 5.3.2 which is an equivalent condition for an M-matrix. This can be found as Lemma 2.1 of [4].

Lemma 5.3.1. *For a nonnegative matrix T, $\rho(T) < 1 \iff (I - T)^{-1}$ exists and is nonnegative.*

Proof. The proof follows the arguments in [4].

($\Rightarrow$) Let $\rho(T) < 1$.

Consider the telescoping series $(I - T)(I + T + T^2 + ... + T^k) = I - T^{k+1}$. As $k \to \infty$,

$$\lim_{k\to\infty}(I - T)(I + T + T^2 + ... + T^k) = \lim_{k\to\infty}(I - T^{k+1}) \tag{5.1}$$

Since $\rho(T) < 1$, $T^{k+1} \to 0$ as $k \to \infty$, so the right-hand side of (5.1) is I. Then,

$$(I - T)\lim_{k\to\infty}(I + T + T^2 + ... + T^k) = I. \tag{5.2}$$

By (5.2), the series $\sum_{i=0}^{\infty} T^i$ inverts $(I - T)$. Since T is nonnegative, $(I - T)^{-1} \geq 0$.

($\Leftarrow$) Suppose $(I - T)^{-1}$ exists and is nonnegative.

By Theorem 5.2.1, $Tx = \rho(T)x$ for some $x > 0$. Then,

$$x - Tx = x - \rho(T)x$$

$$(I - T)x = (1 - \rho(T))x$$

That is, $1 - \rho(T)$ is an eigenvalue of $I - T$. Since the eigenvalues of the inverse of a matrix are the inverse of the eigenvalues,

$$(I - T)^{-1}x = \frac{1}{1 - \rho(T)}x \tag{5.3}$$

Notice that $\rho(T) \neq 1$, as $(I - T)^{-1}$ exists, so (5.3) is well-defined. If $\rho(T) > 1$, then the quantity $\dfrac{1}{1 - \rho(T)} < 0$. Since $x > 0$, the right hand side of (5.3) is negative. But, since the product of a nonnegative matrix $(I-T)^{-1}$ with a nonnegative vector x is always nonnegative, the right hand side of (5.3) is nonnegative. This is a contradiction. Therefore, $\rho(T) < 1$.

■

The first equivalent condition presented is that nonsingular M-matrices are inverse positive. This may be found as Theorem 2.3 N_{38} of [4].

Lemma 5.3.2. *A is a nonsingular M-matrix $\iff$ A has the Z-sign pattern and $A^{-1} \geq 0$.*

Proof. The proof follows the ideas in [4]. By Lemma 5.3.1,

$$\rho(T) < 1 \iff (I - T)^{-1} \geq 0 \tag{5.4}$$

Define $T = B/s$ with $s > 0$. Then (5.4) becomes

$$\rho(B/s) < 1 \iff (I - B/s)^{-1} \geq 0$$
$$\rho(B) < s \iff (I - B/s)^{-1} \geq 0$$

Multiplying the right-hand side by $s^{-1} > 0$ gives

$$\rho(B) < s \iff (sI - B)^{-1} \geq 0$$

Since A has the Z-sign pattern, define $A = sI - B$. Then

$$\rho(B) < s \iff A^{-1} \geq 0$$

That $A = sI - B$ with $\rho(B) < s$ is exactly the statement that A is a nonsingular M-matrix. This proves the lemma.

■

The next condition states that nonsingular M-matrices are positive stable. This is the key property in the proof of the main theorem on R_0, which concerns the stability of a disease-free equilibrium. Furthermore, some references, such as [9], use this condition as the definition of an M-matrix. The lemma is also found as Theorem 2.3 G_{20} of [4]. In the proof, the notation λ_X means λ is an eigenvalue for the matrix X. The set $\{\lambda_X\}$ is the set of all eigenvalues of X.

Lemma 5.3.3. *A is a nonsingular M-matrix $\iff$ A has the Z-sign pattern and is positive stable (that is, the real part of each eigenvalue of A is positive).*

Proof. First, notice that for any matrices A and B, if A and B commute, $\{\lambda_{A+B}\} \subseteq \{\lambda_A + \lambda_B\}$.

Let $\alpha_1, \alpha_2, ..., \alpha_n$ be eigenvalues of A and $\beta_1, \beta_2, ..., \beta_n$ be eigenvalues of B. If A and B commute, they may be simultaneously upper-triangularized according to Theorem 2.3.3 of [8], that is, there is a unitary U such that $U^*AU = T$ and $U^*BU = R$ are both upper triangular with diagonal entries $\alpha_1, ..., \alpha_n$ and $\beta_{i_1}, ..., \beta_{i_n}$, respectively. Then $U^*(A+B)U = T+R$ has diagonal entries and therefore has eigenvalues $\alpha_1 + \beta_{i_1}, ..., \alpha_n + \beta_{i_n}$. These must also be the eigenvalues of $A + B$ since $A + B$ is similar to $T + R$.

($\Rightarrow$) Suppose A is a nonsingular M-matrix, $A = sI - B$.
The eigenvalues $\{\lambda_A\} = \{\lambda_{sI-B}\} \subseteq \{\lambda_{sI} + \lambda_{-B}\} = \{s - \lambda_B\}$ since I and $-B$ commute. That is, any eigenvalue of A can be written as $\lambda_A = s - \lambda_B$. Then,

$$
\begin{aligned}
Re(\lambda_A) &= Re(s - \lambda_B) \\
&= s - Re(\lambda_B) && \text{since } s > 0 \\
&> \rho(B) - \lambda_B && \text{since } s > \rho(B) \\
&\geq 0 && \text{since } \rho(B) \geq \lambda_B \text{ for any eigenvalue of } B
\end{aligned}
$$

Therefore, $Re(\lambda_A) > 0$.

($\Leftarrow$) Let A have the Z-sign pattern and be positive stable.
Since A has the Z-sign pattern, $A = sI - B$ for $B \geq 0$ and $s > 0$. Let λ_B be the an eigenvalue of B. Then,

$$
\begin{aligned}
Bx &= \lambda_B x \\
sx - Bx &= sx - \lambda_B x \\
(sI - B)x &= (s - \lambda_B)x \\
Ax &= (s - \lambda_B)x
\end{aligned}
$$

This final equality states that $s - \lambda_B$ is an eigenvalue of A. Since A is positive stable, $Re(s - \lambda_B) > 0$. Then,

$$
0 < Re(s - \lambda_B) = s - Re(\lambda_B) \leq s - \rho(B)
$$

That is, $s > \rho(B)$, which proves A is an M-matrix.

■

A similar condition may be established for any (singular or nonsingular) M-matrix. This condition is Theorem 4.6 E_{11} of [4].

Lemma 5.3.4. *A is an M-matrix $\iff$ A has the Z-sign pattern and the real part of every nonzero eigenvalue of A is positive.*

Proof. The proof follows the same procedure as the proof of Lemma 5.3.3 with $s \geq \rho(B)$ instead of $s > \rho(B)$ in the appropriate places.

■

The next equivalent condition is that nonsingular M-matrices are semi-positive. This can be found as Theorem 2.3 I_{27} of [4] or Theorem 2.5.3.12 of [9]. Recall the notation $x > 0$ means every entry of the x is strictly positive.

Lemma 5.3.5. *A is a nonsingular M-matrix $\iff$ A has the Z-sign pattern and $\exists x > 0$ such that $Ax > 0$.*

Proof. The proof follows the procedure in [9]. Since A has the Z-sign pattern, write $A = sI - B$ with $s > 0$, $B \geq 0$. First assume that B is irreducible. Then by Theorem 5.2.1(b), $x > 0$ be the Perron-Frobenius right eigenvector of B. Then,

$$Ax = sx - Bx = sx - \rho(B)x = (s - \rho(B))x \tag{5.5}$$

Notice that since $x > 0$,

$$\begin{aligned} A \text{ is a nonsingular M-matrix} &\iff s > \rho(B) && \text{by definition} \\ &\iff Ax = (s - \rho(B))x > 0 && \text{by (5.5)} \end{aligned}$$

This proves the lemma for the case that B is irreducible. If B is reducible, force it to be irreducible by placing sufficiently small $\epsilon > 0$ in the zeros of B. Now, apply Theorem 5.2.1(b) and let $x > 0$ be the Perron-Frobenius right eigenvector of $\tilde{B}$. Following the above procedure, $\tilde{A}$ is an M-matrix $\iff$ $s > \rho(B)$ $\iff$ $\tilde{A}x = (s - \rho(\tilde{B}))x > 0$. Since Ax is sufficiently close to $\tilde{A}x = (s - \rho(B))x > 0$, $Ax > 0$.

■

5.4 Further M-matrix Properties

A common technique to establishing a condition when matrices are singular is to apply a continuity argument, similar to the one in the proof of Lemma 5.3.5. First establish the desired condition for a nonsingular matrix A. Then, replace the singular matrix A by the nonsingular $A + \epsilon I$. Finally, use the continuity of a function in ϵ to obtain the condition for the singular matrix A. This outline and some examples are presented in [16]. The same idea can be applied for M-matrices and will be useful later on. Consider the following continuity condition for an M-matrix which is found in [4] as Lemma 4.1.

Lemma 5.4.1. *Let A have the Z-sign pattern. Then A is an M-matrix $\iff$ $A + \epsilon I$ is a nonsingular M-matrix for all $\epsilon > 0$.*

Proof. ($\Rightarrow$) Let A be an M-matrix. Then $A = sI - B$ with $s > 0$, $B \geq 0$, and $s \geq \rho(B)$. For any $\epsilon > 0$,

$$A + \epsilon I = sI - B + \epsilon I = (s + \epsilon)I - B = \tilde{s}I - B \tag{5.6}$$

Since $\tilde{s} = s + \epsilon > s > \rho(B)$, so $A + \epsilon I$ is a nonsingular M-matrix.

($\Leftarrow$) Let $A + \epsilon I$ be a nonsingular M-matrix.

Then from (5.6), $A + \epsilon I = (s + \epsilon)I - B$ with $s + \epsilon > \rho(B)$. In the limit as $\epsilon \to 0$, $A = sI - B$ with $s \geq \rho(B)$. That is, A is an M-matrix.

■

There are many other interesting properties of M-matrices that can be found in [4] and [9], among other sources. Two more will be useful for defining R_0. The first property will be used to prove the second, which in turn will be used directly in the main theorem. Many of the equivalent conditions from Section 5.3 will be used in the proofs. Lemma 5.4.2 here is found as Lemma 5 of [15].

Lemma 5.4.2. *Let H be a nonsingular M-matrix and suppose B and BH^{-1} have the Z-sign pattern. Then B is a nonsingular M-matrix $\iff$ BH^{-1} is a nonsingular M-matrix.*

Proof. ($\Rightarrow$) This problem is equivalent to one in a slightly different form. Using $F = B^{-1}$ and $G = H^{-1}$, the following will be established: If F and G are nonsingular M-matrices and $F^{-1}G$ has the Z-sign pattern, then FG^{-1} is a nonsingular M-matrix. This claim is exactly the forward implication of the Lemma.

By the equivalent condition Lemma 5.3.5, since G is a nonsingular M-matrix, $\exists x > 0$ such that $Gx > 0$. Consider $F^{-1}Gx$. Define $y = Gx > 0$ by the selection of x.

$$F^{-1}Gx = F^{-1}y \quad \text{where } y > 0$$

By Lemma 5.3.2, since F is a nonsingular M-matrix, $F^{-1} \geq 0$. Then,

$$F^{-1}y \geq 0.$$

The only way $F^{-1}y = 0$ is if F^{-1} has a row or column of zeros, as $y > 0$. But since F^{-1} is nonsingular, this can not happen. Therefore, $F^{-1}y > 0$. That is, $\exists x > 0$ such that $F^{-1}Gx > 0$. By Lemma 5.3.5, $F^{-1}G$ is a nonsingular M-matrix.

($\Leftarrow$) This problem is also equivalent to one in a slightly different form. With $P = BH^{-1}$ and $Q = H$, it will be shown that if P and Q are nonsingular M-matrices and $PQ = B$ has the Z-sign pattern, then $PQ = B$ is a nonsingular M-matrix.

By Lemma 5.3.2, $P^{-1} \geq 0$ and $Q^{-1} \geq 0$. So the product $Q^{-1}P^{-1} \geq 0$. But this product is exactly $(PQ)^{-1}$, so by Lemma 5.3.2 again, $PQ = B$ is a nonsingular M-matrix.

■

The following lemma is used directly in the proof of the main theorem and is found as Lemma 6 of [15].

Lemma 5.4.3. *Let H be a nonsingular M-matrix and suppose $K \geq 0$. Then,*

(a) $(H - K)$ is a nonsingular M-matrix $\iff$ $(H - K)H^{-1}$ is a nonsingular M-matrix

(b) $(H - K)$ is a singular M-matrix $\iff$ $(H - K)H^{-1}$ is a singular M-matrix

Proof. (a) Let $B = H - K$

Consider $B_{i,j}$ for $i \neq j$. $B_{i,j} = H_{i,j} - K_{i,j}$, $H_{i,j} \leq 0$ since H is an M-matrix, and $K_{i,j} \geq 0$ by hypothesis, so $H_{i,j} - K_{i,j} \leq 0$. That is, B has the Z sign pattern.

Similarly, $(BH^{-1})_{i,j} = ((H-K)H^{-1})_{i,j} = (I - KH^{-1})_{i,j}$. By Lemma 5.3.2, $H^{-1} \geq 0$. By hypothesis, $K \geq 0$. So $(I - KH^{-1})_{i,j} \leq 0$ for $i \neq j$. That is, BH^{-1} have the Z sign pattern.

Statement (a) is now a direct application of Lemma 5.4.2.

(b) By the contrapositive of (a), $H - K$ is not a nonsingular M-matrix if and only if $(H-K)H^{-1}$ is not a nonsingular M-matrix. It will be shown that if the M-matrix condition of (a) is kept but the nonsingular condition of (a) is removed, the M-matrix condition still remains true. Notice that

$$\begin{aligned} H - K \text{ is a singular M-matrix} &\iff H - K + \epsilon I \text{ is a nonsingular M-matrix } \forall \epsilon > 0 \\ &\iff (H - K + \epsilon I)H^{-1} \text{ is a nonsingular M-matrix} \\ &\iff (H-K)H^{-1} \text{ is a singular M-matrix} \end{aligned}$$

The first and third statements are due to the continuity argument of Lemma 5.4.1, and the second statement comes from (a). This finishes the proof.

■

5.5 Assumptions

Assume the following hypothesis on an ordinary differential equations model, as in [15]. Suppose the model has the form

$$\dot{x_i} = h_i(\mathbf{x}) = \mathcal{F}_i(\mathbf{x}) - \mathcal{V}_i(\mathbf{x}), \qquad i = 1, ..., \mathrm{M}$$

where $\mathcal{V}_i = \mathcal{V}_i^+ - \mathcal{V}_i^-$. Let the first m components of $\mathbf{x}$ be the disease states. Define the disease-free subspace as

$$\mathbf{X}_s = \{\mathbf{x} \geq 0 | x_i = 0, i = 1, ..., m\}.$$

Then, if an equilibrium $\mathbf{x}^\star \in \mathbf{X}_s$, $\mathbf{x}^\star$ is called a disease-free equilibrium (DFE). Alternatively, if an equilibrium $\mathbf{x}^\star \notin \mathbf{X}_s$, such that at least one of the first m components is nonzero, $\mathbf{x}^\star$ is called an endemic equilibrium (EE). That is, the infection is endemic to the population. First, assume each function is nonnegative:

$$\text{If } \mathbf{x} \geq 0, \text{ then } \mathcal{F}_i(\mathbf{x}),\ \mathcal{V}_i^+(\mathbf{x}),\ \mathcal{V}_i^-(\mathbf{x}) \geq 0 \text{ for } i = 1, ..., \mathrm{M} \tag{A1}$$

Second, if a state is empty, no transfer of individuals can come from that state by death or infection,

$$\text{If } x_i = 0, \text{ then } \mathcal{V}_i^-(\mathbf{x}) = 0. \text{ Moreover, if } \mathbf{x} \in \mathbf{X}_s, \text{ then } \mathcal{V}_i^-(\mathbf{x}) = 0 \text{ for } i = 1, ..., \mathrm{M}. \tag{A2}$$

Third, assume the incidence of infection for uninfected states is zero:

$$\mathcal{F}_i(\mathbf{x}) = 0 \text{ if } i > m \tag{A3}$$

Fourth, if the population is free of the disease, it will remain free of the disease:

$$\text{If } \mathbf{x} \in \mathbf{X}_s, \text{ then } \mathcal{F}_i(\mathbf{x}) = 0 \text{ and } \mathcal{V}_i^+(\mathbf{x}) = 0 \text{ for } i = 1, ..., m \tag{A4}$$

Finally, any disease-free equilibrium $\mathbf{x}^\star$ must be stable in the absence of new infection, so

$$\text{If } \mathcal{F}(\mathbf{x}^\star) = 0, \text{ then all eigenvalues of } Dh(\mathbf{x}^\star) \text{ have negative real parts} \tag{A5}$$

Based on these assumptions, the linearized structure of (2.9) may be partitioned according to the following lemma. This can be found as Lemma 1 of [15].

Lemma 5.5.1. *If $\boldsymbol{x}^\star$ is a disease-free equilibrium and $h_i(\boldsymbol{x})$ satisfies* (A1) *through* (A5)*, then the derivatives $D\mathcal{F}(\boldsymbol{x}^\star)$ and $D\mathcal{V}(\boldsymbol{x}^\star)$ are partitioned as*

$$D\mathcal{F}(\boldsymbol{x}^\star) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, \quad D\mathcal{V}(\boldsymbol{x}^\star) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix}$$

where F and V are the $m \times m$ matrices defined by

$$F = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}(\boldsymbol{x}^\star)\right], \quad V = \left[\frac{\partial \mathcal{V}_i}{\partial x_j}(\boldsymbol{x}^\star)\right] \quad 1 \le i, j \le m$$

Further, F is nonnegative, V is a nonsingular M-matrix and all eigenvalues of J_4 have positive real part.

Proof. Let $\mathbf{x}^\star \in \mathbf{X}_S$, that is

$$\mathbf{x}^\star = [0, \ldots, 0, x_{m+1}, \ldots, x_{\mathrm{M}}]^T$$

By (A3), $\mathcal{F}_i(\mathbf{x}^\star) = 0$ for $i > m$. This is true for any $x_j^\star$, so $\dfrac{\partial \mathcal{F}_i}{\partial x_j}(\mathbf{x}^\star) = 0$ for $i > m$ and any j. In words, there is no incidence of infection *into* uninfected states. By (A4), $\mathcal{F}_i(\mathbf{x}^\star) = 0$ for $i \le m$. Since $\mathbf{x}^\star$ is defined such that the first m elements are 0, this implies that any change in the final $m+1$ to M elements will have no affect on new infections. The rate of change from noninfectious states $j = m+1, \ldots, \mathrm{M}$ to infective states $i = 1, \ldots, m$ is zero,

$$\frac{\partial \mathcal{F}_i}{\partial x_j}(\mathbf{x}^\star) = 0 \quad i = 1, ..., m \quad j = m+1, ..., \mathrm{M}$$

In words, there is no appearance of infection *from* uninfected states. This proves the shape of $D\mathcal{F}(\mathbf{x}^\star)$.

By (A2), $\mathcal{V}_i^+(\mathbf{x}^\star) = 0$ for $i = 1, ..., m$ and by (A4) $\mathcal{V}_i^-(\mathbf{x}^\star) = 0$ for $i = 1, ..., m$. Any change in the final $j = m+1$ to M elements will still result in $\mathcal{V}_i(\mathbf{x}^\star) = \mathcal{V}_i^-(\mathbf{x}^\star) - \mathcal{V}_i^+(\mathbf{x}^\star) =$

$0\ i = 1, \ldots, m$. In terms of a derivative,

$$\frac{\partial \mathcal{V}_i}{\partial x_j}(\mathbf{x}^\star) = 0 \quad i = 1, ..., m \quad j = m+1, ..., \mathrm{M}$$

In words, there is no transfer of infection from uninfected states. This proves the shape of $D\mathcal{V}(\mathbf{x}^\star)$.

Since $\mathbf{x}^\star \in \mathbf{X}_s$, $x_i = 0$ for $i = 1, ..., m$ and $x_i \geq 0$ for $i = m+1, ..., \mathrm{M}$. By (A4), $\mathcal{F}_i(\mathbf{x}^\star) = 0$ for $i = 1, ..., m$. By (A1), $\mathcal{F}_i(\mathbf{x}^\star) \geq 0$ if $x_i \geq 0$ for $i = 1, ..., \mathrm{M}$. These two facts imply that $\mathcal{F}_i(\mathbf{x}^\star)$ can only increase from $\mathbf{x}^\star$ for $i, j = 1, \ldots, m$. That is, $\dfrac{\partial \mathcal{F}_i}{\partial x_j}(\mathbf{x}^\star) \geq 0$ for $i, j = 1, ..., m$. This proves the nonnegativity of F.

To prove that V is a nonsingular M-matrix, consider for $i = 1, \ldots, m$, $i \neq j$,

$$\begin{aligned}
\frac{\partial \mathcal{V}_i}{\partial x_j}(\mathbf{x}^\star) &= \lim_{h \to 0} \frac{\mathcal{V}_i(\mathbf{x}^\star + h\mathbf{e}_j) - \mathcal{V}_i(\mathbf{x}^\star)}{h} && \text{where } \mathbf{e}_j \text{ is the standard basis vector for } \mathbb{R}^n \\
&= \lim_{h \to 0} \frac{\mathcal{V}_i(\mathbf{x}^\star + h\mathbf{e}_j)}{h} && \text{since } \mathcal{V}_i(\mathbf{x}^\star) = 0 \text{ by (A2) and (A4)} \\
&= \lim_{h \to 0} \frac{\mathcal{V}_i^-(\mathbf{x}^\star + h\mathbf{e}_j) - \mathcal{V}_i^+(\mathbf{x}^\star + h\mathbf{e}_j)}{h} && \text{by definition of } \mathcal{V}_i \\
&= \lim_{h \to 0} \frac{-\mathcal{V}_i^+(\mathbf{x}^\star + h\mathbf{e}_j)}{h} && \text{since } \mathbf{x}^\star + h\mathbf{e}_j = 0 \text{ for } i = 1, \ldots, m,\ i \neq j, \text{ so } \mathcal{V}_i^-(\mathbf{x}^\star + h\mathbf{e}_j) = 0 \text{ by (A2)} \\
&\leq 0 && \text{since } \mathbf{x}^\star + h\mathbf{e}_j \geq 0 \text{ so by (A1), } \mathcal{V}_i^+(\mathbf{x}^\star + h\mathbf{e}_j) \geq 0. \text{ for } i = 1, ..., m \text{ and } i \neq j
\end{aligned}$$

This is equivalent to V having the Z-sign pattern. To see that all eigenvalues of V have positive real part, notice that by (A3) and (A4), $\mathcal{F}_i(\mathbf{x}^\star) = 0$ for all i. Then by (A5), if $\mathcal{F}(\mathbf{x}^\star) = 0$, all eigenvalues of $Dh(\mathbf{x}^\star)$ have negative real parts. Notice that

$$Dh(\mathbf{x}^\star)|_{\mathcal{F}(\mathbf{x}^\star)=0} = -D\mathcal{V}(\mathbf{x}^\star) = \begin{bmatrix} -V & 0 \\ -J_3 & -J_4 \end{bmatrix}$$

Since this is a triangular block matrix, the eigenvalues of $Dh(\mathbf{x}^\star)$ are the same as the eigenvalues of $-V$ and $-J_4$. Therefore, all eigenvalues of $-V$ and $-J_4$ have negative real parts, or equivalently, all eigenvalues of V and J_4 have positive real parts.

Finally, since V has the Z-sign pattern and is positive stable, by Lemma 5.3.3, V is a nonsingular M-matrix.

■

5.6 The Main Theorem

The main theorem defining R_0 for ordinary differential equation models is now presented. This is found as Theorem 2 of [15]. Before the theorem is presented, consider the following argument, adapted from [15]. By definition, the i^{th} component of the vector $\mathcal{F}$ describes new infections arising in state x_i. Then the (i, j) component of the matrix F is the rate that new infections appear in state x_i from state x_j. Again by definition, the i^{th} component of the vector $\mathcal{V}$ describes the transfer of existing infections into state x_i. The (i, j) component of the matrix V is the rate of transfer of existing infections into state x_i from state x_j. To determine the interpretation of V^{-1}, consider the fact that

$$\sum_{j=1}^{m} V_{ij} V_{jk}^{-1} = \begin{cases} 1 & i = k \\ 0 & i \neq k \end{cases}$$

Then V_{jk}^{-1} represents the average time an individual in state x_k spends in state x_j. To see this, consider a dimensional analysis argument. Since V_{ij} has units of 1/(time) for an individual in x_i and V_{jk}^{-1} has the units of time for an individual in x_k, then the sum over

all j of the products of $V_{ij}V_{jk}^{-1}$ should be 1 if $i = k$ and 0 if $i \neq k$. This assumes that the population remains near the disease-free equilibrium and hence remains constant.

The (i, k) entry of the Next Generation matrix is the product over all states x_j of the rate new infections appear in state x_i from state x_j with the average time an individual in state x_k spends in state x_j. This is the expected number of new infections in state x_i produced by an individual originally introduced in state x_k. That is,

$$\begin{aligned}(FV^{-1})_{ik} &= \sum_{j=1}^{m} F_{ij}V_{jk}^{-1} \\ &= \sum_{j=1}^{m} (\text{New infections in } x_i \text{ from } x_j) \cdot (\text{Average time } x_k \text{ spends in } x_j) \\ &= \text{New infections in } x_i \text{ produced by } x_k \text{ in all generations}\end{aligned}$$

Thus, the matrix FV^{-1} is aptly defined as the Next Generation matrix. The basic reproduction rate R_0 will be defined as the spectral radius of this matrix.

Theorem 5.6.1. *Consider the disease transmission model given by* $\dot{x}_i = h_i(\boldsymbol{x}) = \mathcal{F}_i(\boldsymbol{x}) - \mathcal{V}_i(\boldsymbol{x}), i = 1, ..., \mathrm{M}$ *with* $\boldsymbol{h}(\boldsymbol{x})$ *satisfying conditions (A1) through (A5). If* $\boldsymbol{x}^\star$ *is a disease-free equilibrium of the model, then* $\boldsymbol{x}^\star$ *is locally asymptotically stable if* $R_0 < 1$*, but unstable is* $R_0 > 1$*, where* $R_0 = \rho(FV^{-1})$.

Proof. Recall the structure of the linearized ordinary differential equation system from Lemma 5.5.1.

$$\begin{aligned}Dh(x_i) &= (D\mathcal{F}(\mathbf{x}^\star) - D\mathcal{V}(\mathbf{x}^\star))(\mathbf{x} - \mathbf{x}^\star) \\ &= \begin{pmatrix} F - V & 0 \\ -J_3 & -J_4 \end{pmatrix} (\mathbf{x} - \mathbf{x}^\star)\end{aligned}$$

The eigenvalues of the linearized ODE system $D\mathbf{h}$ are the eigenvalues of the full system $\mathbf{h}$. Since the Jacobian is block triangular, the eigenvalues of of the linearized ODE system are the eigenvalues of $F - V$ and $-J_4$. By Lemma 5.5.1, the eigenvalues of $-J_4$ have all

negative real parts. If the eigenvalues of $F - V$ have negative real parts, then $\mathbf{x}^\star$ is locally asymptotically stable equilibrium of $\mathbf{h}$. The theorem will be proved using this stability condition.

Let $J_1 = F - V$, or alternatively, $-J_1 = V - F$. By Lemma 5.5.1, V has the Z-sign pattern and F nonnegative. Then, $-J_1$ has the Z-sign pattern by the illustration:

$$\begin{bmatrix} x & & \leq 0 \\ & \ddots & \\ \leq 0 & & x \end{bmatrix} - \begin{bmatrix} & & \\ & \geq 0 & \\ & & \end{bmatrix} = \begin{bmatrix} x & & \leq 0 \\ & \ddots & \\ \leq 0 & & x \end{bmatrix}$$

Or, consider any element of $-(J_1)_{i,j} = V_{i,j} - F_{i,j}$ for $i \neq j$. But $V_{i,j} \leq 0$ and $F_{i,j} \geq 0$, so $-(J_1)_{i,j} \leq 0$.

Lemma 5.3.3 shows that since $-J_1$ has the Z-sign pattern, it is a nonsingular M-matrix if and only if every eigenvalue of $-J_1$ has positive real part. This is equivalent to $-J_1$ is a nonsingular M-matrix if and only if every eigenvalue of J_1 has negative real part. The fact that every eigenvalue of $J_1 = F - V$ has negative real part is the condition required for the local asymptotic stability of $\mathbf{x}^\star$. Therefore,

$$\mathbf{x}^\star \text{ is locally asymptotically stable } \iff -J_1 \text{ is a nonsingular M-matrix} \tag{5.7}$$

Lemma 5.5.1 shows that F is nonnegative. From Lemma 5.3.2, V^{-1} is also nonnegative, as V is a nonsingular M-matrix. Therefore, FV^{-1} is nonnegative. Then, $-J_1V^{-1} = (V - F)V^{-1} = I - FV^{-1}$ has the Z-sign pattern by the same argument that $-J_1$ has the Z-sign pattern. Now, applying Lemma 5.4.2 with $H = V$ and $B = -J_1 = V - F$,

$$-J_1 \text{ is a nonsingular M-matrix } \iff I - FV^{-1} \text{ is a nonsingular M-matrix.} \tag{5.8}$$

Notice that since FV^{-1} is nonnegative, $I - FV^{-1}$ has the Z-sign pattern $A = sI - B$ with $s = 1$. Then by the definition of an M-matrix,

$$I - FV^{-1} \text{ is a nonsingular M-matrix} \iff \rho(FV^{-1}) < 1 \tag{5.9}$$

Combining equations (5.7), (5.8), and (5.9) proves

$$\mathbf{x}^\star \text{ is locally asymptotically stable} \iff R_0 < 1 \tag{5.10}$$

Similarly, since $-J_1$ has the Z-sign pattern, it is a singular M-matrix $\iff$ the real part of every nonzero eigenvalue of $-J_1$ is positive and $-J_1$ has a zero eigenvalue. This follows from Lemma 5.3.3 and Lemma 5.3.4. Equivalently,

$$\begin{aligned} -J_1 \text{ is a singular M-matrix} \iff &\text{every nonzero eigenvalue of } J_1 \text{ has negative} \\ &\text{real part and } J_1 \text{ has a zero eigenvalue.} \end{aligned} \tag{5.11}$$

Since V is a nonsingular M-matrix and F is nonnegative, one can apply Lemma 5.4.3(b) with $H = V$ and $K = F$ to obtain

$$-J_1 \text{ is a singular M-matrix} \iff I - FV^{-1} \text{ is a singular M-matrix.} \tag{5.12}$$

Again by the definition of a singular M-matrix, since $I - FV^{-1}$ has the Z-sign pattern and $FV^{-1} \geq 0$,

$$I - FV^{-1} \text{ is a singular M-matrix} \iff \rho(FV^{-1}) = 1 \tag{5.13}$$

Combining (5.11), (5.12), and (5.13) gives

$$\begin{aligned} &\text{every nonzero eigenvalue of } J_1 \text{ has} \\ &\text{negative real part and } J_1 \text{ has a zero eigenvalue.} \iff \rho(FV^{-1}) = 1 \end{aligned} \tag{5.14}$$

Recall $\mathbf{x}^\star$ is unstable if and only if there exits an eigenvalue of J_1 has positive real part. It follows from (5.14) and (5.10) that

$$\mathbf{x}^\star \text{ is unstable} \iff R_0 > 1 \tag{5.15}$$

This completes the theorem.

■

Chapter 6

MATHEMATICAL FOUNDATIONS FOR R_0 IN MAPS

A similar Next Generation construction of R_0 can be defined for discrete-time models. Here, the Next Generation matrix is $F(I-T)^{-1}$. The (i,j) entry of F is still the rate at which new infections appear in state x_i from state x_j. To determine the interpretation of $(I-T)^{-1}$, consider that one assumption of the theorem is that $\rho(T)<1$. Then, by Lemma 5.3.1, $(I-T)^{-1}=I+T+T^2+T^3+\ldots$. The (k,j) entry of T is the rate of transfer of infected individuals into x_j from x_k in one generation. Similarly, the (k,j) entry of T^n is the rate of transfer of infected individuals into x_j from x_k after n generations. Then, the (i,j) entry of the Next Generation matrix $F(I-T)^{-1}=F+FT+FT^2+FT^3+\ldots$ represents the expected number of new infections in state x_i produced by an individual originally introduced in state x_j over all generations.

$$\begin{aligned}
(F(I-T)^{-1})_{ij} &= F_{ij}+(FT)_{ij}+FT^2_{ij}+\ldots \\
&= F_{ij}+\sum_{k=1}^{m}F_{ik}T_{kj}+\sum_{k=1}^{m}F_{ik}T^2_{kj}+\ldots \\
&= (\text{New infections in } x_i \text{ from } x_j)+ \\
&\qquad (\text{New infections in } x_i \text{ from } x_j \text{ after 1 generation})+\ldots \\
&= \text{New infections in } x_i \text{ produced by } x_k \text{ in all generations}
\end{aligned}$$

6.1 The Main Theorem

Theorem 6.1.1. *Let* (2.1) *be a discrete-time model such that the state vector* $\boldsymbol{x}(t,\boldsymbol{p})$ *is structured with the first* m *components as infected and the remaining* $\mathrm{M}-m$ *components as disease-free, and suppose the following conditions hold:*

1. $\exists!$ *DFE* $\boldsymbol{x}^\star$ *of* (2.1)

2. The linearization of (2.1) *is*

$$X(t+1, \boldsymbol{p}) = \begin{pmatrix} F+T & 0 \\ A & C \end{pmatrix} X(t, \boldsymbol{p}) \tag{6.1}$$

where the matrix $\begin{pmatrix} F+T & 0 \\ A & C \end{pmatrix}$ *is the Jacobian of* $\boldsymbol{h}$ *evaluated at* $\boldsymbol{x}^\star$*, and 0 is an* $m \times (\mathrm{M} - m)$ *matrix of zeros.*

3. The submatrices F *and* T *are nonnegative*

4. $F+T$ *is irreducible*

5. $\rho(C) < 1$ *and* $\rho(T) < 1$ *where* $\rho(\cdot)$ *represents the spectral radius operator*

Then the DFE $\boldsymbol{x}^\star$ *is locally asymptotically stable if* $R_0 = \rho(F(I-T)^{-1}) < 1$ *and unstable if* $R_0 > 1$*, where* I *is the* $m \times m$ *identity matrix.*

Proof. The eigenvalues of the linearized system in (6.1) are the eigenvalues of the full system. Since the linearization is block triangular, the eigenvalues of (6.1) are the eigenvalues of $F+T$ and C. The disease-free equilibrium is stable if these eigenvalues are all less than 1, and unstable if an eigenvalue is greater than one. Since $\rho(C) < 1$, it follows that

$$\begin{aligned} \mathbf{x}^\star \text{ is locally asymptotically stable } &\iff \rho(F+T) < 1 \\ \text{and is unstable } &\iff \rho(F+T) > 1 \end{aligned} \tag{6.2}$$

Note that the theorem is now proved true if R_0 is replaced by the index $r = \rho(F+T)$. The reason for defining $R_0 = \rho(F(I-T)^{-1})$ instead of just using $r = \rho(F+T)$ is to better match the biological definition. The quantity r is not identified as the average number of secondary infections produced from a single infected individual, but rather is identified as the growth factor [10].

The theorem will be proved by proving the following:

$$\begin{aligned} r < 1 &\iff R_0 < 1 \\ \text{and } r > 1 &\iff R_0 > 1 \end{aligned} \tag{6.3}$$

This will be proved using the technique in [10]. Let $r = \rho(F+T)$ and $R_0 = \rho(F(I-T)^{-1})$ and assume $R_0 \neq 0$. Assuming $R_0 \neq 0$ is the same as assuming $R_0 > 0$ by the definition of the spectral radius.

Claim: $\rho(\dfrac{F}{R_0} + T) = 1$ and one of the following holds:

$$r = R_0 = 1, \quad \text{or} \quad 1 < r < R_0, \quad \text{or} \quad 0 < R_0 < r < 1 \tag{6.4}$$

By Theorem 5.2.1, $\exists$ a positive left-eigenvector y of $F(I-T)^{-1}$corresponding to the eigenvalue $R_0 = \rho(F(I-T)^{-1})$. Then,

$$yF(I-T)^{-1} = yR_0$$

Multiplying both sides by $(I-T)$ gives

$$yF = yR_0(I-T) = yR_0 - yR_0T$$

$$yF + yR_0T = yR_0$$

Now divide through by $R_0 \neq 0$,

$$\begin{aligned} \frac{yF}{R_0} + yT &= y \\ y(\frac{F}{R_0} + T) &= y \end{aligned} \tag{6.5}$$

Equation (6.5) implies that 1 is an eigenvalue of $\dfrac{F}{R_0} + T$. Since both F and T are nonnegative, dividing F by $R_0 > 0$ only scales the nonzero entries of $\dfrac{F}{R_0} + T$. Since $F+T$ is irreducible, $\dfrac{F}{R_0} + T$ must also be irreducible. Furthermore, $\dfrac{F}{R_0} + T$ is nonnegative by the assumption that $R_0 > 0$. Then by Theorem 5.2.1(b), since y is a positive eigenvector, it

must be associated with the spectral radius. That is, $\rho(\frac{F}{R_0} + T) = 1$.

Consider the following cases:

(i) $R_0 = 1$.

Then $R_0 = 1 = \rho(\frac{F}{R_0} + T) = \rho(F + T) = r$.

(ii) $R_0 > 1$.

Then by Theorem 5.2.1(c),

$1 = \rho(\frac{F}{R_0} + T) < \rho(F + T) = r < \rho(F + R_0T) = R_0$.

The final equality is established by multiplying $\rho(\frac{F}{R_0} + T) = 1$ through by R_0.

(iii) $0 < R_0 < 1$.

Again by Theorem 5.2.1(c),

$1 = \rho(\frac{F}{R_0} + T) > \rho(F + T) = r > \rho(F + R_0T) = R_0$.

Equation (6.3) is now established under the added assumption that $R_0 > 0$. This assumption can be relaxed by following the procedure in [10] with the added assumption that $F \neq 0$. Note that if $F = 0$, $r = \rho(T) < 1$, so the disease-free equilibrium will be stable, and $R_0 = \rho([0]) = 0$ is also less than 1. This fact can be used to justify the existence of R_0 for discrete background infection models with $\beta = 0$ (the continuous analog is presented in Section 9.2), but if $R_0 = 0$, the infection model is not worth studying.

■

Chapter 7

SENSAI

SENSAI is a hybrid MATLAB/Maple software that simulates large-scale mathematical models and computes sensitivities and elasticities of quantities of interest, including the Next Generation R_0, with respect to parameters and initial conditions. A researcher may construct the model in Maple, where symbolic manipulation is convenient, and simulate the results numerically in MATLAB where numerical simulation and plotting are convenient. SENSAI will automatically compute the solution trajectories of the model as well as the sensitivity and elasticity analysis. Additionally, the user may select a subset of parameters and/or states to compute sensitivity and elasticity information instead of including all of them. Sometimes the quantity of greatest interest to the researcher can be a (possibly nonlinear) function of the states and parameters rather than isolated states, such as the proportion of infected individuals or the number of infected adults, etc. SENSAI allows the user to specify any function of states or parameters as the quantity of interest (QoI). The trajectories, sensitivities, and elasticities of the QoI will also be computed. Finally, if the model is an infection model, the user may specify the equations which describe the infection classes, and SENSAI will compute R_0 via the Next Generation method, if valid, and its sensitivities. The conditions from the theorems will be tested, and if one of the conditions is not met, SENSAI will output a warning statement specifying the condition which is not met. SENSAI uses the MATLAB solver ODE45 to numerically solve the differential equations. The code is freely available from the website

`http://www.math.colostate.edu/~tavener/FEScUE/SENSAI/sensai.shtml`.

Some example models and Maple templates are available at this site.

7.1 Sensitivities and Elasticities

For notational convenience in SENSAI, let the j^{th} initial condition z_j to be parameter $p_{\mathrm{K}+j}$. Re-writing equation (3.4),

$$\left.\begin{aligned} \frac{\partial x_i}{\partial p_{\mathrm{K}+j}}(t+1) &= \left(\sum_{m=1}^{\mathrm{M}} \frac{\partial h_i}{\partial x_m}\,\frac{\partial x_m}{\partial p_{\mathrm{K}+j}}(t)\right) + \frac{\partial h_i}{\partial p_{\mathrm{K}+j}}(t), \\ \frac{\partial x_i}{\partial p_{\mathrm{K}+j}}(0) &= \delta_{ij} \end{aligned}\right\} \; i = 1,\ldots,\mathrm{M},\; j = 1,\ldots\mathrm{M}. \quad (7.1)$$

Solving for both the variables and their sensitivities with respect to the parameters and initial conditions requires solving equations (3.1), (3.3) and (7.1) simultaneously. This is a system of size $\mathrm{M}\cdot(1+\mathrm{K}+\mathrm{M})$. SENSAI evaluates the Jacobian $\partial h_i/\partial x_j,\; i,j = 1,\ldots,\mathrm{M}$ and all partial derivatives $\partial h_i/\partial p_k,\; i = 1,\ldots,\mathrm{M},\, k = 1,\ldots,\mathrm{K}$ symbolically using Maple, and automatically writes the MATLAB routines necessary to evaluate these derivatives.

Once the sensitivities are evaluated, the elasticities are defined according to the scaling from (3.8).

7.2 Quantities of Interest (QoI)

Many times the most valuable sensitivities are calculated from a function of states and parameters. The notation in SENSAI is as follows. Let the QoI be a scalar valued function of time, such that

$$Q(t) = Q(\mathbf{x}(t,\mathbf{p}),\mathbf{p}). \quad (7.2)$$

The sensitivities of the QoI can be computed using the chain rule,

$$\frac{dQ}{dp_k}(t) = \left(\sum_{m=1}^{\mathrm{M}} \frac{\partial Q}{\partial x_m}\,\frac{\partial x_m}{\partial p_k}(t)\right) + \frac{\partial Q}{\partial p_k}(t)\,, \quad k = 1,\ldots,\mathrm{K}+\mathrm{M}. \quad (7.3)$$

The suggested QoI for infection models is the proportion of infected individuals. Suppose the model has a simple SI form, where $x_1 = S$ and $x_2 = I$. The QoI will be defined as

$Q(t) = \dfrac{x_2(t)}{x_1(t) + x_2(t)}$. Then, the sensitivity of the QoI with respect to an arbitrary parameter p_k is

$$\begin{aligned}\frac{dQ}{dp_k}(t) &= \frac{\partial Q}{\partial x_1}\frac{\partial x_1}{\partial p_k}(t) + \frac{\partial Q}{\partial x_2}\frac{\partial x_2}{\partial p_k}(t) + \frac{\partial Q}{\partial p_k}(t) \\ &= \left(\frac{-x_2(t)}{(x_1(t)+x_2(t))^2}\right) S_{1,k}(t) + \\ &\quad + \left(\frac{1}{x_1(t)+x_2(t)} - \frac{x_2(t)}{(x_1(t)+x_2(t))^2}\right) S_{2,k}(t) + \frac{\partial Q}{\partial p_k}(t)\end{aligned} \tag{7.4}$$

7.3 R_0

When the user builds up his or her model in Maple, there is an option of identifying which equations describe the dynamics of the infected classes. If this input is nonzero, R_0 will be computed via the Next Generation method. SENSAI will construct the vectors $\mathcal{F}$ and $\mathcal{V}$ under the following criteria. If a term in an equation describing an infected state involves a noninfectious state or is a term of parameters only, that term belong in $\mathcal{F}$ as it is assumed that term describes an incidence of a new infection. If a term in an infected equation does not involve a noninfectious state but is more than just a product of parameters, that term belongs in $\mathcal{V}$ as it is assumed that term describes the transfer of an existing infection. (Section 9.2 will show that if a term in an equation describing an infected state is only a product of parameters, the Next Generation R_0 is not valid for the model.)

Consider the following traditional SIR model as an example.

$$\left.\begin{aligned}\frac{dS}{dt} &= -\beta SI - \delta S, \\ \frac{dI}{dt} &= \beta SI - \gamma I - \mu I - \delta I, \\ \frac{dR}{dt} &= \gamma I - \delta R,\end{aligned}\right\} \tag{7.5}$$

where β is the infection rate, δ is the natural death rate of the species, γ is the recovery rate, and μ is the disease-specific death rate due. The user must specify equation 2 is the only equation modeling infection classes. Because the noninfectious state S appears in the

term βSI, SENSAI will place that term in $\mathcal{F}$. Since no other term has an occurrence of S or R, but each of these terms are not parameters only, $-\gamma I - \mu I - \delta I$ belong in $\mathcal{V}$.

It has been argued that the generalization of $\mathcal{F}$ and $\mathcal{V}$ is to place the negative terms in $\mathcal{V}$ and the positive terms in $\mathcal{F}$ [11]. However, this generalization fails to accurately identify $\mathcal{F}$ and $\mathcal{V}$, as illustrated by the following example.

Many times the incidence of infection will be modeled not by the probability of a new infection occurring when contact is made with an infected individual, but instead by the probability of remaining disease-free when a contact is made with an infected individual, or the probability of a new infection *not* occurring. Consider the following edition to the SIR model

$$\left.\begin{aligned} \frac{dS}{dt} &= -(1-\bar{\beta})SI - \delta S, \\ \frac{dI}{dt} &= (1-\bar{\beta})SI - \gamma I - \mu I - \delta I, \\ \frac{dR}{dt} &= \gamma I - \delta R, \end{aligned}\right\} \tag{7.6}$$

where the infection rate is given by $1-\bar{\beta}$. Expanding the terms in equation 2 gives the terms $SI - \bar{\beta}SI - \gamma I - \mu I - \delta I$. If all the negative terms are placed in $\mathcal{V}$, $-\bar{\beta}SI$ will be in the wrong place. The entire $SI - \bar{\beta}SI$ describes an incidence of a new infection, so both belong in $\mathcal{F}$. SENSAI will identify this properly with the new generalization of $\mathcal{F}$.

Another common procedure in model development is to scale each term by the total population $N = S + I + R$. In this case, S and R will be located in every term, presenting a potential problem for SENSAI's construction of R_0. To avoid this problem, SENSAI will always replace occurrences of $\sum_{i=1}^{\mathrm{M}} x_i$ with a new variable N. When SENSAI searches for terms with a noninfectious state, N will hide the ones that are there simply for scaling purposes. Consider the equation for infected males from the hantavirus model in (2.8):

$$I_m(t+1) = \left[(1 - e^{-\beta_m I_m(t) - \beta I_f(t)})S_m(t) + I_m(t)\right]\frac{K}{K + (b/2)N} \tag{7.7}$$

This equation has both characteristics described above: the incidence of a new infection is modeled by the probability of an infection *not* occurring when contact is made, and the entire equation is scaled by the total population N. Biologically, the term

$$\frac{(1-e^{-\beta_m I_m(t)-\beta I_f(t)})S_m(t)*K}{K+(b/2)N} \in \mathcal{F},$$

while the term $\dfrac{I_m(t)K}{K+(b/2)N} \in \mathcal{V}$. This is exactly what the algorithm in SENSAI will determine.

7.3.1 Possible Problems in SENSAI

There may be models which have a legitimate Next Generation construction of R_0 that SENSAI will fail to compute correctly. These problems arise from an incorrect identification of which terms belong in $\mathcal{F}$ and which belong in $\mathcal{V}$. Just as it is common to scale by the total population N, it is also common to scale each term by a sub-population N_i. Suppose the model describes two or more interacting species. It may make biological sense to scale the infected class of species 1 by the total population of species 1, and likewise scale the class of species 2 by the total population of species 2. That is, for a model structured with states $(S_1, I_1, R_1, S_2, I_2, R_2)$, it may be accurate to scale the first three equations by $N_1 = S_1 + I_1 + R_1$ rather than by the total population $N = S_1 + I_1 + R_1 + S_2 + I_2 + R_2$. This is difficult to automate for models in general. For instance, while the example of two sub-populations was just described, a model could just as easily have three or more sub-populations and subsequent scalings. If this is occurring in the model, SENSAI will recognize a noninfectious state in these terms and place them in $\mathcal{F}$. This may or may not result in a value of R_0 that is sufficient for the theorem to hold, but will certainly not produce a value that is consistent with the biological definition. In fact, if every term is scaled by some N_i, $\mathcal{V} = 0$ and V^{-1} will not be defined.

7.4 An Alternative to R_0

Sometimes the Next Generation R_0 is not the best tool for the analysis of an infection model. There can be many problems with the Next Generation R_0. Consider the following possibilities.

First, the Next Generation method may not even be applicable. It is possible that in order to accurately describe the dynamics of an infection, one or more of the conditions of Theorem 5.6.1 or Theorem 6.1 will fail. Some examples of this problem will be presented in Section 9.2.

Second, it may be difficult to accurately identify which terms of the infected equations belong in $\mathcal{F}$ and which terms belong in $\mathcal{V}$. A model may be constructed such that the determining factor for a term belonging in $\mathcal{F}$ is not solely that it involves a noninfectious state or is just a product of parameters. The mathematical definitions of $\mathcal{F}$ and $\mathcal{V}$ are not completely generalizable and could present problems for the Next Generation R_0. It is possible that a condition of Theorem 5.6.1 or Theorem 6.1 will fail because of an incorrect $\mathcal{F}$ and $\mathcal{V}$, but it is also possible that all conditions will still hold. If the latter is the case, the value of R_0 will be one that exhibits the threshold criterion, but may not accurately reflect the biological definition of R_0. This problem illustrates that checking to see if the Next Generation R_0 has the threshold criterion may not be enough to ensure the value represents the biological definition of R_0. An example of this problem will be presented in Section 9.1.

Third, the Next Generation R_0 may not accurately predict whether the infection persists in the population if a finite amplitude disturbance is introduced into the infected states, rather than a perturbation. Theorems 5.6.1 and 6.1 only ensure the stability of the disease-free equilibrium under small perturbations. While the disease-free equilibrium is stable if and only if $R_0 < 1$, there may be more than one stable equilibrium for the system. If the initial conditions are in a stable endemic equilibrium's basin of attraction, the infection may persist in the population even though $R_0 < 1$. This is not a failure of the mathematical

theorems, but is a limitation of the Next Generation R_0. An example of this problem will be presented in Section 9.3.

One can easily see how the implementation of R_0 is tenuous, especially for large-scale models in which the biological interpretation of terms can become obscured by complexity. Checking that the Next Generation R_0 passes the conditions of the theorems may not be enough to ensure that it matches the biological definition or that it is even an appropriate index for the analysis.

The most important aspect in the analysis of an infection model is to ascertain the best way to control the infection. The solution trajectories will already indicate whether or not the infection will persist in the population, thus making the threshold characteristic of R_0 obsolete. If the infected trajectories converge to zero in time, one can conclude that $R_0 < 1$ just by this observation. Similarly, if the infected trajectories converge to a nonzero equilibrium, one can conclude that $R_0 > 1$, or at least that it should be. The threshold nature of R_0 is rather unimportant when considering the automatic solving of the model through SENSAI.

If the model projects an endemic equilibrium, using a relevant quantity of interest and calculating its sensitivities and elasticities with the solution trajectories is an ample replacement. For instance, let the QoI be the proportion of infected individuals. That is,

$$QoI = (\sum_{i=1}^{m} x_i) \Big/ (\sum_{i=1}^{\mathrm{M}} x_i). \tag{7.8}$$

If the most sensitive (or elastic) parameters to this QoI are known, one can have a good understanding of how to control the infection through SENSAI. A management strategy developed from this analysis will focus on influencing the proportion of infected individuals most. Some examples will be presented in the following chapter comparing the R_0 analysis to the analysis of the QoI with trajectories.

Chapter 8

EXAMPLES

In this chapter, models will be presented that have a valid Next Generation R_0. The analysis of the model using R_0 and its elasticities will be performed, as well as the analysis of the model using the quantity of interest as the proportion of infected individuals. Finally, comparisons of the two analysis techniques will be made for each example model.

8.1 SIR Model with Logistic Growth

Consider the following continuous-time SIR model that includes logistic growth.

$$\left.\begin{aligned} \frac{dS}{dt} &= rN\left(1-\frac{N}{K}\right) - \beta SI - \delta S, \\ \frac{dI}{dt} &= \beta SI - \gamma I - \mu I - \delta I, \\ \frac{dR}{dt} &= \gamma I - \delta R, \end{aligned}\right\} \tag{8.1}$$

where $N = S + I + R$ is the total population at any time t, r is the per capita growth rate, K is the carrying capacity, β is the infection rate, δ is the natural death rate of the species, γ is the recovery rate, and μ is the disease specific death rate. The parameter values are given in Table 8.1.

The solution trajectories to the model using the initial conditions of adding one infected individual from the disease-free equilibrium are given by Figure 8.1. The equilibrium using the parameter values in Table 8.1 is $(3, 378, 37)$, truncated to whole individuals. The proportion of infected individuals at equilibrium is 90.22% (calculated when the solution is not truncated).

Table 8.1: Parameter Values for SIR Model, dimensions of β, δ, γ, and μ are t^{-1}, dimensions of r and K are population.

Parameter	Numerical Value	Interpretation
r	0.5	Per capita growth rate
K	1000	Carrying capacity
β	0.1	Infection rate
δ	0.2	Natural death rate
γ	0.02	Recovery rate
μ	0.1	Disease-specific death rate

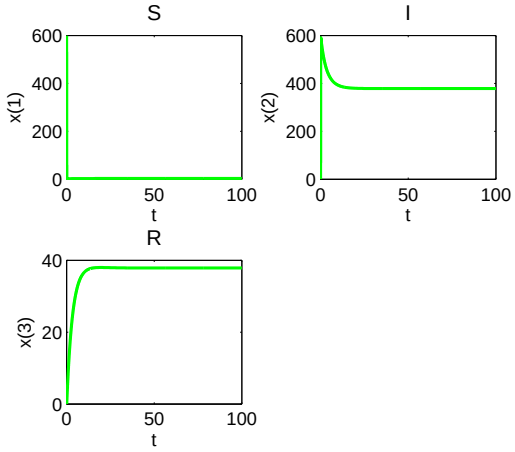


Figure 8.1: Solution of SIR model. The initial conditions are $S(0) = 599, I(0) = 1, R(0) = 0$.

8.1.1 R_0 Analysis

This model has a straightforward construction of R_0. To find the DFE, assume there are no infected or recovered individuals. Setting $\frac{dS}{dt} = 0$ with $I = R = 0$ gives

$$\begin{aligned} rS^\star(1 - \frac{S^\star}{K}) - \delta S^\star &= 0 \\ S^\star(r - \frac{rS^\star}{K} - \delta) &= 0 \\ S^\star = 0 \qquad \text{or} \qquad S^\star &= \frac{r-\delta}{r}K \end{aligned} \tag{8.2}$$

Then, R_0 is given by the Next Generation method:

$$\begin{aligned} R_0 &= \rho(FV^{-1}) \\ &= \rho\left([\beta S^\star][\gamma+\mu+\delta]^{-1}\right) \\ &= \frac{\beta S^\star}{\gamma+\mu+\delta} \\ &= \frac{\beta K(r-\delta)}{r(\gamma+\mu+\delta)} \end{aligned} \tag{8.3}$$

Clearly, R_0 should be greater than one, as it is obvious from the solution trajectories in Figure 8.1 that the infection persists in the population. Moreover, the proportion of infected individuals at equilibrium is 90.22%, so a high value of R_0 is expected. In fact, $R_0 = 187.5$. R_0 is most elastic to $p_4 = \delta$, as indicated by Figure 8.2 and Table 8.2. Because the elasticity

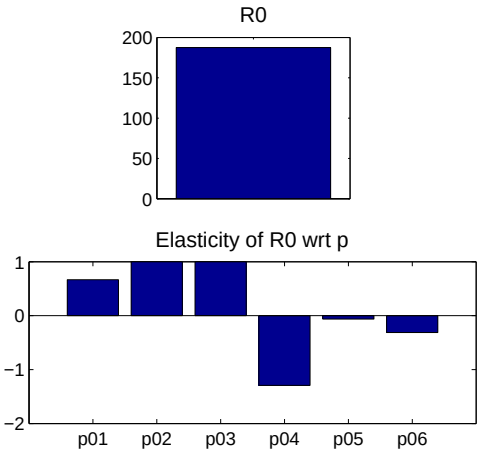


Figure 8.2: R_0 Elasticities. $R_0 = 187.5$

of R_0 to δ is negative, a decrease in δ will result in an increase in R_0. If the desired result is to reduce R_0, the strategy must be to increase δ.

While the sensitivities and elasticities indicate the effects of an infinitesimal change in parameters, a finite disturbance in parameters must be used in practice. One can not change δ by an infinitesimal amount and compute the new trajectories. For comparisons to be made, a relative change of 10% will be made to each parameter. The equilibrium resulting from increasing δ by 10% is $(3, 343, 31)$ as seen from Figure 8.3. The DFE under

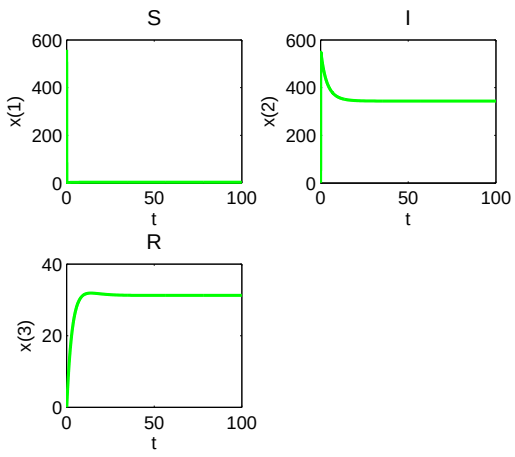


Figure 8.3: Solution after increasing δ by 10%. $R_0 = 164.71$ and $QoI = 90.84\%$.

the change in parameters is $(560, 0, 0)$. The new $R_0 = 164.71$, a relative change of over 12%. This is exactly what one would expect as the elasticity of R_0 to δ is slightly greater than 1 in magnitude. While R_0 was reduced and the infection was reduced by 35 individuals, the proportion of infected individuals actually increased to 90.84%. This is because increasing δ is increasing the death rate. There are fewer secondary infections only because there is a lower population.

Increasing δ is not a very friendly management strategy, so the second most elastic parameter should be analyzed. This can be either $p_2 = K$ or $p_3 = \beta$, as they both have an elasticity of 1. The effects of changing β will be discussed in the following section for the QoI analysis, so K will be chosen. This time, since the elasticity is positive, a reduction in K will result in a reduction of R_0. If K is decreased by 10%, $R_0 = 168.75$, a reduction of 10% as well. This makes sense as the elasticity is exactly 1. The new DFE for the system is $(540, 0, 0)$. If one infected individual is introduced in the population, the endemic equilibrium is $(3, 340, 34)$. The proportion of infected individuals does not change much 90.14%. The solution trajectories in Figure 8.4 are almost identical in shape to the trajectories in Figure 8.1. Reducing the carrying capacity K will reduce the number of individuals in each class proportionally. This is not an effective management strategy.

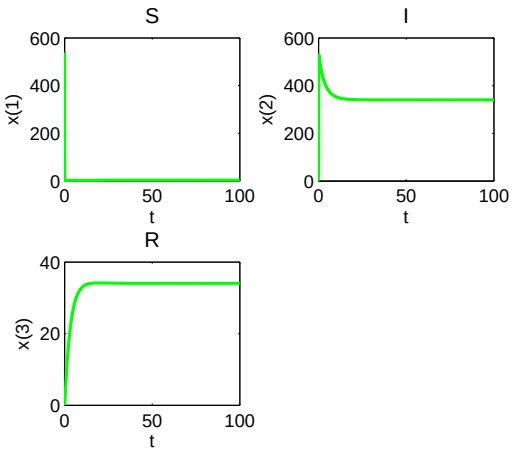


Figure 8.4: Solution after reducing K by 10%. $R_0 = 168.75$ and $QoI = 90.14\%$.

8.1.2 *QoI* Analysis

Let the quantity of interest QoI be the proportion of infected individuals. The QoI is extremely high for this model, 90.22%. Like R_0, the QoI is also elastic (2^{nd} most) to $p_4 = \delta$, *at equilibrium*. Unlike R_0, each of the equilibrium elasticities are extremely small, as indicated by Figure 8.5 or Table 8.2. Furthermore, the elasticity of the QoI to δ is positive.

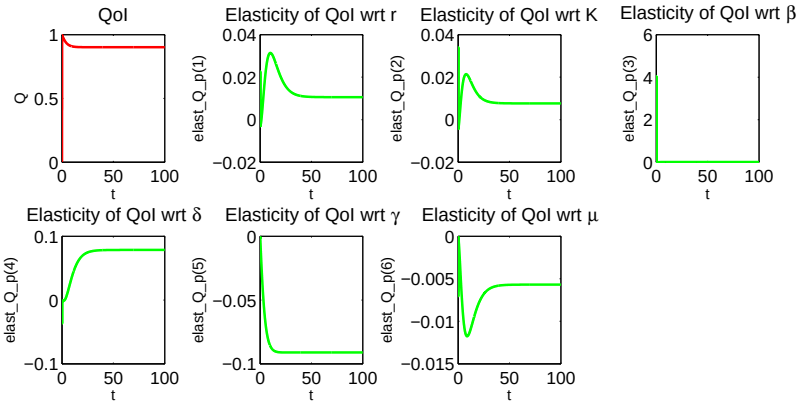


Figure 8.5: Elasticities of the QoI. The initial conditions are $S(0) = 599, I(0) = 1, R(0) = 0$.

If the proportion of infected individuals is to be decreased, the natural death rate δ should be decreased. Even though it is the most elastic parameter, a ten percent change in δ should not affect the proportion of infected individuals at equilibrium. This is observed in Figure 8.3, though δ is changed in the opposite direction. When δ is reduced by 10%, the new QoI

is reduced to 89.41%. The new DFE is $(640, 0, 0)$, and R_0 is increased to 213.33. Again, the QoI at equilibrium is not significantly changed. The endemic equilibrium is $(3, 412, 45)$. There is more infection in the population, but there are also more recovered individuals in the population. This is because every individual lives longer, whether or not they are infected. The solution after reducing δ is shown in Figure 8.6.

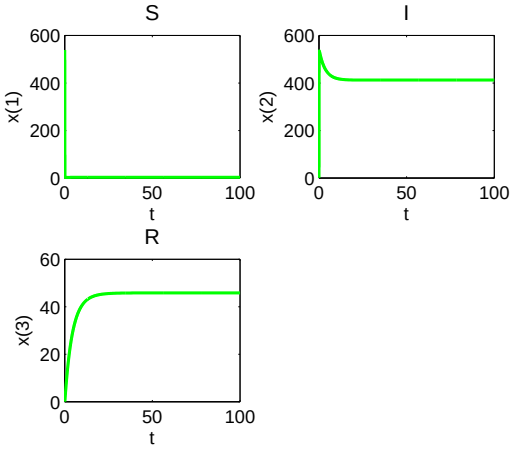


Figure 8.6: Solution after reducing δ by 10%. $R_0 = 213.33$ and $QoI = 89.41\%$.

More information than just the equilibrium elasticities is provided by the QoI analysis. In transience, the QoI is most elastic to $p_3 = \beta$, and it is most elastic by a significant margin. The maximum elasticities of the QoI of any time t, at equilibrium, and the elasticity of R_0 are summarized in Table 8.2.

Table 8.2: Elasticity Values for SIR Model.

Parameter	R_0 elasticity	QoI elasticity at equilibrium	Maximum QoI elasticity
b	0.666667	1.059713×10^{-2}	3.142138×10^{-2}
K	1	7.660186×10^{-3}	3.407802×10^{-2}
β	1	7.660186×10^{-3}	4.025211
δ	-1.29167	7.851908×10^{-2}	7.851908×10^{-2}
γ	-0.06250	-9.108838×10^{-2}	-9.110706×10^{-2}
μ	-0.31250	-5.688001×10^{-3}	-1.176657×10^{-2}

If β is decreased by 10%, as in Figure 8.7, the truncated equilibrium population remains the same. The QoI at equilibrium only changed by fractions of individuals. This is predicted

by the elasticities, as β is only highly elastic in transience. Changing β had negligible effects on the equilibrium solution, though R_0 was reduced to 168.75 (note the elasticity of R_0 to β is 1). The DFE from changing β is still $(600, 0, 0)$.

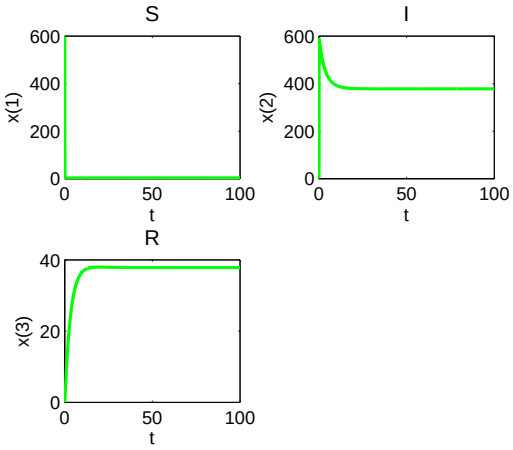


Figure 8.7: Solution after varying β by 10%. $R_0 = 168.75$ and $QoI = 90.14\%$.

The QoI is most elastic to γ at equilibrium. The QoI is also elastic to this parameter during transience (2^{nd} most). When γ is increased by 10%, the DFE remains $(600, 0, 0)$, R_0 is essentially the same value at 186.34, but the endemic equilibrium is now $(3, 376, 41)$. This is a direct transfer of individuals from the infected class to the recovered class, as expected by the function of γ. The equilibrium proportion of infected individuals is reduced to 89.40%. This is still extremely high, but is better than any other strategy attempted yet.

8.1.3 Comparison of Methods

Both the analysis from R_0 and the QoI matched intuition. R_0 is extremely high for this model, and if the largest elasticity is approximately 1.3 in magnitude, a relative change of 10% in that parameter will not eradicate the infection. Similarly, the QoI is extemely high for this model. The largest elasticity is $\mathcal{O}(10^{-2})$ in magnitude, which indicates that a small relative change in that parameter will not significantly change the QoI. The trajectories computed by SENSAI confirm the analyses.

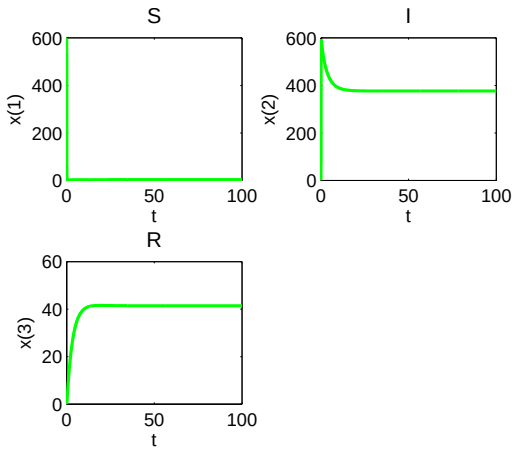


Figure 8.8: Solution after varying γ by 10%. $R_0 = 186.34$ and $QoI = 89.40\%$.

8.2 Typhoid Model

Recall the Typhoid model given by (2.11). If the infected states are considered to be $y = x_3 + x_4 + x_6 + x_7$, as indicated by [2], then the model does not pass assumption (A4) from Section 5.5. If a nonzero density is introduced in either x_2 or x_5, both considered noninfectious, infection enters the solution. The states x_2 and x_5 are incubating noninfectious and sick noninfectious, respectively. One will notice by the equations in (2.11) that the individuals in the "noninfectious" x_2 and x_5 can transfer to an infective state without any contact from an infected state. For example, if $x_2 > 0$ but all infected classes $y = 0$, the equation for $\dot{x_3} = \rho_{23} x_2 > 0$. The only way to ensure a proper Next Generation calculation of R_0 is to assume that x_2 and x_5 are infected states. This may be valid biologically, as an incubating infection is essentially an infection waiting to develop, and a sick noninfectious individual shows signs of an infection. It is peculiar that these states, particularly the state labeled "sick noninfectious," though considered noninfectious, can give rise to the infection just by their presence.

8.2.1 R_0 Analysis

Whether or not x_2 and x_5 are considered infective, if any nonzero population enters any of classes two through seven, the trajectories converge to an equilibrium that contains nonzero infected components. An $R_0 > 1$ is expected for this model. If the assumption that x_2 and x_5 are also infected classes is made, $R_0 = 5.031$.

Since there are six infection classes, SENSAI must compute the inverse of a 6×6 matrix of algebraic equations. Of course, a numerical 6×6 matrix should be easy to solve in MATLAB or Maple, and in fact, SENSAI is capable of producing the numerical R_0 quickly– in just three seconds. But to determine the sensitivities of R_0, an analytical solution must be obtained. Then, since each entry is in the matrix is algebraic, the analytical matrix inverse is a lengthy expression. Since R_0 is given by a long expression, the derivatives of R_0 become extremely involved. When R_0 and its sensitivities are solved from the 6×6 system, SENSAI required 105 minutes of runtime. Nonetheless, SENSAI is capable of computing R_0 for this model.

The most elastic parameter to R_0 is $p_1 = \rho_{12}$, the infection rate from susceptible individuals to incubating noninfectious (but soon to be infected) individuals. R_0 analysis identified six of the twenty-two parameters with an elasticity greater than 0.5 in magnitude and all others 0.1 or less. These six parameters, along with a inelastic $p_{21} = \rho_{91}$ for comparison, are plotted in Figure 8.9.

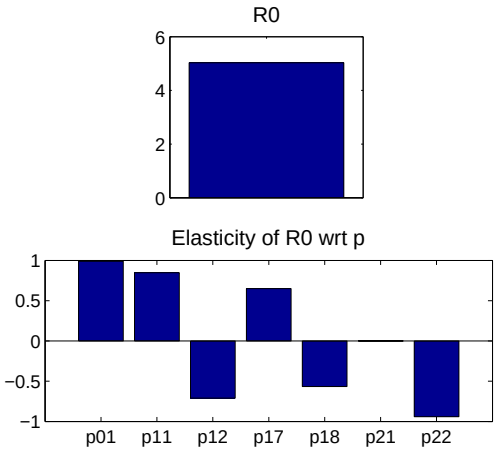


Figure 8.9: Elasticity of $R_0 = 5.031$ to parameters 1, 11, 12, 17, 18, 21, and 22.

A relative change of ρ_{12} by 10% should not reduce R_0 to be less than one. In fact, as the elasticity ≈ 1, a 10% change in p_1 reduces R_0 by 10%, to 4.53. Reducing R_0 to be less than one requires a relative change in ρ_{12} of 81%. This can be seen by solving $R_0 \cdot (1 - x) < 1$ for the relative reduction x. Whether or not this is feasible for this model, when ρ_{12} is reduced this much, $R_0 = 0.995$.

The fact that the populations are modeled as densities may be a point of confusion in the R_0 analysis. As mentioned in Section 4.3, an infinitesimal change is biologically represented as introducing one individual to the population. To find the density corresponding to this change, the total population must be known. If the total population P is 100 individuals, introducing 1 individual corresponds to introducing a density of 0.01 (as is done in Figure 2.2). If the P is 10,000 individuals, introducing 1 individual corresponds to introducing a density of 0.0001. Notice in Figure 8.10 that the infection is removed from the population if the total population is 100 individuals and ρ_{12} is reduced by 81%. A final time of 10,000,000 was used to demonstrate convergence to the DFE.

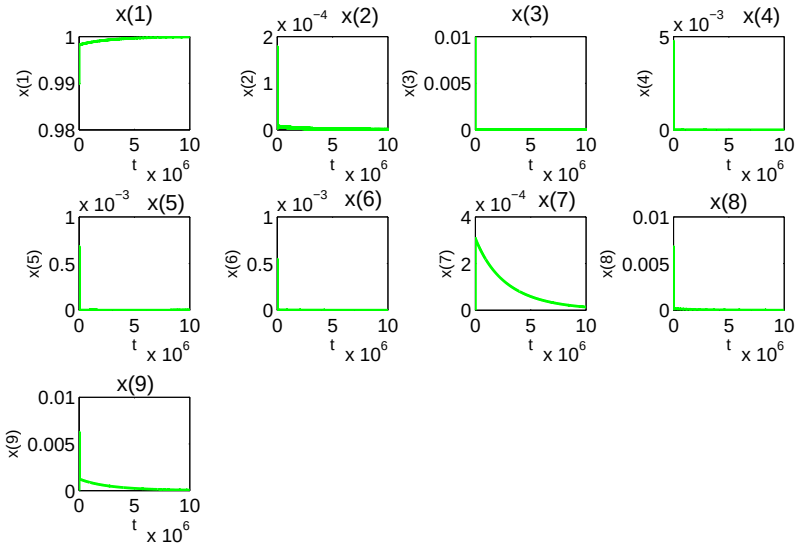


Figure 8.10: Solution to Typhoid model with $R_0 = 0.995$ and $P = 100$. The trajectories approach the DFE.

No matter what the total population P is, the solution will always approach the disease-free equilibrium. This is because the DFE is the only stable equilibrium of the system. This is not guaranteed by Theorem 5.6.1, but is true for this particular model.

8.2.2 *QoI* Analysis

Again, let the *QoI* be the proportion of infected individuals. Note that for this model, the $QoI = \sum_{i=1}^{m} x_i$, since the populations are modeled as densities.

The maximum transient *QoI* analysis also identified ρ_{12} as the most elastic parameter. In fact, the maximum transient *QoI* identified the exact same six most elastic parameters as R_0 did, and the equilibrium *QoI* included these six parameters in its top seven. Figure 8.11 and Table 8.3 show the elasticity results of these seven parameters. A final time of 200,000 was used to ensure the convergence of sensitivities to equilibrium, but the same initial conditions were used as in Section 2.2.1.

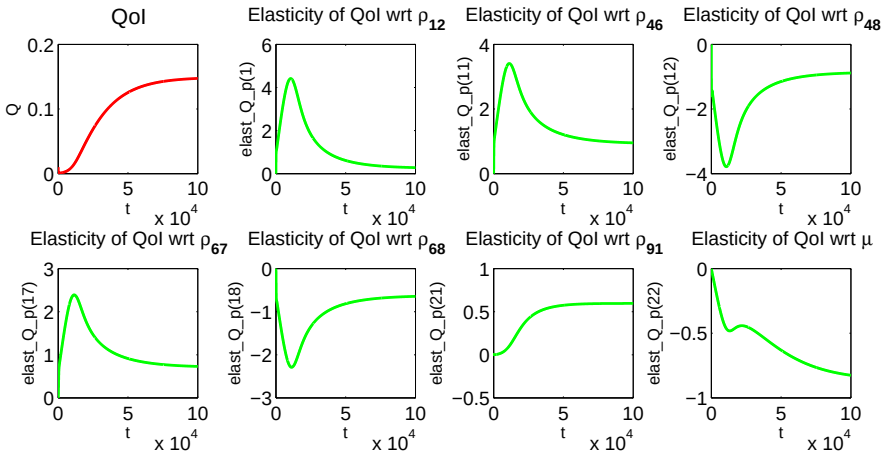


Figure 8.11: Elasticities of the *QoI*. Initial conditions the same as Figure 2.2.

8.2.3 Comparison of Methods

The R_0 and *QoI* analysis are extremely comparable for this model. Six of the twenty-two parameters were identified by the equilibrium *QoI* analysis with an elasticity over 0.5, with all others less than 0.25 with only one parameter different. When the maximum transience

is considered, the missing parameter is added. The only difference between the parameters identified is that the equilibrium QoI was elastic to ρ_{91} the sixth most, but R_0 was not elastic to this parameter at all. Table 8.3 summarizes these results.

Table 8.3: Elasticity Values for Typhoid Model.

Parameter	R_0 elasticity	QoI elasticity at equilibrium	Maximum QoI elasticity
ρ_{12}	0.99039	0.24621	4.4153
ρ_{46}	0.84689	0.92369	3.4093
ρ_{48}	−0.71060	−0.85919	−3.7877
ρ_{67}	0.65054	0.70833	2.3907
ρ_{68}	−0.56677	−0.62541	−2.2921
ρ_{91}	0	0.59451	0.59451
μ	−0.94104	−0.86178	−0.86178

If the R_0 analysis were not available, one would consider varying the parameters most elastic to the QoI at equilibrium and transiently, as done in the previous examples. The parameters ρ_{12}, ρ_{48}, and μ would be identified if the top two parameters to which the maximum QoI is most elastic and the top two parameters to which the equilibrium QoI is most elastic are chosen. This corresponds exactly to the top three parameters to which R_0 is most elastic. Furthermore, if the top three are considered for the QoI analyses, ρ_{46} would be added, which is the fourth parameter to which R_0 is most elastic. If the top four are considered, ρ_{67} would be added, which is the fifth parameter to which R_0 is most elastic. If the top five are considered ρ_{68} would be added, which is the sixth parameter to which R_0 is most elastic. The QoI analysis is quite comparable to the R_0 analysis for this model.

The benefit of the R_0 analysis is that it exactly describes how much change is needed in a single parameter to remove the infection from the population. On the other hand, a reduction of 81% in this parameter was required to reduce R_0 below 1, which could prove difficult in application. This parameter would be reduced by some biologically feasible amount, and then the second most elastic parameter would be evaluated. Once this is reduced by a reasonable amount, the third most elastic parameter would be evaluated, and so on. If this strategy is employed, the R_0 analysis and the QoI analysis would provide the same

strategy. In the R_0 analysis, the effects of the reductions would be checked against the value of R_0. If the reductions in parameters results in $R_0 < 1$, the infection is successfully eradicated. In the QoI analysis, the effects of the reductions would be checked against the solution trajectories. If the solutions converged to a disease-free equilibrium, the infection is successfully eradicated.

8.3 Hantavirus Model

Recall the Hantavirus model given by (2.8). This model passes all the hypotheses of Theorem 6.1, so a valid Next Generation R_0 can be produced, and this index is calculated correctly within SENSAI. The endemic equilibrium for the model is $(375, 125, 375, 125)$.

8.3.1 R_0 Analysis

Again, one can conclude that $R_0 > 1$ just by observing the trajectories of the system from Figure 2.1. Nevertheless, R_0 is computed to be 151.65. Its elasticities are given by Figure 8.12.

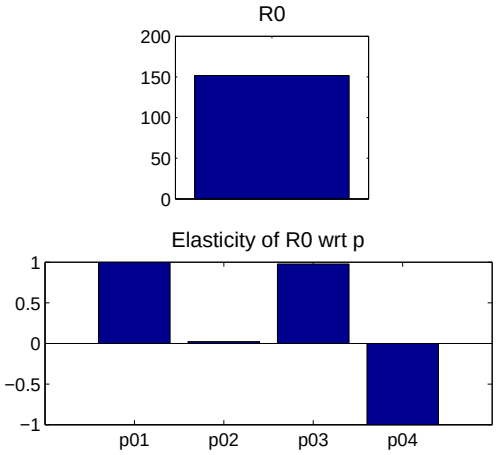


Figure 8.12: Elasticity of $R_0 = 151.65$ to parameters for the Hantavirus model.

R_0 is equally elastic to parameters $p_1 = K$, $p_3 = \beta_m$, and $p_4 = b$. To reduce R_0, one would reduce K and β_m and increase b. These efforts will be made individually to show which is really the most effective.

If p_1 is reduced by 10%, R_0 is reduced to 136.48, a relative change of 10%, as expected by the elasticities. However, since $p_1 = K$, the carrying capacity, reducing this parameter just reduces the total population in every class. The new endemic equilibrium is $(337, 112, 337, 112)$ truncated to the whole individual. The proportion of infected individuals is exactly the same when K is reduced. See Figure 8.13 for the solution trajectories. While the elasticity of R_0 to K is high, changing K seems to be ineffective in controlling the infection.

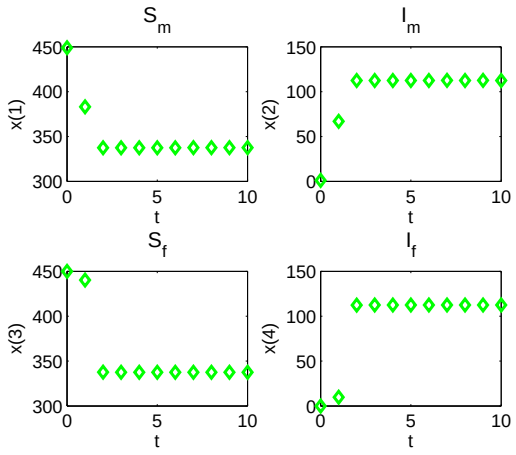


Figure 8.13: Solution of Hantavirus Model when $p_1 = K$ is reduced by 10%. $R_0 = 136.48$. Initial conditions are $(449, 1, 450, 0)$ as the new DFE is $(450, 0, 450, 0)$.

If $p_3 = \beta_m$ is reduced by 10%, R_0 is reduced to 136.85, a relative change of 9.76%. But, the endemic equilibrium is exactly the same before it was reduced. The solution is seen in Figure 8.14. While this reduces R_0, it also seems ineffective in the efforts to control the infection.

Finally, if $p_4 = b$ is increased by 10%, R_0 is reduced to 137.86, a relative change of 9.09%. A 10% increase means that the average litter size is 6.6. This is reasonable for an average and does not need to be a whole number. The new endemic equilibrium is $(383, 116, 383, 116)$,

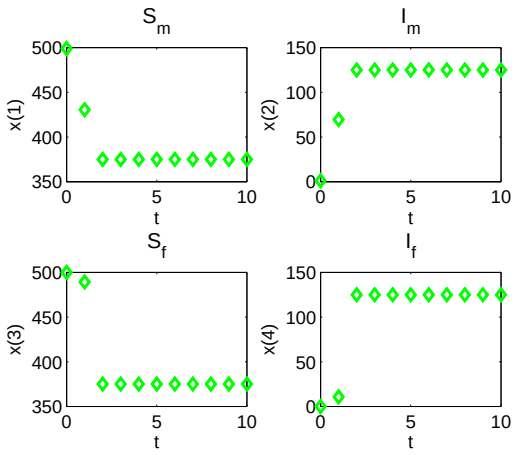


Figure 8.14: Solution of Hantavirus Model when $p_3 = \beta_m$ is reduced by 10%. $R_0 = 136.85$. Initial conditions are $(499, 1, 500, 0)$ as the DFE is $(500, 0, 500, 0)$.

truncated. This by no means eradicates the infection, but does provide a positive change, as the proportion of infected individuals is reduced. The solution trajectories are given in Figure 8.15.

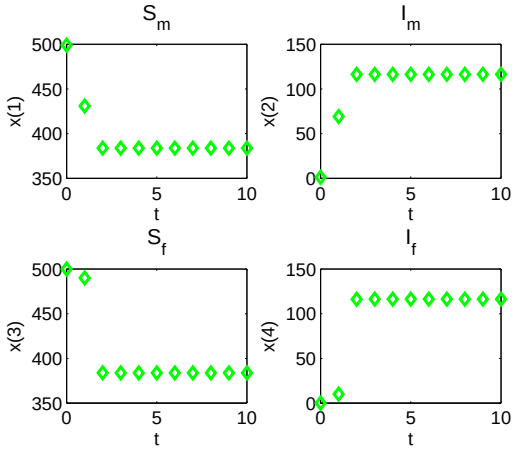


Figure 8.15: Solution of Hantavirus Model when $p_4 = b$ is increased by 10%. $R_0 = 137.86$. Initial conditions are $(499, 1, 500, 0)$ as the DFE is $(500, 0, 500, 0)$

Changing the three elastic parameters by 10% individually did little to remove the infection. Now consider a combined effect. Changing K only seemed to scale the total population. While this reduces the number of susceptibles and therefore reduces the amount of contacts between infected and susceptibles, K will not be attacked heavily as it does not

seem biologically favorable. Consider a reduction of K by 20%. Changing b seemed to have the best effect on the trajectories, so it will be quadrupled. While β_m did not seem to reduce the endemic equilibrium, if R_0 is reduced below 1, the disease will be eradicated. Consider the effects of reducing β_m by 82%. When these changes are made, the new R_0 is still greater than 1, but the elasticities of R_0 to parameters are quite different. See Figure 8.16.

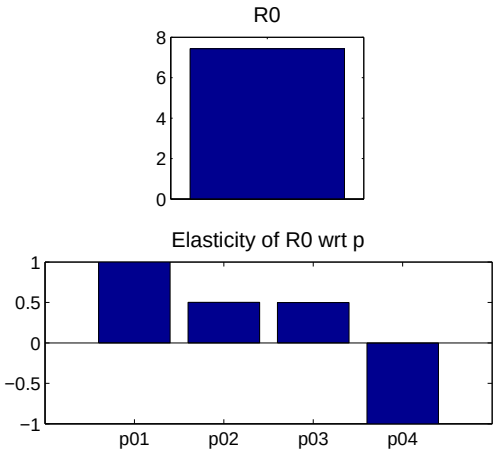


Figure 8.16: $R_0 = 7.43$ and its elasticities after significant changes in parameters.

The new DFE is $(400, 0, 400, 0)$ and $R_0 = 7.43$. The elasticities of R_0 to $p_1 = K$ and $p_4 = b$ are the same as before the changes in parameters, but the elasticity of R_0 to $p_2 = \beta_f$ is now approximately equal to the elasticity of R_0 to $p_3 = \beta_m$. This is simply because β_m reduced it to 0.1620, which is now comparable to the value of $\beta_f = 0.09$. Recall the assumption that $\beta_f << \beta_m$. In efforts to stay consistent with the model formulation, this assumption should be maintained while attempting to reduce R_0 below 1. Staying consistent with the assumption is actually staying true to the elasticities, as continuing the reduce β_m will have less and less affect on R_0. Let β_f be reduced by 75%, and further reduce β_m by 90% of its original value. Now $\beta_f = 0.0225 << 0.09 = \beta_m$ in some sense. The elasticity of R_0 to b is still high and ecologically favorable, so it will be increased further to 50 (about 833% of its original value). The carrying capacity will also be reduced by 50% to 500 individuals. When these changes are made, R_0 is below 1. The new DFE is $(250, 0, 250, 0)$. Whether or not these changes are realistic is unknown. Figure 8.17 shows the trajectories.

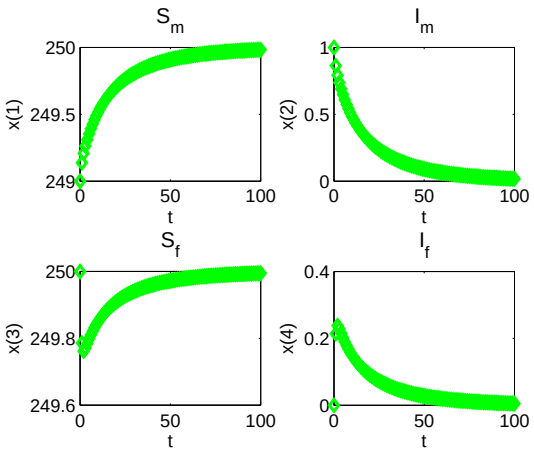


Figure 8.17: Solution after singificant changes to all parameters. $R_0 = 0.9681$ and the infection is not sustained.

8.3.2 *QoI* Analysis

Figure 8.18 depicts the elasticities of the *QoI*, proportion of infected individuals, to parameters for the Hantavirus model.

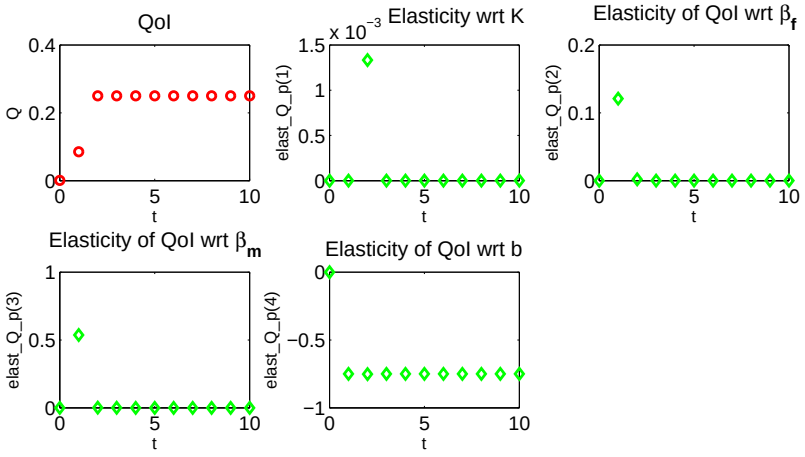


Figure 8.18: Elasticity of the $QoI = 0.25$ to parameters for the Hantavirus model. Initial conditions are $(499, 1, 500, 0)$. Note the scale on the elasticity of K is 10^{-3}

The only parameter with a high elasticity at equilibrium is b. This is consistent with the results from the previous section, as changing K or β_m by 10% did not reduce the *QoI* at all. The *QoI* is also inelastic to β_f, and a change in 10% of β_f results in no change to the *QoI*. The only parameter that changes the *QoI* at equilibrium under a small relative

change is b. A 10% increase to b reduces the QoI to 0.2326. This is not significant, but as seen in the previous section, many changes need to be made to control the infection.

The QoI is also transiently elastic to β_m, with a maximum elasticity of 0.5368. A control strategy of attacking parameters b and β_m is developed from the QoI analysis. If b is increased to 24 as before, and β_m is reduced by 82%, the new QoI is 0.07689, a significant reduction, but not eradication. The disease-free equilibrium is still $(500, 0, 500, 0)$. The elasticities of the QoI also change with this first reduction. Figure 8.19 shows the elasticities after these changes have been made.

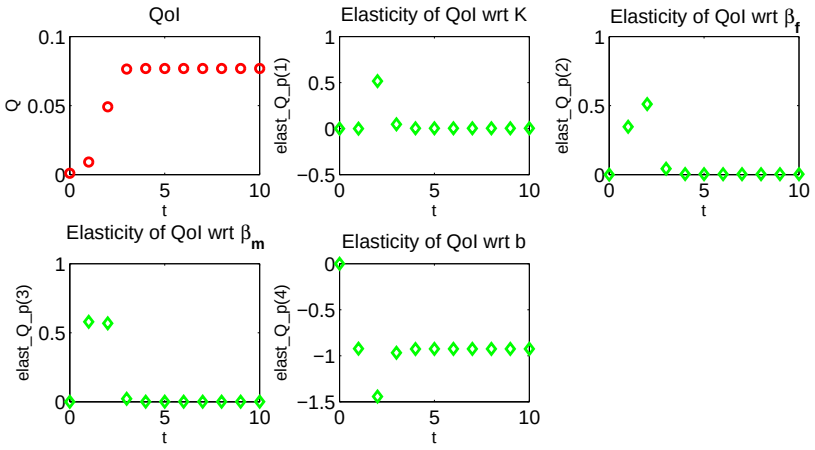


Figure 8.19: Elasticity of the $QoI = 0.077$ to parameters for the Hantavirus model. Initial conditions are $(499, 1, 500, 0)$.

Now the QoI is elastic to all four parameters, at least in transience. As before, the assumption $\beta_f << \beta_m$ should be maintained for the model, so β_f should be reduced as well. This is consistent with the elasticities as the QoI is now elastic to β_f in transience. Let this be reduced by 55% of its original so that $\beta_f = 0.0405 << 0.162 = \beta_m$. Notice that this is a scaling of 4 times; the same scaling is used in the R_0 analysis. The carrying capacity also demonstrates transient elasticity when it essentially did not before. Furthering the control strategy should follow the same procedure as in the R_0 analysis. The parameter that has the highest elasticity should be changed to a biologically reasonable level, and then the next most elastic parameter, and so on, while maintaining the model's assumptions. The QoI analysis

emphasizes increasing b as it is the only parameter with equilibrium elasticity. Assume 70 is the highest b can feasibly reach. Also reduce K by 25% to 750, while maintaining $\beta_m = 0.162$ and $\beta_f = 0.0405$. The new DFE is $(375, 0, 375, 0)$, and the QoI is now 0.01631. The elasticities are given by Figure 8.20.

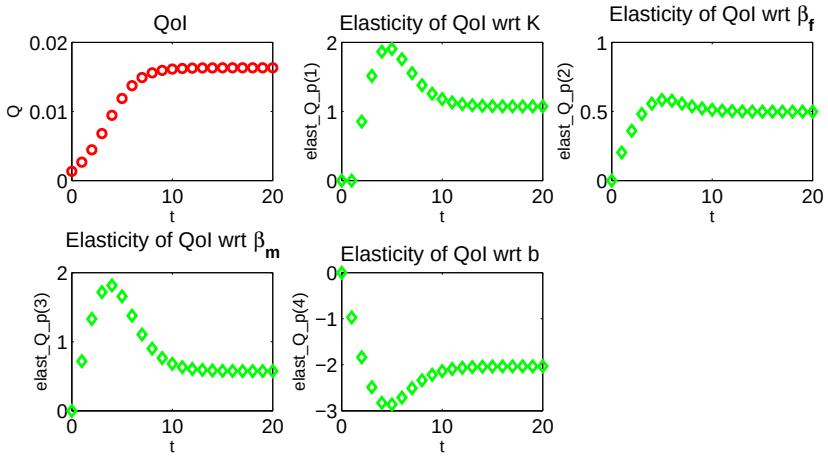


Figure 8.20: Elasticity of the $QoI = 0.016$ to parameters for the Hantavirus model. Initial conditions are $(374, 1, 375, 0)$.

Even though b is the most elastic, it is assumed it can not be increased further. The next best strategy is to reduce K and β_m. If β_m is reduced, β_f will be reduced correspondingly to keep the ratio 4:1. The reduction of K by 50% to 500, β_m by 85% to 0.135, and β_f by 62.5% to 0.03375, while maintianing $b = 70$ effectively removes the infection. The new DFE is $250, 0, 250, 0]$. The final QoI is actually positive valued at 0.001339, implying some infection is in the population. However, the "endemic" equilibrium is $(249.49, 0.51, 249.49, 0.51)$. Truncating to the whole individual results in a "disease-free equilibrium" of $(249, 0, 249, 0)$. This is not really an equilibrium, nor is it actually disease-free. In fact, $R_0 = 1.0373$ with these parameter values.

8.3.3 Comparison of Methods

Both R_0 and the QoI analysis methods led to very similar management strategies for this model. In fact, under certain restrictions, the strategies could be exactly the same. The

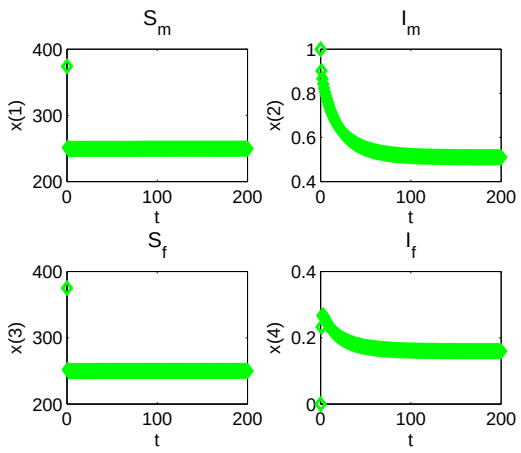


Figure 8.21: Solution after significant changes to all parameters. $QoI = 0.0013$, but the infection is effectively removed from the population.

check for whether the infection persists in the population under the R_0 analysis is too strict when considering the management strategy from the QoI. If individuals are truncated to the whole number, R_0 may be slightly greater than 1 while the infection is removed from the population. This is not a failure of Theorem 6.1 since the disease-free equilibrium is still unstable. The population approached an endemic equilibrium, but that equilibrium is so close to the disease-free equilibrium that the total number of infected individuals, while strictly greater than 0, is also strictly less than 1. When truncated to whole numbers, it is as if infection is removed from the population. If $R_0 \approx 1$, the solution trajectories should be computed to determine whether or not the infection actually persists in the population.

Chapter 9

FAILURES OF R_0

There are models that can be constructed in which a Next Generation R_0 is not well-defined. First, the Next Generation R_0 can fail mathematically as it may not be unique (Section 9.1). Second, the Next Generation R_0 can fail biologically as in models where transmission does not occur only by contact (Section 9.2). Finally, the Next Generation R_0 can fail to predict persistence when a finite amplitude disturbance is introduced rather than an infinitesimal perturbation (Section 9.3).

9.1 Mathematical Failures

Because of the way in which $\mathcal{F}$ and $\mathcal{V}$ are defined, there are models that arise that have the same solution trajectories but different values of R_0. Mathematically speaking, these models are equivalent, thus the concept of R_0 is not mathematically unique. The ideas of this section are an expanded from [11].

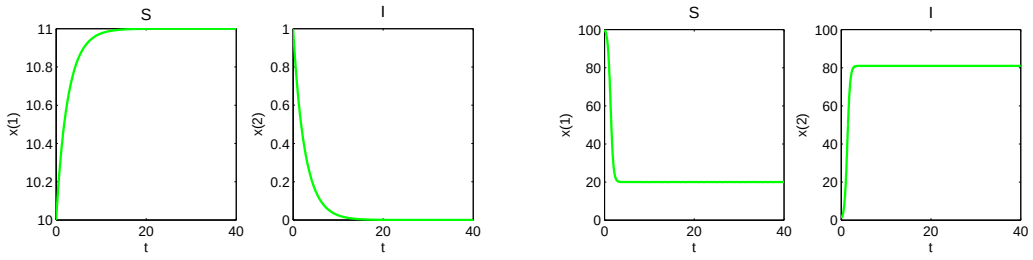
Consider the following SI model, where S represents the number of susceptible individuals in a population, and I represents the number of infected individuals:

$$\left.\begin{aligned} \frac{dS}{dt} &= -\beta SI + \mu I \\ \frac{dI}{dt} &= \beta SI - \mu I \end{aligned}\right\} \tag{9.1}$$

The $+\mu I$ term in the first equation is there only to ensure a constant population by forcing $\dfrac{d(S+I)}{dt} = 0$; the number of new births should be equal to the number of deaths. Under the Next Generation method, the matrices F and V are one-dimensional and equal to βS and μ, respectively. Then, the value of R_0 is given by $R_{0,1} = \rho(FV^{-1}) = \dfrac{\beta S^\star}{\mu}$, where

$S^\star$ is the value of S at the disease-free equilibrium. This R_0 exhibits the threshold criterion such that if $R_{0,1} < 1$, the DFE is stable, but if $R_{0,1} > 1$, the DFE is unstable.

Notice that in this example, R_0 depends on the disease-free equilibrium number of susceptibles, $S^\star$. In this model, there are infinitely many disease-free equilibrium points, since $\left.\frac{dS}{dt}\right|_{I=0} = \left.(-\beta SI + \mu I)\right|_{I=0} = 0$ for any value of β, μ or S. This implies that R_0 depends on the initial conditions for S, as that value will always provide a disease-free equilibrium. Thus, the definition of R_0 is refined to be $R_{0,1} = \frac{\beta S(0)}{\mu}$. Figure 9.1 shows two possible trajectories, one with $R_0 > 1$ and one with $R_0 < 1$. The difference of R_0 values in the two solutions is only due to the initial number of susceptibles. This illustrates the vaccination control strategy: if the number of susceptibles is reduced, the infection can be removed.



(a) $S(0) = 10$ and $R_0 = 0.5$ (b) $S(0) = 100$ and $R_0 = 5$

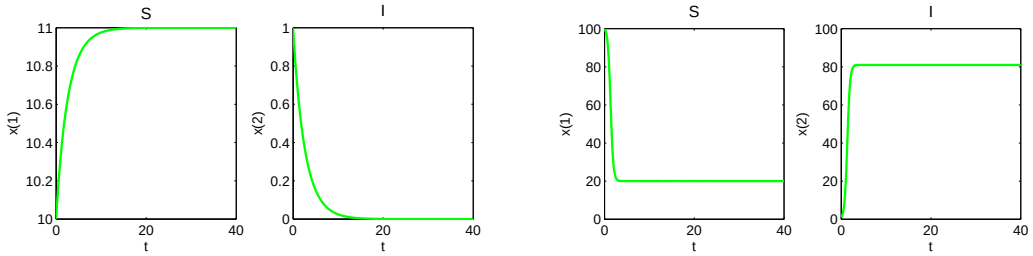
Figure 9.1: SI model trajectories for (9.1). Parameter values are $\mu = 0.8$, $\beta = 0.04$. Initial condition $I(0) = 1$ is used for both.

Now consider the same model with an algebraic manipulation.

$$\left.\begin{aligned} \frac{dS}{dt} &= -\beta SI + \mu I \\ \frac{dI}{dt} &= \beta SI - \mu I - cI + cI \end{aligned}\right\} \tag{9.2}$$

Clearly, this model will have the exact same trajectories for any matching initial conditions and parameter values. Since it is mathematically the same model, the index $R_{0,1}$ is obviously a valid threshold for this model. However, depending on the biological meaning of the $-cI$ and $+cI$ terms, a different R_0 may be determined. Suppose the $-cI$ term

represents a disease specific death rate and the $+cI$ term represents an alternative mechanism for a new infection that just happened to occur at the same rate c. It is appropriate for the $+cI$ term to belong in $\mathcal{F}$ while the (negated) $-cI$ term belongs in $\mathcal{V}$, yielding the matrices $F = \beta S(0) + c$ and $V = \mu + c$. The value of R_0 under these assumptions is then $R_{0,2} = \rho(FV^{-1}) = \dfrac{\beta S(0) + c}{\mu + c}$. If $c = 0.2$, for example, the trajectories for (9.2) are exactly the same as for (9.1), as seen by Figure 9.2, but this time the new $R_0 = 0.6$ instead of 0.5 for Figure 9.2(a), and the new $R_0 = 4.2$ instead of 5 for Figure 9.2(b).



(a) $S(0) = 10$ and $R_0 = 0.6$ (b) $S(0) = 100$ and $R_0 = 4.2$

Figure 9.2: SI model trajectories for (9.2). Parameter values are $\mu = 0.8$, $\beta = 0.04$. Initial condition $I(0) = 1$ is used for both.

$R_{0,2}$ also exhibits the threshold criterion such that if $R_{0,2} < 1$, the DFE is stable, but if $R_{0,2} > 1$, the DFE is unstable.

Proof. Suppose $0 < c < \infty$.

$$\begin{aligned} R_{0,2} < 1 &\iff \beta S(0) + c < \mu + c \\ &\iff \beta S(0) < \mu \\ &\iff R_{0,1} < 1 \\ &\iff \text{the DFE is stable} \end{aligned}$$

A similar argument can be shown for $R_{0,2} > 1$. ■

Clearly, $R_{0,1} \neq R_{0,2}$, yet both are constructed under the same method for two models with the same trajectories. While both $R_{0,1}$ and $R_{0,2}$ exhibit the threshold criterion necessary for R_0, they cannot both satisfy the biological definition for a single model. How can the

average number of secondary infections from one infected individual be both 5 and 4.2 at the same time? It may be easy to determine which terms belong in $\mathcal{F}$ and $\mathcal{V}$ for such a small model, but if the model is constructed progressively as (2.8), it may become difficult to determine the proper biological function of every term.

The difficulty of discovering the true R_0 will certainly increase with the model's complexity. In models that are more than simple SI demonstrations, it should be examined whether the efforts to calculate R_0 are worth the expense when the QoI and solution trajectories can be computed so easily in SENSAI.

9.2 Biological Failures

There is another common class of models where $\mathcal{F}$ and $\mathcal{V}$ are defined correctly according to the epidemiology, but a Next Generation R_0 fails to be well-defined. Consider models that include a background infection rate. Transmission of the infection arises not from contact with an infected individual, but by some alternative source related to the environment of the population. The background transmission occurs as a probability that is independent of the number of infected individuals. An example where background transmission occurs is the model in [6] of White Pine Blister Rust (*Cronartium ribicola*), an infection prevalent in the northwest United States that attacks five-needle, high elevation white pine trees (*Pinus albicaulis* and *P. exilis*). The infection is not transmitted from tree-to-tree contact, but is from an uniformly distributed cloud of spores from flowering plants among the genus *Ribes*. Infection is stored in the *Ribes*, which permeate the forest ground, and transmitted to the pines by a constant probability of infection β, independent of I. Another example comes from Chronic Wasting Disease (CWD) in mule deer (*Odocoileus hemionus*). The model in [14] proposes that the transmission of CWD is primarily through environmental sources and not direct deer-to-deer contact.

For models like these, the Next Generation method of calculating R_0 will never be valid. Assumption (A4) for ODEs (or assumption #5 for maps) fails under all models with

background infection. Because transmission occurs independent of the number of infected individuals, the disease-free subspace is not invariant. That is, if the population is disease-free, infection can still enter the population.

Consider a basic SI model that has a constant background infection rate. Let the number of susceptibles change according to Logistic growth, and let the transmission of infection be independent of the number of infected individuals. Then

$$\left.\begin{aligned} \frac{dS}{dt} &= rN\left(1-\frac{N}{K}\right) \\ \frac{dI}{dt} &= \beta - \gamma I \end{aligned}\right\} \tag{9.3}$$

where $N(t) = S(t) + I(t)$ is the total population, r is the per capita growth rate, K is the carrying capacity, β is the background transmission probability, and γ is the recovery rate.

Notice that there is no nontrivial disease-free equilibrium in this model. This can be seen by solving $\frac{dS}{dt} = 0$ for I. The only solution is $I^\star = \frac{\beta}{\gamma}$. Even if $I(0) = 0$, infection can still occur if $\beta \neq 0$ as seen by Figure 9.3. The only biologically appropriate equilibrium for this system is $S^\star = K - \frac{\beta}{\gamma}$ and $I^\star = \frac{\beta}{\gamma}$. There is another mathematically valid equilibrium for the model where $I^\star$ is the same and $S^\star = \frac{-\beta}{\gamma}$, but negative populations are not biologically realistic.

In fact, there are two problems with this example as far as the construction of the Next Generation R_0 is concerned. First, there is no invariant disease-free subspace; (A4) fails. Second, there is no disease-free equilibrium provided $\beta \neq 0$. The Next Generation method for R_0 describes the stability of the DFE. If there is no DFE, the Next Generation R_0 can not be used.

Because there is no working Next Generation R_0 for this model, the analysis will be done using only the quantity of interest as the proportion of infected individuals. The elasticities of the QoI at equilibrium to parameters $p_2 = \beta, p_3 = \gamma$, and $p_4 = K$ are similar as indicated by Figure 9.4. The only parameter to which QoI is essentially inelastic is $p_1 = r$. All other parameters have an elasticity of 1 in magnitude at equilibrium. The differences between the

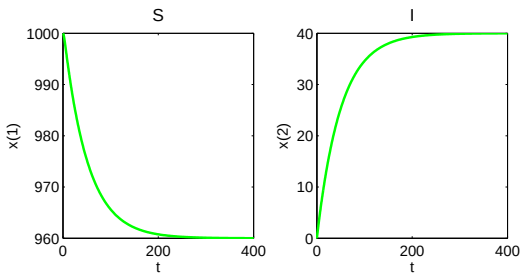


Figure 9.3: Solution to the Background SI model. Parameter values are $r = 0.5$, $\beta = 0.8$, $\gamma = 0.02$, $K = 1000$. The initial condition is disease-free and at carrying capacity: $S(0) = 1000$, $I(0) = 0$, but infection persists in the population.

elasticities of the QoI to β, γ, and K occur in transience. It is easy to see that β is the parameter to which QoI has an elasticity of 1 in the shortest time. In fact, the elasticity of the QoI to β is 1 after a single time step. This is expected, as β is the parameter that determines the new infections. The QoI should be highly elastic to γ at equilibrium, since the equilibrium number of infected individuals is always $\frac{\beta}{\gamma}$. A change in γ will produce a proportional change in I, which will produce a change in the QoI. Similarly, the QoI should be highly elastic to K at equilibrium since the equilibrium number of susceptible individuals is always $K - \frac{\beta}{\gamma}$. A change in K will produce a change in S, which will produce a change in the QoI.

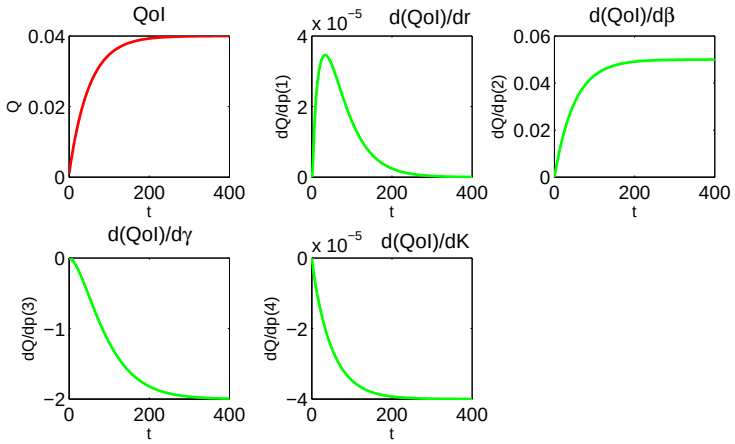


Figure 9.4: QoI and its elasticities for the background infection model. Note the scale on the elasticity of QoI to $p_1 = r$ and $p_4 = K$ is 10^{-5}.

Suppose $\beta = 0$ for this model. Now assumption (A4) is satisfied and a disease-free equilibrium exists, so a Next Generation R_0 is valid. The term β belongs in $\mathcal{F}$ as it is an isolated parameter. This is biologically accurate as β describes new infections from the background transmission. The term γI belongs in $\mathcal{V}$, as no noninfectious state occurs in this term. This is also biologically accurate as recovery is a transfer of existing infections. Then the matrix $F = 0$ and $V = \gamma$, so that $FV^{-1} = 0$, and $R_0 = \rho[0] = 0$. This will always be the case for models where the transmission occurs via a background rate.

The infection rate β should be the most sensitive parameter, as any change of $\epsilon > 0$ will produce a qualitative change in the solution. The disease-free equilibrium will cease to exist, and the solution will converge to an endemic equilibrium instead. The elasticity of any quantity of interest (including R_0) is 0 (or is undefined) with respect to β, as $\beta = 0$ will occur in the numerator of (3.8). Sensitivities will be considered instead of elasticities for this example.

Because R_0 is identically equal to 0, its sensitivities and elasticities will also equal 0. No information can be gleaned from R_0. If disease-free initial conditions are used, the QoI will also be 0. However, unlike R_0, the sensitivities of the QoI are not all 0. Figure 9.5 shows that the QoI is sensitive only to $p_2 = \beta$. This is intuitive, as a change in any parameter

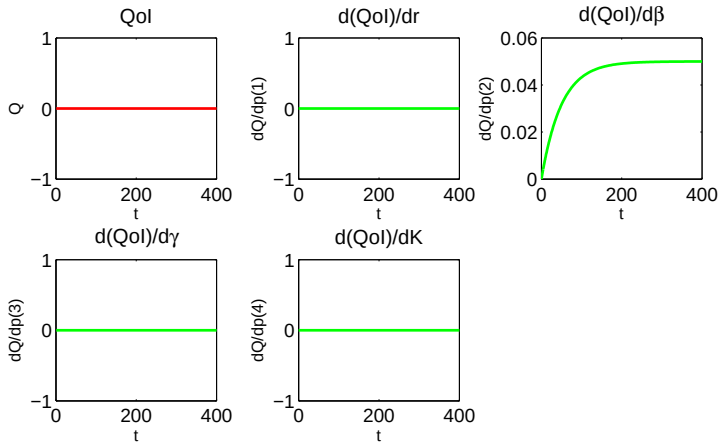


Figure 9.5: QoI and its sensitivities when $\beta = 0$. The only sensitive parameter is $p_2 = \beta$. Initial conditions are at the disease-free equilibrium.

other than β will not change the number of infected individuals, but if β is changed, the number of infected individuals will change.

If infection is introduced in the population, the QoI will not be initially 0. The rate at which the infection decreases is dependent on all parameters, so the QoI will be sensitive to every parameter in this case. In transience, the only parameters with significant sensitivities are β and γ, which makes sense as $I^\star = \dfrac{\beta}{\gamma}$. As the infection is removed from the population, the only sensitive parameter is again β. These results are illustrated in Figure 9.6.

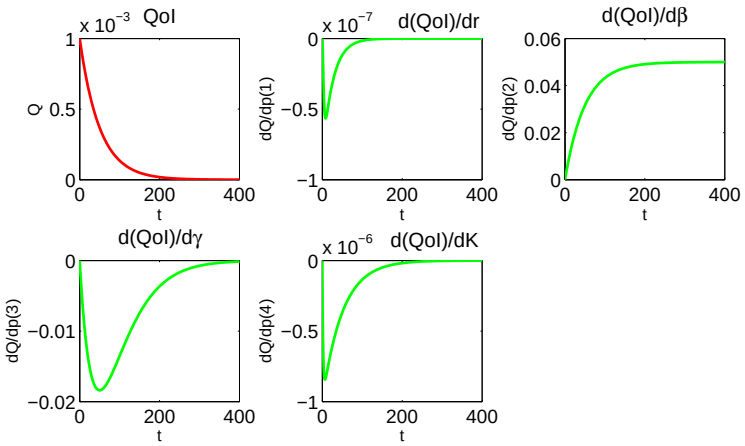


Figure 9.6: QoI and its sensitivities when $\beta = 0$ and initial conditions have infection introduced. $S(0) = 999, I(0) = 1$. Note the scale on $p_1 = r$ is 10^{-7} and the scale on $p_4 = K$ is 10^{-6}.

9.3 Finite Amplitude Disturbances

Finally, there are models where the Next Generation R_0 fails in the sense that it may not accurately predict the persistence of infection if more than one infected individual is introduced to the population. This is not a mathematical failure of the theorems on R_0, nor is it a biological failure of the definition of R_0. Instead, this is a limitation of the concept. R_0 can only be used as an indicator of infection persistence if a single case of infection is originally introduced. If a large number of infected individuals is introduced to a population, R_0 can be misleading.

Consider a model for Dengue fever given by [7]. The model is an $SEIR$ model, where E stands for a class of exposed individuals who have made contact with an infected individual but are still not infectious. Dengue is carried by a vector, mosquitoes, and the dynamics of the vector and human populations are modeled. The equations are as follows:

$$\left.\begin{aligned}
\frac{dS_H}{dt} &= \Pi_H - \lambda_H S_H - \mu_H S_H \\
\frac{dE_H}{dt} &= \lambda_H S_H - (\sigma_H + \mu_H) E_H \\
\frac{dI_H}{dt} &= \sigma_H E_H - (\tau_H + \mu_H + \delta_H) I_H \\
\frac{dR_H}{dt} &= \tau_H I_H - \mu_H R_H \\
\frac{dS_V}{dt} &= \Pi_V - \lambda_V S_V - \mu_V S_V \\
\frac{dE_V}{dt} &= \lambda_V S_V - (\sigma_V + \mu_V) E_V \\
\frac{dI_V}{dt} &= \sigma_V E_V - (\mu_V + \delta_V) I_V
\end{aligned}\right\} \tag{9.4}$$

where $\lambda_H = \frac{C_{HV}}{N_H}(\eta_V E_V + I_V)$ is the human infection rate, $\lambda_V = \frac{C_{HV}}{N_H}(\eta_H E_H + I_H)$ is the vector infection rate, and $N_H = S_H + E_H + I_H + R_H$ is the total human population. The parameters for this model are described and valued in Table 9.1. It is assumed that infected vectors do not recover, so there is no R_V class. This model has a disease-free equilibrium of $(\frac{\Pi_H}{\mu_H}, 0, 0, 0, \frac{\Pi_V}{\mu_V}, 0, 0)$.

The solution trajectories in Figure 9.7 show that although $R_0 < 1$, it is possible for infection to persist in the population. The Next Generation R_0 is a valid technique as all of the conditions of the theorem are met. But, the theorem only proves the stability of the disease-free equilibrium. Since $R_0 < 1$, the DFE is stable for this system. An infinitesimal change from the DFE will not affect the long-term behavior. Biologically, the way to represent an infinitesimal change is to introduce one infected individual, as introducing $0 < \epsilon < 1$ individuals is not biologically realistic.

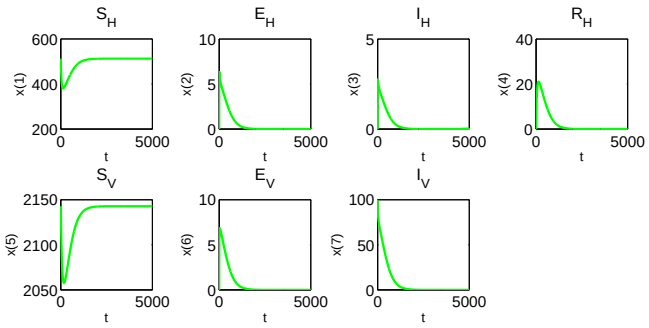
But, if a large enough disturbance is introduced to the population, the long-term behavior can be changed. This is because there is another stable equilibrium that is endemic.

Table 9.1: Parameter Values for Dengue Model.

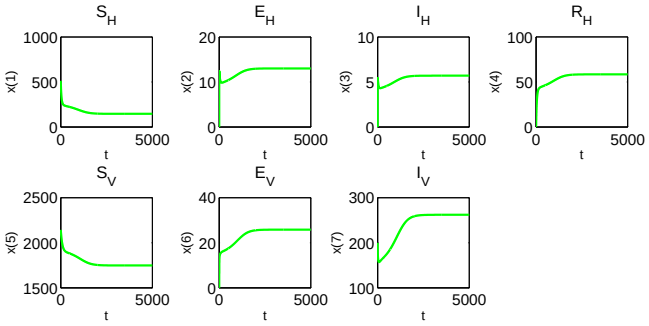
Parameter	Numerical Value	Interpretation
μ_H	0.0195	$1/\mu_H$ is average human lifespan
σ_H	0.5300	Rate of transfer of exposed to infected humans
Π_H	10	Human recruitment rate
δ_H	0.9900	Disease specific human death rate
η_H	0.9900	Infectiousness factor of exposed to infected humans
τ_H	0.2000	Human recovery rate
μ_V	0.0140	$1/\mu_V$ is average vector lifespan
σ_V	0.2000	Rate of transfer of exposed to infected vectors
Π_V	30	Vector birth rate
δ_V	0.0057	Disease specific vector death rate
η_V	0.9800	Transmissibility factor of exposed to infectious vectors
C_{HV}	0.038	Infection rate of mosquitoes

If the disturbance results in a state that is in the basin of attraction of the DFE, as in Figure 9.7(a), the infection will be removed; however, if the disturbance moves the conditions inside the basin of attraction of the endemic equilibrium, as in Figure 9.7(b), the infection will persist.

If the infection is introduced in the population as a single infected individual, consistent with the definition of R_0, the infection will not be sustained. There is no failure in the biological meaning of R_0 or the mathematical definition of R_0. However, if a large number of infected individuals are introduced in the population, R_0 is not a good measure to predict the persistence of the infection. This is a legitimate possibility. Inhabitants of foreign countries have immunities to certain diseases while others do not. Suppose a large influx of individuals who carry a certain disease but have no deleterious effects from that disease arrive in a population of susceptible individuals. R_0 is not a useful measure in such a situation. R_0 may be less than one, but because a large number of infective individuals are introduced, rather than just one, the infection may persist.



(a) $R_0 = 0.9032$ and the infection is removed



(b) $R_0 = 0.9032$ but the infection persists

Figure 9.7: Dengue model trajectories. In (a), $x_0 = (\frac{\Pi_H}{\mu_H}, 0, 0, 0, \frac{\Pi_V}{\mu_V}, 0, 100)$ and the infection is unsustainable. In (b), $x_0 = (\frac{\Pi_H}{\mu_H}, 0, 0, 0, \frac{\Pi_V}{\mu_V}, 0, 200)$ and the infection persists.

Chapter 10

MODELS WITH BLOCK STRUCTURE

Suppose a model is a coupled system of differential equations, such as the hantavirus model in (2.8). There is a clear block structure that results from such a system: the equations for the males is block 1, and the equations for the females is block 2. Can this structure be exploited by separately solving the solutions and sensitivities of each block under an iterative method? More interesting examples than (2.8) come from in-host disease dynamics, where the population of the species is modeled along with the population of the infecting agent. The dynamics of the host population usually occur on a much slower time scale that the dynamics of the infecting agent. If the blocks are solved separately, time and storage space may be saved by solving the slow blocks over a coarser time mesh than the fine mesh required for the rapidly changing block. This chapter will discuss the advantages and disadvantages of decoupling the system of ODEs and more importantly, that of their sensitivity analysis.

10.1 Block Solutions

Assume that the general form of a continuous model (2.9) is a fully coupled, block-structured system. Now, introduce a new function $\mathbf{r} = \mathbf{r}(\mathbf{x})$ that will decouple the system. For simplicity, assume that the system can be split into just two blocks of equations. This can be easily extended to multiple blocks, but the extension will not be discussed here. In the two-block system, $\mathbf{r}$ may be thought of as a vector of two functions, where the first function $r_1 = r_1(\mathbf{x_1})$ depends on the first block, and the second function $r_2 = r_2(\mathbf{x_2})$ depends on the second block. This requires the coupling of a model is involved in only one equation of each block. This may seem strict, but many models exhibit such structure. The set of decoupled

ODEs has the block form

$$\left.\begin{aligned} \dot{\mathbf{x_1}} &= \mathbf{h_1}(\mathbf{x_1}(\mathbf{p}), r_1(\mathbf{x_2}(\mathbf{p})), \mathbf{p}) \\ \dot{\mathbf{x_2}} &= \mathbf{h_2}(\mathbf{x_2}(\mathbf{p}), r_2(\mathbf{x_1}(\mathbf{p})), \mathbf{p}) \end{aligned}\right\} \tag{10.1}$$

where the vector of variables of the first block $\mathbf{x_1} \in \mathbb{R}^{M_1}$, the vector of variables of the second block $\mathbf{x_2} \in \mathbb{R}^{M_2}$, and $M_1 + M_2 = M$. The vector of parameters $\mathbf{p} \in \mathbb{R}^K$, as before.

10.1.1 Piecewise Constant Approximation

In order to explicitly write (10.1), $\mathbf{r}$ must be known at all times t. This can be done through some iteration technique, and the method chosen is Gauss-Seidel. The following algorithm describes the solution technique for a simple piecewise approximation.

Algorithm 1: Piecewise Constant Approximation

1. Approximate $r_1(\mathbf{x_2})$ by assuming it is a piecewise constant function over subintervals of the time domain $[0, T]$.
2. Solve the first block of differential equations
3. Approximate $r_2(\mathbf{x_1})$ by assuming it is a piecewise constant function over subintervals of the time domain $[0, T]$.
4. Solve the second block of differential equations
5. Repeat steps (1) - (4) until convergence

For the first iteration, the initial conditions of $\mathbf{x_2}$ are held constant on the entire interval $[0, T]$ as the input to calculate $r_1(\mathbf{x_2})$. Now $\mathbf{x_1}(t)$ can be solved on the entire time domain $[0, T]$. Once the first block is solved, split up $[0, T]$ into subintervals $[t_i, t_{i+1}]$ and calculate $r_2(\mathbf{x_1})$ by assuming $\mathbf{x_1}$ is a piecewise constant function on the subintervals. This is the piecewise linear constant approximation of the other block.

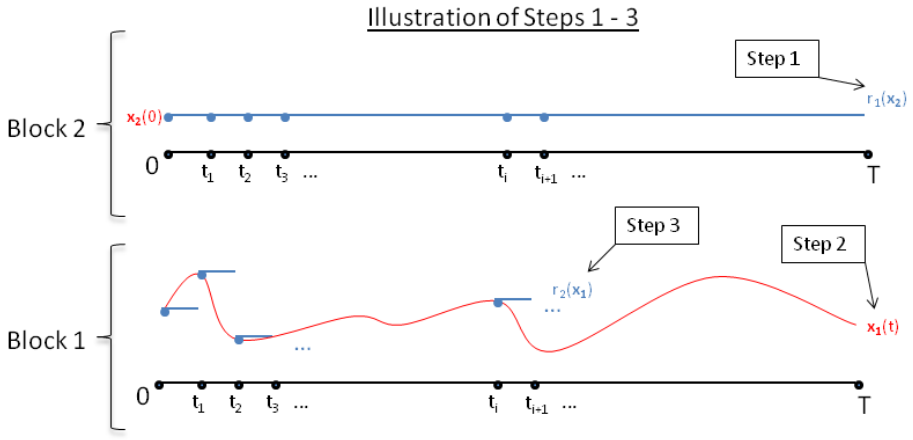


Figure 10.1: Illustration of Steps 1 through 3 of Algorithm 1

After the first step, $\mathbf{x_2}(t)$ can be solved on $[0, T]$. $r_1(\mathbf{x_2})$ is calculated by the piecewise constant approximation of the second block so that $\mathbf{x_1}(t)$ can be refined. The process continues until convergence is achieved.

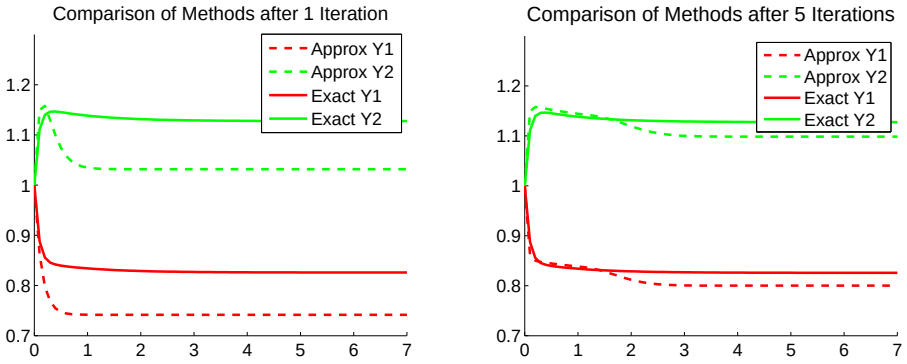
Note that the accuracy of the method described in Algorithm 1 depends on the choice of the splitting of the time domain $[0, T]$. In Figure 10.1, the rate of change of $\mathbf{x_1}(t)$ between $t = t_1$ and t_2 is high in magnitude. The mesh depicted for $r_2(\mathbf{x_1})$ is too large and is a poor approximation of $\mathbf{x_1}$. If a smaller mesh is chosen, the method will be more accurate.

Consider the following pair of differential equations.

$$\begin{aligned}
\begin{pmatrix} \dot{y_1} \\ \dot{y_2} \end{pmatrix} &= \begin{pmatrix} h_1(y_1, r_1(y_2)) \\ h_2(y_2, r_2(y_1)) \end{pmatrix} \\
&= \begin{pmatrix} y_1(1 - y_1) - 7y_1 + 5y_2 \\ y_2(1 - y_2) - 5y_2 + 7y_1 \end{pmatrix} \\
&= \begin{pmatrix} y_1(1 - y_1) - 7y_1 + 5r_1 \\ y_2(1 - y_2) - 5y_2 + 7r_2 \end{pmatrix}
\end{aligned}$$

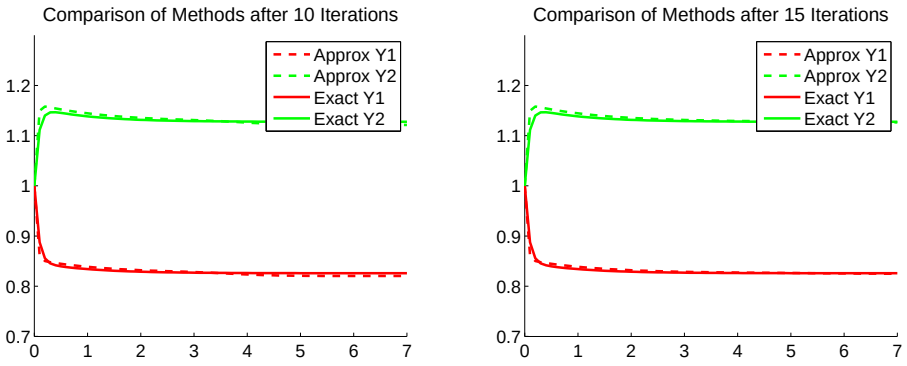
This is a simple model with a bounded solution. It is also easily expressed in block form: the first equation, h_1, is the first block, and the second equation, h_2, is the second

block. Using Algorithm 1, this model can be solved over the interval $t = [0, 7]$ using a mesh of equally spaced time intervals of 0.1 and ode tolerance within MATLAB of 10^{-10}. The fully coupled solution solved in the regular manner using the same ode solver tolerance will be referred to as the exact solution. The norm of the residual of the the iterated solution from exact solution was 5.25×10^{-2}. Gauss-Seidel iteration converged around step 15, within 10^{-5} of the previous step. Figure 10.2 depicts the convergence of the iteration. The dotted lines are the iterated solutions and the solid lines are the exact solutions; and red corresponds to y_1 and green to y_2.



(a) 1 Step GS

(b) 5 Steps GS



(c) 10 Steps GS

(d) 15 Steps GS

Figure 10.2: Piecewise Linear Interpolation with mesh 0.1

Of course, decreasing the mesh size will provide a more accurate interpolation of $\mathbf{r}$. With a mesh of 0.01, the residual had a norm of 1.26×10^{-2}, and with a mesh of 0.001, the residual norm was 3.92×10^{-3}. While the solution became more accurate, the efficiency suffered from the extra precision. As the mesh size is decreased, more steps of Gauss-Seidel

iteration were required to reach convergence. While a mesh of 0.1 converged in 15 steps, a mesh of 0.01 converged in 21, and a mesh of 0.001 converged in 26. This data are illustrated in Figure 10.3.

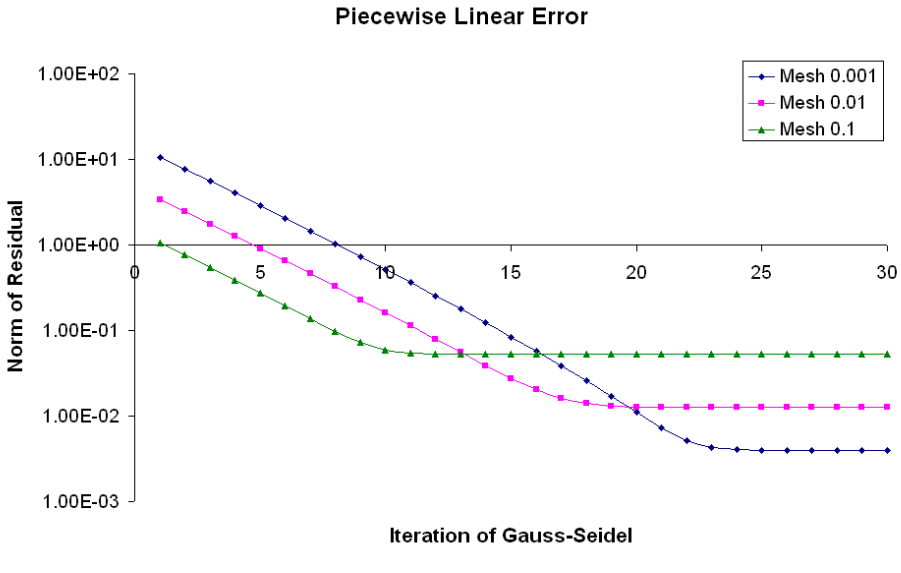


Figure 10.3: Convergence of Gauss-Seidel as Mesh Decreases

The runtime with a mesh of 0.1 was 1 minute, with a mesh of 0.01 was 5 minutes, and with a mesh of 0.001 was 51 minutes. It appears that as the mesh size decreases, the time to convergence increases exponentially.

10.1.2 Spline Interpolation

To improve the accuracy (and efficiency) of the method, a spline interpolation of the other block is used instead of assuming it is a piecewise linear constant. Algorithm 2 describes this procedure.

Algorithm 2: Spline Approximation

1. Compute a spline function of $\mathbf{x_2}$ over $[0, T]$.

2. Approximate $r_1(\mathbf{x_2})$ using the spline over subintervals of $[0, T]$.

3. Solve the first block of differential equations

4. Compute a spline function of $\mathbf{x_1}$ over $[0, T]$.

5. Approximate $r_2(\mathbf{x_1})$ by using the spline over subintervals of $[0, T]$.

6. Solve the second block of differential equations

7. Repeat steps (1) - (6) until convergence

Using the same example in Section 10.1.1 with Algorithm 2, the solutions with a mesh 0.1, 0.01, and 0.001 are given and compared in Figure 10.4. With a mesh of 0.1, the norm of the residual was 9.52×10^{-4}, converging in 25 steps. While this is more steps to convergence than the piecewise linear approximation, because the mesh is still small, the runtime was just 2 minutes. The extra time is worth the accuracy in this instance. Moreover, when the mesh is 0.01, the norm of the residual was 7.38×10^{-8}, converging in 36 steps but requiring only 26 minutes . When the mesh is 0.001, the norm of the residual was 1.85×10^{-11}, converging in 43 steps and requiring 10 hours. Most importantly, with this mesh, the ode tolerance of 10^{-10} is finally achieved. The piecewise linear approximation may never achieve this accuracy.

10.2 SIR Example

Now consider the following example, a simplified version from [13]. This model is an SIR model of Meningitis that describes two interacting populations, Group A and Group B. This example provides a natural block structure among the groups. Group A can contract the disease from Group B, and vice versa; however, a Group A individual will never become a Group B individual. Group A individuals may be thought as susceptible only to type A virus, but the virus can mutate, allowing the infection to be transmitted from a Group B

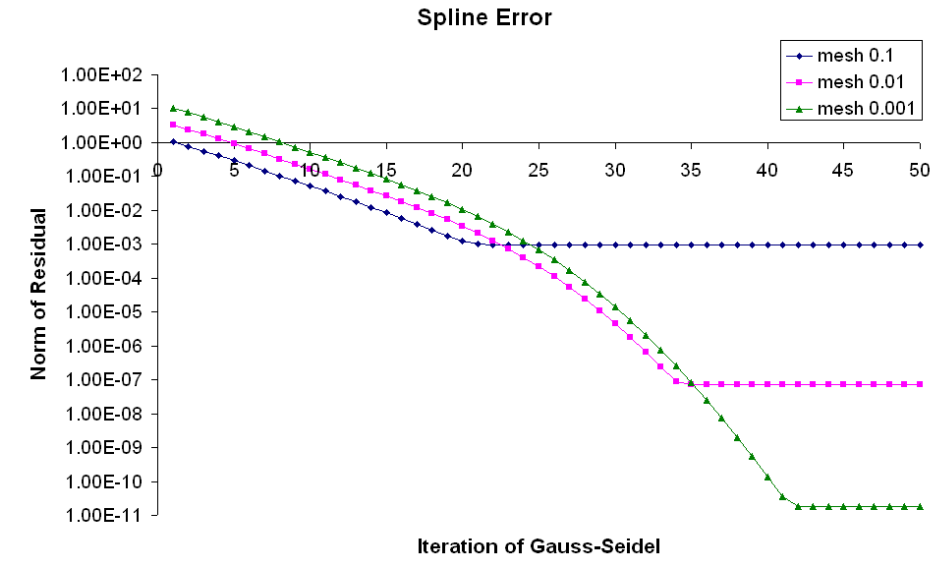


Figure 10.4: Convergence of Gauss-Seidel with Spline Method

individual. The differential equations are:

$$\begin{pmatrix} \dot{S_A} \\ \dot{I_A} \\ \dot{R_A} \\ \dot{S_B} \\ \dot{I_B} \\ \dot{R_B} \end{pmatrix} = \begin{pmatrix} -\beta S_A(I_A + \mu I_B) + \delta(I_A + R_A) \\ \beta S_A(I_A + \mu I_B) - (\rho + \delta) I_A \\ \rho I_A - \delta R_A \\ -\beta S_B(I_B + \mu I_A) + \delta(I_B + R_B) \\ \beta S_B(I_B + \mu I_A) - (\rho + \delta) I_B \\ \rho I_B - \delta R_B \end{pmatrix} \tag{10.2}$$

where β is the transmission rate, μ is the mutation rate of the pathogen (so that a Group A individual can be affected by a type B virus), ρ is the recovery rate, and δ is the death rate. For notational convenience, let $\mathbf{x} = (S_A, I_A, R_A, S_B, I_B, R_B)$ and $\mathbf{p} = (\beta, \mu, \delta, \rho)$. Notice that block 1 ($x_1$ through x_3) depends on block 2 (x_4 through x_6) and vice versa, but only through one state of either block (x_4 and x_2 respectively). Introduce the function $\mathbf{r}$ to "remove" this

coupling. If $r_1(\mathbf{x_2}) = x_5$ and $r_2(\mathbf{x_1}) = x_2$, the same system can be written as two blocks:

$$\begin{pmatrix} \dot{x_1} \\ \dot{x_2} \\ \dot{x_3} \end{pmatrix} = \begin{pmatrix} -p_1 x_1(x_2 + p_2 r_1) + p_3(x_2 + x_3) \\ p_1 x_1(x_2 + p_2 r_1) - (p_4 + p_3)x_2 \\ p_4 x_2 - p_3 x_3 \end{pmatrix} \tag{10.3}$$

$$\begin{pmatrix} \dot{x_4} \\ \dot{x_5} \\ \dot{x_6} \end{pmatrix} = \begin{pmatrix} -p_1 x_4(x_5 + p_2 r_2) + p_3(x_5 + x_6) \\ p_1 x_4(x_5 + p_2 r_2) - (p_4 + p_3)x_5 \\ p_4 x_5 - p_3 x_6 \end{pmatrix} \tag{10.4}$$

Using the initial conditions and parameters described in Table 10.1 and employing Algorithm 2, the solution on the interval $[0, 700]$ can be obtained. Define the exact solution as the solution of the fully coupled system with no iteration. The accuracy of the block solution can be compared using various mesh sizes as before. With the same ode tolerance of 10^{-10}, the norm of the residual generally decreased with mesh size. Define the relative error norm, e, by

$$e = \left\| \frac{\mathbf{x}_{exact} - \mathbf{x}_{iterated}}{\mathbf{x}_{exact}} \right\|_2 \tag{10.5}$$

Table 10.1: Parameter Values for Meningitis Model, units of all parameters are $days^{-1}$.

Parameter	Numerical Value	Interpretation
β	10^{-5}	Transmission rate
μ	10^{-5}	Mutation rate of pathogen
δ	10^{-4}	Death rate
ρ	10^{-2}	Recovery rate

With a mesh of 1.0, $e = 2.38 \times 10^{-6}$. For the remainder of this chapter, the methods will be compared based on the results from this mesh. The relative error results for various mesh sizes is given in Figure 10.5.

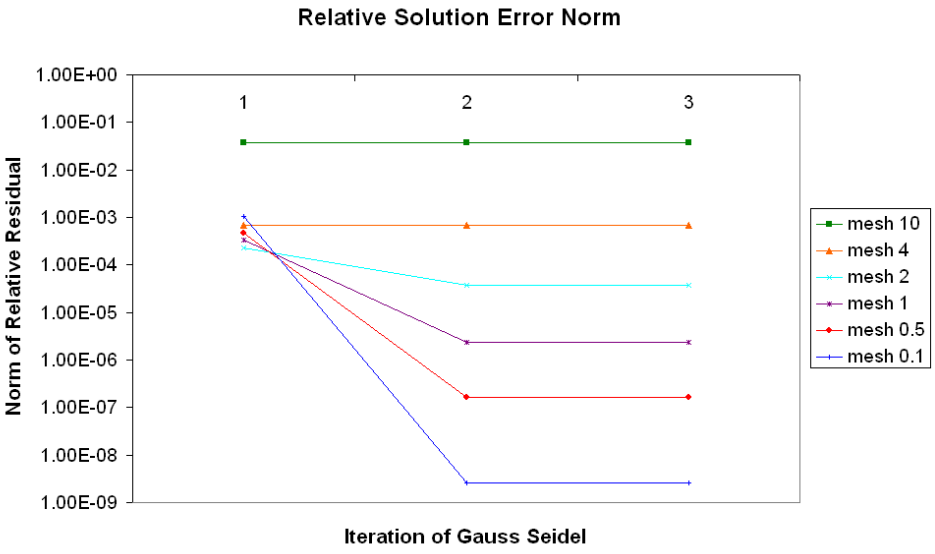


Figure 10.5: Relative Solution Errors for SIR Model

10.3 Sensitivity and Elasticity Analysis

Just as the block structure can be decoupled for the solutions, the same can be done for the sensitivities. Suppose the model is of the form of (10.1). The sensitivity equations have a different form than (3.6). Then by block, the sensitivities become

$$\left.\begin{aligned} \frac{dS_{i,k}}{dt} &= \sum_{m=\mathrm{M}_1+1}^{\mathrm{M}} \left(\frac{\partial h_i}{\partial r_1}\frac{\partial r_1}{\partial x_m}\frac{\partial x_m}{\partial p_k}\right) + \sum_{m=1}^{\mathrm{M}_1}\left(\frac{\partial h_i}{\partial x_m}\frac{\partial x_m}{\partial p_k}\right) + \frac{\partial h_i}{\partial p_k} \qquad i = 1,\ldots,\mathrm{M}_1 \\ \frac{dS_{i,k}}{dt} &= \sum_{m=1}^{\mathrm{M}_1} \left(\frac{\partial h_i}{\partial r_2}\frac{\partial r_2}{\partial x_m}\frac{\partial x_m}{\partial p_k}\right) + \sum_{m=\mathrm{M}_1+1}^{\mathrm{M}}\left(\frac{\partial h_i}{\partial x_m}\frac{\partial x_m}{\partial p_k}\right) + \frac{\partial h_i}{\partial p_k} \qquad i = \mathrm{M}_1+1,\ldots,\mathrm{M} \end{aligned}\right\} \tag{10.6}$$

These equations can be iterated using the same algorithms as the solutions. SENSAI is capable of computing the block sensitivities automatically. The sensitivities of the decoupled, iterated (10.3) and (10.4) when compared to the sensitivities of the fully coupled (10.2) were such that $e = 4.57 \times 10^{-2}$. Figure 10.6 depicts the relative error results.

The elasticity information can be computed using (3.8) as before. The iterated elasticities were such that $e = 1.64 \times 10^{-3}$. This is comparable to the relative errors of the sensitivity analysis. Figure 10.7 shows all of the relative elasticity results.

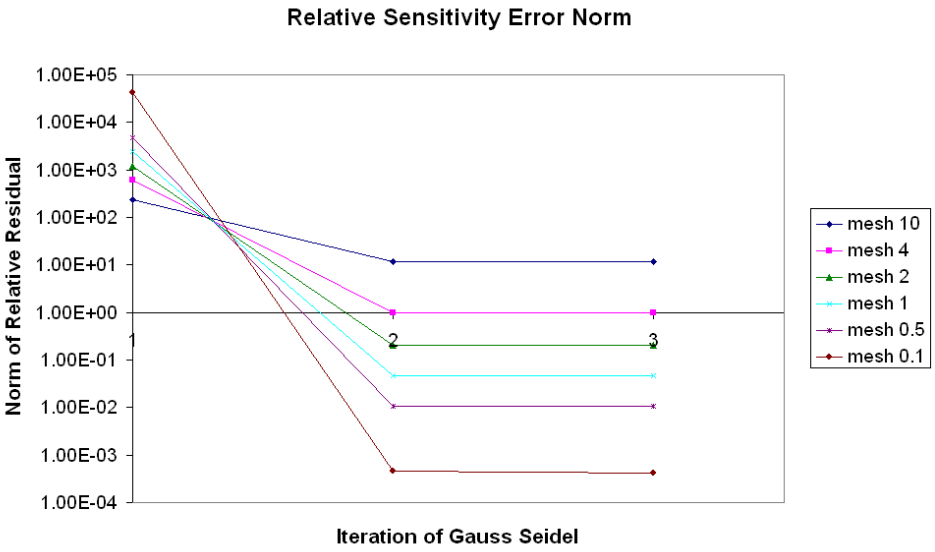


Figure 10.6: Relative Sensitivity Errors for SIR Model

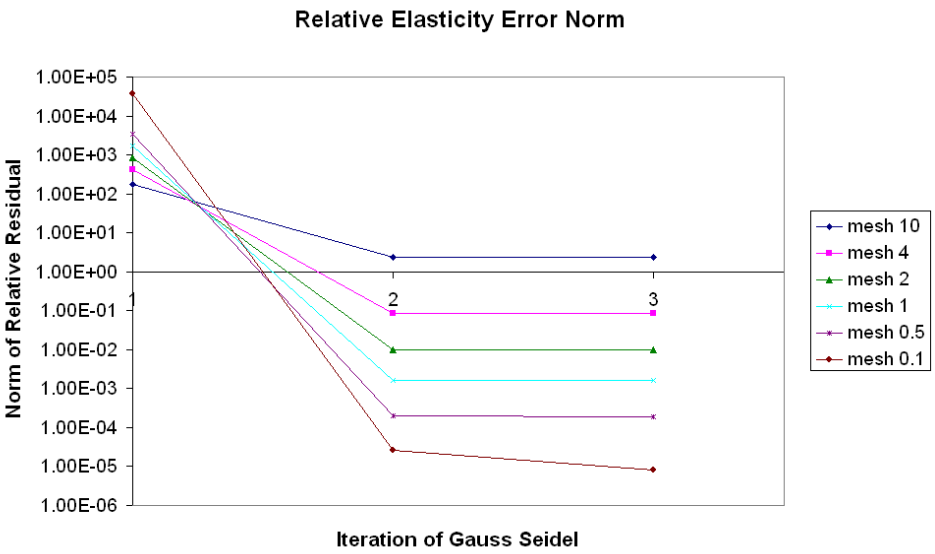


Figure 10.7: Relative Elasticity Errors for SIR Model

10.4 Involving Two Time Scales

Now suppose the model of interest has a block structure such that the first block changes on a fast time scale, but the second block changes on a slow time scale. Examples of this occur widely in biological applications, particularly in-host disease dynamics, as mentioned

previously. The population of infected individuals may change on a much slower scale than the infecting agent itself.

Another interesting example comes from physics. Consider an example from *Estep, et. al*, of a system of masses connected together by a wire [5]. Suppose two of the masses are large and the rest are small. The interaction between the large and small masses is limited to one equation involving the final large mass and the first small mass, so it is compatible with the decoupling algorithms. Moreover, since the large masses move much slower than the small masses, the system changes on two time scales. SENSAI can take advantage of this feature by solving the fast scale on a finer mesh than the slow scale. While a high degree of accuracy is needed to precisely solve the noisy fast scale, a coarse mesh can still be used for the slow scale to save storage space and reduce time to convergence.

A solution (fully coupled) of the wire-mass system described above using 1000 equally spaced mesh points is shown in Figure 10.8. Notice that the first ten equations (the positions and velocities of the small masses) change on a fast scale while the last four equations (positions and velocities of the large masses) change on a slow scale. A fine mesh is required to solve the first block but is not necessary for the second block. As with any iterative method, there is error associated with this. When the first block is solved over a mesh with 1000 time steps and the second block is solved over a mesh of 100 steps, the norm of the error (compared to the fully coupled solution using 1000 steps) is $\mathcal{O}(1)$. But, when the entire system is solved over a mesh with 1000 steps and still solved block-wise, the norm is $\mathcal{O}(10^{-7})$. This is at first startling, but can be explained. The exact solution requires a mesh of more than 1000 steps to compute, so the solution to the fully coupled system which is called the "exact solution" is flawed. The error is most apparent in the smaller mesh of 100. Analysis using a finer mesh was not continued because the time to convergence with a mesh of 1000 steps is 67 hours. Given a proper mesh and enough patience, accuracy for this method may be achieved; however, the inefficiency of decoupling the system is overwhelming.

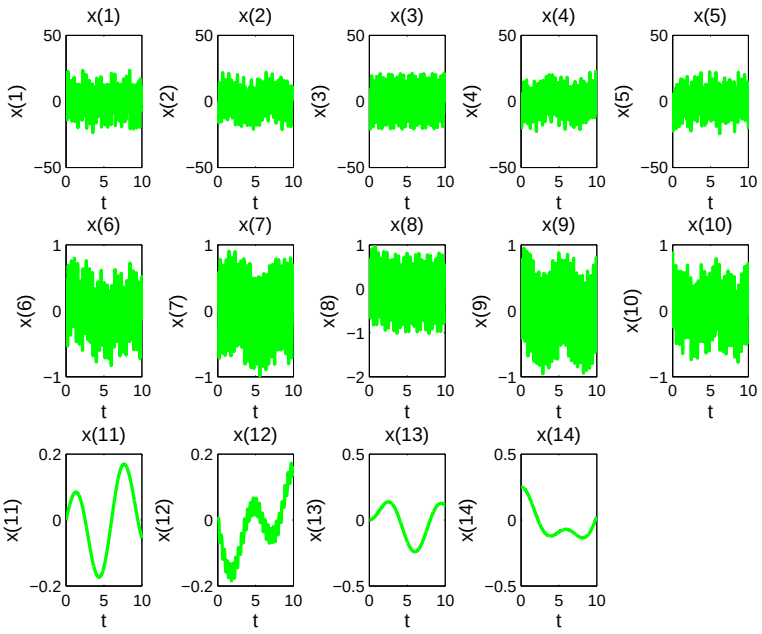


Figure 10.8: Solution to Masses on Wire

Chapter 11

CONCLUSIONS

11.1 R_0

The main focus of this dissertation was to explore the analytical techniques for ecological models, specifically R_0 and sensitivity analysis. R_0 has several advantages when analyzing models. First, it is a single number which, when the conditions of Theorems 5.6.1 or 6.1 are met, has a relevant and clear interpretation. A researcher needs only to know a single number to have a good idea of how hard or easy it will be to control the infection. Second, because the threshold for R_0 is one, the researcher will know exactly how much scaling to a parameter is needed to reduce R_0 to a value less than one by examining its elasticities (as in the Typhoid model in Section 8.2). Finally, the Next Generation construction is automated within SENSAI, and barring any special cases, can be computed with great ease.

Unfortunately, there are also many disadvantages of R_0. First, the Next Generation R_0 is not mathematically unique, as seen by Section 9.1. While the index is guaranteed to be a threshold for the model if it is well-defined, it is not guaranteed the index accurately represents the number of secondary infections from a single infected individual. Second, the Next Generation construction may not be well-defined for the given model. This occurs in models with a background infection rate as Section 9.2, but is not limited to these types of models. Any model where one or more of the assumptions fail from Theorem 5.6.1 for continuous models or from Theorem 6.1 for discrete models will not have a valid Next Generation construction. Furthermore, R_0 may not be an appropriate measure to predict infection persistence if a finite amplitude disturbance is introduced to the population rather than a single infected individual, as seen by Section 9.3. R_0 may be less than one, and this threshold may be mathematically and epidemiologically correct, but if a large number

of infected individuals enter the population at once, infection may still persist. Finally, R_0 may be slightly greater than one with infection effectively removed from the population as in Section 8.3. If the value of $R_0 = 1 + \epsilon$ for sufficiently small ϵ, the trajectories will converge to an endemic equilibrium where the number of infected individuals y is $0 < y < 1$.

Neither the list of advantages nor the list of disadvantages for R_0 are intended to be exhaustive lists.

11.2 SENSAI

Through SENSAI, a researcher can build up his or her model and specify whether or not a Next Generation R_0 is to be computed. The sensitivity and elasticity analysis will be computed automatically within SENSAI for any quantity of interest, including R_0. If a Next Generation R_0 is not valid for the model, such as models with a background infection rate, another quantity of interest should be analyzed. Because SENSAI allows for any quantity of interest to be implemented, an alternative closed form R_0 calculated by a different method than the Next Generation construction may be used. While a Next Generation R_0 is the only method automated in SENSAI, the program allows the user to compute R_0 under any other method outside of SENSAI so that the sensitivity and elasticity analysis can be computed automatically within SENSAI. If R_0 is too difficult to obtain for the model, the quantity of interest of the proportion of infected individuals may be used as a sufficient replacement. This simple quantity will always be valid for an infection model and never has an ambiguous definition or interpretation. Moreover, the information acquired from the sensitivity and elasticity analysis is much the same as that of R_0.

11.3 Block Structure

If the system of equations has a natural block structure, SENSAI can be used to solve the system and sensitivities (and elasticities) using the spline algorithm in Section 10.1.2. Given a small enough splitting of the time domain, the solution and perhaps the sensitivity

analysis can be obtained in the same accuracy as when the system is solved fully coupled. However, due to the enormity of the run time, this method is not cost effective; therefore, the code for the block-wise solutions is not available from the website.

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Appendix A

A PRACTICAL GUIDE TO USING SENSAI GUI

1. Open MATLAB.

2. Within MATLAB, change the directory to the place where the sensai.m program exists (we will call this the SENSAI directory). (e.g. C:/SENSAI/).

3. Open the SENSAI GUI by typing sensai in the MATLAB command window.

4. Using your computer's file browser, find the folder with the Maple file that contains the program and input field for the model (e.g. C:/SENSAI/Examples/ ODE_examples/SIR/, C:/SENSAI/Examples/MAP_examples/SIR/Caswell08/, etc.).

   (a) We will call this the WORKING directory.

   (b) Copy the path of the WORKING directory into the box in the upper right hand within the GUI (e.g. C:/SENSAI/Examples/ODE_examples/SIR/).

   (c) Make sure the Maple file is located in the WORKING directory. Once the file is complete, execute and save the Maple file.

5. Within MATLAB, in the GUI, select "Create MATLAB files using Maple" which creates the files gvec.m, dgvec dxvec.m, dgvec dparam.m, qoi.m and dcp dparam.m within the SENSAI directory. Note: *The active directory within MATLAB must be the same one that contains the sensai.m program, i.e. the SENSAI directory.* Wait until a popup box appears that says "MATLAB files successfully created" before continuing.

6. Within MATLAB, control of the program is through the files user_inputs.m and user_plotdata.m, in the WORKING directory with the Maple file containing the program.

(a) Via user_inputs.m you control parameter values, initial conditions, and the name of the folder in which you wish to save your work (using "JOB").

(b) Via user_plotdata.m you control which solutions (x-values) to output and plot (using "ilist"), and which parameters to have their sensitivities tested (using "klist").

7. Within MATLAB in the GUI, select "Execute MATLAB file created by Maple".

8. All of the plots of the solutions, sensitivities, and elasticities specified in the run of the model, and a file with all of the outputs from the model (output.mat) will be saved in the WORKING directory in a folder named by the variable string "JOB."

   (a) To get the solutions, sensitivity values, and elasticities into data files that can be plotted, either work within MATLAB on the data in output.mat, or ...

   (b) Use the exported information in the text files that can be imported into other programs for plotting (e.g. R). The (large number of) files each contain the solutions, sensitivities, and elasticities for the run specified above.

9. Before carrying out another run using the SENSAI GUI, within MATLAB, return to the SENSAI directory and enter the commands to clear both plots and active memory before moving on:
   >> close all, clear all

   (a) Results from a new run can be saved into another folder in the WORKING directory by changing the name of "JOB" in user_inputs.m

      - (E.g. JOB = "run2").
      - This can also be done by changing this line in the Maple file. *(But this is overkill, since you must go back to step 4.c after this point.)*
        >> JOB_NAME:= "run2"; # Sets the folder name for the output.

(b) Modify values in user_inputs.m and user_plotdata.m in the WORKING directory to explore other values.

(c) Back to step 5.

Appendix B

HOW TO DEFINE R_0 IN SENSAI

SENSAI is capable of automatically defining the basic reproduction ratio, R_0, as defined by the Next Generation method, for appropriate epidemiological models. However, SENSAI is not limited to infection modeling, so specific syntax is required so that SENSAI recognizes if a model is compatible to the definition of R_0. The following guide will instruct the user on how to edit the Maple templates so that SENSAI will produce R_0 and its sensitivity analysis.

1. Edit the Maple templates to define your model equations. These should be stored as the vector $g[i]$, the right-hand side of the equation for the variable $x[i]$.

2. Define which equations from g define the dynamics of infected classes. Store these indices in the variable $NextGen$.

   (a) For example, if the model includes three states, S, I, and R, in that order, $NextGen := [2];$.

   (b) If the model has more than one equation describing an infected class, list them in the order they appear. For example, if the model describes $S_1, I_1, R_1, S_2, I_2, R_2$ in that order, $NextGen := [2, 5];$.

   (c) *If you do not wish to calculate R_0 for the model, define $NextGen = 0$, or let the first state of $NextGen$ be 0.*

3. If the model has four or more infected classes, you may want to consider computing R_0 without its sensitivities. R_0 will be a very lengthy expression for such models, and the derivatives will require a lot of time to compute. If this is the case, define "R0_only" to be 1. If you wish to calculate the sensitivities anyway, define "R0_only" = 0.

(a) While running the SENSAI GUI, you may encounter large delays in "Create MATLAB files using Maple" if R0_only = 0. If your patience has run thin, you must terminate the program through the task manager. The emergency stop in MATLAB of CRTL+c in the command window will not work, as the computation of R_0 is done externally in a Maple procedure call.

4. If the analytical expression for R_0 is already known, it may be faster to use this expression for the quantity of interest (*qoi*) instead of re-deriving the expression during the "Create MATLAB files using Maple" phase.

There are some examples in which the Next Generation construction of R_0 is not valid, or is not compatible with SENSAI. The following are possible problems the user might encounter when trying to define R_0.

1. Problems with ODE models. Recall for ODEs, the Next Generation definition of $R_0 = \rho(FV^{-1})$ where $F = \dfrac{\partial \mathcal{F}_i}{\partial x_j}(x^\star) \quad 1 \leq i, j \leq m$ describes new infections and $V = \dfrac{\partial \mathcal{V}_i}{\partial x_j}(x^\star) \quad 1 \leq i, j \leq m$ describes transfer of existing infections, $x^\star$ is the disease-free equilibrium, the infected classes are $1, \ldots, m$, and $\rho(\cdot)$ denotes the spectral radius operator.

   (a) The fecundity matrix F is not nonnegative. This is part of assumption (A1).

   (b) The transition matrix V is singular. This can occur if an equation is in the model as a placeholder, but the right-hand side is identically 0. This state must be removed from the system for R_0 to be valid.

   (c) The disease-free subspace is not invariant. That is, infection can enter a disease-free population through a nonzero component in a state that is identified as disease-free. This can occur in models with background infection rates, or in models where the infective classes are not identified properly. This is assumption (A4).

(d) The equilibrium is not asymptotically stable in the absence of disease. That is, if $\mathcal{F} = 0$, there is an eigenvalue of the Jacobian of the full system evaluated at $x^\star$ that has a positive real part. This is assumption (A5).

2. Problems with map models. Recall for maps, the Next Generation definition of $R_0 = \rho(F(I-T)^{-1})$, where I is the $m \times m$ identity and F and $-T$ are defined the same as F and V for ODEs, respectively.

   (a) The fecundity matrix F is not nonnegative.

   (b) The transition matrix T is not nonnegative.

   (c) The transition matrix T is singular. This can occur if an equation is in the model as a placeholder, but the right-hand side is identically 0. This state must be removed from the system for R_0 to be valid.

   (d) The transition matrix T is not asymptotically stable. That is, $\rho(T) \geq 1$.

   (e) The equilibrium is not asymptotically stable in the absence of disease. That is, $\rho(C) \geq 1$ where C is the Jacobian of the right-hand side of the noninfectious states.

Notice that assumptions (A2) and (A3) for ODE models are not automatically checked by SENSAI. These assumptions must be verified by the user, but are usually true. For map models, the assumption of a unique DFE is not checked by SENSAI, nor is the condition that $F + T$ is irreducible. These should also be checked by the user to ensure a valid R_0. It is difficult to check both of these conditions, but again, for most models, $F + T$ is irreducible based on the structure of T having a nonzero main diagonal and a sub-diagonal and the structure of F having a nonzero top row.

There are a number of reasons for any of the problems in lists 1 and 2 to occur. Perhaps the model does not have a valid Next Generation construction of R_0. If this is the case, some alternative means to calculate R_0 should be sought, if desired. Alternatively, SENSAI may

not be able to recognize which terms describe new infections and belong in $\mathcal{F}$ and which terms describe transfer of existing infections and belong in $\mathcal{V}$ or $\mathcal{T}$. The following criteria are used by SENSAI to determine the placement of each term. If the terms of the model will not be placed in the biologically correct vectors, SENSAI fails to compute the Next Generation R_0.

1. If the term X in an equation describing an infective class involves a state variable from a noninfectious class, $X \in \mathcal{F}$, unless the occurrence of the noninfectious state variable is part of a sum of all state variables (that is, the term is scaled by the total population).

2. If the term X in an equation describing an infective class does not involve any state variables and is only a parameter, product of parameters, or quotient of parameters, $X \in \mathcal{F}$. If terms like these exist, the disease-free subspace will not be invariant, and the model will not have a valid Next Generation R_0.

3. Every other term X that does not satisfy the above will be placed in $\mathcal{V}$ for ODEs, or $\mathcal{T}$ for maps.