Modeling and Global Stability Analysis of Ebola Models

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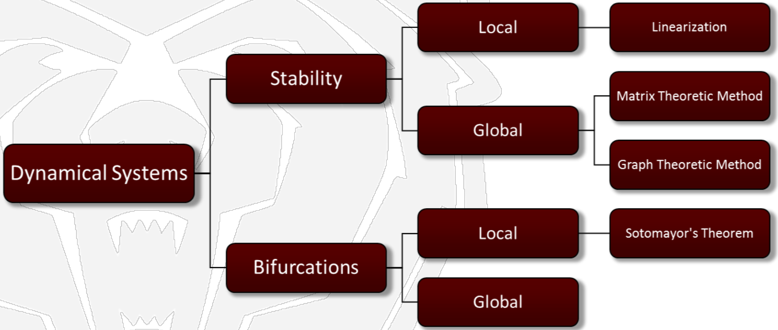
Outline


Dynamical Systems
Stability
Bifurcations
Local
Global
Local
Global
Linearization
Matrix Theoretic Method
Graph Theoretic Method
Sotomayor's Theorem

Dynamical Systems

- A dynamical system may be defined as

$$\dot{\mathbf{z}} = \mathbf{f}(\mathbf{z}, \lambda)$$
$$\mathbf{z} \in \mathbb{R}^n, \ \lambda \in \mathbb{R}^m,$$
$$\mathbf{f} : \mathbb{R}^n \to \mathbb{R}^n.$$

- A system has a equilibrium point when there exists a $\mathbf{z_0} \in \mathbb{R}^n$ such that $\mathbf{f}(\mathbf{z_0}, \lambda) = 0$

Outline

- Dynamical Systems
  - Stability
    - Local
      - Linearization
    - Global
      - Matrix Theoretic Method
      - Graph Theoretic Method
  - Bifurcations
    - Local
      - Sotomayor's Theorem
    - Global

Equilibria Types and Stability Analysis

- Hyperbolic Equilibrium
  - Linearization
  - Stable Manifold Theorem and Hartman-Grobman Theorem
- Non-hyperbolic Equilibrium
  - Center Manifold Theorem
  - Liapunov Functions

Linearization

- Study linear systems $\dot{\mathbf{z}} = A\mathbf{z}$.
- A system is linearized using the Jacobian

$$A = D\mathbf{f}(z_0) = \begin{bmatrix} \frac{\delta f_1}{\delta z_1}(z_0) & \dots & \frac{\delta f_1}{\delta z_n}(z_0) \\ \vdots & \ddots & \vdots \\ \frac{\delta f_n}{\delta z_1}(z_0) & \dots & \frac{\delta f_n}{\delta z_n}(z_0) \end{bmatrix}.$$

- Local stability of an equilibrium point of a linear system is determined by looking at the real part of the eigenvalues of $A = D\mathbf{f}(z_0)$.

Local Center Manifold Theorem

Let $\mathbf{f} \in C^r(E)$ where E is an open subset of $\mathbb{R}^n$ containing the origin and $r \geq 1$. Suppose that $\mathbf{f}(0) = 0$ and that $D\mathbf{f}(0)$ has c eigenvalues with zero real parts and s eigenvalues with negative real parts, where $c + s = n$. The nonlinear system $x' = \mathbf{f}(x)$ can then be written in diagonal form

$$\begin{aligned} \dot{\mathbf{x}} &= C\mathbf{x} + \mathbf{F}(\mathbf{x}, \mathbf{y}) \\ \dot{\mathbf{y}} &= P\mathbf{y} + \mathbf{G}(\mathbf{x}, \mathbf{y}). \end{aligned}$$

where $(x, y) \in \mathbb{R}^c \times \mathbb{R}^s$, $\mathbf{C}$ is a square matrix with c eigenvalues having zero real part, $\mathbf{P}$ is a square matrix with s eigenvalues having negative real part, and $\mathbf{F}(0) = \mathbf{G}(0) = 0$, $D\mathbf{F}(0) = D\mathbf{G}(0) = 0$; furthermore, there exists a $\delta > 0$ and function $h \in C^r(N_\delta(0))$ that defines the local center manifold and satisfies

Local Center Manifold Theorem

$$D\mathbf{h}(\mathbf{x})[C\mathbf{x} + \mathbf{F}(\mathbf{x}, \mathbf{h}(\mathbf{x}))] - P\mathbf{h}(\mathbf{x}) - \mathbf{G}(\mathbf{x}, \mathbf{h}(\mathbf{x})) = 0$$

for $|x| < \delta$; and the flow on the center manifold W^c is defined by the system of differential equations $x' = \mathbf{C}x + \mathbf{F}(x, h(x))$ for all $x \in \mathbb{R}^c$ with $|x| < \delta$.

Basic Reproduction Number

- The reproduction number, R_0, is defined biologically as the average number of individuals infected by a single infected individual entering the susceptible population.
- R_0 is defined mathematically as the spectral radius, $\rho(A)$, of matrix A which is the Next Generation Matrix (FV^{-1}).

Ebola Background Information

- The 2014 Ebola outbreak in West Africa was one of the most devastating disease outbreaks in recent history.
- Ebola virus disease (EVD) is spread through direct transmission, and is often transmitted to those in close contact with infected individuals.
- The average fatality rate of the Ebola disease is around 50%, and case rates have varied from 25% to 90%.
- The Ebola virus has no vaccine, although multiple candidate vaccines are undergoing clinical trial.
- From 2014-2016, the Ebola outbreak in West Africa, primarily in the countries of Guinea, Sierra Leone, and Liberia, had 11,310 confirmed Ebola deaths.

Shen Model

Consider the following 8-dimensional model proposed by Shen et. al. in 2015 to model the Ebola virus

$$
\begin{aligned}
S' &= -\frac{(\beta I+\beta\varepsilon J+\beta_D D)S}{N} - \xi S \\
V' &= \xi S + \frac{(\beta I+\beta\varepsilon J+\beta_D D)\eta V}{N} \\
E_1' &= \frac{(\beta I+\beta\varepsilon J+\beta_D D)(S+\eta V)}{N} - k_1 E_1 \\
E_2' &= k_1 E_1 - (k_2 + f_T)E_2 \\
I' &= k_2 E_2 - (\alpha + \gamma) I \\
J' &= f_T E_2 + \alpha I + \gamma_r J \\
D' &= \delta_\gamma I + \delta_{\gamma_r} J - \gamma_D D \\
R' &= (1-\delta)\gamma I + (1-\delta)\gamma_r J
\end{aligned}
$$

Shen Model

This model has a few major issues including

- Shen assumes a small time scale, so there are no enedemic equilibrium points.
- Shen has no population growth terms, so susceptible individuals can only exist if there is no disease.
- Shen assumes a constant population N. N is defined mathematically as $N = S + V + \cdots + R$ though.

Shen Model Modified

I have proposed the following potential modifications to this original model

- Shen's model could be modified to keep individuals from leaving the system by assuming no individuals die.
- Shen's model could be modified to substitute the summation of variables in for N.
- Shen's model could be generalized by adding natural population growth and death terms, allowing N to represent a maximum population instead of a total population

I have chosen to do stability analysis on the original Shen model, the first proposed modified model, and the generalized Shen model. We will examine the stability of the original and generalized model shortly.

Original Shen Model Local Stability

- The original Shen model has the disease free equilibrium points $DFE_1 = (0, \tilde{V}, 0, 0, 0, 0, 0, \tilde{R})$ with $\tilde{V} \geq 0, \tilde{R} \geq 0$, and $\tilde{V} + \tilde{R} = N$.
- If we assume there is no vaccine, we may also have equilibrium points of the form $DFE_2 = \tilde{S}, 0, 0, 0, 0, 0, \tilde{R})$ with $\tilde{S} \geq 0$, and $\tilde{S} + \tilde{R} = N$.
- While the origin is not biologically relevant due to the assumption that N is a fixed parameter, it is still interesting mathematically.

Theorem 1

Theorem (1)

If the system has initial condition $V_0 = 0$, then the Shen Model is locally asymptotically stable at the origin.

Theorem 1 Proof

Computing the Jacobian of this system and evaluating the Jacobian at the origin gives us:

$$\mathbf{J}(0,...,0) = \begin{bmatrix} -\xi & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \xi & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -k_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & k_1 & -f_T - k_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & k_2 & -a-\gamma & 0 & 0 & 0 \\ 0 & 0 & 0 & f_T & \alpha & -\gamma_r & 0 & 0 \\ 0 & 0 & 0 & 0 & \delta\gamma & \delta\gamma_r & -\gamma_D & 0 \\ 0 & 0 & 0 & 0 & -\gamma(\delta-1) & -\gamma_r(\delta-1) & 0 & 0 \end{bmatrix}$$

which has eigenvalues

$$\lambda = 0, 0, -k_1, -\xi, -\delta\gamma, -\gamma_r, -f_T - k_2, -\alpha - \gamma$$

Theorem 1 Proof Continued(1)

However, since this equation has eigenvalues with zero real part, we want to consider the Jacobian in a block diagonalized form. To do this, we permute the equations of the system to get

$$\begin{aligned}
R' &= (1-\delta)\gamma I + (1-\delta)\gamma_r J \\
V' &= \xi S - \frac{(\beta I + \beta\varepsilon J + \beta_D D)\eta V}{N} \\
E_1' &= \frac{(\beta I + \beta\varepsilon J + \beta_D D)(S + \eta V)}{N} - k_1 E_1 \\
E_2' &= k_1 E_1 - (k_2 + f_T) E_2 \\
I' &= k_2 E_2 - (\alpha + \gamma) I \\
J' &= f_T E_2 + \alpha I - \gamma_r J \\
D' &= \delta\gamma I + \delta\gamma_r J - \gamma_D D \\
S' &= -\frac{(\beta I + \beta\varepsilon J + \beta_D D) S}{N} - \xi S
\end{aligned}$$

Theorem 1 Proof Continued(2)

Computing the Jacobian of this system and evaluating it at the disease free equilibrium gives us:

$$\mathbf{J}(0,\dots,0) = \left[\begin{array}{cc|cccccc} 0 & 0 & 0 & 0 & \gamma(1-\delta) & \gamma_r(1-\delta) & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \xi \\ \hline 0 & 0 & -k_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & k_1 & -f_T - k_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & k_2 & -a-\gamma & 0 & 0 & 0 \\ 0 & 0 & 0 & f_T & \alpha & -\gamma_r & 0 & 0 \\ 0 & 0 & 0 & 0 & \delta\gamma & \delta\gamma_r & -\gamma_D & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\xi \end{array}\right]$$

Theorem 1 Proof Continued(3)

Finally, using a similarity transformation, we find the matrix in block diagonalized form below.

$$\tilde{J}(0,\ldots,0)=\left[\begin{array}{cc|cccccc} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \hline 0 & 0 & -k_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\xi & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\gamma_D & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\gamma_r & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -f_T-k_2 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\alpha-\gamma \end{array}\right]$$

This matrix has eigenvalues

$$\lambda=0,0,-k_1,-\xi,-\gamma_D,-\gamma_r,-f_T-k_2,-\alpha-\gamma$$

Theorem 1 Proof Continued(4)

We now consider the behavior of solutions on the center manifold. Using the center manifold theorem, we rewrite the system as follows.

$$\dot{\mathbf{x}} = \begin{bmatrix} 0 & 0 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} \mathbf{x} \end{bmatrix} + \begin{bmatrix} (1-\delta)\gamma I + (1-\delta)\gamma_r \tilde{J} \\ \xi S - \frac{(\beta\tilde{I}+\beta\varepsilon\tilde{J}+\beta_D\tilde{D})\eta V}{N} \end{bmatrix}$$

$$\dot{\mathbf{y}} = \begin{bmatrix} -k_1 & 0 & 0 & 0 & 0 & 0 \\ k_1 & -(k_2+f_T) & 0 & 0 & 0 & 0 \\ 0 & k_2 & -(\alpha+\gamma) & 0 & 0 & 0 \\ 0 & f_T & \alpha & -\gamma_r & 0 & 0 \\ 0 & 0 & \delta\gamma & \delta\gamma_r & -\gamma_D & 0 \\ 0 & 0 & 0 & 0 & 0 & -\xi \end{bmatrix} \begin{bmatrix} \mathbf{y} \end{bmatrix} + \begin{bmatrix} \frac{(\beta I+\beta\varepsilon J+\beta_D D)(S+\eta V)}{N} \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ -\frac{(\beta I+\beta\varepsilon J+\beta_D D)(S)}{N} \end{bmatrix}$$

Theorem 1 Proof Continued(5)

We now consider the approximation to the center manifold given by:

$$h(x) = \begin{bmatrix} \psi_1 R^2 + \psi_2 RV + \psi_3 V^2 + O(x^3) \\ \psi_4 R^2 + \psi_5 RV + \psi 6 V^2 + O(x^3) \\ \vdots \\ \psi_{16} R^2 + \psi_{17} RV + \psi_{18} V^2 + O(x^3) \end{bmatrix}$$

Substituting $h(x)$ into the equation

$$D\mathbf{h}(\mathbf{x})[C\mathbf{x} + \mathbf{F}(\mathbf{x}, \mathbf{h}(\mathbf{x}))] - P\mathbf{h}(\mathbf{x}) - \mathbf{G}(\mathbf{x}, \mathbf{h}(\mathbf{x})) = 0$$

Theorem 1 Proof Continued(6)

- $$O(x^3) - Ph(x) = 0$$
- Solving for the coefficients ψ_i in Matlab yields that this equation only holds if $\psi_i = 0$ for all i. Hence, we have $h(x) = 0$.
- Substituting $h(x) = 0$ into the approximation to the center manifold $\mathbf{x} = Cx + F(x, h(x))$ we get
- $$\dot{\mathbf{x}} = 0$$

Theorem 1 Proof Continued(7)

$$R = R(0)$$
$$V = S(0)$$

Where $R(0)$ and $S(0)$ correspond to the initial conditions of those equations. $R(0)$ can reasonably be assumed to have intial condition $R(0) = 0$, but V could start from any value. However, using the initial assumption of the theorem, $V(0) = 0$. Therefore, the origin is locally asymptotically stable.

Difficulties of local stability

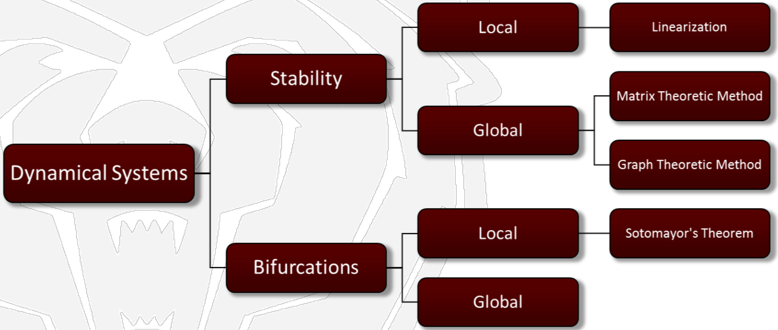
- Computational difficulties of local stability at other equilibrium points
- Computational difficulties with more complex models
- Global Stability

Example Jacobian

$$J = \begin{bmatrix} -\mu-\xi-X & 0 & 0 & 0 & X & X & X & 0 \\ \xi & -\mu-X & 0 & 0 & X & X & X & 0 \\ X & X & -k_1-\mu & 0 & X & X & X & 0 \\ 0 & 0 & k_1 & -f_T-k_2-\mu & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & k_2 & -\alpha-\mu-\gamma & 0 & 0 & 0 \\ 0 & 0 & 0 & f_T & \alpha & -\mu-\gamma_r & 0 & 0 \\ 0 & 0 & 0 & 0 & \delta\gamma & \delta\gamma_r & -\gamma_D & 0 \\ 0 & 0 & 0 & 0 & \gamma(1-\delta) & \gamma_r(1-\delta) & 0 & -\mu \end{bmatrix}$$

The X's in the Jacobian evaluated at the endemic equilibrium point represent very large, real-valued entries that weren't feasible to be displayed here.

Outline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Theorem 2.1 [Shuai and Van Den Driessche]

Goal is to construct a Liapunov function, Q.

If

- $\mathbf{f}(x, y) \geq 0$ in $\Gamma \subset \mathbb{R}_+^{p+q}$,
- $\mathbf{F} \geq 0$, $\mathbf{V}^{-1} \geq 0$, and
- $R_0 \leq 1$.

Then the function

$$Q = \omega^T \mathbf{V}^{-1} \mathbf{x}$$

where ω is the left eigenvector of $\mathbf{FV^{-1}}$ associated with R_0 is a Liapunov function for the system on Γ.

Theorem 2.2 [Shuai and Van Den Driessche]

If

- $\Gamma \subset \mathbb{R}_+^{p+q}$ is compact such that $(0, y_0) \in \Gamma$,
- Γ is positively invariant with respect to the system,
- $\dot{\mathbf{y}} = g(0, y)$ has a unique equilibrium $y = y_0 > 0$ that is GAS in $\mathbb{R}_+^q$,
- $\mathbf{f}(x, y) \geq 0$ with $\mathbf{f}(x, y_0) = 0$ in Γ, and
- $\mathbf{F} \geq 0$, $\mathbf{V}^{-1} \geq 0$, $\mathbf{V}^{-1}\mathbf{F}$ be irreducible.

Then

- If $R_0 < 1$, then the DFE is GAS in Γ.
- If $R_0 > 1$, then the DFE is unstable, the system is uniformly persistent, and there exists at least one endemic equilibrium point.

Original Shen Model

$$
\begin{aligned}
S' &= -\frac{(\beta I+\beta\varepsilon J+\beta_D D)S}{N} - \xi S\\
V' &= \xi S + \frac{(\beta I+\beta\varepsilon J+\beta_D D)\eta V}{N}\\
E_1' &= \frac{(\beta I+\beta\varepsilon J+\beta_D D)(S+\eta V)}{N} - k_1 E_1\\
E_2' &= k_1 E_1 - (k_2 + f_T)E_2\\
I' &= k_2 E_2 - (\alpha+\gamma)I\\
J' &= f_T E_2 + \alpha I + \gamma_r J\\
D' &= \delta_\gamma I + \delta_{\gamma_r} J - \gamma_D D\\
R' &= (1-\delta)\gamma I + (1-\delta)\gamma_r J
\end{aligned}
$$

- First, we proved that we have a feasible region $\Gamma = \left\{z \in \mathbb{R}^8 : z \geq 0, z \leq K\right\}$ which is compact and positively invariant.

Theorem 2.2 [Shuai and Van Den Driessche]

If

- ✓ $\Gamma \subset \mathbb{R}_+^{p+q}$ be compact such that $(0, y_0) \in \Gamma$,
- ✓ Γ be positively invariant with respect to the system,
  - $\dot{\mathbf{y}} = g(0, y)$ has a unique equilibrium $y = y_0 > 0$ that is GAS in $\mathbb{R}_+^q$,
  - $\mathbf{f}(x, y) \geq 0$ with $\mathbf{f}(x, y_0) = 0$ in Γ, and
  - $\mathbf{F} \geq 0$, $\mathbf{V}^{-1} \geq 0$, $\mathbf{V}^{-1}\mathbf{F}$ be irreducible.

Then

- If $R_0 < 1$, then the DFE is GAS in Γ.
- If $R_0 > 1$, then the DFE is unstable, the system is uniformly persistent, and there exists at least one endemic equilibrium point.

Shen Model: Equilibrium Point

- The Disease-Free Equilibrium (DFE) is the origin which is contained in Γ where
- The origin is GAS in the disease-free subsystem because

$$
\begin{aligned}
S' &= -\xi S \\
V' &= \xi S \\
R' &= 0
\end{aligned}
$$

- So we have solution

$$
\begin{aligned}
S &= e^{-\xi t} \\
V &= -e^{-\xi t} \\
R &= R(0)
\end{aligned}
$$

Theorem 2.2 [Shuai and Van Den Driessche]

If

- ✓ $\Gamma \subset \mathbb{R}_+^{p+q}$ be compact such that $(0, y_0) \in \Gamma$,
- ✓ Γ be positively invariant with respect to the system,
- ✓ $\dot{\mathbf{y}} = g(0, y)$ has a unique equilibrium $y = y_0 > 0$ that is GAS in $\mathbb{R}_+^q$,
- $\mathbf{f}(x, y) \geq 0$ with $\mathbf{f}(x, y_0) = 0$ in Γ, and
- $\mathbf{F} \geq 0$, $\mathbf{V}^{-1} \geq 0$, $\mathbf{V}^{-1}\mathbf{F}$ be irreducible.

Then

- If $R_0 < 1$, then the DFE is GAS in Γ.
- If $R_0 > 1$, then the DFE is unstable, the system is uniformly persistent, and there exists at least one endemic equilibrium point.

Shen Model Global Stability at DFE (1)

- First, we considered the global stability of the system at the origin, and then at DFE_1.
- We will be considering the global stability of the system with the assumption that there is no vaccine.

Shen Model Global Stability at DFE (2)

- This gives us the 7-dimensional system

$$
\begin{aligned}
S' &= -\frac{(\beta I + \beta \varepsilon J + \beta_D D)S}{N} \\
E_1' &= \frac{(\beta I + \beta \varepsilon J + \beta_D D)(S)}{N} - k_1 E_1 \\
E_2' &= k_1 E_1 - (k_2 + f_T) E_2 \\
I' &= k_2 E_2 - (\alpha + \gamma) I \\
J' &= f_T E_2 + \alpha I - \gamma_r J \\
D' &= \delta \gamma I + \delta \gamma_r J - \gamma_D D \\
R' &= (1-\delta)\gamma I + (1-\delta)\gamma_r J
\end{aligned}
$$

Shen Model Global Stability at DFE (3)

- The feasible region Γ remains the same.
- $$\dot{x} = \begin{bmatrix} \frac{(\beta I + \beta \varepsilon J + \beta_D D)(S)}{N} \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} - \begin{bmatrix} k_1 E_1 \\ -k_1 E_1 + (k_2 + f_T) E_2 \\ -k_2 E_2 + (\alpha + \gamma) I \\ -f_T E_2 - \alpha I + \gamma_r J \\ -\delta \gamma I - \delta \gamma_r J + \gamma_D D \end{bmatrix}$$

$$\dot{y} = \begin{bmatrix} -\frac{(\beta I + \beta \varepsilon J + \beta_D D)(S)}{N} \\ (1-\delta)\gamma I + (1-\delta)\gamma_r J \end{bmatrix}$$

Shen Model Global Stability at DFE (4)

$$\mathbf{F}(0, y_0) = \begin{bmatrix} 0 & 0 & \frac{(S)\beta}{N} & \frac{(S)\beta\varepsilon}{N} & \frac{(S)\beta_D}{N} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$\mathbf{V}(x, y) = \begin{bmatrix} k_1 & 0 & 0 & 0 & 0 \\ -k_1 & k_2 + f_T & 0 & 0 & 0 \\ 0 & -k_2 & \alpha + \gamma & 0 & 0 \\ 0 & -f_T & -\alpha & \gamma_r & 0 \\ 0 & 0 & -\delta\gamma & -\delta\gamma_r & \gamma_D \end{bmatrix}$$

Shen Model Global Stability at DFE (5)

- $$\mathbf{f}(x,y) = \begin{bmatrix} (\tilde{S}-S)(\frac{\beta I+\beta\varepsilon J+\beta_D D}{N}) \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$
- If $\tilde{S} = N$, then $f(x,y) \geq 0$.
- For now, we will assume $\tilde{S} = N$.

Shen Model Global Stability at DFE (6)

- We calculated FV^{-1} and $V^{-1}F$ explicitly. FV^{-1} is a matrix with positive entries in the first row and zero entries everywhere else. $V^{-1}F$ has two columns of zeros and positive entries everywhere else.

Theorem [Seneta]

Let $A_{n\times n}$ be irreducible and Metzler. Then the eigenvalue with largest real part is real and it has a positive associated eigenvector.

- Using the next generation matrix FV^{-1}, we find R_0 to be

Basic Reproduction Number

$$
\begin{aligned}
R_0 \quad = \quad & \rho(FV^{-1}) = (1-\theta)\beta\frac{1}{\alpha+\gamma} \\
& +\beta\varepsilon\left[(1-\theta)(\frac{\alpha}{\alpha+\gamma})(\frac{1}{\gamma_r}) + \theta\frac{1}{\gamma_r}\right] + \delta\beta_D\frac{1}{\gamma_D}
\end{aligned}
$$

with the substitution $1-\theta = \frac{k_2}{k_2+f_T}$.

Shen Model Global Stability at DFE (7)

- Let w^T be defined as the left eigenvector corresponding to R_0 in $(FV^{-1})^T$.
- $(0, y_0) \in \Gamma$, Γ is positively invariant, $f(x, y) \geq 0$ with $f(x, y_0) = 0 \in \Gamma$, and F and V^{-1} are both non-negative.
- While $V^{-1}F$ is not irreducible, irreducibility was only used to show the non-negative condition of w^T in the proof of Shuai Theorem 2.2.
- Considering the disease free system $\dot{y} = g(x, y)$ with the disease compartment set equal to 0, we have the system

Shen Model Global Stability at DFE (8)

-

$$\begin{aligned} \frac{dS}{dt} &= 0 \\ \frac{dR}{dt} &= 0 \end{aligned}$$

- This has the unique solution

$$\begin{aligned} S &= S(0) \\ R &= R(0) \end{aligned}$$

Shen Model Global Stability at DFE (9)

- Assuming the disease free system starts at values $S_0 = \tilde{S}$ and $R_0 = \tilde{R}$, we find that the disease free system has a unique globally asymptotically stable solution. Therefore, we may conclude by Shuai Theorem 2.2:
- If $R_0 < 1$, then the disease free equilibrium point is globally asymptotically stable in Γ
- If $R_0 > 1$, then the disease free equilibrium point is unstable, and there exists at least one endemic equilibrium point.

Theorem 2.2 [Shuai and Van Den Driessche]

If

- ✓ $\Gamma \subset \mathbb{R}_{+}^{p+q}$ be compact such that $(0, y_0) \in \Gamma$,
- ✓ Γ be positively invariant with respect to the system,
- ✓ $\dot{\mathbf{y}} = g(0, y)$ has a unique equilibrium $y = y_0 > 0$ that is GAS in $\mathbb{R}_{+}^{q}$,
- ✓ $\mathbf{f}(x, y) \geq 0$ with $\mathbf{f}(x, y_0) = 0$ in Γ, and
- ✓ $\mathbf{F} \geq 0$, $\mathbf{V}^{-1} \geq 0$, $\mathbf{V}^{-1}\mathbf{F}$ be irreducible.

Then

- If $R_0 < 1$, then the DFE is GAS in Γ.
- If $R_0 > 1$, then the DFE is unstable, the system is uniformly persistent, and there exists at least one endemic equilibrium point.

Shen Model Global Stability at DFE: Conclusions

- This result may seem quite useful at first glance, but upon examining the assumptions made during this proof we find that this result only holds if $S_0 = \tilde{S} = N$.
- We turn to modified models to attempt to better understand the stability of such a system.

Modified Shen Model

- Consider the following modified Shen Model

$$
\begin{aligned}
S' &= -\frac{(\beta I+\beta\varepsilon J)S}{N} - \xi S \\
V' &= \xi S - \frac{(\beta I+\beta\varepsilon J)\eta V}{N} \\
E_1' &= \frac{(\beta I+\beta\varepsilon J)(S+\eta V)}{N} - k_1 E_1 \\
E_2{}' &= k_1 E_1 - (k_2 + f_T)E_2 \\
I' &= k_2 E_2 - (\alpha+\gamma)I \\
J' &= f_T E_2 + \alpha I - \gamma_r J \\
R' &= \gamma I + \gamma_r J
\end{aligned}
$$

Equilibrium Points, Local Stability, and Global Stability

- Equilibrium points have the form $(0, \tilde{V}, 0, 0, 0, 0, \tilde{R})$ where $\tilde{V} \geq 0$ and $\tilde{R} \geq 0$. Assuming there is no vaccine, equilibrium points may take the form $(\tilde{S}, 0, 0, 0, 0, \tilde{R})$ with $\tilde{S} \geq 0$.
- Local stability and global stability is similar to the original model

Generalized Shen Model

- Consider the following generalized Shen Model

$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda - \frac{(\beta I + \beta\varepsilon J + \beta_D D)S}{N} - \xi S - \mu S \\
\frac{dV}{dt} &= \xi S - \frac{(\beta I + \beta\varepsilon J + \beta_D D)\eta V}{N} - \mu V \\
\frac{dE_1}{dt} &= \frac{(\beta I + \beta\varepsilon J + \beta_D D)(S + \eta V)}{N} - k_1 E_1 - \mu E_1 \\
\frac{dE_2}{dt} &= k_1 E_1 - (k_2 + f_T)E_2 - \mu E_2 \\
\frac{dI}{dt} &= k_2 E_2 - (\alpha + \gamma)I - \mu I \\
\frac{dJ}{dt} &= f_T E_2 + \alpha I - \gamma_r J - \mu J \\
\frac{dD}{dt} &= \delta\gamma I + \delta\gamma_r J - \gamma_D D \\
\frac{dR}{dt} &= (1-\delta)\gamma I + (1-\delta)\gamma_r J - \mu R
\end{aligned}
$$

Equilibrium Points(1)

- The disease free equilibrium point can be easily calculated to be $DFE_1 = (\frac{\Lambda}{\xi+\mu}, \frac{\Lambda\xi}{\mu(\xi+\mu)}, 0, 0, 0, 0, 0, 0) = (\tilde{S}, \tilde{V}, 0, 0, 0, 0, 0, 0)$ by setting the derivatives and disease variables equal to zero.
- To calculate the endemic equilibrium point, we first rewrote E_2^*, I^*, J^*, and D^* in terms of E_1^* and solved for S^*, V^*, E_1^*. We calculated

Equilibrium Points(2)

$$
\begin{aligned}
S^* &= \frac{\Lambda N}{N\mu+N\xi+\beta_D D^*+\beta I^*+\beta\varepsilon J^*}\\
V^* &= \frac{\Lambda N^2\xi}{(N\mu+\beta_D D^*\eta+\beta I^*\eta+\beta\varepsilon J^*\eta)(N\mu+N\xi+\beta_D D^*+\beta I^*+\beta\varepsilon J^*)}\\
E_1^* &= \frac{(\Lambda(\beta_D D^*+\beta I^*+\beta\varepsilon J^*)(N\mu+\beta_D D^*\eta+\beta I^*\eta+N\eta\xi+\beta\varepsilon J^*\eta))}{(k_1+\mu)(N\mu+\beta_D D^*\eta+\beta I^*\eta+\beta\varepsilon J^*\eta)(N\mu+N\xi+\beta_D D^*+\beta I^*+\beta\varepsilon J^*))}\\
E_2^* &= \frac{k_1}{k_2+f_T+\mu}E_1^*\\
I^* &= \frac{k_1k_2}{(\alpha+\gamma+\mu)(k_2+f_T+\mu)}E_1^*\\
J^* &= \frac{k_1(f_T(\alpha+\gamma+\mu)+\alpha k_2)}{(\mu+\gamma_r)(k_2+f_T+\mu)(\alpha+\gamma+\mu)}E_1^*\\
D^* &= \frac{\delta k_1(k_2\gamma\mu+k_2\gamma\gamma_r+\gamma_r\alpha k_2+\gamma_r f_T(\alpha+\gamma+\mu))}{\gamma_D(\mu+\gamma_r)(k_2+f_T+\mu)(\alpha+\gamma+\mu)}E_1^*\\
R^* &= \frac{(1-\delta)k_1(k_2\gamma\mu+k_2\gamma\gamma_r+\gamma_r\alpha k_2+\gamma_r f_T(\alpha+\gamma+\mu))}{\mu\gamma_D(\mu+\gamma_r)(k_2+f_T+\mu)(\alpha+\gamma+\mu)}E_1^*
\end{aligned}
$$

Global Stability of Generalized Shen model

- We now consider the global stability of the disease free equilibrium point for this generalized model.

Theorem (2)

Assume that the initial values of the system satisfies at least one of

- *The total population of the system is less than or equal to* $\frac{\Lambda}{\xi+\mu} + \frac{\eta\xi}{\mu(\xi+\mu)}$
- *The vaccinated population is greater than* $\tilde{V}$

Then the disease free equilibrium point of the generalized Shen model is globally asymptotically stable if the basic reproduction number $R_0 < 1$*, and if* $R_0 > 1$ *the disease free equilibrium point is unstable and there must exist at least one endemic equilibrium point.*

Proof of Theorem 2 (1)

- First we consider the feasible region of this system

$$(S' + V' + \cdots + R') = \Lambda - \mu(S + V + \cdots + R) - \gamma_D D + \mu D$$

- We may assume $\gamma_D > \mu$ without loss of generality (biologically, this should be true for Ebola outbreaks). Hence, we get

$$\begin{aligned} (S' + V' + \cdots + R') &\leq \Lambda - \mu(S + V + \cdots + R) \\ S + V + \cdots + R &\leq \frac{\Lambda}{\mu} + Ce^{(-\mu)t} \\ \lim_{t\to\infty} (S + V + \cdots + R) &\leq \frac{\Lambda}{\mu} \end{aligned}$$

- Thus, we have some feasible region $\Gamma = \left\{ z \in \mathbb{R}^8 : 0 \leq z \leq \frac{\Lambda}{\mu} \right\}$.

Proof of Theorem 2 (2)

$$\dot{x} = \begin{bmatrix} \frac{(\beta I + \beta \varepsilon J + \beta_D D)(S + \eta V)}{N} \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} - \begin{bmatrix} k_1 E_1 + \mu E_1 \\ -k_1 E_1 + (k_2 + f_T) E_2 + \mu E_2 \\ -k_2 E_2 + (\alpha + \gamma) I + \mu I \\ -f_T E_2 - \alpha I + \gamma_r J + \mu J \\ -\delta \gamma I - \delta \gamma_r J + \gamma_D D \end{bmatrix}$$

Proof of Theorem 2 (3)

$$\mathbf{F}(0, DFE_1) = \begin{bmatrix} 0 & 0 & \frac{(\frac{\Lambda}{(\xi+\mu)} + \eta\frac{\Lambda\xi}{\mu(\xi+\mu)}\beta)}{N} & \frac{(\frac{\Lambda}{(\xi+\mu)} + \eta\frac{\Lambda\xi}{\mu(\xi+\mu)})\beta\varepsilon}{N} & \frac{(\frac{\Lambda}{(\xi+\mu)} + \eta\frac{\Lambda\xi}{\mu(\xi+\mu)})\beta_D}{N} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

Proof of Theorem 2 (4)

$$\mathbf{V}(x,y) = \begin{bmatrix} k_1+\mu & 0 & 0 & 0 & 0 \\ -k_1 & k_2+f_T+\mu & 0 & 0 & 0 \\ 0 & -k_2 & \alpha+\gamma+\mu & 0 & 0 \\ 0 & -f_T & -\alpha & \gamma_r+\mu & 0 \\ 0 & 0 & -\delta\gamma & -\delta\gamma_r & \gamma_D \end{bmatrix}$$

$$\mathbf{f}(x,y) = \begin{bmatrix} (\tilde{S}-S+\eta(\tilde{V}-V))\left(\frac{\beta I+\beta\varepsilon J+\beta_D D}{N}\right) \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

Proof of Theorem 2 (5)

- Consider the sign of $f(x, y)$. The sign of the first term of f determines f's sign, so we consider the conditions of its sign.

$$\begin{aligned}(\tilde{S} - S + \eta(\tilde{V} - V)) &= (\tilde{S} + \eta\tilde{V}) - (S+) \\ &= (\tfrac{\Lambda}{\xi+\mu} + \tfrac{\eta\xi}{\mu(\xi+\mu)}) - (S + \eta V)\end{aligned}$$

- Notice that the maximum value that $S + \eta V$ could take is $\frac{\Lambda}{\mu}$, where $V = 0$ and $S = \frac{\Lambda}{\mu}$. However, this would make f negative, so this starting point is not feasible. However, if we assume that $S + \eta V < \frac{\Lambda}{\xi+\mu} + \frac{\eta\xi}{\mu(\xi+\mu)}$, then $f(x, y) > 0$.

Proof of Theorem 2 (6)

- Biologically, the assumptions require that either the population starts below the maximum population by at least $\frac{\Lambda\xi(1-\eta)}{\mu(\mu+\xi)}$, or the population starts with more vaccinated individuals than the equilibrium value for vaccinated individuals $\tilde{V}$. These assumptions, while not ideal, are biologically feasible.
- V^{-1}, FV^{-1} and $V^{-1}F$ were calculated to be very large and non-negative matrices similar in structure to the unmodified Shen model. w^T was again a strictly non-negative vector with large entries, so $V^{-1}F$ does not need to be irreducible.
- We now consider the disease free system with no disease, $\dot{y} = g(0, y)$.

Proof of Theorem 2 (7)

$$\begin{aligned}\frac{dS}{dt} &= \Lambda - \xi S - \mu S \\ \frac{dV}{dt} &= \xi S - \mu V \\ \frac{dR}{dt} &= -\mu R\end{aligned} \tag{1}$$

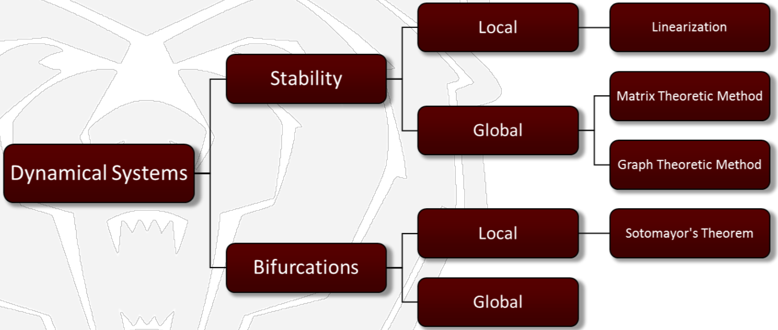
This system has solution

$$\begin{aligned}S &= \frac{\Lambda}{\xi+\mu} \\ V &= \frac{\Lambda\xi}{\mu(\xi+\mu)} + C_1 e^{-\mu t} \\ R &= C_2 e^{-\mu t}\end{aligned} \tag{2}$$

Proof of Theorem 2 (8)

- This solution corresponds to the disease free equilibrium point as time approaches infinity.
- Therefore, by Shuai Theorem 2.2, whose conditions are all met, we have
- If $R_0 < 1$, then the disease free equilibrium point is globally asymptotically stable in Γ
- If $R_0 > 1$, then the disease free equilibrium point is unstable, and there exists at least one endemic equilibrium point.

Outline


Dynamical Systems
Stability
Bifurcations
Local
Global
Local
Global
Linearization
Matrix Theoretic Method
Graph Theoretic Method
Sotomayor's Theorem

Global Stability of EE for Generalized Shen Model

Theorem (3)

If all the conditions for Theorem 2 are met, $R_0 > 1$, $V = 0$ and the maximum population N is biologically reasonable, then the endemic equilibrium point is globally asymptotically stable in Γ.

To prove this theorem, we will look at the system using a graph theoretic method proposed by Shuai.

Theorem 3.5 [Shuai and Van Den Driessche]

Goal is to construct a Liapunov function, $D(z)$.

If

- There exist functions $D_i : U \to \mathbb{R}$ and $G_{ij} : U \to \mathbb{R}$ and
- constants $a_{ij} \geq 0$ such that
- for every $1 \leq i \leq n$, $D_i' \leq \sum_{j=1}^{n} a_{ij} G_{ij}(z)$. And
- for $A = [a_{ij}]$, each directed cycle C of G has $\sum_{(s,r)\in\varepsilon(C)} G_{rs}(z) \leq 0$ where $\varepsilon(C)$ denotes the arc set of the directed cycle C.

Then the function

$$D(z) = \sum_{i=1}^{n} c_i D_i(z)$$

is a Liapunov function for the system.

Generalized Shen Graph Theoretic Method (1)

- We start by differentiating Lotka-Volterra type Liapunov functions.

$$
\begin{aligned}
D_S &= S - S^* - S^* \ln \frac{S}{S^*} \\
D_V &= V - V^* - V^* \ln \frac{V}{V^*} \\
D_{E_1} &= E_1 - E_1^* - E_1^* \ln \frac{E_1}{E_1^*} \\
D_{E_2} &= E_2 - E_2^* - E_2^* \ln \frac{E_2}{E_2^*} \\
D_I &= I - I^* - I^* \ln \frac{I}{I^*} \\
D_J &= J - J^* - J^* \ln \frac{J}{J^*} \\
D_I &= D - D^* - D^* \ln \frac{D}{D^*} \\
D_I &= R - R^* - R^* \ln \frac{R}{R^*}
\end{aligned}
$$

Generalized Shen Graph Theoretic Method (2)

- Before we differentiate, let $x = \frac{\beta I + \beta \varepsilon J + \beta_D D}{N}$ and $x^* = \frac{\beta I^* + \beta \varepsilon J^* + \beta_D D^*}{N}$. We will be using the inequality $1 - x \leq -ln(x)$ in all of the upcoming differentiation.
- Differentiating our D_i's, we find

Generalized Shen Graph Theoretic Method (3)

$$
\begin{aligned}
D_S' &= \left(1 - \frac{S^*}{S}\right)[\Lambda - xS - (\xi + \mu)S] \\
&= \left(1 - \frac{S^*}{S}\right)[x^*S^* - xS + (\xi + \mu)(S^* - S)] \\
&= x^*S^* - xS - \frac{x^*(S^*)^2}{S} + xS^* - \frac{1}{S}(\xi + \mu)(S - S^*)^2 \\
&\leq x^*S^* \left[1 - \frac{xS}{x^*S^*} - \frac{S^*}{S} + \frac{x}{x^*}\right] \\
&\leq x^*S^* \left[\frac{x}{x^*} - \ln\frac{x}{x^*} - \frac{xS}{x^*S^*} + \ln\frac{xS}{x^*S^*}\right] =: a_{1,7}G_{1,7}
\end{aligned}
$$

Generalized Shen Graph Theoretic Method (4)

$$
\begin{aligned}
D_V' &= \left(1 - \frac{V^*}{V}\right)[\xi S - x\eta V - \mu V] \\
\vdots &= \vdots \\
&= \xi S^* \left[\frac{S}{S^*} - \frac{V}{V^*} - \frac{SV^*}{VS^*} + 1\right] := a_{2,1} G_{2,1} \\
&\quad + x^* \eta V^* \left[-\frac{xV}{x^* V^*} + \frac{V}{V^*} + \frac{x}{x^*} - 1\right] =: a_{2,7} G_{2,7}
\end{aligned}
$$

Generalized Shen Graph Theoretic Method (5)

$$
\begin{aligned}
D'_{E_1} &= \left(1 - \frac{E_1^*}{E_1}\right)[x(S + \eta V) - (k_1 + \mu)V] \\
\vdots &= \vdots \\
&\leq x^* S^* \left[\frac{xS}{x^* S^*} - \ln \frac{xS}{x^* S^*} - \frac{E_1}{E_1^*} + \ln \frac{E_1}{E_1^*}\right] =: a_{3,1} G_{3,1} \\
&\quad + x^* \eta V^* \left[\frac{xV}{x^* V^*} - \ln \frac{xV}{x^* V^*} - \frac{E_1}{E_1^*} + \ln \frac{E_1}{E_1^*}\right] =: a_{3,2} G_{3,2}
\end{aligned}
$$

Generalized Shen Graph Theoretic Method (6)

$$
\begin{aligned}
D'_{E_2} &= \left(1 - \frac{E_2^*}{E_2}\right)\left[k_1 E_1 - \frac{k_1 E_1^*}{E_2^*} E_2\right] \\
\vdots &= \vdots \\
&\leq k_1 E_1^* \left[\frac{E_1}{E_1^*} - \ln \frac{E_1}{E_1^*} - \frac{E_2}{E_2^*} + \ln - \frac{E_2}{E_2^*}\right] =: a_{4,3} G_{4,3}
\end{aligned}
$$

Generalized Shen Graph Theoretic Method (7)

$$D_I' = \left(1 - \frac{I^*}{I}\right)\left[k_2 E_2 - \frac{k_2 E_2^*}{I2^*} I\right]$$

$$\vdots = \vdots$$

$$\leq k_2 E_2^* \left[\frac{E_2}{E_2^*} - \ln\frac{E_2}{E_2^*} - \frac{I}{I^*} + \ln - \frac{I}{I^*}\right] =: a_{5,4} G_{5,4}$$

Generalized Shen Graph Theoretic Method (8)

$$D'_J = \left(1 - \frac{J^*}{J}\right)[f_T E_2 + \alpha I + (\gamma_r - \mu)J]$$

$$\vdots = \vdots$$

$$\leq f_T E_2^* \left[\frac{E_2}{E_2^*} - \ln \frac{E_2}{E_2^*} - \frac{J}{J^*} + \ln \frac{J}{J^*}\right] =: a_{6,4} G_{6,4}$$

$$+ \alpha I^* \left[\frac{I}{I^*} - ln \frac{I}{I^*} - \frac{J}{J^*} + \ln \frac{J}{J^*}\right] =: a_{6,5} G_{6,5}$$

We may rewrite $a_{6,5} G_{6,5}$ as

$$a_{6,5} G_{6,5} = \frac{N}{1-\beta} \alpha I^* \left[(\frac{1-\beta}{N})(\frac{I}{I^*} - ln \frac{I}{I^*} - \frac{J}{J^*} + \ln \frac{J}{J^*}) \right]$$

Generalized Shen Graph Theoretic Method (9)

$$D_D' = \left(1 - \frac{D^*}{D}\right)[\delta\gamma I + \delta\gamma_r J - \gamma_D D]$$

$$\vdots = \vdots$$

$$\leq \delta\gamma I^* \left[\frac{I}{I^*} - \ln\frac{I}{I^*} - \frac{D}{D^*} + \ln\frac{D}{D^*}\right] =: a_{7,5}G_{7,5}$$

$$+\delta\gamma_r J^* \left[\frac{J}{J^*} - \ln\frac{J}{J^*} - \frac{D}{D^*} + \ln\frac{D}{D^*}\right] =: a_{7,6}G_{7,6}$$

We may rewrite $a_{7,6}G_{7,6}$ as

$$a_{7,6}G_{7,6} = \frac{N}{1-\beta-\beta\varepsilon}\delta\gamma_r J^* \left[\left(\frac{1-\beta-\beta\varepsilon}{N}\right)\left(\frac{J}{J^*} - \ln\frac{J}{J^*} - \frac{D}{D^*} + \ln\frac{D}{D^*}\right)\right]$$

Generalized Shen Graph Theoretic Method (10)

$$
\begin{aligned}
D_R' &= \left(1 - \frac{R^*}{R}\right)\left[(1-\delta)\gamma I + (1-\delta)\gamma_r J - \mu R\right] \\
\vdots &= \vdots \\
&\leq (1-\delta)\gamma I^* \left[\frac{I}{I^*} - \ln\frac{I}{I^*} - \frac{R}{R^*} + \ln\frac{R}{R^*}\right] =: a_{8,5}\, G_{8,5} \\
&\quad + (1-\delta)\gamma_r J^* \left[\frac{J}{J^*} - \ln\frac{J}{J^*} - \frac{R}{R^*} + \ln\frac{R}{R^*}\right] =: a_{8,6}\, G_{8,6}
\end{aligned}
$$

Generalized Shen Graph Theoretic Method (8)

- Figure 1 shows the how the whole model would be connected with a weighted digraph, and figure 2 shows the graph which represents our model's feasible cycle. While other cycles appear to exist, the G_{ij}'s do not satisfy $\sum G_{ij} \leq 0$ along those cycles.

Figure 1

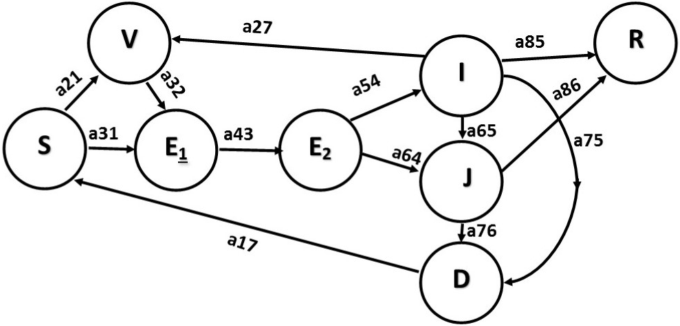
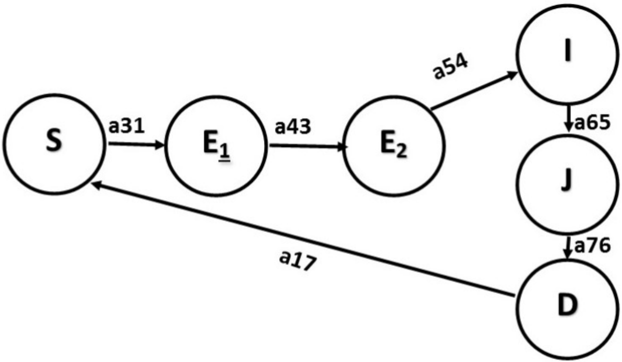


Figure 2



Theorem 3.5 [Shuai and Van Den Driessche]

If

- ✓ There exist functions $D_i : U \to \mathbb{R}$ and $G_{ij} : U \to \mathbb{R}$ and
- ✓ constants $a_{ij} \geq 0$ such that
- ✓ for every $1 \leq i \leq n$, $D_i' \leq \sum_{j=1}^{n} a_{ij} G_{ij}(z)$. And
- for $A = [a_{ij}]$, each directed cycle C of G has $\sum_{(s,r)\in\varepsilon(C)} G_{rs}(z) \leq 0$ where $\varepsilon(C)$ denotes the arc set of the directed cycle C.

Then the function

$$D(z) = \sum_{i=1}^{n} c_i D_i(z)$$

is a Liapunov function for the system.

Generalized Shen Graph Theoretic Method (9)

$$
\begin{aligned}
\sum G_{ij} &= \left(\frac{xS}{x^*S^*} - \ln\frac{xS}{x^*S^*} - \frac{E_1}{E_1^*} + \ln\frac{E_1}{E_1^*}\right) \\
&\quad + \left(\frac{E_1}{E_1^*} - \ln\frac{E_1}{E_1^*} - \frac{E_2}{E_2^*} + \ln -\frac{E_2}{E_2^*}\right) \\
&\quad + \left(\frac{E_2}{E_2^*} - \ln\frac{E_2}{E_2^*} - \frac{I}{I^*} + \ln -\frac{I}{I^*}\right) \\
&\quad +(1-\frac{\beta}{N})\left(\frac{I}{I^*} - ln\frac{I}{I^*} - \frac{J}{J^*} + \ln\frac{J}{J^*}\right) \\
&\quad +(1-\frac{\beta-\beta\varepsilon}{N})\left(\frac{J}{J^*} - \ln\frac{J}{J^*} - \frac{D}{D^*} + \ln\frac{D}{D^*}\right) \\
&\quad + \left(\frac{x}{x^*} - \ln\frac{x}{x^*} - \frac{xS}{x^*S^*} + \ln\frac{xS}{x^*S^*}\right) \\
&= \frac{x}{x^*} - \ln\frac{x}{x^*} - \frac{\beta}{N}(\frac{I}{I^*} - ln\frac{I}{I^*}) \\
&\quad - \frac{\beta\varepsilon}{N}(\frac{J}{J^*} - \ln\frac{J}{J^*}) - (1-\frac{\beta-\beta\varepsilon}{N})(\frac{D}{D^*} - \ln\frac{D}{D^*}) \\
&= \left(\frac{\beta+\beta\varepsilon+\beta_D}{N} - 1\right)\left(\frac{D}{D^*} - \ln\frac{D}{D^*}\right) \\
&\leq 0
\end{aligned}
$$

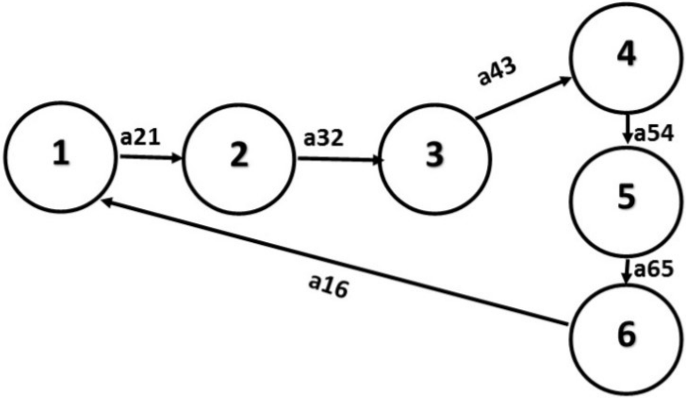
Generalized Shen Graph Theoretic Method (10)

- The last line is true due to the following:

$$
\begin{aligned}
\frac{\beta+\beta\varepsilon+\beta_D}{N} &< 1 \\
\frac{\beta+\beta\varepsilon+\beta_D}{N} &\leq \frac{3}{N} \leq 1
\end{aligned}
$$

- This follows from the earlier assumption that the total population was biologically reasonable.
- We now construct the coefficients of the linear combination of D_i's to create our final Liapunov function. First, we relabel the vertices and a_{ij}'s in our system with indices 1 through 6 starting from S and ending at D (i.e., vertex S is now vertex 1 and directed path a_{31} is now a_{21}).

Figure 3



Theorem's 3.3 and 3.4 [Shuai and Van Den Driessche]

Theorem 3.3

If $a_{ij} > 0$ and $d^+(j) = 1$ for some i, j then

$$c_i a_{ij} = \sum_{k=1}^{n} c_j a_{jk}$$

Theorem 3.4

If $a_{ij} > 0$ and $d^-(i) = 1$ for some i, j then

$$c_i a_{ij} = \sum_{k=1}^{n} c_k a_{ki}$$

Generalized Shen Graph Theoretic Method (11)

Using Shuai Theorem 3.3, we find

$$
\begin{aligned}
c_1 a_{16} &= \sum_{k=1}^{6} c_6 a_{6k} &&= c_6 a_{65} \\
c_2 a_{21} &= \sum_{k=1}^{6} c_1 a_{1k} &&= c_1 a_{11} \\
c_3 a_{32} &= \sum_{k=1}^{6} c_2 a_{2k} &&= c_2 a_{21} \\
&\vdots \\
c_6 a_{65} &= \sum_{k=1}^{6} c_5 a_{5k} &&= c_5 a_{54}
\end{aligned}
$$

Generalized Shen Graph Theoretic Method (12)

Letting $c_1 = 1$ and substituting our a_{ij}'s, we get the following:

$$x^*S^* = c_2 x^* S^* = c_3 k_1 E_1^* = c_4 k_2 E_2^* = c_5 \frac{N}{1-\beta}\alpha I^* = c_6 \frac{N}{1-\beta-\beta\varepsilon}\delta\gamma_r J^*$$

Solving for the coefficients c_i, we get

$$\begin{aligned} c_1 &= 1 \\ c_2 &= 1 \\ c_3 &= \frac{x^*S^*}{k_1E_1^*} \\ c_4 &= \frac{x^*S^*}{k_2E_2^*} \\ c_5 &= \left(\frac{1-\beta}{N}\right)\frac{x^*S^*}{\alpha I^*} \\ c_6 &= \left(\frac{1-\beta-\beta\varepsilon}{N}\right)\frac{x^*S^*}{\delta\gamma_r J^*} \end{aligned}$$

Generalized Shen Graph Theoretic Method (13)

Finally,

$$\begin{aligned} D \;=\; & S - S^* - S^* \ln \frac{S}{S^*} + E_1 - E_1^* - E_1^* \ln \frac{E_1}{E_1^*} \\ & + \frac{x^* S^*}{k_1 E_1^*} \left(E_2 - E_2^* - E_2^* \ln \frac{E_2}{E_2^*} \right) + \frac{x^* S^*}{k_2 E_2^*} \left(I - I^* - I^* \ln \frac{I}{I^*} \right) \\ & + \left(\frac{1-\beta}{N} \right) \frac{x^* S^*}{\alpha I^*} \left(J - J^* - J^* \ln \frac{J}{J^*} \right) \\ & + \left(\frac{1-\beta-\beta\varepsilon}{N} \right) \frac{x^* S^*}{\delta \gamma_r J^*} \left(D - D^* - D^* \ln \frac{D}{D^*} \right) \end{aligned}$$

where D is a **Liapunov Function** for our system. We will now use LaSalle's Invariance Principle and this Liapunov function to determine the global stability of the system.

LaSalle's Invariance Principle

If

- ✓ $\Gamma \subset D \subset R^n$ be a compact positively invariant set,
- ✓ $V : D \to R$ be a continuously differentiable function,
- ✓ $\dot{V}(x(t)) \leq 0$ in Γ,
- $E \subset \Gamma$ be the set of all points in Γ where $\dot{V}(x) = 0$, and
- $M \subset E$ be the largest invariant set in E.

Then every solution starting in Γ approaches M as $t \to \infty$, that is,

$$\lim_{t\to\infty} \left(\underbrace{\inf_{z\in M} \|x(t) - z\|}_{\text{dist }(x(t), M)} \right) = 0.$$

Shen Model: LaSalle's Invariance Principle

$$D' = \left(1 - \frac{S^*}{S}\right) S' + \left(1 - \frac{E_1^*}{E_1}\right) E_1' + c_3 D_3' + \cdots + c_6 D_6'$$

The endemic equilibrium point is the set E, and is also the largest set $M \subset E$. Therefore, by LaSalle's Invariance Principle, if $R_0 > 1$, $V = 0$ and $N \geq 3$, then the endemic equilibrium point is globally asymptotically stable in Γ.Therefore, we have proven Theorem 3!

Future Research

- Continued exploration to deal with the computational difficulties with local stability.
- Confirm numerical simulations are in line with stability results presented.
- Use numerical simulations to verify bifurcation existence, and study using advances with the local stability research.
- Find creative algebraic manipulations to allow graph theoretic cycles including vaccine terms to cancel along the cycles.
- Consider both different models and modifications to the generalized model.
- Proving general results for the graph theoretic method for general dynamical systems

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Stable Manifold Theorem

Let E be an open subset of $\mathbb{R}^n$ containing the origin, let $f \in C^1(E)$, and let ϕ_t be the flow of the nonlinear system. Suppose that $f(0) = 0$ and that $Df(0) = 0$ has k eigenvalues with negative real part and $n - k$ eigenvalues with positive real part. Then there exists a k-dimensional differentiable manifold S tangent to the stable subspace E^s of the linear system at 0 such that for all $t \geq 0$, $\phi_t(S) \subset S$ and for all $x_0 \in S$.

$$\lim_{t \to \infty} \phi_t(x_0) = 0$$

and there exists an $n - k$ dimensional differentiable manifold U tangent to the unstable subspace E^u of the corresponding linear system at 0 such that for all $t \leq 0$, $\phi_t(U) \subset U$ and for all $x_0 \in U$,

$$\lim_{t \to \infty} \phi_t(x_0) = 0$$

Hartman-Grobman Theorem

Let E be an open subset of $\mathbb{R}^n$ containing the origin, let $f \in C^1(E)$, and let ϕ_t be the flow of the nonlinear system. Suppose that $f(0) = 0$ and that the matrix $A = DF(0)$ has no eigenvalue with zero real part. Then there exists a homeomorphism H of an open set U containing the origin onto an open set V containing the origin such that for $x_0 \in U$, there is an open interval $I_0 \in \mathbb{R}$ containing zero such that for all $x_0 \in U$ and $t \in I_0$

$$H \circ \phi_t(x_0) = e^{At} H(x_0)$$

i.e., H maps trajectories of the nonlinear system near the origin onto trajectories of the linear system near the origin and preserves the parametrization of time.

Local Center Manifold Theorem

Let $\mathbf{f} \in C^r(E)$ where E is an open subset of $\mathbb{R}^n$ containing the origin and $r \geq 1$. Suppose that $\mathbf{f}(0) = 0$ and that $D\mathbf{f}(0)$ has c eigenvalues with zero real parts and s eigenvalues with negative real parts, where $c + s = n$. The nonlinear system $x' = \mathbf{f}(x)$ can then be written in diagonal form

$$\begin{aligned} \dot{\mathbf{x}} &= C\mathbf{x} + \mathbf{F}(\mathbf{x}, \mathbf{y}) \\ \dot{\mathbf{y}} &= P\mathbf{y} + \mathbf{G}(\mathbf{x}, \mathbf{y}). \end{aligned}$$

where $(x, y) \in \mathbb{R}^c \times \mathbb{R}^s$, $\mathbf{C}$ is a square matrix with c eigenvalues having zero real part, $\mathbf{P}$ is a square matrix with s eigenvalues having negative real part, and $\mathbf{F}(0) = \mathbf{G}(0) = 0$, $D\mathbf{F}(0) = D\mathbf{G}(0) = 0$; furthermore, there exists a $\delta > 0$ and function $h \in C^r(N_\delta(0))$ that defines the local center manifold and satisfies

Local Center Manifold Theorem

$$D\mathbf{h}(\mathbf{x})[C\mathbf{x} + \mathbf{F}(\mathbf{x}, \mathbf{h}(\mathbf{x}))] - P\mathbf{h}(\mathbf{x}) - \mathbf{G}(\mathbf{x}, \mathbf{h}(\mathbf{x})) = 0$$

for $|x| < \delta$; and the flow on the center manifold W^c is defined by the system of differential equations $x' = \mathbf{C}x + \mathbf{F}(x, h(x))$ for all $x \in \mathbb{R}^c$ with $|x| < \delta$.

Routh-Hurwitz Criterion

Consider a three dimensional system. If the characteristic polynomial

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3$$

satisfies the following:

$$a_1 > 0,$$
$$a_3 > 0,$$
$$a_1 a_2 - a_3 > 0$$

then the equilibrium point is locally stable.

Spectral Radius

The spectral radius of a matrix or bounded linear operator is the supremum among the absolute values of the elements in its spectrum. The spectrum of such a matrix is its set of eingenvalues, but the spectrum of a linear operator $T : V \to V$ is the set of scalars λ such that $T - \lambda I$ is non-invertible.

Partitioned Inversion (Using Shur Complements)

Given a partitioned matrix $\mathbf{M}$:

$$\mathbf{M}^{-1} = \begin{bmatrix} \mathbf{A} & \mathbf{B} \\ \mathbf{C} & \mathbf{D} \end{bmatrix}^{-1}$$

$$= \begin{bmatrix} (\mathbf{M}/\mathbf{D})^{-1} & -(\mathbf{M}/\mathbf{D})^{-1}\mathbf{B}\mathbf{A}^{-1} \\ -\mathbf{D}^{-1}\mathbf{C}(\mathbf{M}/\mathbf{D})^{-1} & \mathbf{D}^{-1} + \mathbf{D}^{-1}\mathbf{C}(\mathbf{M}/\mathbf{D})^{-1}\mathbf{B}\mathbf{D}^{-1} \end{bmatrix}$$

Where

$$(\mathbf{M}/\mathbf{D})^{-1} = \mathbf{A}^{-1} + \mathbf{A}^{-1}\mathbf{B}(\mathbf{M}/\mathbf{A})^{-1}\mathbf{C}\mathbf{A}^{-1}$$

if $\mathbf{A}$ and $\mathbf{D}$ are non-singular

Sotomayor's Theorem

If

- $\mathbf{f}(\mathbf{x_0}, \mu_0) = 0$,
- the $n \times n$ matrix $A = D\mathbf{f}(\mathbf{x_0}, \mu_0)$ has a simple eigenvalue $\lambda = 0$ with eigenvector $\mathbf{v}$, and
- A^T has an eigenvector $\mathbf{w}$ corresponding to the eigenvalue $\lambda = 0$.
- As well as

$$\mathbf{w}^\mathbf{T}\mathbf{f}_\mu(\mathbf{x_0}, \mu_0) = 0,$$
$$\mathbf{w}^\mathbf{T}[D\mathbf{f}_\mu(\mathbf{x_0}, \mu_0)\mathbf{v}] \neq 0,$$
$$\mathbf{w}^\mathbf{T}[D^2\mathbf{f}(\mathbf{x_0}, \mu_0)(\mathbf{v}, \mathbf{v})] \neq 0.$$

Then the system experiences a transcritical bifurcation at the equilibrium point x_0 as the parameter μ varies the the bifurcation value $\mu = \mu_0$.

Liapunov Functions

If

- E is an open subset of $\mathbb{R}^n$ containing z_0,
- $\mathbf{f} \in C^1(E)$ and $\mathbf{f}(z_0) = 0$, and
- there exists $V \in C^1(E)$ satisfying $V(z_0) = 0$ and $V(z) > 0$ if $z \neq z_0$.

Then

(a) if $\dot{V}(z) \leq 0$ for all $z \in E$, z_0 is stable,

(b) if $\dot{V}(z) < 0$ for all $z \in E$, z_0 is asymptotically stable,

(c) if $\dot{V}(z) > 0$ for all $z \in E$, z_0 is unstable.