Introduction: What one must do to analyze any model

- Prove the positivity and boundedness of the solutions
- Determine the disease free equilibrium point and the model reproduction number
- Prove the stability of the disease free equilibrium
- Prove the persistence of solutions
- Prove the stability of the endemic equilibrium point
- Simulate the model

Model Variables and parameters

$S(t)$	Susceptible population
$V(t)$	Vaccinated population
$I(t)$	Infected individuals
$R(t)$	Recovered individuals - recovery with immunity
$B(t)$	Cholera bacteria

The models are based on a paper by X. Zhou and J. Cui

- Model 1: Recovery with immunity

$$
\begin{aligned}
\frac{dS}{dt} &= (1-\rho)\,A - \beta S(t)B(t) + bV(t) - \theta S(t) - \mu_1 S(t) \\
\frac{dV}{dt} &= \rho A + \theta S(t) - bV(t) - \mu_1 V(t) \\
\frac{dI}{dt} &= \beta S(t)B(t) - (d + \alpha + \mu_1) \\
\frac{dR}{dt} &= \alpha I(t) - \mu_1 R(t) \\
\frac{dB}{dt} &= \gamma B(t) + \eta I(t)
\end{aligned}
$$

Recovery without immunity

- Model 2: Recovery without immunity

$$\begin{aligned}
\frac{dS}{dt} &= (1-\rho)\,A - \beta S(t)B(t) + bV(t) - \theta S(t) \\
&- \mu_1 S(t) + \alpha I(t) \\
\frac{dV}{dt} &= \rho A + \theta S(t) - bV(t) - \mu_1 V(t) \\
\frac{dI}{dt} &= \beta S(t)B(t) - (d + \alpha + \mu_1) \\
\frac{dB}{dt} &= \gamma B(t) + \eta I(t)
\end{aligned}$$

Change of force of infection

- Models 1 and 2 assume a mass action force of infection. The assumption is that every one who is in contact with the bacteria is infected
- in reality some people do not catch the disease and so a more appropriate force of infection is

$$\lambda = \frac{\beta S(t) B(t)}{N(t)}$$

where $N(t) = S(t) + V(t) + I(t) + R(t)$ for Model 1 *or* $N(t) = S(t) + V(t) + I$ for Model 2

Positivity and boundedness of solutions of Model 1

- Theorem: Given $S(0) \geq 0, \;\; V(0) \geq 0, \;\; I(0) \geq 0, \;\; B(0) \geq 0$, the solutions $(S(t), \; V(t), \; I(t), \; B(t))$ of Model 1 are positively invariant for all $t > 0$.
- Let $t_1 = \sup\left(t > 0 | S > 0, \; V > 0, \; I > 0, \; B > 0\right)$. From the first equation

$$\frac{dS}{dt} = (1-\rho)\, A - (\beta B(t) + \theta + \mu_1)\, S(t)$$

- The integrating factor is

$$\exp\left(\int_0^t \beta B(s) ds + (\theta + \mu_1)\, t\right)$$

- Multiplying the inequality above by the integrating factor, we obtain

$$\frac{\left[S(t)\exp\left\{\int_0^t \beta B(s)ds + (\theta+\mu_1)\,t\right\}\right]}{dt}$$
$$\geq (1-\rho)\,A\exp\left(\int_0^t \beta B(s)ds + (\theta+\mu_1)\,t\right)$$

- Solving this inequality we obtain

$$S(t)\exp\left\{\int_0^t \beta B(s)ds + (\theta+\mu_1)\,t\right\} - S(0)$$
$$\geq \int_0^t (1-\rho)\,A\exp\{\int_0^\nu \beta B(q)dq + (\theta+\mu_1)\,\nu\}d\nu$$

- Therefore

$$\begin{aligned} S(t) &\geq S(0)\exp\left\{-\int_0^t \beta B(q)dq + (\mu_1+\theta)\,t\right\} \\ &+ \exp\left\{-\int_0^t \beta B(q)dq + (\mu_1+\theta)\,t\right\} \\ &\quad \times \int_0^t (1-\rho)\,A\exp\{\int_0^\nu \beta B(q)dq \\ &+ (\theta+\mu_1)\,\nu\}d\nu > 0 \end{aligned}$$

- Similarly, it can be shown that $(V(t) > 0,\ \ I(t) > 0,\ \ B(t) > 0)$.

Boundedness of the solution

- Theorem: All solutions $(S(t),\ V(t),\ I(t),\ B(t))$ of Model 1 are bounded.
- Proof: Model 1 is split into two, the human population and the pathogen population
- From the first three populations (human populations0, we obtain

$$\begin{aligned}\left(\frac{d\left(S+V+I\right)}{dt}\right) &= A-\mu_1\left(S+V+I\right)-\left(d+\alpha\right)I \\ &\leq A-\mu_1\left(S+V+I\right)\end{aligned}$$

- Then

$$\lim_{t\to\infty}\sup\left(S+V+I\right)\leq\frac{A}{\mu_1}$$

- From the first three equations, we obtain

$$\frac{dS(t)}{dt} \leq (1-\rho)\,A - (S+V+I) + b\left(\frac{A}{\mu_1} - S\right)$$

- Hence

$$S(t) \leq \frac{A\left(b + (1-\rho)\,\mu_1\right)}{\mu_1\left(\mu_1 + b + \theta\right)}$$

- It is easy to show that

$$V(t) \leq \left(\frac{A(\theta + \rho\mu_1)}{\mu_1(\mu_1 + b + \theta)} \right)$$

- For the bacteria we have

$$\frac{dB(t)}{dt} \leq \frac{\eta A}{\mu_1} - \mu_2 B(t)$$

- Hence

$$B(t) \leq \left(\frac{\eta A}{\mu 1 \mu_2} \right)$$

- All solutions of Model 1 are bounded. The feasible region for the human population is

$$\Omega_H = (S,\ V,\ I)\,|S + V + I \leq \left(\frac{A}{\mu_1}\right),\ 0 \leq S \leq S(t)$$
$$\leq \left(\frac{A\left(b + (1-\rho)\,\mu_1\right)}{\mu_1\left(\mu_1 + b + \theta\right)}\right),\ 0$$
$$\leq V \leq \left(\frac{A\left(\theta + \rho\mu_1\right)}{\mu_1\left(\mu_1 + b + \theta\right)}\right),\ I \geq 0,$$

- The feasible region for the pathogen population for Model 1 is

$$\Omega_B = \left(B|0 \leq B \leq \left(\frac{\eta A}{\mu 1 \mu_2}\right)\right)$$

- Define $\Omega = \Omega_H \times \Omega_B$. Let $Int\Omega$ denote the interior of Ω. The region Ω is a positively invariant region with respect to the Model 1. Hence the Model 1 is mathematically and epidemiologically well possed in Ω.

The reproduction number

- Model 1 has a disease free equilibrium given by

$$(S_0,\ V_0,\ 0,\ 0) = \left(\frac{A\left(b + (1-\rho)\,\mu_1\right)}{\mu_1\left(\mu_1 + b + \theta\right)},\ \frac{A\left(\theta + \rho\mu_1\right)}{\mu_1\left(\mu_1 + b + \theta\right)},\ 0,\ 0 \right)$$

- The Model 1 can be written as

$$\frac{dX}{dt} = F - \nu,$$

where

$$F = \begin{pmatrix} \beta SB \\ 0 \\ \\ \\ 0 \end{pmatrix}$$

- and

$$\nu = \begin{pmatrix} (d + \alpha + \mu_1)\, I \\ -\eta I + \mu_2 B(t) \\ -(1-\rho)A + \beta SB + \mu_1 S + \theta S - bV \\ -\theta S + \mu_1 V + bV - \rho A \end{pmatrix}$$

- The Jacobian of $\mathcal{F}$ is

$$\mathbf{F} = \begin{pmatrix} 0 & \beta S_0 \\ 0 & 0 \end{pmatrix}$$

- The Jacobian of ν is

$$\mathbf{V} = \begin{pmatrix} \mu_1 + d + \alpha & 0 \\ -\eta & \mu_2 \end{pmatrix}$$

- The inverse of $\mathbf{V}$ is

$$\mathbf{V^{-1}} = \begin{pmatrix} \dfrac{1}{d + \alpha + \mu_1} & 0 \\ \dfrac{\eta}{\mu_2(d + \alpha + \mu_1)} & \dfrac{1}{\mu_2} \end{pmatrix}$$

- The spectral radius of $\mathbf{FV^{-1}}$ is

$$\rho(\mathbf{FV^{-1}}) = \frac{\eta\beta \mathrm{A}\left[\mathrm{b} + (1-\rho)\mu_1\right]}{\mu_1\mu_2(\mu_1 + \theta + \mathrm{b})(\mu_1 + \alpha + \mathrm{d})}$$

- The reproduction number is

$$R_0 = \frac{\eta\beta A\left[b + (1-\rho)\mu_1\right]}{\mu_1\mu_2(\mu_1 + \theta + b)(\mu_1 + \alpha + d)}$$

Stability of the DFE

- We want to discuss the local and global stability of the DFE of Model 1
- Theorem: The DFE is locally asymptotically stable for $R_0 < 1$ and unstable for $R_0 > 1$.
- to prove this, we define new variables

$$x_1 = S - S_0,\ x_2 = V - V_0,\ x_3 = I,\ x_4 = B$$

- The associated linear system is:

$$\dot{X} = MX$$

- Where

$$M = \begin{pmatrix} -(\theta + \mu_1) & 0 & 0 & -\beta S_0 \\ \theta & -(b + \mu_1) & 0 & 0 \\ 0 & 0 & 0 & \beta S_0 - (d + \alpha\mu_1) \\ 0 & 0 & \eta & -\mu_2 \end{pmatrix}$$

- $X = (x_1,\ x_2,\ x_3,\ x_4)^T)$ and T denotes transpose of a matrix.

Eigenvalues

- Two of the Eigenvalues of M are

$$\lambda_1 = -(b+\mu_1) < 0, \quad \lambda_2 = -(\theta+\mu_1) < 0$$

- The other two are given by

$$\begin{aligned} \lambda_{3,4} &= \frac{1}{2}\left(-\mu_2 \pm \sqrt{\mu^2 + 4\eta(d+\alpha+\mu_1)Z}\right) \\ &= \frac{1}{2}\left(-\mu_2 \pm \sqrt{\mu^2 + 4\eta(d+\alpha+\mu_1)(R_0-1)}\right) \end{aligned}$$

$$Z = \left(\frac{\beta A(b+(1-\rho)\mu_1)}{\mu_1(\mu_1+b+\theta)(d+\alpha+\alpha)} - 1\right)$$

- Both λ_3 and λ_4 are negative hence the DFE is locally stable for $R_0 < 1$.

Global stability of the DFE

- The DFE is globally stable for $R_0 < 1$ and unstable for $R_0 > 1$.
- The Model can be subdivided into two sets $X_1 = (S, V)$ and $X_2 = (I, B)$ so that $X = (X_1, X_2)^T$
- The sub-system X_1 is given by

$$\begin{aligned} \frac{dS}{dt} &= (1-\rho)A - \beta S(t)B(t) + bV(t) - \theta S(t) - \mu_1 S(t) \\ \frac{dV}{dt} &= \rho A + \theta S(t) - bV(t) - \mu_1 V(t) \end{aligned}$$

- The sub-system X_2 is given by

$$\begin{aligned} \frac{dI}{dt} &= \beta S(t)B(t) - (d + \alpha + \mu_1) \\ \frac{dB}{dt} &= \gamma B(t) + \eta I(t) \end{aligned}$$

- It is easy to show that the sub-system $X_1 = (S, V)$ is globally asymptotically stable at

$$X_1^* = \left(\frac{A\left(b + (1-\rho)\,\mu_1\right)}{\mu_1\left(\mu_1 + b + \theta\right)},\ \frac{A\left(\theta + \rho\mu_1\right)}{\mu_1\left(\mu_1 + b + \theta\right)} \right)$$

- The matrix $A_2(X)$ from subsystem X_2 is given by

$$A_2(X) = \begin{pmatrix} -(\mu_1 + d + \alpha) & \beta S \\ \eta & -\mu_2 \end{pmatrix}$$

- The maximum of $A_2(X)$ occurs at the DFE given by

$$A_2(X) = \begin{pmatrix} -(\mu_1 + d + \alpha) & \beta S_0 \\ \eta & -\mu_2 \end{pmatrix}$$

- The spectral bound of $\alpha(A_2(\bar{X})A_2(X))$ is $R_0 \leq 1$.