Mathematics 4MB3/6MB3 Mathematical Biology

2018 ASSIGNMENT 1

Group Name: πrates

Group Members: Adeyemi Fakorede, Megan Hartwell,Ahmad Mahmood, Bradley Montgomery, Courtney Mulholland

1 Analysis of the SI model

The SI model can be written

$$\frac{dI}{dt} = \beta I(N - I)\,, \tag{1}$$

where I denotes prevalence and $N = S + I$ is the total population size.

(a) Prove that the endemic equiliibrium (EE) is a globally asymptotically stable (GAS) equilibrium by finding an appropriate Lyapunov function. Note that "global" here refers to all biologically relevant initial conditions except the (unstable) disease free equilibrium (DFE).
Hint: Lyapunov functions often look paraboloidal.
Note: Notions of stability and Lyapunov functions were discussed in Math 3F03 Lecture 27 in 2013 (http://www.math.mcmaster.ca/earn/3F03).

Proof. An appropriate Lyapunov function to prove that the endemic equilibrium is a globally asymptotically stable equilibrium is given by

$$L = S^2 = (N - I)^2 > 0 \quad \forall X \in \mathcal{O} \setminus X_* \tag{2}$$

$$\dot{L} = 2S\dot{S} = 2(N - I)(-\dot{I}) = -2\beta I^2(N - I)^2 < 0 \quad \forall X \in \mathcal{O} \setminus X_* \tag{3}$$

which satisfies both of the conditions in Theorem 1 (Lyapunov's Direct Method) stated in the section "Notes on Lyapunov functions".

□

(b) In class we proved only stability of the EE, not asymptotic stability. Prove GAS "directly" in two distinct ways:

(i) find the exact solution of the model and take the limit as $t \to \infty$, and conclude that every solution that starts in the interval $(0, N)$ converges to the EE (this approach works only in situations where you can find the exact solution);

Proof. The exact solution of the model can be found by using Bernoulli's Differential Equation

$$\frac{dy}{dx} + p(x)y = q(x)y^n \tag{4}$$

If we let $v = y^{1-n}$ $(n \neq 1)$ then

$$\frac{dv}{dx} = (1-n)y^{-n}\frac{dy}{dx} \tag{5}$$

$$y^{-n}\frac{dy}{dx} = q(x) - p(x)y^{1-n} = q(x) - vp(x) \tag{6}$$

$$\frac{dv}{dx} = (1-n)[q(x) - vp(x)] \tag{7}$$

$$\frac{dv}{dx} + vP(x) = Q(x); \quad P(x) = (1-n)p(x), \quad Q(x) = (1-n)q(x) \tag{8}$$

$$v = \frac{\int e^{\int P(x)dx}Q(x)dx + C}{e^{\int P(x)dx}} = \frac{(1-n)\int e^{(1-n)\int p(x)dx}q(x)dx + C}{e^{(1-n)\int p(x)dx}} \tag{9}$$

$$y = \left(\frac{(1-n)\int e^{(1-n)\int p(x)dx}q(x)dx_C}{e^{(1-n)\int p(x)dx}}\right)^{\frac{1}{1-n}} \tag{10}$$

$$Take \quad n = 2: \quad y = \left(\frac{-\int e^{(-\int p(x)dx}q(x)dx_C}{e^{-\int p(x)dx}}\right)^{-1} \tag{11}$$

$$y = \frac{e^{-\int p(x)dx}}{-\int e^{(-\int p(x)dx}q(x)dx_C} \tag{12}$$

$$p(x) = -\beta N, \quad q(x) = -\beta \implies I(t) = \frac{e^{-\int -\beta N dt}}{-\int e^{-\int -\beta N dt}(-\beta)dt + C} \tag{13}$$

$$I(t) = \frac{e^{\int \beta N dt}}{\beta \int e^{\int \beta N dt}dt + C} = \frac{e^{\beta N t}}{\beta \int e^{\beta N t}dt + C} = \frac{e^{\beta N t}}{(1/N)e^{\beta N t} + C} = \frac{I_0 e^{\beta N t}}{1 + (I_0/N)(e^{\beta N t} - 1)} \tag{14}$$

$$\lim_{t\to\infty} I(t) \approx \frac{I_0 e^{\beta N t}}{1 + (I_0/N)e^{\beta N t}} \approx \frac{I_0 e^{\beta N t}}{(I_0/N)e^{\beta N t}} \approx \frac{N I_0 e^{\beta N t}}{I_0 e^{\beta N t}} \approx N \tag{15}$$

□

(ii) given $\epsilon > 0$, prove that for any $I(0) \in (0, N)$ $\exists t < \infty$ such that $I(t) \in [N-\epsilon, N)$ and use this to establish GAS. (Do not use your exact solution in this part; the point is to use an approach that also works for models that cannot be solved exactly.)

Proof. This proof begins with noticing several things about $\frac{dI}{dt}$. Firstly, $\frac{dI}{dt}$ is strictly positive on the open interval, $(0, N)$. It is also a continuous, smooth, symmetric parabola achieving it's maximum at $I = \frac{N}{2}$. If we are then given values for $I(0) = I_0 > 0$ and ϵ, we can create a closed interval that contains $I(t)$, such that $I \in [I_0, N - \epsilon]$. Now since $\frac{dI}{dt}$ is positive for all I in this interval (and the entire biologically relevant interval), we know that $I(t)$ will increase from I_0 and continue to increase throughout this region since the slope is still positive. We also know the slope is bounded from both above and below since $\frac{dI}{dt}$ is continuous on a closed interval, and both bounds are positive. If we take the lower bound, call this m,

then we know that $\frac{dI}{dt} \geq m \forall I \in [I_0, N-\epsilon]$. If we assume that the slowest speed of increase m is maintained, then we can calculate the maximum time it will take for any trajectory to reach $N - \epsilon$.

$$\begin{aligned} m &= \min(\beta I(N-I), \beta\epsilon(N-\epsilon)) \\ t_f &= \frac{N-\epsilon-I_0}{m} \end{aligned} \tag{16}$$

Thus for any initial condition I_0 and ϵ we can calculate this t_f and we know that $I(t)$ will reach $N - \epsilon$ in time less than t_f. □

2 Analysis of the basic SIR model

The basic SIR model is specified by the following system of differential equations.

$$\frac{dS}{dt} = -\mathcal{R}_0 SI \tag{17a}$$

$$\frac{dI}{dt} = \mathcal{R}_0 SI - I \tag{17b}$$

$$\frac{dR}{dt} = I \tag{17c}$$

The state variables S, I and R are the proportions of the population that are susceptible, infectious and removed, respectively. The parameter $\mathcal{R}_0$ is the basic reproduction number. The time unit has been chosen to be the mean infectious period for convenience.

(a) A quantity of some practical importance is the ***peak prevalence*** of disease in the population, *i.e.,* the maximum proportion of the population that is simultaneously infected. Find an exact expression for the peak prevalence, given initial conditions (S_0, I_0). Why might a public health official want to know this quantity?

Solution. The peak prevalence corresponds to the maximum value of I, which is where the determinant of I is equal to zero.

$$\frac{dI}{dt} = \mathcal{R}_0 SI - I = 0 \implies I = 0 \quad or \quad S = \frac{1}{\mathcal{R}_0} \tag{18}$$

This can then be subbed into the equation for the solution curves in the phase plane as derived in class to find the value of I when $S = 1/\mathcal{R}_0$

$$I + S - (I_0 + S_0) = \frac{1}{\mathcal{R}_0} \log\left(\frac{S}{S_0}\right) \tag{19}$$

$$I = (I_0 + S_0) - \frac{1}{\mathcal{R}_0} + \frac{1}{\mathcal{R}_0} \log\left(\frac{1/\mathcal{R}_0}{S_0}\right) \tag{20}$$

$$I = (I_0 + S_0) - \frac{1}{\mathcal{R}_0} + \frac{1}{\mathcal{R}_0} \log\left(\frac{1}{\mathcal{R}_0 S_0}\right) \tag{21}$$

□

A health official might be interested to know the peak prevalence of an infection so they would be aware of the maximum number of patients they need to be able to treat at one time. This would also be a good indication of the population recovering, since in this model once the maximum of I is reached it will only decrease meaning in the future there will be fewer patients to treat as they move into recovered/removed class.

(b) It would be helpful to have an analytical expression for the solution of the model. Most valuable would be a formula for $I(t)$, which is most closely related to time series data. You probably will not find a formula for $I(t)$ (extra credit if you do!!) but it is definitely possible to find an exact expression that relates R (proportion removed) and t (time).

(i) Find such an expression. *Hint:* Combine the equations for dS/dt and dR/dt into one equation that can be solved for S as a function of R. Then recall that $S+I+R = 1$ and use the dR/dt equation again. *Note:* You will end up with an expression for t as a function of R, not R as a function t.

Solution.

$$\frac{\frac{dS}{dt}}{\frac{dR}{dt}} = \frac{dS}{dR} = \frac{-\mathcal{R}_0 SI}{I} = -\mathcal{R}_0 S \implies S = S_0 e^{-\mathcal{R}_0 R} \tag{22}$$

Recall $S + I + R = 1$ so we have that

$$S_0 e^{-\mathcal{R}_0 R} + I + R = 1 \implies R = 1 - I - S_0 e^{-\mathcal{R}_0 R} \tag{23}$$

From equation (17)

$$\frac{dR}{dt} = 1 - R - S_0 e^{-\mathcal{R}_0 R} \tag{24}$$

We can solve this as a separable equation to get the expression for t(R)

$$t = \int \frac{1}{1 - R - S_0 e^{-\mathcal{R}_0 R}} dR \tag{25}$$

□

(ii) Use your expression for $t(R)$ to find an expression for the time at which peak prevalence will occur. Why might this be useful?

Solution. The peak prevalence corresponds to where the determinant of I is equal to zero:

$$\frac{dI}{dt} = \mathcal{R}_0 SI - I = 0 \implies I = 0 \quad or \quad \mathcal{R}_0 = \frac{1}{S} \tag{26}$$

Since $I = 0$ is trivial, take $\mathcal{R}_0 = 1/S$ and plug this into the expression for t(R) from 2(b)(i) giving

$$t = \int \frac{1}{1 - R - S_0 e^{-R/S}} dR \tag{27}$$

This expression may be useful because the expression relates time to peak prevalence. This means that if one can solve this expression, they will know at what amount of time units peak prevalence will occur.

□

(iii) How could your expressions be used to compare with the time series for pneumonia and influenza in Philadelphia in 1918? (Don't actually do it; just clearly explain your thinking including any assumptions you are making.) Would you advise your assistant who just graduated with a degree in math and biology to do this (to help you prepare your report for the public health agency)? Why or why not?

Solution. The P & I 1918 time series shows deaths as a function of time, whereas the model achieved in this solution is time as a function of those recovered; recovered including both those that died and those that are over the illness and now immune. If the t(R) model from this question was solved explicitly (assuming we could find a solution) and an inverse $t^{-1}(R)$ was solved for explicitly, (one again assuming this exists and can be solved) we would have a model similar to the P & I 1918 model which models recovery as a function of time. One further assumption needed is that all of those belonging to the recovered category in the $t^{-1}(R)$ are dead, since alive and immune is not included in the time series data for P & I 1918. I would not advise my assistant to help prepare a report for the public health agency with this model since the assumptions are too extreme and unreasonable. A better model that has an explicit equation and takes into account those recovered that are alive will do a much better job modelling the P & I 1918 data than the one achieved in this question.

□

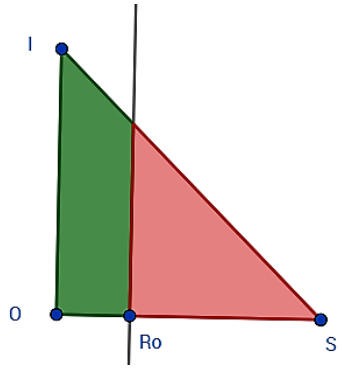
(iv) Is it possible to find an exact analytical expression for t as a function S?

Solution. Yes it is possible to find an exact analytical expression for t(S). The same steps from part (i) can be taken, except R is solved for as a function of S (separable equation) when combining dS/dt and dR/dt, and the dS/dt equation is solved for I to achieve a relation between dS/dt and I to substitute into the$S + I + R = 1$ equation. Carrying on as in part (i) R and I can now be replaced in $S + I + R = 1$ and the equation can be solved as a separable equation, giving t as a function of S or t(S).

□

(c) Prove that all solutions of the basic SIR model approach $I = 0$ asymptotically, and explain why this makes biological sense. *Hint:* Is the function $L(S, I) = I$ a Lyapunov function? Read the Notes on Lyapunov functions below.

Answers. There are several things to be considered at the beginning of this proof. First examine (17) where it can be plainly seen that if $I = 0$ then the system is at an equilibrium. Thus we will only consider cases where $I(0) \neq 0$.



Consider the relative area, as shown here. First we will examine the green area, written as $\mathcal{O} = \{(-\infty, \frac{1}{\mathcal{R}_o}) \times \mathbb{R}\} \cap \Delta$, where $\Delta = \{(S, I) : S \geq 0,\ I \geq 0,\ S + I \leq 1\}$ as shown in the image, and $\mathcal{O}$ is an open subset relative to the area of interest. We will also use the closed set $\mathcal{C} = \{[0, \frac{1}{\mathcal{R}_o} - \delta] \times 0\}, \delta > 0$. As stated previously, any state with $I = 0$ will remain in that set, making $\mathcal{C}$ an invariant set. Knowing this we can now invoke *Lyapunov's Direct Method of Closed Invariant Sets* using the Lyapunov function, $L = I$. It is easily shown that this is a strict Lyapunov function on $\mathcal{O} \setminus \mathcal{C}$ and $\mathcal{C}$ is asymptotically stable.

$$\begin{aligned} L &= I \\ L(X) &= 0 \quad \forall \quad X \in \mathcal{C} \\ L(X) &> 0 \quad \forall \quad X \in \mathcal{O} \setminus \mathcal{C} \\ \frac{dL(X)}{dt} &= \frac{dI}{dt} = I(\mathcal{R}_0 \cdot S - 1) \\ \frac{dL(X)}{dt} &= 0 \quad \forall \quad X \in \mathcal{C} \\ \frac{dL(X)}{dt} &< 0 \quad \forall \quad X \in \mathcal{O} \setminus \mathcal{C} \end{aligned} \tag{28}$$

We now conclude that the set of $I = 0$ is asymptotically stable for any initial conditions in $\mathcal{O}$.

Next we need to show that any trajectories with initial conditions in $\Delta \setminus \mathcal{O}$, in green in the diagram, will eventually land in $\mathcal{O}$ at which point we use the asymptotic stability of $\mathcal{C}$ as we showed above. For any point, $P \in \Delta \setminus \mathcal{O}, P = \{(S, I) | S \geq \frac{1}{\mathcal{R}_0}, I > 0, S + I \leq 1\}$. We can see from (17) that $\frac{dS}{dt} < 0$ for all P. This means that S will decrease and continue to decrease until $P \in \mathcal{O}$, as I will increase while $P \in \Delta \setminus \mathcal{O}$ preventing P from approaching an equilibrium before $P \in \mathcal{O}$. By the asymptotic stability of $\mathcal{C}$ within $\mathcal{O}$, P will proceed to $I = 0$. □

This makes biological sense as any endemic will end eventually, at which point there will be no infectious individuals, so $I = 0$, and $I = 0$ is the only point at which an epidemic will end, as patients will eventually move to the removed class.

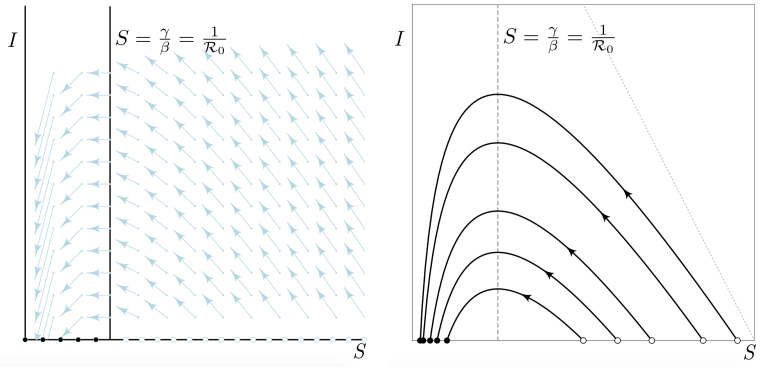
(d) Find and classify the stability of all equilibria of the basic SIR model.

Solution. Equilibrium points are defined where the variables do not change with time:

$$\frac{dS}{dt} = -\mathcal{R}_0 SI = 0, \quad \frac{dI}{dt} = \mathcal{R}_0 SI - I = 0, \quad \frac{dR}{dt} = I = 0 \tag{29}$$

This yields a continuum of equilibrium defined as $(S, I) = (S_0, 0) \quad \forall S_0 \in [0, 1]$.

As can be seen by the nullclines and phase portrait developed in lecture, the equilibrium points with $S < 1/\mathcal{R}_0$ are asymptotically stable and the equilibrium points with $S > 1/\mathcal{R}_0$ are unstable.



□

Notes on Lyapunov functions

Consider Lyapunov's Stability Theorem as stated in Math 3F03 Lecture 28 in 2013:

Theorem 1 (Lyapunov's Direct Method)**.** *Consider an equilibrium X_* of $X' = F(X)$ and an open set $\mathcal{O}$ containing X_*. If $\exists$ a differentiable function $L : \mathcal{O} \to \mathbb{R}$ such that*

(a) $L(X_*) = 0 \quad$ *and* $\quad L(X) > 0 \quad \forall X \in \mathcal{O} \setminus \{X_*\}$ *(L positive definite on $\mathcal{O}$)*

(b) $\dot{L}(X) \leq 0 \quad \forall X \in \mathcal{O} \setminus \{X_*\}$ *($\dot{L}$ negative semi-definite on $\mathcal{O}$)*

then X_* is stable and L is called a ***Lyapunov function****. If, in addition,*

(c) $\dot{L}(X) < 0 \quad \forall X \in \mathcal{O} \setminus \{X_*\}$ *($\dot{L}$ negative definite on $\mathcal{O}$)*

then X_* is asymptotically stable and L is called a ***strict Lyapunov function****.*

Theorem 1 can be generalized for analysis of stability of sets more complicated than isolated equilibria, such as periodic orbits or line segments. If you think through the proof of the theorem above (*e.g.,* [**?**, §9.2, theorem stated on p. 193 and proved on p. 196]), you should be able to convince yourself that the proof still works if the equilibrium X_* is replaced by any *closed forward-invariant set* (often simply called a *closed invariant set*). This observation allows us to state the following more general theorem.

Theorem 2 (Lyapunov's Direct Method for Closed Invariant Sets)**.** *Consider a closed invariant set $\mathcal{C}$ of $X' = F(X)$ and an open set $\mathcal{O}$ containing $\mathcal{C}$. If $\exists$ a differentiable function $L : \mathcal{O} \to \mathbb{R}$ such that*

(a) $L(X) = 0 \; \forall X \in \mathcal{C} \quad$ *and* $\quad L(X) > 0 \quad \forall X \in \mathcal{O} \setminus \mathcal{C}$ *(L positive definite on $\mathcal{O}$)*

(b) $\dot{L}(X) \leq 0 \quad \forall X \in \mathcal{O} \setminus \mathcal{C}$ *($\dot{L}$ negative semi-definite on $\mathcal{O}$)*

then $\mathcal{C}$ is stable and L is called a ***Lyapunov function****. If, in addition,*

(c) $\dot{L}(X) < 0 \quad \forall X \in \mathcal{O} \setminus \mathcal{C}$ *($\dot{L}$ negative definite on $\mathcal{O}$)*

then $\mathcal{C}$ is asymptotically stable and L is called a ***strict Lyapunov function****.*

Note in the above theorems that open sets are defined relative to the subset of interest; in our case this subset is $\Delta = \{(S, I) : S \geq 0,\, I \geq 0,\, S + I \leq 1\}$, not all of $\mathbb{R}^2$. An open set of Δ is a set of the form $U \cap \Delta$ where U is an open set of $\mathbb{R}^2$. (These sets are said to be open in the ***relative topology*** on Δ.) In particular, note that Δ is *open* as a subset of itself, in spite of the fact that it is *not open* as a subset of $\mathbb{R}^2$, whereas Δ is closed in both the relative topology on Δ and the usual topology on $\mathbb{R}^2$.

— END OF ASSIGNMENT —

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