Disease library for COPASI

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Contents

Chapter 1

Introduction

We have compiled a set of compartmental deterministic models for transmissible diseases, ready for use in the COPASI Biochemical System Simulator software (and other SBML standard compliant tools). Models were chosen to represent globally relevant diseases, as well as a diversity of disease types and infection mechanisms. These models aim to exemplify commonly used mathematical analyses, as well as numerical simulations, using COPASI. A primary goal is to provide inexperienced users an amenable introduction to the basics of mathematical modeling of infectious diseases. Provided examples show how one can formulate and numerically explore and analyze a mathematical models. We also aim to promote consistency between modeling efforts by making it easier to use existing standards. This should save people time and effort by enabling them to build from pre-existing models, as well as foster collaboration and reproduceability.

In the sections to follow, we will study basic mathematical models for selected diseases. Chapters 2 through 5 consider diseases by mechanism of infection: water-borne diseases, sexually-transmitted diseases, airborne diseases and vector-borne diseases. Each of these chapters considers each disease case in terms of its epidemiology, a model extracted from literature, a short mathematical analysis, and the COPASI-related code. The following points will be addressed, as relevant for each disease case. These will ultimately relate to specifics in the COPASI model structure and simulation settings.

1. Infection mechanism (E.g. seasonality)

2. Transmission agents (human, vector, animal host, animal reservoir, environment like water bodies, soil, etc.)

3. Mixing structure (homogeneous, age-structured, sex-structured, spatial metapopulation)

4. Region

5. Interventions (Vaccination, social distancing, preventative and curative treatment)

6. Initial conditions (based on the research question) and temporal changes in the interventions (e.g. vaccination is one time phenomenon whereas social distancing may vary over time)

The Generic Models chapter (6) covers slight modifications of the presented models. Chapter 7, The Final Epidemic Size, looks at techniques used to compute the final epidemic size of various models.

The COPASI files for the following models and reproduced results from the respective referenced papers and can be found at https://github.com/mugdhat2/CopasiDiseaseLibrary.

Chapter 2

Water-borne Diseases

2.1 Cholera

Needs paraphrasing to be publishable

Introduction

Cholera is an acute, diarrheal illness caused by infection of the intestine with the toxigenic bacterium *Vibrio cholerae*. It is estimated Cholera is responsible for 2.9 million cases and 95,000 deaths annually worldwide. The infection is often mild or without symptoms, but can be severe. Approximately 1 in 10 people who get sick with cholera will develop severe symptoms such as watery diarrhea, vomiting, and leg cramps. In these people, rapid loss of body fluids leads to dehydration and shock. Without treatment, death can occur within hours.

A person can get cholera by drinking water or eating food contaminated with cholera bacteria. In an epidemic, the source of the contamination is usually the feces of an infected person that contaminates water or food.

Mathematical Model

Assume the health stages Susceptible (S), Infected (I) and Recovered (R), and let B denote the concentration of vibrios in contaminated water. The following [12], two transmission paths for Cholera are considered: environment-to-human transmission and human-to-human transmission.

Susceptible individuals are assumed to be recruited proportionally to the population size, μN, and can become infected by drinking contaminated water at rate $\beta_e \frac{B}{k+B}$, or by contact with infected individuals at rate $\beta_h I$. In addition, susceptible individuals might get vaccinated and become permanently immune at rate ν, or die at rate μ. Infected individuals are assumed to permanently recover on average after $\frac{1}{\gamma}$ days or die at rate μ. Contaminated water is assumed to be generated by infected individuals at rate ξ, and it cleans up by natural vibrios decayment at rate δ or by disinfection at rate c.

The aforementioned disease dynamics are captured in the following system of Ordinary

Differential Equations (ODE).

$$\begin{cases} \frac{dS}{dt} = \mu N - \left(\beta_e S \frac{B}{k+B} + \beta_h SI\right) - \mu S - vS \\ \frac{dI}{dt} = \beta_e S \frac{B}{k+B} + \beta_h SI - (\gamma + \mu) I \\ \frac{dR}{dt} = \gamma I - \mu R + vS \\ \frac{dB}{dt} = \xi I - \delta B - cB \end{cases} \tag{2.1}$$

where μ represents natural birth or death rate, $N(S + I + R = N)$ denotes the total population in China, k corresponds to the concentration of vibrios in contaminated water, ξ is the rate of human contribution to vibrio Cholera, δ is the decay rate of vibrios

With estimated parameters $\beta_e = a \times 10^{-6}$, $\beta_h = b \times 10^{-9}$ and ν.

Model Analysis

The presented mathematical model incorporates population dynamics that allow the model to reach an endemic level (non-zero steady state) in the population. In the absence of cholera, model (2.1), assumes a constant total population since

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dI}{dt} + \frac{dR}{dt} = 0$$

Therefore, it is enough to consider the following equations

$$\begin{aligned} \frac{dS}{dt} &= \mu N - \beta_e S \frac{B}{k+B} - \beta_h SI - \mu S - vS \\ \frac{dI}{dt} &= \beta_e S \frac{B}{k+B} + \beta_h SI - (\gamma + \mu) I \\ \frac{dB}{dt} &= \xi I - \delta B - cB \end{aligned} \tag{2.2}$$

Making system (2.2) equal to zero, and solving for the population variables, we get the disease-free equilibrium (DFE) under control policies (vaccination)

$$E_0 = \left(\frac{\mu N}{\mu + v}, 0, 0\right) \tag{2.3}$$

and the following endemic equilibrium

$$E^* = (S^*, I^*, B^*), \text{ where } I^* = \frac{(\delta + c)B^*}{\xi} \text{ and } S^* = \frac{\mu N \xi - (\gamma + \mu)(\delta + c)B^*}{(\mu + v)\xi}$$

Following the Next Generation Matrix (NGM) approach with infectious compartments I and B, the control reproductive number of system (2.1) is given by Brian's comment: Is "the next generation approach" a formal concept? If so, it should be somehow indicated with capitalization, or something.

$$\mathcal{R}_C = \mathcal{R}_h + \mathcal{R}_e = \beta_h \frac{\mu N}{(\mu + v)(\gamma + \mu)} + \beta_e \frac{\mu N \xi}{(\mu + v)(\gamma + \mu)(\delta + c)k} \tag{2.4}$$

which collects the secondary infections produced by infected individuals during its infectious period $\frac{1}{\gamma+\mu}$ at rate β_h and, the secondary infections produced by contaminated water at

rate $\beta_e \frac{\xi}{\kappa}$ during its contamination period $\frac{1}{\delta+c}$, generated by infected individuals during their infectious period $\frac{1}{\gamma+\mu}$, in a partially susceptible population $S_0 = \frac{\mu N}{\mu+\nu}$.

Notice that the control reproductive number $\mathcal{R}_C$, reduces to the basic reproductive number $\mathcal{R}_0$, in the absence of vaccination. In this case, $S_0 = N$ and the basic reproductive number is given by

$$\mathcal{R}_0 = N\left(\beta_h \frac{1}{(\gamma+\mu)} + \beta_e \frac{\xi}{(\gamma+\mu)(\delta+c)k}\right) \tag{2.5}$$

Simulations

To simulate the model we use the parameters in Figure 2.1.

Initial conditions missing. It would be preferable for the units to be consistent. Rewrite parameter estimate table with final values.

Parameter	Value	Comments	Unit
μ	0.0066	Natural birth or death rate	$year^{-1}$
k	500	Concentration of Vibrio Cholerae in environment	$cells/mL$
N	1.36×10^9	Human number in China	None
β_e	Estimated	Environment-to-human transmission rate	$year^{-1}$
β_h	Estimated	Human-to-human transmission rate	$year^{-1}$
ν	Estimated	Vaccination rate	$year^{-1}$
γ	0.2	Recovery rate	day^{-1}
ξ	10	Rate of human contribution to Vibrio Cholerae	$cells \cdot mL^{-1} \cdot day^{-1}$
δ	1/30	Decay rate of vibrios	day^{-1}
c	4	Disinfection rate	$year^{-1}$

Parameter	Mean	Standard	MCMC error	Geweke
a	2.6699	0.47607	0.055218	0.95468
b	5.3508	2.4914	0.30616	0.99076
v	0.31017	0.040146	0.0047384	0.94347

Figure 2.1: Parameters for Cholera model

Model Remarks

The studied cholera model incorporates several key components: (i) due to the endemic nature of cholera in the affected regions, a model with demographic processes is used; (ii) the water and human based cholera transmission routes require addressing both infection forces in order to appropriately capture disease dynamics and thresholds; (iii) the availability of vaccine makes it important to study cholera dynamics in the absence and in the presence of control measures (vaccination): (a) cholera dynamics in a completely susceptible population and, (b) cholera dynamics in a partially susceptible population, for which disease dynamics exhibits different but related thresholds, ???????????the basic and the control reproductive numbers, $\mathcal{R}_0$ and $\mathcal{R}_C$ respectively.??????????

Finally, notice that $\mathcal{R}_C$ and $\mathcal{R}_0$ of model (2.1), are directly proportional to the population size. This is due to the mass action formulation βSI, as opposed to the standard incidence formulation $\beta S\frac{I}{N}$. The fact that the basic and the control reproduction numbers are functions of the population size, has direct implications to public health policies.

Disease	Cholera
Transmission pathway(s)	- Human-to-human - Water-to-human
Intervention Scenarios	- No Intervention - Disinfection of water (at rate c) - Vaccination (at rate ν)
Model source	[12]
Unique modeling aspect	Simple model with - environmental transmission mode - vaccination
Location	China
Initial conditions	$I_0 = 28$; $B_0 = 500$ (Assumed*)
Parameter estimate remarks	- Sources of parameter estimates not given - For $R_0 < 1$, Figure 5 shows positive equilibrium - Same data used to fit and validate the model (verify)
Data Sources	NA
Reproducibility remarks	Figures 5 and 6 reproduced
Possible extensions	- Waning immunity upon recovery and vaccination - Finer spatial resolution

Table 2.1: Cholera: Summary and reproducibility attributes. * Information missing in paper

2.2 Typhoid

Introduction

Mathematical model

Following the work in [11], we assume the population under study is subdivided in the following health classes: Susceptible individuals (S), Infected and infectious individuals (I), Infected and not infectious individuals due to treatment (T), and Recovered individuals (R). The model also assumes that some susceptible individuals are vaccinated and loss immunity after a period of time (P).

The proposed model assumes that susceptible individuals are being recruited at a constant rate Λ and die at a per-capita rate μ.

The fraction σ of recruited susceptible individuals are assumed to be vaccinated, becoming temporary protected against Typhoid on average for a period of $\frac{1}{\gamma}$. The fraction of non-vaccinated recruited individuals $1-\sigma$ becomes susceptible. Typhoid is transmitted by contacts between infected and susceptible individuals at a rate αSI. Infected individuals either, undergo disease-induced death at a rate δI, go to treatment at a rate βI, or die by other reasons at a per-capita rate μ. Individuals under treatment recovers at a per-capita rate ϵ, loosing natural immunity at a per-capita rate κ, or die out by oher reasons at a per-capita rate μ.

$$\begin{aligned}
\frac{dP}{dt} &= \sigma\Lambda - (\gamma+\mu)P \\
\frac{dS}{dt} &= (1-\sigma)\Lambda + \gamma P - \alpha SI - \mu S + kR \\
\frac{dI}{dt} &= \alpha SI - (\delta+\beta+\mu)I \\
\frac{dT}{dt} &= \beta I - (\mu+\varepsilon)T \\
\frac{dR}{dt} &= \varepsilon T - \mu R - kR
\end{aligned} \tag{2.6}$$

Parameter	Definition	Assumption from [1]	Value
α	Infection transmission coefficient	β_2	0.05
β	Treatment initiation rate	ϕ_2	0.3
δ	Disease induced mortality rate	δ	0.075
ϵ	Recovery rate	ϵ	0.4
γ	Rate of waning immunity of protected individuals	ω	0.5
k	Immunity waning rate of recovered individuals	0	0
Λ	Total recruitment rate of individuals	Λ	200
μ	Natural mortality rate	μ	0.142
σ	Vaccination proportion	τ/Λ	0.092

Table 2.2: Parameter estimates adapted from [1]. Time units in decades.

Disease	Typhoid
Transmission pathway(s)	Human-to-human
Intervention Scenarios	- No Intervention - Treatment - Vaccination
Model source	[11]
Unique modeling aspect	- Capturing water-borne transmission without an explicit class for contaminated water - Waning immunity of vaccination captured - Individuals in treatment are not infectious
Location	Non-specific
Initial conditions	Assumed based on Figures in [1]
Parameter estimate remarks	Assumed based on estimates in [1]
Data Sources	NA
Reproducibility remarks	Simulations approximate Figures 2, 3, 5, 6 and 7 in [1]
Possible extensions	Transmission pathway through contaminated food and water

Table 2.3: Typhoid: Summary and reproducibility attributes

Model Analysis

Simulations

Assumptions:

- I (Infectious individuals) in the coded model is equivalent to I_e (educated infectious individuals) in [1] since the models closely resemble.
- $(P_0, S_0, I_0, T_0, R_0) = (100, 200, 120, 80, 60)$ based on Figures in [1]
- Parameter estimation from [1] as shown in Table 2.2

Model remarks

The proposed model assumes a mass action law in the non-linear term (αSI), which assumes that every susceptible individual makes contacts with every infected individual. This

assumption may be appropriate in the case of small populations, but inaccurate as the total population size increases. A direct consequence of the mass-action assumption is that the basic reproductive number is proportional to the population size. In other words, the model assumes that the number of secondary cases produced by a single infected individual increases as the population size increases.

2.3 Dysentery

Introduction

Dysentery can result from bacteria, virus or parasitic infection. It is commonly caused by shigella dysenteriae serotype 1 (bacillary dysentery) or Entamoeba histolytica (amoebic dysentery). Without adequate hydration, it can be fatal.

Although preventable and treatable, it is common worldwide. Dysentery epidemics regularly occur in less developed areas of Central and South America, Africa, and Asia. It tends to be a major problem among refugee populations, where overcrowding and poor sanitation facilitate transmission.

Mathematical model

Based on the work by Weldegiorgis et.al. [4], the population of interest is subdivided into Susceptible (S), Infected (I) and Recovered (R) individuals. The infectious pathogen is denoted by B.

The proposed model assumes susceptible individuals are recruited at a constant rate Λ, and assumes individuals die out at the per-capita rate μ, regardless of their health status. Susceptible individuals are assumed to become infected by contact with infectious individuals $\left(\lambda_h = \beta_h \frac{I}{N}\right)$ or by ingesting the infectious pathogen $\left(\lambda_B = \beta_B \frac{B}{K+B}\right)$, where β_B represents the rate of ingesting the pathogen from the contaminated environment, and β_h through human to human interaction. The infection due to virus ingestion is assumed to follow a logistic shape, where the 50% chance of acquiring the infection is denoted by K. Infected individuals recover at a per-capita rate γ or die from natural causes or by disease-induced deaths at a per-capita rate d. Recovered individuals die out or are assumed temporarily immune, before becoming susceptible again at a rate α. The infectious pathogen is assumed to be shed by infectious individuals at a rate ϵI, and it is assumed the pathogen clears at a rate σ.

The dynamics of disease progression among individuals in the affected population is described by the following system of ODE's

$$\begin{array}{l} \frac{dS}{dt} = \Lambda + \alpha R - (\lambda_h + \lambda_B + \mu)\, S \\ \frac{dI}{dt} = (\lambda_h + \lambda_B)\, S - (\mu + \gamma + d) I \\ \frac{dR}{dt} = \gamma I - (\mu + \alpha) R \\ \frac{dB}{dt} = \epsilon I - \sigma B \end{array} \tag{2.7}$$

where

$$\lambda_h = \beta_h \frac{I}{N} \text{ and } \lambda_B = \beta_B \frac{B}{K+B} \tag{2.8}$$

Model analysis

Notice that the population is not constant and therefore we start computing the population's steady state. The population size is governed by the equation $\frac{dN}{dt} = \Lambda - \mu N$, with a steady state $N^* = \frac{\Lambda}{\mu}$. Therefore the disease-free equilibrium is given by

$$E^* = \left(\frac{\Lambda}{\mu}, 0, 0\right). \tag{2.9}$$

Using the next generation approach with the infectious compartments I and B, we get the basic reproductive number

$$R_0 = \frac{\beta_h}{(\mu+\gamma+d)} + \frac{\Lambda\beta_B\epsilon}{\mu(\mu+\gamma+d)K\sigma} \tag{2.10}$$

which accounts for the average number of secondary infections produced by a single infected individual $\left(\frac{\beta_h}{\mu+\gamma+d}\right)$, and the average infections produced by the infected environment.

Simulations

Disease	Dysentery
Transmission pathway(s)	- Human-to-human - Water-to-human
Intervention Scenarios	- No Intervention
Model source	[4]
Unique modeling aspect	Waning immunity of recovered people
Location	Ethiopia
Initial conditions	- Values used from Table 3 in [4] - I_0 differs in Table 3 and Figure 4 in [4]
Parameter estimate remarks	Time course for given parameters does not fit the data
Data Sources	Table 2 in [4]
Reproducibility remarks	Figure 4 in [4] reproducible for $K = 28158$, $\alpha = 0.14$, $\gamma = 0.124$
Possible extensions	Age-structure model since children are at most risk

Table 2.4: Dysentery: Summary and Reproducibility attributes

Model remarks

Notice that the birth rate is constant, instead of proportional to the population size. This makes the population size not constant and therefore the analysis requires computation of the population steady state. Alternatively, we could assume the population already reached steady state by using a recruitment rate proportional to the population size (ΛN).

The saturation assumption made in the infectious function of environmental infection makes the model highly sensitive to changes in the K parameter. Notice that λ_B grows linearly with B if $B \ll K$, while if $B \gg K$, λ_B approaches a steady state, with β_B resulting in a saturation state. This impacts the early dynamics of $I(t)$ and $B(t)$.

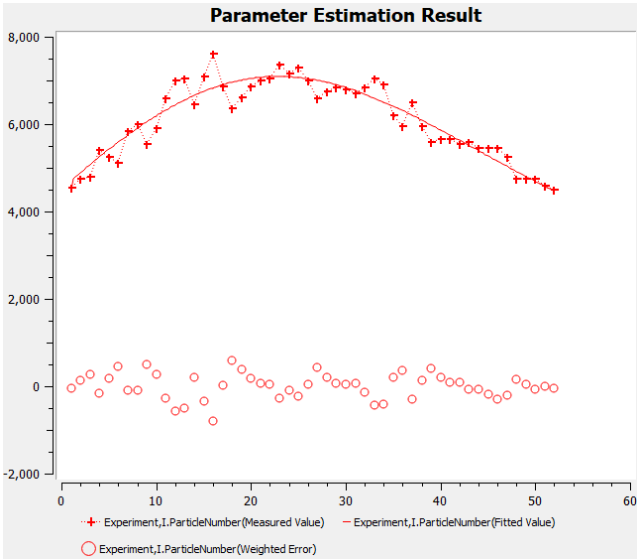

Figure 2.2: Model fitting to reproduce Figure 4 in [4] using COPASI. Horizontal axis is time in weeks.

Chapter 3

Sexually-transmitted Diseases

3.1 Herpes simplex virus (HSV–2)

Introduction

Herpes simplex virus (HSV) is an incurable disease that persists during the lifetime of the human host and produces mucocutaneous infections. There are two types of HSV (HSV-1 and HSV-2). HSV-2 infection in a healthy and non-infected person occurs through sexual contact and direct contact with bodily fluids with an infected person.

Genital herpes infection is common in the United States. The Centers for Disease Control (CDC) estimates that 776,000 people in the United States get new genital herpes infections, annually. Nationwide, 11.9% of persons aged 14 to 49 years have HSV- 2 infection.

Mathematical model

The following model [2] is used to study the effects of early treatment of HSV-2 on its transmission dynamics and control. It considers the U.S. sexually active population with ages between 15 and 49 years. The model considers susceptible individuals (S), individuals in early treatment (X), infected infectious individuals (I), infected individuals under treatment (T), and infected but not infectious individuals in a latent state (L). Susceptible individuals showing symptoms similar to HSV-2 infection can be sent to early treatment X even if they are not HSV-2 infected, at rate $\kappa\eta$. Notice that also false positives may be sent to the X class. After a treatment period, individuals in X come back to S at rate ϕ. Susceptible individuals get infected and progress to I by contacting infectious individuals not in treatment. An infectious individual may go to a Latency state L at rate γ, may go to treatment at rate η, or may die out at rate μ. Individuals under treatment progress to a dormant state L at rate ϕ or dies out at rate μ. Individuals in the latency state may develop symptoms and go to I at rate r or die out at rate μ.

$$\begin{aligned}
\frac{dS}{dt} &= \mu N + \phi X - \frac{\beta SI}{N} - (\mu + \kappa\eta)S \\
\frac{dX}{dt} &= \kappa\eta S - (\phi + \mu)X \\
\frac{dI}{dt} &= \frac{\beta SI}{N} + rL - (\eta + \gamma + \mu)I \\
\frac{dT}{dt} &= \eta I - (\phi + \mu)\,T \\
\frac{dL}{dt} &= \gamma I + \phi T - (r + \mu)L
\end{aligned}$$

Model Analysis

Using the Next Generation Matrix (NGM) to derive the control reproductive number and the basic reproduction number $\mathcal{R}_0$, we define the infectious compartments $\{I, T, L\}$. Since the total population is at steady state $\dot{N} = 0$, the Disease-Free Equilibrium (DFE) in the presence of treatment is given by

$$\left(\frac{N(\mu+\phi)}{\kappa\eta+\mu+\phi}, \frac{N\kappa\eta}{\kappa\eta+\mu+\phi}, 0, 0, 0\right).$$

We define $\mathcal{F} = \begin{bmatrix} \frac{\beta SI}{N} \\ 0 \\ 0 \end{bmatrix}$ and $\mathcal{V} = \begin{bmatrix} (\eta+\gamma+\mu)I - rL \\ (\phi+\mu)T - \eta I \\ (\mu+r)L - \gamma I - \phi T \end{bmatrix}$.

The Jacobian matrices for $\mathcal{F}$ and $\mathcal{V}$ with respect to I, T and L evaluated at the DFE are respectively the following:

$F = \begin{bmatrix} \beta & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$ and $V = \begin{bmatrix} \gamma+\eta+\mu & 0 & -r \\ -\eta & \phi+\mu & 0 \\ -\gamma & -\phi & \mu+r \end{bmatrix}$. The spectral radius of the NGM, FV^{-1} is then

$$\mathcal{R}_C = \frac{\frac{\beta}{\mu+\eta+\gamma} \cdot \frac{\mu+\phi}{\eta\kappa+\mu+\phi}}{1 - \left(\frac{\gamma}{\eta+\mu+\gamma} \cdot \frac{r}{\mu+r} + \frac{\phi}{\mu+\phi} \cdot \frac{\eta}{\eta+\mu+\gamma} \cdot \frac{r}{\mu+r}\right)} \tag{3.1}$$

Notice that $\mathcal{R}_C$ corresponds to the control reproductive number. The basic reproductive number is obtained by setting the control parameters ϕ, η to zero. Therefore

$$\mathcal{R}_0 = \frac{\frac{\beta}{\mu+\gamma}}{1 - \frac{\gamma}{\mu+\gamma} \cdot \frac{r}{\mu+r}}. \tag{3.2}$$

smriti: A little confused here as to how the control reproductive number has been deduced to be as in the equation. (I apologise as I don't have enough background in this area to connect the dots, but maybe a little explanation like in the previous section would be helpful for a person with little background on this to follow ?)

Model remarks

In the proposed model, infected individuals never recovers from the disease. Infectious individuals (I), may progress to a treatment state (T), and then progress to a latent state

(L), from which it is possible to come back to the infectious state. Therefore, a single individual may be in the infectious compartment I many times during his/her lifespan, producing secondary infections during each visit to the I stage. The basic reproductive number takes into account that

$$\mathcal{R}_0 = \frac{\frac{\beta}{\mu+\gamma}}{1-\frac{\gamma}{\mu+\gamma}\cdot\frac{r}{\mu+r}} = \sum_{n=0}^{\infty}\left(\frac{\beta}{\mu+\gamma}\right)\left(\frac{\gamma}{\mu+\gamma}\cdot\frac{r}{\mu+r}\right)^n. \tag{3.3}$$

Chapter 4

Airborne diseases

4.1 COVID-19

Grenfell's SIRS model [3].

Introduction

4.2 Tuberculosis

Introduction

Tuberculosis (TB) is a bacterial disease caused by *Mycobacterium tuberculosis* with at least one-third of the world human population as its reservoir. smriti: A citation might be required here? TB remains the world's deadliest infectious killer. Each day, over 4000 people lose their lives to TB and close to 30,000 people fall ill with this preventable and curable disease. This might not be true as of 2020 since the paper was from 20 years ago.

Following primary tuberculosis (TB) infection, only approximately 10% of individuals develop active TB. Most people are assumed to mount an effective immune response to the initial infection that limits proliferation of the bacilli and leads to long-lasting partial immunity both to further infection and to reactivation of latent bacilli remaining from the original infection. Infected individuals may develop active TB as a consequence of exogenous reinfection, i.e., acquiring a new infection from another infectious individual.

Mathematical Model

The model proposed in [8] stratifies the population under study in Susceptible (S), Exposed (E), Infected (I) and individuals under treatment (T). Due to the worldwide endemic situation of TB, the model incorporates demography processes by assuming a constant recruitment of susceptible individuals (Λ) and average lifespan $\frac{1}{\mu}$.

Susceptible individuals become exposed by direct contacts with infected people at rate $\beta c S \frac{I}{N}$. Exposed individuals are assumed to become infectious by contacts with infected individuals at rate $p\beta c \frac{I}{N}$ or, by endogenous progression at rate κ, otherwise exposed individuals die out at rate μ. Infectious individuals die out at rate μ, receive treatment at rate r or die out at rate d. Finally, individuals under treatment either become infectious

again by contact with infected individuals at rate $\sigma\beta c\frac{I}{N}$ or die out at rate μ. p represents the level of reinfection, c is the per-capita contact rate, and $\leq \sigma \leq 1$ stands for a reduced infectiousness.

$$\begin{aligned}
\tfrac{d}{dt}S &= \Lambda - \beta cS\tfrac{I}{N} - \mu S \\
\tfrac{d}{dt}E &= \beta cS\tfrac{I}{N} - p\beta cE\tfrac{I}{N} - (\mu + k)E + \sigma\beta cT\tfrac{I}{N} \\
\tfrac{d}{dt}I &= p\beta cE\tfrac{I}{N} + kE - (\mu + r + d)I \\
\tfrac{d}{dt}T &= rI - \sigma\beta cT\tfrac{I}{N} - \mu T
\end{aligned} \tag{4.1}$$

where $\mu = 0.016y^{-1}$, $d = 0.1, p = 0.4$, $\sigma = 0.9, \Lambda = 417(\Lambda/\mu = 25000)$, $k = 0.005$, $r = 2$. The value of β is calculated to be $7.465y^{-1}$ for $R_0 = 0.87$ using the expression for the basic reproduction number shown in Equation 4.3. Assuming $c = 1$, the system will show endemic equilibrium even for $R_0 < 1$ for the values of $p > 0.3133$. Refer to Feng et. al. (2000) for the detailed analysis [8].

What is 25000 population of? What are the initial conditions? What region are these parameter values specific for? Original sources of the values required, since mathematical modeling papers use values from different places dated anytime in the past.

Model Analysis

In the absence of TB, the total population in model (4.1) is not constant, but it converges to a steady state

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dT}{dt} = \Lambda - \mu N \tag{4.2}$$

solving (4.2), we get that $N(t) \to \Lambda/\mu$. Using the next generation matrix, we can compute the basic reproductive number

$$\mathcal{R}_0 = \left(\frac{\beta c}{\mu + r + d}\right)\left(\frac{k}{\mu + k}\right), \tag{4.3}$$

the expression (4.3) collects the secondary infections produced by the proportion of exposed individuals $\frac{k}{\mu+k}$, who become infectious and infects at a rate βc during their average infectious period $\frac{1}{\mu+r+d}$.

Notice that the basic reproductive number only captures the first time an individual is infected ($S \to E$) and not necessarily becomes infectious ($E \to I$). Moreover, $\mathcal{R}_0$ does not depend on p.

However, the endogenous infection (κE) and treatment relapse ($\sigma\beta cT\frac{I}{N}$) are not captured in $\mathcal{R}_0$. This generates a *backward bifurcation*. The key components of this type of dynamics are the processes associated to the relapse of individuals in latency state: endogenous progression κ, progression to treatment r and, progression to latency σ.

Model Remarks

The presented model studies the implication of exogenous and endogenous reinfection in the context of TB. The results suggest that these disease dynamics support an endemic equilibrium even when the classic metric $\mathcal{R}_0$ is less than one. This makes TB eradication more challenging because, while taking $\mathcal{R}_0 < 1$ is still necessary, it is not enough to guarantee a disease-free state. In this case, the system exhibits sensitivity to initial conditions if $\mathcal{R}_p < \mathcal{R}_0 < 1$, where $\mathcal{R}_p$ is a second threshold below which a disease-free state is guaranteed.

I was imagining the model remarks to be in terms of simulations and utility of COPASI codes of the diseases. Like "TB is more prominent in one part of the world than other therefore introducing heterogeneity in transmission coefficient is important" or for HSV–2 "women are x% more likely to contract the disease than men, therefore considering sex-segregated model is needed for more accurate and realistic time course simulations". That's a good remark in terms of public health.

4.3 Ebola virus disease

Introduction

Ebola virus disease (EVD) is transmitted to people from wild animals (such as fruit bats, porcupines and non-human primates) and then spreads in the human population through direct contact with the blood, secretions, organs or other bodily fluids of infected people, and with surfaces and materials (e.g. bedding, clothing) contaminated with these fluids. The average EVD case fatality rate is around 50%. Case fatality rates have varied from 25% to 90% in past outbreaks. There is no proven treatment for Ebola but simple interventions early on can significantly improve chances of survival. The 2014–2016 outbreak in West Africa was the largest and most complex Ebola outbreak since the virus was first discovered in 1976. Around 30,000 infected cases and 11,000 deaths were reported during this outbreak.

Mathematical model

In [7], the authors analyze the EVD dynamics in the absence of control measures. The mathematical model structures the population of interest by individuals' health states: susceptible (S), exposed and possibly infectious individuals (E), symptomatic infectious and undiagnosed individuals (I) , disease-induced deaths (D) and recovered (R) individuals, $N = S + E + I + D + R$.

Susceptible individuals move to the infected compartment at rate $\beta\left(\frac{I+\varepsilon D}{N}\right)$ through "effective" contacts with either infected individuals (I) or EVD-infected corpses (D). Infected individuals spend on average $\frac{1}{\kappa}$ days on latency state, without being infectious. After the latency period, individuals become infectious (I) on average during $\frac{1}{\gamma}$ days, after which, individuals either recover with probability $(1 - f_d)$ or die with probability f_d. EVD-infected corpses (D) subpopulation is assumed to increase at rate $f_d\gamma$, and reduced through properly burial on average after $\frac{1}{v}$ days. EVD-infected corpses are assumed to be more infectious than infected individuals due to have the highest viral load, $\epsilon > 1$.

$$\begin{cases} \dot{S} = -\beta S\left(\frac{I+\varepsilon D}{N}\right) \\ \dot{E} = \beta S\left(\frac{I+\varepsilon D}{N}\right) - \kappa E \\ \dot{I} = \kappa E - \gamma I \\ \dot{D} = f_{\mathrm{d}}\gamma I - \nu D \\ \dot{R} = (1 - f_{\mathrm{d}})\,\gamma I + \nu D \end{cases} \tag{4.4}$$

Parameter	Description	Base model values
β	Per susceptible infection rate	0.287
γ	Rate at which an infected recovers or dies	1/7
κ	Per-capita progression rate to latent detectable stage	1/7
ν	Per-capita body disposal rate	1/2
f_d	Proportion of infected who die due to infection	0.7
ε	Scale: Ebola infectiousness of EVD-infected corpses	> 1

Figure 4.1: Parameters for Ebola model

Model analysis

Model (4.4) address a single EVD outbreak where the total population remain constant ($\dot{N} = \dot{S} + \dot{E} + \dot{I} + \dot{D} + \dot{R}$=0). By using the next generation approach, with disease compartments E, I, D; the associated basic reproductive number is

$$\mathscr{R}_0 = \beta \left(\frac{1}{\gamma} + \frac{\varepsilon f_d}{\upsilon} \right). \tag{4.5}$$

The basic reproductive number of system (4.4) captures the average number of secondary infections produced by a typical infectious individual during their infectious period $\left(\frac{\beta}{\gamma}\right)$, and the secondary cases generated by a single EVD-infected corpse, during its disposal period $\left(\frac{\varepsilon \beta f_d}{\upsilon}\right)$, in a totally susceptible population.

Simulations

Units for parameters and references missing. What region are the included parameter values for? What are the initial conditions? Can you please share a screenshot of the figure that can be reproduced in this section?

Model remarks

The 2014 West African Ebola outbreak was a very challenging epidemic in great part due to the limitation of local public health infrastructure. In order to address these challenges, the model (4.4) incorporates two transmission routes: via infected individuals and via infected corpses. The model suggest that, while the main route of infection are the infected individuals, fast removal of infected corpses have a high impact on reducing $\mathcal{R}_0 < 1$ and thus in controlling an EVD outbreak. Since births and deaths are not modeled here, users should run the time course for short time durations for more realistic results. The model can be extended to include control measures.

4.4 Measles

Introduction

Mathematical model

In [13], the author considered a population composed by Susceptible individuals $S(t)$, Exposed individuals, but not yet infectious $E(t)$, Infectious individuals $I(t)$, and Recovered or removed artificially trough vaccination and permanently immune individuals $R(t)$.

$$\begin{aligned}
\frac{dS}{dt} &= b(1-p)N - \frac{\beta SI}{N} - \mu S \\
\frac{dE}{dt} &= \frac{\beta SI}{N} - (\sigma + \mu)E \\
\frac{dI}{dt} &= \sigma E - (\gamma + \mu + \delta)I \\
\frac{dR}{dt} &= bpN + \gamma I - \mu R
\end{aligned} \tag{4.6}$$

4.5 Influenza

Use the one in Generic models chapter?

Introduction

Mathematical model

Model analysis

4.6 Diphtheria

Chapter 5

Vector-borne diseases

5.1 Zika

Introduction

Zika virus disease is caused by the bite of an infected Aedes species mosquito (*Ae. aegypti* and *Ae. albopictus*). These mosquitoes bite during the day and night. smriti: we may be missing a citation here?

Zika virus can be transmitted through sexual intercourse, and it can be passed from a pregnant woman to her fetus. Infection during pregnancy can cause microcephaly and other congenital malformations, known as congenital Zika syndrome. An increased risk of neurologic complications is associated with Zika virus infection in adults and children, including Guillain-Barré syndrome, neuropathy and myelitis. There is no treatment available for Zika virus infection or its associated diseases.

Mathematical model

In [5], authors take into account the human to human infection as well as the vector (mosquito) to human transmission. The model subdivide the total human population, $N_H(t)$, into susceptible humans $S_H(t)$, exposed human $E_H(t)$, infected humans $I_H(t)$, and recovered humans $R_H(t)$, so that $N_H(t) = S_H + E_H + I_H + R_H$. The entire mosquito population, denoted by $N_V(t)$, is partitioned into susceptible vector $S_V(t)$, exposed vector $E_V(t)$ and infected mosquito $I_V(t)$ and hence $N_V = S_V + E_V + I_V$. The proposed model is

$$\begin{cases} \frac{d}{dt}S_h = \Lambda_h - \beta_h S_h \left(I_V + \rho I_h\right) - \mu_h S_h \\ \frac{d}{dt}E_h = \beta_h S_h \left(I_V + \rho I_h\right) - \left(\mu_h + \chi_h\right) E_h \\ \frac{d}{dt}I_h = \chi_h E_h - \left(\mu_h + \gamma + \eta\right) I_h \\ \frac{d}{dt}R_h = \gamma I_h - \mu_h R_h \\ \\ \frac{d}{dt}S_V = \Lambda_V - \beta_V S_V I_h - \mu_V S_V \\ \frac{d}{dt}E_V = \beta_V S_V I_h - \left(\mu_V + \delta_V\right) E_V \\ \frac{d}{dt}I_V = \delta_V E_V - \mu_V I_V \end{cases} \tag{5.1}$$

Mathematical analysis

Notice the host population is not constant, so we start computing the host population steady state

$$N_h' = S_h' + E_h' + I_h' + R_h' = \Lambda_h - \mu_h N_h - \eta_h I_h \tag{5.2}$$

From equation(5.2) we can obtain that in the absence of infection $N_h \to \frac{\Lambda_h}{\mu_h}$ and, in the presence of Zika infections

$$N_h' + \mu_h N_h \leq \Lambda_h.$$

The dynamics of vector population is described by $N_v' = \Lambda_v - \mu_v N_v$ which implies that $N_v' = \frac{\Lambda_v}{\mu_v}$.

The disease free equilibrium is given by $E_0 = \{N_h, 0, 0, 0, N_v, 0, 0\}$, and following the second-generation method

$$F = \begin{pmatrix} 0 & \frac{\rho\beta_h\Lambda_h}{\mu_h} & 0 & \frac{\beta_h\Lambda_h}{\mu_h} \\ 0 & 0 & 0 & 0 \\ 0 & \frac{\beta_v\Lambda_v}{\mu_Y} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, V = \begin{pmatrix} k_1 & 0 & 0 & 0 \\ -\chi_h & k_2 & 0 & 0 \\ 0 & 0 & k_3 & 0 \\ 0 & 0 & -\delta_V & \mu_V \end{pmatrix}$$

where $k_1 = \mu_h + \chi_h, k_2 = (\mu_h + \gamma + \eta)$ and $k_3 = (\mu_V + \delta_V)$. The basic reproductive number of model (5.1) is then the spectral radius of the matrix FV^{-1}

$$\mathcal{R}_0 = \frac{\rho\beta_h\Lambda_h\chi_h}{2\mu_h k_1 k_2} + \sqrt{\frac{\rho^2\beta_h^2\Lambda_h^2\chi_h^2}{4\mu_h^2 k_1^2 k_2^2} + \frac{\beta_h\Lambda_h\chi_h\beta_V\delta_V\Lambda_V}{\mu_h\mu_V^2 k_1 k_2 k_3}}.$$

Further analysis can be done on the endemic equilibria and the backward bifurcation.

Simulations

Some of the parameters don't have the units states in the table. Sources of the parameter values? Region for which these values hold true? Initial conditions?

Parameter	Description	value
β_H	Probability of humans getting infected	0.2 day^{-1}
β_V	Probability of mosquitoes getting infected	0.09
μ_H	Natural death rate in humans	1/(365x60) day^{-1}
μ_V	Natural death rate in mosquitoes	1/14
χ_H	The rate of exposed humans moving into infectious class	0.01
Λ_H	Recruitment rate of humans	100 day^{-1}
Λ_V	Mosquito recruitment rate	1000 day^{-1}
γ	Human recovery rate due to treatment	1000 day^{-1}
ρ	Human factor transmission rate	0.05 day^{-1}
η	Human infected treatment rate	0.2 day^{-1}
δ_V	The rate flow from E_V to I_V	0.05 day^{-1}

Figure 5.1: Parameters for Zika model

Note: Initial condition I_0 different in reported best fit and in the plot in the paper [5]. Estimated $\mu = 0.000457$; Figure 5 uses $\mu = 0.003199$.

5.2 Malaria

Malaria is a life-threatening disease transmitted back and forth between by vectors and hosts. It is caused by parasites transmitted to people through the bites of infected female Anopheles mosquitoes.

Mathematical model

Under the assumption that there are no hosts or vectors disease induced deaths, the hosts and mosquitoes populations remain constant, N_h and N_v respectively.

Following the construction in [6], of a vector borne disease model for Malaria, we get

$$\begin{aligned} S_h' &= \Lambda_h - \beta_h S_h \frac{I_v}{N_v} - \mu_h S_h \\ I_h' &= \beta_h S_h \frac{I_v}{N_v} - (\mu_h + \gamma_h) I_h \\ S_v' &= \Lambda_v - \beta_v S_v \frac{I_h}{N_h} - \mu_v S_v \\ I_v' &= \beta_v S_v \frac{I_h}{N_h} - (\mu_v + \gamma_v) I_v \end{aligned} \tag{5.3}$$

γ_v: Do mosquitoes recover from Malaria in their lifespan?

Model analysis

Notice that in model (5.3) the host population is not constant since

$$N_h' = S_h' + I_h' = \Lambda_h - \mu_h N_h'. \tag{5.4}$$

In order to explicitly find the equilibrium of the host population, we solve equation (5.4). The total host population is then given by

$$N(t) = N(0)e^{-\mu t} + \frac{\Lambda_h}{\mu_h}.$$

By the theory of asymptotic systems, we can analyze system's (5.3) qualitative behavior by assuming the population involved already reached its steady state. Since $N(t) \to \frac{\Lambda_h}{\mu_h}$, we get that model's (5.3) has a disease-free equilibrium $(N_h, 0, N_v, 0)$, where $N_h = \frac{\Lambda_h}{\mu_h}$ and $N_v = \frac{\Lambda_v}{\mu_v}$.

Demographic processes in the hosts and mosquitoes population allow for an endemic equilibrium under the following conditions

$$\begin{aligned} \beta_h S_h I_v &= (\gamma_h + \mu_h) I_h N_v \\ \beta_v S_v I_h &= (\gamma_v + \mu_v) I_h \\ \Lambda_h &= S_h \left(\mu_h + \beta_h \frac{I_v}{N_v} \right) N_h \\ \Lambda_v &= S_v \left(\mu_v + \beta_v \frac{I_h}{N_h} \right) \end{aligned} \tag{5.5}$$

By applying the second generation matrix to compute model's (5.3) basic reproductive number, we get

$$F = \begin{bmatrix} 0 & \beta_h \frac{N_h}{N_v} \\ \beta_v \frac{N_v}{N_h} & 0 \end{bmatrix}, \quad V = \begin{bmatrix} \gamma_h + \mu_h & 0 \\ 0 & \gamma_v + \mu_v \end{bmatrix}$$

where the second generation matrix is

$$FV^{-1} = \begin{bmatrix} 0 & \frac{\beta_h \frac{N_h}{N_v}}{\gamma_v + \mu_v} \\ \frac{\beta_v \frac{N_v}{N_h}}{\gamma_h + \mu_h} & 0 \end{bmatrix}$$

and the basic reproductive number

$$\mathscr{R}_0 = \sqrt{\frac{\beta_h \beta_v}{(\gamma_v + \mu_v)(\gamma_h + \mu_h)}}. \tag{5.6}$$

Model remarks

Notice that following this approach, expression (5.6) envision human-human transmission as a two step process: human-vector and vector-human transmission. However, it may be more appropriate to consider both steps as a single process producing the next generation of infected hosts. Under the former assumption, expression (5.6) becomes

$$\mathscr{R}_0 = \frac{\beta_h \beta_v}{(\gamma_v + \mu_v)(\gamma_h + \mu_h)} \tag{5.7}$$

Discuss about β meaning change if we consider $\frac{I_v}{N_v}$ or $\frac{I_v}{N_h}$.

5.3 Dengue model

Introduction

Mathematical model

$$S_h' = \mu_h N_h - \beta_h S_h \frac{I_v}{N_v} - \mu_h S_h \tag{5.8}$$

$$E_h' = \beta_h S_h \frac{I_v}{N_v} - (\eta_h + \mu_h) E_h \tag{5.9}$$

$$I_h' = \eta_h E_h - (\gamma + \mu_h) I_h \tag{5.10}$$

$$S_v' = \mu_v (N_v - q I_v) - \beta_v S_v \frac{I_h}{N_h} - \mu_v S_v \tag{5.11}$$

$$E_v' = \beta_v S_v \frac{I_h}{N_h} - (\eta_v + \mu_v) E_v \tag{5.12}$$

$$I_v' = q \mu_v I_v + \eta_v E_v - \mu_v I_v \tag{5.13}$$

Model analysis

5.4 Leishmaniasis

5.5 Yellow fever

Chapter 6

Generic Models

6.1 A two-strains model

From the book by Martcheva [10]. Consider an SIR model with genetic variability of a non-fatal infectious pathogen. The population is divided into susceptible individuals S, individuals infected by strain one I_1, individuals infected by strain two I_2, and recovered individuals $R(t)$. Assume recovered individuals get permanent cross-immunity after being infected. In other words, after infected with a strain they can't being infected with the same or the other strain. In addition, assume differential infectiousness on the strains β_1 and β_2 as well as variable serial periods α_1 and α_2.

The previously described model of disease progression is given by

$$\begin{aligned} S' &= \Lambda - \beta_1 \tfrac{SI_1}{N} - \beta_2 \tfrac{SI_2}{N} - \mu S \\ I_1' &= \beta_1 \tfrac{SI_1}{N} - (\mu + \alpha_1) I_1 \\ I_2' &= \beta_2 \tfrac{SI_2}{N} - (\mu + \alpha_2) I_2 \\ R' &= \alpha_1 I_1 + \alpha_2 I_2 - \mu R \end{aligned} \tag{6.1}$$

Adding model's 6.1 equations, we get that the total population N is described by $N'(t) = \Lambda - \mu N$. Model 6.1 has three equilibria: a disease free-equilibrium given by $\mathcal{E}^* = \{\frac{\Lambda}{\mu}, 0, 0, 0\}$, and two endemic equilibria where each of the strains dominates.

Notice that the strain-specific reproduction number are given by $\mathcal{R}_k = \frac{\beta_k}{\mu + \alpha_k}$. Opposite to the single strain SIR model, the DFE $\mathcal{E}^*$ is stable if both reproduction numbers are less than one, and the DFE becomes unstable if at least one of the reproduction numbers is greater than one.

The strain-specific dominance

By changing the model variables to proportions we get that $s = \frac{S}{N}$, $i_k = \frac{I_k}{N}$, and since at the steady state $\Lambda = \mu N$, we get that the equilibria are given by

$$\begin{aligned} 0 &= \mu - \beta_1 s i_1 - \beta_2 s i_2 - \mu s \\ 0 &= \beta_1 s i_1 - (\mu + \alpha_1) i_1 \\ 0 &= \beta_2 s i_2 - (\mu + \alpha_2) i_2 \\ 0 &= \alpha_1 i_1 + \alpha_2 i_2 - \mu r \end{aligned} \tag{6.2}$$

The strain specific dominance is given by the absence of infected individuals of the other strain. Assuming that strain 1 becomes dominant, we get $I_1 \neq 0$ and $I_2 = 0$. Therefore, we get that $s = \frac{\mu+\alpha}{\beta_1} = \frac{1}{\mathcal{R}_1}$. Notice that s is a proportion of the population, so that this holds whenever $\mathcal{R}_1 > 1$.

From (6.2) we get

$$\frac{\mu}{s} = \beta_1 i_1 + \mu \tag{6.3}$$

and

$$\begin{aligned} i_1 &= \frac{\mu}{(\mu+\alpha_1)\mathscr{R}_1} = \frac{\mu}{\mu+\alpha_1}\left(1 - \frac{1}{\mathscr{R}_1}\right) \\ r &= \frac{\alpha_1}{\mu} i_1 = \frac{\alpha_1}{\mu+\alpha_1}\left(1 - \frac{1}{\mathscr{R}_1}\right). \end{aligned} \tag{6.4}$$

Therefore the strain-one dominance equilibrium is given by

$$\mathscr{E}_1 = \left(\frac{1}{\mathscr{R}_1}\frac{\Lambda}{\mu}, \frac{\mu}{\mu+\alpha_1}\left(1 - \frac{1}{\mathscr{R}_1}\right)\frac{\Lambda}{\mu}, 0, \frac{\alpha_1}{\mu+\alpha_1}\left(1 - \frac{1}{\mathscr{R}_1}\right)\frac{\Lambda}{\mu}\right) \tag{6.5}$$

Similarly, the strain-two dominance equilibrium is given by

$$\mathscr{E}_2 = \left(\frac{1}{\mathscr{R}_2}\frac{\Lambda}{\mu}, 0, \frac{\mu}{\mu+\alpha_2}\left(1 - \frac{1}{\mathscr{R}_2}\right)\frac{\Lambda}{\mu}, \frac{\alpha_2}{\mu+\alpha_2}\left(1 - \frac{1}{\mathscr{R}_2}\right)\frac{\Lambda}{\mu}\right) \tag{6.6}$$

This model highlights the **Competitive Exclusion Principle:** When n strains compete in a population, the strain with the largest reproduction number outcompetes the other strains and drives them to extinction.

However, there are mechanisms that allow stable coexistence of multiple pathogens in an epidemic model, namely *mutation, coinfection, superinfection,*

6.2 A model with linear likelihood of infection

From the book by Martcheva [10]. Assume a constant population composed by Susceptible S, Infected I and Recovered R individuals. Assume also the transmission coefficient is linear in the number of infected individuals $1 + \nu I$ where $\nu > 1$, for instance, due to an increase in the number of contacts or an increased probability of infection.

$$\begin{aligned} S'(t) &= \Lambda - \beta(1+\nu I)IS - \mu S \\ I'(t) &= \beta(1+\nu I)IS - (\alpha+\mu)I \\ R'(t) &= \alpha I - \mu R \end{aligned} \tag{6.7}$$

Adding model (6.7) equations, we get that the total population N is described by $N'(t) = S'(t) + I'(t) + R'(t) = \Lambda - \mu N$, which solution converges to the steady state $N^* = \frac{\Lambda}{\mu}$. Therefore the disease free equilibrum always exists and it is given by $\mathcal{E}^* = \{\frac{\Lambda}{\mu}, 0, 0\}$.

The endemic equilibria is obtained by solving

$$\Lambda - \beta(1+\nu I)IS - \mu S = 0 \tag{6.8}$$

$$\beta(1+\nu I)IS - (\alpha+\mu)I = 0 \tag{6.9}$$

$$\tag{6.10}$$

from where we get that

$$(1+vI)\left[\frac{\Lambda}{\mu}-\frac{\mu+\alpha}{\mu}I\right]=\frac{\mu+\alpha}{\beta}. \tag{6.11}$$

Notice that expression (6.11) is a quadratic equation on I, which implies that under some scenarios there may exists one or two endemic equilibria.

Consider the left-hand size of the expression (6.11), and denote it by $f(I)$. The endemic equilibria of model (6.7) are given by the intersections of the parabola $f(I)$ with the horizontal line $y=\frac{\mu+\alpha}{\beta}$. Since $f(I)$ attains its maximum at

$$I_{max}=\frac{1}{2v}\left(\frac{\Lambda v}{\mu+\alpha}-1\right) \tag{6.12}$$

then, there will be two endemic equilibria provided $I_{max}>y=\frac{\mu+\alpha}{\beta}$.

6.3 A model with disease induced-deaths and treatment

From: Mathematical epidemiology - F. Brauer

$$S'=-\beta S[I+\delta T] \tag{6.13}$$
$$I'=\beta S[I+\delta T]-(\alpha+\gamma)I \tag{6.14}$$
$$T'=\gamma I-\eta T \tag{6.15}$$
$$N'=-(1-f)\alpha I-(1-f_T)\,\eta T \tag{6.16}$$

with basic reproductive number

$$\mathcal{R}_0=\frac{\beta}{\alpha+\gamma}+\frac{\gamma}{\alpha+\gamma}\frac{\delta\beta}{\eta} \tag{6.17}$$

6.4 A model with closed solutions

From: Mathematical epidemiology - F. Brauer

Assumes a disease sufficiently debilitates infected individuals so that only susceptible individuals can reproduce. Let us consider the model

$$\begin{aligned} S' &= rS-\beta SI-\mu S \\ I' &= \beta SI-(\mu+\alpha)I \end{aligned} \tag{6.18}$$

notice that, this model is analogous to the predator-prey Lotka-Volterra model of population dynamics.

The model has a disease free equlibrium $(0,0)$ and an endemic equilibrium $((\mu+\alpha)/\beta,(r-\mu)/\beta)$. Consider,

$$\frac{dI}{dS}=\frac{I(\beta S-\mu-\alpha)}{S(r-\beta I)} \tag{6.19}$$

by separation of variables

$$\int\left(\frac{r}{I}-\beta\right)dI=\int\left(\beta-\frac{\mu+\alpha}{S}\right)dS \tag{6.20}$$

and integration gives

$$\beta(S+I) - r\log I - (\mu+\alpha)\log S = c \tag{6.21}$$

where c is a constant of integration. This implies that

$$V(S,I) = \beta(S+I) - r\log I - (\mu+\alpha)\log S \tag{6.22}$$

is constant over each orbit $V(S,I)$ in the SI-plane. These orbits represent periodic solutions

Chapter 7

The Final Epidemic Size

Consider the Kermack-McKendrick model with Susceptible S, Infected I and Recovered R individuals, and assume recovered individuals are permanently immune. Where $\beta > 0$ is the likelihood of infection and $\gamma > 0$ is the recovery rate. Assume that the population at $t = 0$ is totally susceptible, so that $S(0) = N$, $I(0) = 1$ and $R(0) = 0$

$$\begin{aligned}\dot{S} &= -\beta SI \\ \dot{I} &= \beta SI - \alpha I \\ \dot{R} &= \alpha I\end{aligned}$$

Further description of the model can be found in the book *Mathematical Models in Population Biology and Epidemiology*, Section 9.2.

By adding the equations for susceptible and infected individuals we get

$$(S(t) + I(t))' = -\alpha I(t). \tag{7.1}$$

Notice that $S(t) + I(t)$ is a positive ($S(t)$ and $I(t)$ are positive) and decreasing function (its derivative is negative), therefore the limit exists. Recall that the derivative of a positive decreasing function tends to zero, therefore $\alpha I(t) \to 0$, since $\alpha > 0$ this implies $I(t) \to 0$. Hence

$$\lim_{t\to\infty}(S(t) + I(t)) = \lim_{t\to\infty} S(t) + \lim_{t\to\infty} I(t) = S_\infty,$$

integration on both sides of (7.1)

$$\begin{aligned}(S(t) + I(t))' &= -\alpha I(t) \\ -\frac{1}{\alpha}(S(t) + I(t))' &= I(t) \\ -\frac{1}{\alpha}\int_0^\infty (S(t) + I(t))'dt &= \int_0^\infty I(t)dt\end{aligned}$$

$$\begin{aligned}\int_0^\infty I(t)dt = -\frac{1}{\alpha}\int_0^\infty (S(t) + I(t))'dt &= -\frac{1}{\alpha}(S_\infty + \underbrace{I_\infty}_{\to 0} - (\underbrace{S_0 + I_0}_{N})) \\ &= \frac{1}{\alpha}(N - S_\infty)\end{aligned}$$

Now dividing both sides of $\dot{S}$ by S

$$\begin{aligned}
\frac{\dot{S}}{S} &= -\beta SI \\
\int_0^\infty \frac{\dot{S}(t)}{S(t)}dt &= -\beta \int_0^\infty I(t)dt \\
\log(S)\Big|_0^\infty &= -\beta \int_0^\infty I(t)dt \\
\log\left(\frac{S_0}{S_\infty}\right) &= \beta \int_0^\infty I(t)dt \\
&= \beta \frac{1}{\alpha}(N - S_\infty) \\
&= \frac{\beta N}{\alpha}\left(1 - \frac{S_\infty}{N}\right)
\end{aligned}$$

therefore

$$\log\left(\frac{S_0}{S_\infty}\right) = \mathcal{R}_0\left(1 - \frac{S_\infty}{N}\right). \tag{7.2}$$

Equation (7.2) called the final size relation, it relates the basic reproductive number with the final number of infected individuals, the size of the epidemic.

A model for Ebola with quarantine

Assume the total population is composed by Susceptible S, Exposed E, Infected I, Quarantined Q and infectious corpses D. Since the total population of model (7.3) is constant, it is possible to reduce the system to

$$\begin{cases}
N = S + E + I + Q + D + R \\
\dot{S} = -\beta S\left(\frac{I+\varepsilon D+lQ}{N}\right) \\
\dot{E} = \beta S\left(\frac{I+\varepsilon D+lQ}{N}\right) - \kappa E \\
\dot{I} = (1-q)\kappa E - \gamma I \\
\dot{Q} = q\kappa E - \gamma Q \\
\dot{D} = f_{\mathrm{d}}\gamma I - \nu D
\end{cases} \tag{7.3}$$

by assuming $S(0) = N$, $E_(0) = I(0) = D(0) = 0$ and using the notation $\hat{f}(t) = \int_0^\infty f(s)ds$ and $f^\infty = \lim_{t\to\infty} f(t)$; from the first two equations of system (7.3), $\dot{S} + \dot{E} = -\kappa E \leq 0$, which implies $E^\infty = 0$. Similarly it is possible to get $I^\infty = Q^\infty = D^\infty = 0$.

By integrating model's (7.3) first two equations, $S^\infty - N = \kappa\hat{E}$ which implies $\hat{E} = \frac{N - S^\infty}{\kappa_1}$. Similar procedure implies $\hat{I} = (N - S^\infty)\left(\frac{1-q}{\gamma}\right)$, $\hat{Q} = (N - S^\infty)\left(\frac{q}{\gamma}\right)$ and $\hat{D} = (N - S^\infty)\left(\frac{f_d(1-q)}{\nu}\right)$. By integrating model's (7.3) first equation and using similar

derivations than the previous example we get

$$\log\left(\frac{N}{S^\infty}\right) = \left(1 - \frac{S^\infty}{N}\right)\left(q\frac{l\beta}{\gamma} + (1-q)\beta\left(\frac{1}{\gamma} + \frac{\varepsilon f_d}{\nu}\right)\right)$$
$$\log\left(\frac{N}{S^\infty}\right) = \left(1 - \frac{S^\infty}{N}\right)\mathcal{R}_C. \tag{7.4}$$

Equation 7.4 is the typical final size relation, where $\mathcal{R}_C$ represents the *control reproductive number*, the basic reproductive number in the presence of control measures. In the presented model, equation (7.4) relates the number of infected individuals at the end of the outbreak, to the secondary infections produced by quarantined and non-quarantined infectious individuals, and non removed Ebola-infected corpses.

Denote by $s^\infty = \frac{S^\infty}{N}$ the proportion of the susceptible individuals at the end of the epidemic, equation (7.4) yields

$$\log(s^\infty) = (s^\infty - 1)\mathcal{R}_C. \tag{7.5}$$

Letting $y = s^\infty - 1$ denote the proportion of population infected over the course of the epidemic, equation (7.5) becomes

$$y = 1 - \exp[-y\mathcal{R}_c] \tag{7.6}$$

which give us the final proportion of infected individuals, also known as the epidemic *attack rate*.

A model for influenza

(from *Simple models for containment of a pandemic*)

Consider the following model for influenza infections where the population is split into Susceptible ($S(t)$), Latent infected but not yet infectious ($L(t)$), symptomatic Infected ($I(t)$), asymptomatic infectious ($A(t)$), and Removed ($R(t)$) members. Additionally assume that, initially the total population size is K of which a small number I_0 are infectious and the remainder S_0 are susceptible, with $S_0 + I_0 = K$.

Notice that the total population is not constant and it is reduced by disease-induced deaths at a rate $f\alpha I$. That is, only the fraction $f\alpha I$ of infected individuals recover

$$\begin{aligned} S' &= -S\beta(I - \epsilon L + \delta A) \\ L' &= S\beta(I - \epsilon L + \delta A) - \kappa L \\ I' &= p\kappa L - \alpha I \\ A' &= (1-p)\kappa L - \eta A \\ R' &= f\alpha I + \eta A \\ N' &= -(1-f)\alpha L \end{aligned} \tag{7.7}$$

The disease-free equilibrium of the model is given by $S(0) - S_0$ and $L = I = A = R = 0$. The basic reproductive number is

$$\mathcal{R}_0 = S_0\beta\left(\frac{\epsilon}{\kappa} + \frac{p}{\alpha} + \frac{\delta(1-p)}{\eta}\right),$$

Let $\hat{f}(t) = \int_0^\infty f(s)ds$. Then $\int_0^\infty (S' + L') = \int_0^\infty -\kappa L$, from where

$$\hat{L} = \frac{S_0 - S_\infty}{\kappa}.$$

Similarly $\int_0^\infty (S' + L' + I') = -\int_0^\infty (\kappa L(1-p) + \alpha I)$ which implies

$$\hat{I} = (S_0 - S_\infty)\frac{p}{\alpha} - \frac{I_0}{\alpha},$$

following similar procedure, $(S' + L' + I' + A')$ yields

$$\hat{A} = (S_0 - S_\infty)\frac{1-p}{\eta}$$

finally

$$\begin{aligned}
\log\left(\frac{S_0}{S_\infty}\right) &= -\beta\left(\hat{I} - \epsilon\hat{L} + \delta\hat{A}\right) \\
&= -\beta\left[(S_0 - S_\infty)\frac{p}{\alpha} - \frac{I_0}{\alpha} + \epsilon\left(\frac{S_0 - S_\infty}{\kappa}\right) + \delta\left((S_0 - S_\infty)\frac{1-p}{\eta}\right)\right] \\
&= -\beta(S_0 - S_\infty)\left[\frac{p}{\alpha} + \frac{\epsilon}{\kappa} + \delta\left(\frac{1-p}{\eta}\right)\right] + \beta\frac{I_0}{\alpha} \\
&= \mathcal{R}_0\frac{S_0 - S_\infty}{S_0} + \beta\frac{I_0}{\alpha}.
\end{aligned}$$

where the final epidemic size is

$$\log\left(\frac{S_0}{S_\infty}\right) = \mathcal{R}_0\left(1 - \frac{S_\infty}{S_0}\right) + \beta\frac{I_0}{\alpha} \tag{7.8}$$

Equation (7.8) related the basic reproductive number and the final number of susceptible individuals. Notices that, the assumption of an initial number of infectious individuals produce the term $\beta\frac{I_0}{\alpha}$, that accounts for the secondary cases produced by the infected individuals at time $t = 0$ (I_0) during they infectious period $\left(\frac{1}{\alpha}\right)$.

More generally, for the initial conditions

$$L(0) = L_0, \quad I(0) = I_0, \quad A(0) = A_0$$

the term $\beta I_0/\alpha$ in equation (7.8) takes the form

$$\beta\left[\frac{\varepsilon}{\kappa} + \frac{p}{\alpha} + \frac{\delta(1-p)}{\eta}\right]L_0 + \frac{\beta\delta A_0}{\eta} + \frac{\beta I_0}{\alpha}.$$

In this case, the final size relation accounts for the secondary infections of the infectious asymptomatic and symptomatic individuals at time $t = 0$ (A_0 and I_0 respectively), and the average infectious generated by the latent individuals at $t = 0$ (L_0) during their latency period and the weighted (with probabilities p and $1-p$) average secondary infectious generated while progressing to either symptomatic or asymptomatic state.

Summary

Disease	**Transmission pathway(s)**	**Intervention(s)**	**Location**	**Initial Conditions**	**Data Source(s)**	**Source article; Results reproduced?**	**Avenues for extension**
Cholera	Environment-Human; Human-Human	Disinfecting water; Vaccination	China	$I_0 = 28$; $B_0 = 500$ (Assumed)	NA	[12], Yes	
SARS-Cov-2	Human-Human; transmission coefficient dependent on specific humidity	None	New York, USA	$I_0 = 1$	[9]	[3], Yes	Heterogeneous social mixing

Table 7.1: Summary of simulations using COPASI

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7.1 Acknowledgements

Data: The ERA5 data used is publicly available at: https://cds.climate.copernicus.eu/cdsapp#!/dataset/reanalysis-era5-pressure-levels?tab=overview generated by Copernicus Services [2018].