dismolib
COPASI-based infectious disease models library

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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

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 [18], 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
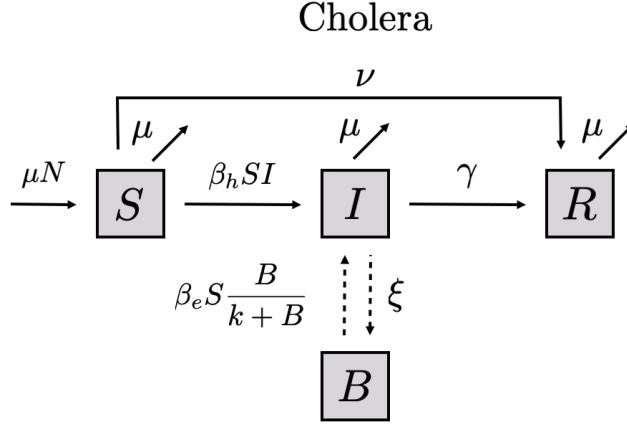
Cholera

Figure 2.1: Flowchart of Cholera disease model

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

$$\frac{dS}{dt} = \mu N - \beta_e S \frac{B}{k+B} - \beta_h SI - \mu S - vS$$

$$\frac{dI}{dt} = \beta_e S \frac{B}{k+B} + \beta_h SI - (\gamma + \mu)I \tag{2.2}$$

$$\frac{dB}{dt} = \xi I - \delta B - cB$$

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

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

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

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

Simulations

To simulate the model we use the parameters in Figure 2.2.

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	$year^{-1}$
v	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 2.2: 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 exhibit, the basic reproductive number and the control reproductive number (disease eradication via control measures), $\mathcal{R}_0$ 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.

2.2   Typhoid

Introduction

Mathematical model

Following the work in [16], 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).
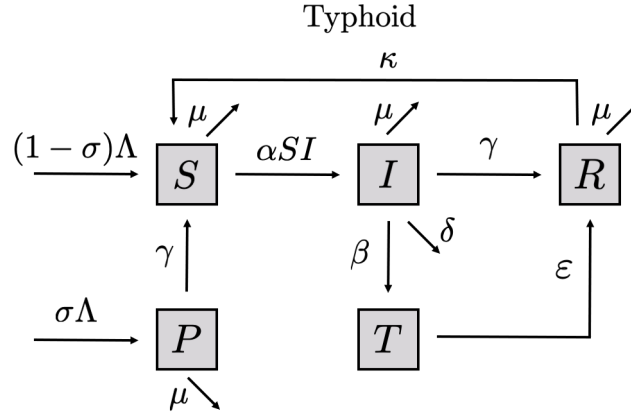

Figure 2.3: Flowchart of Typhoid disease model

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 recover at a per-capita rate ϵ, loosing natural immunity at a per-capita rate κ, or die out by other reasons at a per-capita rate μ.

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

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

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 2.1

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.
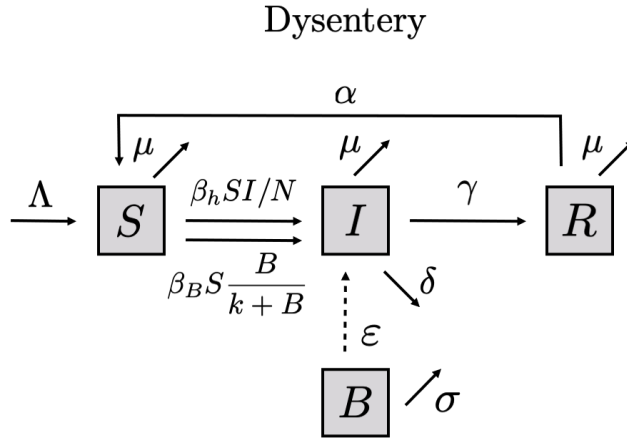

Figure 2.4: Flowchart of Dysentery disease model

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

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

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.
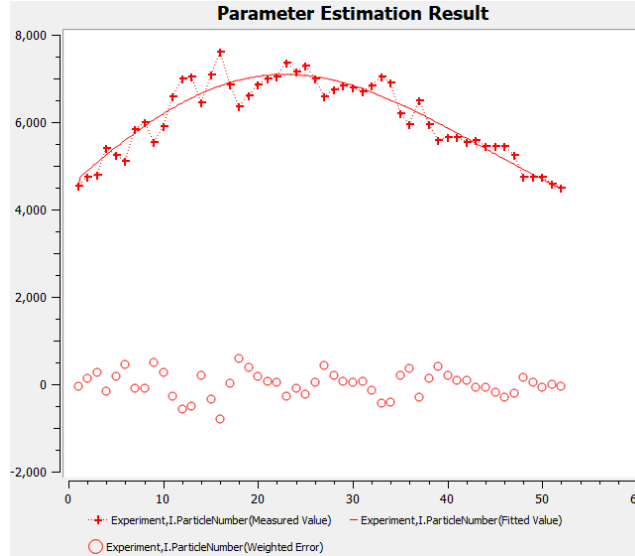
Simulations

Figure 2.5: Model fitting to reproduce Figure 4 in [4] using COPASI. Horizontal axis is time in weeks.

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 $B(t)$.

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.
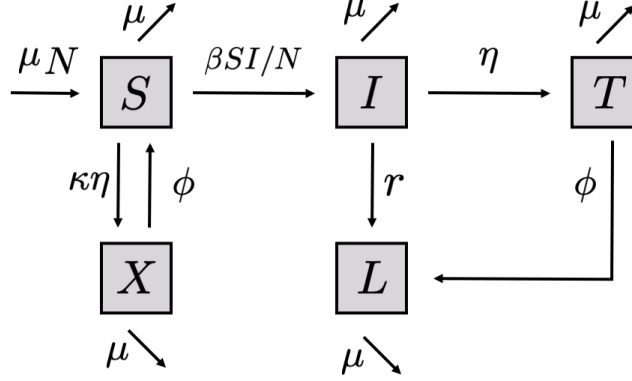
HSV-2

Figure 3.1: Flowchart of HSV-2 disease model

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.

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

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 $\mathcal{F} = \begin{bmatrix} \frac{\beta S I}{N} \\ 0 \\ 0 \end{bmatrix}$ 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

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

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

CoViD-19

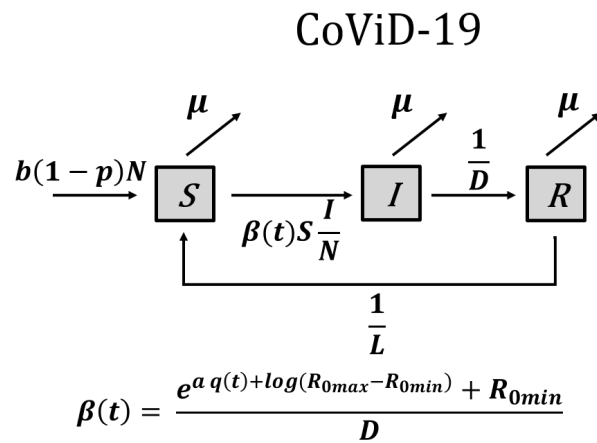$$\beta(t) = \frac{e^{a\,q(t)+log(R_{0max}-R_{0min})} + R_{0min}}{D}$$

Figure 4.1: Flowchart of COVID-19 disease model

4.2 COVID-19 in the Mexican context

4.2.1 Introduction

4.2.2 Model

The model in [17] study SARS-CoV-2 transmission in the Mexican context.

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \mu S - \left(k_v + k_e U + k_i I\right) S \tag{4.1}$$

$$\frac{\mathrm{d}U}{\mathrm{d}t} = \left(k_v + k_e U + k_i I\right) S - \alpha U \tag{4.2}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \alpha U - (\gamma r + \delta d + \epsilon a)I \tag{4.3}$$

$$\frac{\mathrm{d}A}{\mathrm{d}t} = \epsilon a I - [\delta p + \gamma(1-p)]A \tag{4.4}$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \gamma r I + \gamma(1-p)A \tag{4.5}$$

$$\frac{\mathrm{d}D}{\mathrm{d}t} = \delta d I + \delta p A \tag{4.6}$$

4.3 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. TB remains the world's deadliest infectious killer. 1.4 million people died from TB in 2019.

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 [10] 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
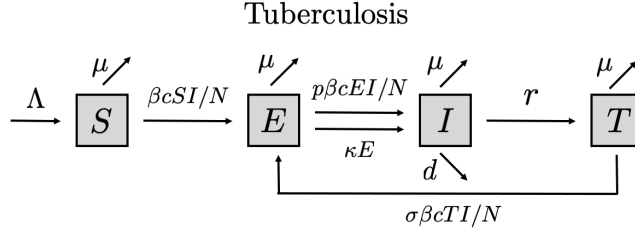
Tuberculosis

Figure 4.2: Flowchart of Tuberculosis disease model

infectiousness.

$$
\begin{aligned}
\frac{d}{dt}S &= \Lambda - \beta c S \frac{I}{N} - \mu S \\
\frac{d}{dt}E &= \beta c S \frac{I}{N} - p\beta c E \frac{I}{N} - (\mu + k)E + \sigma \beta c T \frac{I}{N} \\
\frac{d}{dt}I &= p\beta c E \frac{I}{N} + kE - (\mu + r + d)I \\
\frac{d}{dt}T &= rI - \sigma \beta c T \frac{I}{N} - \mu T
\end{aligned}
\tag{4.7}
$$

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 4.9. 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 [10].

Model Analysis

In the absence of TB, the total population in model (4.7) is not constant, but it converges to a steady state

$$
\frac{dN}{dt} = \frac{dS}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dT}{dt} = \Lambda - \mu N
\tag{4.8}
$$

solving (4.8), we get that $N(t) \to \Lambda/\mu$. Using the next generation matrix, we can compute the basic reproductive number

$$
\mathcal{R}_0 = \left(\frac{\beta c}{\mu + r + d} \right) \left(\frac{k}{\mu + k} \right),
\tag{4.9}
$$

the expression (4.9) 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 ($\sigma \beta c T \frac{I}{N}$) 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.

4.4   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 [9], 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, $N = S + E + I + D + R$.
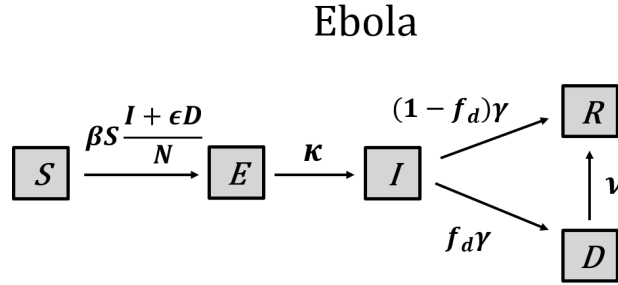

Figure 4.3: Flowchart of Ebola disease model

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, $\epsilon > 1$.

$$\begin{cases} \dot{S} = -\beta S \left(\frac{I+\varepsilon D}{N} \right) \\ \dot{E} = \beta S \left(\frac{I+\varepsilon D}{N} \right) - \kappa E \\ \dot{I} = \kappa E - \gamma I \\ \dot{D} = f_{\mathrm{d}} \gamma I - \nu D \\ \dot{R} = (1 - f_{\mathrm{d}}) \gamma I + \nu D \end{cases} \tag{4.10}$$

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 4.4: Parameters for Ebola model

Model analysis

Model (4.10) 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

$$\mathscr{R}_0 = \beta \left(\frac{1}{\gamma} + \frac{\varepsilon f_d}{v} \right). \tag{4.11}$$

The basic reproductive number of system (4.10) 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 $\left(\frac{\varepsilon \beta f_d}{v} \right)$, in a totally susceptible population.

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 (4.10) 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 periods for more realistic results. The model can be extended to include control measures.

4.5   Measles

Introduction

Mathematical model

In [19], 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 $R(t)$. The previously described disease dynamics are represented in the Figure 4.5
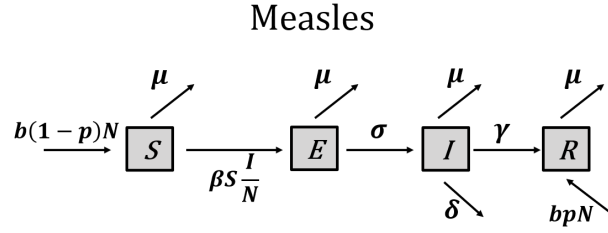

Figure 4.5: Flowchart of Measles disease model

and formalized by the set of ODE's (4.12)

$$
\begin{aligned}
\frac{dS}{dt} &= b(1-p)N - \frac{\beta SI}{N} - \mu S \\
\frac{dE}{dt} &= \frac{\beta SI}{N} - (\sigma + \mu)E \\
\frac{dI}{dt} &= \sigma E - (\gamma + \mu + \delta)I \\
\frac{dR}{dt} &= bpN + \gamma I - \mu R
\end{aligned}
\tag{4.12}
$$

Model analysis

Model remarks

4.6   Influenza

Introduction

Imperfect control measures to mitigate disease transmission are known to be mechanisms that may induce backward bifurcation [11]. For example, imperfect quarantine or vaccines granting partial immunity for significantly short term periods. In this section we use the work in [8] to show how imperfect quarantine is modeled and some of its basic implications.

Mathematical model

Consider the following model for Influenza and quarantine where S, I, Q and R correspond to the number of susceptible, infected, quarantine and recovered individuals, with $S + I +$

$Q + R = N$. In this model

$$\dot{S} = \mu N - \beta S \frac{I}{N-Q} - \mu S,$$
$$\dot{I} = \beta S \frac{I}{N-Q} - (\theta + \gamma + \mu)I, \tag{4.13}$$
$$\dot{Q} = \theta I - (\alpha + \mu)Q,$$
$$\dot{R} = \gamma I + \alpha Q - \mu R.$$

In this model, a policy of perfect quarantine is considered. This impact the incidence term in the form $\beta SI/(N-Q)$ where β is the per-capita effective contact rate. The model assumes constant recovery (γ) and quarantine (θ) per-capita rates. μ is the per-capita birth and death rate, and α is the per-capita recovery rate for isolated/quarantined individuals.

The aforementioned model assumes quarantine is perfect, and quarantined individuals cannot produce secondary infections during their quarantine period. However, in reality this usually is not true and we may expect certain leaking rate so that some quarantined individuals may infect others in the population. The following model incorporates infections of individuals undergoing quarantine

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \mu N - \beta S \frac{I}{N-\sigma Q} - \hat{\beta} S \frac{(1-\sigma)Q}{N-\sigma Q} - \mu S$$
$$\frac{\mathrm{d}I}{\mathrm{d}t} = \beta S \frac{I}{N-\sigma Q} + \hat{\beta} S \frac{(1-\sigma)Q}{N-\sigma Q} - (\theta + \gamma + \mu)I \tag{4.14}$$
$$\frac{\mathrm{d}Q}{\mathrm{d}t} = \theta I - (\alpha + \mu)Q$$
$$\frac{\mathrm{d}R}{\mathrm{d}t} = \gamma I + \alpha Q - \mu R$$

Model (4.14) incorporates imperfect quarantine for $\sigma \in [0, 1]$. $\sigma = 0$ stands for the scenario of totally ineffective quarantine, while $\sigma = 1$ represents a totally perfect quarantine. Therefore, the total number of successfully quarantined individuals is σQ and therefore the total number of individuals who are available to mix homogeneously is $(N - \sigma Q)$. In model (4.14) $\hat{\beta}$ represents the effective rate of contacts between susceptible and imperfectly quarantined individuals. Then, the proportion of contacts made with an infected individual is $I/(N - \sigma Q)$, while the proportion of contacts made with an imperfectly quarantined one is $(1 - \sigma)Q/(N - \sigma Q)$. Therefore, the new force of infection is given by

$$\lambda = \beta \frac{I}{N-\sigma Q} + \hat{\beta} \frac{(1-\sigma)Q}{N-\sigma Q} \tag{4.15}$$

where the new incidences due to contacts with infected individuals are $\beta SI/(N - \sigma Q)$, and due to contacts of susceptible with imperfectly quarantined individuals $\hat{\beta}(1 - \sigma)SQ/(N - \sigma Q)$.

Model analysis

To analyze model (4.14) we normalize the model by assuming $N = 1$ and letting $\hat{\beta} = r\beta$

$$
\begin{aligned}
\frac{\mathrm{d}\bar{S}}{\mathrm{d}t} &= \mu - \beta\bar{S}\frac{[\bar{I} + r(1-\sigma)\bar{Q}]}{1 - \sigma\bar{Q}} - \mu\bar{S} \\
\frac{\mathrm{d}\bar{I}}{\mathrm{d}t} &= \beta\bar{S}\frac{[\bar{I} + r(1-\sigma)\bar{Q}]}{1 - \sigma\bar{Q}} - (\theta + \gamma + \mu)\bar{I} \\
\frac{\mathrm{d}\bar{Q}}{\mathrm{d}t} &= \theta\bar{I} - (\alpha + \mu)\bar{Q} \\
\frac{\mathrm{d}\bar{R}}{\mathrm{d}t} &= \gamma\bar{I} + \alpha\bar{Q} - \mu\bar{R}
\end{aligned}
\tag{4.16}
$$

where $\bar{X} = X/N$ represents the proportion for the population in the health state X, so that $\bar{S} + \bar{I} + \bar{Q} + \bar{R} = 1$.

Stability of the DFE

By setting derivatives of the model (4.16) equal to zero, we get the system has the DFE $E_0 = (1, 0, 0, 0)$ and an endemic equilibrium.

To explore stability of E_0 we linearize the model around E_0 that shows a Jacobian matrix with two eigenvalues $-\mu$ and the eigenvalues of the submatrix

$$
J_0 = \begin{pmatrix} \beta - (\theta + \gamma + \mu) & (1-\sigma)r\beta \\ \theta & -(\alpha + \mu) \end{pmatrix}.
\tag{4.17}
$$

Thus, local stability is given by the conditions

$$
\mathrm{trace}\,(J_0) = \beta - (\alpha + \mu) - (\theta + \gamma + \mu) < 0
\tag{4.18}
$$

$$
\det\,(J_0) = (\alpha + \mu)(\gamma + \mu + \theta) - \beta(\alpha + \mu) - (1-\sigma)r\beta\theta > 0
\tag{4.19}
$$

Re-arranging $\det\,(J_0)$ we get that in order for E_0 to be stable the following condition should hold

$$
1 > \frac{\beta}{\gamma + \mu + \theta}\left[1 + (1-\sigma)\frac{r\theta}{\alpha + \mu}\right] = \mathcal{R}_0.
\tag{4.20}
$$

Therefore, E_0 is stable whenever $\mathcal{R}_0 < 1$, and unstable whenever $\mathcal{R}_0 > 1$.

Furthermore, it is possible to show the model undergoes a Hopf bifurcation in the parameter space $(\sigma, \mathcal{R}_0, \theta)$.

Model remarks

The present model incorporates two key consequences of assuming quarantine or isolation control measures: (i) the proportion of the population homogeneously mixing changes under the assumption of quarantine/isolation, (ii) the imperfect implementation of quarantine/isolation that may generate secondary cases.

4.7   Diphtheria

Introduction

The work in [13] studies the 2017 Diptheria outbreak in Indonesia, that affected 28 provinces

Mathematical Model

$$\dot{S} = A - \frac{(m-c)SI}{N} - (c+\mu)S + \gamma R \tag{4.21}$$

$$\dot{E} = \frac{(m-c)SI}{N} - (\delta+\mu)E \tag{4.22}$$

$$\dot{I} = \delta E - (\beta+\mu)I \tag{4.23}$$

$$\dot{R} = \beta I + cS - (\gamma+\mu)R \tag{4.24}$$

Model analysis

Model remarks

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. 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

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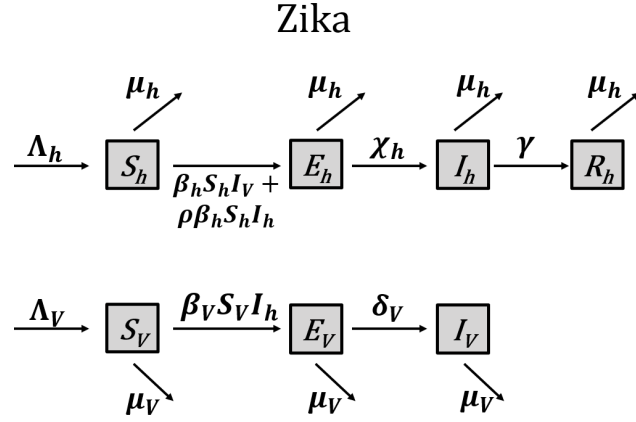\end{cases}
\tag{5.1}
$$

Zika

Figure 5.1: Flowchart of Zika disease model

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

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

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

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 5.2: 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.

Malaria

$$\xrightarrow{\Lambda_h} \boxed{S_h} \xrightarrow{\beta_v S_v I_h / N_h} \boxed{I_h} \xrightarrow{\gamma_h} \boxed{R_h}$$

$$\xrightarrow{\Lambda_v} \boxed{S_h} \xrightarrow{\beta_h S_h I_v / N_v} \boxed{I_h}$$
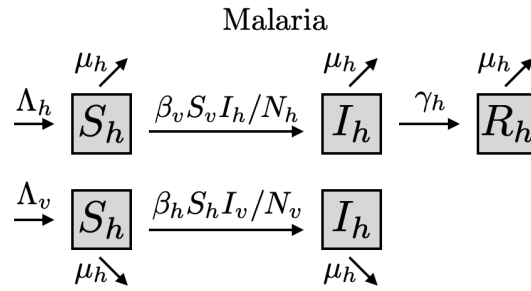
Figure 5.3: Flowchart of Malaria disease model

Following [6], a vector borne disease model for Malaria considers the interaction between the host population and mosquitoes population. Moreover, given that infected mosquitoes remain infected for life and do not recover, the proposed model assumes an SIR-like structure

for both populations, but where mosquitoes never recover

$$S_h' = \Lambda_h - \beta_h S_h \frac{I_v}{N_v} - \mu_h S_h$$

$$I_h' = \beta_h S_h \frac{I_v}{N_v} - (\mu_h + \gamma_h) I_h \qquad\qquad (5.3)$$

$$S_v' = \Lambda_v - \beta_v S_v \frac{I_h}{N_h} - \mu_v S_v$$

$$I_v' = \beta_v S_v \frac{I_h}{N_h} - \mu_v I_v$$

Model analysis

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

$$N_h' = S_h' + I_h' = \Lambda_h - \mu_h N_h'. \qquad\qquad (5.4)$$

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

$$\beta_h S_h I_v = (\gamma_h + \mu_h) I_h N_v$$

$$\beta_v S_v I_h = \mu_v I_v N_h$$

$$\Lambda_h = S_h \left(\mu_h + \beta_h \frac{I_v}{N_v} \right) N_v \qquad\qquad (5.5)$$

$$\Lambda_v = S_v \left(\mu_v + \beta_v \frac{I_h}{N_h} \right) N_h$$

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

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

where the second generation matrix is

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

and the basic reproductive number

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

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

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

Notice that in both cases, the epidemic threshold for disease eradication or disease persistence is the same, $\mathcal{R}_0 = 1$.

5.3 Dengue model

Introduction

Dengue is caused by a virus of the Flaviviridae family, mainly transmitted by the Aedes aegypti mosquito as the primary vector. There are four types of the virus causing dengue fever (DENV-1, DENV-2, DENV-3 and DENV-4). While the number of dengue cases reported to WHO increased over 8 fold over the last two decades, current estimates indicate that 390 million dengue virus infections per year (95% credible interval 284–528 million), of which 96 million (67–136 million) manifest clinically (with any severity of disease). Where reported deaths between the year 2000 and 2015 increased from 960 to 4032, [15].

Mathematical model

By following the model formulation in [6], the proposed model assumes a recruitment rate proportional to the population size for the host and vector populations. Moreover, the vector population's recruitment rate is assumed to be composed by newborn susceptible mosquitoes ($\mu_v(N_v - qI_v)$), and newborn infected mosquitoes ($q\mu_v I_v$).

$$
\begin{aligned}
S_h' &= \mu_h N_h - \beta_h S_h \frac{I_v}{N_v} - \mu_h S_h, \\
E_h' &= \beta_h S_h \frac{I_v}{N_v} - \left(\eta_h + \mu_h\right) E_h, \\
I_h' &= \eta_h E_h - \left(\gamma + \mu_h\right) I_h, \\
R_h &= \gamma I_h, \\
S_v' &= \mu_v \left(N_v - qI_v\right) - \beta_v S_v \frac{I_h}{N_h} - \mu_v S_v, \\
E_v' &= \beta_v S_v \frac{I_h}{N_h} - \left(\eta_v + \mu_v\right) E_v, \\
I_v' &= q\mu_v I_v + \eta_v E_v - \mu_v I_v.
\end{aligned}
\tag{5.8}
$$

Model analysis

Following the second generation matrix with infectious compartments $\{E_h, I_h, E_v, I_v\}$, we get a basic reproductive number of the form

$$\mathcal{R}_0 = \beta_h \beta_v \frac{1}{\mu_h + \gamma} \frac{\eta_v}{\eta_v + \mu_v} \frac{\eta_h}{\eta_h + \mu_h} \frac{1}{\mu_v} + q\mu_v. \tag{5.9}$$

Model remarks

The model assumes a period of latency where neither hosts and vectors are infections, the dynamics of this model are similar to the SIR model where the latency period adds a delay in infections. Furthermore, the model assumes vertical transmission among the infected mosquitoes population (that is, infected mosquitoes produce infected newborns mosquitoes), which in turn impact the basic reproductive number and the disease eradication threshold.

5.4   Leishmaniasis

Introduction

Mathematical model

The modeling work by ELmojtaba et. al. [7], assumes Leishmaniasis dynamics among three independent populations: human hosts (N_H), vectors (N_V) and reservoirs (N_R). Beyond the susceptible, infected and recovered health classes, the model assumes that humans after the treatment of visceral leishmaniasis may develop post kala-azar dermal leishmaniasis (PKDL).

The proposed model assumes two infection cycles: first, the infected reservoir population infect susceptible vectors, and susceptible reservoirs are infected by infected vectors; second, the infected vector population infect susceptible humans hosts, and infected human hosts infect susceptible mosquitoes.
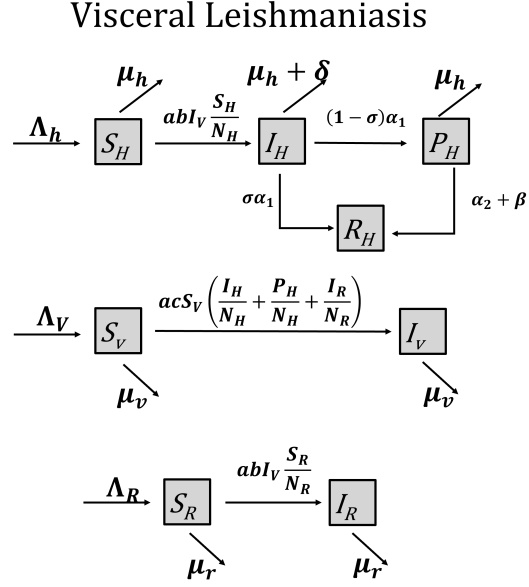
Visceral Leishmaniasis

Figure 5.4: Flowchart of Visceral Leishmaniasis disease model

$$S'_H = \Lambda_H - abI_V \frac{S_H}{N_H} - \mu_h S_H$$

$$I'_H = abI_V \frac{S_H}{N_H} - (\alpha_1 + \delta + \mu_h) I_H$$

$$P'_H = (1-\sigma)\alpha_1 I_H - (\alpha_2 + \beta + \mu_h) P_H$$

$$R'_H = \sigma\alpha_1 I_H + (\alpha_2 + \beta) P_H - \mu_h R_H$$

$$S'_R = \Lambda_R - abI_V \frac{S_R}{N_R} + \mu_r S_R \qquad (5.10)$$

$$I'_R = abI_V \frac{S_R}{N_R} - \mu_r I_R$$

$$S'_V = \Lambda_V - acS_V \frac{I_H}{N_H} - acS_V \frac{P_H}{N_H} - acS_V \frac{I_R}{N_R} S_V - \mu_v S_V$$

$$I'_V = acS_V \frac{I_H}{N_H} + acS_V \frac{P_H}{N_H} + acS_V \frac{I_R}{N_R} S_V - \mu_v I_V$$

Mathematical analysis

The basic reproductive number of the proposed model is

$$\mathcal{R}_0 = \sqrt{\frac{ac\left[\mu_r abm\left(\alpha_2 + \beta + \mu_h + (1-\sigma)\alpha_1\right) + abn\left(\alpha_1 + \delta + \mu_h\right)\left(\alpha_2 + \beta + \mu_h\right)\right]}{\mu_r \mu_v \left(\alpha_1 + \delta + \mu_h\right)\left(\alpha_2 + \beta + \mu_h\right)}} \qquad (5.11)$$

Model remarks

The proposed model assumes a double infection cycle among three independent populations. In consequence, disease eradication is not guaranteed by treating the human host population, since the disease may persist for long periods among vectors and reservoirs.

5.5   Yellow fever

Introduction

Mathematical model

Based in the work by Zhao et. al. [20].

$$S_h' = -ab\frac{I_u}{N_k}S_h - v\left(t - t_0\right)$$
$$E_h' = ab\frac{I_r}{N_h}S_h - \sigma_h E_h$$
$$A_h' = (1 - \delta)\sigma_h E_h - \gamma_h A_h$$
$$I_h' = \delta\sigma_h E_h - \gamma_h I_h$$
$$T_h' = \gamma_h I_h - \kappa_h T_h$$
$$R_h' = v\left(t - t_0\right) + \gamma_h A_h + (1 - \theta)\kappa_h T_h$$
$$D_h' = \theta\kappa_h T_h$$

$$S_v' = B_v(t) - ac\frac{\psi d_h + I_h}{N_k}S_v - \mu_v S_v$$
$$E_v' = ac\frac{\psi A_k + I_j}{N_k}S_v - \sigma_v E_v - \mu_v E_v$$
$$I_v' = \sigma_v E_v - \mu_v I_v$$

(5.12)

Model analysis

The basic reproductive number of the model is

$$\mathcal{R}_0 = \sqrt{\left[\psi \cdot (1 - \delta) + \delta\right] \cdot \frac{a^2 bcm}{\gamma_h} \cdot \frac{\sigma_v}{\mu_v\left(\sigma_v + \mu_v\right)}}$$

(5.13)

Model remarks

Chapter 6

Generic Models

6.1 A two-strains model

From the book by Martcheva [14]. 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

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

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 [14]. 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.

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

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

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

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

$$\tag{6.10}$$

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 equilibrium $(0, 0)$ 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 $R(0) = 0$

$$\dot{S} = -\beta S I$$
$$\dot{I} = \beta S I - \alpha I$$
$$\dot{R} = \alpha I$$

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)

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

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

$$= \frac{1}{\alpha}(N - S_\infty)$$

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

$$\frac{\dot{S}}{S} = -\beta SI$$

$$\int_0^\infty \frac{\dot{S}(t)}{S(t)} dt = -\beta \int_0^\infty I(t)dt$$

$$\log(S)\Big|_0^\infty = -\beta \int_0^\infty I(t)dt$$

$$\log\left(\frac{S_0}{S_\infty}\right) = \beta \int_0^\infty I(t)dt$$

$$= \beta \frac{1}{\alpha}(N - S_\infty)$$

$$= \frac{\beta N}{\alpha}\left(1 - \frac{S_\infty}{N}\right)$$

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

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

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 $s^\infty = \dfrac{S^\infty}{N}$ 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	[18], Yes	
SARS-Cov-2	Human-Human; transmission coefficient dependent on specific humidity	None	New York, USA	$I_0 = 1$	[12]	[3], Yes	Heterogeneous social mixing

Table 7.1: Summary of simulations using COPASI

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