Modelling Infectious Diseases on Small World Network

By

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DECLARATION

This work was carried out at AIMS Rwanda in partial fulfilment of the requirements for a Master of Science Degree.

I hereby declare that except where due acknowledgement is made, this work has never been presented wholly or in part for the award of a degree at AIMS Rwanda or any other University.

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Student: Firstname Middlename Surname

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Supervisor: Firstname Middlename Surname

ACKNOWLEDGEMENTS

I would like to sincerely thank My supervisor and Tutor , Professor Nancy Ann Neudauer and Jan Hazla respectively, for their support and guidance thought this research.

DEDICATION

This is optional.

Abstract

A short, abstracted description of your essay goes here. It should be about 100 words long. But write it last.

An abstract is not a summary of your essay: it's an abstraction of that. It tells the readers why they should be interested in your essay but summarises all they need to know if they read no further.

The writing style used in an abstract is like the style used in the rest of your essay: concise, clear and direct. In the rest of the essay, however, you will introduce and use technical terms. In the abstract you should avoid them in order to make the result comprehensible to all.

You may like to repeat the abstract in your mother tongue.

Contents

1. Introduction

2. Literature Review

Zika virus is a member of the Flaviridae family and the flavivirus genus, it is related to other mosquito borne viruses such as Dengue Virus, Yellow-Fever (YFV) virus and West Nile virus (Dick et al., 1952).The Virus originates from the Zika forest of Uganda and the first case was first isolated in 1947 from a rhesus monkey in the forest. Then later in 1954 a human was diagonised with the virus in Nigeria,(Junior et al., 2015). Since then the virus has spread to different parts o the world. [Jan: Why is "Flaviridae" capitalized and "Flavivirus" not? Why is "virus" capitalized in "Dengue Virus" but not in "West Nile virus"? Capitalization needs to be applied consistently across the thesis.]

[Jan: "first case was first isolated"?]

[Jan: s/diagonised/diagnosed. s/parts o the world/parts of the world. Please spellcheck what you wrote before asking for feedback.]

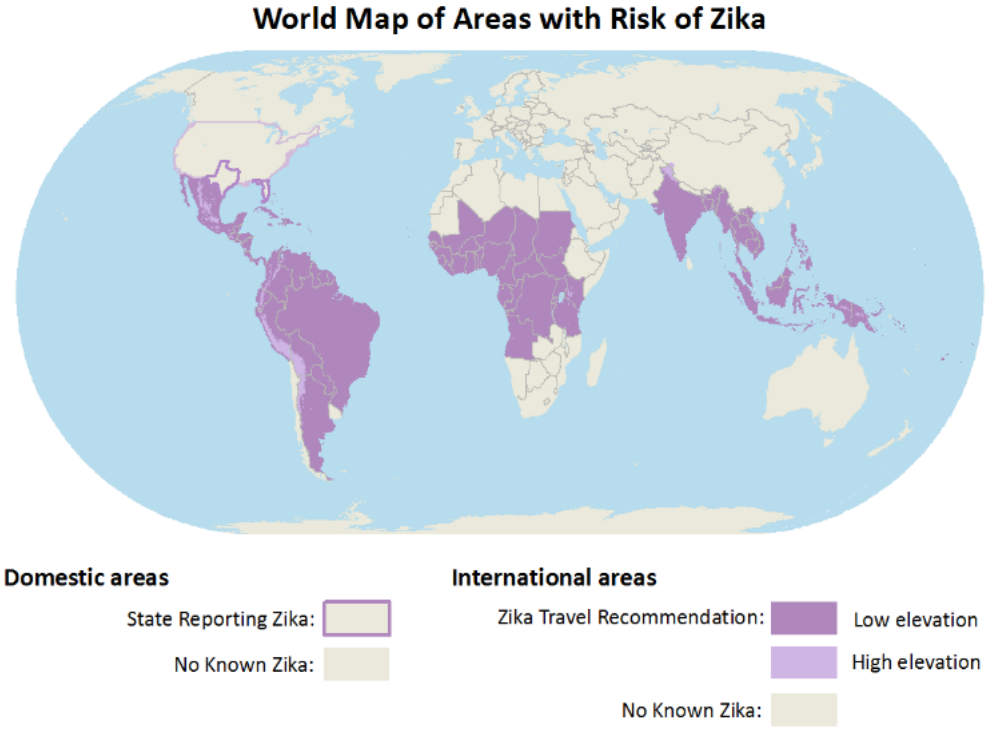


Figure 2.1: Counties with Zika Virus: Source CDC

[Jan: In the caption: s/counties/countries]

Zika Virus is mainly spread by Aedes mosquitoes, when the Mosquito bites an infected person it carries the pathogen and when It bites an infected person it also it leaves the pathogen in them. [Jan: s/Aedes mosquitoes/mosquitoes of genus Aedes. Why is "Mosquito" capitalized? s/it also it leaves/it also leaves] [Jan: "when it bites an infected person it leaves pathogen" What are you

saying here? The person is already infected.] Other ways of by which the virus spreads include, Blood transfusion, Unprotected Sex With an infected person and From mother to child, infected mothers can pass on the virus to their unborn children (Musso et al., 2014). [Jan: s/ways of by which/ways by which] [Jan: Capitalization. Just remove all capital letters.]

Musso et al. (2015), shows that some of the symptoms are papular rash,fever,arthritis or arthralgia. [Jan: Always include a space after comma.] [Jan: \citep is more appropriate here.] In addition , [Jan: Never include a space before comma.] headache, joint pain and red eyes are common symptoms of Zika virus. Simões et al. (2016) state adds that pregnant mothers who are infected with Zika during usually have child bearing defects. [Jan: "state adds"? "during usually"?] [Jan: Again, "X et al. state Y" is not usual way of stating common facts. Better say "Y" and use \citep. For the sentence above: "Children of mothers infected with Zika during pregnancy usually exhibit birth defects \citep {...}"] [Jan: Is it really "usually"?] The Zika virus affect their foetus and development of the baby. [Jan: s/affect/affects] Babies can face a range of neurologic sequelae suc as intellectual disability, hearing loss, vision loss, and seizures. [Jan: s/suc as/such as] These problems can range from mild to severe, are often life-long (Rasmussen et al., 2016). [Jan: This sentence is not grammatical.]

There is no known vaccination to prevent or treat for Zika virus. [Jan: s/treat for Zika/treat Zika] Prevention measures can be taken to prevent the spread of the virus. Preventing mosquito bites, this can be done by sleeping under a mosquito net, using mosquito replant, spraying mosquitos inside and outside among others. [Jan: Sentence above is not grammatical.] [Jan: s/replant/repellent] Another measure of prevention of Zika virus is practising safe sex and avoiding travelling to areas with high prevalence of Zika virus. Drugs for the systems of Zika are administered to patients as a way of treating Zika infected people because of the luck of a vaccination for the virus. [Jan: "Drugs for the systems of Zika" I don't understand what it is.] [Jan: s/luck/lack]

[Jan: The frequency of your language mistakes is not acceptable. You have to read through what you wrote, possibly several times, before handing it in. You have to read every sentence, correcting typos, making sure it is grammatical and meaningful and that the meaning is the intended one.]

[Jan: From now on I will not be marking small mistakes, it is up to you to find and correct them.]

The spread of Zika virus has resulted in Zika epidemics in some part of the world as can be seen in figure 2.1 above. [Jan: Maybe indicate what is the date to which your figure refers.] This cause a worry as the effects of an epidemic are more diver stating and if not controlled can affect the whole country region and World at large.

Mathematical models for disease transmission have been used to link biological processes of disease transmission and emergent of dynamics of infections at the population level. [Jan: s/emergent/emergence] Researchers try to understand the environmental, biological and behavioural infectiousness of a disease .

Environmental infectiousness depends on geographical factors of an infected person. Some pathogens cannot survive inside or outside in given conditions. Thus some diseases or infections spread faster in certain weather conditions(Grassly and Fraser, 2006). Understanding the timing and causes of seasonality offers important insights into how parasite–host systems interact how and when parasite control measures should be applied, and how disease risks will respond

to anthropogenic climate change and altered patterns of seasonality (Altizer et al., 2006). These factors must be captured in the models.

Biological infectiousness depends on the pathogen's life cycle and the individual or host immune system. Some individuals have strong immune system against certain infections. This on the slows down the propagation the infection. On the other hand pathogens that live outside also affect the transmission dynamics of the infection. [Jan: I don't understand how your last sentence connects to the rest of this paragraph.] The interaction of the genetic determinant of disease propagation in the pathogen and host is important in building model for the transmission dynamics of infectious diseases.

Behavioural infectiousness depends on the interaction behaviour of an individual. The contact pattern of the person affect how the individual is likely to propagate the disease. Depending on the nature of disease transmission, if a persons has a lot of contact they are more likely to spread the disease to more people compared to one who has few contacts (Johnson et al., 2001). Contact in this context implies any interaction likely to result in the transmission of an infection.

The susceptibility of and individual largely depend on biological, environmental and behavioural factors of an individual. For example one's contact pattern, immunity and the environmental conditions will highly affect the probability of contracting an infection.

Epidemiologist together with mathematicians have for years been involved in infectious disease modelling to understand the dynamics of the spread of the disease and to come with measures of how the spread can be controls. Recently there has been a growing interest in modelling the spread of Zika virus (Kucharski et al., 2016b).

Over a century, Mathematical representation and analysis of infectious diseases has been the centre of infectious disease epidemiology (Beisner, 2005). Differential equation have been used in the modelling of the dynamics of infectious diseases. They are base on the assumption of uniform mixing, that is everyone in the population has an equal probability of contracting an infectious disease (Kaplan et al., 2002). Compartmental Mathematical models have been used to describe the transmission dynamic of Zika Virus (Gao et al., 2016).

Mathematical modelling of infections diseases, started by the works of Daniel Bernoulli in Bernoulli (1760),in the quest to model the spread of small box and possible eradication. A century later the modelling become well established. The modelling of infectious disease dynamics is important for science and public policy among others. There are three main aims of infectious disease modelling; to is to understand the how the spreading mechanism of the disease, to predict how the disease will progress among the population and to understand how the disease can be controlled.

[Jan: The last few paragraphs are disorganized: you should describe historical development in chronological order.]

Mathematical models of the infectious disease provide tools for investigating and quantifying the spread of disease dynamics. Conducting experimental research on the spread of infectious disease raises a lot of ethical issue and therefore can not be conducted on humans. Mathematical simulations and modelling the disease has helped in providing understanding the impact of the infectious disease on the population and give a guide to new control measures (Ming et al., 2016).

Infectious diseases are transmitted indirectly or directly by contact between the infected and those who are not infected thus models try to capture these interactions (Sattenspiel, 1990).Studies have shown that the Susceptible- Infected- Removed(Recovered)(SIR) models and many of it's [Jan: it's = it is. The possesive is "its" (like "his", "her", etc.).] variants have been useful in the modelling of the spread of infectious diseases (Li and Muldowney, 1995). A number of disease propagation model have being built for various infectious disease among others Malaria, Zika, HIV , Small pox chicken pox (Ding et al., 2016).

Models build on either the SIR or it's variants are either deterministic or stochastic. Deterministic models also know as compartmental describe and explains what happens on average of the population. The assume that the population is homogeneous, that is everyone in the population reacts the same to risks of exposure and infection. This assumption in some cases has proved not to realist and hence the introduction of stochastic models. Stochastic models introduce the idea of randomness in the reaction to risk and infection by individual in the population (Ming et al., 2016). The main advantage of the stochastic model is they take into consideration each individual but the major draw back is that it is laborious to model them as they require a lot of simulation and sometimes become mathematically complex.

[Jan: I looked into this Ming paper and the stochastic model it proposes is different from what you describe. Please make your text and citation consistent.]

Compartmental models of infectious diseases have been built on the assumption of random mixing population. That is the transition from the susceptible to infected compartment is based on the assumption that the population is random. This assumption simplified the model enough to allow meaningful results and intuitions.However real populations do not mix randomly. People tend to mix among people they have something in common more than random people. Gender, age and work some of the important factors that detect the mixing patterns of people (Sattenspiel, 1990).

To build models that incorporate contact patterns of the individuals, Mathematicians have resolved use to use results from the work of Moreno (1945) where he analysed contact patterns of prisoners. This work give basis for understanding or building models based on the contact patterns of individuals in the population (Sattenspiel, 1990). Freeman (2004) characterizes the analysis of social networks by four properties. First,it involves the intuition that links among social actors are important. Second, it is based on the data collection and analysis of data about social relations that link actors.Third,it draws heavily on graphic imagery to reveal and display the patterning of those links and lastly it develops mathematical and computational models to describe and explain those patterns.

Graph theory has over the years grown and has found its application many fields. A graph also known as a network can be defined as triple $G = (V, E, f)$ where V is a finite set of nodes $E \subset V \oplus V = \{e_1, e_2, \ldots, e_m\}$ is a set and f is a mapping which associates some elements of E to a pair of elements of V (Estrada, 2012).

When modelling infectious diseases on networks, individuals or populations are represented by nodes of the network, contacts likely to result in the transmission of disease are represented by edges. Modelling of infectious disease on networks give better models for heterogeneous populations (Ming et al., 2016). One of the major challenges was to capture the contact patterns of individuals, the non availability of such data has lead to mathematicians modelling the spread

of infectious diseases on various simulated network structures (Pastor-Satorras and Vespignani, 2001).

A number of infectious disease model have been built on various network structures. Studies by (Watts and Strogatz, 1998) and Barabási and Albert (1999) have shown that many real world and social networks in which infectious disease propagate are either small world or scale free networks and not random or regular as earlier assumed. The underlying structure of a network influences the effect of that the dynamics of epidemics will have on a population. For example in a small world network, where the network has a high clustering coefficient a shorter average distance. A disease is more likely to spread faster than in a random network or a regular network.

Since the emergence of Zika virus epidemic, there have several studies to model the spread of the virus. Most research on Zika has been modelling the propagation of the infectious using compartmental models as can be seen in the work of Kucharski et al. (2016a), Dantas et al. (2017a) and Bonyah and Okosun (2016), where the used the SEIR compartmental model with vector to model the propagation of Zika. Their main assumption is a well mixed population. That is the population is assumed to be homogeneous.

In this research we will compare the traditional epidemiological model based on the assumption of a well mixed or homogeneous population and the Small world networks to model the population Dynamics in the spread of Zika Virus. The tradition compartmental models assumes that everyone in the population has the same probability of catching the infection. While the model built on a small world network assumes that one infects his close neighbours with a higher probability compared to any other random person in the network (Newman et al., 2002). This is a much more realistic assumption as it captures the contact patterns of individual in the community or network. Zika virus is mainly transmitted through a vector (Mosquito) contact and transmission is in reference to mosquito bite.

[Jan: You cover a lot of ground in this chapter and it feels disorganized. Consider introducing a few sections, topics could be e.g., epidemiology, Zika virus, modeling with DEs, modeling with graphs]. !

3. Background

3.1 Definitions

3.1.1 Epidemic and Pandemic . An infectious disease is a disease that is caused by pathogenic micro organisms, such as bacteria, viruses, parasites or fungi; the diseases can be spread, directly or indirectly, from one person to another.An epidemic is a situation where an infectious disease is affecting many people at a particular time and spread at a very high rate. A pandemic on the other is an epidemic over a large area (Morens et al., 2009).

3.1.2 deterministic and stochastic infectious disease models. The dynamics of infectious disease propagation are modelled as dynamical system. A dynamical system is a system that evolves with time over a state space according to a fixed rule. Thus let $\mathbb{X}$ be a state space $\mathbb{T}$ set of times and $\mathbb{R}$ rule that specifies how the state evolves with time. the rule is a function that whose domain is $\mathbb{XT}$ and co domain $\mathbb{X}$ that is,

$$\mathbb{R} : \mathbb{XT} \longrightarrow \mathbb{X}.$$

[Jan: What is $\mathbb{XT}$? Do you mean Cartesian product? If yes, indicate it explicitly with \times. Also, it would be good to add a citation for this.] !

The population is characterized as $S(t)$, $E(t)$,$I(t)$ and $R(t)$. Where $S(t)$ is the number of individuals susceptible but not infected at time t, $E(t)$ is the number of people exposed or infected but not infectious at time t, $I(t)$ is the number of infected and infectious people at time t and $R(t)$ is the number of people removed from the ability of being infected.Removal is carried by either immunization,death,recovery from the disease. The epidemiological models can be classified as Susceptible,Infected and Recovered (SIR) , Susceptible Infected (SIS or SIS) , Susceptible -Exposed - Infectious and Removed (SEIR) and any other intermediate category can be added. [Jan: It feels to me you are contradicting yourself. If you assume continuous time, I don't think it is accurate to represent the disease evolution as "rule" $\mathbb{R}$.] !

The SIS model assumes that there is no immunity after recovery used to model infections where once a person recovers they become susceptible again for example infectious like flue. SIR model assumes that once a person recovers they become immune to the infection for example chicken pox. The SEIR assumes that onnce a person get becomes infected they do not become infectious intermediately hence the intermediate compartment for exposed. [Jan: s/intermediately/immediately] !

The independent variable in the compartmental model is the time t and the rates of transfer between compartments are expressed mathematically as a result models are formulated initially as differential equations. The most epidemic models are built on the SIR proposed by M'Kendrick (1925). The system can be written as;

$$\begin{cases} \frac{dS}{dt} &= -\alpha S_{(t)} I_{(t)}, \\ \frac{dI}{dt} &= \alpha S_{(t)} I_{(t)} - \gamma I_{(t)}, \\ \frac{dR}{dt} &= \gamma I_{(t)}, \end{cases} \tag{3.1.1}$$

[Jan: Please use consistent notation. $S(t)$ or $S_{(t)}$.]

with assumptions that there is homogeneous mixing in the population. That is the rate of new infections is proportional to the current numbers of susceptibles and infectives in the population. Which the main assumption deterministic models are built on. Deterministic population models are models where the behaviour of the population of determined completely by history and the rules which govern the model. In formulating these models , in terms of derivatives of the sizes of the compartments and it is assumed that the number of members in each compartment is differentiable with time. This assumption is tenable only when the disease outbreak has been established but not valid at the beginning of a disease outbreak, when they are few infectives. When they are a few infectives, the number of infectious depends on random contacts of between small number of individuals. [Jan: Citation would be nice.]

On the other hand Stochastic models are obtained by setting by adding a random variable called noise to the transmission dynamics of deterministic models.These random fluctuations may impact the evolution of the infection. Unlike deterministic model which assume homogeneous mix , an assumption which only holds in small populations. It is quiet unlikely that all people in will be equally susceptible to the disease and effective in spreading it (Ball, 1985). A stochastic model can be further be described as a model in which the distribution of the length of the infectious period as allowed to have any distribution that can be describe by its Laplace transform (Addy et al., 1991). [Jan: This description is vague. Can you give a minimal example of a stochastic model?]

Lets an SIR compartmental model, for $t > 0$, $S(t), I(t), R(t)$ is the number of individuals in susceptible, infectious and removed. $N(t)$ the total number of particles at time t. The Poisson process, which is the underlying structure basic to the class of stochastic models and all Markov chain processes(Greenwood and Gordillo, 2009). [Jan: It is not clear to me what is the relation of Poisson process to the rest. Explain better.] The individuals enter each compartment at random times [Jan: Why random times? I thought it is $t = 0$?] and the initial fixed values , $S(0)$,$I(0)$ and $R(0)$ are fixed for some $\lambda > 0$. [Jan: What is λ?] Letting β to be the average number of contacts an infectious person makes per unit of time that take leads to infection. The probability of a susceptible individual moving from compartment S to compartment I in the time interval $[t, \triangle t]$ that is S $\to S - 1$ and I $\to I + 1$ is β S I $\triangle t + o(\triangle t)$. If it is assumed the an infected person recovers at the rate γ hence the probability of an infected person moving from infected to recovered over an interval $[t, \triangle t]$ given by $\gamma I_{t+\triangle t} - o(\triangle t)$ .It is known that,

$$\begin{aligned} N_t &= S_t + I_t + R_t \\ \Rightarrow R_t &= N_t - S_t - I_t \end{aligned}$$

Which implies that knowing S_t, I_t is knowing R_t. Hence the model becomes an S_t, I_t and thus

the stochastic dynamical system can be written as;

$$P((S_{t+\triangle t}, I_{t+\triangle t} - (S_t, I_t) = (-1, 1)) = \beta SI\triangle t + o(\triangle t). \tag{3.1.2}$$

$$P(((S_{t+\triangle t}, I_{t+\triangle t} - (S_t, I_t) = (0, -1)) = \gamma I_{t+\triangle t} - o(\triangle t). \tag{3.1.3}$$

[Jan: I think you are trying to give an example of a stochastic model, but I realized that only at the end of the paragraph. You should rewrite it. Also give more details about this model. Most important: is time discrete or continuouos?]

3.1.3 Network. A graph also known as a network can be defined as triple $G = (V, E, f)$ where V is a finite set of nodes $E \subset V \oplus V = \{e_1, e_2, \ldots, e_m\}$ is a set and f is a mapping which associates some elements of E to a pair of elements of V (Estrada, 2012). [Jan: I don't get this definition. Since $E \subseteq V \times V$, what is f for?] Nodes can be human beings, cities or houses while edges could be any connection such as friendship, physical connection or road. A network is said to be connected if they exist a path between any two nodes in the network.Distance between any two nodes in a network is defined as the length of the shortest path by each a node can be reached. [Jan: Please fix the preceding sentence.] This can be summed up as the average distance taken over all, pairs of individuals , which gives the idea of the typical distance between nodes in a network or the diameter of the graph which is the largest distance taken over all pairs.

3.1.4 Statistical Characterization. Networks can be characterized by the following statistical properties.

i **Degree distribution** The degree of a node is the number of connection a particular node and is denoted as k and the average distribution of a network is denoted by $< k >$. [Jan: In this context use \langle and \rangle instead of < and >.] Looking at the entire space or network one can obtain a distribution for the degree. Let $n(k)$ be the number of nodes of degree k in a network of size n, $p(k) = \frac{n(k)}{n}$. $p(k)$ represents the probability that a node selected uniformly at random has degree k. the degree distribution is obtained by plotting $p(k)$ against k(Estrada et al., 2015). The common distribution found in network are normal distribution, exponential, power law distribution and poisson distribution.

(Chung and Lu, 2002).

ii **Clustering** A cluster in a network is a collection of nodes which are similar between them and are dissimilar to other nodes belonging to other clusters. Clustering in friendship network may mean friends people have in common. Local clustering in a network is measure by the watts -stoggatz coefficient and the global clustering by Newman clustering coefficients.

watts -stroggatz average clustering coefficient is given by

$$\overline{C} = \frac{1}{n}\sum_i c_i \tag{3.1.4}$$

$c_i = \frac{2t_i}{k_i(k_i - 1)}$ where t_i =e number of triangles attached to node i of degree k_i. [Jan: Mixing formulas and text is bad style. So s/t_i = e number of/t_i is a number of]

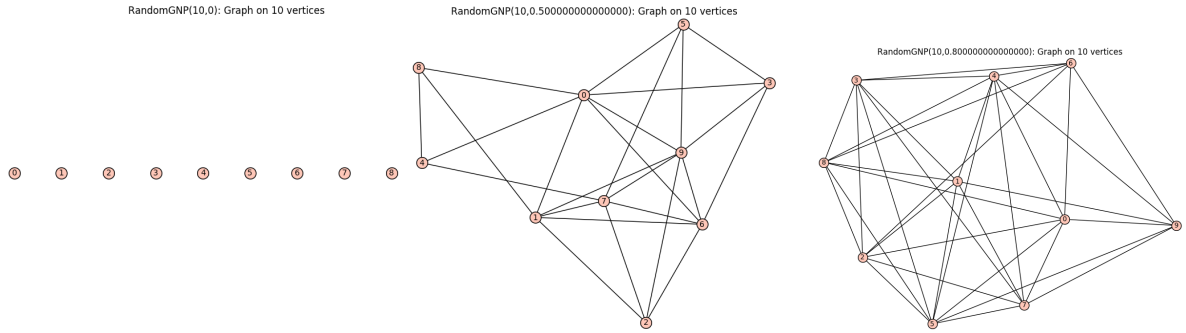
The Newman clustering coefficient is given by

$$c = \frac{3t}{p_2} = \frac{3|c_3|}{p_2} \tag{3.1.5}$$

where $t = c_3$ number of triangle in the network and $|p_2|$ the number of closed paths of length 2.

[Jan: Please give intuitions behind those coefficients as in Phil's lecture.]

3.1.5 Random Graphs. A random graph can be defined as , given a N number of vertices edges between them are drown such that between any pair i, j there is an edge with uncorrelated probability p (Newman et al., 2002). [Jan: No, a random graph can be sampled from any probability distribution. What you describe is usually called "$G(n, p)$ random graph".] For example in 3.1, there are 3 random graphs with 10 vertices, with a probability of nodes i, j being connect being 0, 0.5 and 0.8 in figure 3.1a 3.1b and 3.1c respectively. A random network model can exhibit the small world network property, [Jan: What is small world network property?] it has an average degree $z = pN$. [Jan: Approximately pN (actually $z = p(N-1)$). Also this is the *expectation* of average degree.] Random networks have a a low clustering coefficient $c = \frac{z}{N}$ (Newman, 2003). [Jan: Again, this is just approximation of c.]



(a) $p = 0$ (b) $p = 0.5$ (c) $p = 0.8$

Figure 3.1: Random Graphs

[Jan: Fix the figure: The upper labels are too small and the numbers badly formatted. Also, the labels of vertices are too small to read, just delete them.]

Regular lattices and random graphs have a long history of use in network theory and to model population structures,Harris (1974) gives an example of classic lattice. Models built on latices assume that individuals are located as nodes on a regular lattice and connections are made of some collection of near neighbours or each node. [Jan: Define what a lattice is or at least draw an example.] For example people may be spread out such that connections are made to their four nearest neighbours, one on the left,right, up and down this is called a Neuman neighbours or eight neighbours where four diagonal elements are added to the Neuman neighbours and this is called the Moore neighbour hood (Lloyd et al., 2006).To avoid the effect of the nodes at the end not being connected the last and first neighbours are made neighbours.

The main difference between a random graph and lattices is that interactions are local, that is individuals are only related to their neighbours. Where as in random networks the connections are made are global, that is connections are made without taking spatial locations of an individual into consideration.

Small world networks were first introduced by Watts and Strogatz as an intermediate between the regular lattice and randomly rewiring certain proportions p of the network links(Watts and Strogatz, 1998). The small world networks allows for random contacts across the network. That is in addition to near neighbours as in a regular lattice, each node has a random distant neighbour connected to it (Watts and Strogatz, 1998). [Jan: Give more precise definition and/or add an example.]

4. Compartmental and Stochastic Models

4.1 Deterministic Models

4.2 SIR Model

In the model the population is partitioned into three compartments. Susceptible, Infected and Recovered this is the basis for most epidemiological models. (M'Kendrick, 1925). In building the model the number of individuals Susceptible, Infected and Recovered is assumed to be differentiable over time. The simple epidemic model is given by.

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI, \\ \frac{dI}{dt} &= \beta SI - \gamma I, \\ \frac{dR}{dt} &= \gamma I, \end{aligned} \tag{4.2.1}$$

[Jan: I think it's better to use \align instead of \equation with an array inside. You can look it up in "not so short introduction to latex".] $N = S + I + R$ The model is based on the assumption that susceptible individuals become infected at a rate β proportional to the number of people infected and susceptible at time t and Infected people recover at γ rate. The reciprocal $\frac{1}{\gamma}$ is referred to as the average infectious period . Another assumption in this model is that the population remains constant, thus it does not take int account the demographic changes of the population.

4.2.1 Model Analysis. We determine the equilibrium and the stability of 4.2.1, but since $N = S + I + R$ knowing S and I implies that we can solve for R. Hence our system of equations can be reduced to

$$\frac{dS}{dt} = -\beta SI. \tag{4.2.2}$$

$$\frac{dI}{dt} = \beta SI - \gamma I. \tag{4.2.3}$$

[Jan: Fix alignment (align has only two columns, usually you separate them after the equal sign).] With $S(0) > 0$, $I(0) > 0$ and $R(0) = 0$ as the initial conditions for the model. We now calculate the disease free equilibrium and endemic equilibrium by equating 4.2.2 and 4.2.3 to zero then solving them. Despite its extreme simplicity, this model 4.2.1 cannot be solved explicitly.That is, we cannot obtain an exact analytical expression for the dynamics of S and I though time, instead the model has to be solved numerically.

The equation 4.2.2 gives two import insights in understanding the spread of disease and has since been used in infectious disease modelling for along time.

4.2.2 Threshold Phenomenon. Its is important to determine whether the infection will result into an epidemic or not and what factors could determine this. Consider the initial stage after $I(0)$ individuals have been infected in a population with $S(0)$ susceptible. Equation 4.2.3 can be rewritten as,

$$\frac{dI}{dt} = I\left(\beta S - \gamma\right) \tag{4.2.4}$$

In equation 4.2.4 if the initial susceptible (S(0)) is less than $\frac{\gamma}{\beta}$. Then $\frac{dI}{dt} < 0$. This implies that there will be no epidemic in this case. [Jan: "This implies" is not a good choice of words here. I think it gives a good intuition why there will be no epidemic, but the proof is more complicated than that, right?] This result was coined by M'Kendrick (1925) and is what is refereed to as the threshold phenomenon. The initial S(0) must exceed the threshold $\frac{\gamma}{\beta}$ for an epidemic occur.In other words the relative removal rate $\frac{\gamma}{\beta}$ must be small enough to allow the occurrence of the epidemic.

The reciprocal of the of relative removal rate is called the basic reproductive ratio and is one of the most important quantities in epidemiology . Basic reproduction ratio is defined as the average number of secondary cases arising from an average primary case in an entirely susceptible population. It measures measures the maximum reproductive potential for an infection. For the our SIR model in equation 4.2.1 it is given by:

[Jan: Equation missing here.]

For initial susceptible $S(0) = 1$, if $R_0 > 1$ then there will be an outbreak if $R_0 < 1$ the will be no outbreak. It can be noted that every disease has a different R_0 value and also depending on the population's contact pattern the R_0 value will differ.

$$R_0 = \frac{\beta}{\gamma} \tag{4.2.5}$$

4.2.3 Epidemic Burnout. The threshold phenomena give a description of what happens in the initial stages after introduction of an infection. Another important quantity we get from the SIR model is the long term state infection. From they system in equation 4.2.1 we take

$$\frac{dS}{dt} = -\beta SI \tag{4.2.6}$$

$$\frac{dR}{dt} = \gamma I \tag{4.2.7}$$

dividing equation 4.2.4 by equation 4.2.7 we get

$$\frac{dS}{dR} = \frac{-\beta S}{\gamma} \tag{4.2.8}$$

$$= R_0 S \tag{4.2.9}$$

[Jan: Just put whole equation above on one line.] Differentiating equation 4.2.9 with respect to R we get [Jan: Differentiating? You are integrating, no?]

$$\int \frac{dS}{S} = \int R_o dR \tag{4.2.10}$$

$$e^{lnS} = e^{-R_0 R + k} \tag{4.2.11}$$

$$S(t) = e^{-R_0 R(t)} e^{k} \tag{4.2.12}$$

assuming R(0) = 0

$$S(t) = S(0) e^{-R_0 R(t)} \tag{4.2.13}$$

[Jan: Add one more step between the first and second equation above.] Hence as the epidemic develops the number of susceptible reduce, taking into consideration the infectious period there is a lag but eventually the number of recovered start to increase. There number of susceptible in the population will always be above zero as can be seen in equation 4.2.13.

The epidemic burnout gives the intuitive idea that the chain of transmission eventually breaks due to the decline in infectives not due to lack of susceptibles. [Jan: I don't see this intuition. Can you explain more and/or add citation?]

4.2.4 Disease free equilibrium. Adding demographic parameters to 4.2.1 we get a new system of equations. [Jan: Explain what is the interpretation of "demographic parameters".]

$$S' = \mu - \beta SI + \mu S \tag{4.2.14}$$

$$I' = \beta SI - \gamma I - \mu I \tag{4.2.15}$$

$$R' = \gamma I - \mu R \tag{4.2.16}$$

[Jan: Be consistent with notation: S' or dS/dt? Don't you have a typo in the first equation?] Using the procedure we used to get equation **??** it can be shown that the R_0 for this model is

$$R_0 = \frac{\beta}{\mu + \gamma} \tag{4.2.17}$$

Now e calculate the equilibria of the model by setting equation 4.2.14, 4.2.15 and 4.2.16 to zero.Then solving for I,S and R.

from equation 4.2.15 we get,

$$I(\beta S - (\gamma + \mu)) = 0 \tag{4.2.18}$$

thus we get

$$I = 0 \rightarrow S = \frac{\gamma + \mu}{\beta} \tag{4.2.19}$$

Therefore the disease free equilibrium is $I^* = 0$ and $S^* = \frac{\gamma+\mu}{\beta}$. [Jan: What are I^* and S^*? It seems to me that disease-free equlibrium is $S = \mu N$ and $I = 0$, please double-check and make corrections.] This implies that there will be no epidemic when the number there is no infection in the population. [Jan: Of course there is no epidemic with no infection, there is no need to write that. The point of computing equilibria is different.]

To calculate the endemic equilibrium, we take $I \neq 0$ and solve (4.2.16). Since $S + R + I = 1$

$$\gamma I - \mu(1 - S - I) = 0 \tag{4.2.20}$$
$$\gamma I - \mu I - \mu(1 - S) = 0 \tag{4.2.21}$$
$$I = \frac{\mu}{\beta} R_0 \left(1 - \frac{1}{R_0}\right) \tag{4.2.22}$$
$$I = \frac{\mu}{\beta}(R_0 - 1) \tag{4.2.23}$$

[Jan: I could not follow the computation above, please state clearly what you are substituting for what.] Thus the endemic equilibrium point (S^*, I^*, R^*) is $\left(\frac{1}{R_0}, \frac{\mu}{\beta}(R_0 - 1), 1 - \frac{1}{R_0}\frac{\mu}{\beta}(R_0 - 1) - \frac{1}{R_0}\right)$

4.2.5 stability of the model. Once an out break occurs its important to understand the long term behaviour of the out break and finding the stability of the model gives an insight on this. In other words calculating the stability of the model is establishing at which point the epedemic burn out will occur.

4.2.6 SEIR Model. The susceptible, Exposed, Infected and Recovered models add a new compartment to the previously discussed SIR Model. The earlier models assume that once a person is infected they become infectious immediately. In this model an assumption is made that one a person is exposed there is an intermediate stage between the time of infection and when they become infectious, this maybe refereed to as the latent or incubation period of the infection. The will system of equations will be;

$$S' = \mu - \beta SI\mu S \tag{4.2.24}$$
$$E' = \beta SI - (\mu + \gamma)E \tag{4.2.25}$$
$$I' = \gamma E - (\alpha + \mu I) \tag{4.2.26}$$
$$R' = \alpha I - \mu R \tag{4.2.27}$$

where β is the rate at which susceptible individuals become infectious, γ the rate at which exposed people become infection. The quantity $\frac{1}{\gamma}$ is called the latent period of the infection. α is the recovery rate. In this model the total infected individuals is given by $E + I$ and we assume that our system is density dependant thus $S + E + I + R = 1$ and that the population is constant implying that birth rate (μ) = death rate (μ).

Since $R = 1 - S + E + I$ [Jan: Typo here] it can be dropped from the system and our new system of equations would be,

$$\begin{aligned} S' &= \mu - \beta SI\mu S \\ E' &= \beta SI - (\mu + \gamma)E \\ I' &= \gamma E - (\alpha + \mu I) \end{aligned} \tag{4.2.28}$$

[Jan: No need to write exactly the same equations right after the original ones, just say you are dropping the last one. Also correct typo in thefirst equation.] We calculate equilibrium point by equating all the equations,in the the system 4.2.28 to 0 and solving them.

The disease free equilibrium of the system $S^*, E^*, I^* = (1, 0, 0)$. [Jan: No, I don't think that is correct disease-free equilibrium.] Thus is there are infections there will be no epidemic. When $I^* \neq 0$ we find the disease pandemic equilibrium, which is given by

$$S^*, E^*, I^* = \left(\frac{(\alpha+\mu)(\gamma+\mu)}{\beta\gamma}, \frac{\alpha+\mu}{\gamma} I^*, \frac{\mu}{\beta S*} \frac{\mu}{\beta} \right).$$

The reproductive number R_0 is given by the spectral radius FV^{-1}. Where $V = \left[\frac{\partial V_i(x*}{\partial j} \right], F = \left[\frac{\partial F_i(x^*)}{\partial j} \right]$, x^*, $V_i(x)$ the disease equilibrium and transition rate from one component to the other respectively. $F_i(x^*)$ is the number of infections in component i and is a non singular matrix. [Jan: Where does this come from? Give citation or explanation.]

Therefore,

$$FV^{-1} = \begin{pmatrix} 0 & 0 \\ \beta & 0 \end{pmatrix} \begin{pmatrix} \frac{1}{(\gamma+\mu)} & \frac{-\gamma}{(\alpha+\mu)+(\gamma+\mu)} \\ 0 & \frac{1}{\alpha+\mu} \end{pmatrix} = \begin{pmatrix} 0 & 0 \\ \frac{\beta}{(\gamma+\mu)} & \frac{-\beta\gamma}{(\alpha+\mu)+(\gamma+\mu)} \end{pmatrix} \tag{4.2.29}$$

The equation 4.2.29 has eigenvalue values λ_1 , $lambdad$ as 0 and $\frac{-\beta\gamma}{(\alpha+\mu)+(\gamma+\mu)}$ respectively.

$$R_0 = max|\lambda_1||\lambda_2| \tag{4.2.30}$$

Thus the R_0 for the system will be $\frac{-\beta\gamma}{(\alpha+\mu)+(\gamma+\mu)}$.

It can be shown that the stationary point (1,0,0) is asymptotically stable which implying that $R_0 < 1$ and the pandemic equilibrium $R_1 > 1$ meaning the disease will persist. [Jan: I don't understand your last sentence.]

4.2.7 Other Compartmental Models.. There are several other types of compartmental model and epidemiologist tend to include additional components. Here are some of the models that can be used to model infectious diseases.

4.2.8 SI. The susceptible infected model assumes that once someone is infected there is no recovery. Hence it has only two components and it is used to model infectious like HIV and other incurable infectious diseases. The description of the short term and long term behaviour of the model can be calculated similar to the SIR model.

5. Testing

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