A survey of epidemiological modeling on networks and investigation of the relationship between the fraction of epidemics that take-off and the endemic level in a network

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Chapter 1

Introduction: Understanding R_0 and Infectious Disease Modeling

1.1 General Overview of Infectious Disease Modeling

Infectious diseases are a pressing issue for civilization today. In recent years a number of significant disease out breaks have affected human populations [20] [59] [23]. Additionally, outbreaks in domestic animal populations have consequences for the livelihoods of farmers [28][55] and epidemics in wildlife populations can alter entire ecosystems [19]. To combat these infections one must first understand how they spread and determine the optimal strategies to control them. Infectious disease modeling uses different forms of mathematical equations and tools to build a quantitative picture of various infectious agents and how they spread in different populations.

1.1.1 History of Disease Modeling

Daniel Bernoulli developed one of the earliest examples of a model for an infectious disease in the 1760s. He attempted to determine the increase in life expectancy from birth for an individual inoculated against smallpox. At the time the procedure to inoculate was extremely controversial and the quantitative understanding of the risks versus rewards provided by his work helped increase acceptance of the procedure [18]. His work was one of the first examples of a compartmental model as he divided the population into susceptible and infectious states and applied an age-specified force of infection [8].

In its early forms disease modeling also involved using statistics to understand disease patterns and their affects. Two pioneers in this field were William Farr and John Snow. They both examined the cholera epidemics occurring in London during the mid 1800s. Farr, a qualified doctor, helped pioneer the use of statistics to understand disease spread. His analysis of clinical cohorts was much ahead of its time . He tracked cases from beginning to end without losing site of a case. This

specificity allowed him to accurately determine mortality for smallpox by correctly ascertaining the probability of recovery or death based on full tracking of a large number of cases [24]. While his use of statistical analysis was ahead of its time, his conclusion that incidence of cholera was related to elevation and belief that the cause was airborne would not stand up to further testing.

John Snow disagreed with Farr's assessment of cholera as an airborne infection. He used Farr's statistics to support his theory that the cause of cholera was tainted water. Farr was not converted to Snow's view until 1866 when Snow definitively traced the source of an outbreak to a tainted well [22].

Dynamical Systems Based Model

Dynamical systems were first applied to the problem of disease modeling at the beginning of the 20th century, laying the foundations of modern disease modeling [15]. Kermack and McKendrick (1927) [37] proposed the most famous of these early dynamical systems models in their landmark series of papers titled, "A Contribution to the Mathematical Theory of Epidemics" [15]. A special case of their model remains one of the most commonly studied examples of a basic infectious disease model. Further descriptions of models based on their original appear in Section 1.1.3.

Stochastic Model

Shortly after Kermack and McKendrick developed their model, another approach to disease modeling was developed by two professors at John Hopkins University, Reed and Frost. Their model focused on the idea that events in nature, while controlled by overlying principles are inherently random. They did not consider their model worthy of publication, and neither of the original authors ever published on it. Instead they used the model in a course jointly taught by the departments of epidemiology and biostatistics [53].

The Reed-Frost model as it became known is a chain binomial model that predicts the number of individuals infectious in the next generation of a disease based on the number infectious in the current generation. As in the Kermack and McKendrick model, every individual in the population is in one of three states: infectious, susceptible, immune. The following expression describes the distribution of successive generations in the model:

$$C_{t+1} \sim Binomial(S_t, 1 - q^{C_t})[1].$$

In this expression C_t denotes the number of infectious individuals at time t and S_t is the number of susceptible individuals at the same time [17]. The q is equal to $1 - p$, where p is the probability that any two individuals selected at random will make an infectious contact, a contact sufficient to pass on infection, in a given time step. The model assumes the infection possesses a short infectious period relative to

the latent stage. During the latent stage an individual has been infected, but is not yet infectious to other individuals. This assumption allows for the models definition of distinct generations to be defined because the latent period creates a seperation between successive generations [17].

At the very beginning of an epidemic it is reasonable to simplify this model to an approximate birth death problem, which allows for an estimation of the fraction of seeded epidemics that will actually take-off. The full explanation and derivation of this process is discussed further in Section 1.3.2 and provides a part of the basis for the work disscussed in Section 3.1. Stochastic models can also be examined with contact processes especially dealing with how they take off [27].

The model developed by Reed and Frost resembles work done thirty five years earlier by a Russian mathematician P. D. En'ko. En'ko developed a chain binomial model to which he fit predictions to years of observations with strikingly good results [16]. The model he developed in 1889 is represented by three equations written here in the same notation as used by Reed and Frost:

$$\begin{aligned} C_{t+1} &= S_t\left\{1-\left(1-\frac{C_t}{N_t-1}\right)^{kN_t}\right\} \\ S_{t+1} &= S_t\left(1-\frac{C_t}{N_t-1}\right)^{kN_t} \\ N_{t+1} &= N_t - C_t \end{aligned}$$

where again C_t represents the number of infectious individuals at time t, S_t provides the number of susceptible individuals and N_t is the size of the population. The k parameter provides the number of contacts made by each susceptible individual [17]. The model is based around the binomial distribution, which requires the exponent to be an integer and thus requires that each susceptible make the same number of contacts. Reed and Frost developed their model independently of En'ko as his work was not well known in the west until the past 30 years [16].

1.1.2 Criss Cross Model

Finally, no discussion of the general history of infectious disease modeling would be complete without mentioning two other individuals who worked independently on a model examining the prevalence and persistence of malaria. Ross and Macdonald developed a deterministic, differential equation based model to represent the spread of malaria. Their model is of particular significance because it was one of the first examples of a multi-species model [40].

Malaria infects both humans and mosquitoes, but infection only occurs from human to mosquito and vice versus. In order to model the system one needs to use two sets of equations one for the mosquito population and another for the human

population. As with all of the models discussed previously the model can be adjusted for varying degrees of complexity and corresponding accuracy.

1.1.3 Basic Deterministic Models

As stated above the Kermack and McKendrick model is still in use today. Individuals in the model exist in three categories based on disease status. They are susceptible to disease, infectious, or recovered from the infection (no longer able to be infected). These classes, represented with the letters S, I and R respectively, give rise to the name of the model S-I-R.

Since Kermack and McKendrick first published their paper in 1927, many variations and additions to this model have been developed. Researchers now work on models where individuals return to the suseptible class after infection called S-I-S models and additional states have been added to the original S-I-R model to make the models better reflect real life diseases. Examples of these variations are found in Section 1.1.4.

Susceptible-Infectious-Recovered

Kermack and McKendrick's original model was an S-I-R model, which used differential equations to represent the changing numbers of individuals within a population. The model using current notation is represented by three equations:

$$\frac{dS}{dt} = -\beta S(t)I(t) \tag{1.1}$$

$$\frac{dI}{dt} = \beta S(t)I(t) - gI(t) \tag{1.2}$$

$$\frac{dR}{dt} = gI(t). \tag{1.3}$$

The S, I, and R represent the fraction of a population that is in each of the states susceptible, infectious, or resistant at any given point in time. The other two parameters β and g relate to the specific infection and population being modeled. The rate of recovery is g and β is the transmission parameter.

While this model appears simple, due to the non-linear term $\beta S(t)I(t)$ it lacks an explicit analytic solution and numerical methods are necessary to solve it. An approximate solution was offered by Kermack and McKendrick at the time using a Taylor expansion to the second degree. They did some work fitting their model to data and achieved quite a good fits considering the simplicity of the model [17].

Their main case study remains one of the most commonly used illustrations of a model fitted to data and is shown in Figure 1.1. It involves an outbreak of plague in Bombay from December 1905 to January 1906. In order to solve the model they had to make several significant assumptions about the population and size of the epidemic. By assuming the population is a closed system and all individuals in one

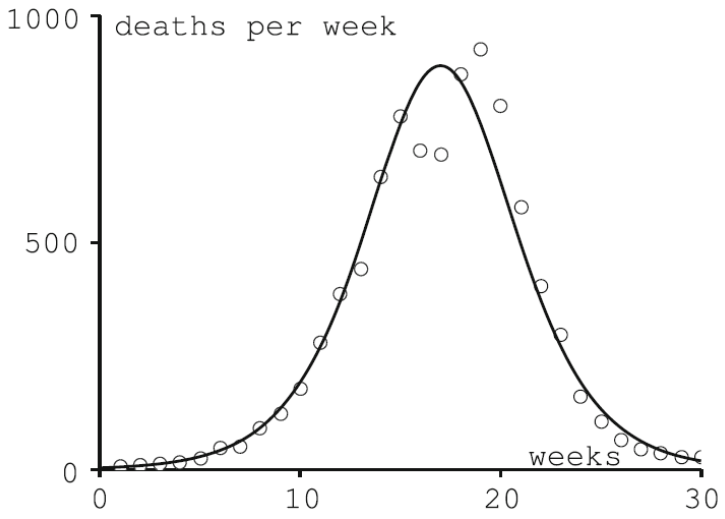

Figure 1.1: One of the most commonly used illustrations of a model fitted to data from a report of the Advisory Committee appointed by the Secretary of State for India [5].

of the three states the model can in fact be defined by two of the three equations. Therefore, it is possible to remove the I class of individuals from consideration if one divides $S(t)$ by $R(t)$ to obtain:

$$\begin{aligned} \frac{dS}{dR} &= \frac{-\beta S(t)}{g} \\ &= -R_0 S(t), \end{aligned}$$

where R_0 is the basic reproductive number equal to β/g and explained in detail in Section 1.1.3 and all other values are the same as described for the original model. This equation represents the rate of change of susceptible versus recovered individuals. By further integrating, one can obtain a value for S in terms of R:

$$S(t) = S(0)\exp(-R(t)R_0). \tag{1.4}$$

Then returning to the original equations and using the assumption of $S(t) + I(t) + R(t) = 1$, the system is closed and all individuals are in one of three states, Equation 1.3 can be rewritten in terms of S and R, and then solely in terms of R by using Equation 1.4:

$$\frac{dR}{dt} = g(1 - S(t) - R(t)) \tag{1.5}$$

$$\frac{dR}{dt} = g(1 - S(0)\exp(-R(t)R_0 - R(t))). \tag{1.6}$$

While Equation 1.6 cannot be solved outright, if one assumes that the $R_0R(t)$ term is small then a Taylor expansion can be performed for the exponential term and after some somewhat messy calculations an approximate solution is obtained:

$$R(t) = \frac{1}{R_0^2 S(0)}\left(S(0)R_0 - 1 + \alpha tanh\left(\frac{1}{2}\alpha g t - \phi\right)\right),$$

where

$$\alpha = [(S(0)R_0 - 1)^2 + 2S(0)I(0)R_0^2]^{\frac{1}{2}},$$

and

$$\phi = tanh^{-1}\left[\frac{1}{\alpha}(S(0)R_0 - 1)\right].$$

This solution can then be used to obtain the epidemic curve of the number of recovered individuals with respect to time, which is how Kermack and Mckendrick obtained their approximate solution for the Bombay plague. For the curve in Figure 1.1 the solution is $890/cosh^2(0.2t - 3.4)$ [5].

Significant assumptions are required to obtain this solution. The requirement of $R_0R(t)$ to be small, means that this solution is not likely to be valid for a number of infections where the R_0 value is high. Additionally, the solution will be most accurate at the beginning of an epidemic when the value of $R(t)$ is also very small.

Furthermore, as commented by Bacaer in a recent article it is important to consider the assumptions made in the conditions of the model. He makes the case that while the 1905 plague epidemic is a famous example of the application of the Kermack and McKendrick model, it is not necessarily a good one. Plague at that time in Bombay had a remarkable pattern of seasonal epidemics from 1897 through to 1911. So it is more likely that the 1905 epidemic was seasonal in nature [5].

Another classic case study for the basic SIR model comes from an outbreak of Influenza in an English boarding school in 1978. This case fits the assumptions of the basic model very well. All but a few of the boys resided at the boarding school, which made the school a relatively closed system. Additionally, none of the boys had been previously exposed to the virus making the entire school susceptible, and one sick boy initiated the infection. This epidemic was reported in the "British Medical Journal", and fits very well to the pattern predicted by the basic SIR model. By the end of the epidemic 512 boys had become ill over the course of the epidemic, which lasted approximately two weeks [4]. The size and course of the model fits well with the predictions of the basic SIR model. This epidemic was severe so the weak epidemic assumptions applied to the plague model cannot be used and numerical methods are required to analyze the full system [43].

The Basic Reproduction Number (R_0) for the S-I-R Model

Kermack and Mckendrick first introduced the idea of the basic reproduction number as the threshold theorem. It provided a quantitative measure for determining whether an epidemic would take-off in a population. The phenomenon occurs because for an epidemic to progress the differential equation, $dI/dt = \beta S(t)I(t) - gI(t)$, must be positive. The number of infectious individuals must be growing. Therefore, $\beta S(t) > g$ and $S(0) > g/\beta$ in order for an epidemic to spread in a population. The relative removal rate g/β must be small enough to permit the infection to take-off.

The inverse of the relative removal rate at the start of an epidemic is the formula for the basic reproduction number, R_0, for the given model. It approximates the number of secondary cases per a primary case in an entirely susceptible population [35]. When R_0 is known then the likelihood of an epidemic can be ascertained. The basic reproduction number represents the maximum reproductive potential for an infectious agent in a population [14]. It also can inform about a number of other properties of an infection, such as what level of vaccination would be required to prevent an outbreak and the likely severity of an outbreak.

1.1.4 Variations of the Basic Model

Susceptible-Infectious-Susceptible

In one variation of the S-I-R model individuals recover from infection and return to the susceptible class. This model requires one less equation than the S-I-R model. It is defined by:

$$\begin{aligned} \frac{dS}{dt} &= -\beta S(t)I(t) + gI(t) \\ \frac{dI}{dt} &= \beta S(t)I(t) - gI(t), \end{aligned}$$

where S and I again represent the portion of the population in the susceptible and infectious states, β is the transmission parameter, and g is the recovery rate.

Basic assumptions of the model include a closed population, $S(t) + I(t) = 1$, making every individual either susceptible or infectious. The model can then be written with a single equation. Assuming, $S(t) = 1 - I(t)$:

$$\frac{dI}{dt} = (\beta - \beta I(t) - g)I(t) = \beta I(t)((1 - 1/R_0) - I(t)), \tag{1.7}$$

where $R_0 = \beta/g$ as in the S-I-R model. The formula of R_0 is derived from the equation representing infectious individuals in the model and as the equation is identical to the S-I-R model, its derivation is the same as seen in Section 1.1.3. Equation 1.7 is a logistic equation which can be solved by equilibrium analysis [9].

The equation dI/dt is set to zero to determine the steady state values of the system. Thus the two steady states of the system are the disease free equilibrium where, $I(*) = 0$, and endemic equilibrium, $I(*) = 1 - 1/R_0$. While the zero equilibrium is relatively uninteresting, the second equilibrium relates the prevalence of an infection in a population directly to the basic reproduction number. This analysis further illustrates the requirement for R_0 to be greater than one for the infection to remain in the population. For R_0 less than one the endemic equilibrium is negative making it infeasible. Thus in order for an infection to persist in a population R_0 must be greater than one.

This type of model has applications in any number of infections where immunity is not conferred after an infection. Sexually transmitted infections (STIs) are one of the major applications of SIS models currently. Most STIs do not impart immunity and individuals return to the susceptible class when they recover from infection. Additionally, many bacterial and parasitic infections fit within the SIS mold as individuals can continue to be infected with subsequent exposures.

Models with Additional States

As more knowledge has entered the field of epidemiology about the biological characteristics of specific infections, models have been adapted to account for these characteristics. One of the most common examples is the inclusion of a latent period in the S-I-R model. The latent period accounts for the delay, present in many common infections such as flu, between the contact with the infective virus and the onset of symptoms when an individual generally becomes infectious. The addition of a state to the system requires the addition of an equation:

$$\begin{aligned}
\frac{dS}{dt} &= -\beta S(t)I(t) \\
\frac{dE}{dt} &= \beta S(t)I(t) - aE(t) \\
\frac{dI}{dt} &= aE(t) - gI(t) \\
\frac{dR}{dt} &= gI(t).
\end{aligned}$$

All the variables for this equation are the same as for the original S-I-R model, but with the addition of the latent state, E, and the rate of transition from latency to infection,a.

The expression for R_0 remains the same as for the S-I-R model and one might assume that the inclusion of the latent class is an unnecessary complication of the S-I-R model because the basic dynamics of the model remain the same. However, the inclusion of the latent period causes the model to behave differently at the outset of an epidemic, with the latent class slowing the dynamics [35]. Most forms of influenza

possess a latent period, so inclusion in the model is important to accurately match the model to data. One example of this type of model was used to determine the basic reproduction number for the 1918 pandemic influenza [12] and in models for the recent outbreak of Swine Flu [51].

Another model with an additional state reflects infections where not all individuals recover. Some retain chronic infections and continue to transmit infection for a long period of time. This model can be written as:

$$\begin{aligned}
\frac{dS}{dt} &= -\beta S(t)I(t) - \epsilon\beta C(t)S(t) \\
\frac{dI}{dt} &= \beta S(t)I(t) + \epsilon\beta C(t)S(t) - gI(t) \\
\frac{dC}{dt} &= gqI(t) - \Gamma C(t) \\
\frac{dR}{dt} &= gI(t) - gqI(t) + \Gamma C(t).
\end{aligned}$$

The new carrier state is represented by C, with q determining the proportion of infecteds that enter the carrier state, ϵ accounting for the decreased rate of transmission from individuals in the carrier state and Γ determining the rate of recovery from the carrier state. This model has a different formula for the basic reproduction number as it must account for both the number of individuals entering the carrier state and the affect of additional infections from carriers. The formula for R_0 for this model is:

$$R_0 = \frac{\beta}{g} + \frac{qg}{g}\frac{\epsilon\beta}{\Gamma} = \frac{\beta}{g}\left(1 + \frac{qg\epsilon}{\Gamma}\right)).$$

The first term mirrors the original form of R_0, while the second part accounts for the carriers. Examples of infection models that might include a carrier state would be herpes or hepatitis B [60]. Additionally, many STIs might be effectively modeled with a carrier state because if individuals do not present symptoms and are not tested then they can continue to pass on the infection for long periods of time.

Models with waning immunity

Some infections are best represented with a hybrid of the S-I-R and S-I-S models. In these models called S-I-R-S immunity is conferred from an infection, but over time the immunity is lost and the individual returns to the susceptible class. As one might expect the dynamics of this model fall in-between the S-I-R and S-I-S models. The level of infection does eventually reach an endemic equilibrium when $R_0 > 1$ as seen for the S-I-S model.

However, in moving toward this equilibrium the population will experience various epidemics, with dynamics that more closely mirror the classic S-I-R model.

After an epidemic the pool of susceptible individuals will be diminished, but it is replenished with the loss of immunity over time such that another large outbreak can occur. The equations for this model are very similar to the original SIR model, but with the addition of one term ω representing the rate at which immunity is lost:

$$\begin{aligned} \frac{dS}{dt} &= \omega R(t) - \beta S(t) I(t) \\ \frac{dI}{dt} &= \beta S(t) I(t) - g I(t) \\ \frac{dR}{dt} &= g I(t) - \omega R(t). \end{aligned}$$

One example of a model with waning immunity was developed by Grassly et al. 2005 [26]. They use an S-I-R-S model to show that the 8-11 year period between major outbreaks of syphilis is due to the natural dynamics of the disease where immunity is obtained for a period of time after infection. Previously the periodicity of epidemics had been attributed to changes in sexual behavior over the previous 50 years. They compared the pattern of major outbreaks of syphilis to the lack of oscillations observed for gonorrhea cases, which do not offer any period of immunity .

Including Demography

Further adaptations of the basic model can be used to even better reflect reality. In the simple S-I-R model, the population is a closed system thus when an infection invades causing an epidemic, then a large portion of the population is removed and would not be susceptible to further infection. However, data from measles, mumps, rubella, and chicken pox show that epidemics of these infections occur repeatedly in the same population. This pattern occurs because the population itself is not a closed system. Instead babies are born and individuals migrate renewing both the number of susceptibles and the possibility of a pathogen being introduced from the outside [13]. At the same time some in the population are passing away decreasing the number of individuals in all states. Incorporating these values into the model allows it to better reflect the true dynamics of the system.

The basic demographic model is nearly identical to the S-I-R model, but with the addition of a parameter to account for new births in a population and deaths. For simplicity in many models, to keep the size of the population constant, the death rate is assumed to equal the birth rate although this condition is not necessary. Additionally for simplicity, the most basic model assumes that individuals die at equal rates proportional to the number of individuals in their given state. Thus the assumption that the infection does not increase the chance of dying is incorporated

into the model. The simple demographic model:

$$\begin{aligned}
\frac{dS}{dt} &= \mu - \beta S(t)I(t) - \mu S(t) \\
\frac{dI}{dt} &= \beta S(t)I(t) - gI(t) - \mu I(t) \\
\frac{dR}{dt} &= gI(t) - \mu R(t)
\end{aligned}$$

represents the birth rate with a constant, μ, and assumes that all individuals are susceptible at birth. In some cases, such as with measles immunity may be conferred to newborns through the birth process, which can last approximately six months to a year after birth [39]. This immunity could be accounted for with an additional parameter in the model, however, in the case of measles where the average age of infection is school age (approximately five or six years old) the limited immunity at birth is unlikely to significantly affect the outcomes of the model [3].

One of the simplest and most common methods for approximating μ is to assume that $1/\mu$ is the mean lifespan for the population. Thus individuals suffer natural mortality, independent of infection status at a total rate of μ. As illustrated by the model the number of deaths from each category is scaled to the portion of the population in that infection state. The population birth rate is then assumed to be μ in order to keep the population size constant.

With the inclusion of demography the formula for R_0 must be adjusted to account for the additional deaths. The new formula is:

$$R_0 = \frac{\beta}{g + \mu}.$$

With the reseeding of susceptible individuals over time, the dynamics of the model begin to appear similar to the S-I-S model from Section 1.1.4. If R_0 is greater than zero than the level of infection in the population will tend toward an endemic equilibrium. However, its path toward that equilibrium is quite different from the S-I-S model and involves a number of epidemics of decreasing size. Generally, the inclusion of demography will generate an oscillatory pattern of epidemics as was the case for the plague in Bombay, which Kermack and McKendrick modeled. If one looks at the course of epidemics over years than clear oscillatory dynamics emerge [5]. Alternatively, in the absence of infection, the demographic SIR model is an Immigration-Death process.

One important quantity that is unique to demographic models is the ability to determine average age at infection. For a basic demographic model the mean age of infection is:

$$A \approx \frac{1}{\mu(R_0 - 1)} \text{[35]}. \tag{1.8}$$

This relationship can be very useful in that it relates the parameters of the model to a measure of infection that is relatively easy to obtain. Age stratified seroprevalence data can be obtained from a careful sampling of the population. This information can then be used with Equation 1.8 to approximate the value of R_0 for the infection. Obtaining parameters based on population data improves the accuracy of the model.

Including Population Structure

Additionally, in attempting to make models more realistic one can incorporate population structure. This component is important because general mean-field mixing models treat the whole population as a collection of particles interacting at random where any individual in the population is equally likely to interact with any other individual. While this type of model is useful, it is not generally a good representation of real world behavior. Animals as varied as Tasmanian devils and humans display structure in their contact patterns [29]. When modeling human infections, accounting for this population structure improves the accuracy of the model. While these models still utilize mean-field mixing assumptions, with the inclusion of structure the mixing occurs within smaller groups in the population.

In human populations, individuals tend to interact primarily with a portion of the population, such as within their age demographic and much less outside of it. Therefore school age children are most likely to interact with other children their own age, with limited contact to adults primarily their parents and teachers. Alternatively, adults are more likely to interact and have close contact with other adults. Work has been done by a number of different groups to quantify these patterns with the development of social contact networks [42] [33]. These networks have been very useful in revealing tendencies in contact patterns, but they also have limitations based on the sample used to create the network.

One method for exploiting these tendencies in models is to create sub-groups within the models for different groups. Individuals interact with their demographic counterparts at different rates than they interact with other groups in the population. In these models children interact with other children their own age at a much greater level than they interact with adults and vice versus [11].

1.1.5 Pair Approximations

Another type of deterministic model that has seen increasing use involves incorporating the probabilities of the system being in a given state at any time. This type of model, which makes use of Kolmogorov forward equations, also known as master equations, is deterministic. It produces the same results every time as the differential equation based model does. However, models based on master equations can provide additional insight into the system because they do not provide a single solution for the state of the system, but instead offer a distribution of the likelihood of a given state of the model for any point in time.

The pair-approximation model focuses on pairs of individuals. The S-I-R formulation for the basic pair approximation model appears below

$$\begin{aligned}
[\dot{SS}] &= -2\tau[SSI] \\
[\dot{SI}] &= \tau([SSI] - [ISI] - [SI]) - g[SI] \\
[\dot{SR}] &= -\tau[RSI] + g[SI] \\
[\dot{II}] &= 2\tau([ISI] + [SI]) - 2g[II] \\
[\dot{IR}] &= \tau[RSI] + g([II] - [IR]).[36]
\end{aligned}$$

In this model the S, I, and R represent susceptible, infectious, and recovered individuals respectively. The symbol τ is the transmission rate across an edge equal to β/n where n is the mean number of connections per an individual. The recovery rate is represented by g. While there are nine distinct types of pairs in this model, on a symmetric network pairs such as$[SI]$ and $[IS]$ are equivalent. Additionally, since the sum over all pairs is constant the model is fully defined by just five pair-wise equations. The values of individuals within the model can still be defined in the pair-wise model

$$\begin{aligned}
[\dot{S}] &= -\tau[SI] \\
[\dot{I}] &= \tau[SI] - g[I] \\
[\dot{R}] &= g[I].
\end{aligned}$$

The resemblances to the basic mean-field pair based model should be clear from looking at the equations for individuals. However, the pair equations show that significantly more equations are required to represent this model than the basic model because of the need to define each potential pair. Thus where the addition of a state in the basic model requires only one additional equation, for the pair-based model additional states have a multiplicative affect.

Additionally, in the pair approximation model, one must know or assume facts about the structure of the population in order to solve the model. As can be seen above, this model includes not only relationships of pairs of individuals, but relationships of three individuals. In order to 'solve' the model, one must define these triples and potential correlations in terms of pairs and individuals. One technique for doing this is a moment closure approximation. With a moment closure approximation the ratio of open and closed triples, triangular clustering, must be considered. This relationship is important to the model because closed triples will have stronger correlations between the states of individuals than open triples. The use of the moment closure approximation incorporates the structure of the network into the model and allows for the definition of the triples in terms of pairs.

While the pair approximation model shows significant improvement in fit, which has helped prompt its more wide-spread use, it also requires assumptions which may not always prove to be accurate. The moment closure approximation requires an estimate of triangular clustering, which may not always be accurate or known. The model is closed at the level of triples and may not accurately represent infections on networks with strong degrees of quadratic or higher order clustering.

1.1.6 Stochastic Mean-field Models

While deterministic models are important for their ability to define a system clearly with a set of equations and the analysis that this allows, they also have significant limitations. Deterministic models produce the same answer every time they are run. They predict the same size epidemic and peak time, but in real life these values are not always reached and sometimes they are exceeded. The real-world offers variability in the exact course of an epidemic, it will be different every time. To incorporate this realism into mathematical representations of outbreaks, researchers incorporate stochasticity into models.

Noisy Deterministic Models

There exist several different methods for mimicking the uncertainty present in real-world systems. One method is to incorporate noise into the deterministic equations described in the earlier sections. This noise can be incorporated through observational uncertainty, that is recognizing the uncertainty inherent in the parameters selected for the model and the values it could be fitted to. In a real system the values for β and g will never be exact, but instead can vary within the epidemic and possess a degree of experimental uncertainty. Cases are often missed for infections in the real world, which can be asymptomatic or individuals can be misdiagnosed [31]. While these cases become unimportant in large systems, when populations are small they can have a significant impact.

The problem with these types of models is that they tend to differ significantly from their pure mean-field counterparts only at the beginning of an epidemic or when a population is small. However, in both of these circumstances the accuracy of the model itself is questionable. Thus the paradigm that when these noise inclusive deterministic models are most useful they are also the least accurate.

Gillespie's Algorithm

Variations of Gillespie's algorithm for simulating an epidemic are the most common form of stochastic model in use today. In this method probabilities are generated for certain events based on transition rates that appear very similar to the differential equation based models disscussed earlier. In this model random numbers are drawn to determine the time until the next event and what the event will be.

This type of model incorporates the uncertainty inherent in real-life systems. While a system may possess a value for the basic reproduction number much greater than one, a chance always exists that the epidemic never takes-off because the first individual recovers before passing on infection to anyone else. For small populations or at the beginning of an epidemic this type of model possesses the greatest degree of similarity to real life systems.

Additionally, this method is relatively flexible in incorporating additional states into the system. It is able to include latent states and other such modifications without drastically changing the computational power required for the model. In small populations it is a very feasible method for modeling.

However, when one wishes to build the model for very large populations, then it can become computationally expensive. The need to draw two random numbers for every event can become a drag on the model. With the computer power available today, however, this barrier is becoming less of a problem, which should allow for more complex models of large populations.

1.2 Limitations of mean-field models

As discussed earlier deterministic mean-field models have produced tremendous results in epidemiological research. They have provided insight into the basic dynamics of infection and sometimes produce very counterintuitive results as evidenced by the work on Rubella and the vaccination threshold [2]. However, they also have significant limitations in the ability to represent epidemics in small populations or the beginning of an outbreak. Differential equation based deterministic models also possess only a limited ability to address underlying relationships and structures in systems. With the increasing computational power available today stochastic models and pair based deterministic models developed from master equations have been able to overcome many of these limitations.

Both types of models can be run on networks that provide a complete underlying structure for a population. The inclusion of networks in models, however, has presented problems of its own. The concept of the basic reproduction number, which is very thoroughly developed for mean-field models does not translate easily to network based models.

1.2.1 Finding a threshold on a network

The basic reproduction number is a fundamental quantity in epidemiology that represents the threshold for when an epidemic will take-off. For the majority of work in disease modeling, determining the likelihood of an epidemic is a crucial point. This threshold is important in evaluating control measures and predicting final size. The formulation for R_0 in mean-field models is well settled, along with the formulation for the basic S-I-R and S-I-S models of $R_0 = \beta/g$, with modifications for models with additional states and parameters.

While the basic reproduction number has been well defined for mean-field models, its definition on network models is much less clear. As discussed in Section 2.1.3 the basic reproduction number for a basic S-I-R model on a simple network is different than the mean-field model. Furthermore, application of this work to the S-I-S model shows that unlike the mean-field case on a network the simple S-I-R and S-I-S models have different thresholds.

1.3 Further characteristics of R_0 on mean-field models

The goal of this work is to use characteristics of the basic reproduction number on mean-field models to investigate the threshold for when an epidemic will take off on different networks. Two specific characteristics of the mean-field definition of R_0 are of interest in this work.

1.3.1 Endemic level of infection

The first of these characteristics relates to the level of the endemic state of the S-I-S model and can be related to the system value of R_0. The endemic level of infection in an S-I-S system is related to the value of the basic reproduction number.

The endemic state is associated with the steady state of the system and thus the differential equations defining the system are each equal to zero. One can then rearrange the equation for dI/dt and set it equal to zero to get, $0 = (-\beta S + g)I$. If I were to equal zero there would be no disease in the population so the interest is in the alternative solution when $-\beta S + g = 0$. This equation can be rearranged to obtain a value for the number of susceptible individuals in the population, $S = g/\beta$. Substituting this value back into the definition of R_0 with a population size N, one obtains $R_0 = N/S$ [41]. A rearrangement of this equation produces, $1/R_0 = S/N$. Further rearrangement reveals the relationship $R_0 = 1/S_\infty$ when S_∞ is defined as a fraction of the population.

1.3.2 Fraction of epidemics that take-off

The other characteristic of the mean-field mixing model that is of interest in this work is the fraction of epidemics that take off in a stochastic system. When a stochastic model is seeded with a single infectious individual there is a significant probability that the infectious individual could recover, never pass on the infection and the epidemic would fail to take off. At the beginning of an epidemic the stochastic dynamics dominate and any set threshold is suspect. However, one can examine what happens near this threshold.

To do this one examines the probability of infection and removal events occurring

in a small time interval $(t, t+h)$. This probability is represented as:

$$\begin{aligned} \Pr\{(S,I) &\rightarrow (S-1, I+1)\} = \beta SIh \\ \Pr\{(S,I) &\rightarrow (S+1, I-1)\} = gIh. \end{aligned}$$

An approximate solution for the early stages of an epidemic can be obtained by noting that in the beginning of an epidemic with one initial infective the transition probabilities of βSI are $\beta(N-1)$, $\beta(N-2)2$, $\beta(N-3)3$, ..., where $N = S + I$. For small numbers of infectious individuals, I, these transition probabilities are approximately βNI. At the beginning of an epidemic these transition probabilities can be represented by a birth-death process. The "birth" rate is $\lambda = \beta N$, an infection event, and the "death" or recovery event rate is $\mu = g$. For a birth-death process the probability of extinction is:

$$q = \begin{cases} \frac{\mu}{\lambda} = \frac{g}{\beta N} = \frac{1}{R_0} & \text{if } \lambda > \mu, \text{ i.e. if } R_0 > 1 \\ 1 & \text{if } \lambda \leq \mu, \text{ i.e. if } R_0 \leq 1. \end{cases}$$

Based on this approximation of extinction in the early stages of an epidemic a stochastic threshold is approximated. If $R_0 \leq 1$ than a major outbreak cannot occur. For $R_0 > 1$ the probability of a major epidemic, $1 - \frac{1}{R_0}$. [50] The probability of a major outbreak is equivalent to the fraction of epidemics that take off when many simulations are run. Thus the fraction that take off of a large number of simulations is $F = 1 - \frac{1}{R_0}$ so $R_0 = \frac{1}{1-F}$ [50].

Chapter 2

Networks in Disease Modeling

2.1 Overview of Networks

Human and animal populations include structure and thus mass action models are limited. In order to develop models that accurately predict outbreaks in structured populations then that structure must be included in the model. One method currently being developed and increasingly used to incorporate this structure into models is network based models.

In the modern world networks appear just about everywhere. They appear in information systems, wildlife studies, food chains, and human behavior [29] [42] [33] [32]. Models built around understanding the spread of diseases on networks could have far reaching applications. Models developed to understand the spread of a human infection might be relevant to tracking a computer virus.

One of the chief advantages networks offer in modeling is that they limit the number of contacts an individual can have in the population which better reflects reality. Infections can only spread across pairs of susceptible and infectious individuals. This limitation changes some of the base values that one might derive from the mass action models.

2.1.1 Network Types

There are a number of different networks used in disease modeling. In this work six general network types are investigated. Each of these network types are described in detail below.

Poisson Distributed Random Networks

A poisson distributed random network is a random network with a binomial distribution, which is Poisson in the limit of a large number of nodes. This type of network was first discovered by Solomonoff and Rapoport and later independently by Erdos and Renyi [47].

In there 1951 paper Solomonoff and Rapoport postulated about 'random nets' [56]. They describe several problems in mathematical biology where random nets could occur and one of those problems was epidemiological modeling. Their discussion begins by considering the probability of transmission between each pair of individuals. Then they consider the number of individuals infected at a specific time t, in infinite time, or the probability that the entire population will be infected. If the probability of transmission is constant for all pairs of individuals, the same condition applied to the S-I-R mass action model, then the problem can be defined with a random net.

The paper describes 'weak connectivity' versus 'strong connectivity' in an epidemiological network. Weak connectivity represents the likely number of individuals who will contract the infection eventually, while strong connectivity is the probability that starting from a random point on the network every individual will ultimately succumb to infection [56]. These ideas relate to the ultimate connectivity of the network, with strong connectivity relating to a fully connected network and weak connectivity representing the size of the component associated with the node upon which the infection began.

Rapoport conducted further work in which he collected data on a model of students in a high school and created acquaintance chains based on the students responses. He then used random nets to trace the acquaintance network. The original data was then replicated with a random net trace. Rapoport also extended his work to nonrandom nets by incorporating "biases", the preference for certain type nodes to connect to like types, his results for both attempts show that only two parameters are enough to build a good fit to the original data [49].

Alternatively Erdos and Renyi developed a simple method to produce the network by taking a predetermined number of nodes n and connecting each pair with probability p. They define $G_{n,p}$ as the ensemble of all networks with these values where the probability of a given graph with m edges is $p^m(1-p)^{M-m}$ where $M = n(n-1)/2$ or the maximum number of edges that could be connected to a given node [47]. Thus when a random graph is created with n vertices and m edges, one is in fact choosing uniformly at random from all networks that possess this property.

The probability of choosing a specific network is $P(G) = 1/\Omega$, where Ω is the total number of simple graphs with n nodes and m edges. This fact is useful in determining generic properties of these networks. For example the diameter (the largest number of connections separating any two nodes on a network) of a random network with these conditions would be:

$$\langle l \rangle = \sum_G P(G) l(G) = \frac{1}{\Omega} \sum_G l(G).$$

This definition represents the mean diameter across all networks with n nodes and m edges. While some individual networks, might possess extremely large or small

diameters this calculation recovers the mean value [45]. It is useful for analytic formulation and addressing the most represenative scenario, which is useful in interpreting model results.

Poisson random networks are the most closely related network to the traditional mass action models of epidemiological modeling. By simply changing the probability p of connecting any pair of nodes in the network to one then the network is fully connected and a model run on it will recover the results of the mean-field model. All individuals have equal probability of interacting with any other individual in the population. Random graphs then should maintain some degree of similar results even when they are created to be sparser. This similarity is also a weakness of this type of network because like the mass action model it cannot incorporate complex structure, which is common in natural and human networks.

Poisson random graphs are not generally considered the best representations of networks that occur in the natural world. The distribution of edges across the network tends to be normal and lacks the extremes that are more common in networks, which appear in the real world. Additionally, their random distribution does not reflect the contact biases generally found between contacts on different networks.

Small-world

The small-world effect is most often associated in the popular mind to the idea of "six degrees of separation" discovered by Milgram in a famous series of experiments conducted in the 1960s. In Milgram's experiments individuals were asked to pass on a letter to an acquaintance in an attempt to get it to an ultimate target individual that was unknown to the original sender. While many of the letters were lost approximately a quarter of the letters reached their target individual. On average the letters that reached their target passed through only six individuals to reach the final recipient [57]. Thus the term "six degrees of separation" was coined years later by a playwright J. Guare [47].

Milgram was operating in the field of psychology, but his work illustrates a very significant property of many networks found in nature and human society, the mix of local and long-range connections. In small-world networks the majority of connections are local. However, if only local connections were present then the path length of the network would be extremely large. Small-world networks incorporate a few long range connections, which drastically reduce the path length across the networks. These long range connections allow an infection to skip to an entirely new part of a network or a letter to be passed to an individual in only a few steps. The network is both globally and locally efficient [38].

In a follow up to his original 1967 study, Miligram partnered with Travers to conduct a similar study, where participants were in two different geographical regions. One group was based in Nebraska, while another group lived in Boston. Both groups of participants were attempting to get a letter to an individual based in Boston. While the mean chain length was longer for letters being sent from Nebraska than

from Boston, on average only an extra 1.5 links was necessary to transport a letter more than 1,300 miles. This study shows even more firmly the effects of long-range jumps that are present in many networks. While the letters that began in the Boston area were generally within a 25 mile radius of the ultimate recipient, the highly local nature that characterizes most social contacts still required an average of 4.6 intermediaries before reaching the final recipient [58].

A systematic methodology for creating a network with the specific small-world properties was first put forth by Watts and Strogatz in 1998 [61]. They propose a network that can be oscillated between order and disorder by changing the probability of rewiring connections. The network starts as ring lattice of size n where each node has k edges. The ring lattice, also called a great circle, is discussed further in Section 2.1.1. In brief it is a circular shaped network where each individual is connected to its k nearest neighbors. Edges in the network are then rewired with probability p and the network can then be toggled between order and disorder by changing p. For $p = 0$ the network remains a ring lattice or great circle. Alternatively, $p = 1$ returns the network to a Poisson random graph with no underlying structure. Watts and Strogatz investigated the values of p between one and zero, which had previously not been studied [61].

To quantify their results Watts and Strogatz choose two measures of network connectivity, average path length $L(p)$ and the clustering coefficient $C(p)$. The average path length is the number of steps required to reach any two nodes in the network, while the clustering coefficient measures how interconnected local areas of the network are. In a highly clustered network individuals are very likely connected to their nearest neighbors. They then vary the value of p beginning with small values close to zero and moving toward one.

Even for very small values of p dramatic decreases in $L(p)$ occur. This effect shows that even a few long range connections in a network can have a dramatic affect. Conversely, the clustering coefficient, $C(p)$, showed very little decrease initially. As the initial ring lattice is highly clustered, the clustering coefficient can only decrease as its edges are removed and thus it can only scale linearly [61]. The result of this is that $L(p)$ drops rapidly while $C(p)$ remains practically unchanged. At the local level then, the small-world effect can be imperceptible, while having a large affect on a global scale. Based on their published results for this type of network structure, a value for p of approximately 0.01 appears to cause a large drop in average path length while maintaining a high level of clustering.

Further work conducted by Newman, Moore and Watts in 2000 developed an analytic formula which is exact in the case of large networks for determining the effect of adding connections or "short cuts" on the average path length in a small world network. A short cut is a connection randomly added between two points in the network. Their final scaling function appears as:

$$f(x) = \frac{1}{2\sqrt{x^2 + 2x}} tanh^{-1} \frac{x}{\sqrt{x^2 + 2x}},$$

where x is the number of connections added to the network [46]. This result is particularly relevant because it allows for a network creator to determine the exact decrease in path length desired and choose the number of "short cuts" required.

Scale-free Random Networks

Scale-free networks are extremely common in nature. Networks often appear random, but rarely do they follow the Poisson distribution discussed earlier. Instead real world networks generally exhibit a selection bias as they form. One of the earliest identified examples of this type of network, is a study of scientific citations conducted by Derek de Solla Price in 1965. He showed that papers with a larger number of citations at a given point in time are more likely to be cited later than a paper with fewer citations [48]. The papers with large numbers of citations are likely better papers, or simply more well known, but either way these few papers will garner many more citations than the majority of papers that receive only a few.

Scale-free networks generally possess a power law or exponential degree distribution of edges [47]. The majority of nodes in the network are only connected to a few other nodes, but certain key nodes possess a large number of edges.

In idealized form these networks possess some convenient properties that make them attractive for mathematical study. One example presented by Newman in his 2003 survey paper involves a scale-free network [47], with a power law distribution:

$$p_k = \begin{cases} 0 & \text{for } k = 0 \\ k^{-\alpha}/\zeta(\alpha) & \text{for } k \geq 1. \end{cases}$$

This network is defined by the degree distribution p_k, which is the fraction of nodes in the network with degree k, the constant α, and $\zeta(\alpha)$ is the Riemann function used as a normalizing constant. With this definition the phase transition point can be determined for the network, for when a giant component will occur. In this example the phase transition occurs at:

$$\zeta(\alpha - 2) = 2\zeta(\alpha - 1),$$

which solves to a critical value for α of $\alpha_c = 3.4788...$ Using this value the point at which a giant component will appear in the network can be determined. A giant component is when majority of the points in a network are joined together so that any point in the component can be reached from any other point. Further calculations found in Newman's paper [47] show that for values of α below two, the giant component encompasses the whole network. However, for values between $\alpha = 2$ and $\alpha_c = 3.4788...$ a giant component exists, but does not necessarily encompass the whole network, thus the network could be disconnected. The affect of this disconnect could be relevant for modeling an infection on the network, as some individuals could be inherently protected from infection by virtue of having no contact path from the

original infected individual. This type of disconnect could effect population level results for an infection model.

Price first recognized this type of network in his paper on scientific paper citations [48], but his work was not well known in the scientific community. It was not until a method for the development of generalized random networks was developed by Albert-Laszlo Barabasi years later that his method of network development now known as 'preferential attachment' was widely acknowledged [47].

Barabasi proposed a model for a network that removes two characteristics of previous networks, constant size and random attachment. In the previously discussed Erdos Renyi random network and even the small-world network of Watts and Strogatz, population sizes are held constant and individuals are connected or reconnected at random. In nature by contrast, networks are generally growing as new individuals are added to the population. Additionally, a new node added to a network is more likely to be connected to a well connected node than to a node with only a few edges.

To build this network he began with a small number of nodes m_0 and add a new node possessing m edges at every time step, with $m \leq m_0$. The 'preferential attachment' of the network is brought in by defining the probability, Π, of a new vertex connecting to a preexisting vertex i as dependent on the number of contacts, k_i, of vertex i so:

$$\Pi(k_i) = \frac{k_i}{\sum_j k_j}.$$

Over time this network develops a power-law distribution of edges, which is independent of the scale of the network [7]. Additionally, with his algorithm for creating a scale free network, it is easy to create a network of a specified size or with a set number of edges as the size of the network is simply $m_0 + t$ with mt edges.

One area of current research with these types of networks and particularly relevant to disease modeling is the resilience of the networks to attack. Networks with a highly skewed distribution of contacts are unique in being both resilient and vulnerable. Networks of this type such as the World Wide Web are very resilient against the random removal of nodes. However, they are quite vulnerable to the targeted removal of a few key nodes [10].

With epidemic prevention, one desires to break up the network. Techniques such as vaccination to remove nodes or social isolation to remove links could be targeted to specific key points instead of random. The use of scale-free networks that reflect real life systems to determine the affects of random or targeted vaccination is important for potential strategic implementation in the case of an outbreak.

K-regular Local Networks

Thus far the discussion of networks has tended from a purely random graph, toward more heterogeneous networks represented by the small-world and scale-free

networks. At the other end of the spectrum are highly structured, local networks. These networks are generally k-regular, all individuals have the same number of connections, and complete homogeneity. They are generally referred to as lattices. The great circle or ring lattice was mentioned earlier as a commonly used starting point for the small-world network. Other common lattice structures include a triangular lattice where each individual has three contacts or square lattice with four contacts per an individual. Occasionally these networks are constructed such that they are not homogeneous or k-regular on the boundaries, but in the limit of large networks this effect is negligible.

Square Lattice

The square lattice is a k-regular network and completely homogeneous, with the same degree of clustering for every node in the network. It has four contacts per a node. The only exception to it homogeneity would be when boundaries are present that would only be connected to two or three nodes instead of four.

Great Circle

A great circle network, is a network where every node is connected to its nearest neighbors. For the network to be a connected network every individual must be connected to at least its nearest neighbor. If more than two connections per a node are desired than edges can be added connecting each individual to its next nearest neighbors, repeating the process until the desired degree is reached [6].

K-regular Random Networks

K-regular random networks have the k-regular contact distribution of the lattice networks. However, instead of the pattern of contacts being completely local as with the various lattice networks, the contacts are randomly assigned across the network. This type of network is the only k-regular network type which can incorporate heterogeneity, but it can also be structured to approximately maintain homogeneity across the network. It can be described quite succinctly, as compared to the other random networks and does not have the same highly localized transmission that exists in the various lattice networks.

These types of networks are open to the same criticisms as the Poisson random because their regular distribution of contacts is not common in nature. However, they are useful mathematical tools for analytic analysis of the spread of an infection.

2.1.2 Other Characteristics of Networks

The networks described above represent a sampling of basic networks commonly used in disease modeling. They possess varying degrees of heterogeneity, structure, and clustering. While these are important characteristics there are a number of

other traits that can be considered in analyzing and creating networks that are not represented in these networks.

First, all of the networks described above are undirected, all contacts are bi-directional. Many networks are instead directed, with contacts traveling from one individual to another. Price's original model for scientific paper citations is such at network [48].

Additionally, in the physical world, rarely will a network have uniform strength across all edges. Instead edges possess varying weights with stronger and weaker connections. Weighting has been used in network models for a number of years. With the inclusion of weights, a simple homogeneous network such as the square lattice can be made extremely heterogeneous. The weighted lattice network can simply represent many of the trends seen in networks with more complex connection patterns. Heterogeneity in the weight of edges can cause patchiness in the spread of an epidemic and cause it to have a qualitatively different epidemic pattern than the fully connected network model would predict [52].

Additionally, in the networks considered above, all nodes are of the same type. In the natural world, many networks involve nodes of different types. The inclusion of multiple node types opens up a number of other characteristics that can be considered on a network. One example is the mixing pattern between different node types. The degree of mixing has a special name in social networks, it is called assortative mixing or homophily [47]. This term describes the amount that individuals in a social network interact with others of a different type. Types can be anything from age, race, or gender to income level, education status, occupation or any number of other determinants.

This type of mixing can be quantified with the "assortativity coefficient" Q:

$$Q = \frac{\sum_i P(i|i) - 1}{N - 1}$$

where N is the number of individuals in the population and $P(j|i)$ is a conditional probability representing the likelihood that a neighbor is of type j if a node is type i. When contacts in a network only interact with their own type, then the coefficient is zero. If they are randomly mixing than it is one [47].

The "preferential attachment" tendency of scale-free networks also mimics a special kind of assortative mixing, called degree correlations. These correlations develop in one of two ways. High degree individuals either prefer to associate with other high degree individuals or alternatively they prefer individuals with only a few contacts. Both situations lead to interesting network dynamics [47].

Finally, in networks with distinct social characteristics where individuals prefer to interact with like kinds, sub communities can develop within the larger population of the network.

2.1.3 Disease Modeling on Networks

A lot of work has been done in modeling epidemics on different types of networks. The following is a survey of a sampling of that work.

Correcting R_0 on the K-regular Random Network

In a 1999 paper Keeling presented a correction to the traditional formula for R_0 for an S-I-R epidemic on a K-regular random network [36]. His work illustrated the importance of the limiting nature of a sparse contact network in the ability of an epidemic to take-off. In mean field models infectious individuals have access to every other individual in the network, but in networks they have direct access only to their immediate contacts. If an individual has three contacts then once one neighbor is infected only two individuals are available to be infected by the second generation. Furthermore, after the initial generation of infection each new infected contact has at best one less contact available for infection. Thus the correlations in the contact network limit the spread of the infection.

In a network where triangular clustering is assumed to be zero throughout the network he finds a value for R_0 of:

$$R_0 = \left(1 - \frac{2}{n}\right)\frac{\beta}{g},$$

where n is the number of connections per a node and all other values are the same as the mean-field model [36]. The results Keeling obtained in this derivation for an S-I-R network differ from the results for the S-I-S system. Following the same derivation, with a transmission rate of τ, one obtains a value for R_0 for an S-I-S epidemic of:

$$R_0 = \frac{\beta - g - 2\tau + \sqrt{(g + 2\tau - \beta)^2 + 4g\beta}}{2g} [54].$$

This difference is interesting because the results for R_0 in the mass action models considered earlier are the same for the S-I-S and S-I-R systems. While interesting, the result is not necessarily surprising. If one considers the correlation discussion from earlier in this section, in an S-I-R system when an individual is infected they are permanently unavailable for infection, which could as correlations develop limit the ability of the infection to spread. Alternatively, in the S-I-S system after an individual recovers from infection it returns to the susceptible pool, which changes the limiting effects of the correlations seen in the S-I-R model.

Networks in Modeling Intervention Strategies

Networks often offer more realistic representations of population interaction than mean-field mixing models, making them inherently useful in modeling intervention

strategies for potential epidemics. One of the first challenges in building models to test intervention strategies is building an accurate network upon which to model. The networks discussed earlier are all idealized to some degree in order to build general conclusions about how epidemics behave on different networks. However, for an epidemiologist looking to model intervention strategies, accuracy is paramount, while generality and mathematical elegance are less important.

One method for building an accurate network is to collect data directly. The use of contact surveys is a common method for building networks of sexual contacts. It can also be used with more general social contact.

In 2008 Read et al. conducted a contact survey of 49 adults on 14 non-consecutive days [33]. They asked individuals to record all face to face encounters and as much as possible the name or a unique identifier for the contact so that repeat contacts could be accounted for. Participants also recorded the contact type and social context. While the results showed that in wider social contexts a lot of random contacts occur, in more intimate social settings the repeated close contacts are very measurable. With this data they built a weighted contact network on which epidemics could be simulated. One strength of their network is the ability to study the affect of contacts in different settings.

They used the network developed from the contact survey for simulating epidemics and evaluating control strategies. Because their survey included information on the strength of contacts, a weighted network was used to simulate an epidemic and determine the effects of vaccination strategies.

They tested targeted vaccination strategies for an epidemic that unchecked would likely affect approximately half of the population. The total degree of a node, the number of other nodes to which it links, total weight, the sum of the total degree multiplied by the effective strength of contacts, secondary cases, the expected number of individuals a contact is likely to infect, daily degree, and the number of contacts of an individual on a random day are all used as methods for targeting individuals for vaccination. In the end, all of these measures improved significantly on random vaccination as control strategies for preventing an outbreak [21]. Their work shows that detailed, precise knowledge of a social network is not necessary for targeted vaccinating to be effective. Even with approximate knowledge of basic parameters such as daily number of contacts, vaccinating individuals at higher risk for spreading an outbreak is a good use of limited resources.

Alternatively a group in the Sandia National Laboratories in the United States used a simulated network of a small community to test social distancing strategies for intervening in an epidemic where a vaccine or antidote may not be available. To simulate the community, the researchers used a combination of small random networks and a ring lattice. They attempted to estimate the life patterns of typical individuals in the community across all age groups. The network is extremely complex and specific. It is likely to be quite accurate for the community of 10,000 individuals it is meant to simulate, but its complexity points to the limitations of this strategy. While a small community can be modeled with relative accuracy, a

city of millions such as London or New York with many more people and much more diversity in types of individual behavior would be impossible to capture accurately. Additionally, one would need separate networks to represent each individual community.

For the small town modeled, this work showed that social distancing strategies are effective in limiting the spread of an epidemic. School closures and keeping children home can be especially effective in addressing influenza, which is primarily spread among young individuals. For an epidemic that is more likely to affect the adult population then work place closures would need to be considered. The affect of out lying communities that might not be employing the same strategies was also considered. While these communities might continue to import infectious contacts, prolonging the epidemic, it would ultimately be held to a manageable level for local hospitals [25]. This type of modeling is especially important because control strategies such as social distancing can carry very significant economic costs and be unpopular to implement. Their effectiveness needs to be convincingly proven through modeling before they are likely to be implemented in the face of an epidemic.

2.1.4 Network generation

Great circle network

An algorithm is written for generating each type of network. The generation of the great circle or ring lattice is very straight forward with no room for variation. Each individual numbered one through N, the size of the network, is connected to its n nearest neighbors. Special cases are used for the first and last few nodes to connect the ends of the network.

Square lattice network

A similar procedure is used for the square lattice network. In three-dimensional space the network would be shaped as a taurus so that it is k-regular across all nodes and does not have any boundary exceptions. Each individual is again numbered and then connected to their equivalent neighbors on either side and above and below. This network is defined by two parameters M and N, which when multiplied together determine the size of the network, or the population being modeled.

Poisson random network

The Poisson Random network is created using an existing algorithm in Matlab to create a sparse random network of size N with a Poisson distribution centered on a mean of n neighbors or contacts per an individual. The network created by the Matlab function `sprand` for sparse random network is then modified so that it is a network comprised solely of ones and zeros like the other networks and is not weighted.

K-regular random network

For the K-regular random network a procedure used by House and Keeling [30] adapted from Watts Strogatz small world is implemented. The algorithm begins with the creation of a ring lattice of size N, with n connections per a node. Then beginning with the first node and moving around the network, one of its connections is broken. A second node is chosen from the network at random that was not already connected to the first node, then one of this second node's connections is also selected and broken. The second chosen node is then rewired to the first and the two nodes that were broken are then rewired. This procedure is followed moving around the circle a total of five times. By that point the network is completely rewired such that connections are no longer local, but entirely random.

This procedure is similar to the algorithm proposed by Watts Strogatz for the original Small World network, however, this network must remain k-regular so where ever a node is wired one of the corresponding nodes for the receiving individual must also be broken and enough connections are rewired to lose all of the initial structure.

Small world network

The small world network is created using the original algorithm created by Watts and Strogatz, without the condition of k-regularity. A value for p, the fraction of nodes rewired, is set at $p = .1$ corresponding to the value found by Watts and Strogatz where local clustering is maintained while the average path length of the network is drastically reduced.

Scale free network

To build the scale free model the algorithm developed by Barabasi and Albert of preferential attachment is used. In the beginning a very small network with a few random connections is created. Then edges are added to the network at random, but with a higher probability of attaching to nodes with more connections already then nodes with fewer connections. As the network grows and more individuals become connected to the higher degree nodes then the probability of new nodes connecting to the original is very strong with lesser probability of connecting to any other given node.

Chapter 3

An investigation of the epidemic threshold phenomenon in complex networks

3.1 Problem Definition

As the previous discussion has shown, the basic reproduction number R_0 is a fundamental quantity in infectious disease modeling. Its main purpose is in informing whether or not an epidemic could take-off in a population. Additionally, networks are increasingly used to form more accurate views on how an infection would be likely to spread. Unfortunately, these two concepts do not merge well. The formulations for R_0 developed for mean-field models do not directly translate to models developed on networks.

Models built on networks incorporate limitations on the ability of an infection to transmit in a population and can include correlations between susceptible and infectious pairs. Various efforts have been made to define R_0 on networks. While these efforts have made inroads in defining R_0, a clear universal definition for a quantity equivalent to the basic reproduction number for networks in general has not been found.

In the earlier discussion, a number of relationships between R_0 and various characteristics of epidemics in different systems have been shown. Two of these characteristics are of interest in this work. The first characteristic is the relationship between R_0 and the endemic state of the S-I-S system. For the basic, mean-field S-I-S model, $R_0 = 1 - 1/I(\infty)$. This relationship comes from the deterministic model defined by the differential equations introduced in Section 1.1.4. The second relationship on the other hand comes from the stochastic model. The stochastic model is built around the idea that, in the real world, epidemics seeded with a single individual often do not take-off even if they have parameter values that make them likely to take-off. From this uncertainty, a relationship to the basic reproduction number can

be defined. The derivation is in Section 1.3.2 and the relationship is $R_0 = 1/(1-F)$.

As they have been defined for the mean-field model, both the endemic level of infection and the fraction of epidemics that take-off have direct relationships to the basic reproduction number and so one could postulate that they would have a relationship even when defined on a network for which the basic R_0 might not apply. By considering the extreme cases, a nice pattern begins to show. In the case where the probability of an infection taking-off is zero, the mean number of infectious individuals in the steady state must also equal zero. Conversely, when the probability of take-off is one, the value of the recovery parameter g must be zero. If g is not equal to zero than there would exist some probability of an infectious individual recovering and not passing on the infection. Since g is zero when the infection has been established and is in its steady state, then the entire population will be infected, corresponding to a fraction infected of one. Thus, in a network with one strongly connected giant component, defined in Section 2.1.1, a relation between the fraction that take-off and the endemic level of an S-I-S system must pass through the points $(0, 0)$ and $(1, 1)$. The interest of this work is to examine the relationship between these two quantities in different networks and to determine if this relationship could bring insight into the problem of defining a threshold for when an epidemic can take-off. This relationship has been shown to hold for the great circle network [44].

3.2 Method for investigation

The approach taken here is to use two simulators based on Gillespie's algorithm to run stochastic simulations of S-I-S epidemics on six different general networks. One simulator is formulated to run one long simulation in order to obtain an endemic value for a given parameter set and network. The other simulator runs a large number of simulations until a cut-off value where the infection is endemic in the population and considered to have taken off. This second simulator then outputs the size of each epidemic run so that the number of epidemics that take-off can be determined.

For this work six networks are chosen that represent different types and levels of heterogeneity and structure. The six networks chosen are: great circle, lattice, k-regular random, Poisson random, small-world, and scale-free. The great circle, lattice, and k-regular networks each have four contacts per an individual, and the Poisson random and small-world networks have a mean of four contacts across the network. By its nature the scale-free network has a much larger distribution of contacts than any of the other networks. The great circle and lattice networks are constructed to be completely homogeneous with no boundaries and highly structured, while the scale-free network is extremely heterogeneous and unstructured. Considering a range of networks should allow for insight into any patterns that might be distinct to one type of network and not universal.

A representative network of each type is created and then the same network is

used repeatedly in all simulations in order to avoid any variance based on random differences between different individual networks in the same class. All networks consist of 20,000 individuals. This network size is deemed as optimal size in order to overcome a challenge for defining the endemic level near the threshold, but still retain computational efficiency.

All results for the fraction of epidemics that take-off are based on running one million simulations and results for the endemic level are developed after running the endemic simulator for four million events. The large number of simulations run is to ensure the degree of accuracy required to obtain a clear relationship free from noise. The code used to generate the simulations for the endemic level and fraction that take-off is attached as Appendices A and B.

3.2.1 Challenges of Investigation

Several challenges arise in properly determining both the endemic levels and the fraction that take off on the different networks.

Determining the endemic level

The first challenge is simply to define the endemic level based on a simulation of an outbreak. In the deterministic, differential equation based models the endemic level is a single value, but in a stochastic simulation the exact level of infection in the population is constantly changing. The value oscillates around the steady state, but judgment must be used to determine when the infection has reached its steady state. For the higher levels of infection this point is very clear, as illustrated in Figure 3.1. For low values of infection determining exactly when an infection is endemic

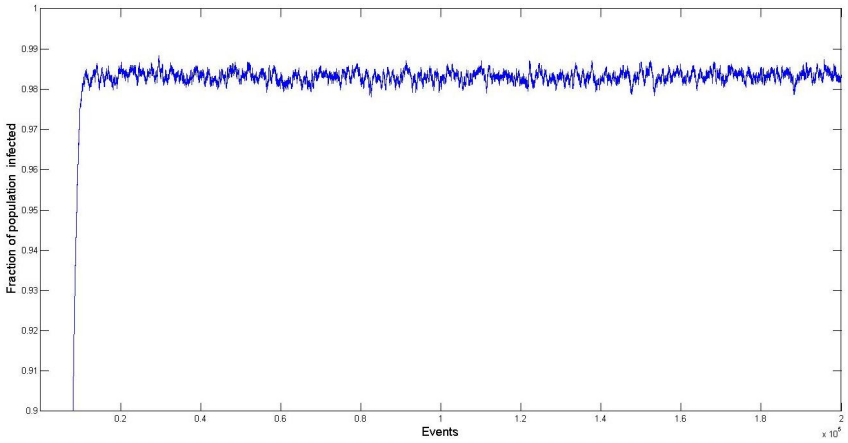

Figure 3.1: A sample of a network with a high infection rate. The level of infection quickly reaches a point where it stabilizes around the assumed endemic level.

is challenging. Figure 3.2 illustrates this challenge as the epidemic appears to be

decreasing to what might be a steady state, but it is not very clear. One way to

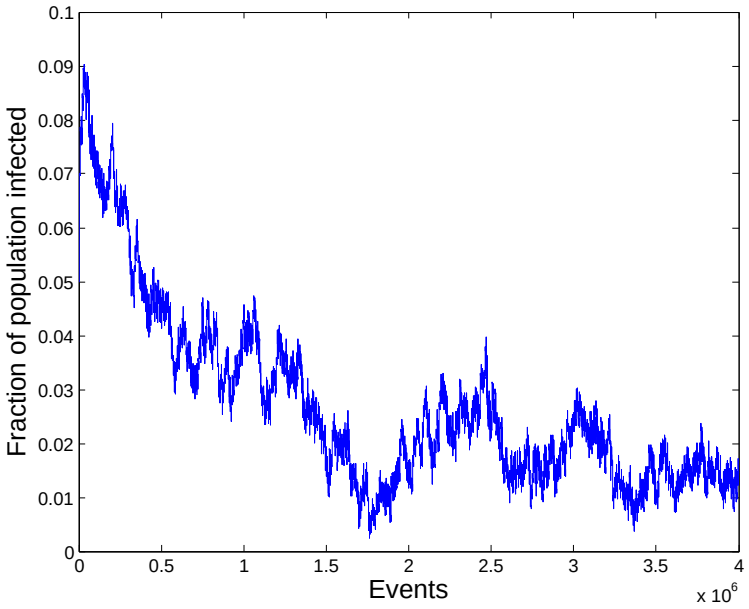

Figure 3.2: This infection has a very low infection rate and whether it has stabilized to an equialibrium is unclear.

attempt to get a clearer view is to run the simulation for more events. In this work events were used instead of set times, however, the varying time between events was accounted for in the compilation of the data. However for low values of infection this exacerbates the problem of stochastic fade out. As Figure 3.3 illustrates if an infection is oscillating around a small enough value then it is highly susceptible to reaching zero infectives after a short time, which kills the epidemic.

Stochastic fade-out

Stochastic fade-out occurs when an infection is endemic in a population, but at such a low level that it randomly dies out. If run long enough, all SIS epidemics with $g > 0$ on a closed population of size N will eventually go extinct. Stochastic fade-out is problematic to this work when it occurs before an endemic level can be ascertained. This problem can be avoided by automatically re-seeding an infection if it ever reaches zero in the population. However, this method is not desirable for this work as it might affect the value obtained for the endemic level. Instead the size of the network is an important consideration.

As the level of infection in a population is not an absolute value, but instead a fraction of the population a larger population allows for the consideration of smaller fractions without the problem of stochastic fade out. This desire for a larger network to prevent stochastic fade-out must be balanced against the need to keep the networks

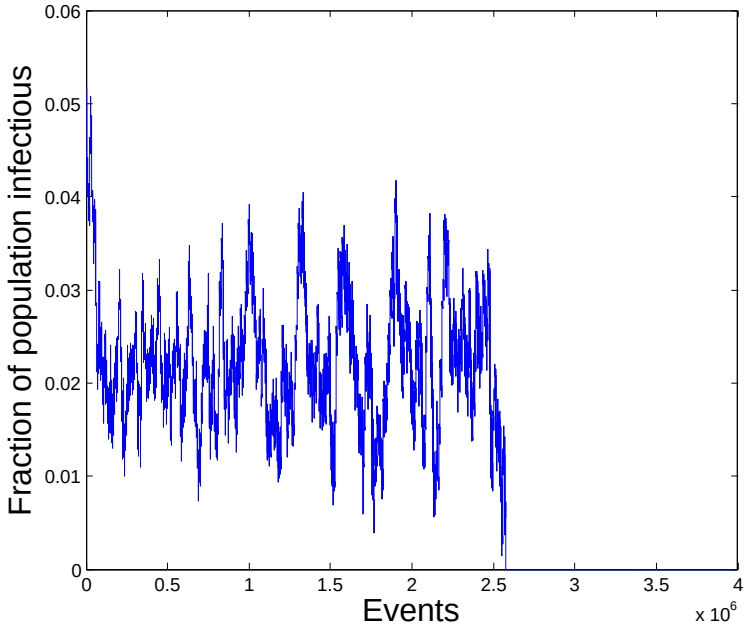

Figure 3.3: An epidemic, which has sucumbed to stochastic fade-out.

at a reasonable level for computation speed. To this end three different networks sizes were tested to find an optimal size. Networks of 10,000, 20,000, and 30,000 were all tested. Figure 3.4 shows the results of runs for the stochastic system on one network of each size. The network of 20,000 was determined to be optimal because it had a marked improvement in how small of values could be tested without fadeout over the 10,000 node network while the 30,000 node network did not offer noticeable further improvement.

Determining when an epidemic has taken-off

Another challenge arises in determining exactly when an epidemic has taken-off. The determinant for this work is the standard of bi-modal behavior. If the results of the large number of runs is bi-modal then there is a clear gap between small epidemics that die out quickly and those that become entrenched in the population, as Figure 3.5 shows. As with the endemic level, this distinction is very clear for the higher values of infection illustrated by Figure 3.5, but it is more difficult to determine as the infection level nears the threshold shown in Figure 3.6. When one moves even closer to the threshold the distinction disappears completely as Figure 3.7 shows. Ultimately, by raising the cut-off for the simulator to a high enough value bi-modal behavior can be determined to very low values of infection on the different networks.

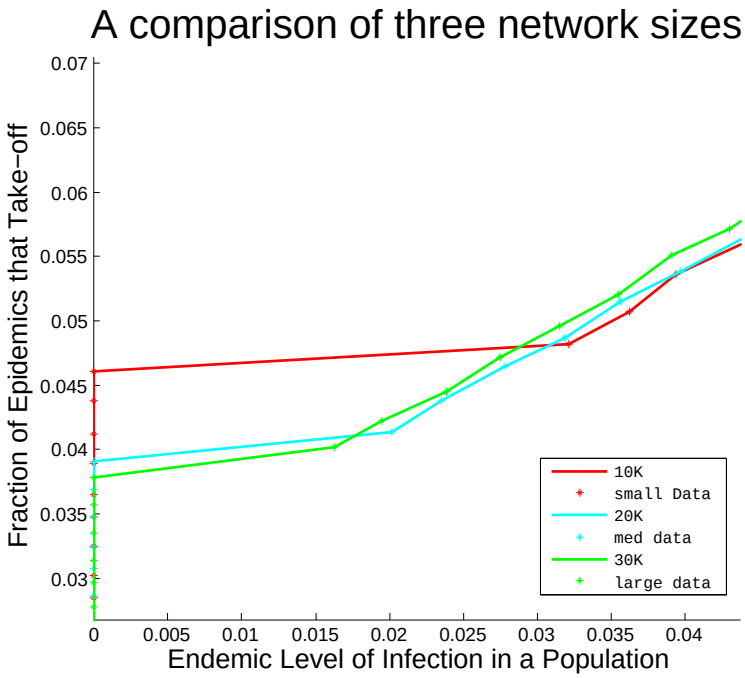

Figure 3.4: This graph illustrates the effect of size on point of stochastic fade-out. All three networks showed a small amount of noise at these low values, but the larger networks of 20,000 and 30,000 individuals appeared to to reach lower values for infection rate without fading out.

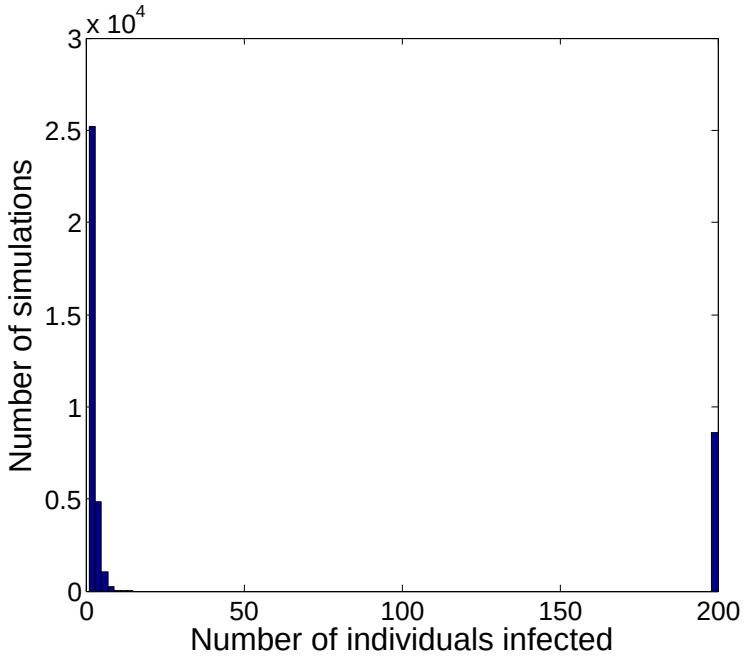

Figure 3.5: This graph illustrates the results of a network that was deemed bi-modal. Note the large gap between the number of individuals infected in epidemics that took off versus those that did not.

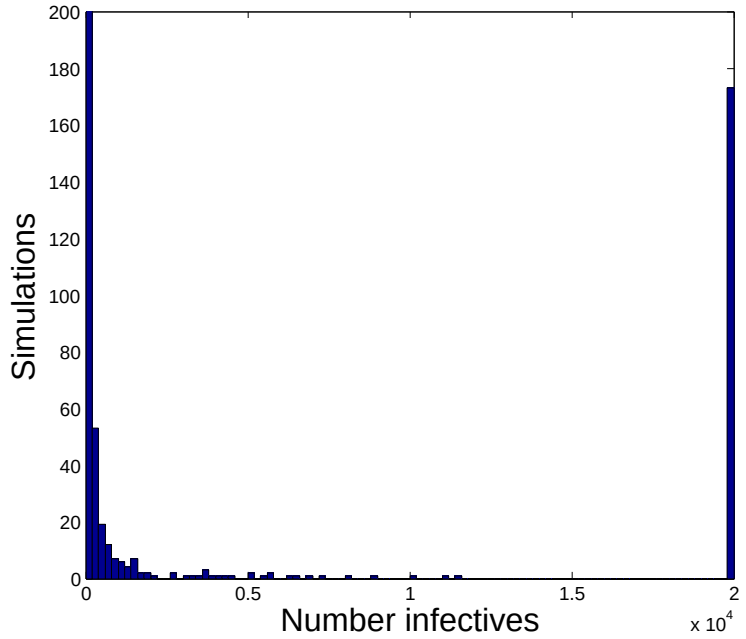

Figure 3.6: As one attempts to model lower infection rates the distinction between epidemics that took-off and those that died becomes less clear.

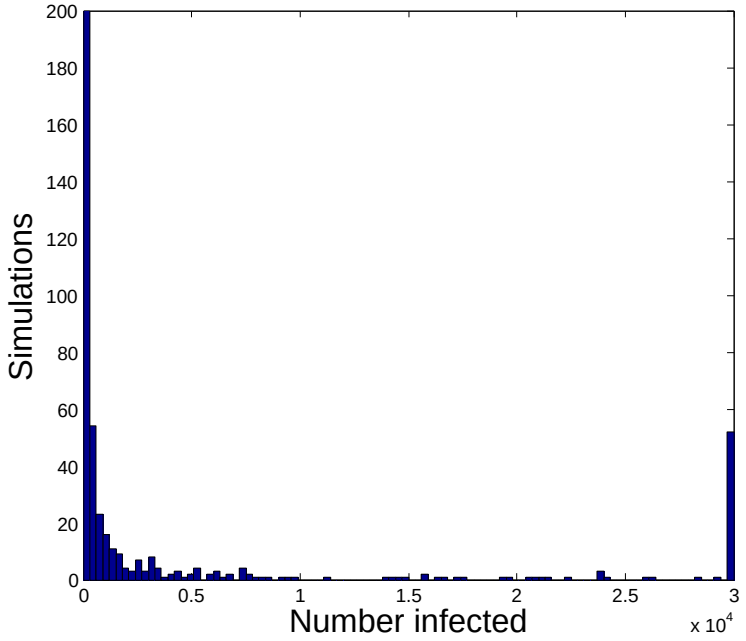

Figure 3.7: In a network close to the threshold there is no clear distinction between epidemics that took off and those that died.

3.3 Results

In each of the networks the same pattern appears. Each of these networks show a linear relationship between the endemic level of infection and the fraction of epidemics that take-off.

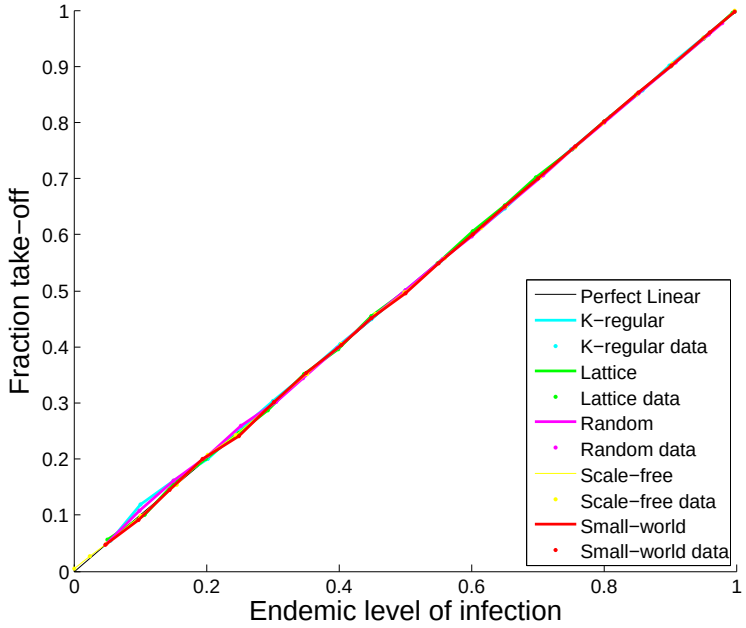

Figure 3.8: The results of the fraction of epidemics that take-off plotted against the endemic level of infection.

As Figure 3.8 shows, the linear relationship holds through the spectrum of parameter values for each network. The cut-off point where the relationship can no longer be ascertained, however, does vary for each of the networks. This variation is likely caused by the differing thresholds existent on each network. Figure 3.9illustrates the difference between the endemic level of infection and fraction of epidemics that take-off throughout the parameter spectrum. It shows the noise that is present in the current data and how different networks can only be measured to different infection levels. At a point in each of the networks results could not be found do to stochastic fade-out and the definition of an epidemic take-off becoming murky do to the loss of bi-modal behavior. Addressing both of these issues would allow for examining the relationship even closer to the threshold and closer to the $(0, 0)$ point.

The difference in the threshold for each of the networks is not surprising because the structure of the network effects the point at which an infection is sustainable in a population [36]. While a mean-field model offers $N - 1$ opportunities for direct contact, in a network an individual can only directly contact the n individuals it is connected to, which is often a very small fraction of the population. Additionally,

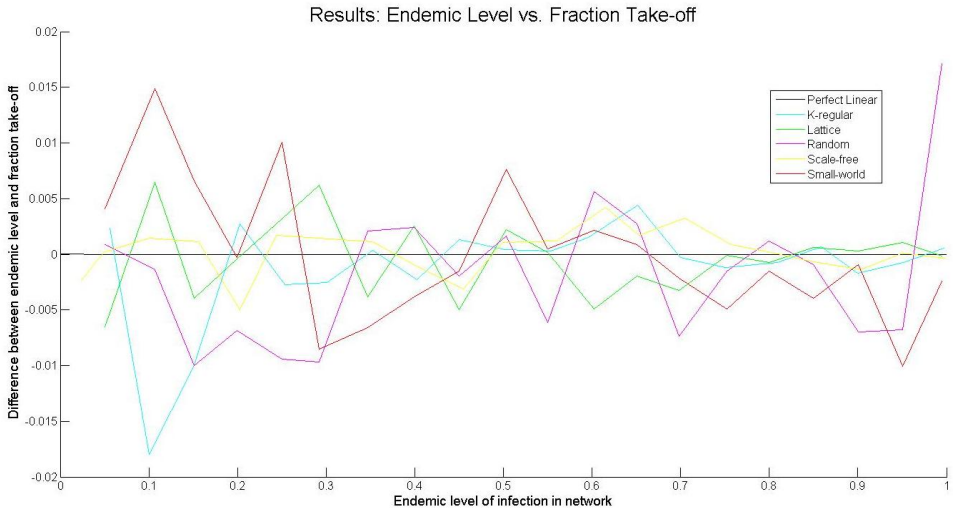

Figure 3.9: A graph of the difference between the endemic level and fraction of epidemics that take-off at different infection rates.

the degree of correlation between neighbors that is emphasized in pair-based models varies significantly by network. In highly clustered networks such as the great circle or square lattice the spread of the infection is limited by the boundaries of the spreading infection and the need to have contact with a susceptible individual in order to pass on infection. In random or small world networks where the average path length on the network is much shorter it is possible for an epidemic to spread more quickly throughout the network as it is not limited to one section but can instead move throughout.

3.4 Application to real-world networks

While this work appears to hold well in all five of the networks chosen which represent varying degrees of heterogeneity and clustering, the real test of this relationship would be on a much more heterogeneous network, particularly a network generated from data, which would not follow exactly any of the standard network attributes existent in all of the above networks. While the linear relationship has held on the scale-free network, which is very heterogeneous, it is still very simple and idealized compared to many data derived networks.

To test this assertion a network is selected, which is about as complex as can be found. It is heterogeneous, asymmetric, weighted, and has multiple disjointed components. This network, a representation of relationships between fisheries in the UK [34], was chosen because it is completely opposite of the networks studied previously. All networks studied thus far are symmetric, unweighted, and have a

single giant component. Figure 3.10 shows the results of a few initial runs on this network. The initial results are not promising as the linear relationship appears to completely disappear especially at higher values of R_0.

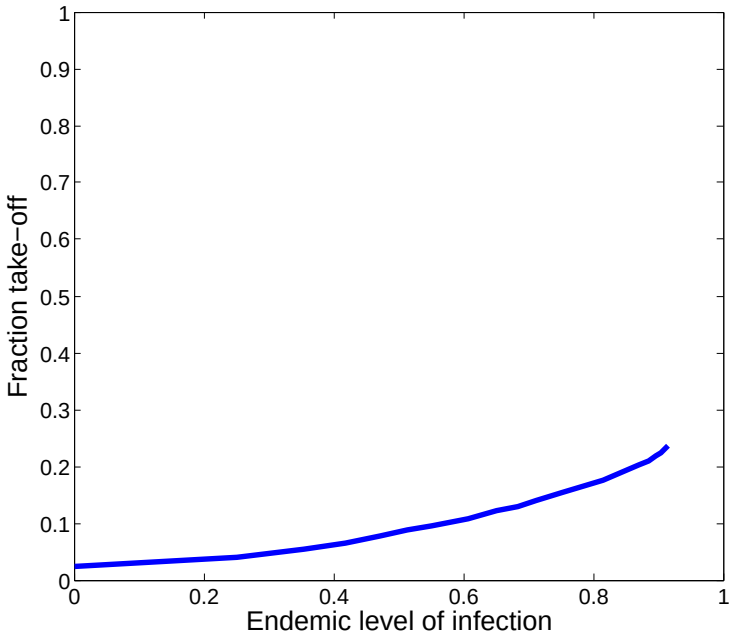

Figure 3.10: Initial results for a real-world network do not appear to show the linear relationship demonstrated on the idealized networks.

This limited investigation leads to the conclusion that the connectivity of the network is a condition for this relationship on asymmetric networks. In asymmetric networks where individuals have directed edges it is possible to have nodes that can be reached from one direction and thus would be possibly infected in the endemic state but, if they have no connections directed outward into the rest of the network, then they are unable to pass on the infection if it was seeded with that individual. Figure 3.11 illustrates an example of such a disjointed asymmetric network. An epidemic seeded with individuals 4 or 8 would take-off with probability 0. However, in an endemic state it is very possible for them to be infectious. This type of property likely is the cause for the skewed initial results on the asymmetric network of fisheries tested [34]. A number of nodes exist at the end of chains where they do not have the ability to initiate an infection even while they can be infectious in the endemic state.

If we would like to examine the possibility of a one-to-one relationship than it is necessary to identify the giant component within this network. In the giant component any node can be reached from any other node via some path through the network. In figure 3.11 all nodes are in the giant component except for nodes 4 and

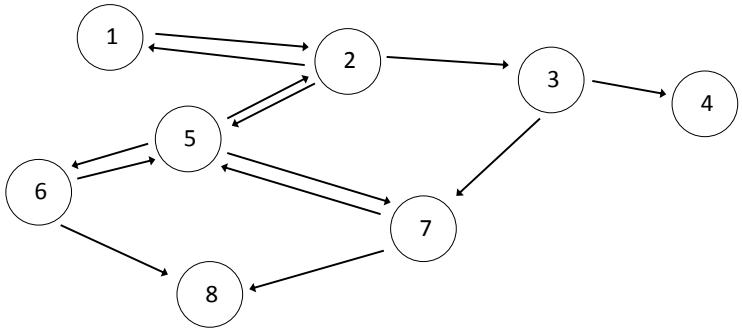

Figure 3.11: An illustration of an asymmetric network.

8 discussed earlier.

3.5 Areas for further development

There are several areas for further development of this work.

3.5.1 Determining Source of "Wobbles"

The term "near linear" is used because while there appears to be a clear linear relationship across all networks, it contains noise whose source has yet to be identified. Figure 3.8 illustrates the results for each of the six networks with a straight line representing the perfect linear relationship, which can be used for comparison.

With this significant number of simulations run, the continued presence of noise in the linear relationship can only be put down to a yet undetected bug in the simulator program or a real artifact of the system that is currently not understood. As follow up work done by another researcher did not include "wobbles" and thus they are determined to be the result of a bug in the code.

3.5.2 Focus on the individual level

The first area for further development is in examining correlations between individuals in the network. What is the degree of correlation between the likelihood that an individual is infected in the endemic state and the likelihood of an epidemic taking off seeded from that individual? While some amount of agreement seems likely, whether a clear pattern or relationship can be established deserves deep consideration.

This examination could be particularly relevant because it might help bring insight into the role that different key areas in a network, such as "super spreaders" in a scale free network might have on the persistence of an infection in the endemic state and the possibility of initiating an epidemic. It might be possible that in the

initial stages of an epidemic, if certain areas could be protected, then the infection would not be allowed to become endemic in the population.

3.5.3 Pushing to the threshold

Finally, as this work appears to show a clear linear relationship between the endemic level and the likelihood of an epidemic taking off, pushing this relationship closer to the threshold is desirable. However, in order to show the validity of the relationship at values very close to the threshold of R_0 further investigation is required. Clearer definitions of what it means for an epidemic to take-off and to be established in a population must be created or much larger networks must be used to obtain a clearer view of behaviors near the threshold.

Defining bi-modal behavior

The current definition for whether an epidemic has taken off or not, as discussed in Section 3.2.1, is reliant on bi-modal behavior of the system where epidemics either clearly do not take-off and only a few individuals are infected or they become entrenched and a large number of individuals are infected. The challenge of this condition is that there is not a definitive, quantitative method for distinguishing the mode of an individual epidemic when an overlap between the modes exists. In the work conducted here a judgment is made by the researcher as to which outbreaks belong to each mode. For larger values of R_0 this behavior is very distinct, but for lower values it is very much a judgment call. A different judgment might lead to a different answer.

One possibility for attempting to draw a clearer picture of bi-modal behavior closer to the threshold is to attempt to model in successively larger networks. The use of larger networks might help prevent stochastic fade out that comes from an infection that has reached an endemic state, but the amplitudes of its oscillations around the endemic level exceed the number of individuals infected at the endemic level. This fade out is likely responsible for a number of epidemics that appear to infect a significant number of individuals and be entrenched in the population, but fadeout before reaching the defined cutoff to determine bi-modal behavior. If the population size is larger, then the absolute endemic level is raised so that the oscillations are less likely to hit zero and cause stochastic fadeouts.

However, it is also important to consider that at some point the loss of bi-modal behavior will correspond with the instability of the endemic steady state do to reaching and passing the disease threshold. At this point corresponding to $R_0 \leq 1$ than by definition an epidemic cannot take-off in the population corresponding to the point $(0, 0)$.

Defining endemic level

A similar problem exists in measuring the endemic level of infection. Not only does one run into the issue of stochastic fade-out as mentioned in Section 3.2.1, but the definition of the steady-state for a stochastic system is not clear. For higher values of the basic reproduction number this state is clear from examining a graph and is reached quickly. However, for parameter values near the threshold, judgment is involved in attempting to discern when an infection has reached its endemic state.

The challenge of stochastic fade-out is that sometimes it is unclear if an infection with certain parameter values has a potentially valid steady state that should be measured or if an infection is just very slow in fading out and no steady state in fact exists. This challenge could be addressed by running simulations near the threshold for longer periods of time in larger networks where stochastic fadeouts are less likely. Additionally, comparisons might be made back to the fraction of epidemics that take-off. If bi-modal behavior has been lost in that system for a given set of parameter values than it is likely that even if there appears to be the possibility of an endemic steady state, it is unlikely to be stable.

3.5.4 Attempting different models

This work has been attempted on the basic S-I-S model because it is a simplistic model and possesses a steady state. As has already been shown by comparing the original R_0 correction presented by Keeling in his 1999 paper for the S-I-R model to a correction derived from the same process for the S-I-S model in Section 2.1.3, these models differ in their thresholds. Thus the relationship between an endemic level determined by an S-I-S model and an epidemic take-off threshold determined from the S-I-R model will not be one to one, but it could still be defined and useful in attempting to discern the likelihood of an outbreak with a given set of parameters

Another model that might be worth investigating is an S-I-R model with demography. Unlike the basic model, the S-I-R model with demography does eventually reach a steady state, but it tends to oscillate a lot more in reaching the steady state than the S-I-S model and will still have periods of low disease prevalence intermixed with epidemics. Again however, if a relationship could be determined it is likely to be useful in a real world context. Additionally, S-I-R models with demography are more realistic than the basic models so it is closer to a real world system.

Beyond these examples there are any number of other systems which could be tested. Models with additional states such as the S-E-I-R model, which includes the latent period, or S-I-R-S model, with waning immunity, might both prove interesting. While the relationships might not be linear they could still be useful. Only testing of these additional examples will be able to determine if the relationship shown here can be applied to more complex models in addition to differing networks.

3.6 Conclusions

The goal of this research was to determine the relationship between the endemic level of infection in a population and the fraction of epidemics that take-off on various networks. Results obtained so far appear to support the hypothesis that there is a relationship, and the nature of this relationship appears to be linear. While this result is not entirely unexpected it is nice that it appears to hold for all of the networks despite extreme examples of localization illustrated by the great circle and square lattice and heterogeneity illustrated by the scale free network. As the results have held across this variety of networks, the probability of them holding on further types of networks is very high.

These results could useful in practice if the results are proved to be robust across extreme real-world networks. However there are limitations in the real world applications as early results from the asymmetric fish network show. For directed networks the linear relationship is only likely to hold for the giant component in the network. While the linear relationship may not hold for the entire network in cases of directed networks where the network is not covered by the giant component, the measure of individuals might still prove useful. These investigations would further solidify the robustness of this relationship between the endemic level of infection and the likelihood of an epidemic taking off.

Appendix A

MATLAB code for simulating fraction of epidemics that take-off

```
% clear; close all
profile on

%Transmission network generation
k=5;
N=500;
g=1;


tic

% T=make_homogeneous_symmetric_network(N,k);%note that this does not always converge to a
solution
% T=make_random_network(N,k);%
% T=make_lattice_network(M,N);
% T=make_scale_free(N,k); %k is min number contacts per individual
% T=make_small_world;

% Predicted_R0=tau*k/g

No_sims=2000;

outMat=[];

tau=[.31];
no_trials=length(tau);
Frac_take=zeros(2,length(tau));
for i=1:no_trials
    T=T~=0;
    T=tau(i).*T;
FracTake=SIS_frac_sim(T,g,No_sims);
Frac_take(:,i)=[tau(i); FracTake];
end
Frac_take
toc
profile off
```

```
function FracTake=SIS_frac_sim(T,g,No_sims)

Fail_Vec=[]; I0=randsample(length(T(:,1)),1);

for i=1:No_sims
       Fail=simulate(T,I0,g);
       Fail_Vec=[Fail_Vec Fail];
       FracTake=(length(Fail_Vec)-sum(Fail_Vec))/length(Fail_Vec);
end

function Fail=simulate(T,I0,g)
Fail=[]; No=length(T(:,1));

I_vec=zeros(1,No);I_vec(I0)=1;
S_vec=ones(1,No);S_vec(I0)=0;
S_tot=sum(S_vec);I_tot=sum(I_vec);

M=I_vec*T; P_vec=S_vec.*M; P=max(sum(P_vec),eps);

current_time=0; infection_time=current_time+exprnd(1/P);

R=max(g*sum(I_vec),eps); recovery_time=current_time+exprnd(1/R);
event=0; t_max=1000; I_max=20;

while I_tot<I_max
event=event+1;
    if I_tot>0
    %find next event
    [time_to_next_event,event_type]=min([infection_time,recovery_time,t_max+1]);
    current_time=time_to_next_event;

    if event_type==1 %infection
        A=P_vec/P;
        edges=[0,cumsum(A)];
        [F,farm_index]=histc(rand,edges);
        S_vec(farm_index)=0; I_vec(farm_index)=1;
        M=M+T(farm_index,:);
        P_vec=max(S_vec.*M,0); P=max(sum(P_vec),eps);
        infection_time=current_time+exprnd(1/P);
        R=max(g*sum(I_vec),eps);
        recovery_time=current_time+exprnd(1/R);
        S_tot=S_tot-1; I_tot=I_tot+1;
    elseif event_type==2 %recovery
        A=I_vec/sum(I_vec);
        edges=[0,cumsum(A)];
        [F,farm_index]=histc(rand,edges);
        I_vec(farm_index)=0; S_vec(farm_index)=1;
        M=M-T(farm_index,:);
        P_vec=max(S_vec.*M,0); P=max(sum(P_vec),eps);
        infection_time=current_time+exprnd(1/P);
        R=max(g*sum(I_vec),eps);
        recovery_time=current_time+exprnd(1/R);
        I_tot=I_tot-1;  S_tot=S_tot+1;
    end
    else
       Fail=1;
       return
    end
end

if     I_tot==I_max;  Fail=0;  end
```

Appendix B

MATLAB code for simulating endemic level of infection

```
clear; close all
profile on

%Transmission network generation
k=5;
N=2000;
g=1;


tic


T=make_homogeneous_symmetric_network(N,k);%note that this does not always converge to a
solution
% T=make_random_network(N,k);%
% T=make_lattice_network(M,N);
% T=make_scale_free(N,k); %k is min number contacts per individual
% T=make_small_world;

% Predicted_R0=tau*k/g

event_max=10*length(T);
startCount=1000;

outMat=[];

tau=[.29];
no_trials=length(tau);
infMat=zeros(2,length(tau));
for i=1:no_trials
    T=T~=0;
    T=tau(i).*T;
[out inf]=steady_state_sim(T,g,event_max,startCount);
outMat=[outMat out(:,3)];
infMat(:,i)=[tau(i); inf];
end
infMat
toc
profile off
```

```
function [out inf]=steady_state_sim(T,g,event_max,startCount)

N=length(T);
I0=randsample(length(T(:,1)),.05*N); %The second value is the number of individuals
seeding the epidemic.
No=length(T(:,1));

I_vec=zeros(1,No);I_vec(I0)=1;
S_vec=ones(1,No);S_vec(I0)=0;
S_tot=sum(S_vec);I_tot=sum(I_vec);

M=I_vec*T; P_vec=S_vec.*M; P=max(sum(P_vec),eps);

current_time=0;

infection_time=current_time+exprnd(1/P);

R=max(g*sum(I_vec),eps); recovery_time=current_time+exprnd(1/R);
event=0; t_max=2*event_max;

out=zeros(event_max,3);
while event<event_max && I_tot~=0
    event=event+1;
    out(event,:)=[current_time,S_tot,I_tot];

    %find next event
    [time_to_next_event,event_type]=min([infection_time,recovery_time,t_max+1]);

    current_time=time_to_next_event;

    if event_type==1 %infection
        A=P_vec/P;
        edges=[0,cumsum(A)];
        [F,farm_index]=histc(rand,edges);
        S_vec(farm_index)=0; I_vec(farm_index)=1;
        M=M+T(farm_index,:);
        P_vec=max(S_vec.*M,0); P=max(sum(P_vec),eps);
        infection_time=current_time+exprnd(1/P);
        R=max(g*sum(I_vec),eps);
        recovery_time=current_time+exprnd(1/R);
        S_tot=S_tot-1; I_tot=I_tot+1;
    elseif event_type==2 %recovery
        A=I_vec/sum(I_vec);
        edges=[0,cumsum(A)];
        [F,farm_index]=histc(rand,edges);
        I_vec(farm_index)=0; S_vec(farm_index)=1;
        M=M-T(farm_index,:);
        P_vec=max(S_vec.*M,0); P=max(sum(P_vec),eps);
        infection_time=current_time+exprnd(1/P);
        R=max(g*sum(I_vec),eps);
        recovery_time=current_time+exprnd(1/R);
        I_tot=I_tot-1; S_tot=S_tot+1;
    end
end
if I_tot==0
    out='ERROR'
    return
end
outInfVec=out(:,3);
outInfVec=outInfVec(startCount:event_max);
inf=mean(outInfVec)/N;
```

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