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On-the-fly Modelling and Prediction of Epidemic Phenomena

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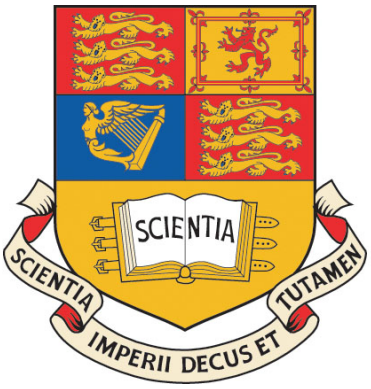

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Abstract

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I would like to thank all my mates who without my mates I would not be able to do my project, like at all.

1 Introduction

1.1 Overview

This project provides a framework with which the dynamics of an epidemic event composed of multiple, overlapping sub-epidemics may be modelled and forecasted in real time. We aim to provide an optimised model fit to a given set of epidemic data where all model parameters are assumed to be unknown. The challenge of considering various candidate model types is also considered. Unlike previous approaches, the presented framework is implemented in object oriented style using a general purpose programming language, allowing improved customisability and speed. Furthermore, we attempt to implement a maximum likelihood based fitting procedure, which has previously only been considered for single epidemic models.

1.2 Motivation

Epidemic spreading processes can be observed in a wide range of fields. Any type of interaction between individuals will allow the propogation of ideas or parasites through a population, with some spreading processes arising unexpectedly in excess of baackground levels. In the case of infectious diseases, such outbreaks are termed epidemics. Indeed, many significant historical events have been heavily influenced by epidemics, and the WHO estimates that infectious diseases account for more than 13 million deaths per year.[1] It is therefore no wonder that epidemiology, the study of the mechanisms and population dynamics of infectious diseases, has become a central field of research. With the advancement of computing technology and methodology, new opportunities to develop complex mathematical and computational models of real-time epidemics have emerged.

Although the study of infectious disease spread continues to be an area of particular research focus, globalisation and advances in communication technologies have led to a new and rapidly developing type of internet based epidemic. With the entire world connected online, new ideas, trends and information can disseminate through the world wide web almost instantaneously, and as these spreading processes become increasingly central to modern day life, interest from academic, commercial and social fields continues to increase. One highly relevant theory is that of 'memes' as proposed by Richard Dawkins, who suggests that ideas, behaviours and styles spread like "mind viruses" between individuals within a culture.[2] The adaptation of this term to describe the spread of fads on the internet demonstrates the relevance of studying the dynamics of epidemic processes over the internet. [6]

Research into the dynamics of internet-based phenomena are largely at an early stage, and have mostly focused on Online Social Networks (OSNs) such as Facebook and Twitter, and content sharing websites such as YouTube.[3, 4] The analogy between infectious diseases and the spread of content online is easy to consider: the social networks formed on OSNs simulate physical interactions in real life as users interact and share content on their profiles, whilst viewing and subsequently sharing a YouTube video may be compared to contracting and spreading an infectious disease. There is a growing body of research that aims to use ideas from epidemiology to better understand the spread of internet-based phenomena. [5, 6, 7] Taking inspiration from epidemiology, the study of internet-based epidemic phenomena has investigated the applicability of both locally and globally driven models. For example, some studies have investigated the use of diffusion models to describe the disemmination of influence, whilst others have investigated the use of global mathematical models.[5, 6, 7, 8]

Whilst these studies have shown generally promising results, a recent study highlighted the limitations of the single epidemic based approach.[5] The co-occurence and interaction between diseases and with environmental factors is increasingly realised as important, and the authors suggest that the corresponding field of *synepidemiology* can be applied to internet-based epidemics.[9, 10] The authors go on to coin the term *synthedemics* to describe the co-occurence of a set of infections that may or may not be dependent on each other.[11] Taking inspiration from Fourier analysis, the study goes on to investigate how an incoming epidemic signal can be broken down and described in terms of multiple epidemic components (Figure 1). Furthermore, the authors build on a previous study to allow models to be fit in real time without making assumptions regarding the initial model parameters.

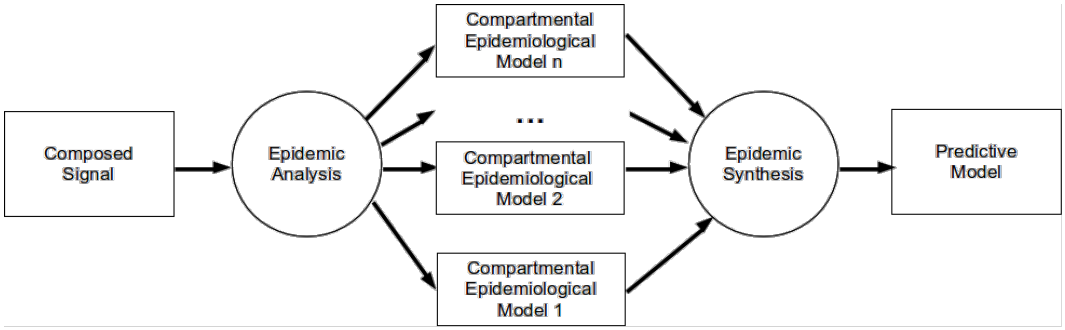

Figure 1: Model construction framework as proposed by Nika et al. 2014.[11]

1.3 Objectives

The aim of this project is to implement a real time model fitting framework with which epidemic phenomena might be characterised and forecasted. When provided with epidemic data up to an arbritary time point, we attempt to fit an appropriate number of sub-epidemics of various types to best describe the current data, and to allow future time points to be predicted. The course of the project can be split up into the following sub goals:

1.3.1 Single Epidemics

The first objective of this project is to implement a single epidemic fitting framework, treating the growth and recovery rates of the epidemic as unknown parameters. This framework is then extended to additionally consider the initial number of susceptible individuals and the actual epidemic start time as unknown parameters. The model fitting procedure is undertaken using optimisation with both least squares and maximum likelihood estimations. The framework allows for 'on the fly' fitting, such that a model may be fit to the data as the epidemic unfolds and more data points are obtained.

The initial implementation of this framework is initially undetaken using the R statistics programming environment due to the availability of useful packages and functions. For example, the *deSolve* for solving first-order ordinary diffierential equations (ODEs), the *optim* function for optimising a set of model parameters, and the *bbmle* package for maximum likeliihood based fitting.

An extension of this objective that arose during the course of the project is the implementation of the fitting framework in C++ 'from scratch'.

1.3.2 Multiple Epidemics

Not all epidemic phenomena are constrained to a single population, and the single epidemic fitting methodology is therefore inadequate in characterising all epidemics. For example, the measure of *YouTube* video views over time might be composed of multiple spikes of interest as the video is shared in new online social groups. This limitation also affects to infectious disease dynamics, wherein the total number of infected individuals in a country might be affected by the penetration of the disease into different cities. The second objective of this project is therefore to implement a model fitting framework that can simultaneously fit and combine multiple sub epidemics into a single model.

As in the single epidemic fitting framework, the multiple epidemic fitting framework makes no assumptions regarding model parameters such as growth rate, recovery rate, start time and number of susceptibles. As above, an initial implementation will be attempted using R. However, as the computational difficulty of fitting multiple sets of parameters simultaneously increases as the number of sub epidemics increases. We therefore provide a final 'from scratch' implementation in C++.

A significant extension of this fitting methodology is to allow different epidemic models to be considered. That is, which one of a number of model equations can be used to best describe the data? An object-oriented C++ implementation is therefore provided to consider the addition and removal of various candidate models to describe a set of data.

1.3.3 Maximum Likelihood Estimation

A novel objective of this project is to use maximum likelihood rather than least squares to find an optimised model fit. A significant challenge of this is to implement an efficient likelihood function in C++ with which a set of parameters might be optimised in reasonable time. An advanced extension of this objective is to generate confidence intervals characterise uncertainty in the optimised parameters.

1.3.4 Evaluation

All of the above objectives must be validated, and we use a number of data sources to assess the model fitting framework. Synthetic data provides the core of the evaluation, as it allows for the retrieval of known parameters from artificially generated data. Finally, we consider the framework's ability to provide model fits to historic infectious disease data and online epidemic phenomena.

1.4 Contributions

1.5 Report Structure

2 Background

2.1 Modelling Infectious Disease Dynamics

Throughout history, infectious diseases can consistently be cited as one of the leading causes of death across the world. Whilst many such diseases may be endemic in a population, a large proportion of diseases may outbreak as epidemics. That is, a disease may arise in a community, region or even worldwide in excess of normal levels following a particular outbreak. In an age of increasing urbanisation, global connectivity and a larger immuno-compromised population, monitoring and controlling the spread of epidemics is absolutely paramount.[12] Recent events such as the 2009 flu pandemic highlight the incredible need for a solid understanding of the underlying mechanisms of such diseases. This section will discuss the history and current standards in epidemiology.

A general understanding of infectious disease behaviour can be seen as early as the 8th century A.D., when the Indians and Chinese used a rudamentary form of vaccination known as variolation to control smallpox.[14] Even earlier than this, Hippocrates (c. 460-c. 370 BC) was amongst the first to propose that disease spread could be explained rationally through human behaviour and environmental factors.[15] Unfortunately, the understanding of infectious disease dynamics appeared to regress until the 17th century when the collection of the first public health statistics allowed for a more scientific approach.

One of the first predictive mathematical models was by Bernoulli in 1760, who used mathematical techniques to establish that variolation for smallbox could help increase the life expectancy in the French population.[16] Similarly, another systematic study of disease dynamics took place in 1854 by John Snow, who identified a single water pump in London as the likely source of a Cholera epidemic.[17] However, it was the early 1900s in which the most fundamental advances in mathematical epidemiology were made. Firstly by Ross in 1911, who used a spatial model to describe the spread of malaria due to mosquitoes.[17] This study was the first to demonstrate that infectious diseases could be controlled by reducing the population of infected individuals below a certain threshold. The next and arguably most central breakthrough was then made by Kermack and McKendrick in 1927, who proposed the use of ordinary differential equations (ODEs).[18] ODEs represented the first deterministic, general epidemic model to describe mass action. The general idea behind ODE models in the context of epidemiology is that individuals in a given population are members of various compartments depending on their relationship to the infection (eg. infected, recovered), and individuals switch between compartments as described by these ODEs.

The most basic form of the model prosed by Kermack and McKendrick's ODEs is the Susceptible-Infected-Recovered (SIR) model. Given a population of size N, individuals are divided into three states or compartments:

1. Individuals that are susceptible to the infection, denoted by $S(t)$
2. Individuals that are infected with the disease and are therefore capable of infecting others, denoted by $I(t)$
3. Individuals that have been removed from the population or recovered, denoted by $R(t)$.

Individuals move between compartments in the following order:

$$S \Longrightarrow I \Longrightarrow R$$

Simply, individuals start off as being free of the disease, but susceptible to infection. Individuals are then infected with the disease and begin to display symptoms, thereby becoming infectious themselves. After a certain period of time, individuals are no longer infectious as they recover and become immune to the disease. In this model, the population size is assumed to be fixed such that:

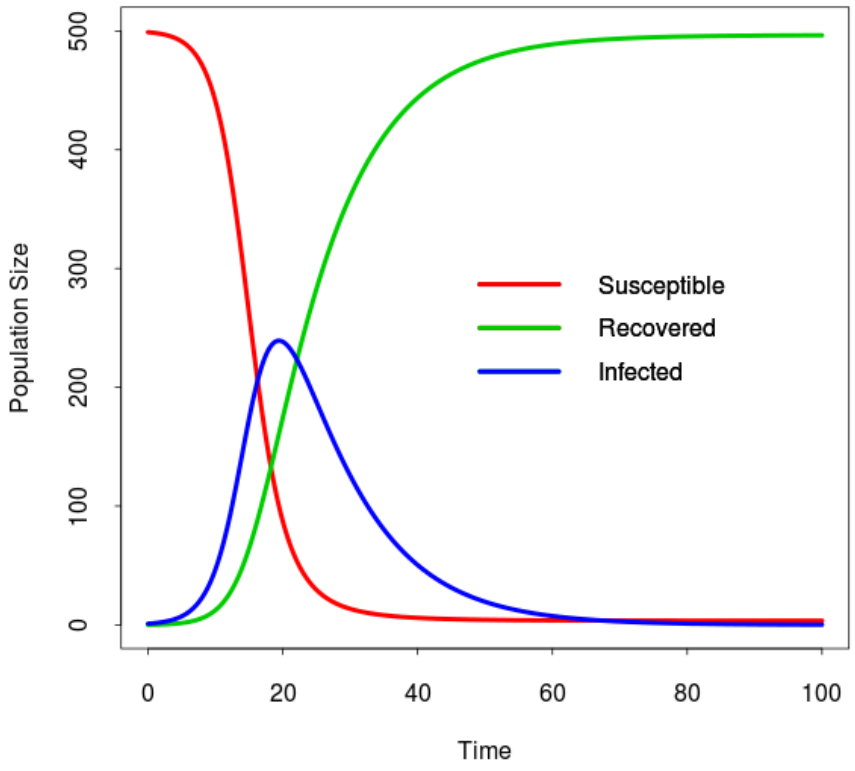

Figure 2: Generic example of the classic SIR model demonstrating the change in population size for each compartment as the epidemic unfolds

$$N = S(t) + I(t) + R(t)$$

The way in which individuals individuals move between these compartments are described by the following set of ODEs:

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

The dynamics of these ODEs are influenced by two key parameters: the contact rate, β, and the recovery rate, γ. β describes the probability of an infected person coming into contact with any

susceptible person per unit time, whereas γ describes the rate at which an individual recovers from the disease. When β is large, the contact rate between individuals is high, and the disease spreads rapidly. Similarly, when γ is large, then individuals recover rapidly and move to the recovered compartment quickly. Note that these parameters make global assumptions about the population, in that all individuals have an equal chance of interacting, and all individuals recover at the same rate. Infected individuals therefore come into contact with βN individuals per unit time. Only susceptible individuals may become infected, and the number of new infections per unit time is therefore $\beta N(S/N)$, resulting in a new infection rate of $\beta N(S/N)I = \beta SI$. Finally, as individuals recover with rate γ, they are removed from the infected compartment and enter the recovered department with rate γI.

Considering these parameters allow for useful insights into the dynamics of a given disease: a disease with a high β and lower γ will obviously spread more than one with a lower contact rate and higher recovery rate. With this in mind, we can make the intuitive leap to conclude that an infection will either: spread as an epidemic when each individual is causing more than one secondary infection; remain endemic in a population when each individual causes exactly one further infection before recovering; will die out when each individual causes less than one secondary infection before recovering. This idea is formalised by the concept of a *basic reproductive number*, R_0 (not to be confused with $R(0)$, which denotes the initial size of the recovered population!). R_0 denotes the number of secondary infections caused by a single infected individual when introduced into an initial susceptible population, $S(0)$. As this infected individual will come into contact with βN individuals per unit time over a period of $1/\gamma$ (the mean infectious period), the reproductive number will be given as the number of secondary infections per unit time multiplied by the amount of time that an individual can infect others:[20, 21]

$$R_0 = (\beta N)/\gamma$$

R_0 describes the number of secondary infections resulting from one individual in a completely susceptible population; however, this rate will obviously decrease as the proportion of susceptible individuals in the population decreases. Rather than considering the initial reproductive number, it is often more useful to consider the effective reproduction number, R_n . In simplest terms, $R_n = R_0 \times s$, where s is the proportion of the population that is susceptible $(S(t)/N)$.

As an aside, it should be noted that calculating R_0 is a crucial stage in understanding how a disease will spread. A high R_0 (eg. malaria) means that the disease will spread rapidly, with each individual causing a high number of secondary infections, whereas a low $R0$ (eg. monkeypox) means that a disease will spread slowly.[19] As discussed above, an R_0 greater than 1 is necessary for an epidemic to take hold. Even at an early stage of an epidemic, R_0 can be estimated based on the growth rate of an epidemic, as was the case during the 2003 SARS virus.[31] Therefore, decreasing the proportion of sucseptible individuals below a certain level (ie. through vaccination) will result in an effective reproduction number of less than 1, preventing the epidemic from taking hold. This critical threshold is defined as the *herd immunity threshold*, and provides a crude but often effective target for immunization programmes:[30]

$$HIT = 1 - \frac{1}{R_0} = \frac{R_0 - 1}{R_0}$$

The model shown above describes three compartments, however there are a number of extensions to this model where different compartments and interactions might be appropriate. For example,

an "exposed" compartment might be added which encompasses individuals that have been exposed to the disease, but are not yet infectious. Such a model is known as the SEIR model. As well as additional compartments, the transitions between these compartments might be varied. For example, in cases where immunity is only transient, individuals might be able to re-enter the susceptible compartment following recovery (the SIRS model). Choosing the model structure is dependent on the nature of the disease and population under consideration. For example, using an SIS (infected individuals return to the susceptible state) to model HIV, or an MSIR model (initial maternal-derived immunity) in the case of measles.[19]

It should be noted that there are further considerations to take when modelling real epidemics. For example, the inclusion of birth and death rate, seasonal dynamics, stochasticity and age-dependent interactions.[19] However, the basic principles discussed above are sufficient to begin considering how we might model the spread of other epidemic processes.

With the solid theoretical basis described above, advanced mathematical and computational models are becoming increasingly central to making public health decisions. One recent application of mathematical models in epidemiology was to describe and predict the dynamics of an epidemic in real time.[32] A study by Tizzoni et al. used a Monte Carlo Maximum Likelihood (MCML)-based approach on historical data from the 2009 flu pandemic to develop a global stochastic simulation model, referred to as GLEAM, to obtain basic model parameters.[34, 35] (Note that this project will aim to similar methodologies to fit epidemic models in real time, and a brief overview of maximum-likelihood estimation and least squares estimation is provided in Box 1). Tizzoni et al. used GLEAM to estimate the seasonal transmission ability of the 2009 H1N1 pandemic, generating forecasts for the activity peaks in the northern hemisphere. The robustness of this stochastic forecast was also explored as a function of data completeness by fitting the model using only partial data.[33]

Tizzoni et al. showed that the GLEAM model was in good agreement with the actual 2009 epidemic data, even when only partial data was used (for example, pre-exposure immunity and adherence to vaccination campaigns. However, a key feature of the model is that it accounts for the way in which populations interact and connect, and it was shown that model accuracy was reduced considerably when using only a partial dataset for population mobility. The GLEAM model uses three layers: a population layer (a grid representing the population of the world); a mobility layer (using real flight data to represent travel between cells in the grid); and an epidemic model (consisting of susceptible, latent, symptomatic infectious able to travel, symptomatic infectious unable to trabel, asymptomatic infectious and permanently covered compartments). Indeed, consideration of multiple networks layers in epidemic modelling is a growing area of consideration for real infectious diseases, as it alows for the consideration of more realistic population dynamics.[36]

2.2 Development Environment

2.2.1 Programming Languages

There were a number of candidate programming languages, each with their own strengths and weaknesses. In the end, R and C++ were chosen for intitial and final implementations. Previous approaches to epidemic and synthedemic model fitting frameworks use R due to its

readily available ODE solvers, optimisation functions and graph plotting functionality.[5, 11] R therefore provided an ideal means to implement the single and multiple epidemic fitting frameworks initially. Once this initial model fitting framework was implemented, we went on to provide a C++ implementation with the aim of providing a faster, more transparent 'from scratch' fitting methodology.

At the start of the project, it was desirable to begin exploring and understanding the theory behind epidemic modelling and otpimised model fitting. As such, the first development consideration was to decide on a language that was well adapted for easy implementations with a large number of available packages and functions. R and Matlab were candidates for this initial approach. Whilst Matlab has an arguably better programming environment with better documentation, R has already been shown to be effective in epidemic model fitting. The R community provides a number of statistical analysis tools and is suited to dealing with non-typed data sets, making it an ideal choice. These packages can easily be obtained via the Comprehensive R Archive Network (CRAN).

The nature of parameter optimisation means that fitting a large number of parameters simultaneously can be extremely slow, and an approach to providing a faster implementation was to reimplement the model fitting procedure in C++. C++ has been shown to be considerably faster than both R and Matlab when solving stochastic neoclassical growth models, suggesting that an efficient C++ implementation might provide a much faster fitting framework than an R counterpart.[13] However, the trade off with run time speed is the fact that coding the same algorithms and functions in C++ is very time consuming. Whilst there are R packages readily available that allow parameter fit optimisation, maximum likelihood estimations and graph plotting in only a few lines of code, the equivalent functionality in C++ had to be implemented from scratch. A significant challenge of this project was therefore to find, adapt or create source code for the essential functions of the model fitting framework. For graph plotting, a Gnuplot iostream was called from C++ code.

Python and Java were also considered as potential languages for a faster implementation. However, the relatively lower speed of Python and unfamiliarity with Java meant that C++ remained the ideal choice.

It should be noted that whilst C++ provides an ideal way of speeding up computational bottlenecks in the model fitting procedure (namely the optimisation step), it it may still be desirable to call R functions from within the C++ program. For example, the generation of a likelihood profile. This can be achieved using the Rcpp library if needed. Furthermore, the quick generation of synthetic data with which to evaluate and develop the fitting framework is clearly not a limiting factor. R therefore remained the ideal language for syynthetic data generation using *GillespieSSA* package, exporting the data as a .csv file to be imported in the C++ implementation.

3 Single Epidemic Fitting

In this section we explore the theory and implementation behind a model fitting framework for single SIR models with unknown parameters. To provide a simulation of real time model fitting, we iteratively fit a new optimised model at each data point. Firstly, a least-squares fitting procedure is implemented in R for a single SIR epidemic where beta, gamma and S0 are assumed to be entirely unknown. We then extend the implementation to include the start time of the epidemic, t0 as a fourth unknown parameter. This also raises the issue of epidemic outbreak detection and model selection, which we will revisit in section SECTIONNNN!. We go on to use a maximum likelihood based approach which allows for the generation of confidence intervals. Finally, we reimplement the above approaches in C++ to provide a much faster implementation.

3.1 Parameter Optimisation

As discussed in SECTION BACKGROUND, the ultimate aim of the optimisation procedure is to find the set of parameters for a set of ODEs that, when solved, best fit the given data.

3.1.1 The Nelder-Mead Algorithm

3.2

4 Multiple Epidemic Fitting

5 Evaluation

6 Conclusions and Future Work

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Appendix