

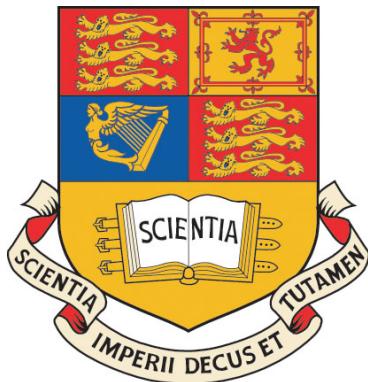
IMPERIAL COLLEGE LONDON

DEPARTMENT OF COMPUTING

On-the-fly Modelling and Prediction of Epidemic Phenomena

Author:
James HAY

Supervisor:
Dr. William KNOTTENBELT



Submitted in partial fulfilment of the requirements for the MSc Degree in Computing Science of Imperial College London

September 2014

Abstract

Text of the Abstract.

Acknowledgements

I would like to express (whatever feelings I have) to:

- My supervisor
- My second supervisor
- Other researchers
- My family and friends

Dedication

Dedication here.

‘Quote text here.’

Guy Quoted

Contents

Abstract	i
Acknowledgements	iii
1 Introduction	1
1.1 Overview	1
1.2 Motivation	1
1.3 Objectives	3
1.3.1 Single Epidemics	3
1.3.2 Multiple Epidemics	4
1.3.3 Maximum Likelihood Estimation	4
1.3.4 Evaluation	4
1.4 Contributions	5
1.5 Report Structure	5
2 Background Theory	6
2.1 Modelling Infectious Disease Dynamics	6
2.2 Epidemic Phenomena on the Internet	15
2.3 Networked Epidemiology and Social Networks	23
2.4 Summary	24
2.5 Development Environment	26
2.5.1 Programming Languages	26
3 Single Epidemic Fitting	28
3.1 Epidemic Data	28
3.2 Solving Candidate Models	29
3.3 Parameter Optimisation	34
3.3.1 Initial Test Parameters	34
3.3.2 The Objective Function	35

3.3.3	Optimisation Algorithm	35
3.3.4	Parameter Transformations and Bounding	40
3.4	Evaluating Goodness of Fit	40
3.5	Iterative Least Squares Fitting Framework	42
3.5.1	R Implementation	42
3.5.2	C++ Implementation	45
3.6	Maximum Likelihood Based Estimation	46
3.7	Alternative Candidate Models	46
3.7.1	Additional Models	47
3.7.2	Selecting a Model	52
3.8	Initial Results	53
3.8.1	Known Model Types	53
3.8.2	Unknown Model Types	54
3.8.3	CDC Influenza Data	58
3.8.4	Internet Epidemic Data	59
3.9	Chapter Summary	60
4	Synthedemic Modelling	61
4.1	Identifying Sub Epidemic Start Time	61
4.1.1	Epidemic Detection	62
4.1.2	Optimising Epidemic Start Times	62
4.2	Initial Approach	62
4.2.1	Practicality Considerations	63
4.2.2	Initial Testing	64
4.2.3	Parameter Transformations and Bounding	65
4.3	Implementation Revision with Parameter Bounding	66
4.4	Final Implementation	68
4.5	Real Data Testing	69
5	Evaluation	71
5.1	Single Fitting Framework Evaluation	71
5.2	Mutliple Candidate Models	71
5.3	Synthedemic Fitting Framework	71
5.4	Limitations	72
6	Conclusion	73
6.1	Summary of Thesis Achievements	73

6.2 Applications	73
6.3 Future Work	73
Bibliography	73

List of Tables

List of Figures

1.1	Model construction framework as proposed by Nika et al. 2014.[?]	3
2.1	Generic example of the classic SIR model demonstrating the change in population size for each compartment as the epidemic unfolds	8
2.2	Examples of the statistical distributions considered in Bauckhage et al.[?]	16
2.3	Graph <i>Facegroup</i> depicting the uptake of the "Commander Hadfield" YouTube video, demonstrating the "growth" model as proposed by <i>Facegroup</i> .[?]	19
2.4	Graph from <i>Facegroup</i> depicting the uptake of the "Dove Real Beauty Sketches" YouTube video, demonstrating the "spike" model as proposed by <i>Facegroup</i> .[?]	19
3.1	Example synthetic epidemic data generated using the <i>GillespieSSA</i> algorithm in <i>R</i> . In this model: $\beta = 0.0015$, $\gamma = 0.1$, $S_0 = 800$, $I_0 = 1$.	29
3.2	Implementation of the SIR model using the <i>GillespieSSA</i> package	30
3.3	Implementation of the Kermack-McKendrick SIR model	30
3.4	Graph demonstrating various levels of model fit	31
3.5	Least Squares Fitting Objective Function	36
3.6	The Gillespie algorithm is run with original parameter values of $\beta = 0.001$, $\gamma = 0.1$, $S_0 = 500$. The <i>optim</i> function returns fitted parameter values of $\beta = 0.0008018066$, $\gamma = 0.1273486$, $S_0 = 618$. This results in a SSE of 5120.06.	37
3.7	A) Reflection. B) Expansion. C) Outside contraction. D) Inside contraction. E) Shrink transformation	39
3.8	Control flow of the basic model fitting framework	42
3.9	Iterative model fitting over time using least squares minimisation.	43
3.10	Iterative model fitting over time using least squares minimisation. I_0 , S_0 , β and γ unknown.	44
3.11	Goodness of fit reduced when inaccurate parameter assumptions are made.	44
3.12	UML diagram of the model fitting framework	45

3.13 Graphical output of the C++ single model fitting framework. Beta = 0.001, gamma = 0.1, S0 = 1000, I0 = 1	46
3.14 1) SIR model. 2) SEIR model. 3) Exponential decay model. 4) Modified SErIR model. 5) irSIR model	48
3.15 Dynamics of candidate models with similar parameters and starting susceptible population of 1000	51
3.16 Samples graphs of various candidate model fits (true parameter values in brackets): 1) SIR (0.0015,0.05,1000); 2) EXP (0.15,800); 3) SEIR (0.02,0.02,0.05,800); 4) irSIR (0.0003,0.0001,2000); 5) SErIR (0.005,0.002,0.002,0.01,1500)	55
3.17 Model fitting over time on an irSIR model with parameters of beta = 0.0001, gamma = 0.0005, and S0 = 2000	56
3.18 Model fits of an SErIR and SEIR model where unrealistic values provide a decent model fit .	56
3.19 Fitting procedure on an SIR model where the model type is assumed to be unknown	57
3.20 Interchangeable selection of the similar SErIR and SEIR model types	57
3.21 Fitting procedure on the 2013-14 H1N1 CDC flu data	58
3.22 Fitting procedure on the 2010-11 AH3 CDC flu data, with I0 considered unknown	59
3.23 Fitting procedure on the 2013 viral hit, “The Fox (What does the Fox say?)”	60
4.1 Multiple epidemic fitting procedure on two overlapping SIR models	64
4.2 Multiple epidemic fitting procedure on two overlapping SIR models with logistic bounding .	67
4.3 Multiple epidemic fitting procedure on an SIR and EXP models with logistic bounding . .	67
4.4 Multiple epidemic fitting procedure on the number of <i>BitTorret</i> downloads of the song “Blurred Lines” by Robin Thicke. Number of downloads on the y-axis and day on the x-axis	69
4.5 Second multiple epidemic fitting procedure on “Blurred Lines” download data using addi- tional logistic binding and modified Nelder-Mead algorithm	70

Chapter 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 propagation of ideas or parasites through a population, with some spreading processes arising unexpectedly in excess of background 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.[?] 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.[?] 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. [?]

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.[?, ?] 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. [?, ?, ?] 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 dissemination of influence, whilst others have investigated the use of global mathematical models.[?, ?, ?, ?]

Whilst these studies have shown generally promising results, a recent study highlighted the limitations of the single epidemic based approach.[?] The co-occurrence 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.[?, ?] The authors go on to coin the term *synthedemics* to describe the co-occurrence of a set of infections that may or may not be dependent on each other.[?] 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.

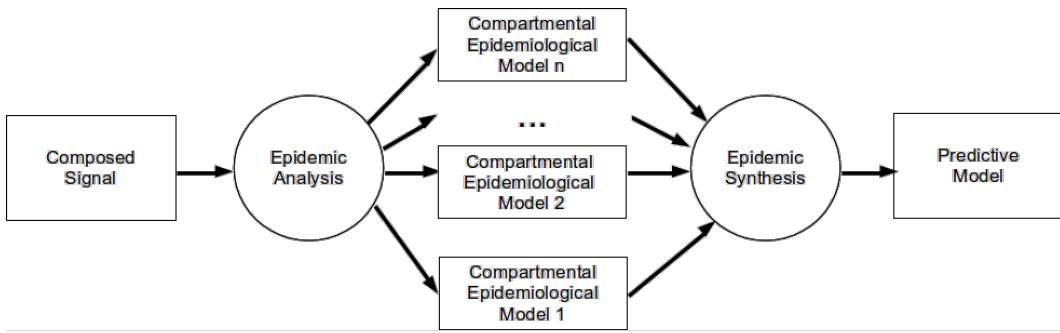


Figure 1.1: Model construction framework as proposed by Nika et al. 2014.[?]

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 arbitrary 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 undertaken using the R statistics programming environment due to the availability of useful packages and functions. For example, the *deSolve* for solving first-order ordinary differential equations (ODEs), the *optim* function for optimising a set of model parameters, and the *bbmle* package for maximum likelihood 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

Contributions here.

1.5 Report Structure

Statement here.

Chapter 2

Background Theory

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.[?] 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 rudimentary form of vaccination known as variolation to control smallpox.[?] 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.[?] 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 smallpox could help increase the life expectancy in the French population.[?] 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.[?] 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.[?] 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).[?] 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:

$$S \implies I \implies R$$

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:

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

The way in which individuals move between these compartments are described by the following

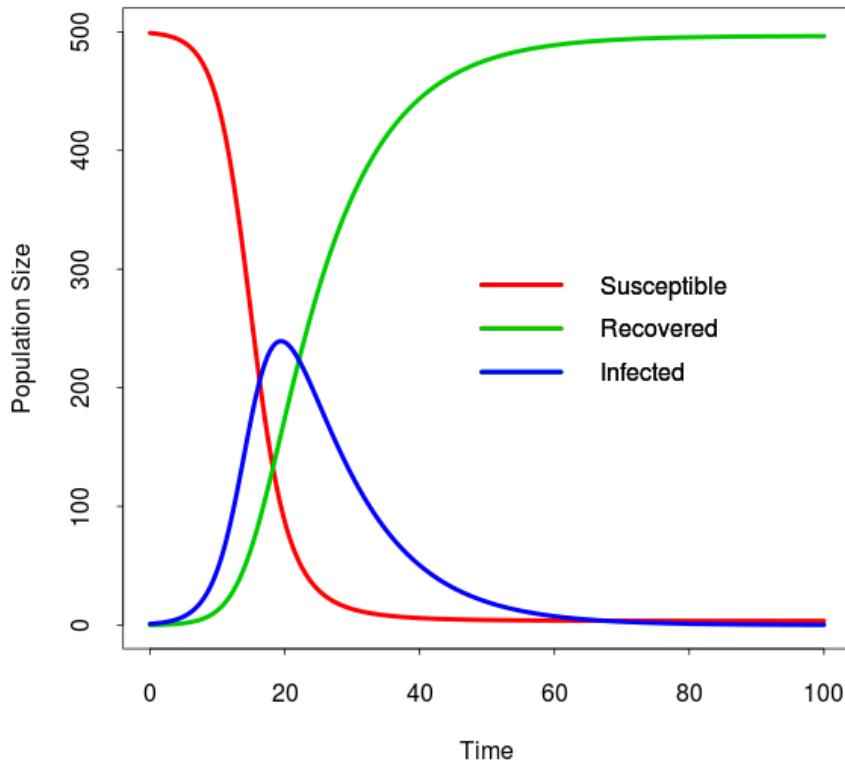


Figure 2.1: Generic example of the classic SIR model demonstrating the change in population size for each compartment as the epidemic unfolds

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 $\beta N(S/N)I = \beta SI$.

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:[?, ?]

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

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 R_0 (eg. monkeypox) means that a disease will spread slowly.[?] 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.[?] Therefore, decreasing the proportion of susceptible 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:[?]

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

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.[?]

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.[?] 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.[?] 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.[?, ?] (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.[?]

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 represent-

ing 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 travel, 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 allows for the consideration of more realistic population dynamics.[?]

Box 1

To fit model parameters in real time, we consider two methods to fit a continuous-time model to a given set of data: least squares and Maximum Likelihood Estimation (MLE).

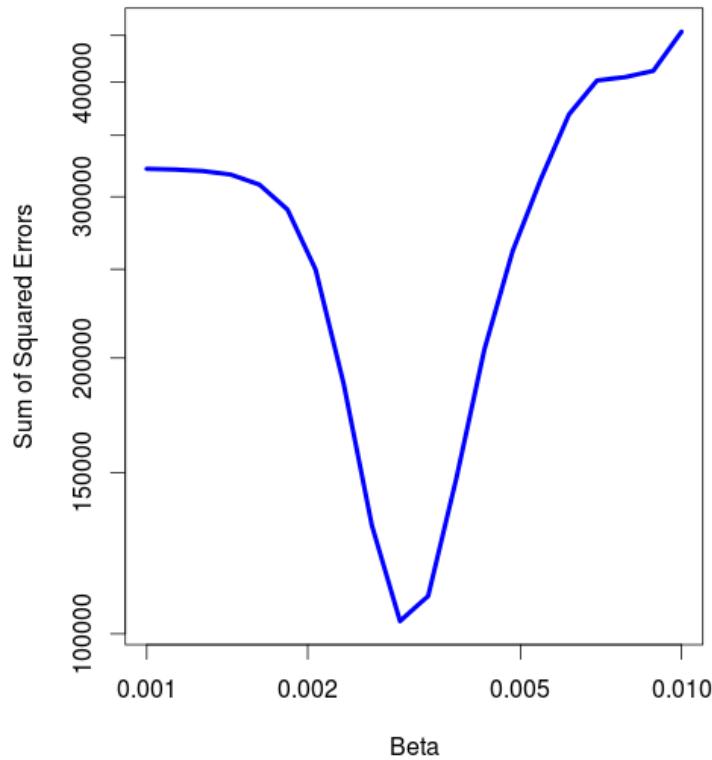
Least squares is the simpler of the two approaches, and assumes that the only source of variability in the data is measurement error (which is distributed symmetrically with a constant variance eg. Gaussian). By estimating the "least squares" for a set of parameters, we aim to find the set of parameters that minimises the sum of the squares of the errors (ie. the difference between an observed value and the fitted value).

More formally, given a simple data set of n points of the form (x_i, y_i) , we aim to minimise the following formula:

$$S = \sum_{i=1}^n r_i^2$$

Where r_i is the residual for each point, given by the difference between the actual value of the dependent variable and the variable fitted by the model: $r_i = y_i - f(x_i, \beta)$

In the context of our SIR model, we aim to find the β and γ values that provide the best fitting SIR model for a given epidemic dataset (we will use the Nelder-Mead algorithm with R).[?]

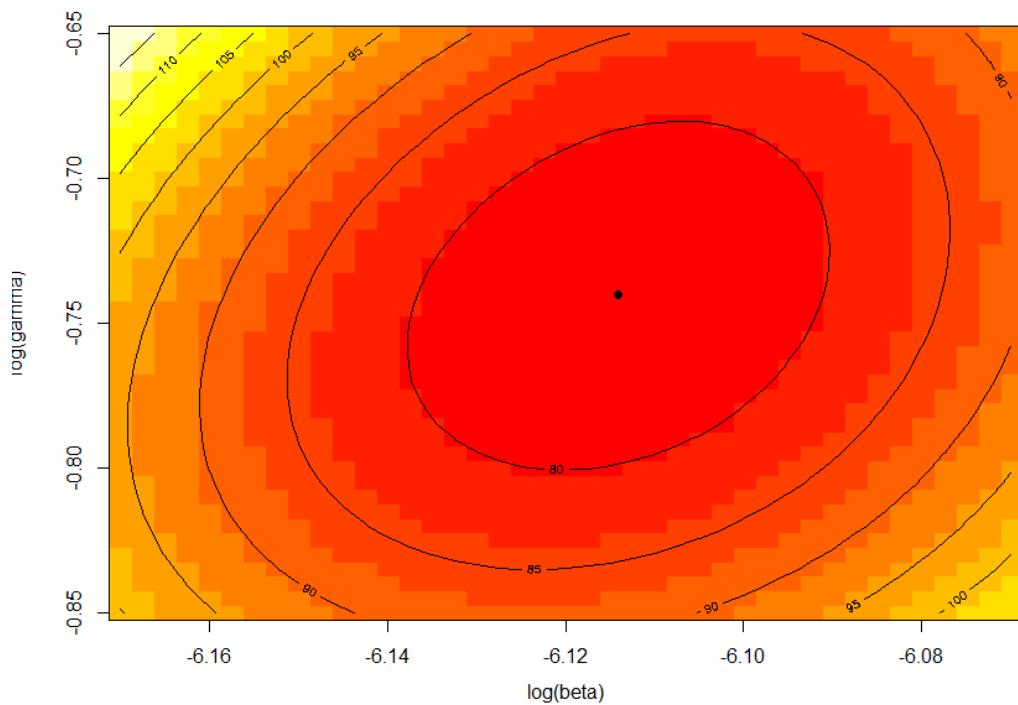


Shown above is an example sum of squared errors (SSE) plot demonstrating how a particular value for β minimises the SSE to a given dataset at around 0.003. This plot was created using a test flu dataset. Note that this plot assumes a γ value of 1, though multiple parameters may be optimised simultaneously using R's *optim* (Nelder-Mead) function.

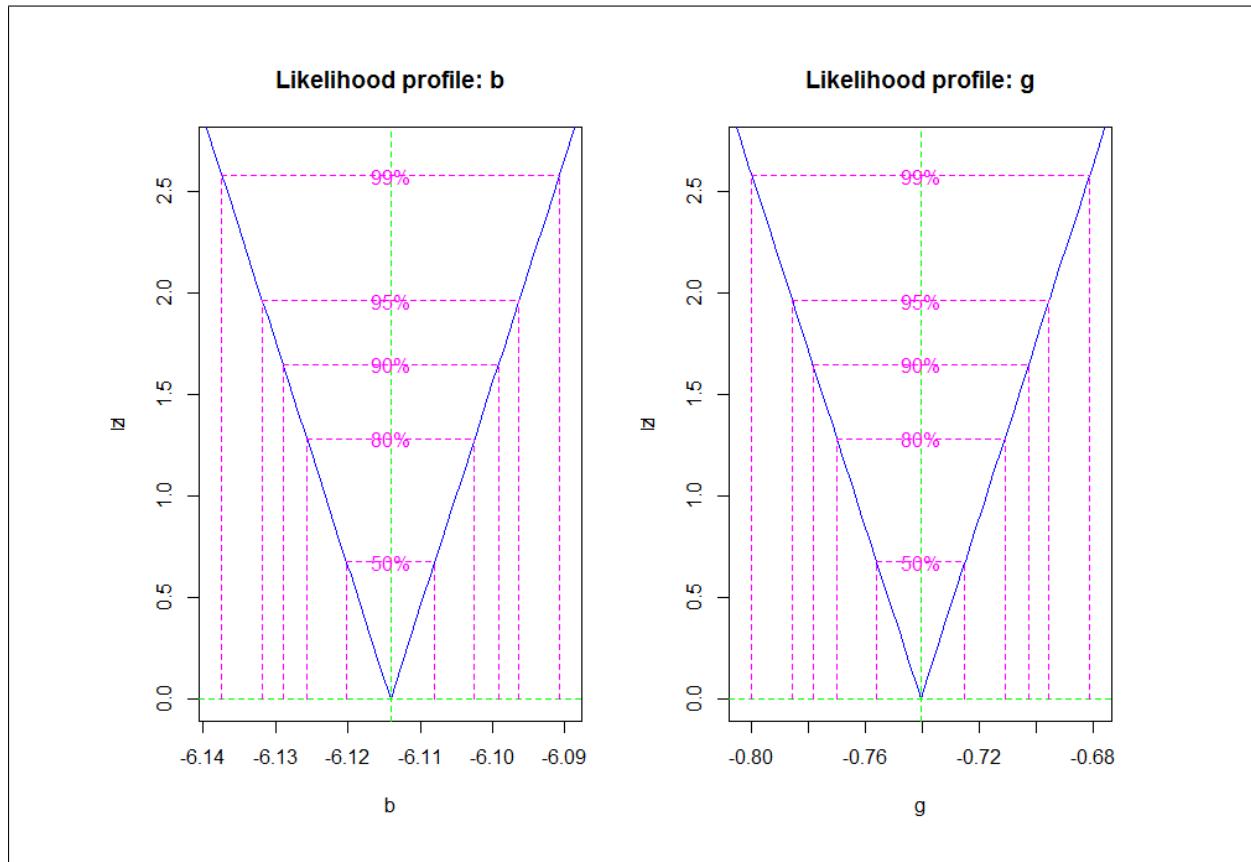
Maximum-likelihood estimation (MLE) is the method of estimating the parameters of a statistical model based on a given hypothesis and a set of data that has occurred. This method essentially selects the set of values for the model parameters that maximise the likelihood function:

$$\mathcal{L}(\theta|x) = P(x|\theta)$$

In other words, we aim to find the set of parameters that provide a model fit would be most likely to produce our given data. As above, we aim to find the set of parameters, β and γ that maximise this likelihood function. Specifically, we calculate the negative log-likelihood of the data given some combination of parameters. Methods using MLE are very common when fitting epidemic models in real time.[?, ?, ?]



The graph above depicts the two-dimensional parameter space (the likelihood surface) for beta and gamma when fit to a set of epidemic data. Note that we use log values to avoid underflow/overflow. Each point represents a separate fit to the data, and the height of the surface shows the negative log-likelihood of that parameter combination. In this particular example, we find that a $\log(\text{beta})$ value of -6.11 and a $\log(\text{gamma})$ value of -0.74 provide the best fit. We can also show the confidence intervals for each parameter in the form of a likelihood profile, as shown below.



2.2 Epidemic Phenomena on the Internet

A more recent application of epidemic modelling methods is to the spread of information and trends. In particular, the continual development of the internet has opened up a vast area of research into the dynamics of social networks, viral marketing and computer security. It is quite easy to see the analogy between the spread of an online trend to the spread of an infectious disease: individuals have either been exposed to the trend or not; may be actively spreading the trend; or may have lost interest in the trend. The relatively recent surge of interest in online social networks and rapidly rising occurrence of viral phenomena has brought with it an interest in understanding and modelling these trends. In this section, we will briefly discuss the history of epidemiology-based analyses of information dissemination and the resulting application of classical epidemiology to online phenomena.

The first application of epidemiology in a social context was made by Goffman and Newill in 1964 who directed attention to the analogy between the spreading of an infectious disease and the dissemination of information.[?] This was closely followed by Daley and Kendal, who examined the spreading of rumours using mathematical epidemiology.[?] As in Kermack and McKendrick's SIR model, Daley and Kendal used three compartments to describe their population: those individuals that had not heard the rumour, those that

were actively spreading the rumour and those that were no longer spreading the rumour. The way in which these compartments interacted was described by parameters indicating those that heard the rumour and those that lost interest or ‘forgot’ the rumour, corresponding to β and γ . Daley and Kendal found that the fit was somewhat limited by the difference in behaviours of a rumour and an infectious disease. Specifically, the way in which individuals “lost interest” in the rumour was not comparable to recovery from an infectious disease. Although not a perfect fit, Daley and Kendal’s study did highlight the potential application of mathematical epidemiology in a social context.

More recently, the ever increasing relevance of the internet to modern day life has resulted in more studies being undertaken to model and predict the spread of trends and information on the internet. Bauckhage et al. present one such study, investigating the application of statistical models in describing the spread of internet memes.[?] That is, viral catch phrases, images or videos that spread through instant messaging, blogs, forums and social networking sites. Bauckhage et al. use *Google Trends* data as an indicator of search frequency and therefore interest in the internet population. Classifying these as ‘fads’, Bauckhage et al. go on to fit established statistical distributions to over 200 meme related time series compared to a fitted Log-Normal model. Using a multinomial maximum likelihood fit, the authors find that the Weibull, Gompertz and Frechet distributions all provided a better model of general trends for meme related search activity, suggesting that growth dynamics cannot be attributed to chance. The authors conclude that these dynamics can be described as a ‘hype cycle’, encompassing a period of rapid uptake followed by a gradual loss of appeal. Although Bauckhage et al. did not use epidemic modelling, they demonstrated that mathematical modelling could be effectively used to describe online trend dynamics.

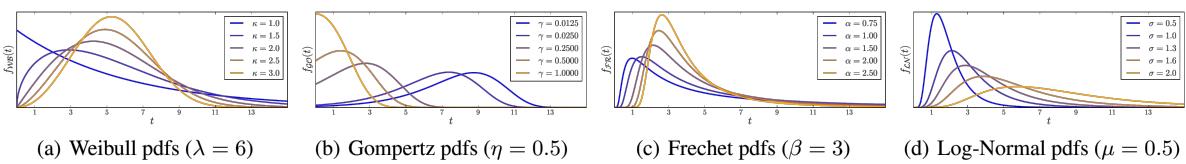


Figure 2.2: Examples of the statistical distributions considered in Bauckhage et al.[?]

The study by Bauckhage et al. demonstrates the applicability of mathematical modelling to the dynamics of internet memes, however research has also been undertaken to describe the spread of internet ‘celebrities’. Tweedle and Smith undertook one such study, investigating the usefulness of SIR modelling in describing the spread of popularity of the music artist, Justin Bieber.[?] Tweedle and Smith demonstrated that an SIR model could be fit to *Google Trends* search data relatively well. Furthermore, the study investigated how ‘media effects’ might impact epidemic spread (for example, an album release or television appearance). It was found that the inclusion of media effects improved the usefulness of the model in describing the search trend data. Although a fairly ‘tongue in cheek’ study, Tweedle and Smith demonstrated that SIR modelling

could be successfully used to describe the spread of online popularity, particularly when additional media effects are considered.

A recent study by Nika et al. showed the potential for epidemiology to explain and predict outbreaks of internet-based information spreading, with the novelty that the size of the initial susceptible population was assumed to be unknown.[?] The aim of this study was to fit SIR and SEIR models to celebrity outbreaks on the internet in real time, improving model fit as the epidemic progresses. Using the Nelder-Mead algorithm with a least-squares-based objective function to fit SIR and SEIR models in real time (see Box 1), Nika et al. were able to demonstrate real time model fitting with unknown initial parameters. The authors validate their approach on synthetic epidemic data, a historical influenza epidemic and BitTorrent and YouTube video views. Both the SIR and SEIR models fit the synthetic and historical data well, and showed good predictive power. However, whilst the models were fit to the internet-based data with some success, the authors acknowledge limitations in their methodology, such as the generation of confidence intervals without due regard for parameter uncertainty. This study demonstrates a promising framework for fitting parameters to data in real time, though highlights the limitations of classic SIR modelling in its basic form.

One recent study using similar methodology that recently received public interest was by Cannarella and Spechler, who investigated the use of SIR modelling in describing public interest in OSNs, namely MySpace and Facebook.[?] Cannarella and Spechler used an adapted SIR model that modified the dynamics of the recovering population such that contact between recovered and infected individuals was required for recovery. That is, individuals would only stop using the OSN if they came into contact with someone who had already stopped using it. The authors named this adaptation the ‘irSIR’ model. As in the above studies, Cannarella and Spechler used *Google Trends* search data as a proxy for service usage. Similar to Nika et al., the authors used the Nelder-Mean algorithm to find a best fit curve based on sum of squared error, also assuming that all initial parameters, including population size are unknown. The study found that in the case of MySpace, whilst the basic SIR model did not fit particularly well, the modified irSIR model provided a good fit to the adoption and abandonment phases of the OSN. When applied to the ongoing OSN, Facebook, the authors found that Facebook had reached peak popularity in 2012 and was in the early stages of abandonment, predicting that the OSN would reach 20% of its maximum size by the end of 2014. The authors do concede that there exists an infinite range of possible slower declining solutions.

Facebook posted a rebuttal to the study, using similar methodology to show that Princeton would cease to exist by 2021 based on Google search results.[?] Although not a formal, peer reviewed study, Facebook’s rebuttal did highlight some shortcomings with the methodology employed by Cannarella and Spechler. Namely the assumption that Google searches were an indicator of usage, and also the flawed assumption

that Facebook would not ‘evolve’ to keep users. These studies highlight the importance of making valid assumptions and using appropriate data when attempting to study a rapidly evolving area such as OSNs.

With huge implications for marketing and commercial success, Interest in viral phenomena has become an area of particular interest outside of the academic community. As a result, commercial circles have also taken an interest in attempting to understand the spread of online trends. A review posted by the global strategic insight agency, *Facegroup*, inadvertently touched upon the application of SIR modelling in explaining the spread of viral videos.[?] The main conclusion that *Facegroup* came to was that there is no single model of virality. Rather, different types of viral videos could be spread in different ways, proposing ‘spike’ and a ‘growth’ types depending on their spreading pattern. In the ‘spike’ case, videos tend to peak early and drastically drop in views within a week. In the latter case, videos achieve their peak views after a few days and decline slowly, interrupted by secondary peaks of interest.

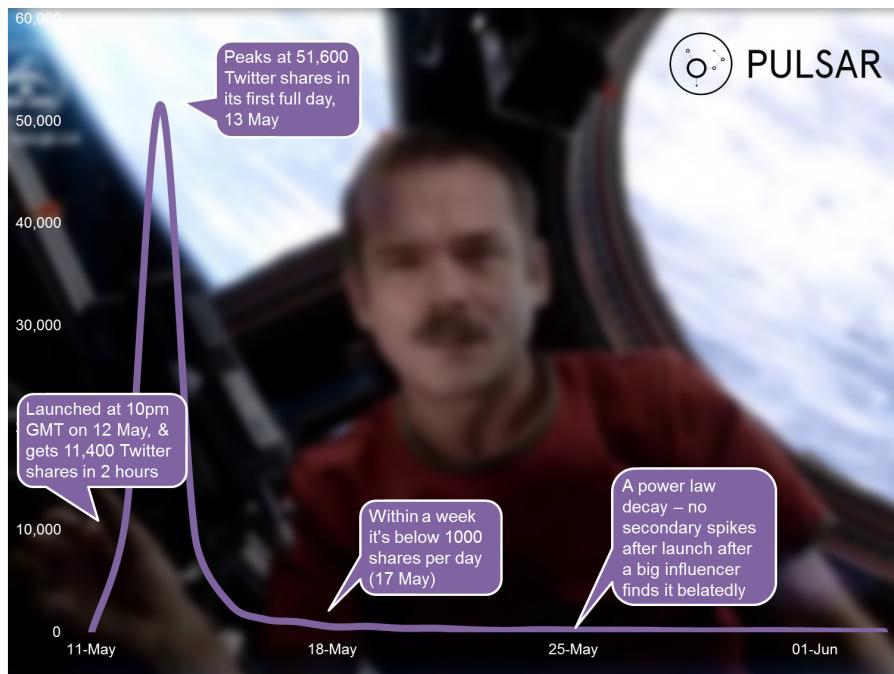


Figure 2.3: Graph *Facegroup* depicting the uptake of the "Commander Hadfield" YouTube video, demonstrating the "growth" model as proposed by *Facegroup*.[?]

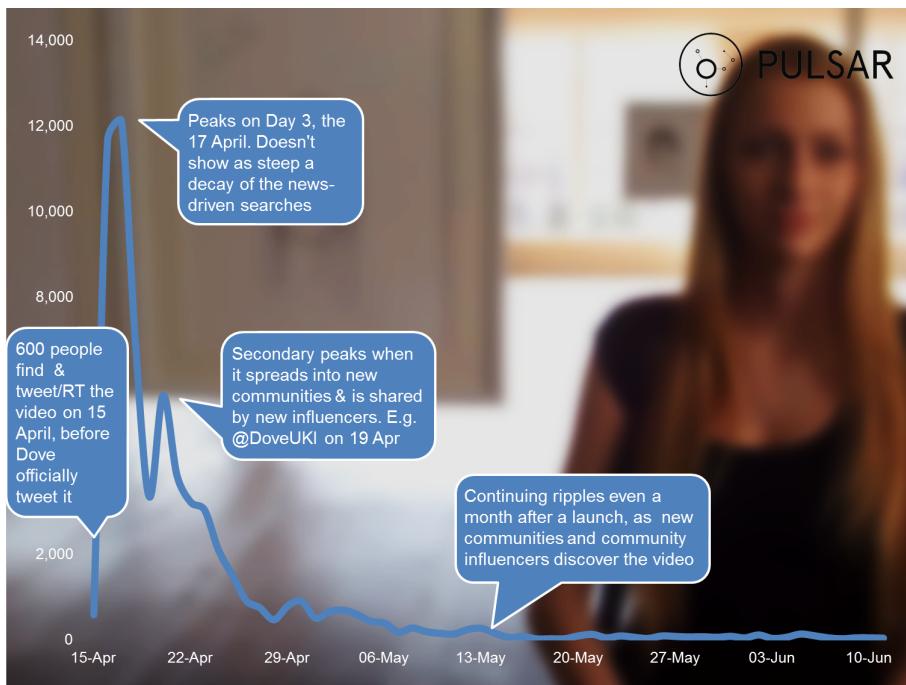


Figure 2.4: Graph from *Facegroup* depicting the uptake of the "Dove Real Beauty Sketches" YouTube video, demonstrating the "spike" model as proposed by *Facegroup*.[?]

Returning to an academic setting, Nika et al. recently undertook another study to improve the fit of their real time fitting framework, stating that, based on their previous study, a single epidemic is inadequate to characterise a complex internet-based phenomena. This may be because internet based trends may be influenced by multiple underlying spreading mechanisms at different times, similar to the ‘media effects’ as described by Tweedle and Smith in their analysis of ‘Bieber Fever’. Nika et al. took inspiration from Fourier analysis, proposing that modelling and predicting internet-based phenomena could be better described by considering multiple compartmental epidemiological models. That is, an epidemic signal can be broken down into a number of sub-epidemic models which, when recombined, can be used as a predictive model (see Figure 1). Nika et al. go on to coin the term *synthedemic* from the field of syndemics - the idea that infections can co-occur and interact with each other as well as environmental factors.

The term synthedemic is used to describe the co-occurrence of a set of infections, whether they are dependent or not. The aim of the study was to account for the potential influence of multiple underlying spreading mechanisms which may begin at different times by breaking an incoming epidemic signal into component parts, and selecting the model that best explains each component. Using only a classical SIR model and exponential decay model as candidates, Nika et al. are able to adequately characterise the evolution of synthetic data and four real-world data sets from internet trends (BitTorrent downloads and daily YouTube views) well. Please refer to Box 2 for a detailed explanation of the theory used by Nika et al. Using synthetic double epidemic data, the model by Nika et al. successfully predicts two overlapping epidemics, predicting the peak of the second, spike epidemic with a high R² value. The model is also fit successfully to the BitTorrent downloads of two popular songs and a viral YouTube video; detecting the presence of multiple outbreaks and exponential decay of interest.

Box 2**Methodology:**

The modelling procedure begins by considering a small, truncated dataset of an epidemic outbreak. At each time point, an additional data point is added until the end of the considered time frame is reached. This might be a synthetic epidemic dataset, a historical infectious disease epidemic, or some measure of interest in an online phenomena (Nika et al. use BitTorrent downloads and daily YouTube views). Nika et al. propose two candidate models that provide theoretical analogues to the *growth* and *spike* trends as proposed by *Facegroup*: an SIR model to represent gradual growth, and an exponential model to represent a rapid outbreak and decay of public interest.[?]

At every time point, the multiple epidemic is optimised by attempting to minimise the sum of squared error of the model against the data. At each stage of fitting, the latest residuals are checked at each additional time point for the presence of an additional epidemic outbreak. If detected, a new epidemic is temporarily added to the model from the list of candidate models. If the addition of this model improves the R^2 value, then this additional epidemic is included in all future model fittings. After the multiple epidemic model has been optimised, an autoregressive model is fitted to capture the remaining variability in the data. Finally, the fit of the multiple epidemic AR model is assessed against benchmarked fitting procedures, such as a single epidemic model, using a range of statistical tests, including rSquare comparison.

Candidate Models:

Let M be the class of sub epidemic models under consideration:

$$M = \{f_1^{(i)}, f_2^{(i)}\}$$

Where $f_1^{(i)}$ and $f_2^{(i)}$ are defined as follows:

- A. $f_1^{(i)}$ denotes the SIR model $f_1^{(i)}(\theta^{(i)}, t)$ with parameter vector $\theta^{(i)} = [I_0^{(i)}, S_0^{(i)}, \beta^{(i)}, \gamma^{(i)}]$

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

B. $f_2^{(i)}$ denotes the Exponential decay model $f_2^{(i)}(\theta^{(i)}, t)$ with parameter vector $\theta^{(i)} = [I_0^{(i)}, \gamma^{(i)}]$

$$\frac{dI}{dt} = -\gamma I$$

Parameter t denotes a particular time, where $S_0^{(i)}$ and $I_0^{(i)}$ denote the initial number of susceptible and infectious individuals at time t , whilst $\beta^{(i)}$ and $\gamma^{(i)}$ denote the infection and recovery rate. Furthermore, the current number of sub epidemics within the overall model is given by k , where the combined value of the epidemic model at time t is given by the following formula:

$$\hat{y}(\theta, t) = \sum_{i=1}^k f^{(i)}(\theta^{(i)}, t)$$

Global mathematical models of epidemic processes provide a useful insight into infectious disease dynamics; however, they make a number of potentially unrealistic assumptions. Most notably, SIR models assume complete mixing of the population. That is, each individual in the population has an equal chance of coming into contact with every other individual in the population. Although this assumption may hold in certain scenarios (it is generally safe to assume that the internet population observes random mixing), it may not be applicable to many systems that are affected by local dynamics. Consider the population of a town comprising of schools, offices and homes. Obviously a student will mix much more frequently with other students and their family rather than office workers. In such cases, the approach of SIR based modelling may not be sufficient to capture the underlying dynamics of the population. Many researchers have therefore developed extended models to investigate stochasticity, multiple compartments representing different subpopulations, branching processes and chain-binomial models.[?]

One recent approach of particular relevance to the study of epidemic phenomena in a social context is that of networked epidemiology: an approach that encompasses individual behaviour, heterogenous multiscale networks and the dynamical processes on these networks. Although this particular project focuses on the application of classical SIR modelling, it is worth discussing networked epidemiology in brief to give a complete picture of the field.

2.3 Networked Epidemiology and Social Networks

We have briefly touched on the idea of networks in epidemiology with reference to multi-layered epidemic models, however it is worth discussing the basics behind network considerations.[?, ?] Networked epidemiology takes its inspiration from graph theory, using nodes to denote individuals and edges to denote interactions.

Let $G(V, E)$ denote a contact graph on a population of V individuals, where each edge, $e = (u, v) \in E$ denotes those individuals, $u, v \in V$ that come into contact. As in the SIR model, each node might be in the S , I or R state. However, the key difference is that the infection may only spread from u to v along an edge with a probability of $\beta(e, t)$ at time instant t after u has become infected. Similarly, a node only remains infected for a set amount of time denoted by $\tau(u)$. After this time, the node u switches to state R . By considering this network model over a given number of time steps, the dynamics of an epidemic taking place in a network can be modeled. With this basic idea, it is easy to see how real world networks structures and data can be used to vastly improve models of epidemic processes in reality, thereby improving approaches to vaccination and disease control programmes.[?] On the other hand, the reality of transmission networks is not quite so ideal, with information regarding population connectivity and interactions being limited. In this section, we will discuss a sample of studies that build on the concept of local network approaches, and discuss some approaches that have been taken towards applying these to online trends.

With the basis for another approach to epidemic modelling, we can begin to consider general frameworks to describe local dynamical processes. One such approach is called the graphical discrete dynamical system (GDDS)[?], which is defined as a tuple (G, F, π) , where: $G = (V, E)$ represents the underlying contact network; $F = \{f_v | v \in V\}$ is a set of local functions for each node, v , to compute the state of v based on its neighbours; and π is a schedule that specifies the order in which the stages of the nodes are updated. It is possible to view the configuration space of a GDDS as a Markov chain, M , where each node in M is the state vector of the node states in the GDDS, G . For example, in the SIR model these three states correspond to the susceptible, infectious and recovered states.

A conceptually simpler approach to local network modelling is that of a cellular automata model. Cellular automata models take into consideration local behaviour and heterogeneity by ascribing each individual to a particular cell as part of a grid. Individual cells may have a certain state, such as infected or susceptible, and may interact with other cells depending on the assumptions made. Turner et al. provide one such example of this type of model, proposing two spatial host-pathogen models that are described as equivalent to a density and frequency dependent global model.[?] Another example is provided by Zanette and Risau-Gusman,

who investigate the effect of evolving connections between individuals affects the spread of an infection. Zanette and Risau-Gusman use an SIS based model where susceptible agents are able to break their links with infected agents either temporarily or permanently, showing that a moderate contact reconnection frequency is sufficient to suppress infection.[?] It is possible to stretch the analogy of human networks to the internet, with towns and cities representing various internet communities. However, the drastically higher level of connectivity and transmission speed on the internet does limit the applicability of these locally driven models.

Global models may provide a more appropriate approach to global internet trends compared to locally driven models; however, research into using network based models to describe the dynamics of social networks has recently shown some success. The aim of such models are largely to predict future viral trends. One such example is a study by Altshuler et al., who investigated the use of social diffusion models in trend prediction in an online social trading community.[?] Altshuler et al. set out to answer the following question: given a snapshot of a social network with some behaviour occurrences, what is the probability that these occurrences will result in a viral diffusion and a wide-spread trend? The authors model the diffusion process using scale-free networks (ie. probability that v has d neighbours follows a power law); taking into account local fluctuations and heterogeneity. From this, Altshuler et al. develop a theoretical mathematical model to understand trend diffusion in social networks. However, as the authors points out, their framework needs to be tested in the field by conducting an active experiment in which the emergence of a trend is predicted in real time.

2.4 Summary

Research into the mathematical modelling of epidemic processes is now an established field, with the majority of work based on the original SIR model as proposed by Kermack and McKendrick.[?] Extensions of the SIR model take into account additional compartments and inter-compartment dynamics, such as the inclusion of an ‘exposed’ group or of births and deaths. By customising model parameters and structure, public health authorities and researchers can improve their understanding of the way in which infectious diseases spread. 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.[?] Understanding these population dynamics in combination with the critical vaccination threshold, given by the reproductive ratio of the virus, allows for effective vaccination and control strategies. Particular topics of note in recent years are the use of multi-layered epidemic models and the use of maximum-likelihood estimations to predict

the spread of an epidemic in real time. [?, ?, ?, ?, ?]

Although infectious diseases are the focus of mathematical modelling of epidemic processes, a novel application is in the modelling of internet-based phenomena and trends. As online social networks and content sharing site become increasingly popular, the relevance of understanding the dissemination of information online becomes an increasingly important area of research both from an academic and commercial perspective.[?, ?] Studies in this area are still at an early stage, though a few recent studies have shown promising early results. [?, ?, ?] The study by Nika et al. shows promising results by considering the presence of multiple, overlapping epidemics to describe one epidemic phenomena in real time using a least-squares based fit. That is, the popularity of a single online trend may be described through considering its underlying sub-epidemic components. Nika et al. consider two types of sub epidemic model as proposed by the strategic insight agency, *Facegroup*, and is the first study to consider multiple overlapping epidemics to explain the spread of internet trends.

Although applying epidemic modelling techniques to the spread of internet trends has shown promising results, there are a number of limitations and flawed assumptions that must be considered. Firstly, the analogy between an internet trend and an infectious disease is limited. Nika et al. point out that whereas normal SIR modelling will be able to make realistic assumptions or measurements regarding the size of the initial susceptible population, this is not possible when considering online trends. This S_0 value must therefore be treated as an additional unknown parameter.[?] Furthermore, the spreading mechanisms and lifecycle of internet trends are different to those of infectious diseases. Whereas infectious diseases must be passed on through physical contact, internet trends can be spread instantaneously to any other user through a ‘tweet’ or ‘share’. Trends such as online videos or memes may also typically experience media spikes when a video or celebrity is shown on television or highly frequented web pages. The dangers of making such assumptions can be observed in the study by Cannarella et al. who attempted to show that Facebook would be abandoned by 2015, neglecting to consider that Facebook will continue to ‘evolve’ to keep users.[?, ?] Proxies for interest in internet trends such as *Google Trends* search results should therefore be used with caution.

Despite these limitations, promising early results encourage the pursuit of further research. There are a number of other techniques and models currently being investigated in infectious disease modelling that might be applicable to the spread of internet trends. For example, the use of maximum-likelihood estimations rather than least squares;[?] the use of multi-layered epidemic models that might account for underlying social network structure (for example, the spread of a viral video on or between social network sites);[?, ?] and the consideration of alternative compartmental models or statistical distributions.[?]

With so many potential routes to follow, this project will focus on furthering the work done by Nika et al. to fit a multiple epidemic model in real time to the spread of online phenomena.

2.5 Development Environment

2.5.1 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 initial and final implementations. Previous approaches to epidemic and syndemic model fitting frameworks use R due to its readily available ODE solvers, optimisation functions and graph plotting functionality.[?, ?] 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 optimised 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.[?] 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 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 synthetic data generation using *GillespieSSA* package, exporting the data as a .csv file to be imported in the C++ implementation.

Chapter 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, independently optimised model at each data point. Firstly, a least-squares fitting procedure is implemented in R for a single SIR epidemic where beta and gamma are assumed to be entirely unknown. We then extend the implementation to include the number of initial susceptible individuals, S_0 ; the start time of the epidemic, t_0 ; and the initial number of infected individuals, I_0 . This also raises the issue of epidemic outbreak detection and candidate 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 fitting framework.

3.1 Epidemic Data

The data that we wish to characterise is the change in number of infected individuals over time. In this context, the term ‘infected individuals’ may be defined as individuals infected with a disease, or individuals that have viewed a particular *YouTube* video or ‘liked’ a particular *Facebook* post. Examples of this type of data are shown in Figure 3.1. *R* is ideally suited for the easy management and manipulation of data through the use of the ‘data frame’ type. In C++, we import data as .csv files and carry out all manipulation and use using vectors.

We use the results of solving ODEs with known parameters and independent runs of the *GillespieSSA* algorithm to test the framework’s ability to find the true model parameters. *GillespieSSA* provides an easy

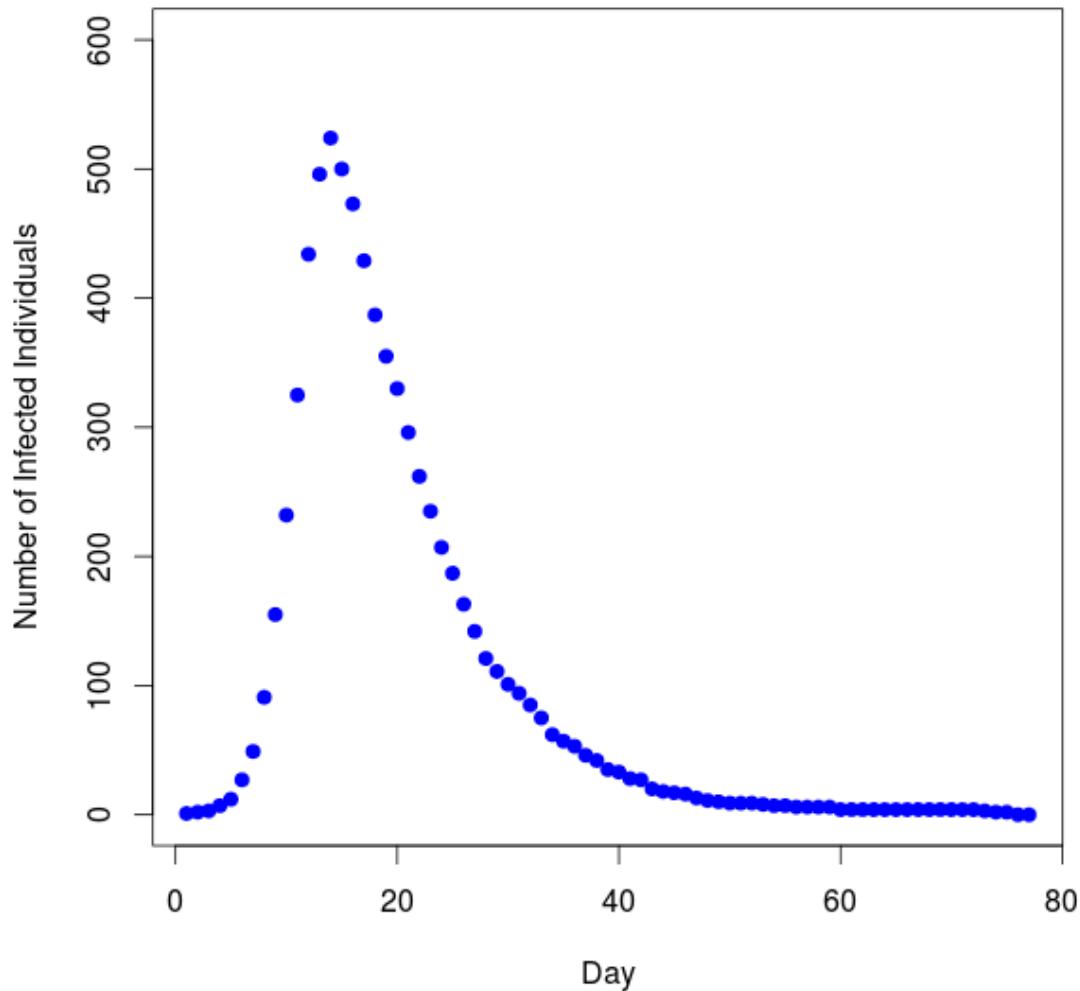


Figure 3.1: Example synthetic epidemic data generated using the *GillespieSSA* algorithm in R. In this model: $\beta = 0.0015$, $\gamma = 0.1$, $S_0 = 800$, $I_0 = 1$.

to use, extensible means of generating simulated trajectories of finite population continuous-time models. Algorithm 1 shows a basic implementation of the SIR model in R using *GillespieSSA* for generation of synthetic data.

3.2 Solving Candidate Models

As we aim to find a model that best describes our data, the next consideration is the generation of model data that might fit our epidemic data. With a candidate set of model equations in mind, namely the *SIR* model, and a set of candidate parameters (β , γ and S_0), we solve the model ODEs to generate a series of discrete data. We can then assess how well this chosen model fits the epidemic data.

Figure 3.2 Implementation of the SIR model using the GillespieSSA package

```

function GILLESPIE.SSA.SIR(params, I0, time, i)
  # Define parameters
  parms ← c(beta=params[1], gamma=params[2])

  # Define system
  x0 ← c(S=params[3], I=I0, R=0)                                ▷ Initial state vector
  nu ← matrix(c(-1,0,1,-1,0,1), nrow=3, byrow=T)                  ▷ State-change matrix
  a ← c("beta*S*I", "gamma*I")                                     ▷ Propensity vector
  tf ← time                                                        ▷ Final time

  # Run the simulations
  nf ← layout(matrix(c(1,2,3,4), ncol=2, byrow=T))

  # Direct method
  set.seed(i)
  out ← ssa(x0, a, nu, parms, tf, method="ETL", tau=1, simName, verbose=FALSE)
  return out.data
end function

```

When implementing the model fitting framework in *R*, we utilise the *ode* function from the *deSolve* package to return sub-population values calculated from a given set of parameters, a set of ODEs and a desired time frame. A simple *R* implementation of the *SIR* is shown in Figure ???. In the C++ implementation, an ODE solving framework is written from scratch.

Figure 3.3 Implementation of the Kermack-McKendrick SIR model

```

function CLOSED.SIR.MODEL(time, data, parameters)
  S ← data[1]
  I ← data[2]
  R ← data[3]

  beta ← parameters[1]
  gamma ← parameters[2]

  dS ← -beta*S*I
  dI ← beta*S*I - gamma*I
  dR ← gamma*I

  list(c(dS, dI, dR))
end function

```

With a model solving framework and a set of data that we wish to fit, one can begin to visualise how the model fitting process might take place. Even with completely unknown parameters, candidate models can be generated by choosing parameters that might fit the data. Figure 3.4 depicts how using various model parameters results in different shaped curves.

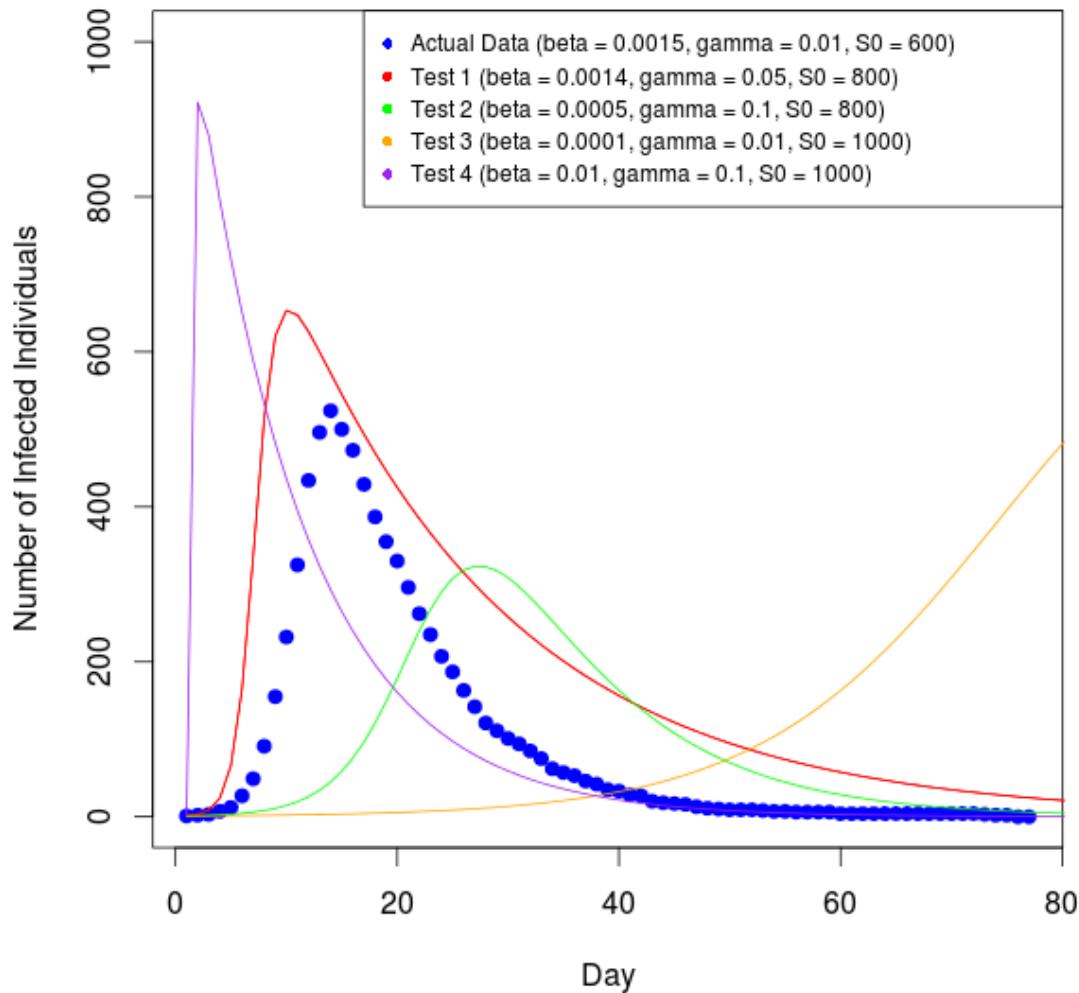


Figure 3.4: Graph demonstrating various levels of model fit

As a theoretical aside, it should be highlighted that the `ode` function uses the LSODA integration method by default, based on FORTRAN code. The benefit of the LSODA method is that it automatically switches between stiff and non-stiff systems, and is very robust. However, in our C++ implementation, we provide a ‘from scratch’ ODE solver using the Runge-Kutta method in an attempt to speed up the model fitting process. A theoretical introduction to ODE solving is provided in Box 4.

Box 4: Solving Ordinary Differential Equations

The epidemic models take the form of ordinary differential equations (ODEs), wherein the dynamics of the population are described by the transition of individuals between different compartments. In the case of the the *SIR* model, individuals transition from susceptible, to infected and finally to recovered. As discussed in Box 1, the rate of transition between these states depends on the model parameters (namely beta and gamma), as well as the number of individuals currently in each compartment.

For the purpose of model fitting, it is necessary to calculate the number of individuals in each compartment at each time point. This requires the set of ODEs to be solved. Given a set of parameters and initial compartment sizes, we wish to find the number of individuals over the course of the epidemic at each time point. For a simple differential equation, it is possible to find the closed form solutions. Given a function, g , we wish to find the solution such that:

$$\begin{aligned} Y'(t) &= g(t) \\ Y(t) &= \int g(s)ds + c \end{aligned} \tag{3.1}$$

where c is an arbitrary constant, and the value of $Y(t)$ can be obtained at a given time point:

$$Y(t_0) = Y_0 \tag{3.2}$$

In the case of first-order differential equations (as is our case), we take the above equation as the initial value condition and are presented with an initial value problem of the form:[?]

$$\begin{aligned} y'(t) &= f(t, y(t)), \\ y(t_0) &= y_0 \end{aligned} \tag{3.3}$$

It is often impractical to derive analytical solutions to differential equations. In the case of models in epidemiology, the first-order different equations are often non-integrable.[?] Considerable work has been undertaken to attempt to solve *SIR* models analytically using Lie analysis and homotopy analysis.[?, ?] Such approaches are difficult to implement and are not fit for the purpose quickly solving ODEs in a

generalisable way. We therefore turn to numerical analysis.

Numerical methods are used to find numerical approximations to the solutions of ODEs rather than solving them analytically. For the purpose of obtaining population values that can be used in model fit assessment, such numeric approximations are sufficient. The simplest numerical method for solving the initial value problem is *Euler's method*, which involves finding an approximate nearby point on the curve by moving along a line tangent. Euler's method forms the basis for a highly popular group of methods for solving initial value problems known as Runge-Kutta methods, which are relatively easy to implement.

The most basic member of the Runge-Kutta methods is simply known as the “classical Runge-Kutta method”, and is the method that we chose to implement in C++. Given the above initial value problem and an initial condition, we can attempt to find later values of $y(t)$ with the following definitions:

$$\begin{aligned} y_{n+1} &= y_n + \frac{h}{6}(k_1 + 2k_2 + 2k_3 + k_4) \\ t_{n+1} &= t_n + h \end{aligned} \tag{3.4}$$

for $n = 0, 1, 2, 3\dots$, using

$$\begin{aligned} k_1 &= f(t_n, y_n), \\ k_2 &= f\left(t_n + \frac{h}{2}, y_n + \frac{h}{2}k_1\right), \\ k_3 &= f\left(t_n + \frac{h}{2}, y_n + \frac{h}{2}k_1\right), \\ k_4 &= f(t_n + h, y_n + hk_3) \end{aligned} \tag{3.5}$$

Note that y_{n+1} is the Runge-Kutta approximation of $y(t_{n+1})$, where y_{n+1} is determined by the weighted average of four increments of y_n at interval size, h , with the estimated slope specified by the right hand side of the differential equations. Note that greater weighting is given to the increments at the midpoint of the chosen interval.

3.3 Parameter Optimisation

We now have now clearly identified our problem and the means by which we can attempt to solve it. That is, can we find a set of ODE parameters that generate a model that accurately fits our epidemic data. Given an initial set of test parameters, we attempt to optimise these parameters to best fit our data using an optimisation algorithm alongside an objective function measuring model fit.

3.3.1 Initial Test Parameters

In classical epidemiology, it is often possible to obtain estimates of many important model parameters based on disease biology and population dynamics. For example, the initial susceptible population of an isolated influenza outbreak might be estimated as the school-aged population of a country. Similarly, the infection and recovery rates of a new strain of virus might be estimated based on phylogenetic relationships to previous viruses of known parameters.[?] Another potential method is to measure transmission rates in experimental populations, as demonstrated by Bouma et al., who estimated the transmission parameters of the H5N1 avian influenza virus using a small number of birds in an experimental transmission study.[?] However, it is easy to imagine situations where parameter estimation might be infeasible. Estimating the susceptible population size for a viral *YouTube* video, for example, might be difficult. Do we assume that the entire internet population is at risk of exposure, or will the video be limited to only certain internet communities? Such a scenario is not unimaginable for infectious diseases. Should a new, uncharacterised disease arise in only an unknown demographic, the task of estimating model parameters becomes very difficult.

In scenarios where parameter estimation is infeasible, we aim to find the true model parameters without making any assumptions as to where they might lie other than within a realistic range. In the presented model fitting framework, we begin the parameter optimisation procedure with random parameter values taken from a realistic range with reasonable limitations imposed. For example, we seed the optimisation procedure with a random beta value between 0.0001 and 0.01. It is also important to ensure that a number of realistic conditions are adhered to:

1. The basic reproductive ratio must be sufficient to allow an epidemic to take off, $R_0 > 1$. For this to be adhered to, gamma must be greater than beta.
2. The initial number of susceptible individuals, S_0 must be positive and within a reasonable range. Seeding with an very high or low values might prevent the optimisation procedure from converging on an optimal solution.

3. The initial number of infected individuals, I_0 , must be greater than 0. Whilst I_0 does not necessarily need to be bound from above by S_0 , it is generally the case that S_0 is much greater than I_0 .

One heuristic for estimating the start value of I_0 is to take the first data point as the initial number of infected individuals. However, this causes the model to be highly dependent on the first data point, neglecting to consider that the first data point might not represent the start of the epidemic. A more reasonable approach would be to consider I_0 as another unknown parameter to be optimised, or to assume that there is initially only one infected patient, or ‘patient zero’. In the case of online phenomena, an I_0 of 1 may represent the initial posting of a video or meme. In the case of infectious disease dynamics, I_0 might need to be seeded higher. For example, multiple infecteds might enter a population simultaneously on the same flight. We initially make the assumption that I_0 is always 1, and then go on to adapt our implementation to include I_0 as an unknown parameter.

3.3.2 The Objective Function

With a set of model equations, potential model parameters and the resulting model data at each time point, the next step is to assess how well the proposed model fits the given data. It is only through quantifying this measurement that we can then go on to find the best fitting model parameters. As discussed in section BACKGROUND, the first assessment of fit that we implement is the least squares fit. This uses the total squared difference between each model value and dataset value at each time point. The smaller this ‘sum of squared errors’ (SSE), the better the model fit. Clearly our aim is to find the set of parameters that minimises this SSE. A central part of the model fitting framework is therefore the implementation of this ‘objective function’ (Figure 3.5). Once the objective function is defined, the final step in the optimisation procedure is to transform the model parameters until the SSE is minimised.

3.3.3 Optimisation Algorithm

The next step in the model fitting framework is an implementation of an optimisation procedure to find the set of parameters that minimise the result of the objective function. In the initial *R* implementation, this is done by passing the initial seed parameters, the objective function and the data to the *optim* function. *Optim* uses the Nelder-Mead algorithm to find the set of parameters in the parameter space that return the minimum objective function value. That is, the set of parameters that evaluate to a model that most closely fits the provided data. Box 4 provides a theoretical overview of the Nelder-Mead algorithm.

Figure 3.5 Least Squares Fitting Objective Function

Takes a set of parameters and a set of epidemic data. The *ode* function then uses the LSODA solver to evaluate the *SIR* model. The sum of squared errors is then calculated from the generated model and provided data.

```
function SIR.SSE(params, data)
  t ← data[,1]
  cases ← data[,2]

  beta ← params[1]
  gamma ← params[2]

  S0 ← params[3]
  I0 ← 1
  R0 ← 0

  out ← as.data.frame(ode(y=c(S=S0,I=I0,R=R0), times=t,closed.sir.model,parms=c(beta,gamma),
  atol=1e-15,hmax=1/120))
  sse ← sum((out$I-cases) $\hat{2}$ )
end function
```

The *optim* function also provides the option to use other optimisation methods, including the “BFGS” quasi-Newton method, the “CG” conjugate gradients method and the “L-BFGS-B” method. However, we settle on the Nelder-Mead due to its robustness, and in the case of C++, its ease of implementation.

Figure 3.6 illustrates the results of running *optim* on a *GillespieSSA* generated model with known parameters.

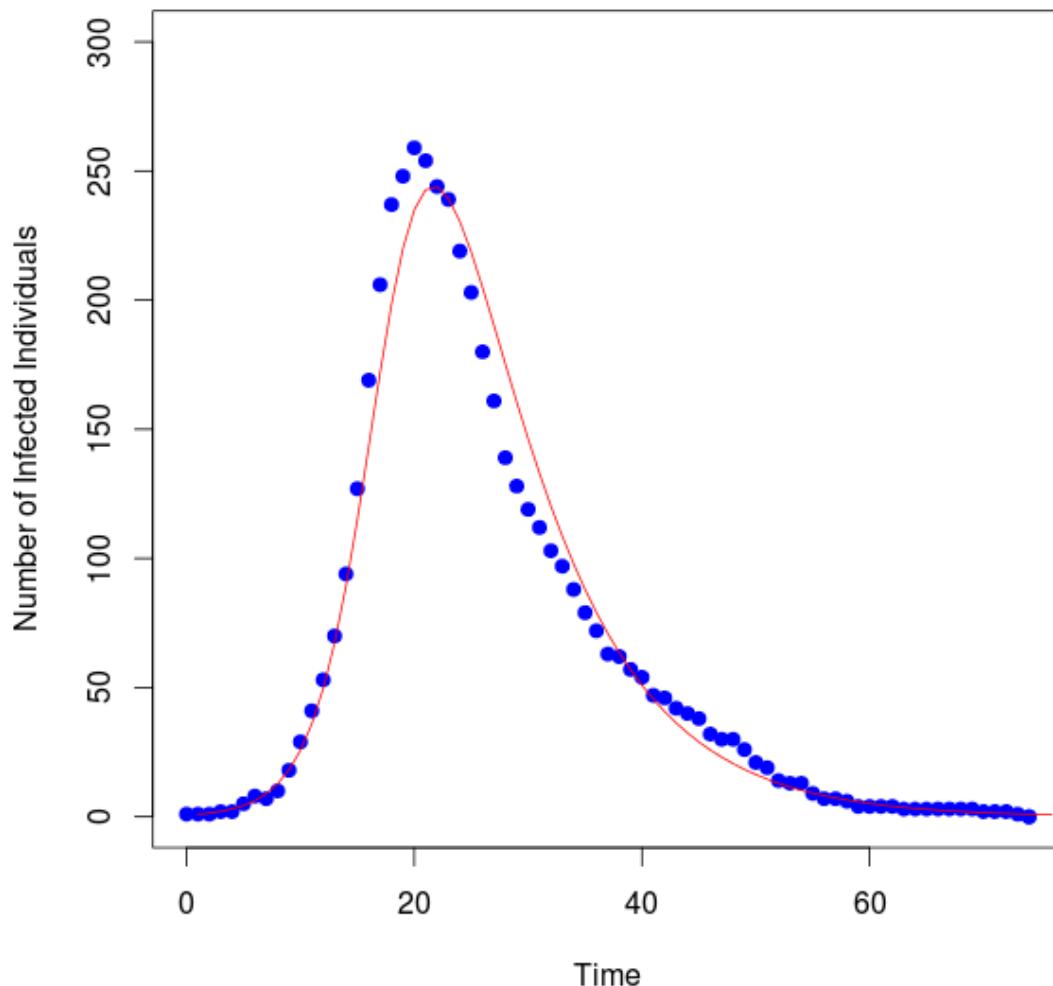


Figure 3.6: The Gillespie algorithm is run with original parameter values of $\beta = 0.001$, $\gamma = 0.1$, $S_0 = 500$. The *optim* function returns fitted parameter values of $\beta = 0.0008018066$, $\gamma = 0.1273486$, $S_0 = 618$. This results in a SSE of 5120.06.

Box 5: The Nelder-Mead Algorithm

The Nelder-Mead algorithm, or simplex search algorithm, is one of the best known and commonly used algorithms for multidimensional unconstrained optimisation without derivatives. The algorithm is relatively simple to understand and implement, which makes it an ideal candidate for solving parameter estimation problems. The method ultimately approximates a local optimum of a problem with N variables when provided with an objective function to be minimised.

Given a nonlinear function, $f : \mathbb{R}^n \rightarrow \mathbb{R}$, the Nelder-Mead algorithm uses a simplex-based search method to minimise f , where a simplex, S in \mathbb{R}^n is defined as the convex hull of $n + 1$ vertices, $x_0, \dots, x_n \in \mathbb{R}^n$. In the case of \mathbb{R}^2 , the simplex is a triangle, whereas in the case of \mathbb{R}^3 , the simplex is a tetrahedron. In the case of epidemic model fitting, each vertex of the simplex corresponds to a set of model parameters.

Starting with a set of $n + 1$ points (the initial ‘seed’ parameters) and a corresponding set of function values at the vertices, $f_i := f(x_i)$, for $j = 0, \dots, n$, the Nelder-Mead method performs a sequence of transformations on the working simplex S with the aim of decreasing the function values at its vertices. Once the method has satisfied some minimisation condition, whether it be a number of steps or a desired minimisation range, the final simplex can be used to return the optimised parameters.

The Nelder-Mead algorithm follows the following set of steps:

1. Construction of the initial working simplex, S , around an initial point based on initial parameters
2. Repeat the following steps until maximum number of iterations reached or minimisation condition satisfied:
 - (a) Calculate the function value for the current working simplex
 - (b) Check if termination criteria met
 - (c) If not met, transform towards the best vertex of the working simplex to give new vertex values with the following sub steps:
 - i. Determine the order of vertices in terms of function values (from best to worst)
 - ii. Calculate the centroid, c of the side opposite the worst vertex

- iii. Compute a new working simplex from the current simplex using a series of transformations
3. Return the best vertex of the current simplex, S, along with its associated function value.

In the transformation step, replacing the worst vertex is achieved by reflection, expansion or contraction with respect to the best side. Firstly, the worst vertex is replaced with a reflection of the best vertex. If this point provides an improvement on the current best value, then the simplex is expanded towards the new point. Otherwise, the simplex is contracted towards the current best point. If successful, then the new point replaces the worst vertex of the working simplex. If not, then the simplex is shrunk towards the best vertex. A later addition of the algorithm is to shrink the entire simplex in the event of failed contractions, though this is a rare and slow step.

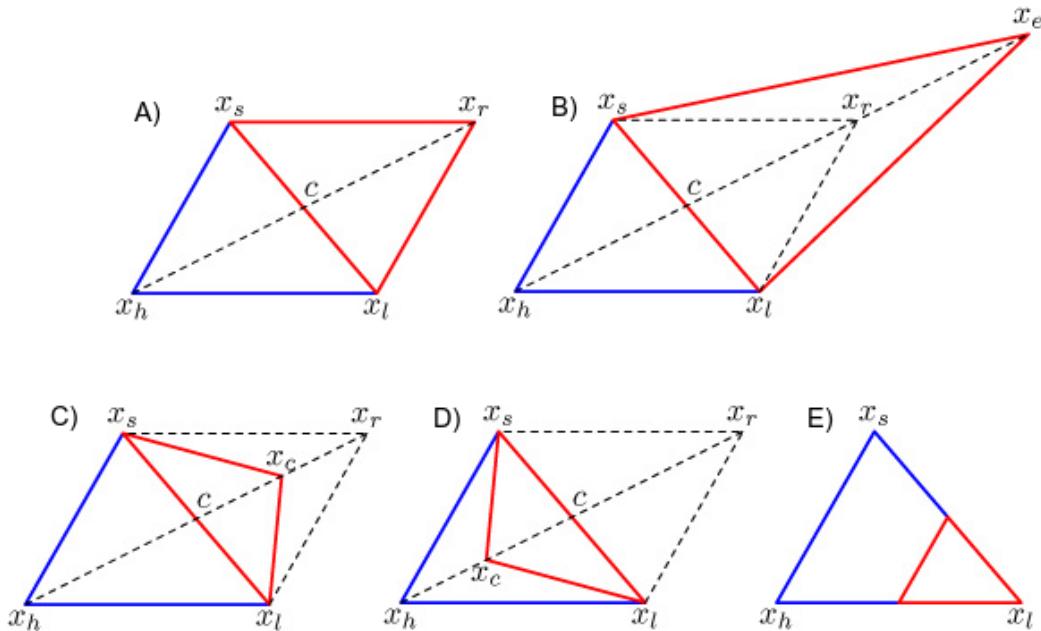


Figure 3.7: A) Reflection. B) Expansion. C) Outside contraction. D) Inside contraction. E) Shrink transformation

The Nelder-Mead method is a fast and relatively simple algorithm for obtaining a good reduction in function value in a relatively small number of function evaluations. For optimisation problems where a precise optimum (eg. parameters are subject to noise) is not necessarily required, the Nelder-Mead method is ideal. However, it is possible for the Nelder-Mead algorithm to undertake an extremely high number of iterations with little to no function value improvement at a region far from the actual minimum. A heuristic solution to this problem is to restart the algorithm at multiple start points and to only allow a small number of iterations during each run.[?, ?]

3.3.4 Parameter Transformations and Bounding

When left unmodified, the Nelder-Mead algorithm will search the parameter space in the range of $-\infty$ to $+\infty$. However, in the context of epidemic modelling, it does not make sense to consider negative parameters. By doing so, we increase the chance of the algorithm getting stuck in a local minimum and therefore returning infeasible results. We therefore carry out a *log transformation* on each parameter, only carrying out the reverse *exp* transformation within the objective function. This constrains the search space to between 0 and $+\infty$, ensuring that we do not generate meaningless parameter vectors.

3.4 Evaluating Goodness of Fit

Although the SSE provides a value which the optimisation process can aim to minimise, its magnitude is largely meaningless without appropriate context. We therefore use the coefficient of determination, R^2 , to provide an evaluation of model fit. R^2 is a widely used measure of goodness of fit in statistical modelling, and provides an ideal means for comparison between different model fits. R^2 provides a measure of what proportion of total variation in the data is explained by the model. A mathematical definition of the R^2 measure is provided in Box 5.

Box 6**The Coefficient of Determination:**

Consider a data set with observed values y_i . We would like to assess how well a set of predicted values f_i fits our data. Firstly, we consider the amount of variability in our data set using the sum of squares:

$$SS_{tot} = \sum_i (y_i - \bar{y})^2 \quad (3.6)$$

Where \bar{y} denotes the mean of the observed:

$$\bar{y} = \frac{1}{n} \sum_{i=1}^n (y_i) \quad (3.7)$$

Next, we calculate the sum of squares of the residuals. That is, the amount of discrepancy between the data and the predicted values:

$$SS_{res} = \sum_i (y_i - f_i)^2 \quad (3.8)$$

The final step is then to evaluate the amount of unexplained variance of the model with the total variance of the data. This gives us the *coefficient of determination*, R^2 :

$$R^2 \equiv 1 - \frac{SS_{res}}{SS_{tot}} \quad (3.9)$$

The resulting value is usually a number between 0 and 1, where 1 suggests that the predicted values explain all of the variance of the data (a perfect fit), and a value close to 0 implies that it explains very little of the data variance (a poor fit). Values of less than 0 are also possible, which indicates that the mean of the data provides a better model fit than the model.

3.5 Iterative Least Squares Fitting Framework

3.5.1 R Implementation

Due to the availability of relevant packages and its suitability for data manipulation, the initial fitting framework was implemented in R. The flow of control of the basic implementation is depicted in Figure ???. The framework takes a matrix or data frame of epidemic data to be fit and begins the optimisation procedure. Random seed parameters are generated and given to the optimisation function, *optim*, along with the objective function to be minimised. As the Nelder-Mead algorithm can converge on sub-optimal solutions due to the presence of local minima, the optimisation function is restarted twenty times with different seed parameters. The best fitting set of parameters are stored and passed to the analysis procedure, which evaluates the model for the given parameters and calculates the accompanying R-Square value. Finally, all of the results are passed to the output procedure for graph plotting and results saving.

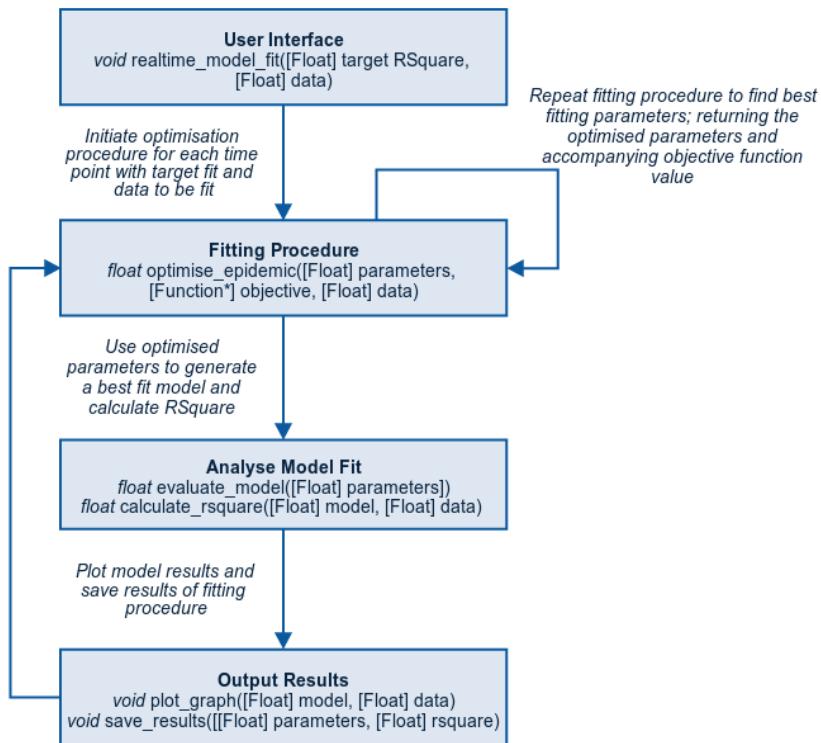


Figure 3.8: Control flow of the basic model fitting framework

To begin with, the optimisation procedure only considers beta and gamma to be unknown. The other important model parameters, S_0 , I_0 and R_0 are set to the correct values. We then adapt the framework to also consider S_0 to be a completely unknown parameter. Figure 3.9 shows how the optimisation procedure unfolds over time. The framework fits the available data points well early on; however, it does not accurately predict the main peak until sufficient data has become available. By the 40th data point, a very high

R-Square value is achieved, with parameters that closely match the ground truth parameters ($\beta=0.00111$, $\gamma=0.0946$, $S_0=506$). The inclusion of S_0 as an additional unknown parameter allows a closer model fit to be calculated.

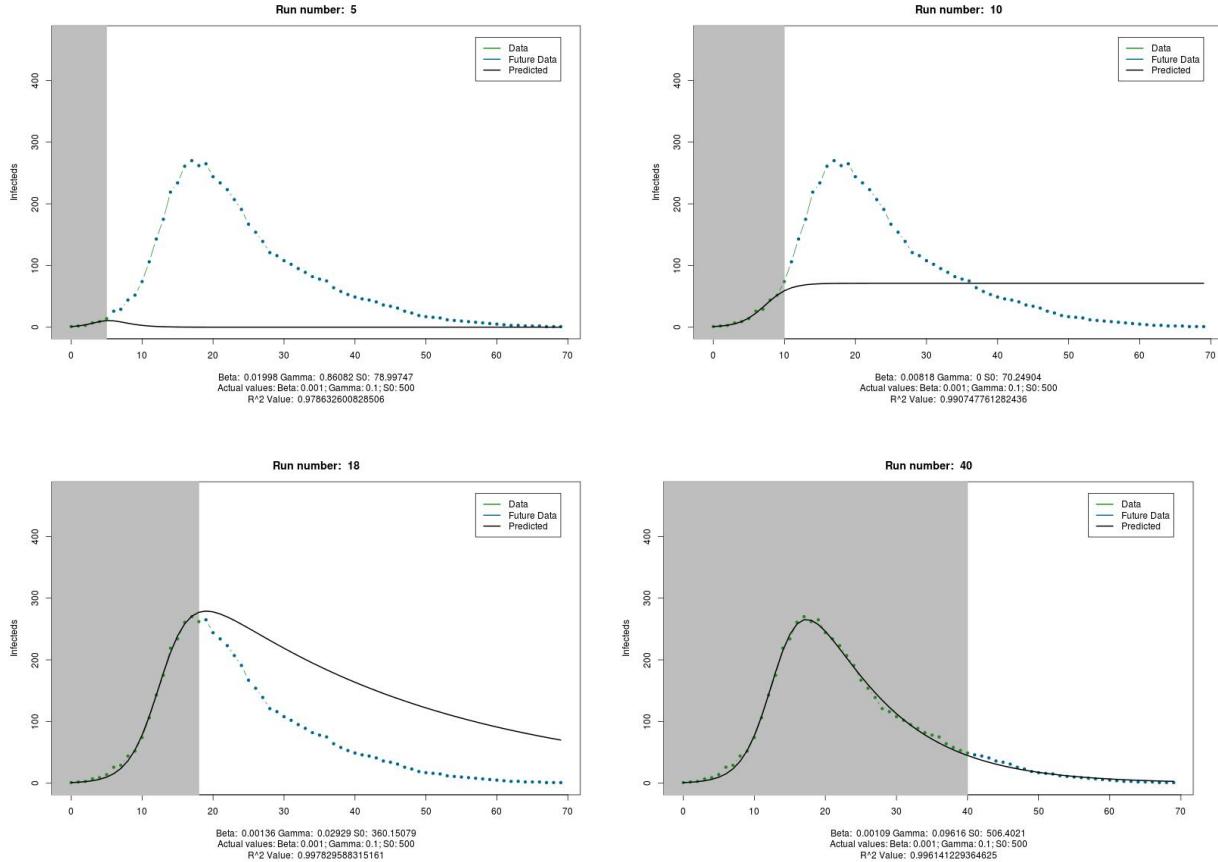


Figure 3.9: Iterative model fitting over time using least squares minimisation.

The model fitting procedure can be extended further to include the number of initial infected individuals, I_0 . Data from real epidemic phenomena might not become available until well into the start of the epidemic, and number of initial infected individuals might not immediately be available. For example, consider a *YouTube* video where views data are not collected until the video has already become viral. By including I_0 in the optimisation procedure, we are able to predict the dynamics of the epidemic as soon as it is detected. Including additional unknown parameters in the optimisation procedure provides a closer model fit but runs the risk of increase instability during optimisation as parameter transformations have a greater impact on the objective function. Figure 3.10 shows the run of the optimisation procedure where beta, gamma, S_0 and I_0 are all assumed to be unknown. Although the fits seem comparable to Figure 3.9, Figure 3.11 demonstrates how the goodness of model fit is reduced when our initial assumptions about I_0 are incorrect.

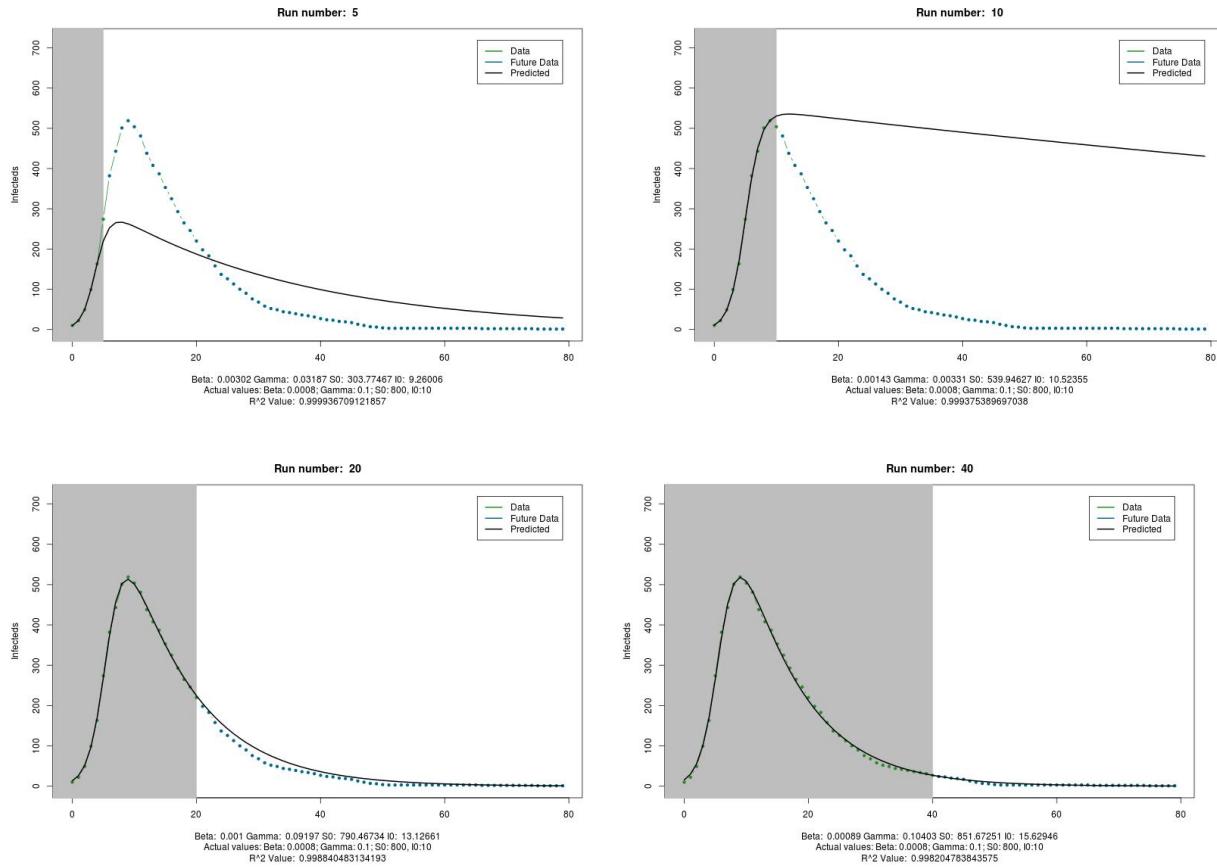


Figure 3.10: Iterative model fitting over time using least squares minimisation. I0, S0, beta and gamma unknown.

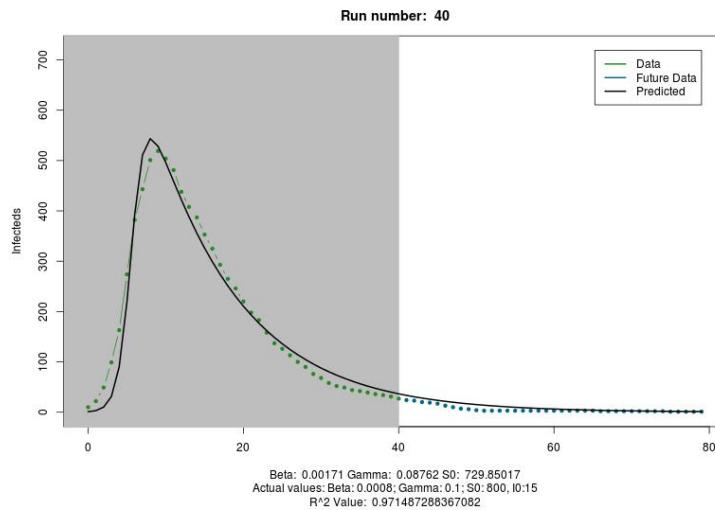


Figure 3.11: Goodness of fit reduced when inaccurate parameter assumptions are made.

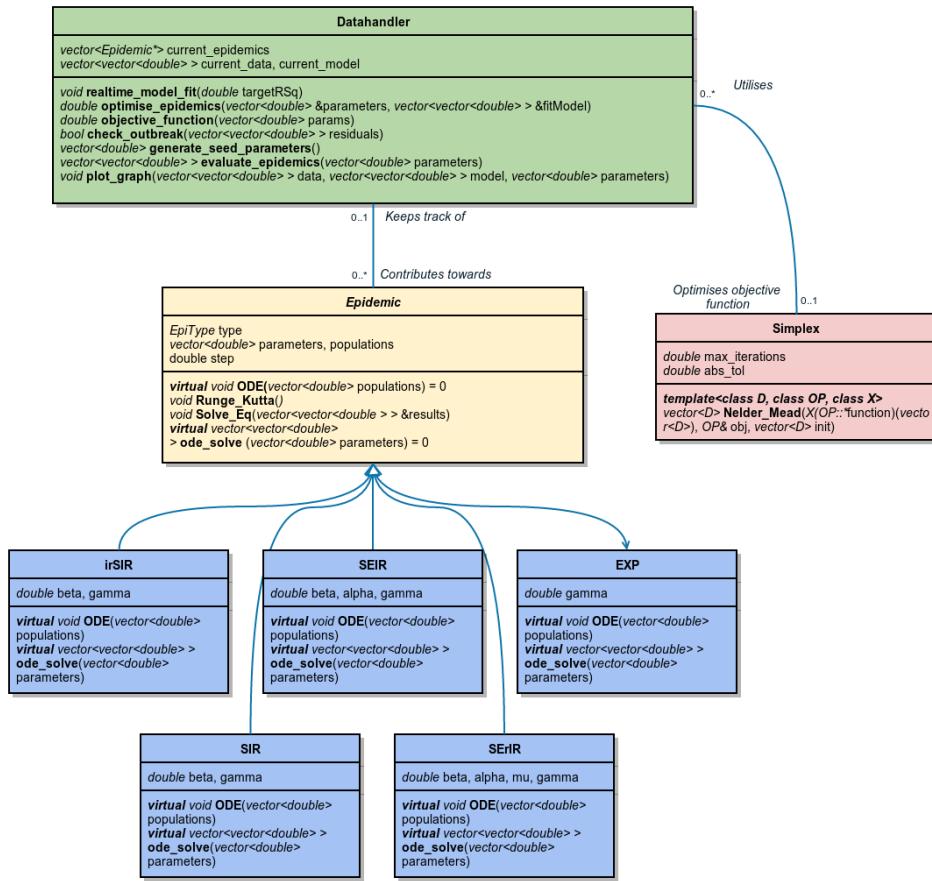


Figure 3.12: UML diagram of the model fitting framework

3.5.2 C++ Implementation

Although the implementation in R provides a simple and relatively quick fitting framework, it depends heavily on independently provided packages. By implementing the fitting framework from scratch, we are able to address any potential bottlenecks to performance. Furthermore, it has been found that C++ is much faster than R in modelling tasks.[?] On the flip side, the lack of available methods imposes a significant cost in terms of coding time on the project. A significant contribution of this project is the implementation of model fitting framework from scratch using a generalisable, objected oriented approach, allowing for the easy addition of candidate epidemic models. Figure 3.12 depicts a simplified UML diagram of the object oriented model fitting framework.

The Datahandler class keeps track of the currently available data, best fitting parameters, current model and currently active epidemics. The fitting procedure is initiated with a desired fit level, and the Datahandler proceeds to manage the overall fitting process. An objective function is formed by solving and summing the ODEs for each active epidemic, and calculating the SSE against the available epidemic data. This objective function is passed to the Simplex class, which carries out the Nelder-Mead algorithm to return an optimised

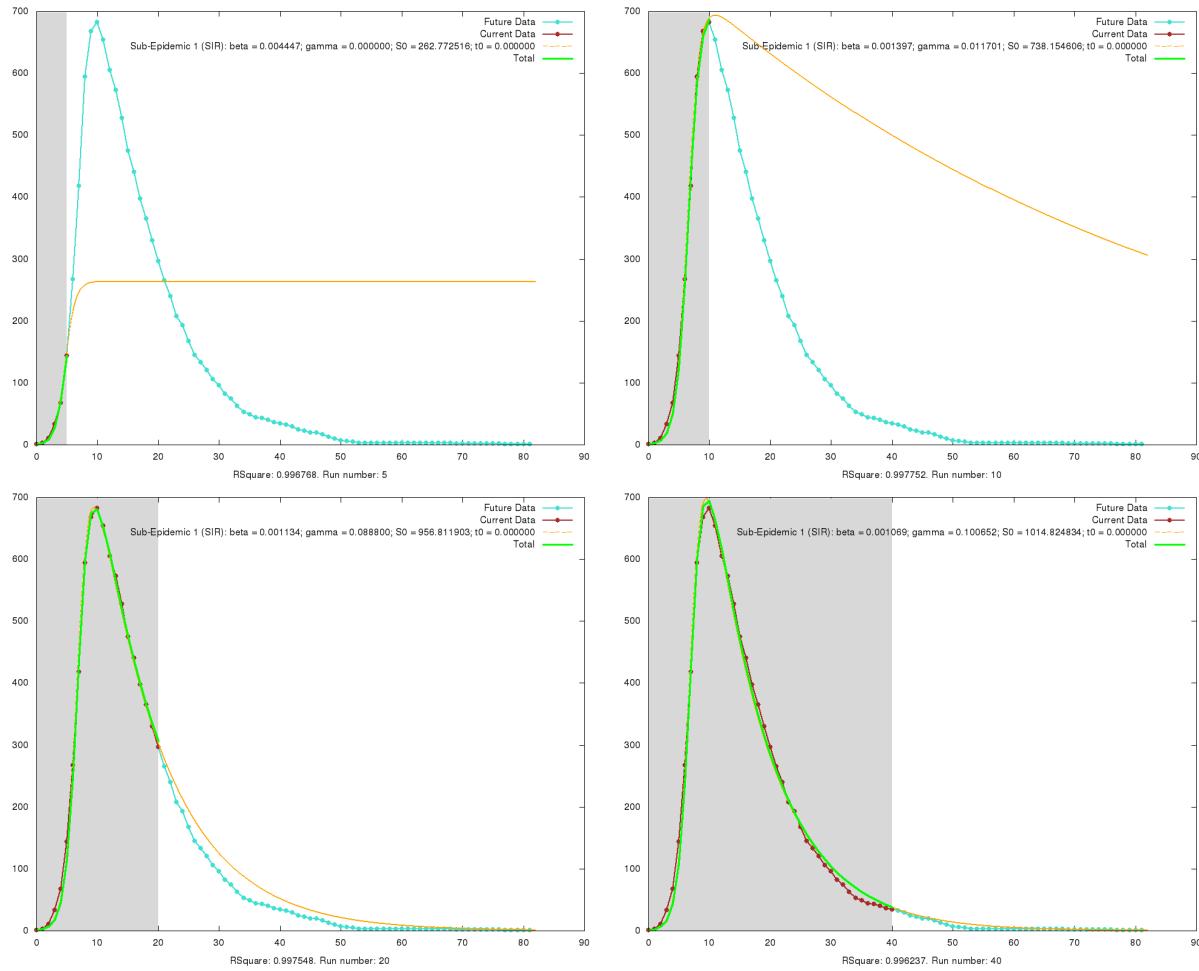


Figure 3.13: Graphical output of the C++ single model fitting framework. Beta = 0.001, gamma = 0.1, S0 = 1000, I0 = 1

set of parameters. Note that the `Epidemic` class is an abstract class, with each sub class having its own set of parameters and set of ODEs. The `Epidemic` class also holds the Runge Kutta method for solving a given set of ODEs. This allows the framework to be easily extendible to include additional types of candidate model. The `Datahandler` class also manages the analysis of model fit and the plotting of any desired graphs through the use of Gnuplot. Figure 3.13 shows the output of the iterative fitting procedure on synthetic data, where beta, gamma and S0 are assumed to be unknown.

3.6 Maximum Likelihood Based Estimation

3.7 Alternative Candidate Models

The generalised C++ implementation allows for alternative candidate models to be fit to our epidemic data. In classical epidemiology, many infectious diseases are better explained by adaptations of the *SIR* model.

For example, The HIV virus is best explained by the *SIS* model, where infected individuals do not recover but rather return to the susceptible compartment.[?] Similarly, some online epidemic phenomena have been shown to be better described by an adaptation of the *SIR* model known as the *irSIR* model, which suggests that the recovery rate is additionally dependent on the number of recovered individuals (as themes become ‘out of fashion’).[?] As discussed in section BACKGROUND, it has also recently been proposed that online viral trends might spread as either gradual “growth” or sudden “spike” epidemics, depending on whether the trend is spread slowly through social networks, or rapidly through mass exposure. An improved model fitting framework would therefore allow for the selection of a best fitting candidate model from a list of potential models.

3.7.1 Additional Models

The present fitting framework considers the SIR and SEIR as initially described in classical epidemiology.[?] We also include the Exponential Decay model to represent a “spike” epidemic and the irSIR mdoel as proposed by Cannarella et al.[?] Furthermore, we propose a novel adaptation of the SEIR model named the SErIR model. In this model, we consider the number of exposed individuals rather than the number of infected individuals as our population of interest. The rationale behind this is that in online phenomena, an individual is recorded as having seen or viewed a video regardless of whether or not they are actively spreading the epidemic. Furthermore, this model adds an additional parameters, π , which represents the rate at which individuals who are exposed to the ‘infection’ move to the recovered compartment without spreading the infection.

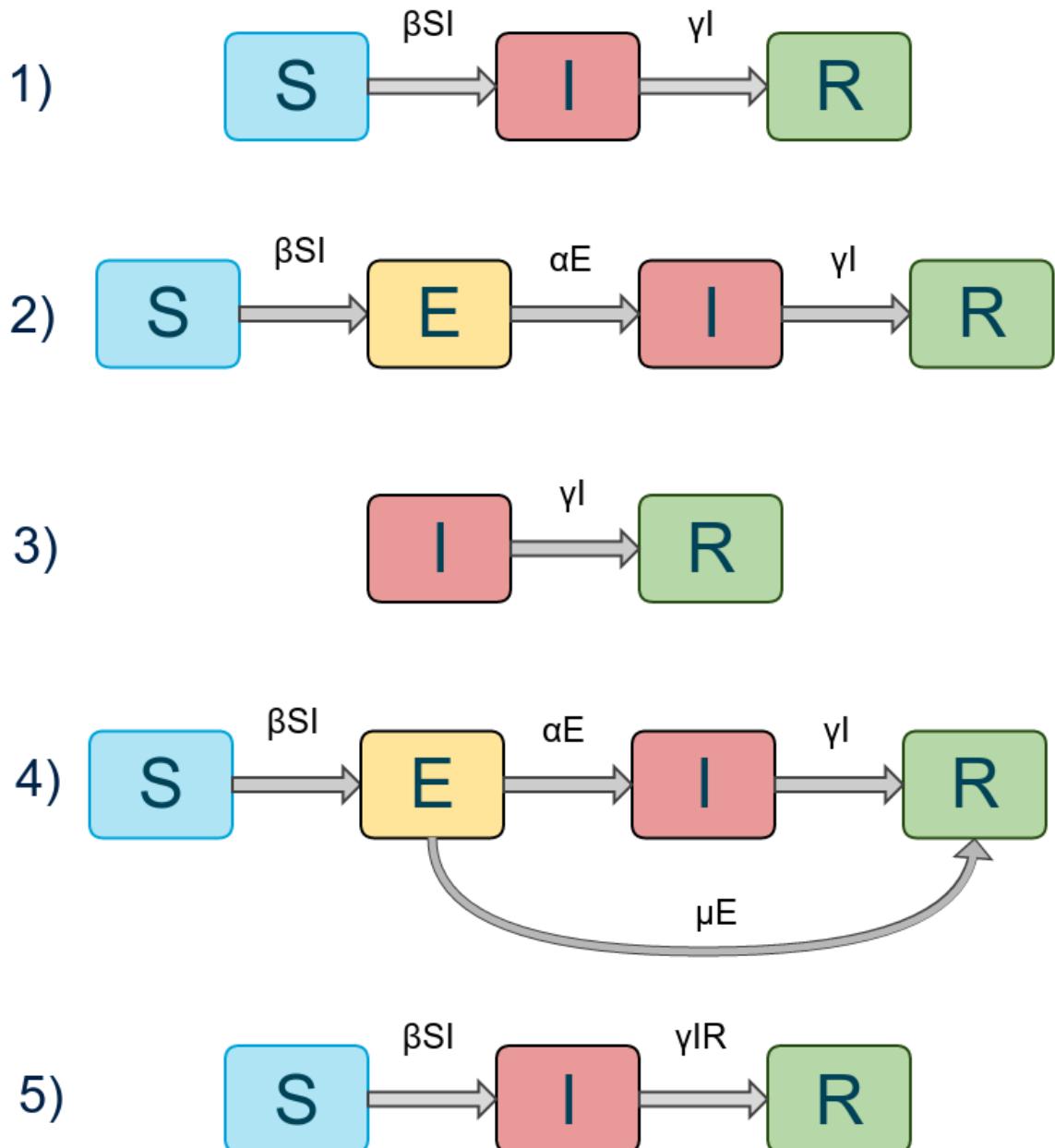


Figure 3.14: 1) SIR model. 2) SEIR model. 3) Exponential decay model. 4) Modified SErIR model. 5) irSIR model

Box 5: Candidate Epidemic Models

In addition to the *SIR* and *Exponential Decay Model* described in Box 2, we include the following epidemic models in our fitting framework:

The irSIR Model

Originally proposed by Cannarella et al., the *irSIR* model is an adaptation of the *SIR* model to consider that the rate of recovery depends on the number of recovered individuals. The classic *SIR* model considers that infected individuals recover with a set rate, γ as they fight off the infection. The idea behind the *irSIR* model is that an individual is more likely to recover from an infection if they come into contact with an already recovered individual. For example, Cannarella et al. suggest that individuals are more likely to stop using a social network site as overall usage decreases. The *irSIR* model has the following parameter vector and set of equations:

$$\theta^{(i)} = [I_0^{(i)}, S_0^{(i)}, \beta^{(i)}, \gamma^{(i)}] \quad (3.10)$$

$$\begin{aligned} \frac{dS}{dt} &= -\beta IS, \\ \frac{dI}{dt} &= \beta IS - \gamma IR, \\ \frac{dR}{dt} &= \gamma IR \end{aligned} \quad (3.11)$$

The SEIR Model

The *SEIR* is another simple adaptation of the *SIR* model that aims to better describe the course of a disease. Rather than transitioning from susceptible to infected immediately, many diseases go through a long incubation period before the infected individual becomes infectious.[?] This incubation period is described by the parameter α , where $1/\alpha$ is the mean latent period of the disease. The *SEIR* model has the following parameter vector and set of equations:

$$\theta^{(i)} = [I_0^{(i)}, S_0^{(i)}, \beta^{(i)}, \alpha^{(i)}, \gamma^{(i)}] \quad (3.12)$$

$$\begin{aligned}\frac{dS}{dt} &= -\beta IS, \\ \frac{dE}{dt} &= \beta IS - \alpha E, \\ \frac{dI}{dt} &= \alpha E - \gamma IR, \\ \frac{dR}{dt} &= \gamma IR\end{aligned}\tag{3.13}$$

The SErIR Model

A novel candidate model proposed here is the *SErIR* model; an adaptation of the SEIR model that takes into account incomplete infection spreading. Whereas individuals affected by an infectious disease will invariably spread the infection upon contact, individuals that are exposed to online viral phenomena might not go on to become spreaders. Furthermore, the measure interest becomes the ‘exposed’ rather than ‘infected’ compartment, as non-spreaders will contribute towards the data of interest. Consider the example where an individual views a *YouTube* video, but does not go on to ‘share’ the link with anyone else. We introduce the parameter, π to describe the rate at which individuals move from the exposed to the recovered compartment, where $1/\pi$ might be termed the “ignoral rate”. The *SErIR* model has the following parameter vector and set of equations:

$$\theta^{(i)} = [I_0^{(i)}, S_0^{(i)}, \beta^{(i)}, \alpha^{(i)}, \pi^{(i)}, \gamma^{(i)}]\tag{3.14}$$

$$\begin{aligned}\frac{dS}{dt} &= -\beta IS, \\ \frac{dE}{dt} &= \beta IS - (\alpha + \pi)E, \\ \frac{dI}{dt} &= \alpha E - \gamma IR, \\ \frac{dR}{dt} &= \gamma IR + \pi E\end{aligned}\tag{3.15}$$

Figure 3.15 shows the trajectories of the various candidate models when seeded with similar parameters. As individuals move out of the compartment of interest at a greater rate (namely in the *irSIR* model), the peak becomes much lower. Furthermore, the introduction of an incubation period as in the *SEIR* and *SErIR* models delays the peak of the epidemic.

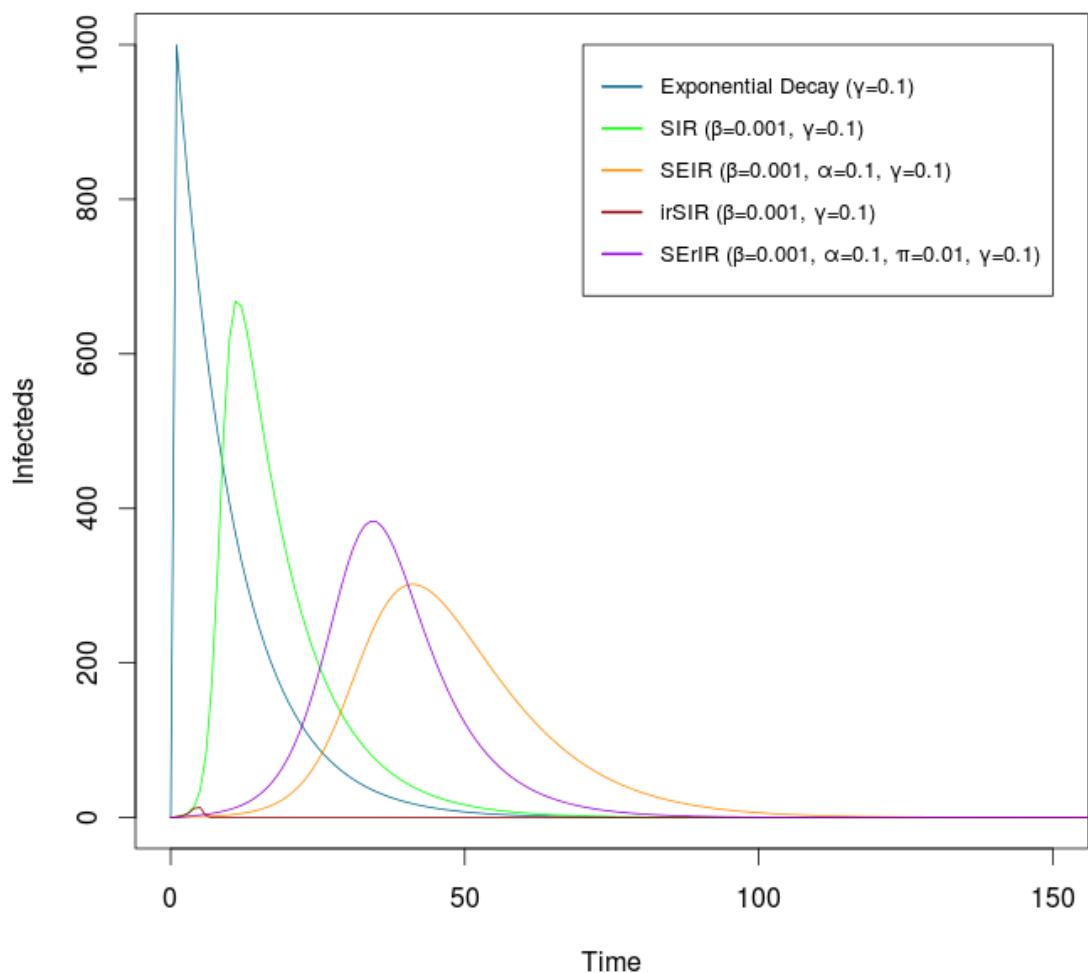


Figure 3.15: Dynamics of candidate models with similar parameters and starting susceptible population of 1000

3.7.2 Selecting a Model

The implementation described here allows the user to either fit a specified epidemic type to the set of data. All relevant transition rate parameters (eg. beta, gamma) and S0 are included in the optimisation process, and we allow the user to optionally include I0 as an unknown parameter. The user may also decide to allow the fitting framework to select the best fitting model for the data. In this case, the framework attempts to fit each candidate model and tracks the best fitting result, settling on the candidate model that best describes the data. This process is not as simple as choosing the model with the best R Square value. The shape of models with more parameters is much more adaptable by nature, as the increased number of parameters results in more inflection points. As all of the candidate models are extensions of the *SIR* model, the more complex models (*SEIR*, *SErIR*) will tend to be selected simply due to their increased complexity. To prevent this overfitting, the relative model complexity must also be taken into consideration when selecting the best candidate model.

The aim of the candidate model selection procedure is therefore to select the simplest model that provides a good fit to the data. A heuristic approach to this problem is to select the model with the fewest parameters that provides a sufficiently good fit. When considering which model to add, we first check the R Square value for each model type and only consider those models that provide a fit above a pre specified threshold. If more than one model provides a sufficiently good fit, we choose the model with the fewest parameters. If two or more models have the same number of parameters and provide a sufficiently good fit, then we are able to choose the with the highest R Square value.

A formal measure of the above heuristic is known as the *Akaike information criterion*, or *AIC*.^[?] Based on information theory, the *AIC* is a measure of statistical model quality for a given set of data that takes into account both goodness of fit and model complexity. In general terms, the *AIC* value of a model is defined as:

$$AIC = 2k - 2\ln(L) \quad (3.16)$$

where k is the number of free model parameters, and L is the maximised likelihood function. The preferred candidate model is that with the minimum *AIC* value, which therefore minimises information loss. As we are only interested in the comparative *AIC* values, we can use the δAIC value between two models. Furthermore, we can also make adjustments for small sample sizes, as is the case with our epidemic data early on in the fitting procedure. This *AICc* puts a greater penalty on complex models than the basic *AIC* score, and is defined as:

$$AICc = -2\ln(L) + 2k + \frac{2k(k+1)}{n-k-1} \quad (3.17)$$

In the scenario where we use the residual sum of squares as our objective function value, we use the following *AIC* definition:

$$AIC = n \ln(RSS/n) + 2k \quad (3.18)$$

where n is the number of data points and RSS is the residual sum of squares.

In terms of implementation, we calculate the *AICc* value for each candidate model and track the candidate model with the lowest *AICc* value. Once all candidate models have been considered, the final model with the lowest *AICc* value is chosen as the best fitting candidate model. As the first window of data points might not be representative of the entire data set, we perform this selection every 10 data points to ensure that the best model is chosen in light of recent data.

3.8 Initial Results

Due to the much greater speed of the C++ implementation along with comparable fitting accuracy, we present here the initial results of the various candidate model fitting frameworks from the C++ implementation. A more detailed comparison of the two implementations is provided in section EVALUATION. The single model fitting framework was first tested in its ability to fit synthetic epidemic data of known parameters and types. We then go on to see how well the *AICc* model selection criteria is able to identify the correct model type. Finally, we test our implementation on real influenza data from the H1N1 virus during the 2013-2014 season and the number of BitTorrent downloads of the briefly viral “*The Fox (What Does the Fox Say?)*” song.

3.8.1 Known Model Types

The model fitting framework is able to accurately and consistently fit all five types of candidate model at each time point, as depicted in figure 3.16. All of the R Square values are upwards of 0.98, which shows a very high level of model fit, and the model fit remains high throughout the fitting procedure as shown in figure 3.17. Even in the case of the more complex *SErIR* and *SEIR* model, the framework is able to produce a good model fit. An important observation is that the framework provides an optimised fit to only the available data points. This has implications for the framework’s predictive ability, which will often over or under estimate the peak of the epidemic based. Furthermore, due to the variation provided by the *GillespieSSA* algorithm, the best fitting model at some time points does not necessarily match the true data

parameters. However, once the epidemic peak has been reached, the framework is able to find values close to the true parameters and to predict the future dynamics of the epidemic with good accuracy.

In the case of the *SErIR* and occasionally the *SEIR* model, the model fitting framework occasionally produces a model fit with parameter values that are quite different to the true values. This isn't particularly surprising, as the higher number of parameters results in a higher number of high fitting models due to the highly malleable curve shape.

One important observation that was made when testing the single epidemic fitting framework was that the optimisation procedure occasionally settles on values widely outside of a realistic range that still provide a good model fit. This was particularly prevalent at earlier data points for the more complex models, possibly due to the much larger parameter search space. Figure 3.18 shows some examples of this problem. In the case of the first *SErIR* graph, the S_0 value is found to be almost 17000000000, which greatly differs from the true value of 1500. The algorithm is able to still provide a decent fit by using very high recovery values (μ and γ). A solution to this problem that is explored in the next chapter when fitting multiple epidemics is to bound the possible parameter search space to a pre defined realistic range.

3.8.2 Unknown Model Types

The next step in testing the model fitting framework is to assess how well it is able to choose the correct model type for a given data set when the model type is entirely unknown. At the start of the fitting procedure, the best of twenty optimised fits are found for each candidate model, and the model which produces the lowest AIC_c value is chosen as the correct model. To prevent the framework from becoming stuck with the wrong model type early on in the fitting process, we reconsider each candidate model every ten data points.

The model fitting framework still manages to produce a good model fit for each of the tested synthetic data sets. In the case of the synthetic *SIR* data, the fitting framework is able to correctly select the *SIR* model. This is depicted in figure 3.19, where despite choosing to use an *SErIR* model at one point during the fitting procedure, the framework is able to correctly return to using an *SIR* model. It should be noted that the best fitting model type might vary over the course of the run due to variation in the data itself.

Despite penalising more complex models using the AIC_c criteria, the fitting framework often selects an *SIR* model in place of an *EXP* model. This is unsurprising, as the *EXP* model is simply a special case of the *SIR* model when beta is very high (and susceptible individuals therefore move into the infected compartment almost instantly). Furthermore, we see in figure 3.21 that the framework often chooses between the *SErIR* and *SEIR* interchangeably. Again, the two models are closely related. As μ tends to 0, the *SErIR* model

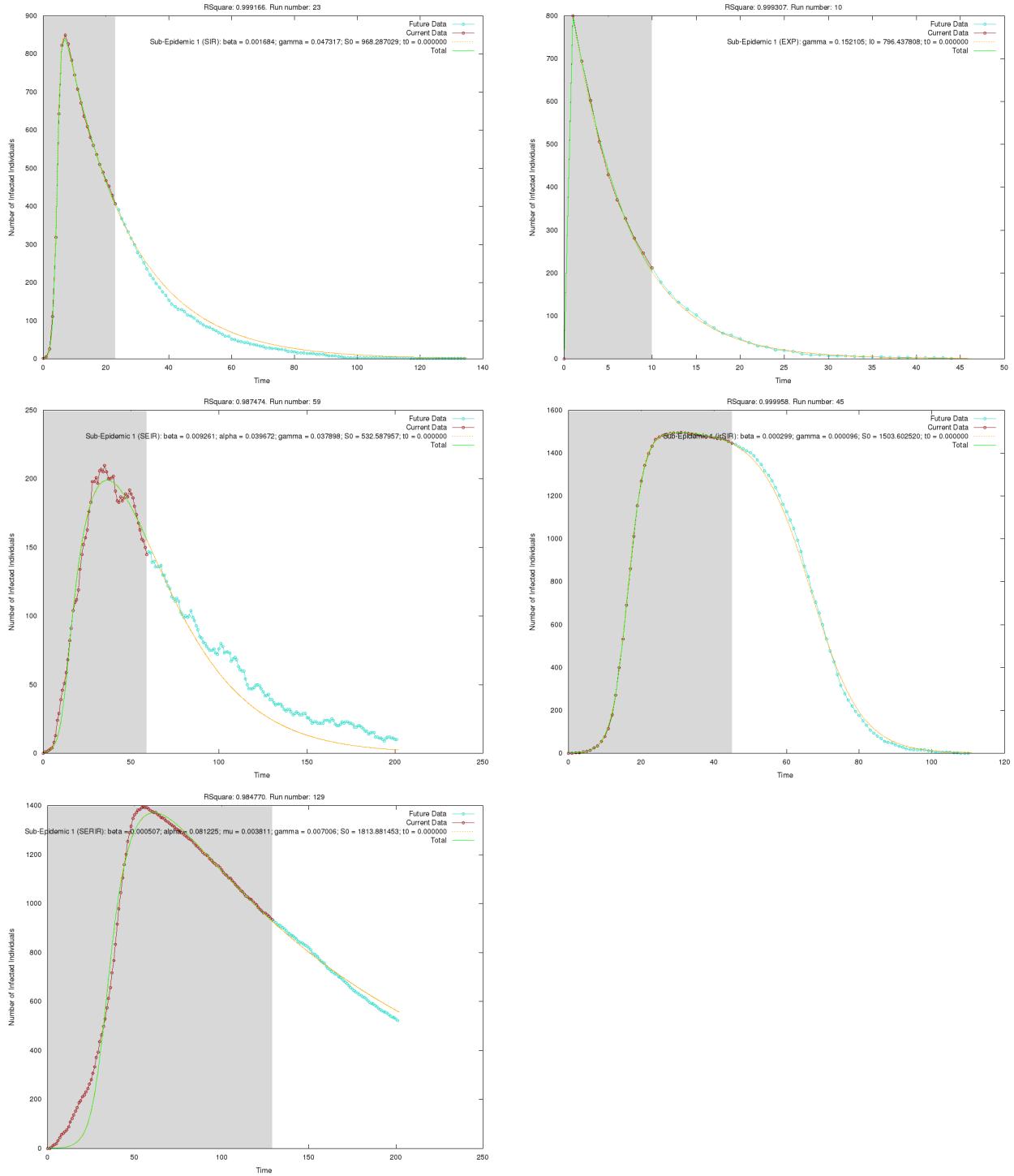


Figure 3.16: Samples graphs of various candidate model fits (true parameter values in brackets): 1) SIR (0.0015,0.05,1000); 2) EXP (0.15,800); 3) SEIR (0.02,0.02,0.05,800); 4) irSIR (0.0003,0.0001,2000); 5) SERIR (0.005,0.002,0.002,0.01,1500)

tends to the equivalent *SEIR* model.

Although all of the models can produce similar shapes due to their high level of similarity, we would still expect the *AICc* criteria to penalise any model that is unnecessarily complex such that the simplest model is chosen. This case is only satisfied in the situation that a maximally optimised fit is produced for each candidate model. However, by choosing random parameters to start each optimisation, the optimisation

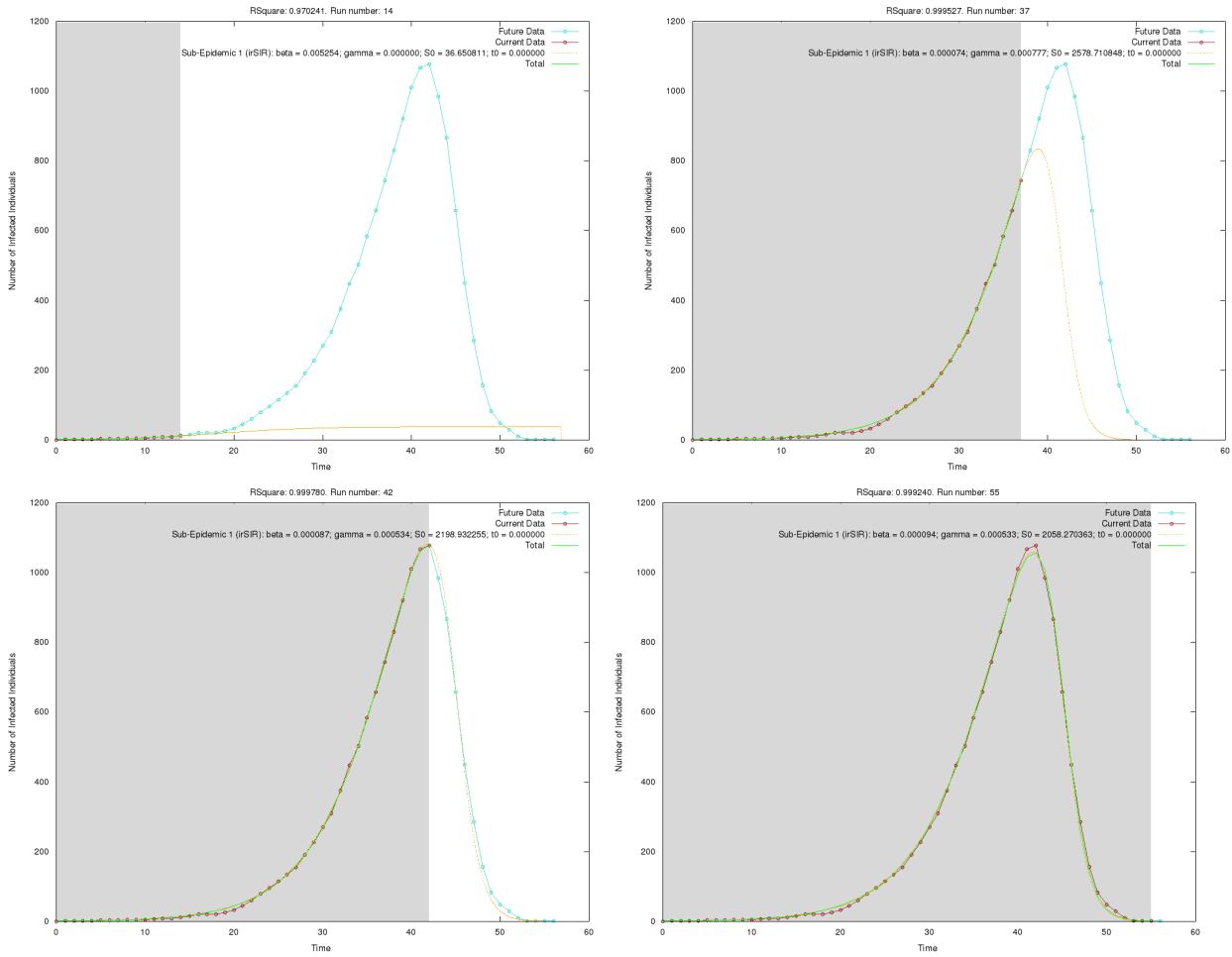


Figure 3.17: Model fitting over time on an irSIR model with parameters of $\beta = 0.0001$, $\gamma = 0.0005$, and $S_0 = 2000$

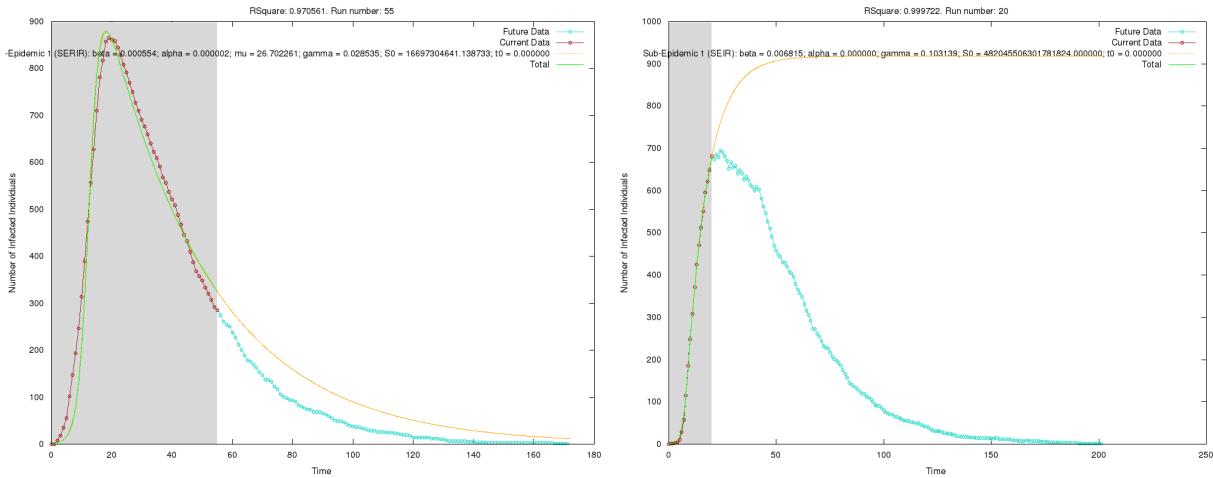


Figure 3.18: Model fits of an SEiR and SEIR model where unrealistic values provide a decent model fit

might return slightly sub optimal parameters some of the time. For example, the best run from random parameters for an *SIR* model might produce an R Square of 0.97, whereas the run using an *SEiR* model might produce a fit of 0.99 simply as a result of being seeded with better initial parameters.

The problem of incorrect model selection might be countered by using a greater number of random runs

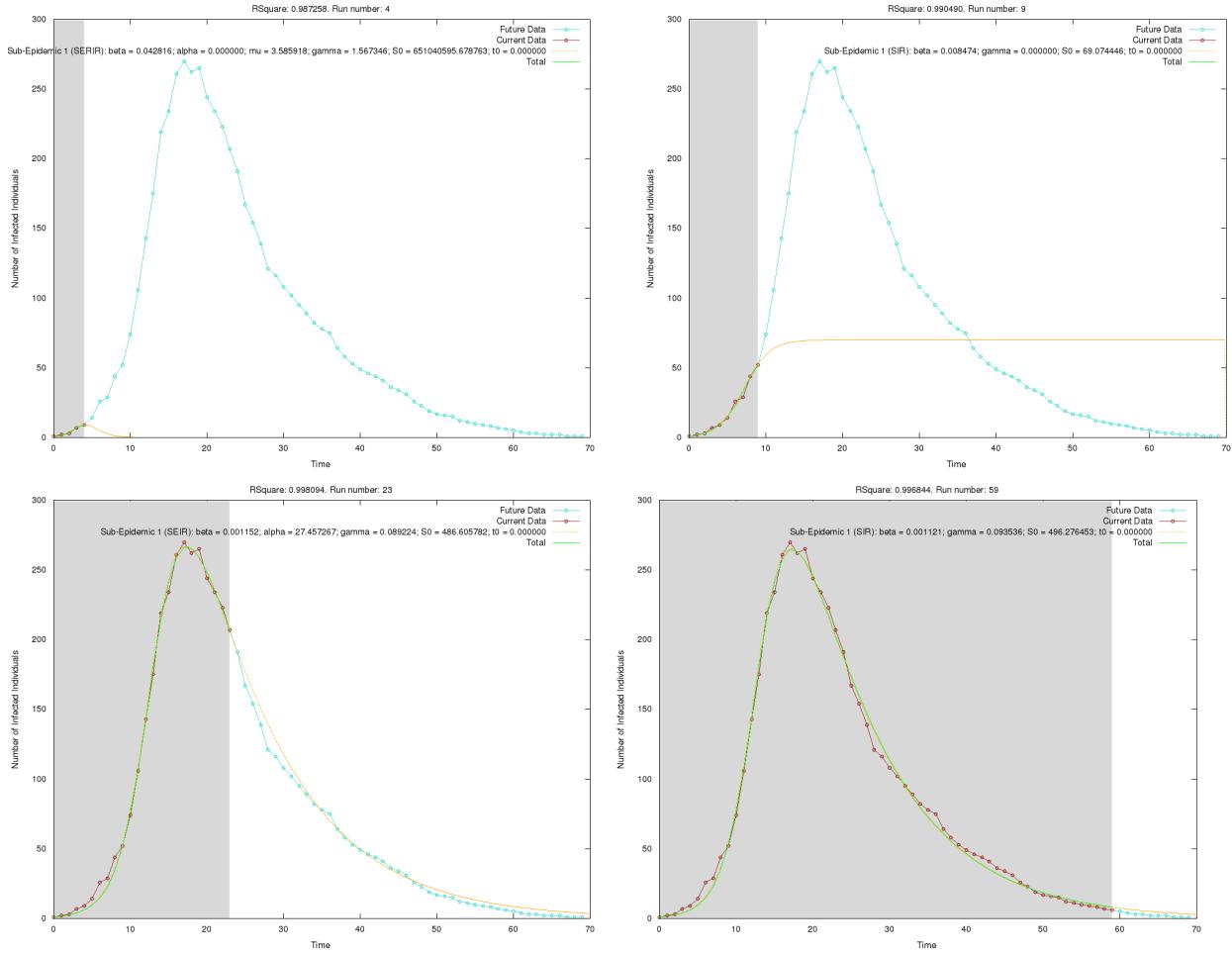


Figure 3.19: Fitting procedure on an SIR model where the model type is assumed to be unknown

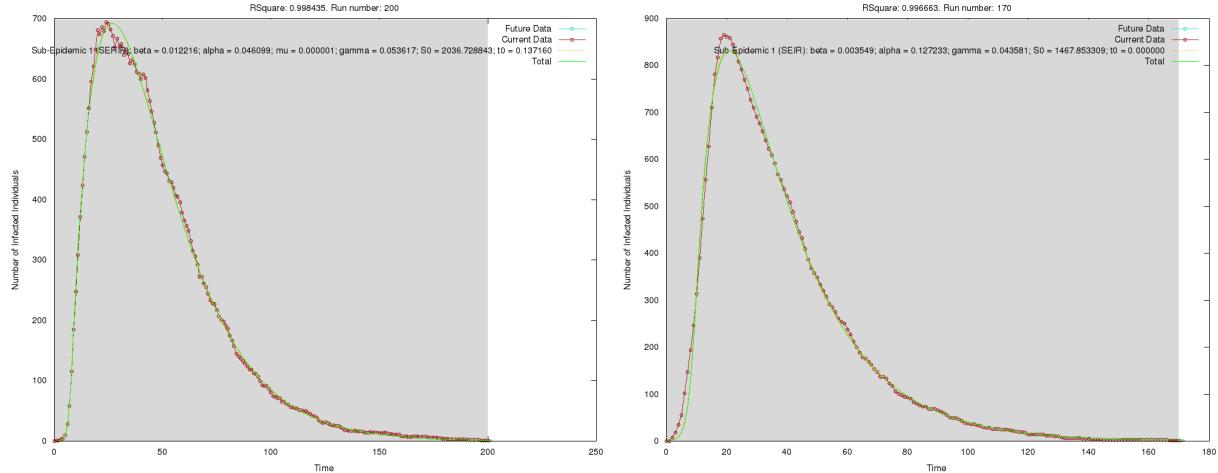


Figure 3.20: Interchangeable selection of the similar SERIR and SEIR model types

and by decreasing the error tolerance of the Nelder-Mead algorithm to ensure that all model fits find the global minimum rather than a similar local minimum. Similarly, we might also increase the max number of iterations allowed in the Nelder-Mead algorithm, but this limit is not currently reached. However, these adjustments will drastically increase the amount of time taken for a full optimisation run. This therefore represents an important trade off to be considered when deploying the fitting framework. Another potential

solution would be to use alternative means of model selection. The $AICc$ score may not sufficiently penalise more complex models when the difference in number of parameters is minimal and the number of data points is high. An alternative might be to simply select the model with the fewest parameter that satisfies some desired fit value.

3.8.3 CDC Influenza Data

To put the model fitting framework to the test, we attempt to characterise the CDC infected data for the H1N1 virus during 2013 to 2014. The fitting framework is able to choose and fit a model to the data with very high accuracy, selecting the *SIR* model for the duration of the fitting procedure, and generating an R Square value of over 0.99 consistently once the peak is reached. The predicted trajectory of the epidemic matches the future data well.

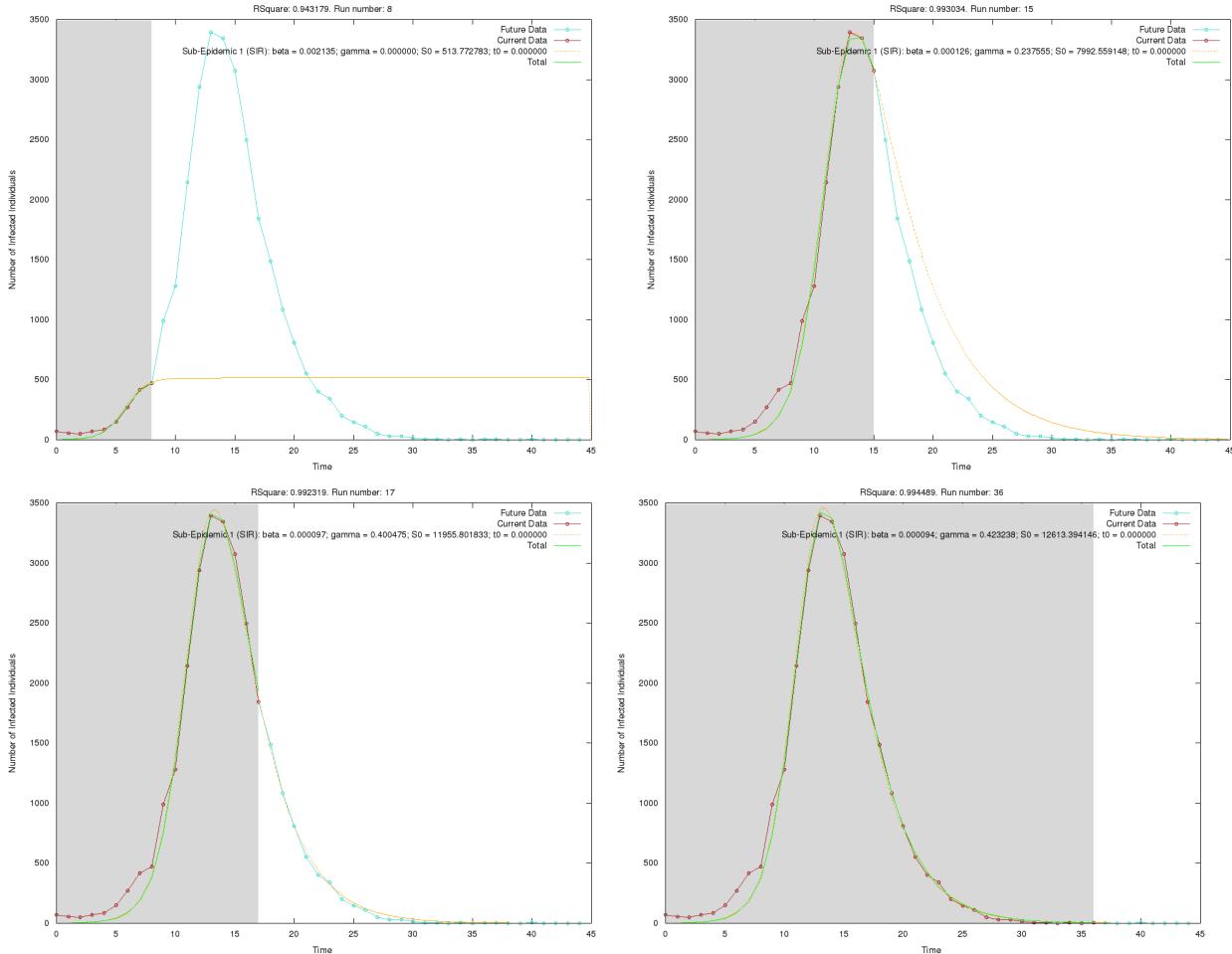


Figure 3.21: Fitting procedure on the 2013-14 H1N1 CDC flu data

We go on to test the fitting framework on the AH3 virus during 2010 to 2011, but this time include the initial number of infected individuals, I_0 , as an additional unknown parameter. Again, the framework is able to characterise the data with a high R Square value throughout. In this case, the type of model chosen changes

during the fitting, but settles on a high fitting *SIR* model by the end.

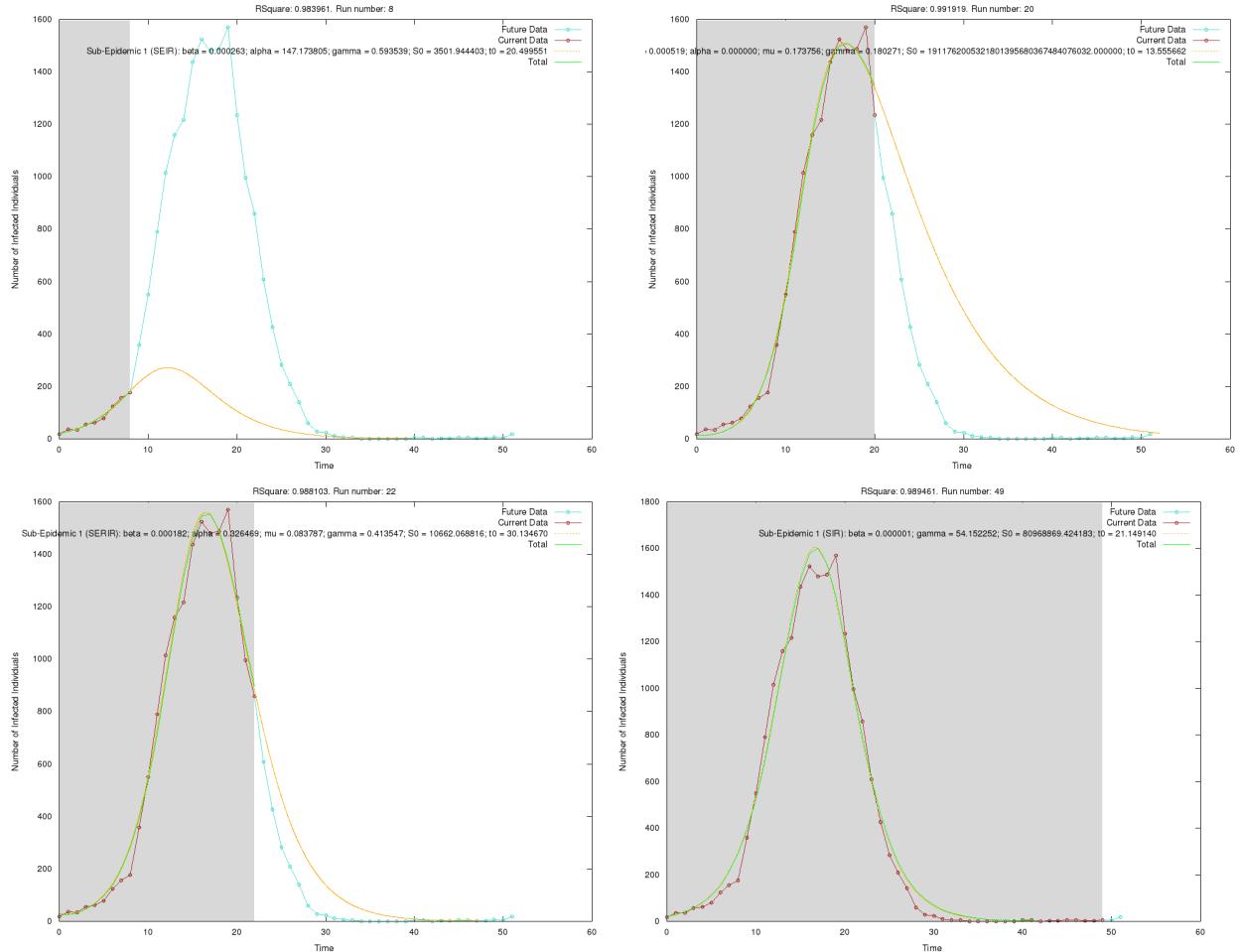


Figure 3.22: Fitting procedure on the 2010-11 AH3 CDC flu data, with I_0 considered unknown

3.8.4 Internet Epidemic Data

In addition to conventional infectious disease epidemic data, we wish to test how well the model fitting framework can characterise epidemic phenomena on the internet. Figure 3.23 shows the application of the fitting framework to the number of daily *BitTorrent* downloads of the viral song “*The Fox (What does the Fox say?)*” between September 2013 and August 2014. The large peak corresponds to the single release in Norway on October 11th 2013. The framework detects and characterises the initial small peak accurately, and adapts to characterise the overall peak as the fitting procedure continues. By the end of the fitting, the framework has characterised the data with an *SERIR* model with an R Square value of 0.909.

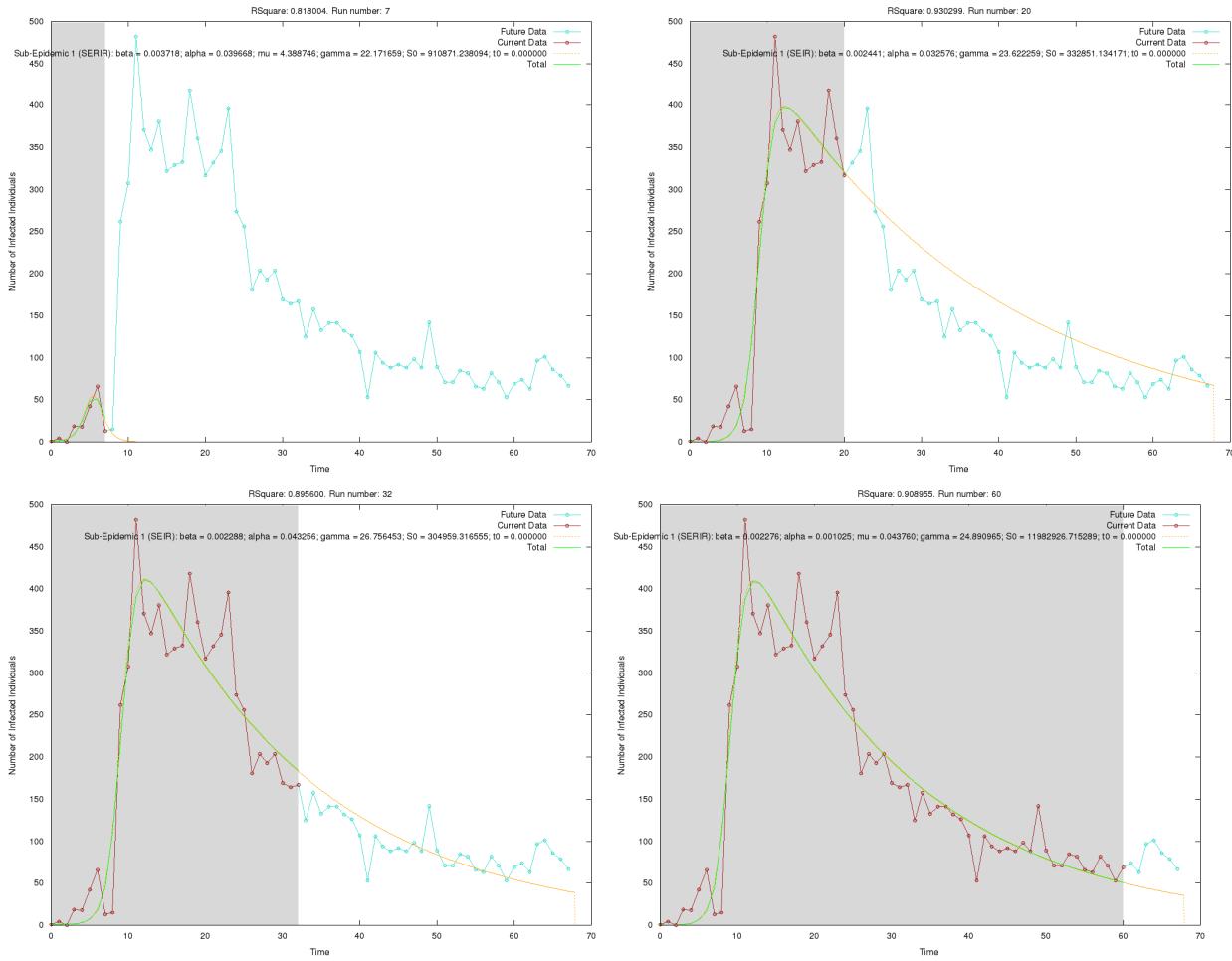


Figure 3.23: Fitting procedure on the 2013 viral hit, “The Fox (What does the Fox say?)”

3.9 Chapter Summary

In this section we have discussed the implementation and trial of an R and C++ model fitting framework. The C++ framework is implemented from scratch, using the Runge-Kutta method for solving ODEs, and the Nelder Mead algorithm for optimisation. We assume that the transition parameters and initial number of susceptibles, S_0 , are entirely unknown, and also consider the case where I_0 is known. We include five types of candidate model and attempt to select the best fitting model using the $AICc$ score, and show reasonable success. The framework is tested using synthetic data, real influenza data, and *BitTorrent* download data. In all cases we are able to provide a model with a high R Square fit.

Chapter 4

Synthedemic Modelling

The classic epidemic model brings to mind images of a single curve with a single peak. When measuring the spread of a single infectious disease within a closed population, this is often a realistic characterisation. For example, the number of people in London infected with a new strain of flu virus might resemble this curve.

Recent work has highlighted the limitations of the single epidemic based approach in characterising certain epidemic phenomena, particularly with regards to viral internet trends.[?, ?] A recent adaptation of the field of *synepidemiology* termed *synthemics* has been proposed as a potential avenue of further research. The key challenges of the synthedemic modelling procedure are to identify the number of underlying epidemics, to identify when these sub epidemics start, and to identify the type of epidemic model that best describes each sub epidemic. Furthermore, as the number of included sub epidemics increases, so to do the number of parameters to be optimised the corresponding parameter search space.

In this section we discuss an implementation that aims to address these challenges, and the particular problems and solutions that arise during the course of the project.

4.1 Identifying Sub Epidemic Start Time

In the single epidemic fitting framework, it is assumed that there is only one epidemic in the dataset, and that it can be considered to have started right from the start of the data, t_0 . However, when considering multiple epidemics simultaneously, it is not possible to make this assumption, as multiple sub epidemics might start and finish during the iterative fitting procedure. Furthermore, when multiple epidemics are progressing simultaneously, it might not be possible to detect the start of a new epidemic until it is well underway. The

start time of the epidemic therefore might (and probably will not) match the detection time. The first step in developing a synthedemic model fitting framework is therefore to implement a means to detect and record epidemic start times, and to consider how these start times will be included in the optimisation procedure.

4.1.1 Epidemic Detection

4.1.2 Optimising Epidemic Start Times

Once an epidemic outbreak has been detected, the next challenge is to find the actual start time of the epidemic. Simply using the detection time of the sub epidemic as the actual start time is unsatisfactory, as it assumes that the detection procedure will pick up a new outbreak as soon as it starts. Some sub epidemics will be hidden within larger outbreaks and may not be detected until well into their course.

An initial naive approach to finding the start time of each sub epidemic might be to consider each possible combination of epidemic start times. If we consider every possible start time, this would result in n optimisations for a single epidemic, where n is the number of data points currently available. As soon as multiple epidemics are considered simultaneously, this quickly becomes infeasible as the complexity increases with the number of sub epidemics. An heuristic adaption to this is to only consider a subset of start time combinations. For example, we can consider only the start times within a window of the detection time, and assume that the ordering of start times does not matter. This results in tCn combinations of start times, where t is the number of time points under consideration, and n is the number of epidemics to be fit.

Although such heuristics might provide a conceptually simple optimisation approach, they avoid the problem of including t_0 in the optimisation procedure directly. Doing so allows for the start time of each sub epidemic to be found precisely. Furthermore, doing so allows us to consider the start time as a continuous variable, making the model fit much more accurate. We therefore chose to initially include t_0 as an unknown parameter in the optimisation procedure. Giving the Nelder Mead algorithm a completely random time as a seed value risks producing an extremely high initial SSE value. We therefore use the detection time minus a small value (to account for delayed detection) of the epidemic as the seed value for the optimisation procedure.

4.2 Initial Approach

The initial approach aims to iterate over a set of epidemic data, where it is not assumed that there is an ongoing epidemic from the start. We include the transition parameters, beta and gamma, as well as S0 and

t_0 in the optimisation procedure. As in the single fitting framework, at each time point we produce random seed values and choose the best run from ten independent as the best fitting model. T_0 is seeded as the detection time of the epidemic. We first fit the currently known k epidemics, and then consider the addition of an epidemic when the model fit has deteriorated sufficiently and the latest residual is a certain number of standard deviations away from the previous residuals' mean. By only adding an additional epidemic when the model fit has deteriorated sufficiently, we avoid needlessly overfitting the data when an outlying data point might falsely suggest the start of a new epidemic.

We initially consider only SIR models, which result in a combined parameter set of $(\beta^{(k)}, \gamma^{(k)}, \S_0^{(k)}, t_0^{(k)})$ to be optimised. One risk of only considering the addition of epidemics is that we risk overfitting the data. To avoid this, we also consider the removal of a sub epidemic at each time point. This is done by removing each sub epidemic from the current set in turn and reoptimising the remaining model. If this fit of $k - 1$ epidemics is sufficient, we permanently remove the epidemic from the list.

4.2.1 Practicality Considerations

As the fitting process is a computationally time intensive procedure, we adhere to the following heuristics to prevent the run time from becoming infeasible:

1. Only one epidemic is added or removed at each stage.
2. For SIR epidemics (and sub types in later implementations) we assume that the number if initial infected individuals is 1.
3. For EXP epidemics, the number of infected individuals is included as an unknown parameter. A potential simplification of this is to use the difference between the current best fitting model and the time point at which the epidemic is detected. However, this does not allow for the possibility that our current best fitting model might not be optimal.
4. The seed time for t_0 for SIR type epidemics is taken as the detection time minus 10, and searched within the range $t - 50 \leftarrow t$, where t is the detection time.
5. At each time point, we choose the best of 10 independent optimisation runs for k epidemics and $k - 1$ epidemics, testing the removal of all current epidemics to prevent overfitting. When adding epidemics, we consider adding each candidate model if the latest residual is over three standard deviations away from the mean residual size.

4.2.2 Initial Testing

The multiple epidemic fitting framework was firstly tested using synthetic data generated by the *GillespieSSA* algorithm in R. To simulate multiple overlapping epidemics, we run *GillespieSSA* for each sub epidemic and offset the values by the desired t_0 ; adding the infected values of each sub epidemic on the corresponding time points. Two *SIR* models were combined with the following parameters:

$$\beta^1 = 0.001, \gamma^1 = 0.1, S_0 = 500, t_0 = 10$$

$$\beta^1 = 0.0008, \gamma^1 = 0.008, S_0 = 800, t_0 = 30$$

The initial implementation detected the start of the first epidemic at $t = 14$, and proceeded to accurately fit the the epidemic. At around $t = 30$, the second epidemic was detected and added to the optimisation procedure. The R Square value for the model fit to the currently known values remains high throughout the fitting procedure at over 0.99, though it does occasionally fall to around 0.95. This is likely due to poor initial seed values.

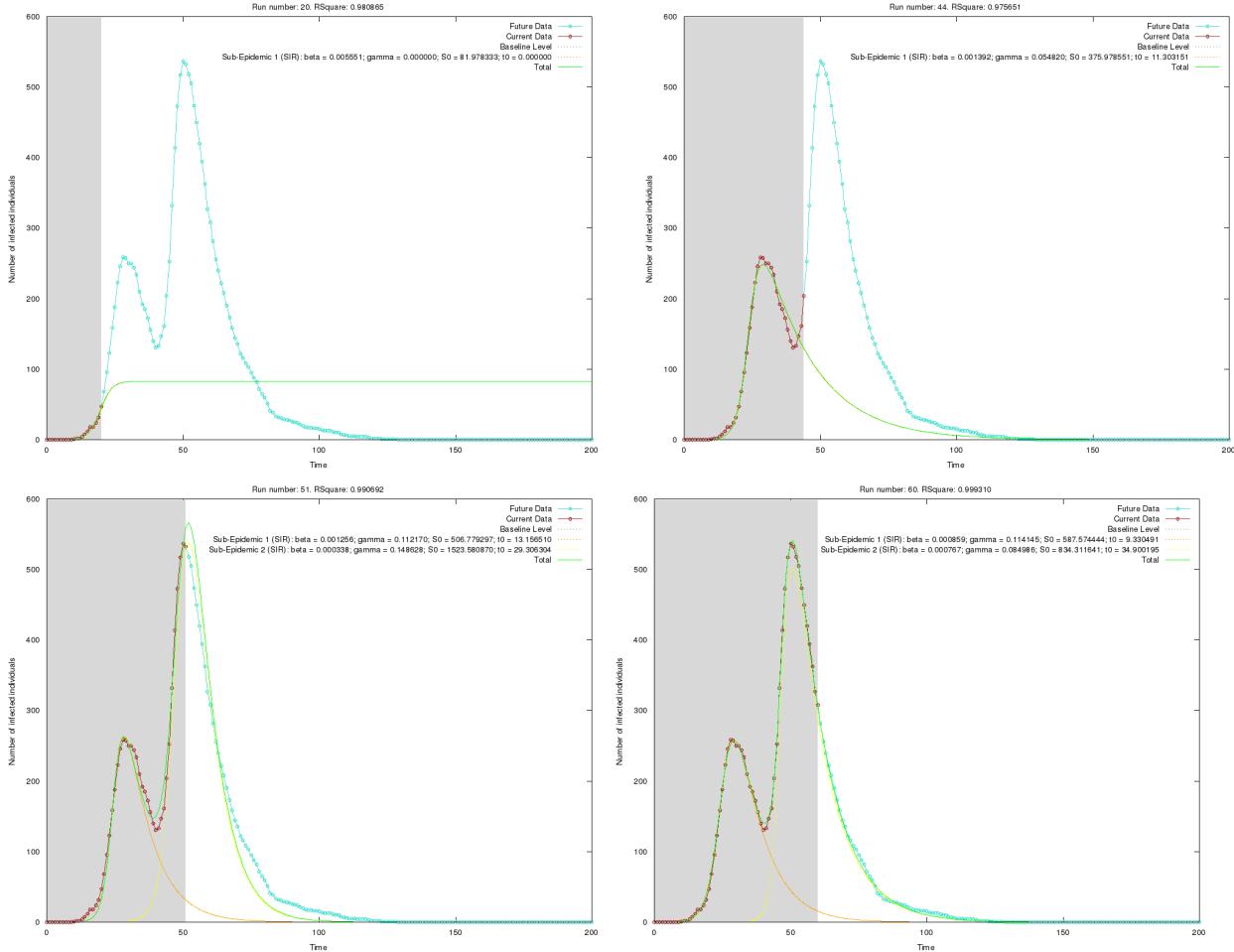


Figure 4.1: Multiple epidemic fitting procedure on two overlapping SIR models

As in the single epidemic fitting framework, a problem that occasionally occurred was that the the optimisa-

tion procedure occasionally tended towards values far outside the range of realistic values. For example, the optimisation makes S_0 very large as it explores a particular local minimum. Furthermore, the inclusion of t_0 as an additional parameter makes the optimisation procedure much less stable, particularly when uncertainty in other model parameters is high. This results in a model fit that is not quite as good as we might hope, particularly when considering earlier sub epidemics.

4.2.3 Parameter Transformations and Bounding

A potential way of limiting the space in which the Nelder-Mead algorithm searches for parameters is to bound the parameters. As discussed in section SECTION, it is often desirable to transform the model parameters into log space. Another potential transformation that may be applied is through the use of the *logistic* function. Originally studied in the context of population growth, maps the parameter search space from between 0 and 1 to between $-\infty$ and $+\infty$. The function is defined as:

$$\text{logistic}(x) = \frac{1}{1 + e^{-x}} \quad (4.1)$$

The inverse of the logistic function, the *logit* function, can therefore be used to map the search space of a parameter, p , from between $-\infty$ and $+\infty$ to between 0 and 1. The logit function is defined as:

$$\text{logit}(p) = \log\left(\frac{p}{1 - p}\right) \quad (4.2)$$

The logit function can be modified to transform the search space from between 0 and 1 to one between 0 and \max as follows:

$$\text{newLogit}(x) = \frac{\max}{1 + e^{-x}} \quad (4.3)$$

with the inverse defined as:

$$\text{newLogistic}(x) = \log\left(\frac{x}{\max - x}\right) \quad (4.4)$$

The logic behind this modification can be expanded further to use the logistic function to provide lower bounds as well as upper bounds. As $x \rightarrow +\infty$, $\text{logit}(x) \rightarrow 1$. Similarly, as $x \rightarrow -\infty$, $\text{logit}(x) \rightarrow 0$. We can therefore modify the logistic function as follows:

$$f(x) = \frac{x_{\max} - x_{\min}}{1 + e^{-x}} + x_{\min} \quad (4.5)$$

We can see that as $x \rightarrow +\infty$, $f(x) \rightarrow x_{max}$, and as $x \rightarrow -\infty$, $f(x) \rightarrow x_{min}$. By limiting the parameter search space to a predetermined range of expected values, we ensure that the optimisation procedure does not get stuck in a local minimum far away from the actual parameter values. However, doing so requires us to make assumptions regarding where the real parameter values might lie. Whilst a good model fit might be produced within a provided range of parameter values, this fit might be sub optimal compared to the model produced from a set of entirely unexpected parameters.

An alternative, simple approach to bounding parameter values in the optimisation procedure is to modify the results returned by the objective function. As the Nelder Mead algorithm transforms parameter values with the aim of minimising the objective function, we can direct the parameter search by ensuring that the objective function returns high values when venturing into an undesirable parameter space. For example, we can include a simple check of each parameter with each call of the objective function; returning a high SSE value if the parameter is outside our desired range. This method was implemented initially; however, it appeared to result in the Nelder Mead algorithm returning nonsense values more frequently as it failed to identify any local minima. This is due to the fact that the optimisation surface becomes much less smooth, as each check outside of the specified bounds results in a sudden spike in function value.

Using the above methodology, we initially add constant limits to S_0 and t_0 ; ensuring that S_0 stays within the range 100-15000, and t_0 stays within the range of data (typically 0-200). Although this did improve the stability of the fitting procedure, it was found that the range of possible t_0 values could be limited further. Rather than using 0-200, we use a window of time around the detection time. We use the detection time of the epidemic as the upper bound of the transformation, and $t - 40$ as the lower bound.

4.3 Implementation Revision with Parameter Bounding

Figure 4.2 shows the results of the fitting procedure on the same two overlapping SIR models usnig logistic bounding on S_0 and t_0 . As in the previous implementation, the fitting procedure maintains a high R Square value throughout, and accurately detects the second epidemic. With an effective multiple SIR fitting framework, we then attempt to consider the addition of an EXP model. As dicussed in the context of single epidemic model fitting, we add the candidate model that produces the best model fit in terms of $AICc$ value. For t_0 bounding, we use a very narrow optimisation for the EXP epidemic. Figure 4.3 shows that the framework is able to accurately detect and fit both the SIR and EXP model throughout the fitting procedure.

The true parameters used in figure 4.3 are:

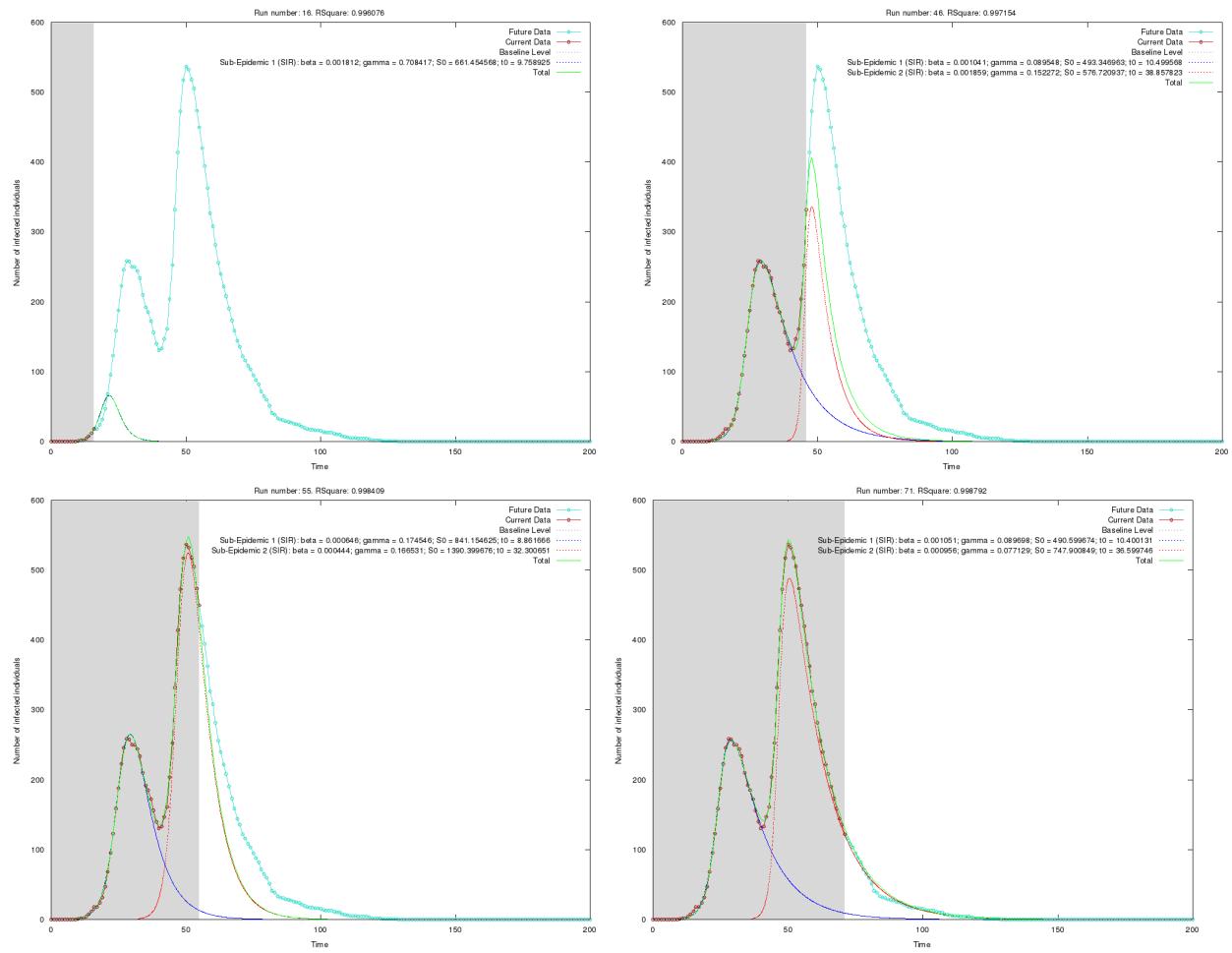


Figure 4.2: Multiple epidemic fitting procedure on two overlapping SIR models with logistic bounding

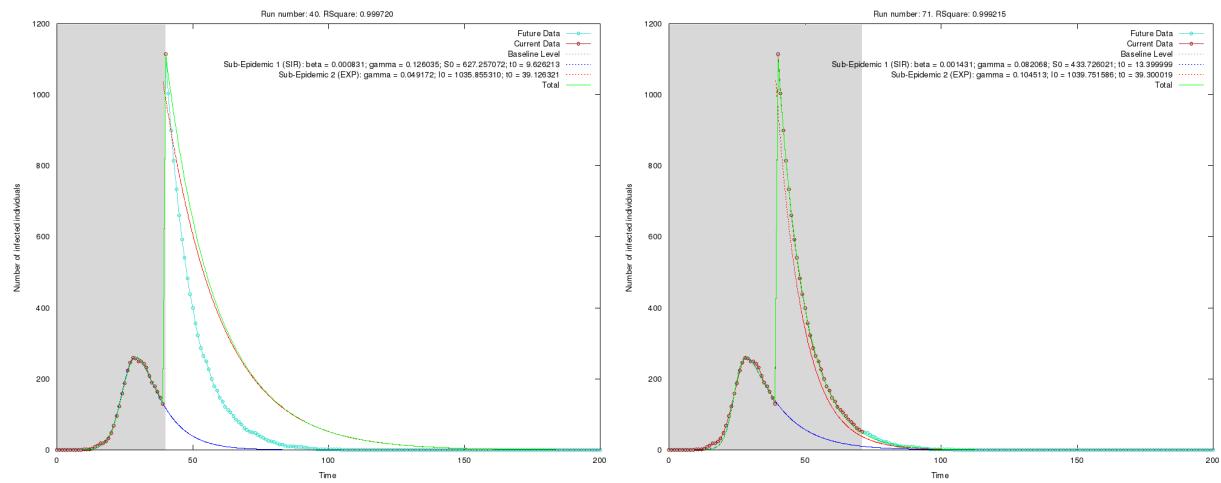


Figure 4.3: Multiple epidemic fitting procedure on an SIR and EXP models with logistic bounding

SIR : beta = 0.001, gamma = 0.1, S₀ = 500, t₀ = 10

EXP : gamma = 0.1, S₀ = 1000, t₀ = 40

4.4 Final Implementation

With a multiple epidemic fitting framework implemented, we then went on to test our epidemic fitting framework on real epidemic data. To put the framework to the test, we firstly attempted to characterise the viral internet sensation, “Blurred Lines” by Robin Thicke. To speed up the fitting process, we only consider SIR and EXP models. We use the number of *BitTorrent* downloads between As a first attempt, the model provided a reasonable fit to the data, characterising the overall shape fairly well. However, as can be seen in figure 4.4, there are a number of shortcomings in the present approach:

1. The characterisation of the first SIR epidemic worsens during the fitting procedure, particularly towards the end.
2. The long term projection of the epidemic varies throughout the run. For example, whereas the first graph predicts that there will constantly be around 4000 infected individuals, the second graph predicts that the epidemic will eventually die out.
3. The procedure is unable to pick up the epidemic peaks at around day 180 and day 220.

The main reasons for the this instability and inaccuracy can be attributed to the following:

1. **Problem:** Not constraining the transition parameters (eg. beta and gamma) results in a number of optimisation runs that do not converge on a decent fitting solution. Furthermore, using a potential seed range of parameters that are too far from the correct value results in a number of unstable runs. For example, if the basic reproduction number, R_0 is less than one (where $R_0 = \frac{\beta}{\gamma}$), then the epidemic will not take off. It was found that seeding the optimisation with a high value of S_0 often produced non convergent runs.

Solution: The seed times of the transition parameters should be adapted to ensure that they are within a reasonable range. Secondly, we can use the logistic transformation to bound these parameters within a sensible range. We also seed S_0 with a lower than expected value and allow the optimisation algorithm to ‘grow’ the value.

2. **Problem:** The detection threshold for new epidemics is set too high. In the above run, we use a threshold R Square value for 0.8, which potentially allows for outlying data points to be ignored.

Solution: The target R Square value is increased, and the distance to latest residual from the mean of the residuals is reduced to two standard deviations.

3. **Problem:** The time taken to run ten optimisations is longer than desirable.

Solution: We investigated the effect of changing the scaling parameters in the Nelder-Mead algorithm

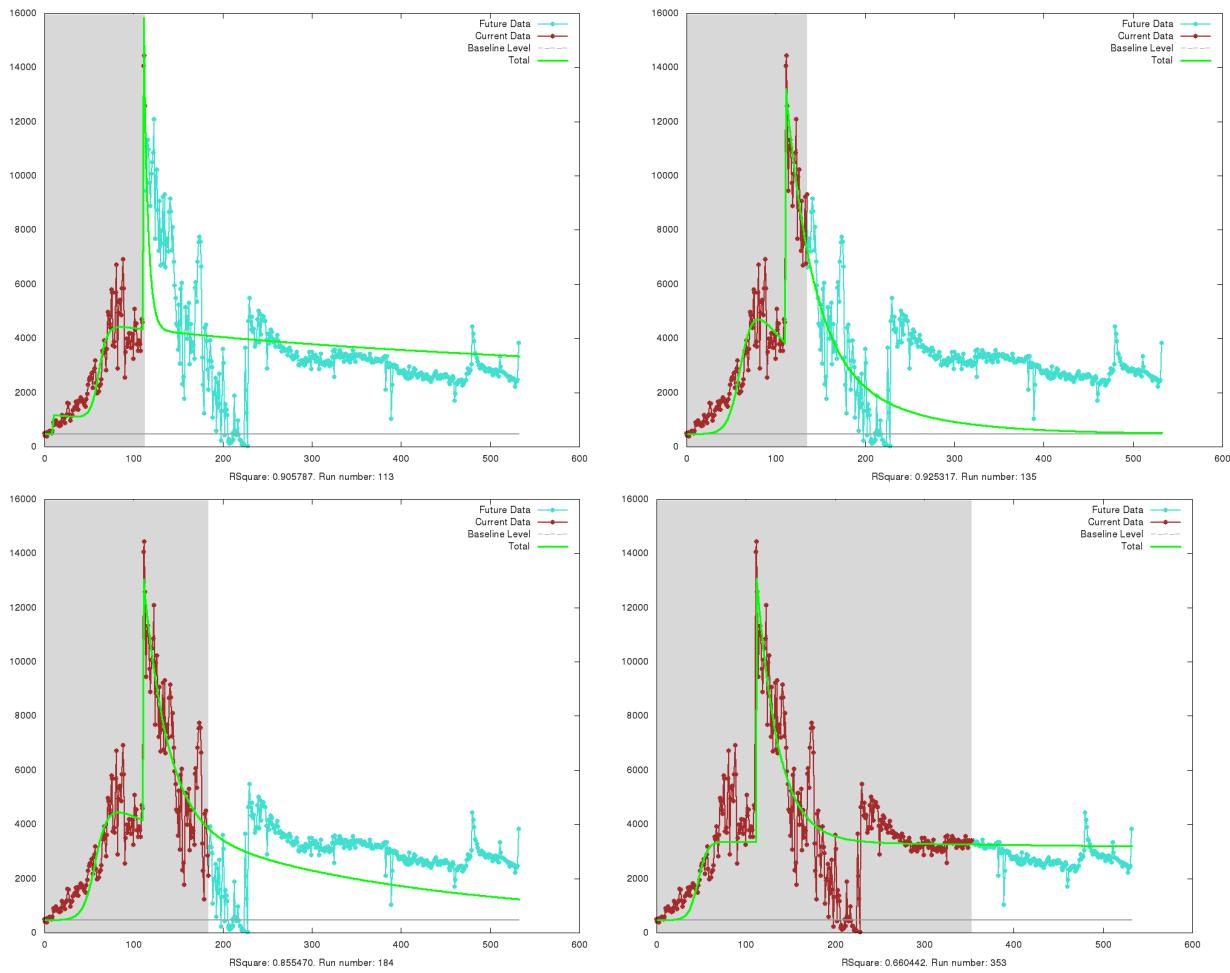


Figure 4.4: Multiple epidemic fitting procedure on the number of *BitToret* downloads of the song “Blurred Lines” by Robin Thicke. Number of downloads on the y-axis and day on the x-axis

itself. We initially used parameter values of 1.0, 1.0, 0.5 and 0.5 for reflection, expansion, contraction and secondary contraction respectively. The expansion parameter is particularly troublesome, as it currently does not stretch the simplex towards the best vertex. We therefore changed these values to 1.1, 1.5, 0.4 and 0.4 respectively, which resulted in a significant decrease in optimisation time.

Following the above modifications, the framework was rerun on the “Blurred Lines” download data as shown in figure 4.5. Note that the number of data points is reduced by taking every fourth data point to reduce run time.

The updated implementation provides a much better fit throughout the course of the run, and accurately locates the initiation of

4.5 Real Data Testing

- Present synthetic data - Present real influenza data - Present Robin Thicke data final - any others?

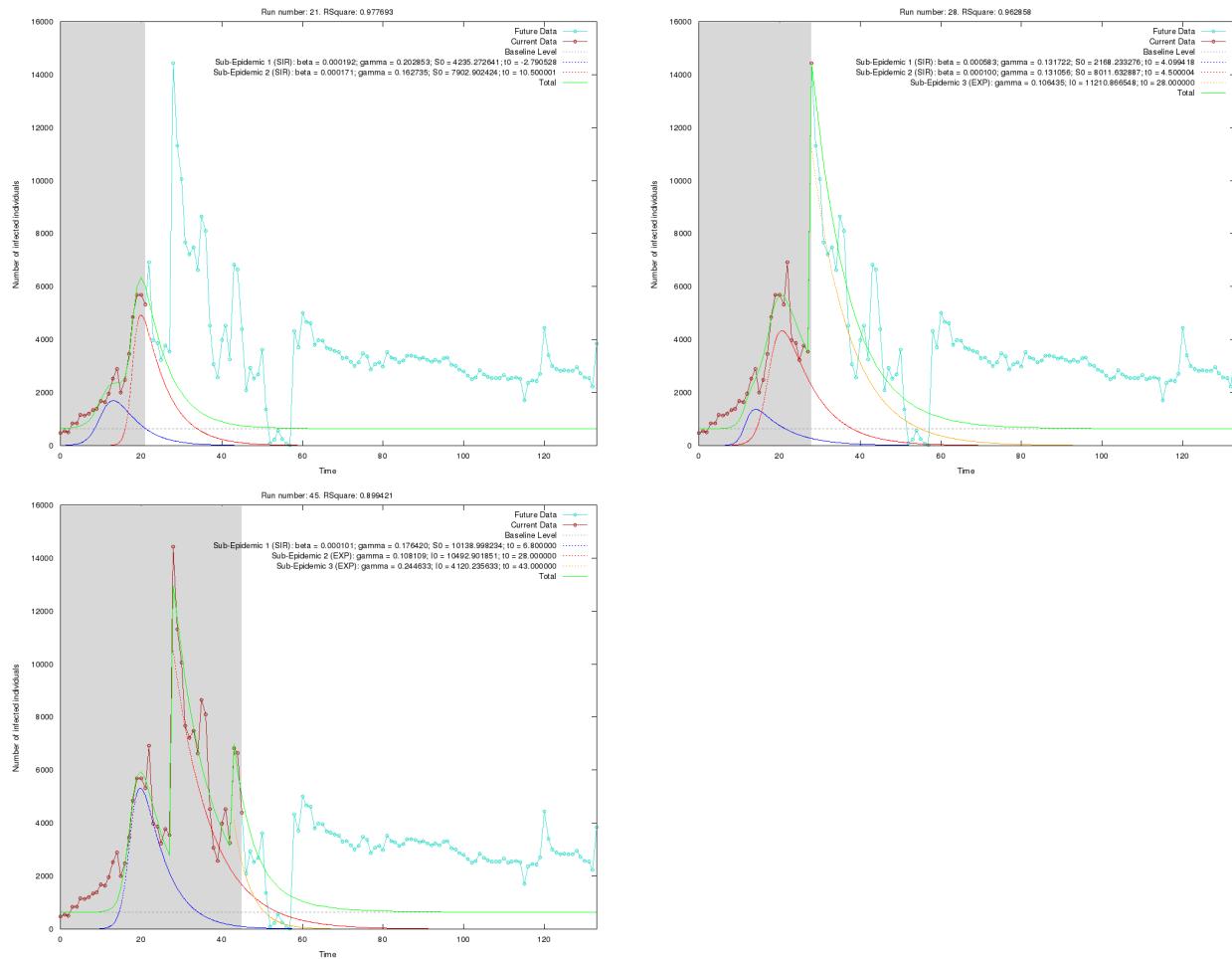


Figure 4.5: Second multiple epidemic fitting procedure on “Blurred Lines” download data using additional logistic binding and modified Nelder-Mead algorithm

Chapter 5

Evaluation

- Aim of model fitting framework - How this is assessed

5.1 Single Fitting Framework Evaluation

- We have implemented a framework in R and C++ - Rational is to provide a faster, customisable implementation - Therefore need to compare accuracy of fit and speed - Show graphs of RSquare - Show mean RSquare - Compare times
- Conclude that C++ implementation is much faster and has comparable accuracy

5.2 Multiple Candidate Models

- Quantify accuracy of model classification - Show that model selection is often accurate by the end, but often - chooses the incorrect model initially.

5.3 Synthemic Fitting Framework

- Plot RSq over time. - Summarise end results on different data sets in a table - Perhaps compare to single fitting framework - Perhaps future RSquare values

5.4 Limitations

- Target RSquare threshol - Robustness of the Nelder-Mead implementation to bad intial starting - values - Speed and accuracy when high number of parameters - Limitation of including t0 in optimisation - Epidemic detection - Epidemic classification - Confidence intervals

Chapter 6

Conclusion

6.1 Summary of Thesis Achievements

Summary.

6.2 Applications

Applications.

6.3 Future Work

Future Work.