PINNING CONTROL OF DISEASE NETWORKS

by

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SUMMARY

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Department:	Electrical, Electronic and Computer Engineering
University:	University of Pretoria
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The modelling of contagion spread on contact networks provide valuable insights to epidemiologists and policymakers trying to control and eradicate diseases. This thesis proposes, implements and analyses a methodology for inserting disease contact networks of HIV into feedback control loops and applying open-loop pinning control to their nodes. Pinning control aims to medicate only a portion of an entire network in order to achieve the same outcomes that would be seen when all nodes are controlled. The control loops are simulated using networks ranging from size $N = 100$ nodes to $N = 10000$ nodes. Simulations aim to control the average maximum incidence in the networks by first estimating the reference average transmissibility from the statistical physics technique known as bond percolation. Once the average transmissibility is known, node-, network- and population mass-action models can be measured for incidence. Two selective pinning control strategies, namely proportional feedback and nonlinear model predictive control (NMPC), are compared with one another and also with a random pinning strategy. The budget, measured in quality-adjusted life years (QALYs), is added to the cost-function for NMPC control. It is shown that budget can indeed be controlled while incidence varies, while incidence may be controlled as budget varies. Pinning control of disease networks is a feasible methodology to analyse the future and steady-state outcomes of interventions in fast-spreading (high-risk) disease contact networks.

OPSOMMING

PENBEHEER VAN SIEKTEVERSPREIDINGS-NETWERKE

deur

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Modellering van die verspreiding van siektes oor kontak-netwerke verskaf waardevolle inligting aan beleidmakers en epidemioloë wat besluit op maatreëls vir voorkoming teen die siekte. Hierdie proefskrif hou 'n metode voor wat gebruik word om siekteverspreidings-netwerke te simuleer en te analiseer. Dit word gedoen op netwerke met nodusse wat varieer tussen $N = 100$ en $N = 10000$. Netwerke waarin HIV versprei word gebruik. Penbeheer word in 'n ooplus-konfigurasie op elke nodus toegepas binne 'n geslote terugvoerlus op netwerkvlak. Penbeheer se doel is om slegs sekere nodusse te beheer om dieselfde uitkomste vir die voorkoms van HIV tydens 'n epidemie te meet. Die doel is om die gemiddelde waarskynlikheid vir oordrag van die siekte tussen nodusse te beheer en sodoende, deur middel van die tegniek genaamd "bond percolation", te bepaal hoe groot die finale epidemie gaan wees. Sodra die gemiddelde waarskynlikheid bekend is, kan nodus-, netwerk- en populasiemodelle saamgestel word. Twee selektiewe penbeheer-strategieë (proporsioneel, en NMPC) word met mekaar en met 'n derde willekeurige tegniek vergelyk. Die beheer van begrotings, gemeet in "quality-adjusted life years" (QALYs), word deur die NMPC strategie hanteer. Siektes binne kontaknetwerke kan dus beheer word met selektiewe penbeheer. Penbeheer-strategieë word ook vergelyk op grond van die dosisse wat hulle benodig, asook die akkuraatheid van die bestendigde-toestand resultate. Penbeheer van siekteverspreidings-netwerke is 'n werkbare metode om toekomstige en bestendigde-toestand uitkomste van mediese ingrepe op netwerke mee te analiseer.

LIST OF ABBREVIATIONS

ARV	Antiretroviral
ART	Antiretroviral Treatment
HIV	Human Immunodeficiency Virus
LSQ	Least-Squares
MSF	Master Stability Function
NMPC	Nonlinear Model Predictive Control
QALY	Quality Adjusted Life Year
PGF	Probability Generating Function
PrEP	Pre-exposure Chemoprophylaxis
RTI	Reverse Transcriptase Inhibitor
SARS	Severe Acute Respiratory Syndrome
SEIR	Susceptible-Exposed-Infected-Recovered Model
SI	Susceptible-Infected Model
SIS	Susceptible-Infected-Susceptible Model
SIR	Susceptible-Infected-Recovered Model
SIRS	Susceptible-Infected-Recovered-Susceptible Model
STD	Sexually Transmitted Disease
WHO	World Health Organisation

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"We make no apologies for making these excursions into other fields, because the separation of fields, as we have emphasized, is merely a human convenience, and an unnatural thing. Nature is not interested in our separations, and many of the interesting phenomena bridge the gaps between fields."

Richard Feynman (1918-1988)

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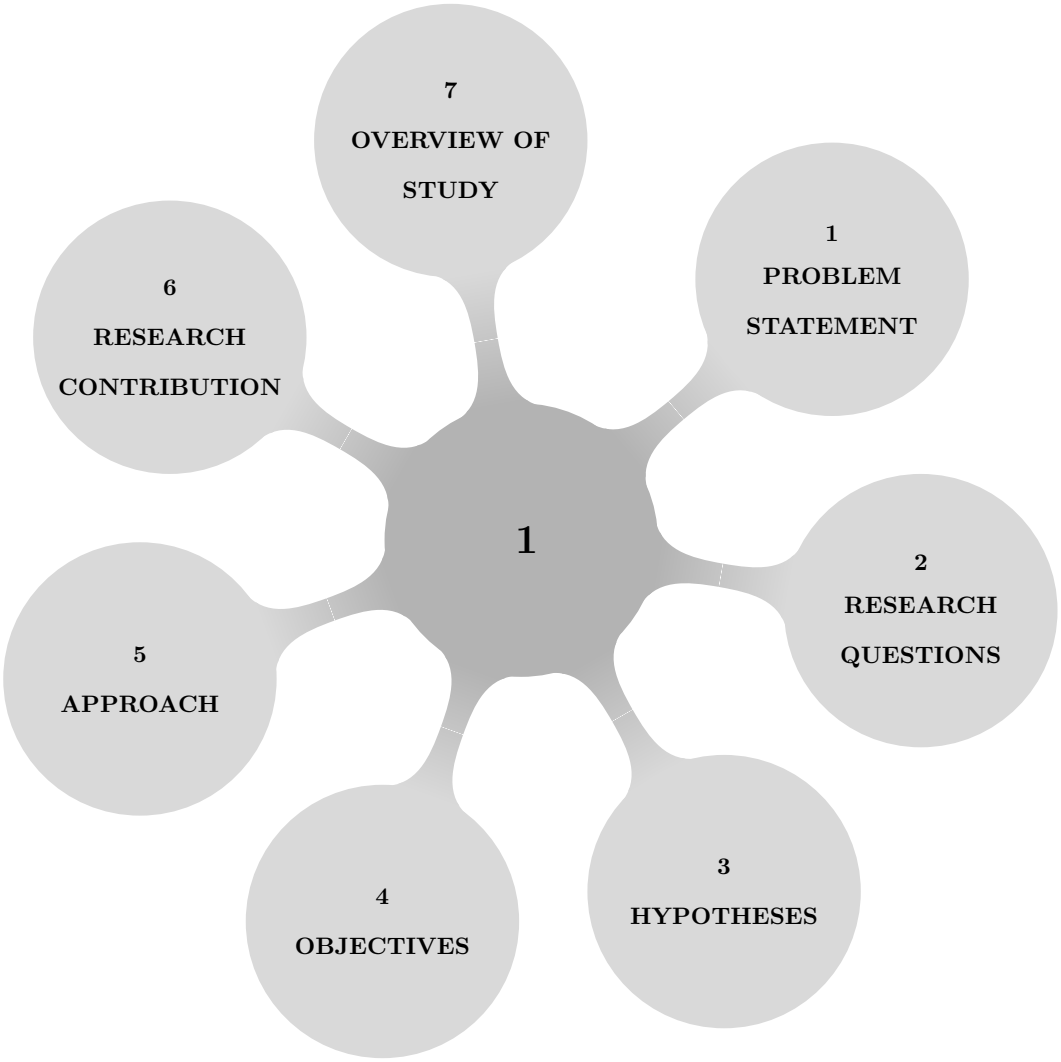
CHAPTER 1

INTRODUCTION



1.1 PROBLEM STATEMENT

What problem is addressed in this thesis?

The present-day public health interventions (for example antiretroviral medicine) applied to large complex networks of individuals that transmit a virus among each other are generally effective but usually costly and probably not optimal.

What is the anticipated solution?

The anticipated solution is defined as using a new control systems methodology to simulate, analyse and establish cost-effective interventions on complex networks that potentially have the same epidemiological effect as mass-action interventions used today.

1.1.1 Context of the problem

Within our world, multiple populations are afflicted with numerous diseases. Diseases spread between people in various ways and affect the quality of life of many. Where the focus of public health policymakers is to deliver medical interventions on a large scale to unhealthy populations, multiple challenges face these efforts. The challenges range from access to medicine, uptake of the medicine when access has been established, budget, to efficiency of the drugs and the presence of additional risk factors that add to these challenges. Beneath these problems lie the dynamics of how disease is spread in societies and the need for comprehensive knowledge on how this spread can be slowed down and even completely stopped. A further level down, the impact of the health or immune response of the individuals in the network affect the aforementioned transmission of disease. Not only is insight into the current state of disease burden important, but also the ability to mathematically predict probable outcomes when given historical data. This is what the realm of modelling can offer.

It has been established that medical interventions that focus on the provision of medicine on a large scale to populations are effective in general but very costly [1, 2]. A great need thus exists for better planning and the opportunity to optimise the implementation of an intervention. It also presses the scientific community to devise lateral, multi-disciplinary approaches to solving this problem. This thesis exists within this context.

The use of control systems to find solutions to immune system and drug dosage-related prob-

lems has been a research focus point in the past [3, 4, 5]. This research focused on within-host dynamics of viral pathogen, after which the identification and estimation of model parameters [6, 7] and the analysis of timing planned control action [8] could be proposed. The field of epidemiology also offers insight into similar problems, but on the scale of large groups of people and populations. Normally, in such studies, several assumptions are made about the individuals in the population, the risk factors that affect them, their levels of exposure to disease and their general demographics. People are thus normally seen as homogenous entities inside a population with equal risk profiles. To combine the two worlds, that of the individual and that of the population (or immunology and epidemiology), an idea for the field of immunoepidemiology was proposed. Although the field of immunoepidemiology has not matured as perhaps anticipated, the needs and conclusions voiced by [9] included the following:

1. There is a need for better measurement. Realistic experiments should be performed which measure values directly relevant to disease transmission and host immune responses.

2. Better models should be developed. The dynamics of the immune response of a person and the dynamics of transmission between persons should be captured in such models.

3. Epidemiological studies should focus on cohorts, providing longitudinal information. This could be formal cohort studies or longitudinal surveys.

4. There is a need for statistical techniques that can be applied to the analysis of large sets of data.

5. An overall improvement in the standardisation of the collection of data is needed.

Of the above needs, the fields of physics (graph theory) and specifically complex networks offer analysis of the spread disease spread between networked agents [10, 11, 12]. Three fields are thus consulted with this research: complex networks, epidemiology and control systems. This thesis proposes a methodology to fulfil the need for more sophisticated models that capture both host and interaction dynamics. The methodology may be used to analyse the important issue of node heterogeneity [13] and the ability to estimate individualised parameters based on real-world measurements of immune response markers.

1.1.2 Research gap

Model-based simulations of contact networks and disease spread and percolation studies have not, until now, considered the internal dynamics of the connected nodes. Rather, most studies emulate knowledge of the general distribution of nodes based on general and trivial sets of stylised facts. In this respect, this work offers to cover this gap in the body of scientific knowledge by simulation of the spread of disease based on per-node models flowing into broader network models. The final analysis can then be made using classical epidemiological techniques, such as Susceptible-Infectious-Removed (SIR) models, risk ratios and hazard ratios. Very little research currently addresses this need. It is the primary motivation for performing this research and bridging the identified gap.

1.2 RESEARCH QUESTIONS

The research questions that arise from the problem statement in Section 1.1 are provided below. The questions aim to address the research gap that has been identified in Section 1.1.2:

Research questions

1. Could less control action (applied doses of medicine) on disease contact networks still provide the same epidemiological outcomes? Outcomes include the average maximum size of the epidemic and the intervention budget measured in quality-adjusted life years (QALYs).
2. Could limited resources or eventual impact be defined as an input or reference signal for the planned control action, and the system be driven to the desired steady-state?
3. Could a multi-disciplinary approach with a primary focus on control systems provide feasible solutions to this problem?
4. Could public health specialists or funders use the researched information to supplement decision-making for interventions?

1.3 HYPOTHESES

This thesis aims to analyse the results of the following three hypotheses. The outcomes are listed in Section 9.3.

1.3.1 Hypothesis 1 : Selective pinning significance

H_0: Control of specific nodes in a network (selective pinning control) is not using significantly less control action, on average, than pinning all infected nodes in order to achieve the same average maximum epidemic level, with a p value of less than 0.01.

H_A: Control of specific nodes in a network (selective pinning control) is using significantly less control action, on average, than pinning all infected nodes in order to achieve the same average maximum epidemic level, with a p value of less than 0.01.

Testing approach: A statistical analysis of the control action (doses of medicine) is performed. The analysis first investigates the distribution of doses for both strategies, then proceeds to test whether the distributions are originating from different sampling populations. Lastly, depending on the distributions, the average or the median number of doses are compared and a result for accepting or rejecting the null-hypothesis obtained.

1.3.2 Hypothesis 2 : Optimal pinning control significance

H_0: Control of specific nodes using nonlinear model predictive control (NMPC) is not significantly more accurate to using conventional proportional feedback control techniques to achieve the same average maximum reference epidemic levels, with a p value of less than 0.01.

H_A: Control of specific nodes using NMPC provides a significant improvement in accuracy over conventional proportional feedback control techniques to achieve the same average maximum reference epidemic levels, with a p value of less than 0.01.

Testing approach: A statistical analysis of the control action (doses of medicine) using NMPC is performed. The analysis compares the distribution of doses for NMPC with the distribution of doses for proportional selective pinning. A further comparison of both these two strategies

is also made with random pinning. The average or the median number of doses are compared and a result for accepting or rejecting the null-hypothesis obtained.

1.3.3 Hypothesis 3 : Budget control significance

H_0: The intervention budget, measured in QALYs, cannot be specifically controlled in a complex static network, using pinning of selective nodes.

H_A: The intervention budget, measured in QALYs, can be controlled to specific reference levels in a complex static network.

Testing approach: After applying selective pinning control of the budget using NMPC, the results are measured according to the steady-state error. If the error is less than 10% for all reference values tested, the null-hypothesis shall be rejected.

1.4 OBJECTIVES

The research objectives given in this section provide the list of specific research goals that shall be performed. Each objective contributes towards successful testing of the hypotheses and addressing the research questions that are defined. The objectives are given as:

1. Develop a method by which the spread of disease on complex networks can be analysed from a node-level model through to network- and population-level models.

2. Control the spread of disease on complex networks to pre-defined average maximum levels.

3. Control the budget spend on disease contact networks, measured in QALYs.

4. Clearly define a control methodology for the spread of disease on networks by primarily using control-theoretic concepts as well as drawing from the disciplines of complex networks and epidemiology.

5. Use models and parameters available and verified from literature as part of the proposed methodology, for scientific soundness.

6. Compare different control strategies and comment on their similarities and differences.

7. Comment on the research contribution and usability of this research for practical implementation in the engineering and public health fields.

1.5 APPROACH

The research approach specifies the philosophy followed to address the research questions and goals.

The following general steps define the scientific approach followed in this thesis:

1. Establish the current state of literature and background information on the topic of control of disease networks. The fields of control systems, complex networks and epidemiology were used as part of this investigation. The results of the literature review can be seen in Chapter 2.

2. Select and design the appropriate models to use for the research. This includes a node model, a network model and a mass-action population model.

3. Ensure that the models have parameters available from literature.

4. Build a tiered mathematical model structure that can be used for simulation from an individual's contribution towards population outcomes.

5. Provide simulation flexibility on the use of immune response dynamics, the network types and the epidemiological parameters that could be measured. Ensure that node heterogeneity and network variability can be simulated in any reasonable way desirable.

6. Program the simulation platform in C++. This includes the immune response model, network model, parameters, control algorithms and algorithms for numerical integration and recursive calculation of results.

7. Simulate the desired network experiments on a parallel computing cluster.

8. Analyse the results in Matlab and use the R statistical programming language for

hypothesis testing and reporting.

9. Present the results in journal publications and in a complete report (this thesis).

1.6 RESEARCH CONTRIBUTION

This research offers a methodological contribution as well as experimental results-based contributions to the control and evaluation of the spread of diseases in complex static networks. The additions to scientific literature can be seen in Table 1.1.

Table 1.1: Peer-reviewed scientific contributions

No.	Citation / Status
1	E. F. du Toit and I. K. Craig, "Quantifying the impact of two pinning control strategies on HIV incidence," in Proceedings of the 19th IFAC World Congress, 2014.
2	E. F. du Toit and I. K. Craig, "Selective pinning control of the average disease transmissibility in an HIV contact network," Physical Review E, vol. 92, no. 1, p. 012810, 2015.
3	E. F. du Toit, I. K. Craig, and M. Nieuwoudt, "Non-linear model-predictive pinning control of an HIV contact network with budget adherence," Submitted to Mathematical Biosciences, July 2015.
4	E. F. du Toit, "A control systems methodology for intervention in the spread of diseases on networks," Abstract accepted for Contagion '15 at the Conference on Complex Systems (CCS), September 2015

1.7 OVERVIEW OF STUDY

The design of this study and thesis is represented graphically in Figure 1.1 at the hand of a control feedback loop. The relevance and applicability of each chapter to the control loop is shown in greyed circles.

Chapter 1 provides an introduction to this research. The problem statement gives a central focus to the study and provides the context and the research gap identified in the scientific body of knowledge. The research questions, hypotheses, objectives and particular approach

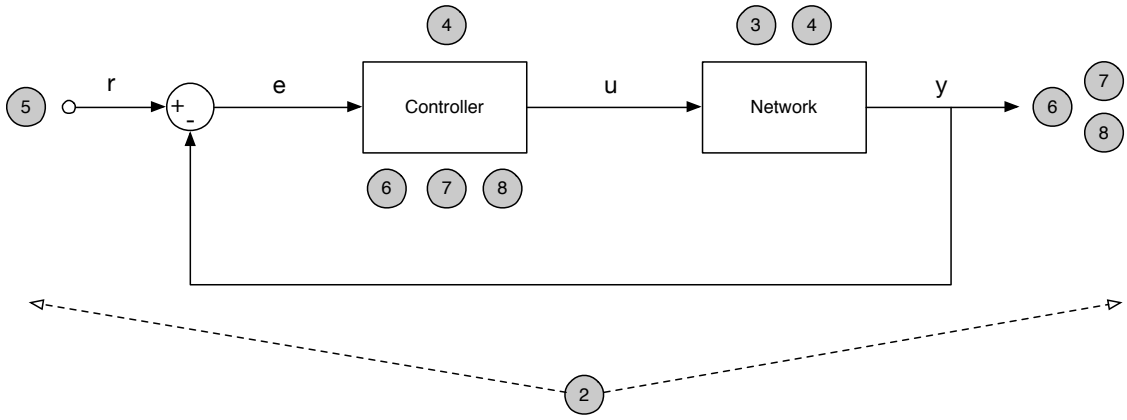


Figure 1.1: Overview of the applicability of the chapters of this thesis to the general feedback control loop. Each greyed circle contains the number of the chapter that applies to that portion of the control loop.

followed in addressing the questions are discussed. Finally, the contribution to science is highlighted, and an overview of the thesis given.

Chapter 2 is a comprehensive literature study supporting the background, context and contribution made by this research. The research inputs to this study from the fields of control systems, complex networks, public health and epidemiology are presented and disseminated.

Chapter 3 presents the models used in this work. The links between the models are discussed and the various simulation options in using these models are presented.

Chapter 4 clearly describes the concept of pinning control and show how this is mathematically represented. The different sub-types of pinning control are discussed.

Chapter 5 presents the concept of bond percolation, as defined from the field of statistical mechanics. The primary focus of using this technique as part of this research is presented, namely for the use as a reference signal to the control systems in this thesis.

Chapter 6 compares a random pinning control strategy with a selective pinning control strategy implemented on a proportional feedback control loop. A description of how each control philosophy is implemented is given and the advantages, improvements, differences

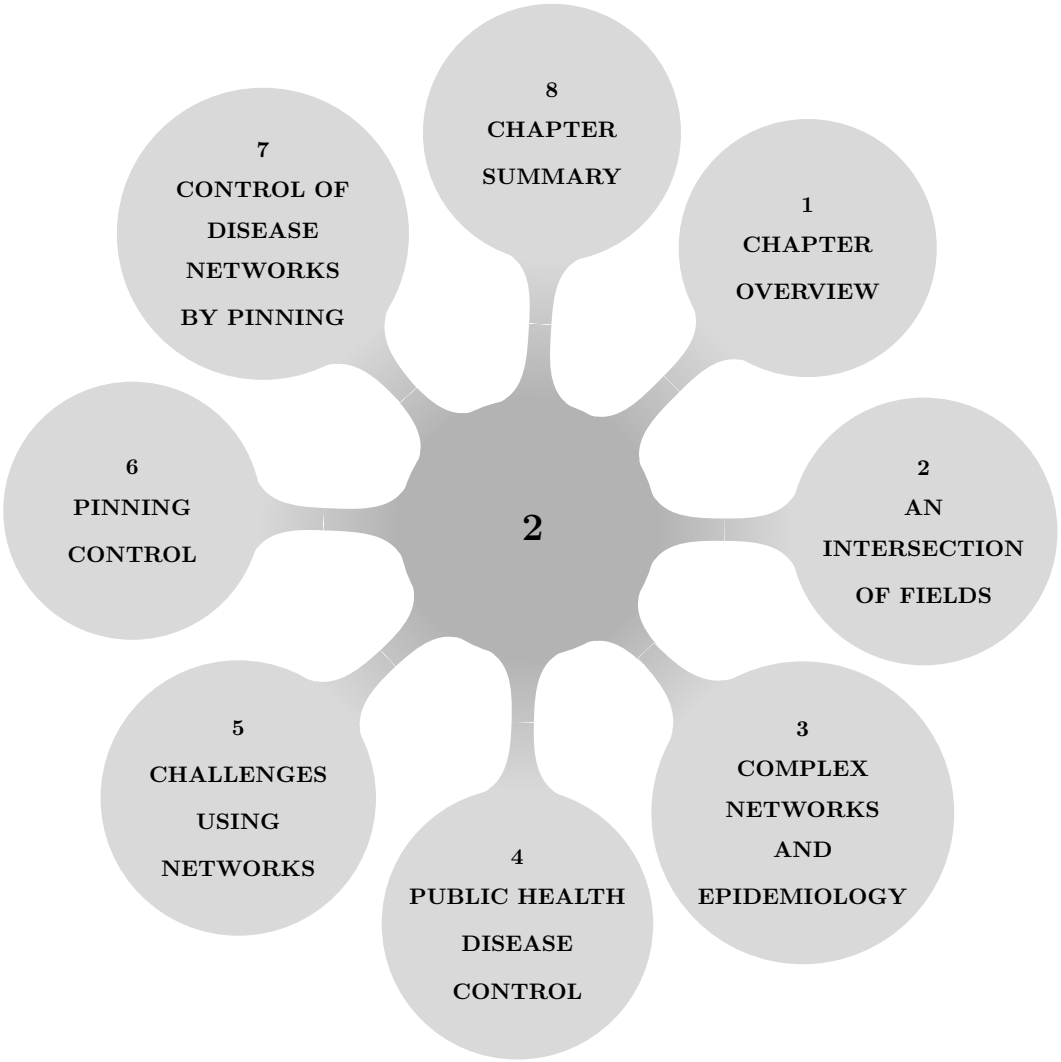
and impact of both strategies are clearly laid out.

Chapter 7 presents the use of NMPC implemented on pinning control feedback loops of disease spread networks. A comparison of the control action needed with NMPC is done with the random and selective schemes from Chapter 6.

Chapter 8 uses NMPC to indicate how pinning control may be applied to budgets for public health, measured in Quality-Adjusted-Life-Years (QALYs). The cost-effectiveness of different incidence reference levels and budget reference levels are discussed.

CHAPTER 2

BACKGROUND



2.1 CHAPTER OVERVIEW

This chapter provides an overview of the background research that forms the foundation upon which this research is built. The aim of the chapter is to inform the reader how the fields of epidemiology, complex networks (or graph theory) and control systems intersect, as these are the primary bodies of scientific knowledge that contribute to this thesis. The further objective of the chapter is to ensure that the study herein is relevant and that no duplication of published work already undertaken in these fields have been performed. To this end, the title of the thesis ("Pinning control of disease networks") provides guidance on the background information that had to be placed under scrutiny: Disease spread is looked at from a public health and epidemiological viewpoint. The control measures for epidemics in populations are discussed. The theory of mathematical pinning control is presented. Complex networks, their links to the modelling of disease spread and the derivation of what constitutes contacts between nodes are shown. The chapter concludes with a brief overview of the author's published research on pinning control of disease networks.

2.2 AN INTERSECTION OF FIELDS

This is a study about controlling the spread of disease over contact networks. The nodes are persons, and at least one node is infected at the start of any given period of investigation. Ideally, as in many control systems, control action should be used sparingly. Control action in this study is medicine, and this is given to the nodes (persons) in the networks at various times. The outcome is favourable for the nodes, as it improves their health. But what if infection of the nodes can be avoided to begin with? Herd immunity is an epidemiological concept that implies that if an unprotected node is surrounded by immune neighbour nodes, that node is implicitly protected from infection. This leads to the question: What if control of a specific number of individual nodes in a complex disease network is enough to infer protection upon the rest of the network? Furthermore: What if it is possible to control the threshold of maximum infection in the network, thus implying that one may possibly drive a network towards a particular epidemiological outcome? The unique application of pinning control theory to a disease network with the aim of predicting network steady states places this work at an intersection of three fields, namely epidemiology, graph theory (complex networks) and control systems as illustrated in Figure 2.1.

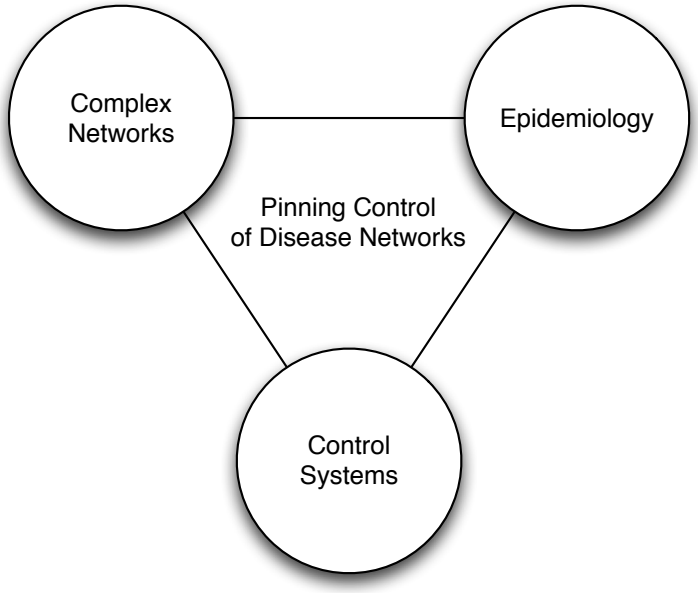


Figure 2.1: At an intersection of fields

The aim of doing multi-disciplinary work such as this is to gain insight into what new ideas may be extracted from blending different fields. One approach is to explore the possible benefit from each pair of fields. To illustrate: What may be gained from the overlap between complex networks and epidemiology? Accurate models of disease propagation in populations may be produced. What may be learned from applying control to the nodes of complex networks? Pinning control of entire oscillating networks can be achieved with very few nodes under control. How does epidemiology relate to control systems? If interventions are seen as control action, and the desired effects of the interventions as reference signals, then the techniques of control theory might be applied to study the outcomes of interventions applied to epidemiological models. Then, as three fields converge, the important question should be asked: How may the new knowledge and experimental results be useful? Indeed, the application to real-life disease networks would be the ultimate goal. To reach this goal, yet more fields should be considered: Ethics, logistics, demography, sociology and public health. A study such as this cannot be made too broad, as it will lose its focus and possibly its statistical power. It is the aim of this work to build upon the expertise of each of the three proposed fields and supply a new method for synergy and analysis spanning these domains.

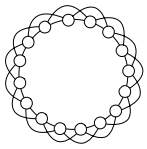
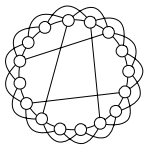
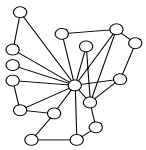
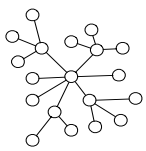
2.3 COMPLEX NETWORKS AND EPIDEMIOLOGY

Complex networks, from the domain of graph theory, can be described as a collection of nodes (or vertices) linked to another in such a way that the links (or edges) are not all uniformly distributed nor the connections trivial. A wide variety of real-world complex networks exist: The network of World Wide Web links [14, 15, 16], social networks [17, 18, 19, 20, 21], opinion-formation networks [22], road transport [23] and cargo ship networks [24], human mobility networks [25], earthquake networks [26], academic citation networks [27], Hollywood actor networks [28], human genome disease networks [29, 30, 31] and, of particular interest here, disease contact networks [32].

2.3.1 Types of complex networks

Network classification (Table 2.1) depends on topology, captured mainly by the node degree distribution. This is the distribution of the number of links to each node.

Table 2.1: Main types of complex network models

Network Type	Degree Distribution	Ref.	Visual
Erdös Rényi (Random)	$p_k = \binom{n-1}{k} p^k (1-p)^{n-1-k}$	[33]	
Small-world	$p_k = e^{-cp} \times \frac{(cp)^{k-c}}{(k-c)!}$	[34]	
Exponential (Random)	$p_k = Ce^{-\lambda k}$	[35]	
Scale-free (Power-law)	$p_k = Ck^{-\alpha}$	[36]	

Real-world networks may be represented by a mixture of the models in Table 2.1, but most notably the power-law network. Power-law networks tend asymptotically to scale-free networks [37].

2.3.2 Complex networks of disease propagation

Following on research in the theoretical field of complex networks, the practical application to networks of epidemiological significance emerged with the work on the transmission of HIV and the social network dynamics that influence its spread [38]. The term "contact network" describes an important way to look at disease spread, namely a collection of connections that are formed between nodes on a regular basis leading to the potential transfer of a pathogen across these links [39, 40]. In this type of network, the connections are normally defined as some type of close-proximity behaviour such as sexual contact (for example an HIV contact network) or being in the close presence of another person on a regular basis (for example a TB network). The network connectivity structure (or topology) greatly depends on the type of transmission a particular disease exhibits. Diseases may transmit by airborne contamination after coughing and sneezing (measles, chickenpox, SARS, TB), sexual contact with exchange of body fluids (HIV, hepatitis-B, chlamydia), by eating contaminated food (cholera, salmonella), through the skin by touch (herpes simplex virus) and also by animals (rabies) and insect vectors (malaria, dengue fever). The effect of network topology on the rate and pattern of this spread has been analysed by [41]. Most studies make the assumption that infectious individuals in populations all have the same probability of spreading disease to any other individual in the population. Such an approach was novel in the field of epidemiology, as it allowed the analysis of the mean effect of large numbers of infective people in a population as a function of time. This is why most epidemiological networks since 1927 represented individuals as being grouped together or compartmentalised according to their disease status. Nodes were either susceptible to getting a disease, infected by a disease or recovered from a disease [42]. The classical Kermack-McKendrick compartmental population-based model is represented as follows:

$$\begin{aligned} \dot{S} &= bN - \lambda S - dS \\ \dot{I} &= \lambda S - gI - dI \\ \dot{R} &= gI - dR \end{aligned} \tag{2.1}$$

In this model, S is the number of people susceptible to disease, I is the number of infected individuals and R is the number of individuals that have recovered from the disease. The parameters are fully described in Table 2.2.

Table 2.2: Summary of the Kermack-McKendrick SIR model parameters.

Parameter	Description
S	Susceptible persons in the population.
I	Infectious persons in the population.
R	Recovered (Removed) persons in the population.
N	Size of the population.
b	The birth rate.
d	The natural death rate.
g	The rate of recovery from infection.
λ	The force of infection ($S \rightarrow I$).

A simplified version of this model is used in this thesis, given in (3.9). Equations may be removed from or added to (2.1) to suit the type of disease. In the case of sexually transmitted diseases, where repeat infections are common, only the susceptible and infected states may be used (SIS-model). Theses types of models assume that risk factors are spread randomly and uniformly across the population, with no particular insight into the specific dynamics that govern how disease spreads between individuals. Towards the purpose of capturing person-level transmission dynamics, disease network models based on the mathematical field of graph theory were developed.

Disease networks have been included into the fray of complex networks with fundamental reviews by [12] and [43], as well as the simulations of several types of contact networks of infectious diseases by [44] and the concise description of networks and epidemic models by [45].

In seminal work by [46], it was shown that the within-host dynamics and immune responses of nodes could be linked into the network-based interactions leading to the spread of disease.

In this case, a general viral-antibody network model was used:

$$\begin{aligned} \dot{a_i} &= \lambda_i - \mu_i a_i + \epsilon_i a_i v_i \\ \dot{v_i} &= r_i v_i - \gamma_i a_i v_i + F\left[\sum_{j \neq i}^{n} \beta_{ji} v_j\right] \end{aligned} \tag{2.2}$$

Here, briefly, the parameters are: a_i represents the antibodies of node i and v_i the viral load of node i; λ_i is the antibody production rate; μ_i is the death rate of antibodies; ϵ_i is the rate of antibody production induced by a single virus; r_i is the growth rate of the viral population; γ_i is the rate of destruction of viruses by a single antibody. The coupling strength between nodes of the network is indicated by F, whilst the coupling matrix is β. The coupling matrix indicates which nodes are connected to which other nodes. It is a square matrix of dimensions $n \times n$, where n is the number of nodes in the network. The matrix has an element value of 1 if a node is connected to another, and an element value of 0 if not. By adapting the model in (2.2), specific disease immune-response network models can be analysed. In this thesis, HIV spread is analysed using a similar modelling framework.

A further important contribution made by [46] was to analyse network-based spreading of disease at the hand of the Kermack-McKendrick population model seen in (2.1). All infected individuals form part of the I population, whilst uninfected and susceptible persons are in the S group. Individuals that were infected but recovered from the infection are grouped into the R compartment. This transition to macroscopic, population-level models allow for an analysis of the maximum eventual epidemic size.
The spread of a disease on networks has been widely analysed, particularly on small-world networks [47, 48], scale-free networks [49] and on networks containing heterogenous nodes [50]. A summary of the various network and epidemic models has also been provided by [45]. To be able to solve the evolution of epidemiological models and spread of a disease on a complex network, the theory of site and bond percolation [51, 47, 39, 52, 44, 53] and generating function methods (Chapter 5) can be used. An introduction and overview of networks in epidemic modelling has been contributed by [54].

2.3.3 Real-world contact networks

A wide variety of real-world disease-spreading networks have been modelled by using the mathematical framework of contact networks. For instance, the web of human sexual contacts

have been found to follow a power-law degree-distribution [55]. The spread of computer viruses on the Internet was found to approximate a scale-free network [56], with the surprising evidence that in these types of networks, asymptotically, the epidemic threshold (where the basic reproductive number $\mathcal{R}_0 = 1$) seems to be absent [49]. This means that new control strategies, different from the classical random medicating of nodes, should be employed if an epidemic is to be avoided. Indeed it has been indicated that policies that discriminate between the different types of nodes and focus on highly connected nodes can restore the epidemic threshold and potentially eradicate a virus from scale-free networks [57]. In the world of mobile phone connectivity, virus spreading patterns have been analysed to understand the risks involved and prevent costly outbreaks [58]. When diseases that are spread between humans are considered, similar scale-free contact and spreading patterns have been observed. These observations have been analysed for various diseases, including avian influenza (H5N1) [59], Severe Acute Respiratory Syndrome (SARS) [60], pertussis (whooping cough) [61], HIV [38, 62, 63] and tuberculosis [64, 65, 66, 67].

2.4 PUBLIC HEALTH CONTROL OF DISEASE SPREAD

Public health aims to control both communicable and non-communicable diseases mainly by removing or reducing risk factors for the spread or incidence of such diseases. Control methods include prophylactic medication (mainly vaccination), treatment medication (such as ARVs) and quarantine measures (often in the case of highly contagious (like SARS) or non-treatable diseases (like EBOLA). When an outbreak of a disease is noted, the core group of individuals investigated for possible intervention are the contacts of identified cases. Another method of intervention aims at behavioural change by the dissemination of important information into a population. One example of this is the governmental promotion of condom use in South Africa to curb the spread of HIV.

2.4.1 Quarantine

During the 2003 outbreak of SARS in Toronto it was necessary to isolate and quarantine up to 100 contacts of every case identified [68]. In addition to this, every expected case of SARS was treated for the illness until a clear diagnosis could be made. As a final measure, after the outbreak was under control, systematic measures of screening for SARS were implemen-

ted in all hospitals in Toronto. For the 2014 epidemic of EBOLA in West Africa, similar case and community isolation strategies were implemented, but on a larger scale [69]. The impact of school closures, protection during burying rituals, rapid and active case-finding, household protective kits and isolation and social distancing interventions were all assessed and implemented [70, 71].

2.4.2 Vaccination as prophylaxis

The application of vaccines to populations are amongst the greatest public health achievements of the twentieth century [72, 73, 74]. Vaccination of children against the famous MMR trio of diseases (measles, mumps and rubella) has led to its indigenous eradication in many countries [75]. One of the strategies for controlling further spread of a highly contagious sickness such as EBOLA was proposed as ring vaccination [76]. This is the explicit targeted vaccination of the exposed contacts of individuals that are infected. An investigation into the plausibility of herd immunity and disease eradicability as a result of voluntary vaccination programmes has also been done [77]. Herd immunity is described as the protection of unvaccinated individuals because of close-proximity contacts being vaccinated on a broad scale in a population.

2.4.3 Direct treatment

The most prevalent form of intervention in disease networks is patient-based application of medicine. The best-known medicines for treatment are classified into the categories of antivirals and antibiotics, the former for viruses and the latter for bacterial infections. Treatment interventions are also tested through the most noteworthy form of epidemiological studies performed, namely that of randomised controlled trials [78, 79].

2.4.4 Behavioural interventions

Behavioural interventions follow from regressive studies that indicate personal behaviour as a large risk factor for disease spread. One of the largest non-communicable diseases, obesity, is a focus point for behavioural change [80]. The intervention in this case would be the development, promotion and implementation of strategies for weight reduction by means of a balanced diet and physical activity. Another type of behavioural intervention, awareness of

disease spread, can have such a large impact on the spread of disease that it may be prevented from growing into an epidemic [81]. Abstinence, partner reduction, condom use and delay in onset of first intercourse may also be seen as behavioural interventions on networks where HIV and other sexually transmitted diseases (STDs) are prevalent [82].

2.5 CHALLENGES IN USING CONTACT NETWORKS FOR EPIDEMIOLOGY

The predominant modelling and analysis approach in public health is the use of mean-field compartmental, population-based models. In general, two facets are always compared: Results from a model without intervention and results from a model that includes intervention. Translating this homogenous, average-effect approach into the domain of dynamic processes flowing through a network structure is challenging. Some of the important challenges to consider in using contact networks in epidemiological modelling have been highlighted by [83] and [84]:

1. **Heterogeneity and epidemic outcomes:** In a population-based model that can be analysed in the large population limit, well-defined relationships for fundamental epidemiological parameters such as the final size of an epidemic and the basic reproductive number $\mathcal{R}_0$ exist. In a network, these parameters greatly depend on the network degree distribution. Differences in node disease transmissibility (as modelled and shown in this thesis) also affect the final size of an epidemic. It is thus important that node heterogeneity be carefully considered when causal inference is made between mean-field model results and contact network model results [85]. Such comparisons may be subject to rather using the counterfactual model of outcomes, which stresses that the exchangeability of populations be carefully considered before inference is made [86].

2. **Static complex disease networks:** Various models exist that aim to represent realistic graphs. The complexity of such graphs are inversely proportional to the ability to generalise the results from simulation. The majority of network-based research focus on approximations of real-world networks by using static representations. Nodes do not enter or leave the population, although their roles and states may differ. Network structure thus stays constant. For SIR population models, thorough analytical analyses are possible. When using static networks it is imperative to use a network model that

fits to well-established epidemic models such as this.

3. **Dynamic complex disease networks:** In most real-world networks, the links between different nodes are not identical. As is shown in Section 3.3.2, contacts between nodes in the network are made with varying probabilities for transmission of disease. The approach to model this heterogeneity is to use weighted networks. Each node in such a network thus has a specific, and mostly unique potential to transmit a disease to another node. Dynamics that may influence the epidemiology of a disease on a network include:

   - The work done by [87] incorporate births, deaths, social relationships, economic changes and node mobility.
   - Node behaviours (partnership or contact formation and contact dissolution) have been analysed by [88].
   - Adaptive behaviour of nodes towards other nodes that are infectious and symptomatic [89, 90].
   - Public health interventions such as vaccinations [91] and antiviral drugs [92].
   - Node behaviours of recovered individuals (such as sexual abstinence after having recovered from a sexually transmitted disease or STD).
   - The effect when a network's links also depict dynamical behaviour [93].

   Network studies of pathogen spread could be made more scientifically sound if the link strength (probability of transmission) of the disease could be properly defined, modelled and quantified using available data. Detailed measurements of the dynamic links between nodes would allow us to understand how contact networks evolve in response to a disease. The impact of highly-connected nodes called "super-spreaders" should be considered [94]. Dynamic network structures may be used and reported on, but the locality of the specific structures should be kept in mind. Dynamic structures vary by geographic location.

4. **Waning immunity in epidemic models:** SIR models are by far the most widely researched epidemiological population-based models. This is because many diseases lead either to eventual immunity, or death, or complete recovery. The analysis of a SIR model is much simpler compared to a Susceptible-Infected-Susceptible (SIS) or a Susceptible-Infected-Recovered-Susceptible (SIRS) model. SIR models are simpler to analyse because, from a network perspective, node states are mainly dependent on their neighbours, and would only go through at most two state transitions ($S \rightarrow I$ and $I \rightarrow R$). When waning immunity is at play (nodes lose their immunity after some time), nodes might possibly go through an infinite number of state transitions due to the feedback loop that exists in the SIS and SIRS model structures. This makes it very difficult to analyse final epidemic size. Few such models have been thoroughly analysed in literature, with the possible exception of the so-called "contact process" (asynchronous SIS model) [95].

5. **Approximation schemes for epidemics on networks:** There are many methods that can be used to approximate and validate epidemiological results on contact networks. These methods include pair approximations [96] and effective-degree approaches [97]. Approximations readily rely on assumptions, such as that the networks representations being studied are selected uniformly at random from the set of all graphs having specified properties. The ideal approximation relies on finding an asymptotic mathematical representation under which the approximation becomes exact as the population size tends to infinity.

6. **Network properties and epidemic outcomes:** Network characteristics affect important epidemiological quantities. As an example, the basic reproductive number $\mathcal{R}_0$ and the probability and size of an epidemic depends on the degree of clustering in a network [53, 98]. What is important is that networks with different topological structures may exhibit the same amount of clustering [99]. Other network properties that influence epidemic outcomes include the distribution of link weights [100], the relationship between nodes having many contacts and the weight of each of those contacts (degree correlation with link weights) [101], partner concurrency in sexual contact networks [102], contact repetition [103] and neighbour exchange [104].

7. **Using relevant real-world data:** The most important supporting factor for influencing the accuracy of theoretical models for disease spread on networks should be the focus for data collection. An information feedback loop should exist between the development of models and the validation of these models by actual data. Models and experiments should also guide data collection and highlight which data affects epidemic outcomes the most. An important development is that of "big data", which raises the possibility for contact tracing and determining network structure. The need thus perpetually exists for better data and the appropriate use of that data.

8. **Further challenges:** It is clear that many challenges exist for modelling disease spread on contact networks. In addition to the challenges listed, some more are given below:

   - Network structure may be exploited for interventions by targeting highly connected nodes and also central nodes (in the field of complex networks this is called "betweenness centrality"), for larger fragmentation into subgroups to hamper disease spread. To achieve this, the network structure should be very well understood.

   - Individuals' behavioural reactions to interventions may change network structures.

   - It is very difficult to define exactly what constitutes an infectious contact. One might be able to define the cause of a respiratory disease (for example a droplet containing a pathogen is inhaled by another person), but not exactly how it happens when two persons are in close proximity to another. It is thus important to identify the dominant mode of transmission, and what types of interaction matter.

2.6 PINNING CONTROL

2.6.1 Overview

Pinning control is a control-theoretic technique by which particular nodes of a coupled network are controlled with local feedback. It may also be called pinning synchronisation [105]. Primarily, control of such a sub-set of an entire network's nodes has the effect that the entire network synchronises to a particular steady-state outcome. Reviews of the topic of synchronisation [106] and of pinning control to achieve synchronisation [105] have been performed. Research into this phenomenon has been approached by analysing the relationship between

network topology and network dynamics. This has been done by varying the structure of networks from small-world [107] and scale-free [108] and testing the synchronisability of each. To qualify, a small-world network's nodes are mostly not neighbours with each other, but can be reached over a short node-to-node distance. A scale-free network's degree distribution (average number of incoming plus outgoing connections per node) follows a power law, if at least considered asymptotically.

Pinning control of lattice-type networks has been explored as early as 1997 [109]. The study, from the physics domain, aimed to comment on the optimal placement of controlled nodes in the lattice and found it to be greatly dependent on the structure of the network. A number of years later, in 2002, this idea has been brought into the electrical engineering domain by Xiao Fan Wang and Guanrong Chen in their work on pinning both small-world networks [107] and scale-free dynamical networks [110]. In particular, they simulated a model of connected Chua's oscillator circuits to indicate synchronisation in such a network.

2.6.2 Main research considerations

The main considerations for analysis and research in the field of pinning control were presented in [111] as:

1. **Behaviour of the nodes (The node models)**: Assumptions are normally made regarding the nodes. These are usually either homogeneity or autonomy. Mostly, in literature, nodes are analysed with the assumption that their dynamic behaviours are all the same.

2. **Network topology**: Topology may be varied in three broad categories. Firstly, network structure may vary from random through to scale-free. This means that all nodes may have exactly the same number of neighbours (random degree distribution), or roughly the same number of neighbours with a few nodes having slightly more neighbours than the rest (small-world) or networks that exhibit a power-law in their degree distributions (scale-free). The latter has a couple of nodes that act as hubs in the network, with a large proportion of nodes connected to them. The second manner in which network topology may differ is in the coupling strength between nodes. Networks with nodes that are coupled exactly in the same way are unweighted networks, and net-

works with nodes that differ in their coupling are called weighted networks. The last topological feature of networks that may be varied is their directivity. Networks may have nodes that accept coupling both to and from other nodes. Other networks may have nodes that only allow incoming or outgoing connections. Such networks are called directed, or semi-directed networks. Depending on the selection of different topology features for a network being analysed for pinning synchronisation, the behaviour and impact of pinning could have very different outcomes.

3. **Coupling strength between nodes**: Coupling strength refers to the ability of the coupled states of two nodes to relay information between another. It is always assumed that the coupling method does not differ within a single network.

4. **Control for synchronisation or stability**: The purpose of controlling a network by pinning is mainly for synchronisation to a particular reference outcome or to stabilise the networks. Synchronisation readily assumes that nodes are modelled with oscillating dynamics, which would further imply that such oscillations would be damped until settling to a steady-state value. Many works focus on the coupled dynamics of oscillators [112, 113, 114]. The reason for this is the ability to construct a real-world network of such oscillators for analysis and observation [115].

5. **Control methods**: The methods for applying pinning control to a network may vary extensively. The most common method is to apply local linear feedback injections to particular nodes [116]. The selection of which nodes to pin may be random or very specific, such as pinning according to nodes' degrees [112]. Other methods of selecting nodes include pinning according to node betweenness centrality, clustering coefficient and closeness [117].

6. **Methods for analysing the stability of pinned networks**: Stability of pinned networks may be analysed using three main techniques:

   (a) The Lyapunov stability theorem [118].

   (b) The master stability function (MSF) [119].

   (c) Fundamental stability theory of a linear system (Routh-Hurwitz array stability).

7. **Implementing the control**: The main decisions to be made are the number of nodes to pin, in which manner they will be pinned and which specific nodes in the network will be pinned. Mainly, the two schemes employed for pinning are called *selective pinning* and *random pinning*. Selective pinning indicates that the nodes with the most number of connections (highest degree) in the network are pinned and random pinning that control is applied at random to nodes in the network. Several comparisons of these two main methods were made through extensive simulation [120, 114, 121].

2.6.3 The number of pinned nodes

An approximation of the number of pinned nodes to be pinned for stability of a network of coupled oscillators has been attempted by [113]. It has also been shown that, if the coupling strength between nodes is chosen to be large enough, control of even a single node is sufficient in order to achieve network synchronisation [122].

2.6.4 Pinning controllability

2.6.4.1 Local pinning controllability

Local pinning controllability can be analysed by using the Master Stability Function (MSF) approach [123]. In general, the following $N+1$ dynamical systems y_i, linked in network form, can be defined as:

$$f(y_i) = \sigma \sum_{j=1}^{N+1} a_{ij}\, h(y_j)\,, \qquad i = 1\,, 2\,, \ldots\,, N+1 \tag{2.3}$$

Here, σ is the coupling strength and $a = \{a_{ij}\}$ is a square matrix with dimensions $N+1$, given as:

$$\begin{pmatrix} \mathcal{L}_{11} + \delta_1\kappa_1 & \mathcal{L}_{12} & \ldots & \mathcal{L}_{1N} & -\delta_1\kappa_1 \\ \mathcal{L}_{21} & \mathcal{L}_{22} + \delta_2\kappa_2 & \ldots & \mathcal{L}_{2N} & -\delta_2\kappa_2 \\ \vdots & & \ddots & & \vdots \\ \mathcal{L}_{N1} & \mathcal{L}_{N1} & \ldots & \mathcal{L}_{NN} + \delta_N\kappa_N & -\delta_N\kappa_N \\ 0 & 0 & \ldots & 0 & 0 \end{pmatrix}$$

and given that $\delta_i = \sum_{k=1}^{n} \delta(i - c_k)$. The eigenvalues of a are then $\{\lambda_i = \lambda_i^r + j\lambda_i^i\}$, and assuming they are ordered, could be given as $\lambda_1^r \leq \lambda_2^r \leq \ldots \leq \lambda_N^r$. It has been shown by

[124] that $\lambda_i^r \geq 0 \, \forall \, i$. Sufficient conditions now exist to apply the MSF to (2.3). It was shown by [123] that, for synchronisable networks, the reference state $y_1(t) = y_2(t) = \ldots = y_N(t) = y_{N+1}(t)$ is stabilisable or controllable for a finite range of coupling gains $\sigma = [\sigma_a \, \sigma_b]$.

2.6.4.2 Global pinning controllability

The conditions for global pinning controllability of complex networks was analysed and proposed by [125] using an approach based on the Lyapunov stability theorem. This work has further been extended in [126] to optimise the control performance in synchronising a network. The general method for arriving at the proof of sufficient conditions for global controllability is given below. The proof indicates that, with a limited number of pinned nodes, global stability and controllability can be reached by selecting the correct values of the coupling strength and the feedback gain. A network of coupled oscillators is assumed, similar to the network represented in (2.3), but given in this case as

$$\begin{aligned} \dot{x}_i = f(x_i(t)) = \sigma \, B \sum_{j=1}^{N} l_{ij} \, x_j(t) + u_i(t) \\ x_i(t_0) = x_{i0}, \;\; i = 1 \, , \ldots , N \, , t \geq t_0 \end{aligned} \tag{2.4}$$

Here, B is the inner linking matrix, which couples the states (x_i) of the nodes and l_{ij} are the elements of the network's Laplacian L. The control input is given as $u_i(t) = p_i \, K \, e_i(t)$, where p_i equals 1 if a node is pinned and zero otherwise. K is the feedback gain matrix, and e_i is the error of node i in following the reference signal $s(t)$. This means that $e_i(t) = s(t) - x_i(t)$. The errors of all nodes i are then combined into a vector $e(t) = 1_N \otimes s(t) - x(t)$. Then, the system in (2.5) is defined as an asymptotic stability problem about the origin:

$$\dot{e}(t) = 1_N \otimes f(s(t)) - [1_N \otimes f](x(t)) - \sigma L \otimes B e(t) - P \otimes K e(t) \tag{2.5}$$

The null space of the Laplacian is given by 1_N, which is $L 1_N = 0$. The error dynamics can now be represented as

$$\dot{e}(t) = \mathcal{F}(e(t), t) \, e(t) - (\sigma L \otimes B + P \otimes K) e(t) \tag{2.6}$$

where

$$\mathcal{F}(e(t), t) = \text{Diag}[F_{s(t), s(t) - e_1(t)} \, , \ldots , F_{s(t), s(t) - e_N(t)}] \tag{2.7}$$

Now, it can be said that the system in (2.5) is globally pinning-controllable if the system in (2.6) is globally asymptotically stable about the origin.

The proof of a sufficient condition for this stability has been given in [125].

2.7 CONTROL OF DISEASE NETWORKS BY PINNING

2.7.1 Stability of the infection process

When contact networks and the transmission of disease are considered, stability of compartmental population-based epidemic models have been considered by [127] and [128]. Global stability of the infection process in complex networks has also been shown [129, 130] and comprehensively discussed and presented in [131]. It is important here to define the concept of the *epidemic threshold*. When a disease is spread in a network or population, this spread happens at a particular rate. A quantity called the basic reproduction number, or $\mathcal{R}_0$, describes the average number of secondary infections that result from a single infected node in a population that is completely susceptible during this infection process. The infection happens through β contacts, giving rise to new infections with a mean infectious period of $1/Y$. This means that $\mathcal{R}_0 = \beta/Y$. There are three scenarios for spread, related to $\mathcal{R}_0$:

1. $\mathcal{R}_0 < 1$: In this case, the infection would probably not be passed to a susceptible individual during the infectious period, and the infection process will eventually die out.

2. $\mathcal{R}_0 > 1$: This scenario is known as an *epidemic*. It means that each infected member of the population on average infects more than one susceptible member of the population.

3. $\mathcal{R}_0 = 1$: The rate of infection stays consistent in the population, and the disease becomes *endemic*.

The proof that the process of spreading infection through a network is globally stable, as defined in [131], was approached from the viewpoint of the different values that the basic reproductive number may assume:

1. Stability above the epidemic threshold: When $\mathcal{R}_0 > 1$, infected nodes that have a particular degree are independent from the number of infected nodes observed initially. This indicates that the process of infection is globally stable, as originally proven by [129].

2. Stability below the epidemic threshold: When $\mathcal{R}_0 < 1$, the spread of disease will die out eventually. This, in turn, means that the disease-free equilibrium of the spreading process is globally asymptotically stable.

3. Stability when the basic reproductive number is equal to 1: When $\mathcal{R}_0 = 1$, the disease-free equilibrium is unstable.

The analysis of the epidemic threshold has been done with a focus on dynamic contact networks [132], the effect of the interconnected network structure [133] and scale-free networks [49].

2.7.2 Pinning disease networks

Controlling of a disease network with open-loop pinning was presented by [121]. This idea was further developed and refined and the comparison of open-loop random and selective pinning of high-risk HIV networks shown in [134].

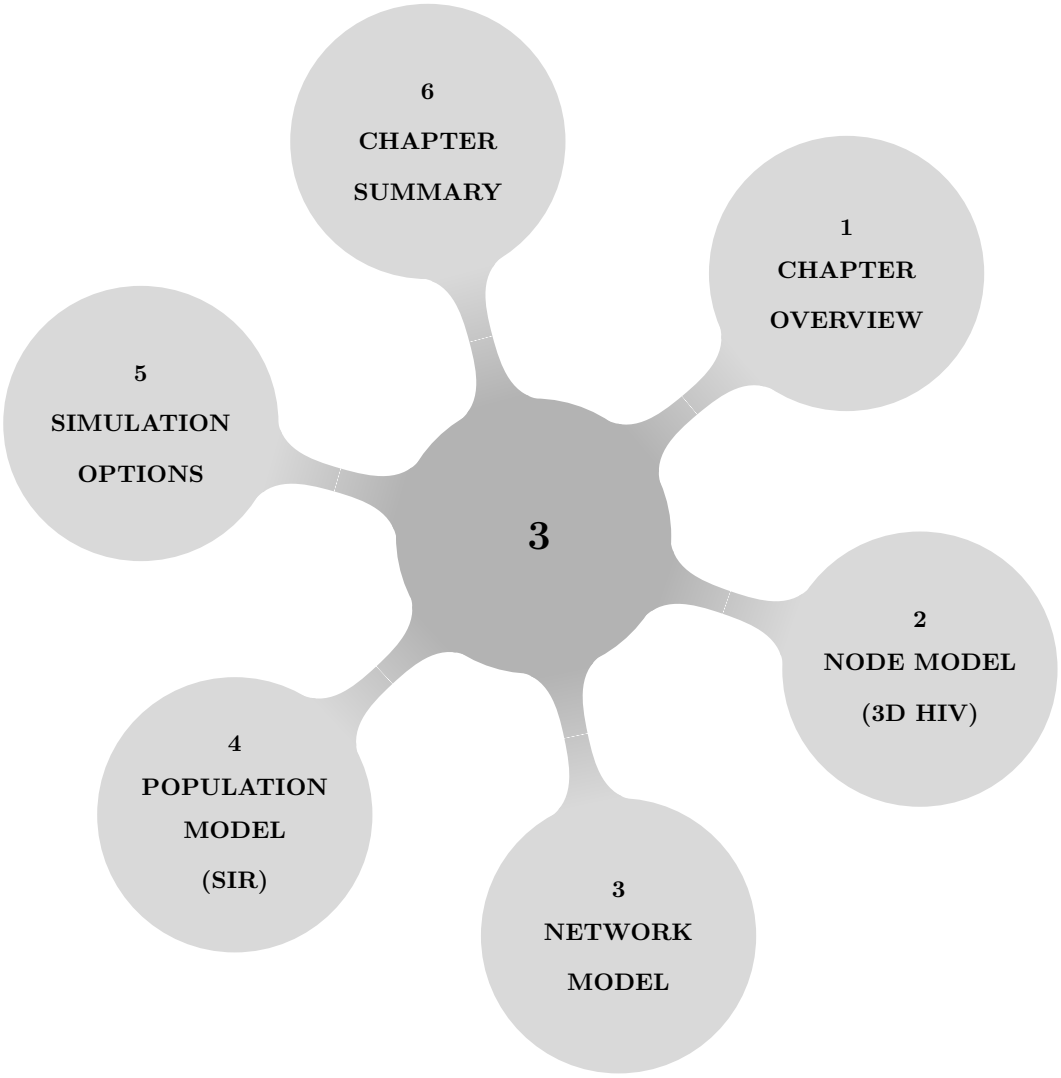
In the real world, pinning control would entail having an intimate knowledge of the network contact structure of individuals as a first prerequisite. To apply the controls, further knowledge is needed of which nodes are infected. This can normally only be achieved through active case finding.

2.8 CHAPTER SUMMARY

In this chapter, the background literature on the synergy between control systems, complex networks and epidemiology were discussed. The intersection of these fields is the main focus point of this thesis. Complex network models relevant to the spread of disease were presented, including a discussion on population-level models and real-world disease networks. The public health control measures for the spread of disease created a basis from which the discussion of challenges in networks modelling for epidemiology could take place. The main research considerations in the field of pinning control followed from this discussion. A brief overview of the infection process on disease networks, and the stability of this process, was given. The chapter concluded with a brief section on the author's contribution.

CHAPTER 3

MODELS



3.1 CHAPTER OVERVIEW

In this chapter, all the models used in this thesis, their parameters, their purpose, function and inter-relationships are explained. The modelling framework consists of three levels: node, network and population levels, as seen in Figure 3.1. At the node level an immune-response model of HIV is used to simulate the dynamics of a person's changing viral load over time. The viral load is directly related to the risk or probability of transmission (called "transmissibility") of virus to another person when nodes are linked in a network structure. The network model is that of a sexual contact network for which a suitable network topology is formed by a degree distribution function with both an exponential portion and a power law portion. Lastly, the modelling chapter concludes with a population Susceptible-Infected-Removed (SIR) model that is analogous to the network model. The population model allows the number of susceptible, infected and removed nodes to be measured over time.

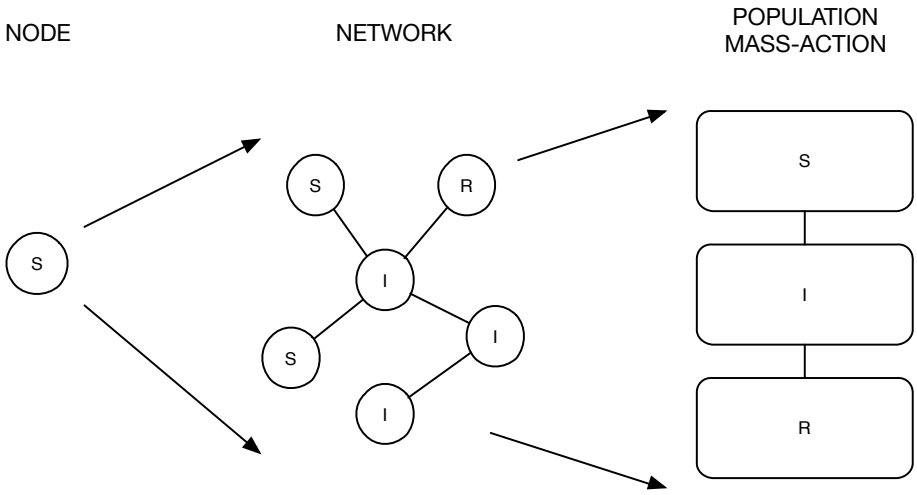


Figure 3.1: Three tiers of models are used in this thesis. A node-model is connected into a network of multiple nodes. The nodes of the network are then compartmentalised according to their susceptible (S), infected (I) or removed (R) status, thus forming a population mass-action SIR model. (Reprinted figure with permission from E. F. du Toit and I. K. Craig, Physical Review E, 92, 012810, 2015. Copyright 2015 by the American Physical Society. See Appendix D for further information.)

3.2 NODE MODEL: 3D MODEL OF HIV

Considering a single person's immune response as foundation from which the dynamics of viral load variation can be modelled, the well-researched three-dimensional model of HIV *in vivo* is used. This model, shown in (3.1), was originally proposed by [135] and later refined in [136]. It assumes three states corresponding to three cell types involved: the viral load v, the CD4+ T-cell count T and infected CD4+ T-cells T^*.

$$\begin{aligned} \dot{T} &= s - dT - \theta T v \\ \dot{T^*} &= \theta T v - \delta T \\ \dot{v} &= kT^* - \mu v \end{aligned} \tag{3.1}$$

In this model, s depicts the source term for production of new CD4+ T-cells, d is the death rate of uninfected T-cells, θ is the infectivity rate of free virus particles, δ is the natural death of T-cells, k is the rate at which virions are produced per infected T-cell and μ is the natural death rate of virus. The parameter values chosen from literature for this model are shown in Table 3.1.

3.2.1 Parameter identifiability

Identifiability of any system is a property that indicates whether the parameters of the system can be identified given a series of samples of the outputs of the system. The technique for algebraic identifiability of the parameters of the three-dimensional model was first proposed by [7] and [137], and also implemented with real-world data by [4]. Further study by [138] found that if the viral load is the only measurable output of the model, then the source term s and rate of virion production per infected T-cell k cannot be determined, although their product (sk) is identifiable. In this thesis it is assumed that all individuals of each of the contact networks simulated employ the immune response model in (3.1). The initial conditions and parameters for each node are thus the same. Model parameters were obtained from [4] and are given as $\hat{\chi} = \{s;\ d;\ \beta;\ \delta;\ \mu;\ k\} = \{10.7;\ 0.015;\ 4.5 \times 10^{-6};\ 0.58;\ 2.05;\ 896.49\}$, with the initial conditions for an infected node given as $\mathbf{I_0} = \{T_0;\ T_0^*;\ v_0\} = \{1000;\ 1;\ 100\}$. It should be noted here that only one node was randomly chosen to be infected at the start of a simulation, and that the initial conditions for all other nodes were $\mathbf{U_0} = \{T_0;\ T_0^*;\ v_0\} = \{1000;\ 0;\ 0\}$.

Table 3.1: Summary of all node model parameters used in this thesis.

Parm.	Description	Value / Range	Source
T_i	Uninfected CD4+ T-cells	– copies/mm^3	–
T_i^*	Infected CD4+ T-cells	– copies/mm^3	–
v_i	Free virions	– copies/mm^3	–
T_{i0}	Initial uninfected CD4+ T-cells of first infected patient	1000 copies/mm^3	[4]
T_{i0}^*	Initial infected CD4+ T-cells of first infected patient	1 copy/mm^3	[4]
v_{i0}	Initial free virions of first infected patient	100 copies/mm^3	[4]
s	Source term for uninfected CD4+ T-cells	10.7 / (mm^3 day)	[4]
d	Death rate of uninfected CD4+ T-cells	0.015 / (mm^3 day)	[4]
θ	Infectivity rate of free virus particles	4.5×10^{-6} / (mm^3 day)	[4]
δ	Natural death of infected CD4+ T-cells	0.58 / day	[4]
k	Rate of virions produced per infected CD4+ T-cell	896.49 virions / (cell day)	[4]
μ	Natural death rate of virus	2.05 / day	[4]

3.2.2 Benefits of using this model

The main benefits and the reasons for choosing this model to represent the dynamics of nodes as part of this thesis are:

1. It captures the dynamics between HIV and a person's immune response.

2. The model is one of the simplest of its kind for HIV dynamics, which means that scaling networks to tens of thousands of nodes should most likely be computationally feasible.

3. The impact of a dose of medicine on the HIV infection of a node is measurable.

4. The model, its parameters and controllability has been thoroughly analysed.

3.3 NETWORK MODEL

3.3.1 Topology

One of the most important risk factors for the transmission of HIV is the number of sexual partners per individual [139]. If one represents the sexual partners of each person as a real-world contact network, the proportion of high-risk people with many partners will be small and the proportion with only one or a few partners comparatively large [140, 141]. Networks with such a degree distribution are typical in the real-world and can be modelled by the degree distribution proposed by [41], shown in (3.2).

$$p_k = \begin{cases} 0, & \text{for } k = 0 \\ \frac{k^{-\alpha} e^{-k/\kappa}}{Li_\alpha(e^{-1/\kappa})}, & \text{for } k \geq 1 \end{cases} \tag{3.2}$$

Note here that $Li_\alpha(x)$ represents the nth polylogarithm of x, where the polylogarithm (known as Jonquière's function) is defined mathematically by the following Taylor Series expansion:

$$Li_s(z) = \sum_{k=1}^{\infty} \frac{z^k}{k^s} = z + \frac{z^2}{2^s} + \frac{z^3}{3^s} + \dots \tag{3.3}$$

The distribution p_k chosen for this thesis, with power-law exponent $\alpha = 2$ and degree cutoff at $\kappa = 5$, is shown in Figure 3.2.

The investigation of asymptotically scale-free networks is not included in this thesis due to the absence of an epidemic threshold in such networks [49]. This result implies that the probability of an epidemic persisting on a scale-free network is very high, even when medicine is applied generously. In contrast to this notion, it has been suggested by [57] that focusing medication on the "hub" nodes in a network may bring the virus spreading rate to below the epidemic threshold and potentially eradicate the virus. Even policies that offer moderate success could be effective in restoring the epidemic threshold in a network, although the most effective policies should drive this threshold to below β_c, the critical transmissibility.

Representing disease spread via proliferation through a contact network opens up the possibility to model and simulate the spread of HIV between nodes over time, especially given that the infection process is globally stable for all infection rates apart from the

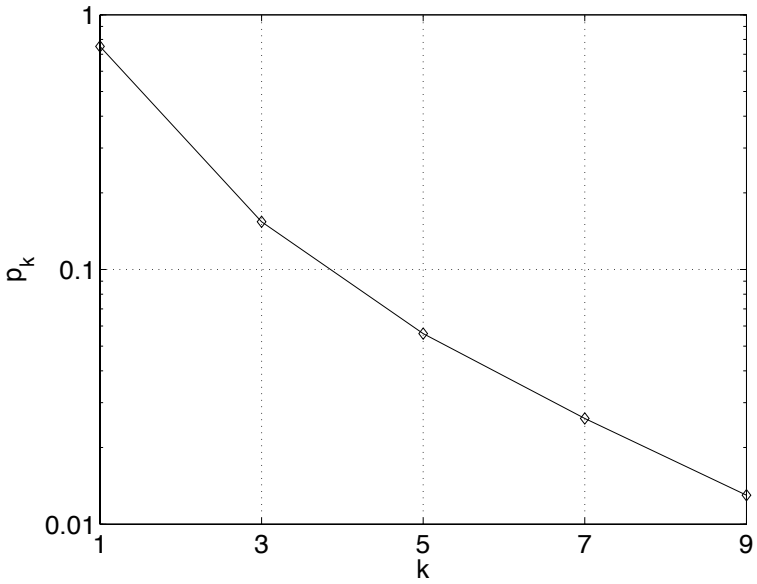


Figure 3.2: Normalised degree distribution (p_k) of the simulated networks. The distribution is normalised to a fraction between zero and one. Parameters are fixed at $\alpha = 2$ and $\kappa = 5$. The average number of links (M) for each network of N nodes are: $N = 100$ ($M = 280$), $N = 1000$ ($M = 2792$), $N = 5000$ ($M = 13968$), $N = 10000$ ($M = 27938$). All networks have a mean degree of 2.8. (See Appendix D for copyright information.)

epidemic threshold T_c [131]. The influence of any intervention on a contact network can also be determined and optimal solutions can be sought.

3.3.2 Transmission function

The node model incorporates the immune response of an individual to HIV infection. For this work, the node model is represented by the well-known 3D model of HIV *in-vivo* [142, 135, 136]. This model was the basis of the question for the control of HIV asked in [5], with parameters listed in Table 3.2, as estimated in [4]. Each infected node has an inherent probability of transmitting disease to another node, influenced mainly by its viral load level. It is assumed that nodes receiving the infection are all equally susceptible and that nodes transmitting infection do so at the highest probability reachable given their risk profile. Additional risk is added via a factor R_f, and high risk is represented by $R_f > 100$. Additional risk factors that are included into the risk factor R_f include the presence of STDs, drug use and frequency of intercourse without protective measures such as condoms.

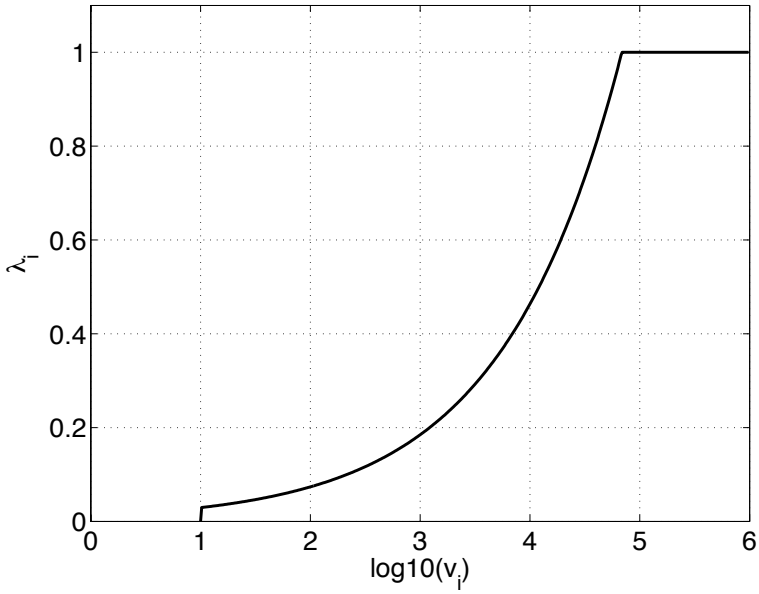


Figure 3.3: Example transmission function (λ_i), where the added risk factor $R_f = 500$ indicates a very high risk HIV spread. The function is chosen to saturate just below a log-viral load of 5, for 100% transmission. (See Appendix D for copyright information.)

The highest risk groups are represented by the simulations in this work in order to suitably use an SIR model at the population level and to achieve disease spread above the epidemic threshold. Under normal risk circumstances HIV is not nearly as transmissible as represented here, but for the purpose of comparing control strategies this is a feasible configuration.

The per-sexual-act transmission probability of the i'th node is λ_i, with increased risk added via the risk factor R_f as represented by Eq. (3.4) and shown in Figure 3.3. The input to the function is node i's viral load v_i [143].

$$\begin{aligned} \lambda_i(t) &= R_f * \left(1 - \left[1 - 9.36 \times 10^{-4}\right]^{e^{(.92*(log_{10}(v_i(t))-4))}}\right), \\ &\quad \text{with } 0 \leq \lambda_i(t) \leq 1 \\ &\quad \text{and } \lambda_i(0) = 0, \quad \text{for } v_i(0) = 0 \end{aligned} \tag{3.4}$$

Nodes are linked via the viral load state of the immune response model of each node, into a network represented by Eq. (3.6). All parameters used in Eq. (3.6) are obtained from literature. Here v_i is the viral load from the node model of the i'th node; T_i^* is the infected CD4+ T-cells; μ is the natural death of virus in the body; a_{ij} is the connectivity matrix of the network and $\Gamma(x)$ is the activation function for transmission in the network. Given in

Iverson Notation, where $[v_j > 0]$ evaluates to 1 if the condition in the bracket is *true*:

$$\begin{aligned} \dot{T}_i &= s - dT - \theta T v \\ \dot{T}_i^* &= \theta T v - \delta T \\ \dot{v}_i &= kT_i^* - \mu v_i + \Gamma\left(\lambda_i(t)\right) \sum_{j \neq i}^{N} a_{ij}[v_j > 0] \end{aligned} \tag{3.5}$$

3.3.3 Open-loop pinning control term

All control at node-level in this thesis are open-loop. This means that no node is singularly aware of feedback regarding its states. Control is added as a single term to two of the 3D HIV model states, exactly as proposed by [144].

Addition of the control term u_i to the complete network model gives:

$$\begin{aligned} \dot{T}_i &= s - dT - \theta T v + \Delta_i u_i \\ \dot{T}_i^* &= \theta T v - \delta T - \Delta_i u_i \\ \dot{v}_i &= kT_i^* - \mu v_i + \Gamma\left(\lambda_i(t)\right) \sum_{j \neq i}^{N} a_{ij}[v_j > 0] \end{aligned} \tag{3.6}$$

In (3.6), "pinning" a node is defined as the control u_i being activated by a member i of the activation matrix Δ as follows:

$$\Delta_i u_i = \begin{cases} 0, & \text{for } \Delta_i = 0 \\ \varepsilon_{RTI} \beta T v, & \text{for } \Delta_i = 1 \end{cases} \tag{3.7}$$

and the function $\Gamma(x)$ is defined by:

$$\Gamma(x) = \begin{cases} 0, & \text{for } U([0,1]) \leq x \\ 1, & \text{for } U([0,1]) > x \end{cases} \tag{3.8}$$

where $U([0,1])$ is a uniformly distributed random number between 0 and 1.

The final controlled network model (3.6) can now be described: At each time step of simulating the network model, transmission of a single virion from a neighbour j to node i is possible with probability λ_i, only if node j is already infected.

Table 3.2: Summary of all network-specific model parameters used in this thesis.

Parm.	Description	Value / Range	Source
$\Gamma(x)$	Activation probability function for transmission	$0, 1$	[134]
I_{max}	Maximum incidence of HIV for a network	$0 - 100\%$	[134]
λ_i	Transmissibility of node i	$0 - 1$	[134]
R_f	Added risk factor for HIV transmission	500	[134]
N	Total number of network nodes	100	–
$\Delta_i \times c_i$	Node-level control (medicine) from [134]	$0 - 1$	[134]

3.4 POPULATION MODEL

3.4.1 Susceptible-Infected-Removed (SIR) model

A Susceptible-Infected-Removed (SIR) model to capture epidemic dynamics as originally proposed by [42] is used in this thesis. This model allows the simulation of epidemics that reach a maximum number of infected nodes (incidence) and then declines. This maximum (I_{max}) represents the "steady-state" in context of the simulations done in this thesis. The assumption of random mixing (homogeneity) applies with compartmental SIR models: Each susceptible person in the population is assumed to have an equal probability of becoming infected after contact with an infected node. In a complex network where disease is being spread, it has been shown by [41] that individual transmissibilities make no difference and that the disease will propagate between nodes as if all transmissibilities are equal to β. This proof allows networks to be solvable on population models such as the SIR model in this section.

The SIR model modified from (2.1) is given as

$$\begin{aligned} \dot{S} &= -\beta IS \\ \dot{I} &= \beta IS - \nu I \\ \dot{R} &= \nu I \end{aligned} \tag{3.9}$$

The values used for the parameters of this model are supplied in Table 3.3. The number of susceptible nodes in the population is given by S; the number of infected nodes is given by I and the number of removed nodes by R. The transmissibility rate of the infective pathogen

is β, and the rate at which infected nodes are removed from the population is ν. Graphically, this model can also be represented as given in Figure 3.4 and a typical simulation of the model can be seen in Figure 3.5.

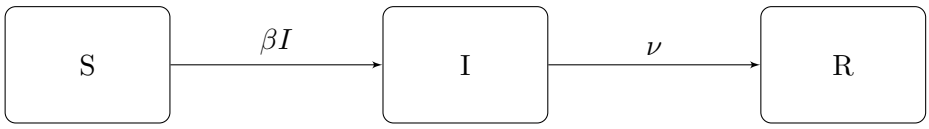


Figure 3.4: Graphical representation of the SIR population-based model and its parameters.

Table 3.3: Summary of all population model parameters used in this thesis.

Parm.	Description	Value / Range	Source
S	Number of nodes susceptible to HIV infection	$0 - N$	–
I	Number of infected nodes	$0 - N$	–
R	Number of removed (by death) nodes	$0 - N$	–
β	Average transmissibility of the network and population	$0 - 1$	–
ν	Mean probability of death for infected nodes	0.05	–

3.4.2 Linking the SIR and network models

In order to couple the population SIR model (3.9) to the complex network model (3.6), the viral load of all nodes is assessed. If the viral load of a node is above one, this adds one to the total number of infected nodes (I). If the viral load is zero, the number of susceptible nodes increases by one. All remaining nodes are classified as removed (R). This calculation can be represented using Iverson notation as shown in (3.10). By definition the expression in square brackets evaluates to an outcome of one or zero.

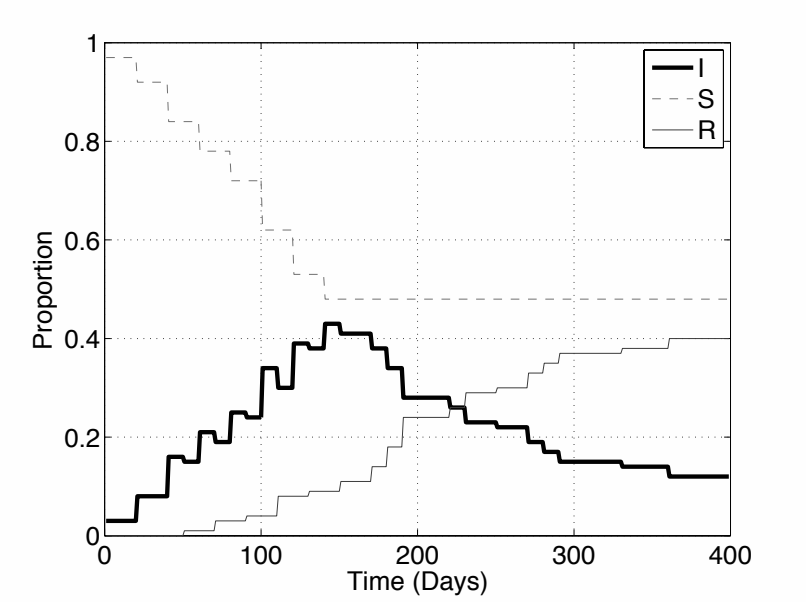


Figure 3.5: A typical example of SIR model dynamics can be seen in this graph. The number of infected nodes reach a peak (in this instance, at about 145 days), while the number of susceptible nodes decrease monotonically over time. The number of removed (R) nodes increase monotonically over time.

$$\begin{aligned} S &= \sum_{i=1}^{N} [v_i = 0] \\ I &= \sum_{i=1}^{N} [v_i > 0] \\ R &= N - S - I \end{aligned} \tag{3.10}$$

N is the total number of nodes in the network or population. The transmissibility of a specific node was given in (3.4). The average transmissibility (β) of the network and the SIR model is taken as the sum of the individual transmissibilities from each of the infected nodes in the network as presented in (3.4), divided by the total number of infected nodes (I):

$$\beta = \frac{\sum_{i=1}^{N} \lambda_i}{I} \tag{3.11}$$

With the SIR model, the incidence I reaches a specific maximum number of newly infected nodes when $dI/dt = 0$ and then declines. This work aims to control I to reach this point when $I = I_{ref}$.

3.5 SIMULATION OPTIONS

The three-level tiered modelling architecture presented in this chapter (shown visually in Figure 3.1) allows several options for simulation and analysis. These possibilities are described in the following sections.

3.5.1 Varying node heterogeneity

Many networks studies focus on nodes where the dynamics of all nodes are homogenous. Although, in this thesis, the same node model and parameters are chosen for all nodes, this can easily be adjusted to create completely heterogenous dynamics across all nodes. For example, the network may include a percentage of nodes that are co-infected by tuberculosis to assess the impact on the majority of HIV-infected nodes. Initial conditions of infection for each node can also be separately defined and adjusted.

3.5.2 Adapting the network structure

The networks studied are random, with power-law degree distributions. This structure may be adjusted to incorporate studies of scale-free networks which, asymptotically, do not resemble the property of an epidemic threshold [49]. This analysis could be evaluated for a variety of networks adjusting for the scale-free power factor γ seen in Table 2.1 in Section 2.3.1. Depending on the type of pathogen and the dynamics of its transmission, a suitable network with appropriate degree distribution is generated. As an example, tuberculosis is a disease which people may recover from and become susceptible for infection again. This could allow connected network "triangles" to form, which would make exponential random graphs the appropriate network structure for modelling TB statically [145], or with varying degree distributions over time [146].

3.5.3 Comparisons with real-world population epidemic results

Calibration of network models with real-world population interaction data is possible by using statistical tests [147]. A large number of studies exist that perform compartmental analyses of diseases. Any such model can be fitted to the population-based model simulated in this architecture. Attempts can be made to adjust the transmissibility of the network to compare it to population model outcomes.

3.5.4 Simulation of intervention policies

A wide variety of interventions may be simulated and compared using the modelling architecture in this chapter. As an example, the 2014 World Health Organisation (WHO) guidelines for antiretroviral treatment administration [148] recommend that treatment be given to all individuals that test positive for HIV irrespective of their CD4 count. The South African Department of Health announced in the South African Antiretroviral Treatment Guidelines of 2015 [149] that ARVs should be given to all infected individuals with a CD4+ T-cell count of less than 500 copies/ml. This strategy can be tested on a network and compared with, for instance, a selective approach. Selective approaches look at nodes that are most likely to transmit a virus to other nodes, after which medicine doses are given to them.

3.5.5 Reaction of networks to control set-points

Control set-points for the following targets can be set:

1. Control set-point for the maximum incidence (I_{ref}) in a network, which translates into an average transmissibility set-point $\hat{\beta}_{ref}$ as explained in Chapter 5. Analysis of the average maximum incidence should be done for a statistically signifiant number of networks as explained by the definition of bond percolation average epidemic sizes.

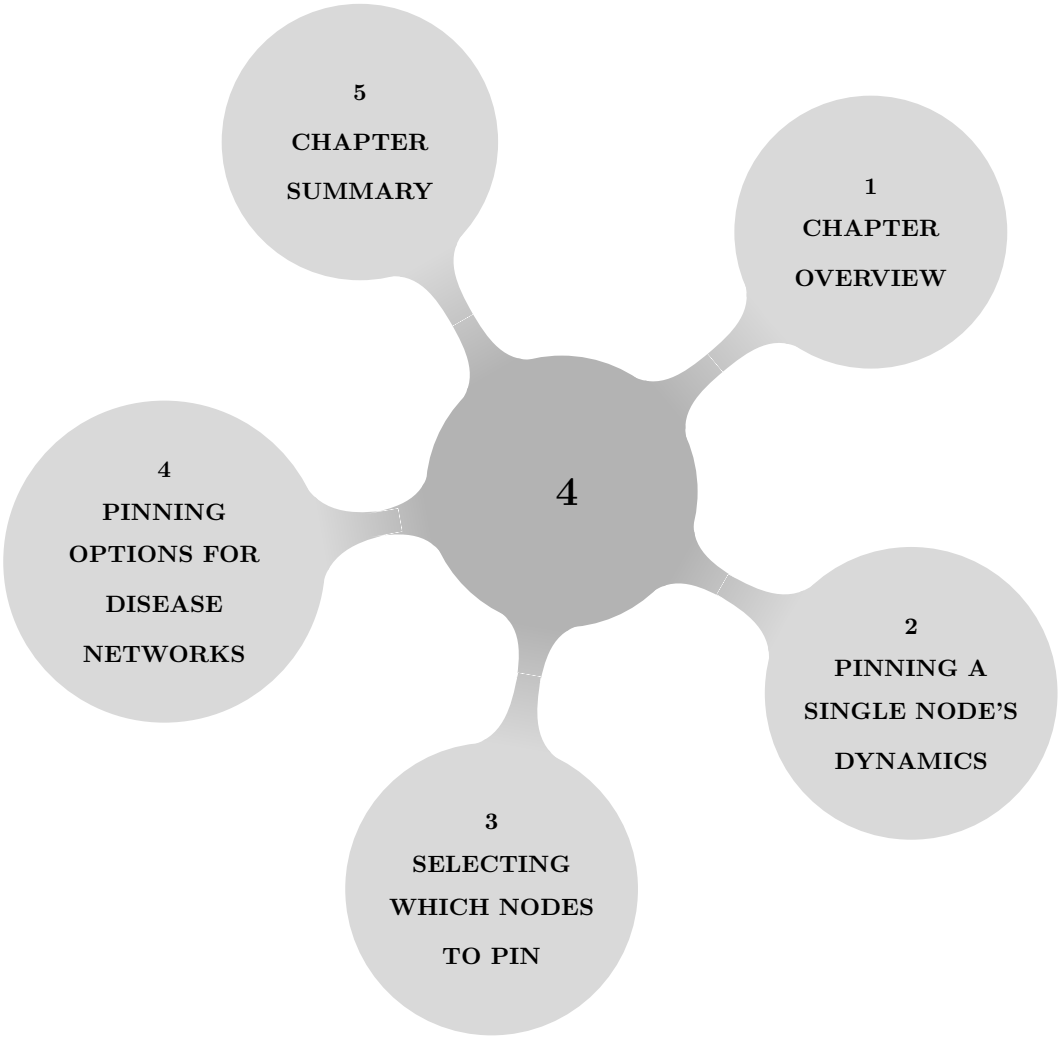
2. Control set-point for budget (Q_{ref}) measured in QALYs as explained in Chapter 8. Budget is determined with a quality-of-life function linked to the CD4+ T-cell count of patients. By measurement and feedback of the T-cells, the utility function can be determined and the system can react and control for QALYs.

3.6 CHAPTER SUMMARY

In this chapter, the models used in this thesis were presented. Three tiers of models are used: A node, network and population-level model. The link between each level was presented. The node models are linked via each viral load state in order to spread and propagate disease throughout a network. The network spreads disease at an average transmissibility which also represents the average transmissibility in the population-level SIR model. In the next chapter, two methods of pinning control are presented. These methods are later applied to the models that were presented in this chapter (See chapters 6 and 7).

CHAPTER 4

PINNING CONTROL



4.1 CHAPTER OVERVIEW

Pinning control is a network-based intervention. On contact networks, this intervention is used to limit disease spread. The networks simulated in this thesis apply different pinning control schemes: At the node-level, open-loop pinning is applied. At the network-level, selective pinning is applied. Pinning control is thus a control-theoretic technique where the dynamics of network nodes are manipulated by adding an open-loop control term or closed-loop reference and control terms to network node models. On disease networks, pinning implies giving a dose of medication to a person. In this chapter, the pinning control options for disease networks are presented and discussed. Two options, open-loop and closed-loop pinning, apply specifically to the node model dynamics, whilst random and selective pinning apply to the network model dynamics and outcomes.

4.2 PINNING A SINGLE NODE'S DYNAMICS

4.2.1 Open-loop pinning control

Open-loop pinning indicates that a control term is added to the dynamics of nodes in a network, but without reference-error dynamics as in the closed-loop scenario [116]. The control in (4.1) is added, for example, to the three-dimensional model of HIV (4.2) and the effect on the overall network outcome is measured. The difference to closed-loop pinning is thus that open-loop pinning focuses not on the particular outcome for individual nodes, but rather on an average outcome for the entire network, whilst closed-loop pinning focuses on synchronisation of all nodes' dynamics to a particular set-point.

The approach of using antiretroviral drugs as control inputs to an immune response model is not new and was effectively demonstrated by [8]. In the example, the control is the application of a Reverse Transcriptase Inhibitor (RTI) to any number of nodes in a network, and is represented as proposed by [144], preventing the infection of healthy CD4+ T-cells by the virus:

$$u_i = \varepsilon_{RTI} \beta v T \tag{4.1}$$

In this equation, ε_{RTI} is the efficiency of the RTI. The drug used to simulate medication is a reverse transcriptase inhibitor named Tenofovir with an average efficiency chosen for this

thesis of 65%. Combination-drugs, for example using a Protease Inhibitor (PI) together with an RTI, was not studied in this work. This means that the final controlled network model of HIV in this case is represented as in (3.6), provided here again as:

$$\begin{aligned} \dot{T}_i &= s - dT - \beta T v + \Delta_i u_i \\ \dot{T}_i^* &= \beta T v - \delta T - \Delta_i u_i \\ \dot{v}_i &= k T_i^* - \mu v_i + \Gamma\left(\lambda_i(t)\right) \sum_{j \neq i}^{N} a_{ij}[v_j > 0] \end{aligned} \tag{4.2}$$

In the model Δ_i is a function representing whether a node is controlled or not, of the form:

$$\Delta_i = \begin{cases} 1 & : \text{node controlled} \\ 0 & : \text{node not controlled} \end{cases} \tag{4.3}$$

For the random pinning control scheme (Section 4.3.1), Δ_i would thus be equal to 1 for each node included in the randomly pre-determined percentage of pinned nodes in the network. For the selective pinning control scheme, Δ_i would be equal to 1 for each of one of the highest-degree network nodes selected for control. In either control scheme, the specific percentage of pinned nodes was determined before the simulation commenced.

4.2.2 Closed-loop pinning control

Closed-loop pinning control of a network of oscillating nodes has been demonstrated by [105]. Local feedback injections are made to nodes and the solution to an isolated, master node provides the reference trajectory for the network. To illustrate this, a network of oscillators are constructed as follows [126]:

$$\dot{x}_i(t) = f(x_i(t)) - \sigma \sum_{j=1}^{N} l_{ij} h(x_j(t)) + u_i(t) \tag{4.4}$$

where $x_i(t)$ is the state of the ith oscillator and the function f describes an individual oscillator's dynamics. When oscillators are coupled to each other, the function h describes the links between their states. The parameter σ is the coupling strength between oscillators and $u_i(t)$ is the control of node i. The matrix elements l_{ij} describe the graph topology (which nodes in the network are linked to each other).

Closed-loop pinning control inputs are applied to nodes with the main aim of synchronising

their dynamics to a reference trajectory $s(t)$. This trajectory is independently applied to the network as $\dot{s} = f(s(t))$.

The state feedback control law can then be defined as follows:

$$u_i(t) = k_i\Big(h(s(t)) - h(x_i(t))\Big) \tag{4.5}$$

with k_i the control gain applied to node i. For nodes that are not pinned, $k_i = 0$.

The definition of the pinning control problem in this section is the same definition used by many works in literature [105, 112, 113, 150]. An illustration of closed-loop pinning control is given in Figure 4.1.

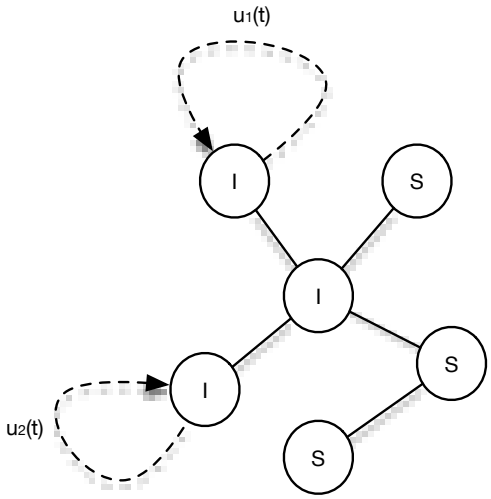


Figure 4.1: An illustration of closed-loop pinning in a network. Some controlled nodes implement a feedback loop towards achieving a common reference trajectory $s(t)$.

4.3 SELECTING WHICH NODES TO PIN

4.3.1 Random pinning

Random pinning can be applied to networks in a number of ways. Two of the options are:

1. Randomly select any number of nodes to be pinned in a network without regard for their internal dynamics and any predefined categorical status of the nodes.

2. Pin nodes with a particular categorical status or dynamic characteristic resulting from a random process (such as disease-transmitting contacts) on a network [121].

In networks containing synchronising oscillators Option 1 would apply, whilst in networks of disease spread and percolating dynamics both options are feasible. As an example of a real-world public health implementation of Option 2: The recommendations for administering antiretrovirals in South Africa in 2014 [151] indicate that all individuals with a CD4+ T-cell count of less than 350 copies per ml should be offered antiretroviral treatment. In 2015, this threshold changed to 500 copies per ml [149]. There is an increasing drive by the World Health Organisation (WHO) for test-and-treat strategies [152] as well as ART for prophylaxis in a strategy called PrEP (Pre-exposure chemoprophylaxis) [153, 154]. Test-and-treat (as proposed by the WHO) means that, if a person is tested positive for HIV when visiting a clinic, they would be given treatment. Ideally, if all cases of HIV went for testing, they would all be treated. What gave rise to their having HIV in the first place is a sexual contact network. This means that to "test-and-treat" is exactly the same strategy as random pinning with Option 2.

In this thesis, random pinning implies that nodes are given medication based only on their infection status (susceptible, infected or removed). The infection process is stochastic in itself, which implies that the pinning process is also random. With the random pinning strategy, nodes are thus given medication whenever they become infected. Random pinning is illustrated in Figure 4.2. Selective pinning control has, in general, been found to require a much smaller pinning fraction than random pinning to achieve the same steady-state in networks comprised of chaotic oscillators [120].

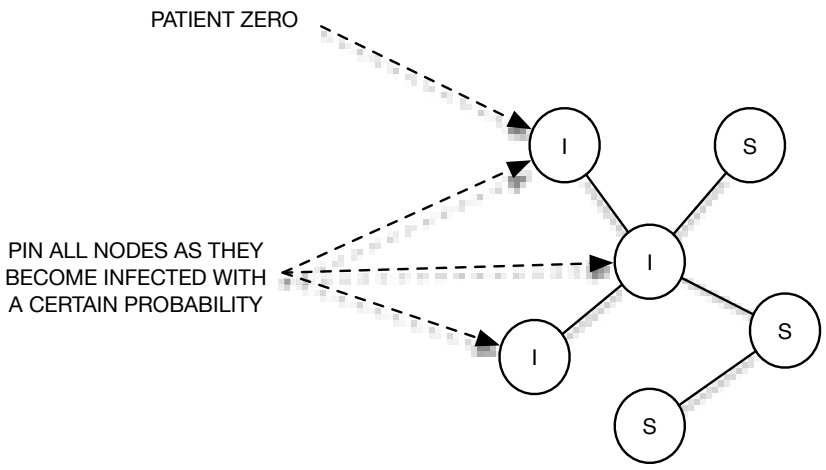


Figure 4.2: Depiction of random pinning in a network. All nodes that become infected (I) with a certain probability are pinned at each time step. The probability of a node i becoming infected at any time point is the average probability that one if i's neighbours j will infect it. This probability is $(\sum \lambda_j) \,/\, N_i$ for all j with transmission probability λ_j connected to i. N_i is the total number of neighbours to i.

4.3.2 Selective pinning

Selective pinning reserves control action for nodes that adhere to some pre-defined criteria. Before pinning, nodes are prioritised and sorted according to criteria that range from node betweenness centrality [155] to node degree [123] and also other proposed criteria such as the node energy index [156]. In this thesis, an adapted version of the degree-sorting criteria is used to pin nodes: Nodes with the highest number of susceptible nodes connected to them are pinned first when a feedback loop suggests the number of nodes to be pinned. The implementation of the feedback loop is explained in Chapter 6. At each time step, the nodes are ranked according to their number of connected susceptible neighbour nodes, from highest to lowest, and pinned. A proportion of nodes equal to the control input to the network, selected from the total number of nodes N would be pinned at each time step. Selective pinning is depicted in Figure 4.3.

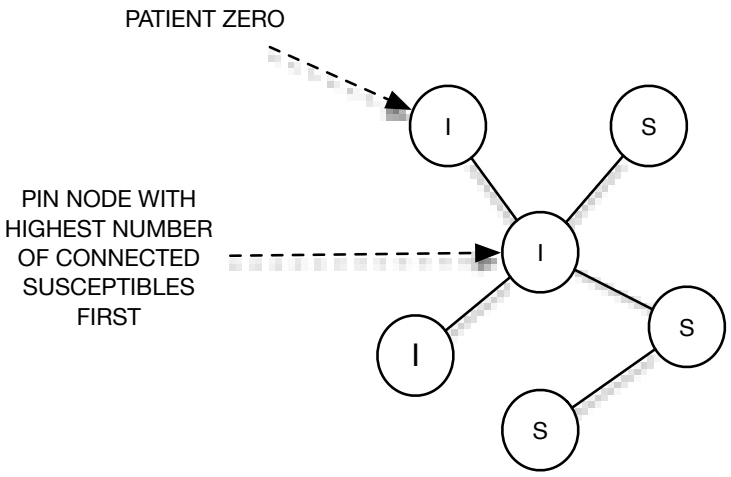


Figure 4.3: Depiction of selective pinning in a network. A proportion of nodes are pinned, as dictated by the network feedback loop. Nodes are pinned according to priority: Nodes with the most number of connected susceptible neighbours are pinned first.

4.4 PINNING OPTIONS FOR DISEASE NETWORKS

Closed-loop pinning at the node level is not applied to the networks studied in this thesis. The aim of control for disease networks is not to synchronise the dynamics of all nodes to a particular equilibrium. It is to ensure an average, statistically significant network-level outcome over several instances of networks. Relevant outcomes are the average maximum incidence and budget.

The control system design at the individual level could be (and more often is) a feedback control that is added [8], but in the case of the nodes of the HIV disease network represented in this work, this node-level control is open-loop. The treatment is antiretroviral medicine applied to infected nodes. This manner of pinning nodes (or influencing the microscopic dynamics of a network), can drive the network towards a particular equilibrium [116]. With unsynchronised or oscillating networks, pinning control has the capability to synchronise the complete network towards a particular steady-state by pinning only a few nodes [112], or in some cases by pinning only a single node [122]. For disease networks, which are already synchronised by virtue of their steady-state characteristics, the primary focus is on the impact of the pinning control method on this steady-state rather than on synchronisation.

When the node immune response model is extended to form part of a network of individuals linked through their sexual partnerships and hence the possible transmission of HI virions, similar to the work done by [46], the viral load equation becomes:

$$\dot{v_i} = kT_i^* - \mu v_i + \Gamma\left(\lambda_i(t)\right) \sum_{j \neq i}^{N} a_{ij}[v_j > 0] \tag{4.6}$$

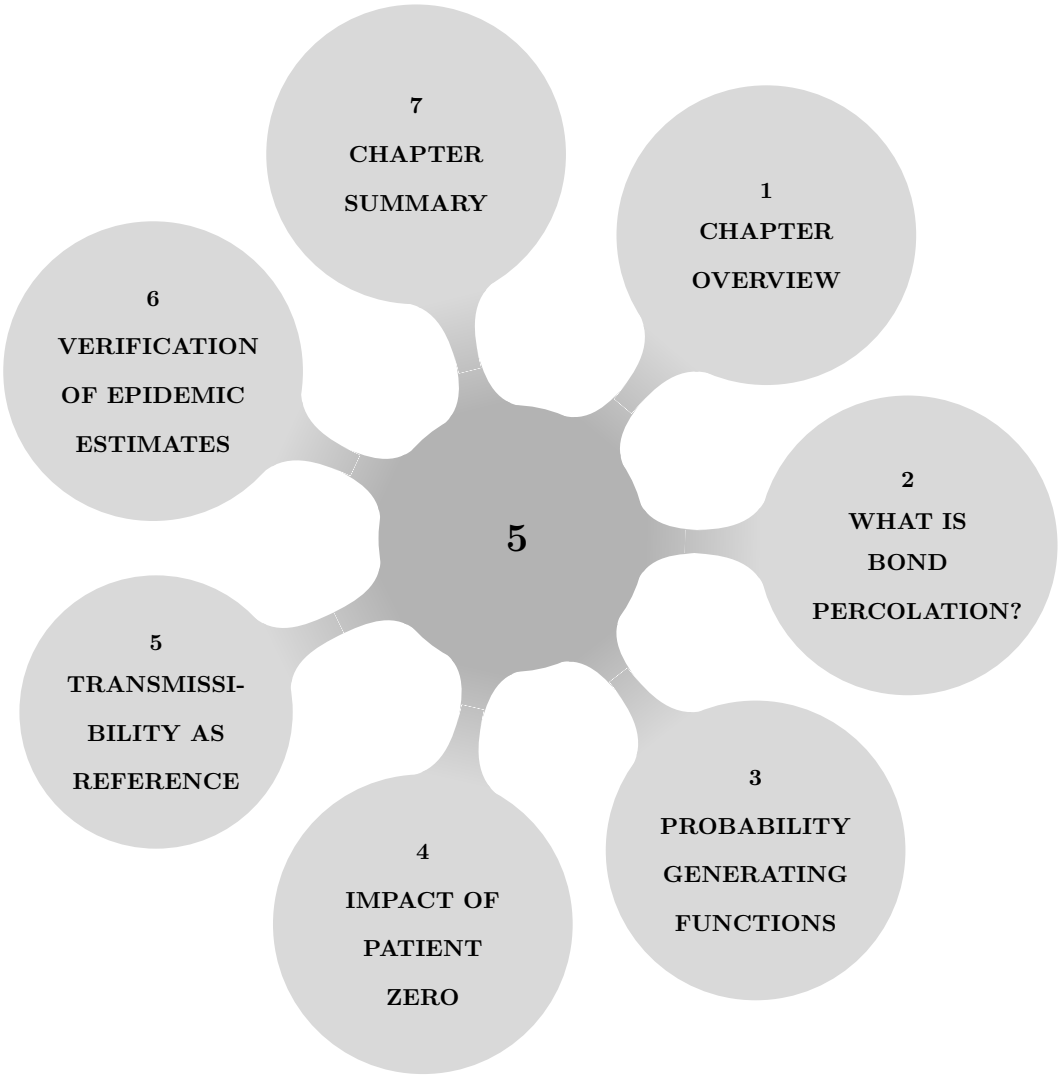
In (4.6), the matrix a_{ij} represents the network structure, hence it indicates which nodes are connected to node i. The matrix Γ represents the coupling of the viral load response of this node to the viral load of the node's neighbours; v_j is the viral load of a node connected to node i.

4.5 CHAPTER SUMMARY

In this chapter, the pinning control method has been discussed from the node and network levels. At the node level, the dynamics can be manipulated by open-loop or closed-loop pinning by addition of the appropriate control terms to the node model. It was discussed how open-loop pinning is an appropriate option for disease contact networks. At the network level, two general strategies exist to select the nodes which would be pinned: Random pinning and selective pinning. Both strategies were explained and illustrated. The remainder of this thesis uses open-loop pinning at the node level and compares random and selective pinning at the network level for all simulated networks.

CHAPTER 5

BOND PERCOLATION: PREDICTING INCIDENCE STEADY-STATE



5.1 CHAPTER OVERVIEW

This chapter presents and applies the concept of bond percolation to disease networks. It is a technique originating from statistical mechanics which is used to analyse the spread of a disease process on complex networks with the aim of predicting the average maximum epidemic size and average outbreak size that might be observed. The inputs to this method are the network topology, network node degree distribution and the average probability of transmission between nodes (transmissibility). The controlled variable is the average transmissibility and the control set-point is determined by providing the final epidemic size required and then recursively finding the average transmissibility that would satisfy the given final epidemic size. Verification simulations of the epidemic estimates are performed for set-points spaced 0.02 percent apart and ranging from 0 to 1. Each set-point is simulated 50 times, and the average maximum incidence at that point is recorded. It is found that, for the random networks simulated in this thesis, bond percolation estimates hold well for networks ranging from size $N = 100$ to $N = 100000$ [41].

5.2 WHAT IS BOND PERCOLATION?

To predict the maximum number of individuals that will become infected in a network, this work draws on percolation theory [157], and in particular on bond percolation applied to epidemic networks [41]. Bond percolation theory sees the links between nodes as entities that may be "occupied" or "not occupied" at a point in time. This theory relies heavily on the degree distribution of nodes in a contact network (reflected in Figure 3.2). An analogous technique called "site percolation" see the nodes (vertices) themselves as entities which may be occupied or not. If bond percolation is applied to the spread of disease [40], the probability that an infected node transmits a pathogen to any of its connected nodes is calculated. If its neighbour nodes are not yet infected, and the probability for transmission is sufficient, the disease is percolated throughout the network.

Percolation happens at an average transmissibility β in the network, and if this average can be determined for the entire period that the infection process in a network is under scrutiny, the maximum number of infected individuals in the particular network can be determined. The assumption here is that infected individuals change state twice, first when

they become infected and again when they recover or are removed from the network. The population model would then be a Susceptible-Infected-Removed (SIR) model.

The average transmissibility of a disease in a bond percolation model is also known as the bond occupation probability. For an outbreak of a disease to occur on a network, it has to spread from an initially infected node to other nodes in the network across the links between the nodes. This means that if one were to indicate that such transmission occurred across a particular set of links (or occupy such links in a bond percolation model, which happens with probability β), the eventual maximum size of the epidemic would be the same as the size of the cluster of nodes reachable from the initially infected node through traversing only across infected (known as “occupied") links [39].

5.3 PROBABILITY GENERATING FUNCTIONS

Probability generating functions, originally proposed by [158], are used in this thesis for easier analysis of a network topology’s disease percolation characteristics. Instead of working directly with the probability distributions, functions are defined that, when called, would generate the necessary distributions. The logical links between the generating functions in this section are represented graphically in Figure 5.1. The functions as described in this section have been defined by [41]. In general, the m’th power of a generating function generates the sum of a property k of an object. In this case the object is a node and k is the node degree. The sum is generated over m independent realisations of that object, which are the m nodes of the network. The first derivative of the generating function then produces the mean of the probability distribution of the property k, which in this case is the mean degree.

The generating functions that follow are thoroughly described in [159]: First, $G_0(x)$ seen in (5.1) provides the degree distribution.

$$G_0(x) = \sum_{k=0}^{\infty} p_k x^k \tag{5.1}$$

with p_k the probability that a node has degree k.

Including a disease into the network, propagating at average transmissibility β, the equation becomes:

$$G_0(x;\beta) = G_0(1 + (x-1)\beta) \tag{5.2}$$

The following generating function constitutes the excess degree. This means that it generates a distribution equal to the degree of nodes minus the occupied or infected links to those nodes. The generating function $G_1(x)$ is given by:

$$G_1(x) = \sum_{k=0}^{\infty} q_k x^k \tag{5.3}$$

where q_k can also be calculated as:

$$q_k = \frac{(k+1)p_{k+1}}{z} \tag{5.4}$$

with $(k+1)$ signifying the actual degree of a node and k the number of links by which infection did not spread to the node, with the average degree z of nodes in the network given by:

$$z = \dot{G}_0(1) = \sum_k k p_k \tag{5.5}$$

Similarly as for $G_0(x)$, Eq. (5.3) is extended to include the propagation of disease on the network, given by:

$$G_1(x;\beta) = G_1(1 + (x-1)\beta) \tag{5.6}$$

From [54], one can see that the basic reproductive number ($\mathcal{R}_0$) is defined as given in (5.7). This number signifies the average number of secondary infections resulting from a single node in the network:

$$\mathcal{R}_0 = \beta \dot{G}_0(1) \tag{5.7}$$

The epidemic threshold transmissibility β_c is defined as the specific average transmissibility in the network at which the average number of secondary infections resulting from a single node is greater than 1. For this, $\mathcal{R}_0$ is equal to 1, and:

$$\beta_c = \frac{1}{\dot{G}_1(1)} \tag{5.8}$$

Following this, the generating function $H_1(x)$ for the total number of nodes that are reachable by following a specific link in the network is given by:

$$H_1(x;\beta) = xG_1(H_1(x;\beta);\beta) \tag{5.9}$$

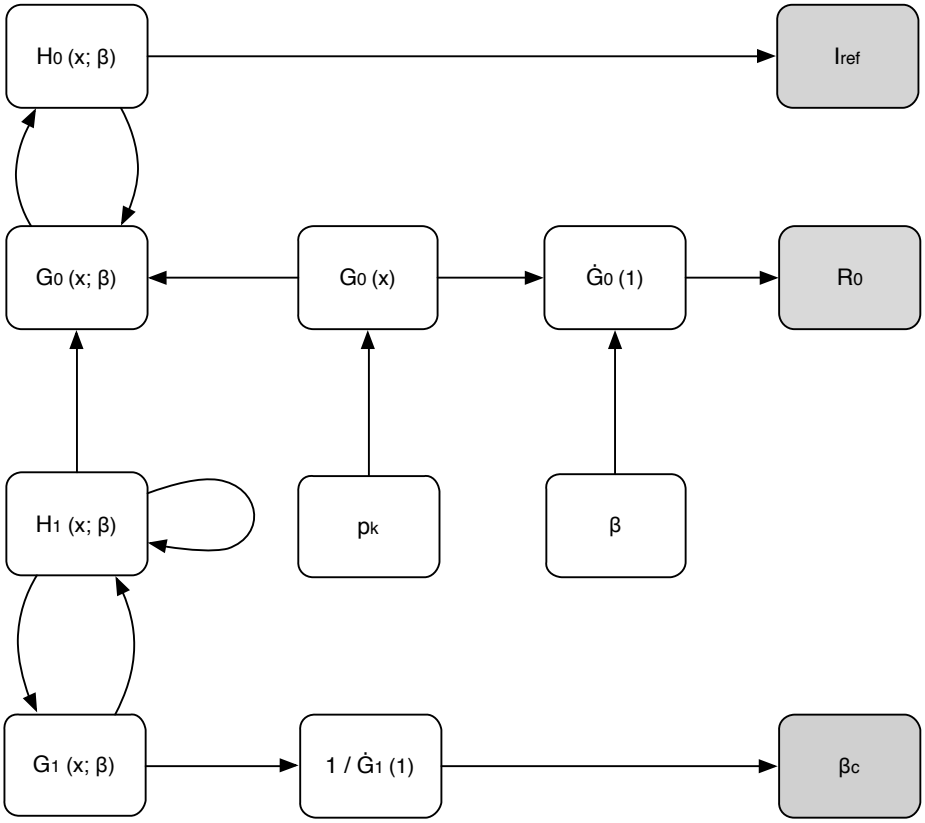


Figure 5.1: Flow-diagram depicting the connections between probability generating functions and the outputs that are obtained from these links. The reference incidence for all control systems depicted in this thesis is determined following this flow.

The generating function for the distribution of the total number of nodes that are reachable from a node chosen at random is given by:

$$H_0(x;\beta) = xG_0(H_1(x;\beta);\beta) \tag{5.10}$$

When $\beta_c \leq 1$ (below the epidemic threshold $\mathcal{R}_0$), the network will experience outbreaks of average size $\langle s \rangle$ [41], where:

$$\langle s \rangle = 1 + \frac{\beta \dot{G}_0(1)}{1 - \beta \dot{G}_1(1)} \tag{5.11}$$

Above the epidemic threshold, a fraction $S = I_{ref}$ in the network will become infected. The proportion of the network that will become infected can be estimated by:

$$I_{ref} = 1 - H_0(1;\hat{\beta}_{ref}) \tag{5.12}$$

where $\hat{\beta}_{ref}$ is the solution of β that satisfies (5.12) given a particular I_{ref} within the constraint of $0 \leq I_{ref} \leq 1$. The prediction of the final epidemic size may then be used as the control input reference for the networks studied in this thesis.

The solution of the probability generating function $H_1(x;\beta)$, applicable to SIR models, is not trivial. The solution cannot be determined analytically and was consequently established numerically. In this thesis, repeated calculation by recursive function was used, with the following Matlab code:

```
% Generating function H1(x;T)
function val = H1_xT(x, Pk_n, kmax, T, num)
  val = 0;
  if (num == 0)
    val = 0;
    return;
  else
    val = x * G1_xT( H1_xT(x, Pk_n, kmax, T, num-1), Pk_n, kmax, T);
  end;
end
```

In the code listing, x takes the most recent value of $H_1(x;\beta)$, the normalised degree distribution is Pk_n, the maximum degree in the network is k_{max}, the average transmissibility β is represented by T and the number of recursions to perform is given by num.

5.4 THE IMPACT OF PATIENT ZERO ON AN EPIDEMIC

To determine whether the initially infected node is likely to start an epidemic, the degree k of patient i in a network may be used. It has been found that the likelihood of an outbreak is a monotonically increasing function of the degree of patient zero [60]. Furthermore, if the disease is spreading at an average transmissibility β below the epidemic threshold β_c (5.8), the probability that the first patient will spark an epidemic is equal to:

$$\varepsilon_k = 1 - (1 - \beta + \beta_u)^k \tag{5.13}$$

As described by [60] the probability that patient zero with degree k will start an epidemic is equal to the probability that transmission along one of the edges of that node will cause an epidemic. The probability that the disease will not be transmitted across one of the links to that node is $(1-\beta)$ and β_u is the probability that even if the disease were to be transmitted it will not cause an epidemic. Using (5.13) we can thus step through all the subsequent connections in the network from an initially infected node and determine whether that node will indeed cause an epidemic along any of the original transmission routes or edges connected to it. The average transmissibility has been chosen such that the probability of an epidemic is always equal to 1. This means that $\beta > \beta_c$ for all simulations performed in this thesis. The selection of the initial node for infection will thus not have an impact on the final outcomes measured in this thesis. The assumption is thus that epidemics will definitely occur and a comparison of the final epidemic sizes should be the main focus. For the networks utilised in this thesis, $\beta_c = 0.14$.

5.5 TRANSMISSIBILITY AS CONTROL REFERENCE

Bond percolation is used to determine the reference average transmissibility $\hat{\beta}_{ref}$ needed to reach a given final epidemic size I_{ref}. The value $\hat{\beta}_{ref}$ is then used as input to the control system applied to the network. To be able to do this, verification is done to determine whether the bond percolation estimates indeed produce final epidemic sizes in the SIR model as proposed, given a particular average transmissibility. The desired epidemic size is then

translated back to the verified average transmissibility β and an attempt is made to control the network to this value. Considering what is measured in the network, the average transmissibility is the key parameter. When the output incidence I is used by itself in the feedback control system for a network without taking β into consideration, the network will not reach the required target incidence.

In this thesis the epidemic size is used as reference input I_{ref} to the pinning control system and the average transmissibility $\hat{\beta}_{ref}$ needed to reach I_{ref} is calculated numerically. The bond percolation functions $H_0(x;\beta)$ and $H_1(x;\beta)$ are simulated numerically, using a recursive function as shown in Section 5.3, to converge to the required solution.

5.6 VERIFICATION OF THE ACCURACY OF EPIDEMIC SIZE ESTIMATES

When random networks with the degree distribution given in (3.2) are considered, for large networks ($N = 100000$) bond percolation estimates have been verified by [41]. Smaller networks ($N = 100$) were verified here to assess the validity of using the predictions across all sizes of networks. In Figure 5.2, the solid line represents the bond percolation estimates of the epidemic size, given a particular average transmissibility. Each circle on the graph represents the simulated average outcome of maximum incidence across 300 networks after 5 years of simulation for each networks. Each network was simulated at the fixed average transmissibility provided on the x-axis of the graph. It can be seen that percolation estimates slightly overestimate the epidemic size at lower transmissibilities and slightly underestimate the epidemic size at higher transmissibilities. This verification confirms, by inspection, that the predictions may be used as input to the control system proposed.

To obtain the estimated average transmissibility given the epidemic size (I_{ref}), requires the calculations used to produce Figure 5.2 and the numerical solution of β from:

$$G_0(H_1(1;\hat{\beta}_{ref});\hat{\beta}_{ref}) = 1 - I_{ref} \tag{5.14}$$

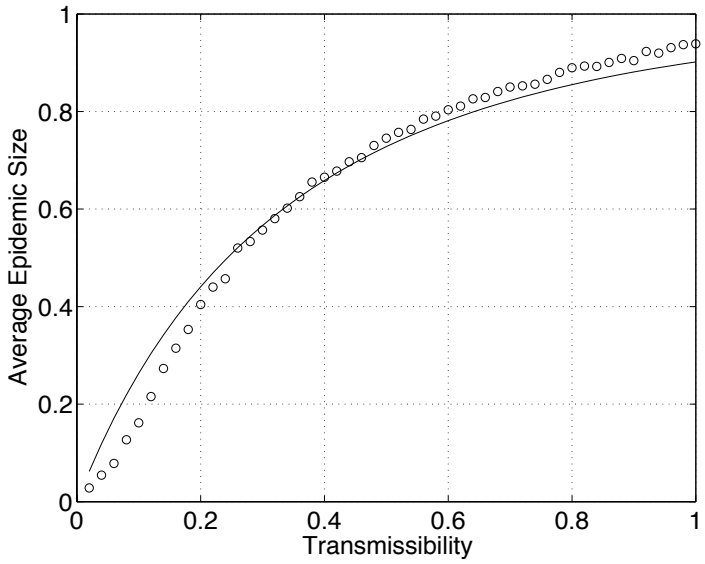


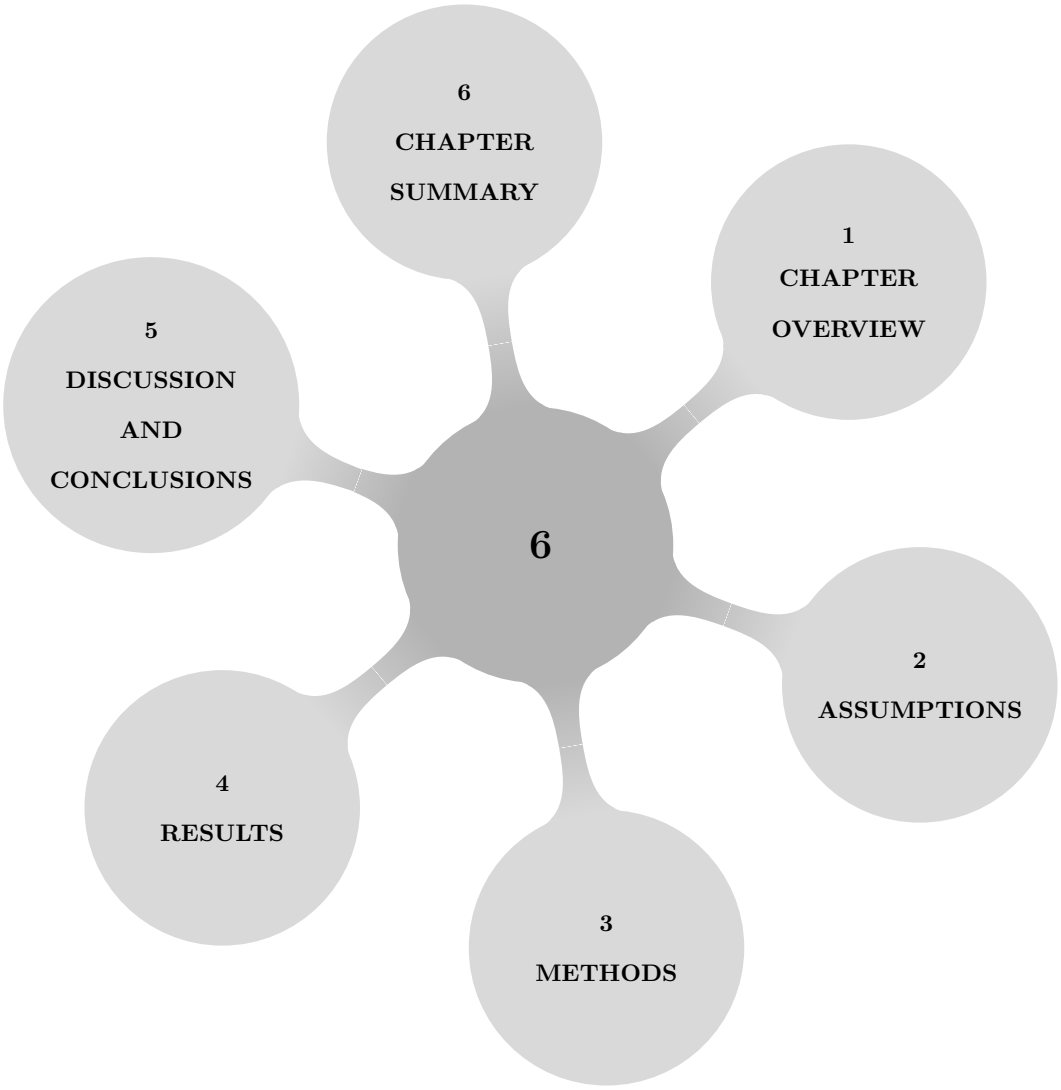
Figure 5.2: Bond percolation estimates of the epidemic size (in this thesis I_{ref}) plotted against the average transmissibility β. Estimates are represented by the solid line and each circle represents the simulated average of 300 independent networks of size $N = 100$. Similar results were presented by [41], for networks of size $N = 100000$, verifying the estimates for scale. (See Appendix D for copyright information.)

5.7 CHAPTER SUMMARY

The statistical mechanics technique of bond percolation was presented in this chapter. Its use and application to the work in this thesis was highlighted. Predictions of the final epidemic size in SIR-model networks can be made using bond percolation. In turn, the final maximum epidemic size prediction is used as the control input reference in the remainder of this thesis. Verification of the bond percolation estimates was shown for 300 networks of size N per data point for verification. It was found that bond percolation estimates fit very well with the simulated average maximum epidemic sizes in the networks assessed. In the next chapter, bond percolation estimates are applied as the control reference in a proportional feedback scheme. The aim is to control the average transmissibility in order to reach an average maximum epidemic size.

CHAPTER 6

SELECTIVE PINNING WITH PROPORTIONAL FEEDBACK



6.1 CHAPTER OVERVIEW

This chapter proposes a methodology to integrate an HIV contact network into the classic feedback control system in the manner shown in Figure 1.1 in Chapter 1. Given a list of assumptions, the feedback control system is simulated for networks with $N = 100$, $N = 1000$, $N = 5000$ and $N = 10000$ nodes. The feedback control system takes as its input the reference incidence I_{ref} as explained in Chapter 5. Two pinning control strategies are compared using this methodology: Random pinning and selective pinning. A comparison of the median of the number of doses administered reveals that selective pinning as applied in this chapter uses 51.3% less medication than random pinning when applied to HIV contact networks.

6.2 ASSUMPTIONS

When simulating models with a large number of parameters and variability, it is important to make reasonable assumptions to simplify the analysis. The main assumptions made in this chapter in using the proposed methodology are:

1. Nodes in the network are homogenous regarding their immune response, implying that all nodes use the same immune response model given by (3.1).

2. When given medication at any time point, each node receives one dose.

3. Sexual contact between nodes is assumed to be heterosexual, thus the network links represent a heterosexual network of sexual contacts. This said, no distinction is made between male and female nodes.

4. Reverse Transcriptase Inhibitors (RTIs) alone are effective in limiting the spread of HIV in the network. Multiple drugs, as recommended by the World Health Organisation (WHO) standard treatment guidelines are not used in this work.

5. A single virion is transferred at infection.

6. Sexual relationships are not broken during the time of the simulation. The network is static.

In light of the given assumptions, this chapter aims to show how a control-theoretic strategy could possibly be used by public health specialists to assess the number of medicine doses needed to control the level of HIV incidence in a population to a set value. The results achieved could be made more realistic by relaxing the assumptions in this section in a systematic manner. This is the aim of future work based on the proposed methodology.

6.3 METHODS

6.3.1 Feedback on/off pinning control of a network

The purpose of using feedback control is to be able to compare the ability of two strategies of medication to control contact networks towards a target epidemic size. The two strategies are random pinning and selective pinning (Section 4.3). Random pinning is applied to a network by providing medication to all infected nodes. Selective pinning medicates a proportion of the infected nodes, starting with the node that has the highest number of susceptible nodes connected to it, and thereafter in order of highest degree to lowest degree.

A feedback control system of the form shown in Figure 6.1 is implemented and the controlled "plant" or "process" is an HIV contact network of the form in (3.6). The average

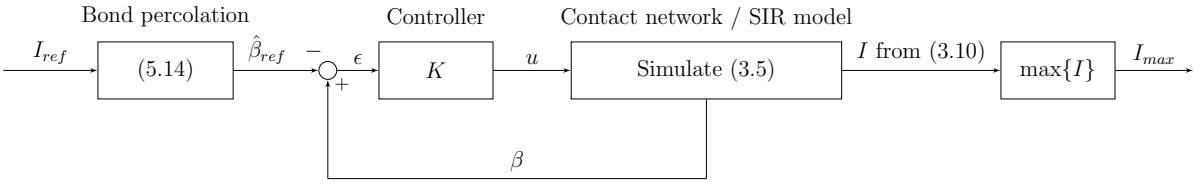


Figure 6.1: Feedback control system for an HIV contact network. The reference signal is determined by using bond percolation to predict the necessary average transmissibility $\hat{\beta}_{ref}$ needed to reach an average maximum incidence I_{ref}. (See Appendix D for copyright information.)

transmissibility β of nodes infected with HIV in the network is measured and fed back to the reference summation point. The system proportionally medicates more (or less) people based on the difference between the bond percolation predicted reference transmissibility and the actual transmissibility. The medication is given in an on-off pulsed manner to

represent doses, where pulses are made when $\beta \geq \hat{\beta}_{ref}$ and no pulsing when $\beta < \hat{\beta}_{ref}$. A single network node is controlled (pinned) by setting Δ_i from Eq. (3.7) equal to 1 (pin the node) or equal to 0 (don't pin the node).

A summary of all the control and performance parameters used in this section is given in Appendix B.1. The flow of the feedback control system shown in Figure 6.1 is described in the next subsections.

6.3.1.1 Reference incidence as input

The input to the feedback loop is the required average maximum network incidence I_{ref}. Given the outcome of bond percolation estimates from which $\hat{\beta}_{ref}$ is estimated as the average epidemic size, the target incidence can only be reached by taking the average across several hundred network simulations using this architecture, given the definition of bond percolation estimates from which I_{ref} is calculated (Chapter 5). The equation provided in (5.12) is used to numerically determine the value of $\hat{\beta}_{ref}$ that would lead to the required reference incidence I_{ref}.

6.3.1.2 Input translation

The input I_{ref} is translated to an average transmissibility $\hat{\beta}_{ref}$ by numerically solving Eq. (5.14). Another method to determine $\hat{\beta}_{ref}$ is to fit a model to the actual data points of Figure 5.2. This could be done by regression that forms part of system identification theory [160]. Specifically, an ARX (autoregressive with extra input) model may be used. In this thesis, the method of numerical analysis was chosen to estimate the average transmissibility needed.

6.3.1.3 Error calculation

The difference between the estimated transmissibility $\hat{\beta}_{ref}$ and the simulated average network transmissibility β is calculated at the summing junction and used as input to the controller.

The error is bounded by the following limits:

$$-1 \leq \epsilon \leq 1, \quad \text{where} \quad \epsilon = \begin{cases} -1, \text{when } \beta = 0\,, \hat{\beta}_{ref} = 1; \\ 1, \text{ when } \beta = 1\,, \hat{\beta}_{ref} = 0; \\ (-1, 1), \text{ when } 0 < (\beta; \hat{\beta}_{ref}) < 1. \end{cases} \tag{6.1}$$

The average transmissibility β of the network is bounded at its upper limit at a value of 1 due to the bounded definition of the transmission function (3.4). If the calculated average transmissibility is higher than 1 due to selection of a very high risk factor, the boundaries of β (6.1) will not be violated because $\lambda_i(t)$ is bounded at 1 for all i.

6.3.1.4 Controller

The controller selects the proportion u of individuals in the network to receive medication. The ith node is pinned by setting its Δ_i parameter to 1 in (3.7). The output of the controller is limited to 1, given that this represents the control of all nodes in the sexual contact network. If the random pinning strategy is used, all infected nodes receive medication regardless of their infection status. This strategy is deemed random due to the stochastic term used in the transmission function (3.4). Nodes become infected due to the activation of the probability of transmission calculated from the transmission function. If the selective pinning strategy is used, the proportion of infected nodes to receive medication is calculated by (6.2). Nodes are then pinned in order of the highest number of connected susceptible individuals to them until the proportion u is reached. The control output u saturates at 1.

$$u = \begin{cases} 0, \text{for } \beta < \hat{\beta}_{ref}; \\ K \times (\beta - \hat{\beta}_{ref}), \text{for } \beta \geq \hat{\beta}_{ref}; \\ 1, \text{for } \beta \geq (2 \times \hat{\beta}_{ref}). \end{cases} \quad \text{with } 0 \leq u \leq 1 \tag{6.2}$$

6.3.1.5 Gain

The controller gain K is chosen to be 1 in this thesis. A higher gain may be selected to allow more control action when the selective pinning control strategy is used. As $K \to \infty$, the selective pinning control strategy approaches the random control strategy by definition of the number of nodes pinned given in the previous section. To discern any differences between

the two strategies, the value of K should be bound by the following condition (graphically depicted in Figure 6.2):

$$K < \left[1/(\beta - \hat{\beta}_{ref})\right], \quad \text{if } (\beta - \hat{\beta}_{ref}) > 0 \tag{6.3}$$

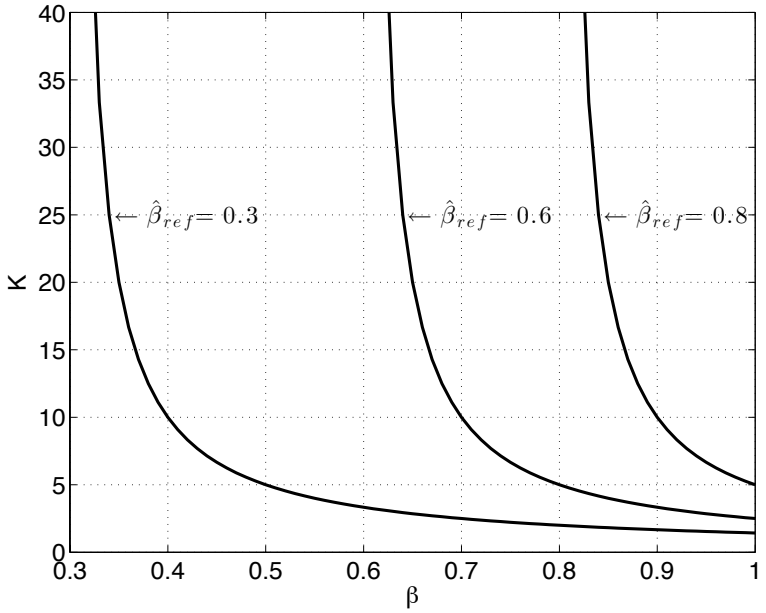


Figure 6.2: Upper bounds of the gain K for ensuring the doses administration of the selective pinning control strategy is distinguishable from the random pinning control strategy. K should be chosen such that $(\beta - \hat{\beta}_{ref})$ doesn't exceed 1 for all values of β. For example, if $\hat{\beta}_{ref} = 0.8$, then K should be less than 5 to ensure the most conservative use of control action for all values of β. If $\hat{\beta}_{ref}$ is 0.3, then choosing $K < 5$ would have selective pinning perform exactly the same as random pinning for $\beta > 0.5$.

6.3.1.6 Actuator

The actuator is the application of medication to the immune response systems of the pinned nodes in the network. Providing antiretroviral (ARV) doses to nodes affect their immune response models (3.6) and this in turn influences the entire network's dynamics. A node is pinned by setting Δ_i from Eq. (3.7) equal to 1. The drug used to simulate medication in this thesis is a reverse transcriptase inhibitor (RTI) named Tenofovir with an average efficiency chosen for this thesis of 65% [161]. The assumption made with the use of such an actuator

is that the drug may be administered as often as necessary to all patients and that no side-effects would impact on the nodes. The use of drug combinations as prescribed by the World Health Organisation (WHO) is also possible with this methodology. The node model may be amended according to [144] to include protease inhibitor (PI) drugs. This amendment would result in the following controlled network model:

$$\begin{aligned} \dot{T}_i &= s - dT - \theta T v + \Delta_i u_{i(RTI)} \\ \dot{T}_i^* &= \theta T v - \delta T - \Delta_i u_{i(RTI)} \\ \dot{v}_i &= \Delta_i u_{i(PI)} + kT_i^* - \mu v_i + \Gamma\left(\lambda_i(t)\right) \sum_{j \neq i}^{N} a_{ij}[v_j > 0] \end{aligned} \tag{6.4}$$

with the control term for RTIs given by:

$$\Delta_i u_{i(RTI)} = \begin{cases} 0, & \text{for } \Delta_i = 0 \\ \varepsilon_{RTI} \beta T v, & \text{for } \Delta_i = 1 \end{cases} \tag{6.5}$$

If a protease inhibitor (PI) drug were to be used, the control term is given by:

$$\Delta_i u_{i(PI)} = \begin{cases} 0, & \text{for } \Delta_i = 0 \\ -\varepsilon_{PI} k T_i^*, & \text{for } \Delta_i = 1 \end{cases} \tag{6.6}$$

In the equation (6.5), the term $u_{i(RTI)}$ is the addition of RTIs to a node, with the effect of hampering the infection process of the CD4+ T-cells. The prevention of the development of virus particles into becoming infectious is done by adding $u_{i(PI)}$ as shown in (6.6). The use of combination drug therapies (HAART) has been shown to be more effective than using single drug therapies [162]. The effectiveness of different drug administering strategies can be explored using the proposed feedback pinning control methodology in this chapter.

6.3.1.7 Process

The controlled process is the entire disease contact network (3.6) and the SIR model encapsulating it (3.9). The input to the process is the number of nodes to be pinned (controlled) and the output is the current incidence of HIV in the network. The process is pre-configured with the pinning strategy that will be applied when it receives an input from the controller. When an input to the process is received ($0\% - 100\%$), depending on the pinning control strategy selected, nodes in the network are open-loop pinned (Section 4.2.1) by setting Δ_i for the i'th node equal to 1 in (3.7).

6.3.1.8 Feedback

The feedback from the network process is the average transmissibility β. If the process output, I, was chosen as the feedback variable, the force of infection is not controlled and the likelihood for very high steady-state error exists. Even though a network may be driven towards a particular maximum incidence in this manner, a large $\mathcal{R}_0$ may exist (much greater than β_c, the critical transmissibility) which could lead to an outcome with large steady-state error. As an example: Because the maximum size of an epidemic is equal to the probability of an epidemic [54], at the point where a network reaches the reference incidence (say, 0.5), the average transmissibility may be close to 0.8. This means that it is highly likely the process output would have a maximum close to 0.8 instead of the intended 0.5. Transmissibility is thus the key factor that should be controlled to maintain the desired levels of incidence in the network [134].

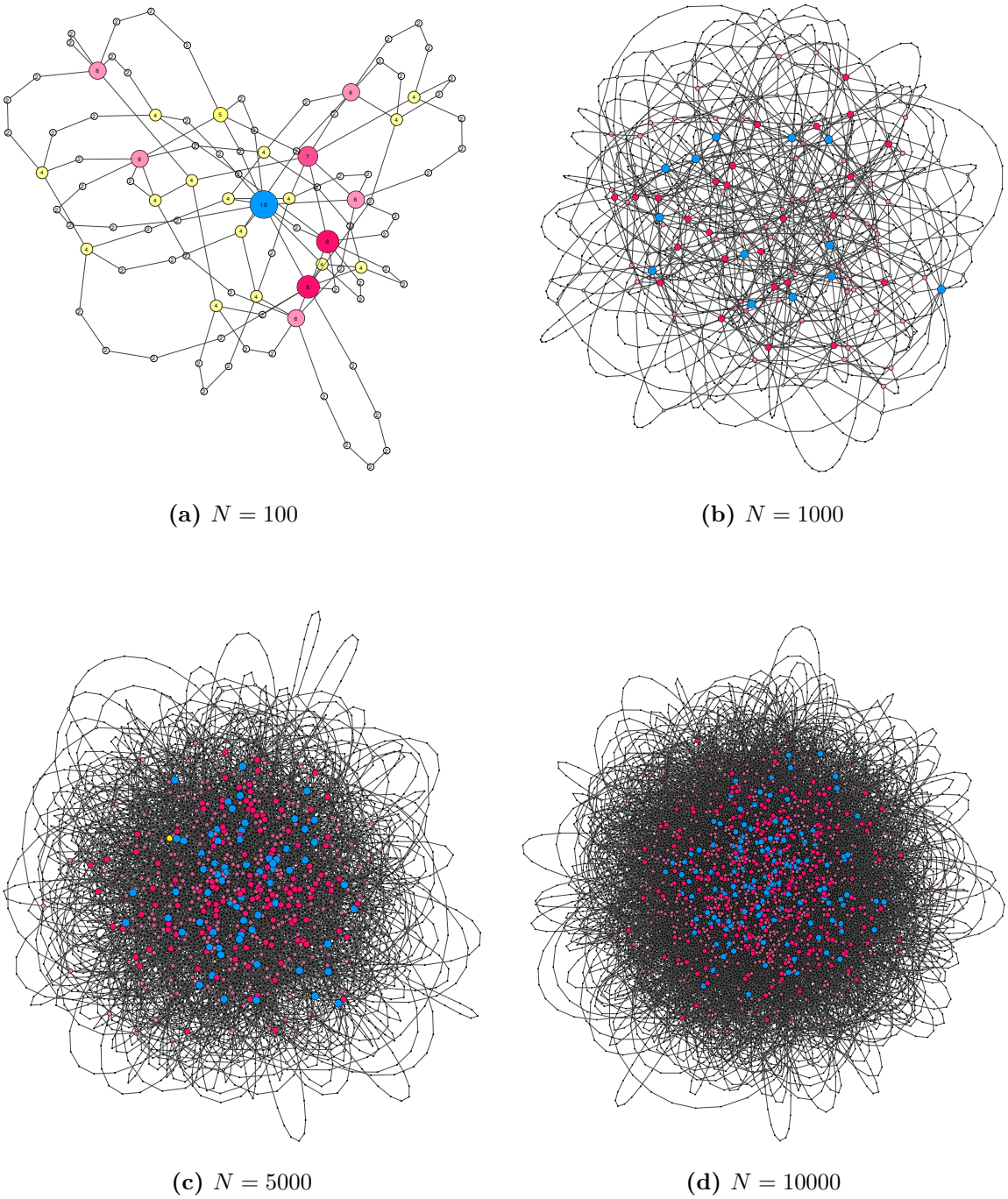
6.3.1.9 Output

The process output is the current disease incidence in the network. The output is measured to determine the maximum (I_{max}), which is then measured across several hundred instances of networks controlled in this manner to be able to comment on whether the target average maximum incidence I_{ref} has been satisfied. The bond percolation definition of the progression of a disease at an average transmissibility regardless of the individual transmission probabilities between nodes forms the basis for the solution of the controlled system output [41].

6.3.2 Simulations

Simulations of all networks are done over a maximum of 2000 days. Network sizes of nodes $N = 100$, $N = 1000$, $N = 5000$ and $N = 10000$ are used. Visual examples of each size network is given in Figure 6.3.

Random and selective pinning are applied to 300 independent realisations of connected networks without isolated components, for each reference incidence level from 20% to 60% in increments of 10%. For the control system shown in Figure 6.1 to function correctly, the average I_{max} of the 300 realisations for each I_{ref} was taken.



(a) $N = 100$ **(b)** $N = 1000$

(c) $N = 5000$ **(d)** $N = 10000$

Figure 6.3: Visualisations of the different sizes of the random combination exponential and power-law networks used in this chapter, with degree distribution defined in (3.2). Nodes with a higher degree are indicated with a larger size where distinguishable.

6.4 RESULTS

6.4.1 Controlled β and incidence

Having applied the random and selective pinning strategies to varying sizes of networks, the outcomes of I_{max} for different levels of I_{ref} can be seen in Figure 6.4.

6.4.1.1 Accuracy

For all investigated reference transmissibilities, the control performance (over- or undershooting of the target) for both strategies are similar. At lower references of around 20%, for networks larger than $N = 100$, the incidence is controlled to within 5% of the reference. For small networks of $N = 100$, the control of incidence performs to within 5% for references of 30%, 40% and 50%. As the network size increases beyond $N = 100$, the less accurate the control to higher reference incidences (above 20%) becomes, although the differences with the set-points are fairly similar for networks of $N = 1000$, $N = 5000$ and $N = 10000$ nodes. The constant control gain value of $K = 1$ is the most likely explanation for this from a control perspective. From a network perspective, this means that larger networks are impacted differently by control than smaller networks. The analogous result is that larger networks seem to be impacted by proportional feedback control in a similar manner, given the same offsets in control error for networks of $N = 1000$, $N = 5000$ and $N = 10000$. At higher transmissibilities and with larger networks ($N \geq 1000$), both control strategies are unable to reach the target incidence if the gain is kept constant.

6.4.1.2 Finite size effects

There seems to be a bounded impact of network size on both control strategies' ability to reach the reference values. This boundedness can be seen in the comparable steady-state error differences at all transmissibilities, as network sizes increase from $N = 1000$ to $N = 10000$. An increase in network size seems to be associated with a larger reduction in accuracy between $N = 100$ and $N = 1000$ than any consecutive increase. The also appears to be a slight increase in accuracy when the network size is increased from $N = 5000$ to $N = 10000$. It can thus be said that ever-increasing network sizes do not necessarily imply that the ability

of the networks to reach a controlled steady-state value become less accurate. Measurements were repeatable for networks of $N = 1000$, $N = 5000$ and $N = 10000$.

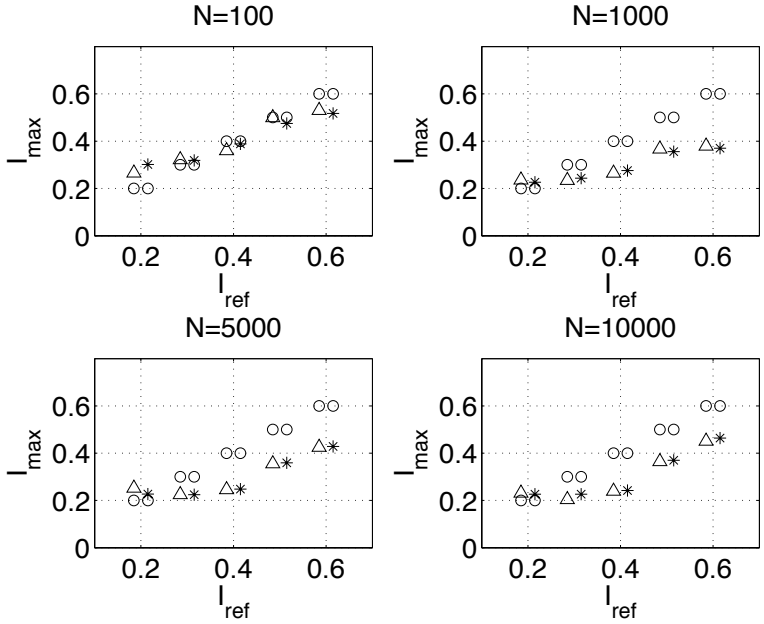


Figure 6.4: The average maximum incidence for each reference signal I_{ref}. Each marker represents the average of 300 independently simulated networks. Asterisks (*) are randomly pinned networks (all nodes pinned) and triangles (△) represent selectively pinned networks. The reference points, I_{ref}, are represented by circles (○). (See Appendix D for copyright information.)

6.4.2 Effect of the critical transmissibility β_c

The critical transmissibility (or epidemic threshold) for networks in this thesis is set at $\beta_c = 0.1426$. This means that the estimations of epidemic size for transmissibilities below 0.1426 are invalid using the epidemic estimate equation in (5.12). The equation for the average outbreak size should be used below $\beta_c = 0.1426$. This equation is given in (5.11). Plotting the estimates of outbreak size for $\beta = [0\ 0.2]$ provides the graph in Figure 6.5.

Figure 6.5 indicates that simulations that operate close to the epidemic threshold transmissibility β_c result in average incidence levels that are higher than anticipated (this result is seen in Figure 6.4 for all networks sizes at $I_{ref} = 0.2$). This under-estimation of the true epidemic size is a direct result of the use of epidemic-measures rather than outbreak-measures and

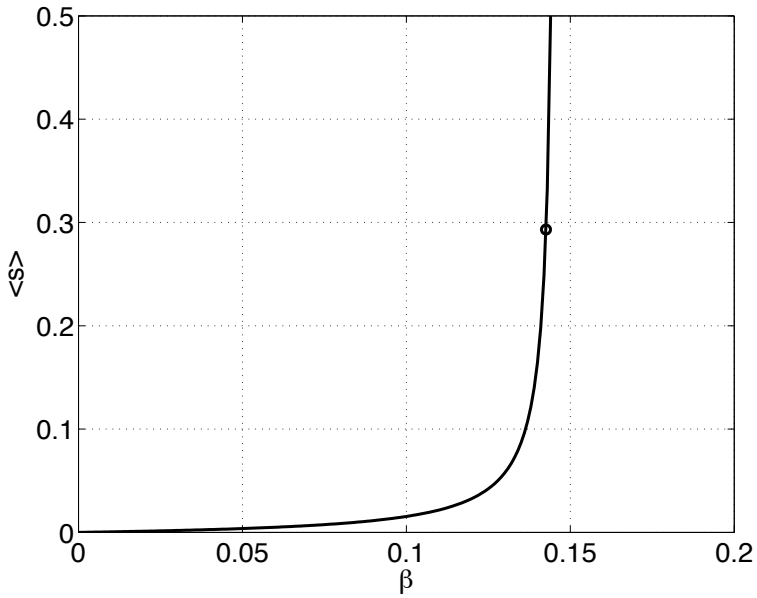


Figure 6.5: The average outbreak sizes $\langle s \rangle$ for average transmissibilities (β) between 0 and 0.2. The estimate for the critical transmissibility β_c approaches infinity ($\beta_c \to \infty$) as ($\beta \to \beta_c$). If the estimate of β_c is rounded off so that $\beta < \beta_c$, but $\beta \approx \beta_c$, then the effect seen in this graph is noticed. The circle ($\circ$) represents the approximated β_c. The associated outbreak size is 0.3, which is a higher estimate than when the epidemic-related equations are used.

equations for this estimation. The asymptotic singularity in Figure 6.5 and the computed, rounded estimation of β_c thus result in higher estimates of the true epidemic sizes (or in this case outbreak sizes) at transmissibilities close to the epidemic threshold.

6.4.3 Average steady-state error

The average steady-state error (I_{sse}) simulation results can be seen in Figure 6.6. The incidence markers ($\triangle$ and $*$) each represent a mean value over 300 networks' data, with $\triangle$ depicting the selective pinning strategy and $*$ the random pinning strategy. The closer these markers are to zero, the more accurately the control system drove the network towards the desired reference. By inspection, there is almost no difference in steady-state error between selective and random pinning, for all sizes of network investigated. With both random and selective pinning, the lower references (around 20%) resulted in negative errors for all sizes of network. This indicates overshooting of the target reference at low incidence reference

levels (Chapter 8 provides an explanation for this at the hand of the characterisation graph in Figure 8.2. This graph indicates that there is an overestimation of the true epidemic size for transmissibilities below 0.2 in the networks studied). An incidence level of 20% can thus be achieved by using a reference average transmissibility of less than 0.1.

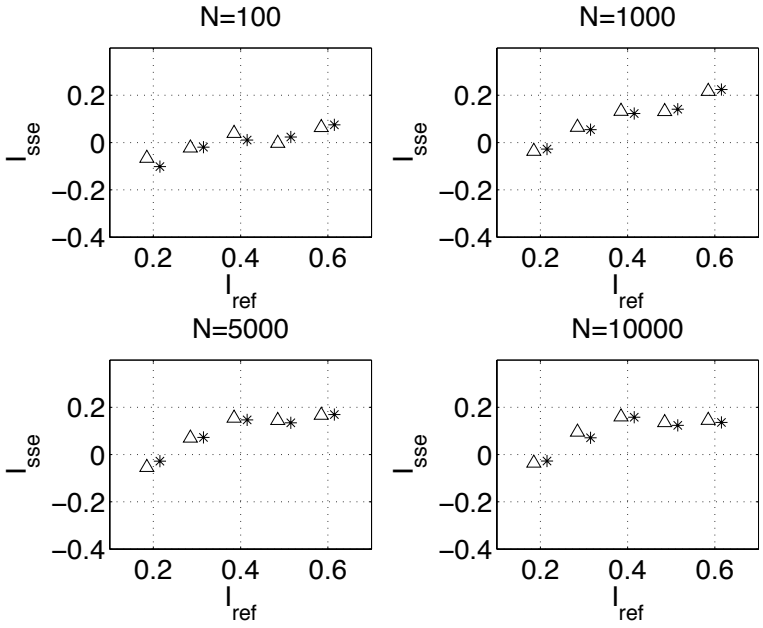


Figure 6.6: The average steady-state error between the average maximum incidence and the reference maximum incidence. Each marker represents the average of 300 network simulations with asterisks (*) the random pinning strategy and triangles (△) the selective pinning strategy. (See Appendix D for copyright information.)

6.4.4 Control effort

Control effort expenditure is reported as the comparison between the medians of the number of doses used for each pinning control strategy. The use of the median as opposed to the mean of the data is necessary because neither distribution of doses is Gaussian normal.

The measure of doses itself is obtained by taking the sum of all control action pulses over time, per network instance, and multiplying this with the total number of nodes N in a network. Thereafter, the sum of the control action across all 300 network instances per data point is taken to obtain the total control action for the respective data point.

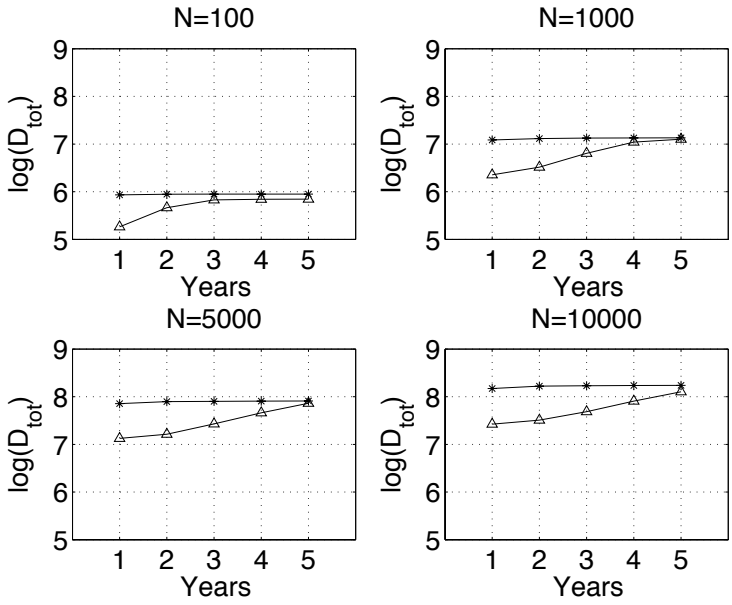


Figure 6.7: The log of the cumulative total doses, $log(D_{tot})$, for the two types of pinning control strategies over 5 years. Asterisks (*) represent random pinning and triangles (△) selective pinning. Each yearly data point is the cumulative control effort from 1500 independent networks spanning the studied reference levels I_{ref}. (See Appendix D for copyright information.)

After a period of 5 years, the calculated total doses per strategy appears to be much closer in value to each other than in preceding years. Each year of simulation presents the selective pinning control as using cumulatively more control action than the year before, whilst the random pinning strategy seems to cumulatively use all its control action within the first year of simulation. Thereafter, the cumulative random pinning does not vary considerably. This effect can be seen in Figure 6.7.

A statistical analysis was performed on the cumulative doses after 5 years, both for networks stratified according to size and across network sizes. The results can be seen in Table 6.1. Firstly, the normality of the data across all network sizes for selective pinning and random pinning was compared with respect to their distributions. The data was not normally distributed, and the two strategies differed in their fundamental distributions. The Kolmogorov-Smirnov (KS) test for non-parametric data was used to confirm that the distributions of both dosing strategies are different, with p-value of less than 2×10^{-16}. The ratio of the medians of the two sets of overall data suggests that, for the simulations

performed, selective pinning control uses 51.3% less doses compared to random pinning after 5 years. The difference was statistically significant using the Mann-Whitney U-test, with a p-value less than 2×10^{-16}. Stratifying for network size, the medians suggest that selective pinning uses 76% less doses for $N = 100$, 48% less doses for $N = 1000$, 24% less doses for $N = 5000$ and 44% less doses for $N = 10000$ nodes.

Table 6.1: Descriptive statistics for the doses applied under the two pinning control strategies of Selective ($\triangle$) and Random ($*$) pinning across all values of I_{ref}, after 5 years.

N	Statistic	Selective ($\triangle$)	Random ($*$)
100	Sample Size	1500	1500
	Median	145.87	600
	Inter-quartile range (IQR)	[73.55, 672.70]	[400, 800]
	Median Ratio ($\triangle$:$*$)	0.24	
1000	Sample Size	1500	1500
	Median	4641	9000
	Inter-quartile range (IQR)	[1052, 8436]	[5000, 12000]
	Median Ratio ($\triangle$:$*$)	0.52	
5000	Sample Size	1500	1500
	Median	38030	50000
	Inter-quartile range (IQR)	[5943, 80160]	[30000, 75000]
	Median Ratio ($\triangle$:$*$)	0.76	
10000	Sample Size	1500	1500
	Median	56070	100000
	Inter-quartile range (IQR)	[10840, 147200]	[60000, 170000]
	Median Ratio ($\triangle$:$*$)	0.56	
All	Sample Size	6000	6000
	Median	6823.0	14000
	Inter-quartile range (IQR)	[872.7, 43150]	[1000, 70000]
	Median Ratio ($\triangle$:$*$)	0.48	

6.5 DISCUSSION AND CONCLUSIONS

Two network-wide control strategies, random and selective pinning, were proposed. Both strategies were implemented with an On/Off type controller that medicates (with one dose each) a specific number of nodes when the actual incidence is above the reference incidence. It has been shown that contact networks with a high transmissibility and removal of nodes can be controlled to a target incidence by On/Off proportional control, although a constant gain results in an increasing steady-state error as the network size increases. The control schemes proposed here have an important impact on HIV incidence, in particular, the maximum incidence can be controlled to within 20% with either strategy using a constant gain controller.
Selective pinning results in a similar average steady-state error for the target incidence. This means that neither strategy outperforms the other on accuracy.

The statistical analysis performed on the total control effort applied across all simulations per strategy suggests, by comparing the medians of the dosing data, that *selective pinning uses* 51.3% *less medicine compared to random pinning.* Although this result is statistically significant, further work should test even larger networks ($N > 10000$) in a similar manner.
The main limitations of this work due to the assumptions in Section 6.2 are:

1. In real-world HIV networks, each individual's immune response is different. The node models would need to be updated for each node for more accurate results. To obtain enough information to estimate the parameters of each individual is a very resource-intensive task.

2. HIV rarely spreads with such high rates of transmissibility as used in this work. The results here therefore only apply to very high risk HIV contact networks.

3. For simplicity, a single drug (an RTI named Tenofovir) has been used with an efficiency of 65% [161]. Multiple drugs are the recommended treatment scheme, hence the node models should be updated before comparing the results obtained to a real-world scenario.

This work quantified the impact of two different pinning control schemes on high-risk contact networks in which HIV is transmitted. The average transmissibility could be controlled to reach a particular target average maximum incidence in the simulated networks. It was found that selective pinning is equally as accurate as random pinning in reaching the reference incidences. A statistical analysis of the two dosing strategies suggested that selective pinning requires, according to the median of doses, 51.3% less medication (control action) compared to random pinning. The control gain was set to $K = 1$ in producing this result.

6.6 CHAPTER SUMMARY

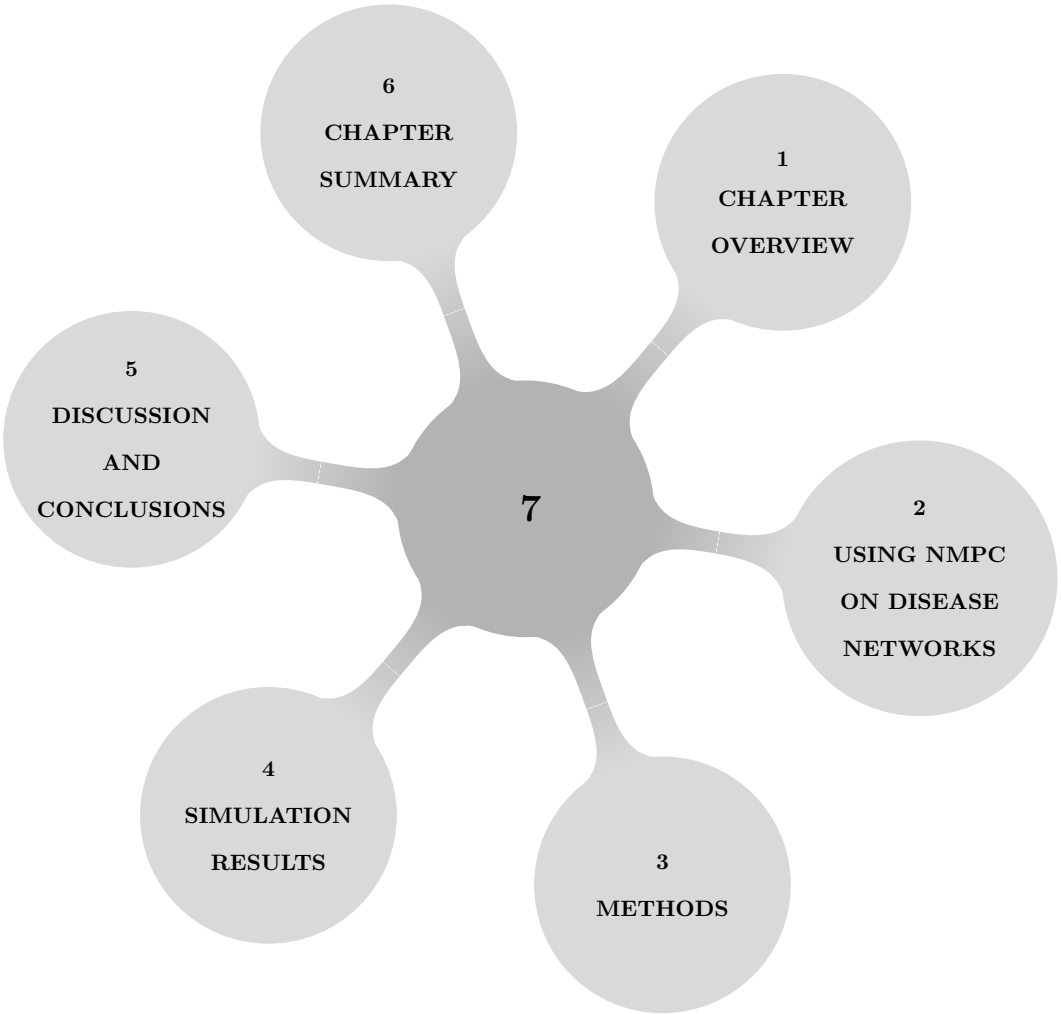
This chapter provided a methodology to insert network-level dynamics into a feedback control loop to be able to control incidence through controlling the average transmissibility β between nodes of the network. Bond-percolation was used to establish suitable epidemic estimates used as reference signals to the control system. A controller was designed such that the boundaries of β, the feedback error ϵ, the controller gain K and the control output u were respected.

It was found that networks could be controlled using feedback loops at the network-level combined with open-loop pinning at the node level. This control could be limited to finite, repeatable steady-state errors using the required incidence translated to average transmissibility by bond percolation as reference signal. The results obtained from this chapter's work included a statistical analysis of the median doses per network size per strategy. The main result from this analysis was that selective pinning, on average, use about 51% less medication than random pinning to achieve the same levels of incidence on average in the power-law exponential networks used in this thesis. Disease immune response models can be varied using this methodology to capture a broader range of epidemiological effects, such as dynamic formation of networks, co-infection with multiple dependent or independent diseases, such as HIV and TB [163], ART as prevention [153], a variety of control strategies such as variation of the timing of ART with minimum frequencies [164].

The challenge with simulating HIV disease networks lies in the systematic removal of assumptions made regarding sexual behaviour, quantifying viral transfer, finding frequencies of sexual intercourse and modelling the broad range of population risk factors.

CHAPTER 7

OPTIMAL PINNING CONTROL OF DISEASE NETWORKS



7.1 CHAPTER OVERVIEW

This chapter explores how the use of nonlinear model predictive control (NMPC) may benefit and possibly improve upon the selective pinning control methodology proposed in Chapter 6. Nodes are pinned according to the outcome of an optimisation process that seeks to minimise a cost function. The cost function is of the least-squares (LSQ) type and includes the use of the target incidence, the control input, and the average transmissibility of the network. The addition of the proposed budget, measured in QALYs, to the cost function equation is discussed in Chapter 8. Optimal control of HIV incidence is simulated for networks subjected to the highest risk circumstances. Additional risk is assumed for nodes through the uniform presence of drug usage, unprotected sexual behaviour and the presence of STDs. These additional risks means that the progression of HIV may be modelled at the population level using a SIR model. The prevalence of death is thus high due to the added risk assumed for these networks. Control is performed on networks with $N = 100$ nodes, each simulated over 365 days. It is shown that disease incidence can be controlled with an average accuracy improvement on the target incidence of 6.25% over the selective pinning control scheme in [134]. It is also shown that the use of bond percolation to estimate the final disease incidence through control of the average transmissibility is a suitable control methodology.

7.2 USING NMPC ON DISEASE NETWORKS

Controlling the transmission of any disease between individuals is an important public health aim. The 2014 EBOLA epidemic in West Africa is an example of the importance of viral transmission control [70, 165]. Research in the field of control engineering has already explored individual-based immune-response viral load control [6, 5], HIV model parameter estimation [4, 138], and optimal drug scheduling [8, 166]. This work builds on the control of disease spread proposed in [134], and extends the use of optimal control beyond the individual to drive a network of disease spread to a desired outcome.

As a disease is spread, an ever-increasing proportion of a population becomes infected and the likelihood for further spread increases, assuming individuals stay in the population or only slowly leave it. If the proliferation is fast enough, above what is called the epidemic threshold, a large proportion of such a network will become infected and this is known as an

epidemic. Financing and budgets for the costs of interventions play a large role in keeping the size of an epidemic to within a particular maximum proportion [167].

From a biological point of view, the probability for the spread of HIV during sexual intercourse is predominantly a function of the viral load of a person [168], with viral load modelled as part of the immune response [142]. To link people (or nodes) together into a network of HIV transmission, the links of the network are defined as the sexual relationships between the nodes [55]. When transmission of the disease occurs, it is assumed here that a single virion is passed from one individual to the next, and so the virus proliferates in the network. A similar, more generic model for extending immune response models into networks has been shown in [46].

To control disease networks, the node immune responses should be manipulated to limit the transmission of the disease between nodes. Pinning control has been presented in Chapter 4 to be a control systems technique by which particular nodes of a network are controlled in order to synchronise the entire network to a particular outcome. This has been specifically used on networks of coupled oscillators [126, 116, 122]. For the disease networks studied, pinning control has been applied in a proportional feedback scheme in Chapter 6 by selectively medicating nodes with the highest number of uninfected neighbours. This means that the highest risk is addressed first, and the second-highest risk thereafter, and so forth. The alternative would be to medicate all infected nodes, and indeed this is standard ethical practice world-wide for HIV treatment. This work focuses on the minimal, optimal intervention that could be performed, given all the relevant measurement incidence and transmissibility data from the node, network and population models. The controller used to perform this optimisation implements a nonlinear model predictive control (NMPC) scheme. [169]. MPC, in its linear form, has already been applied to structure optimal disease treatments at the individual node level, from control of hyperthermia [170] to glucose concentration in diabetes patients [171] and to HIV drug scheduling [172, 173].

Nonlinear model predictive control (NMPC) is a form of model predictive control that uses a nonlinear model to predict the system states at future times $k + i$, for each sampling time k, up to a horizon H. The predictions are then used to establish the next control to use, which will minimise a cost function over the specified horizon. NMPC is usually used in the chemical and biochemical process control industries [171, 174, 175, 176],

but here it is applied to optimising the resource usage of a medical intervention (medicine doses) in a network of sexually connected individuals spreading HIV. In networks comprising of 100 individuals (nodes), the optimal number of nodes to receive medication at each sampling time over the course of 365 days is evaluated, given either a particular budget, or a particular incidence to reach over the year. The network size is important here, as this has been specifically chosen to be able to deal with the computational complexity (see Section 7.3.4) of running an NMPC optimisation algorithm and simulating entire networks in a feedback loop. The problem of controlling disease spread is not uniquely addressed in this work, but the approach to this problem is new. Pinning control applied at the node-level allows for simulation of the disease state of each individual connected in the network. Because the states are measurable in the simulated model, it allows for the calculation of transmissibility and incidence estimates for use in the NMPC algorithm.

7.3 METHODS

7.3.1 The control problem

Having considered medicine doses applied to infected individuals in disease contact networks using proportional feedback control in Chapter 6, this chapter now considers the optimal way in which to apply medicine doses. In particular, a cost function approach with input-output constraints is considered. The control problem is defined as: Control the application of medicine doses to a selective number of HIV-positive people at each time step (u_k^* in Figure 7.2) within a sexual contact network such that the minimum number of doses to achieve a particular average maximum disease incidence are administered, given input and output constraints. The node level control is applied in an open-loop configuration in the same manner as in Chapter 6.

7.3.2 Assumptions

The assumptions made in this chapter are:

1. Nodes are homogenous, with any node capable of transmitting the virus to any of its susceptible, connected nodes at a probability β_i, for node i.

2. The study design of using 250 networks of size $N = 100$, each simulated over 365 days, is sufficient to estimate a statistical difference in medicine doses when this strategy is compared to a proportional pinning control strategy.

7.3.3 NMPC control

NMPC is applied to disease networks of size $N = 100$ nodes, on which HIV is spread from one initially infected node (patient zero) to the rest of the network. An NMPC scheme is chosen because a linear deterministic model for the network node interaction and disease propagation cannot be formulated. To limit the computational intensity of the simulations performed to achieve the results in Section 7.4, the prediction horizon was chosen as $H = 4$ as explained in Section 7.3.4. The controller and system architecture used in this thesis is depicted in Figure 7.1.

7.3.3.1 General NMPC formulation

The model used for NMPC in this work is of the discrete form, with the following general formulation:

$$\begin{aligned} x_{k+1} &= f(x_k, u_k) \\ y_k &= h(x_k) + v_k \end{aligned} \tag{7.1}$$

Here, x is the system state at time k consisting of the average transmissibility β_k, the disease incidence I_k and the budget spent Q_k. The system state is a function of itself and the control input u_k. The input u_k is the percentage of highest-connected nodes to receive medication. The function $f : \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}^n$, which denotes an n-dimensional state vector multiplied by an m-dimensional control vector, is numerically simulated from the network in Eq. (3.6).

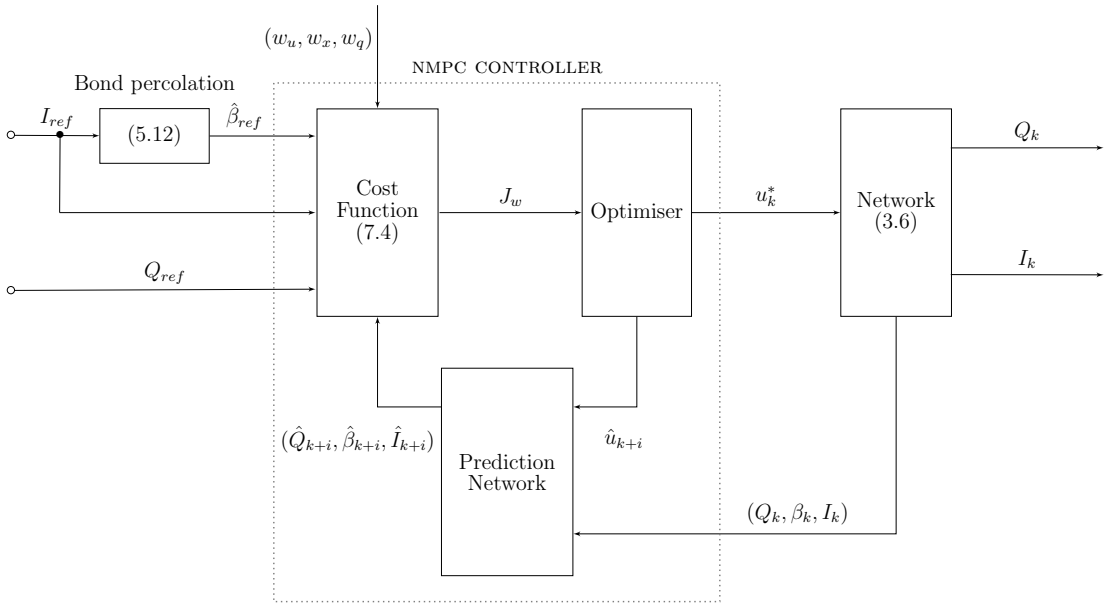


Figure 7.1: NMPC feedback control system architecture. Incidence is provided as reference I_{ref}, translated to a reference average transmissibility $\hat{\beta}_{ref}$. The feedback system states at time k are the QALYs Q_k (discussed in Chapter 8), average transmissibility β_k and disease incidence I_k. The prediction network returns $\hat{Q}_{k+i}, \hat{\beta}_{k+i}$ and $\hat{I}_{k+i}$. The optimal control is u_k^*.

The measured output y_k is a function of the system state x_k, and consists of Q_k, I_k and β_k. Random disturbances are modelled as v_k, but because the system is already configured to contain random disturbances, with the function $\Gamma(x)$ seen in (3.8), the value of v_k is set to zero in this thesis.

7.3.3.2 Algorithm

In general, an MPC algorithm utilises the following main mathematical components:

1. The process model used internally in the controller as an estimation of the true process dynamics.

2. A vector or matrix of historical control actions taken.

3. A cost function J_w to determine the priorities of the controller with respect to the system being controlled.

The process under control is a static network of disease spread, modelled in (3.6). For this reason, the internal process model applied to the NMPC controller is the same network duplicated from the actual controlled network at time k. The entire state of the actual network is "copied" to the controller model at each time k and simulated during subsequent times $k+i$ up to the horizon $(H-1)$. Each such simulation is performed with the goal of finding the optimal trajectory of the control u, denoted as u^*, that satisfies the minimum of the cost function J_w. Formally, the control algorithm can be formulated as proposed in [169]:

At each sampling instant $i = 0, 1, 2, ...$, perform the following steps:

Algorithm 1: NMPC control optimisation

1 Measure x_i, the state of the system.

2 Set $x_0 = x_i$

3 Solve the following optimal control problem:

Given the input and output constraints:

$$u_{min} \leq u_i \leq u_{max}$$
$$y_{min} \leq y_i \leq y_{max} \tag{7.2}$$

at each time step k, determine:

$$\min_{\{u_i\}_{i=0}^{H-1}} \{J_w(u_i, x_i, y_i)\} \tag{7.3}$$

where J_w is the cost function seen in Eq. (7.4), and u_i is the control input at time i, with x_i the state vector and y_i the output vector.

7.3.3.3 Cost Function

To design a suitable cost function for the control problem, the priorities of what the control should achieve must be defined. Priorities are given in the desired order as:

1. Minimise the control action (medicine doses) applied.

2. Minimise the steady-state error between the reference average transmissibility and the measured average transmissibility.

3. If selected, and applicable to Chapter 8, minimise the steady-state error between the reference budget and the actual budget measured in QALYs.

4. Minimise the steady-state error between the reference maximum disease incidence and the actual maximum disease incidence.

The next step, after setting the control priorities, is to select the weights of the cost function terms based on the defined priority sequence above.

After provision of the priorities for the control system, it is important to weight the cost function accordingly. Four weights are necessary, one for each of the priorities. The control input weight is w_u, the controlled variable (average transmissibility) weight is w_x and the budget optimisation weight is w_q. Because the average transmissibility and the disease incidence are directly related to another, the same weight with a constant offset is applied to the disease incidence as $(0.1 \times w_x)$. The controllability of the epidemic network incidence is directly related to the average transmissibility when bond percolation methods are applied, taken from (5.12). For this reason, through w_x, transmissibility is weighted ten times more than reaching the reference incidence in the cost function in (7.4). The complete least-squares cost-function can now be given as:

$$\begin{aligned} J_w(x,u) &= \sum_{i=0}^{H-1} w_x \times (\hat{\beta}_{ref} - \hat{\beta}_{k+i})^2 \\ &+ (0.1 \times w_x)(I_{ref} - \hat{I}_{k+i})^2 \\ &+ w_u \times (\hat{u}_{k+i})^2 \\ &+ w_q \times \Big[(Q_{ref} - \hat{Q}_{k+i})^2 \end{aligned} \tag{7.4}$$

The function is evaluated at each sampling instant k, from day 1 to day 365 to be representative of 1 year of simulation. It is of the least-squares (LSQ) type, and summated towards the control horizon $(H-1)$ for all time instances over 1 year. Any one of the cost function weights (w_u, w_q, w_x) may be set to zero to force the optimisation route to ignore the particular portion of the cost function. The parameter would thus be uncontrolled and the input will not have any effect on the NMPC control system.

7.3.3.4 Inputs

The inputs to the control systems are the reference disease incidence I_{ref}, the estimated average transmissibility in the network $\hat{\beta}_{ref}$ [134] and the budget reference Q_{ref} measured in QALYs. The budget reference signal is discussed and applied in Chapter 8, but presented here as part of the overall NMPC control scheme implemented. Using the numerical solution of (5.14), the reference incidence is translated to the estimated average transmissibility $\hat{\beta}_{ref}$.

The input constraints are given by:

$$\begin{aligned} 0 \leq \quad & I_{ref} \quad \leq 1, \\ 0 \leq \quad & \hat{\beta}_{ref} \quad \leq 1, \\ 0 \leq \quad & Q_{ref} \quad \leq (Y \times N). \end{aligned} \tag{7.5}$$

for networks of size N simulated over Y years or $(Y \times 365)$ days. Incidence is a proportion of the total network size, with a value of 1 equal to the entire network. Transmissibility is a probability, hence a value between 0 and 1 and Q is measured in QALYs, which are the number of years lived in full health. With $N = 100$ nodes, this means that 100 people living 1 year in full health would constitute 100 QALYs. (See Section 8.2.)

7.3.3.5 Optimiser

The optimiser in the control scheme used in this thesis implements a solver for smooth nonlinear programming problems that uses a sequential quadratic programming algorithm. Practically, a Fortran-based industrial implementation of this solver named NLPQLP, as described in [169], is used. The only difference is that this thesis implements the solver in a strictly monotone search direction, meaning the horizon is always approached from the current time incrementally to $H - 1$ for all optimisation trajectories considered. In general, the optimiser takes as input a continuously differentiable cost function $f(x)$, defined in this thesis by (7.4), and tries to minimise it. A quadratic programming problem is solved at each iteration by approximating a Lagrangian function. The description of the complete SQP algorithm provided here is supplied by [177]:

First, the Lagrangian function is defined, given by:

$$L(x,u) := J_w(x,u) - \sum_{j=1}^{m} u_j g_j(x) \tag{7.6}$$

where $J_w(x,u)$ is the cost function (7.4), u_j are multiplier vectors used to estimate the control trajectory and $g_j(x)$ are constraint functions of the iterates x that are zero for $j \leq m_e$ and non-zero above m_e, where $1 \leq m_e \leq m$. The solution of the quadratic programming problem can now be obtained by the minimum of the following Tailor expansion:

$$\min \left\{ \frac{1}{2} d^T \mathbf{H} d + \nabla f(x_k)^T d \right\} \tag{7.7}$$

where $\mathbf{H}$ is the Hessian of the Lagrangian in (7.6) and d is a solution of the problem. If d_k is now the optimal solution, u_k the multipliers, α_k the step length and v_k an approximation of the multipliers, then each subsequent iterate is given by:

$$\begin{pmatrix} x_{k+1} \\ v_{k+1} \end{pmatrix} := \begin{pmatrix} x_k \\ v_k \end{pmatrix} + \alpha_k \begin{pmatrix} d_k \\ u_k - v_k \end{pmatrix} \tag{7.8}$$

The step length parameter α_k is critical to ensure global convergence of the SQP method. This parameter should satisfy a decrease condition of the merit function:

$$\phi_r(\alpha) := \psi_r \begin{pmatrix} x \\ v \end{pmatrix} + \alpha \begin{pmatrix} d \\ d - v \end{pmatrix} \tag{7.9}$$

where ψ_r is a penalty function described by:

$$\psi_r(x,v) := J_w(x,v) - \sum_{j \in J} \left(v_j g_j(x) - \frac{1}{2} r_j g_j(x)^2 \right) - \frac{1}{2} \sum_{j \in K} v_j^2 / r_j \tag{7.10}$$

in which the sets are $J := \{1, ..., m_e\} \cup \{j : m_e < j \leq m, g_j(x) \leq v_j / r_j\}$ and $K := \{1, ..., m\} \backslash J$. The penalty parameters r_j should be chosen to guarantee a descent direction of the merit function in (7.9). This means that

$$\phi'_{r_k}(0) = \nabla \psi_{r_k}(x_k, v_k)^T \begin{pmatrix} d_k \\ u_k - v_k \end{pmatrix} < 0 \,. \tag{7.11}$$

As a last step in the SQP sub-problem solution, the Hessian matrix $\mathbf{H}$ should be approximated. The standard approach to do this is by using the Broyden-Fletcher-Goldfarb-Shanno (BFGS) quasi-Newton formula:

$$B_{k+1} := B_k + \frac{q_k q_k^T}{p_k^T q_k} - \frac{B_k p_k p_k^T B_k}{p_k^T B_k p_k} \tag{7.12}$$

in which $q_k := \nabla_x L(x_{k+1}, u_k) - \nabla_x L(x_k, u_k)$ and $p_k := x_{k+1} - x_k$.

The complete optimisation process is summarised in Figure 7.2.

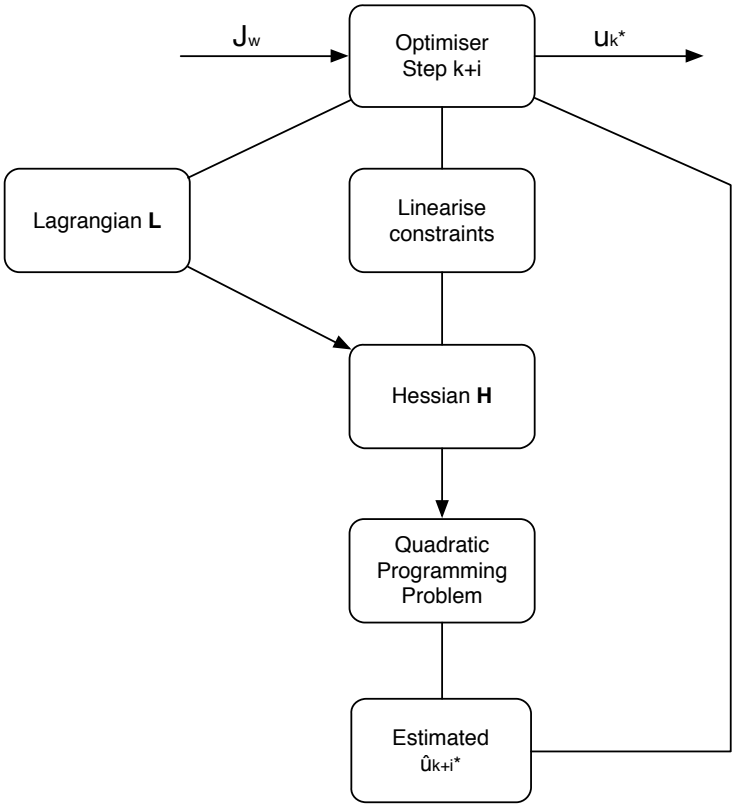


Figure 7.2: Summary of the optimiser algorithm followed in the NMPC control system architecture seen in Figure 7.1.

7.3.3.6 Prediction Network

The prediction network is exactly the same nonlinear process used as the simulated network, and given by (3.6). If the prediction network system of equations is defined as $\dot{\mathbf{P}}_k$ at time k and the set of actual network equations in (3.6) given as $\dot{\mathbf{X}}_k$, then at each iteration k of the control system and at each return to time k as part of the sub-problem optimisation process in Section 7.3.3.5, the following system re-initialisation of the prediction network is done:

$$\begin{aligned} p_{jk} &= x_{jk}, \\ \text{for all} \quad x_j &\text{ at time } k, \\ j &\in \{1, 2, 3\}, \end{aligned} \tag{7.13}$$

where $p_1 = T$ (CD4+ T-cells), $p_2 = T^*$ (Infected T-cells) and $p_3 = v$ (Virus).

7.3.3.7 Feedback

Feedback signals at time k from the simulation network include the average transmissibility β_k, the QALYs indicated by Q_k and the incidence I_k. These parameters are fed into the optimiser by means of the cost function in (7.4).

7.3.4 Computational time complexity and the choice of horizon

The choice of the control horizon H primarily depended on the computational time complexity of the algorithms and the available technology to simulate them in a reasonable time period for analysis. In Table 7.1, an experimental listing is shown of comparative scenarios that were used as inputs in this consideration. The values in the table were generated using a curve fitted to the observations of time and complexity during a variety of simulations. A graph of the time complexity can be seen in Figure 7.3.

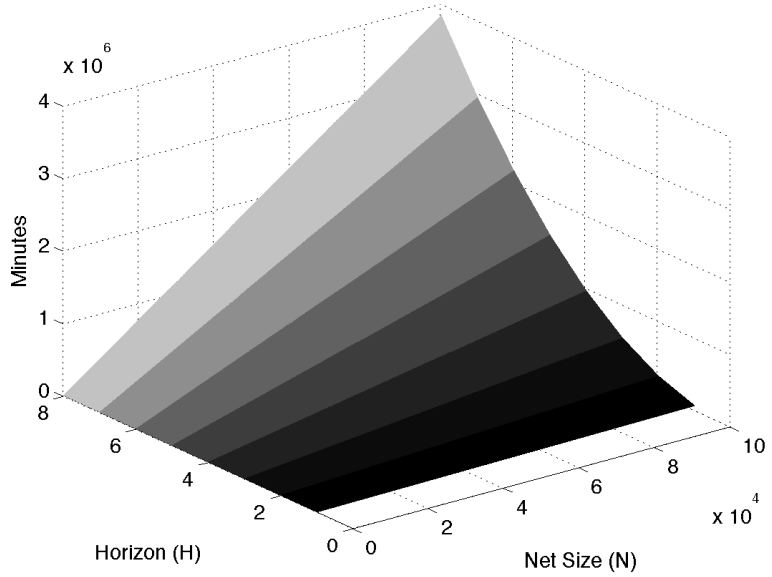


Figure 7.3: A depiction of the time complexity of the NMPC control algorithm implemented on networks of size N, with a control horizon H.

The complete NMPC algorithm implemented on a simulation of a complex disease-spreading network scales at $\mathcal{O}(H^2 * N)$ in the direction of an increase in horizon (H), and at $\mathcal{O}(N)$ in the direction of an increase in network size (N). The worst case performance is thus $\mathcal{O}(H^2 * N)$. This means that any simulation on a network under the same circumstances that contains ten times more nodes will take ten times longer to finish. Any network simulated with an increase in horizon by 1 will experience an increase in time proportional to the square of the horizon.

From the above data, to be able to present reasonable results using an available cluster of 10 machines, with 8 cores per machine, of which 6 were available for use (thus 60 parallel processes maximum at any one time), networks of $N = 100$ and a horizon of $H = 4$ were chosen for this part of the thesis.

Table 7.1: Time complexity of an increase in horizon for the NMPC algorithm on networks of increasing size. The assumption is that a cluster of 10 machines, each capable of running 6 processes in parallel, are employed. This makes for 60 parallel processes maximum at any time.

N	H	Ref. levels	Nets per ref.	ETA: (Hours)
100	1	5	300	0.42
100	2	5	300	1.7
100	3	5	300	3.75
100	4	5	300	6.7
1000	1	5	300	4.2
1000	2	5	300	16.7
1000	3	5	300	37.5
1000	4	5	300	66.7
10000	1	5	300	41.7
10000	2	5	300	166.7
10000	3	5	300	375
10000	4	5	300	666.7

7.4 SIMULATION RESULTS

7.4.1 No control

To establish a baseline against which to measure the improved health states of the network, 300 uncontrolled networks were simulated for each level of incidence considered (levels of 20%, 30%, 40% and 50% were used). An average maximum incidence of 72% was observed over all networks simulated for 365 days.

7.4.2 Control of incidence

Controlling the average maximum HIV incidence, reference levels of 20%, 30%, 40% and 50% were used. The results are shown in Figure 7.4.

Over a total simulation time of t_f, the average steady-state error I_{sse} is calculated by averaging $I_{sse} = |I - I_{ref}|$ at $t = t_f$ across several networks. Using this calculation, the results shown in Table 7.2 indicate that the proportional feedback scheme for 100-node networks in [134] could limit I_{sse} to within 32%, whereas NMPC could reduce I_{sse} to 12% or less of the reference values. The average steady-state error with NMPC was 5.75%, while for proportional feedback control it was 12% and for random pinning 16%. Thus, for 100-node networks, NMPC could control to the reference incidence 6.25% more accurately than the proportional selective pinning strategy from [134].

It is important to note here that, because steady-state error is reported as a percentage of the absolute difference in incidence percentage relative to a reference value, a small difference at a lower reference could constitute a large steady-state error.

Table 7.2: Average steady-state error of three control strategies implemented on 100-node networks compared. Random (RND) and Proportional Selective (SEL) pinning from [134] is compared to NMPC pinning control.

$I_{ref}[\%]$	$\overline{I}_{sse}[\%]$ for (RND)	$\overline{I}_{sse}[\%]$ for (SEL)	$\overline{I}_{sse}[\%]$ for (NMPC)
20	50	32	1
30	6.2	7.3	2
40	3	10	12
50	5	5	8
Avg	16.1	12	5.75

From Table 7.2, the following trends are noted:

1. The value of I_{sse} is higher for smaller references with both the random and selective pinning strategies. The reason for this is that these strategies have no predictive capabilities and the gain is kept constant at $K = 1$. A higher gain at lower references (which are more difficult to control accurately in disease spreading networks) could likely improve the steady-state error in these pinning control strategies.

2. The value of I_{sse} is lower for smaller references with the NMPC strategy. A constant gain is not a problem for this strategy as it directly calculates the needed control action based on predictions. One reason that may be offered for the increase in I_{sse} at larger references is the relative weight of control action and incidence in the cost function seen in (7.4). Investigations into the nature of this phenomenon should be done in further work.

7.4.3 Total doses

A statistical comparison of the NMPC selective strategy with the random and selective pinning strategies for the 100-node networks from [134] was done. The normalised frequency distribution of the total number of doses across the three strategies of pinning control are displayed in Figure 7.5. Samples of the number of doses were generated for each of the three

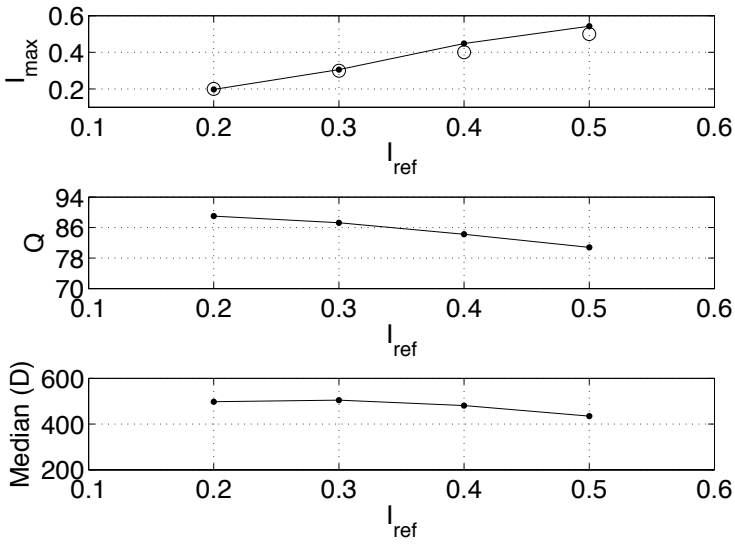


Figure 7.4: NMPC control of HIV incidence. Reference levels of 0.2, 0.3, 0.4 and 0.5 for incidence were used. Circles (∘) indicate the reference levels and solid dots (•) indicate the resulting simulated data points.

methods (Selective pinning: 1500, Random pinning: 1500, NMPC selective pinning: 1000). Descriptive statistics, including the median and interquartile range, were calculated for each set of samples. Histograms were generated and the vertical (sample frequency) axis normalised to percentage to enable a visual comparison between the distributions of the three methods. Comparisons between the methods were made using median difference tests and the non-parametric, Wilcoxon Rank (WR) sum and Kilmogorov-Smirnov (KS) tests for location and distribution respectively.

The results in Figure 7.5 and Tables 7.3 and 7.4 suggest that the NMPC method requires a lower dosing sampling frequency than either the selective pinning or random approaches from [134]. The NMPC method further requires a higher median number of doses than the random method but lower than the selective approach. There were significant differences in the medians of all 3 methods. There were also significant differences in characteristics of both location (WR) and distribution (KS) between the methods. None of the methods were distributed in a Gaussian normal manner.

The doses datasets of all the strategies are all non-parametric as well as from different dis-

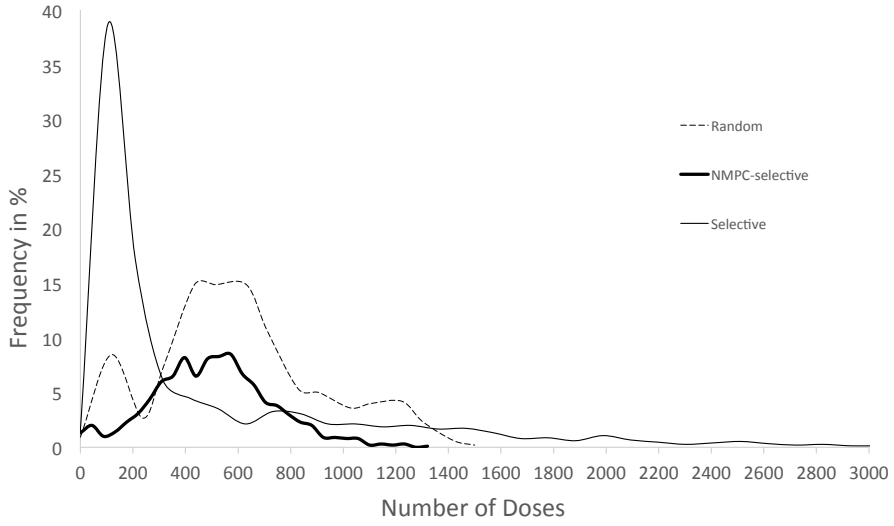


Figure 7.5: Normalised frequency distribution of usage of doses between three pinning control strategies. Selective pinning used the widest bandwidth of doses (between 0 and 3000 doses per network per year) and NMPC selective pinning the narrowest bandwidth (between 0 and 1350 doses per network per year). Bandwidth is indicative of the variability of the strategy for practical implementation. Selective pinning has a very high frequency peak. This indicates that a large proportion of networks under selective pinning control received around 160 doses per year in total. The narrower the bandwidth, the more generalisable the result is, but with selective pinning it came at a cost of 6.25% steady-state accuracy as seen in Table 7.3. It can thus be said that selective pinning control uses less doses per network per year, but more often than the other strategies on 100-node networks over 1 year.

tributions as shown in the test results in Table 7.3.

Table 7.3: Statistical significance of the difference in doses data between pinning methods. Selective pinning (SEL), random pinning (RND) and NMPC selective pinning are compared.

Statistic	Selective (SEL)	Random (RND)	NMPC Selective
Median	146.3	600	479.7
IQR	(73.6-672.7)	(400-800)	(333.3-619.7)
Sample size	1500	1500	1000

Table 7.4: Descriptive statistics from the comparison of pinning methods: Selective (S), Random (R) and NMPC Selective (N).

Methods	Median ratio	Median test (p)	KS-test	WR-test
S : R	0.244	$< 1 \times 10^{-6}$	$< 1 \times 10^{-6}$	$< 1 \times 10^{-6}$
S : N	0.305	$< 1 \times 10^{-6}$	$< 1 \times 10^{-6}$	$< 1 \times 10^{-6}$
N : R	0.799	$< 1 \times 10^{-6}$	$< 1 \times 10^{-6}$	$< 1 \times 10^{-6}$

7.5 DISCUSSION AND CONCLUSIONS

An analysis of using different pinning control schemes applied to disease networks was done in [121]. Following this, a proportional feedback methodology was proposed in [134]. This chapter captures the formal analysis of using optimal feedback control on disease spread in complex networks. For the purpose of providing an evaluation tool to public health specialists, the main focus of this chapter is on incidence control. It was shown that NMPC may be combined with network simulations to provide insight into optimal dosing strategies. The size of the network and the choice of the control horizon were both problems related to the computational complexity of the NMPC algorithm and the addition of network dynamics to this algorithm, as discussed in Section 7.3.4. Using the resources available (computational cluster of 10 machines, with 8 cores each of which 6 were allocated for use), the horizon choice of $H = 4$ resulted in simulations that could finish in a reasonable time. The control strategy proposed through the use of such a controller implies that, practically, case-finding for the disease should be implemented and the contact networks thoroughly assessed. The spread of disease is highly reliant on contact network structure, hence an assumption was made in this thesis that a general random exponential-power-law model would be used. The engineering method used in this thesis to analyse HIV contact networks resulted in the following major conclusions after analysis:

1. NMPC pinning control is 6.25% more accurate than selective proportional pinning control and 10.35% more accurate than random pinning control studied in [134]. Accuracies are based on analyses and comparisons of the steady-state error of the disease incidence of all control schemes, reflected in Table 7.3.

2. NMPC control has the lowest bandwidth of administered doses per network per year, compared to random pinning and selective proportional feedback pinning. Narrower bandwidths of doses are easier to implement in a real-world setting.

3. The maximum number of doses administered during any single year (doses bandwidth) on a single network of 100 nodes under NMPC control were around 1350. For selective pinning this number was around 3000, and for random pinning around 1500. The highest proportion of yearly doses for NMPC control of 100-node networks was between 400 and 700 doses.

4. NMPC selective pinning control uses a higher median number of doses than proportional selective pinning when only 100-node networks are considered. In contrast, the NMPC method uses a lower median number of doses compared to random pinning. The gain for the higher usage of doses of the NMPC strategy is seen in its accuracy, where it improves upon the random pinning strategy by a 10.3% reduction in steady-state error.

Control of the incidence in disease contact networks is possible using nonlinear model predictive control. This control improves upon the existing proportional feedback strategy published in [134] in terms of accuracy. The improved strategy and method can be used by public health intervention sponsors to analyse the trade-off between budget and incidence. The analysis of the spread of other disease, such as resource allocation to eradicate EBOLA, can also be done using this technique.

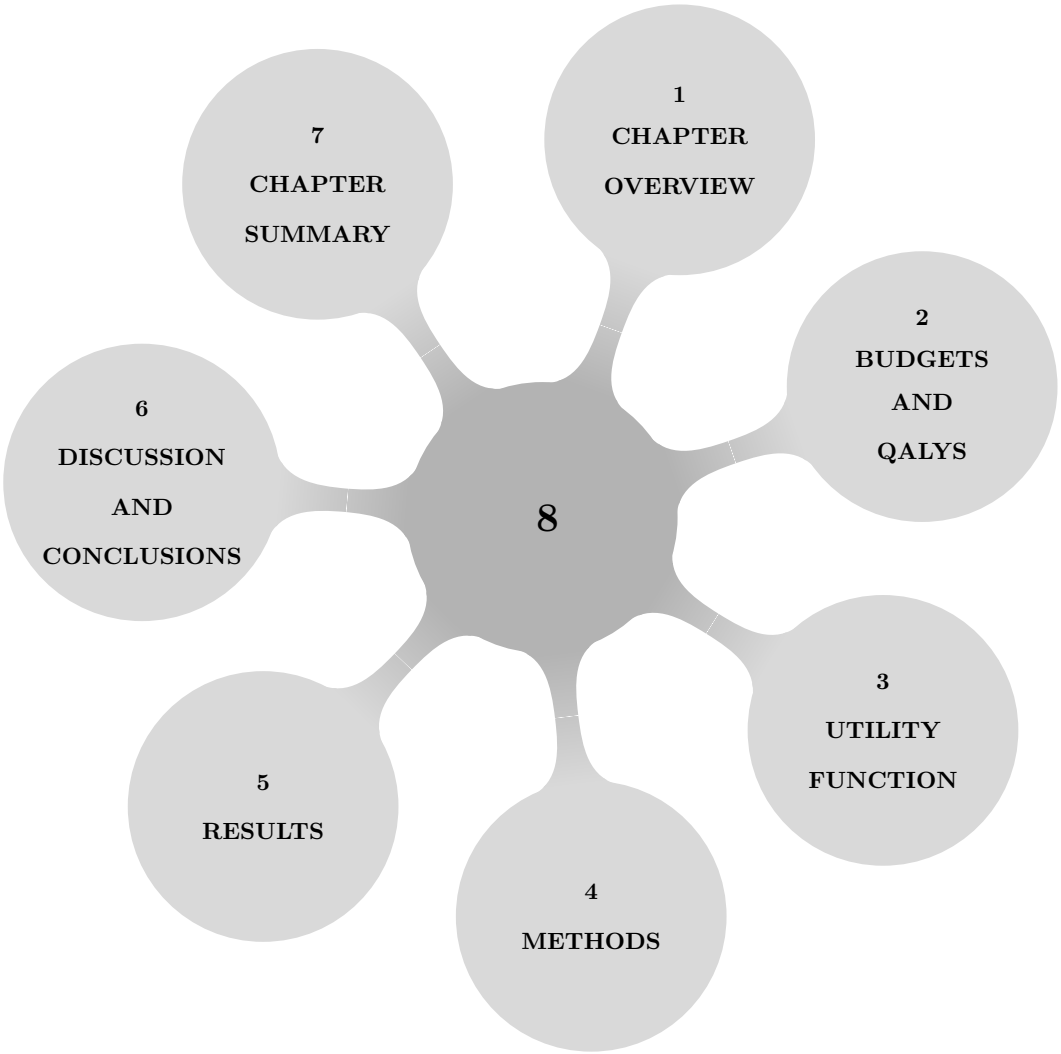
In order to scale the NMPC control method to a real-world disease control scenario, a high resolution of data measurement in the population under control would be needed. The presence (and absence) of regular contacts would be needed to assess network structure and the identification of highly-connected individuals would flow from this. After analysis of the network structure and current infections, NMPC simulations should be performed to obtain the optimal number of highest-connected nodes to pin. If the public health study protocol allows this, these individuals should then be targeted for intervention and receipt of medication. Very few (if any) studies would allow this from an ethical perspective under highly-resourced circumstances. Given medicine-scarcity and large numbers of infections, this approach might become more feasible and practical, as less individuals would need medication than otherwise possible.

7.6 CHAPTER SUMMARY

In this chapter, the impact of an optimal drug dosing strategy for a variety of HIV incidence set-points were explored. NMPC was implemented with average transmissibility and disease incidence feedback. Contact network sizes were fixed at $N = 100$ nodes due to the time complexity of the NMPC algorithm attached to network simulations. It was found that networks controlled for incidence by the NMPC controller were 6.25% more accurate than the selective pinning feedback strategy proposed in Chapter 6 when the median doses were compared. In contrast, NMPC control used a median of 69.5% more doses. Considering the median number of doses used on 100-node networks over 1 year, proportional selective pinning uses the least number of doses and random pinning is the least accurate. NMPC pinning uses more doses than selective proportional feedback pinning and less doses than random pinning. It is more accurate than any of the other strategies. The bandwidth of doses by using the NMPC strategy was the lowest, which makes it more logistically practical to implement than the other compared strategies. The bandwidth for the proportional feedback selective pinning strategy was the highest.

CHAPTER 8

PINNING CONTROL OF INTERVENTION BUDGETS



8.1 CHAPTER OVERVIEW

This chapter builds on the NMPC selective pinning strategy and architecture proposed in Chapter 7. Controlling and limiting the transmission of disease are important public health problems, with available financial resources being a driving factor when deciding how and whether to implement any medical intervention [178]. There are many scenarios where budgets are limited. Focus is placed on a population or network's QALY measurement to establish the financial impact of the controls applied on the ability of the population to live healthy lives [179]. The QALYs measurement has long been the subject of criticism in its application [180]. This debate will not be discussed in the scope of this thesis, but it is important to know about this measurement instrument's limitations. These include the possibility of bias due to self-reporting of health states, confounding elements such as misinterpretation of questions asked during measurement, the omission of important health outcomes by virtue of QALYs providing a single outcome value only and the debate around the bias away from mental and emotional health problems.

Three control options for budget are explored: (1) Establishing an up-front budget and controlling the network towards this budget, (2) controlling towards a particular disease incidence over 1 year and reporting the budget spent to achieve this and (3) attempting to control the incidence and budget simultaneously. For all strategies, value-for-money is also determined from the ratio of medicine doses used to QALYs saved in relation to no intervention.

8.2 INTERVENTION BUDGETS USING QALYS

QALYs are used by public health practitioners to measure the burden of disease in a population. Health is reflected as a function of both the quality and quantity of life. It was first implemented by [181]. In particular, it is used to assess the value-for-money of a public health intervention. Practically, companies funding interventions are interested in the number of QALYs that can be saved relative to no intervention in a population, and normally assign a budget per QALY saved. The QALY measurement expresses the number of years of life lived in a particular state of health. Each year in perfect health is assigned the value of 1.0 and time spent being sick or infected is attributed a value of less than 1.0. This is called

the utility value of a person. The equation for calculating QALYs is shown as:

$$QALY = Y \times Q_w, \quad Q_w \leq 1 \tag{8.1}$$

The QALY depends on the product of two values. The first, Y, is the number of years lived (in this work chosen as $Y = 1$ year), and the second is a utility value (Q_w) depicting the quality of life during this time. A large variety of public health measurement instruments are used to calculate the utility value, largely based on patients' self-assessment of their state of health according to different categories such as mobility, self-care, the ability to perform usual activities, the amount of pain experienced and the degree of depression felt. The most widely used measures to collect data on utility values Q_w are the standard gamble approach, time trade-off (TTO) approach, visual analogue approach and the rating scale measure [182]. Indirect measures of utility are normally done using generic preference instruments such as the EQ-5D, SF-6D and HUI methods. The next section includes a description of the EQ-5D method. This method is normally preferred.

Several studies have been performed to assess health-related quality of life (HRQoL) retrospectively [183, 184]. Proprietary measures such as the Health Utilities Index (HUI) [185] and the EuroQol (EQ5D) [186] systems have been used to convert HRQoL data to utility values for providing Q_w in (8.1) [187]. The standardised and widely used EQ-5D survey methodology for determining the quality of life associated with a particular health state such as being infected with HIV and having a particular CD4+ T-cell count, works as follows:

1. Participants fill in a questionnaire to reflect their current health state. The questionnaire focuses on the following five dimensions of health:

   A. Anxiety and Depression

   B. Mobility

   C. Pain and Discomfort

   D. Usual Activities

   E. Self-care

2. For each dimension of health, a participant would select one of three levels: (1) no

problem, (2) some problems or (3) extreme problems.

3. The answers are then coded into five digits, for e.g. 11111 would indicate no problems on all five dimensions.

4. Proportional values may then be attached to the outcomes measured, across all dimensions and across all patients.

5. A final summary index value is determined. Such values may be stratified according to age or any other risk factor measured in the target population. For the purposes of this thesis, the EQ5D results matched to a particular CD4+ T-cell count by the CDC (Table 8.1) are used.

Due to the subjective nature of determining the utility value Q_w for quality-of-life of a person, it is widely criticised for its accuracy. It is important to note that the best practice in obtaining measurements from real people involve considering the ethics of the exercise. Utility values, and the associated standard instruments that measure it, represent the most ethical approach to this problem by basing the result on self-reporting.
To supply more objectivity to the value of Q_w, the economics of the circumstances of each person might be considered. Socio-economic state, age, sex and income may all influence an individual's perception of their own health and could be considered to adjust the self-reported value of utility.

8.3 CHOOSING A SUITABLE UTILITY FUNCTION

Utility values for HIV are widely available for various populations and epidemiological studies performed [188, 189]. Utility values are by definition categorical variables, resulting in a function that is not smooth and differentiable. For the specific optimisation algorithm used in this work, based on Sequential Quadratic Programming (SQP), a smooth cost function is a prerequisite otherwise controllability according to budget is greatly impaired. A smooth utility function was obtained by using utility values from a meta-analysis of HIV-specific measures [190], and fitting a function to the mean of the categorical data in Table 8.1. The function has the following form:

$$Q_k = \frac{L}{\left(1 + e^{(-k \times (x - x_0))}\right)} \tag{8.2}$$

where $0 \leq Q_k \leq 1$. The input to the utility function should be a measured variable x. In the simulated networks of HIV, all the state variables are available for measurement. The most appropriate variable to use is the CD4+ T-cell count. The Center for Disease Control has classified the stages of HIV based on CD4+ T-cell count [191]. The input to the utility function is thus defined, with categorical input/output values for utility listed in Table 8.1. The next step is to define a smooth utility function. To this purpose the average utility for medicated and non-medicated individuals is taken and a logistic function of the form seen in (8.2) is fitted to it. The fitted function parameters are $L = 1$, $k = 0.0031$ and $x_0 = 0$.

Table 8.1: QALY utility values per CDC state of HIV ([190, 191]).

CDC Stage	CD4+ T-cell count	Utility (Q_w) (on medication)	Utility (Q_w) (not on medication)
A - Asymptomatic	> 500	0.94	0.68
B - Symptomatic	$200 - 499$	0.82	0.56
C - AIDS	< 200	0.7	0.44

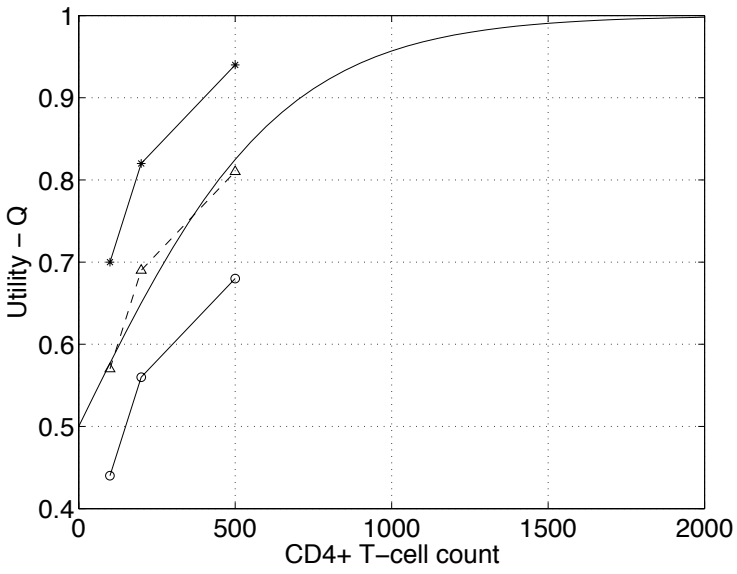


Figure 8.1: Plot of the applied smooth utility function in (8.2), with $L = 1$, $k = 0.0031$ and x_0=0. Asterisks ($*$) indicate the utility when receiving medication, and circles ($\circ$) indicate the utility without medication. The dotted line and triangles ($\triangle$) represents the average utility between medicated and unmedicated people infected with HIV.

8.4 METHODS

8.4.1 The control problem

The control problem addressed in this chapter is defined as: Control the application of medicine doses optimally to a selective number of HIV-positive people at each time step within a sexual contact network such that the minimum number of doses are used to maintain a defined budget measured in QALYs. Additionally, attempt to control budget and QALYs simultaneously. QALYs are applied in two ways in this thesis: (1) As reference signal for the control system and (2) as measured output when the disease incidence is set as the reference signal.

8.4.2 Assumptions

The assumptions made in this chapter are:

1. Quality of life (QoL) and budget target values are estimates. In this thesis, specific references have been chosen to represent these measures. Each particular study should seek and refine its own, accepted quality-of-life measures and specific budget function needed.

2. Nodes that die continue to contribute their last known quality-of-life values to the budget function. This ensures that the cost function stays smooth for controllability.

8.4.3 Characterisation of incidence and budget

Incidence and budget are coupled by the immune response models of the network nodes. Respectively, incidence depends on the viral load of nodes and budget depends on the CD4+ T-cell count of nodes. It is thus necessary to characterise the relationship between these outputs by simulating the budget (Q) for each reference control level of incidence. A simulation was performed on 50 networks for each 1% of incidence from 1% to 100% reference incidence levels. The average maximum incidence (I_{max}) for each reference level was obtained, with the result shown in Figure 8.2.

This result suggests that the controllable references fall within the interval $I_{ref} = [0.14, 0.76]$. Beyond these reference values the controlled maximum incidence become inaccurate and diverge to more than 15% of the reference signal. Regarding controllability, the QALY (Q) graph depicts a similar result to the incidence (I_{max}) graph. Below $I_{ref} = 0.14$, the QALYs are close to 90 and above $I_{ref} = 0.76$, the QALYs are close to 75. This suggests that the useable reference values for QALYs should fall within this interval.

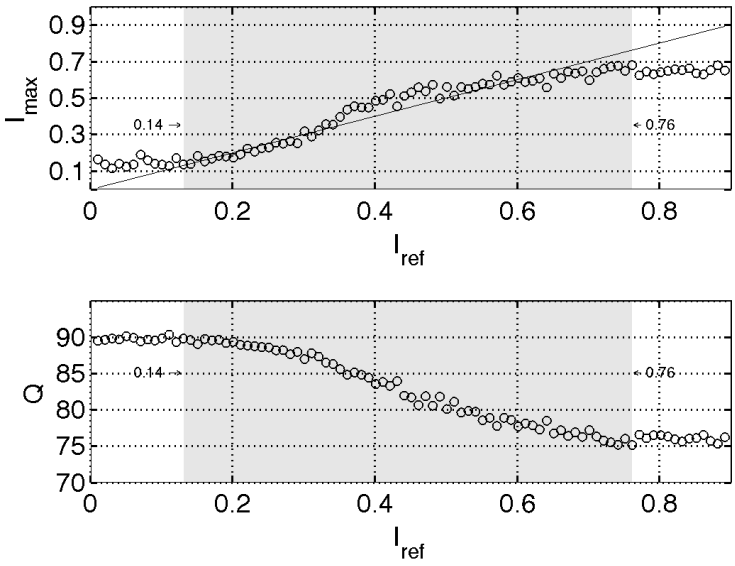


Figure 8.2: Characterisation of incidence and budget is done by noting the QALYs spent for each reference level of incidence from 1% to 100%. Each data-point represents the average of 50 networks. The greyed area represents the reference incidence levels for which I_{max} has an error of less than 15%. This area corresponds to the interval $I_{ref} = [0.14, 0.76]$.

8.5 SIMULATION RESULTS

8.5.1 No control

To establish a base-line for improved health, 250 uncontrolled networks per reference level were simulated. The average QALYs measured across all of these networks was 72.07.

8.5.2 Control of budget

Control of budget was done according to the reference levels of QALYs that fall within the controllable range seen in Figure 8.2 for networks containing 100 nodes. The range for Q is thus [0, 100] when 100 indicates the entire network of $N = 100$ is completely healthy. Budget was noted as being inversely proportional to incidence in all cases. Control at lower QALY levels (between 74 and 78 QALY) were more accurate than higher QALY levels (between 78 and 86). The error increased as the QALY reference level increased. The steady-state errors for reference levels of 74, 78, 82 and 86 were 0.6%, 1.1%, 3.7% and 6.4% respectively and the corresponding median doses needed were 65, 110, 110 and 126. The median doses varied significantly and were much less when compared to control of HIV incidence only as seen in Figure 7.4.

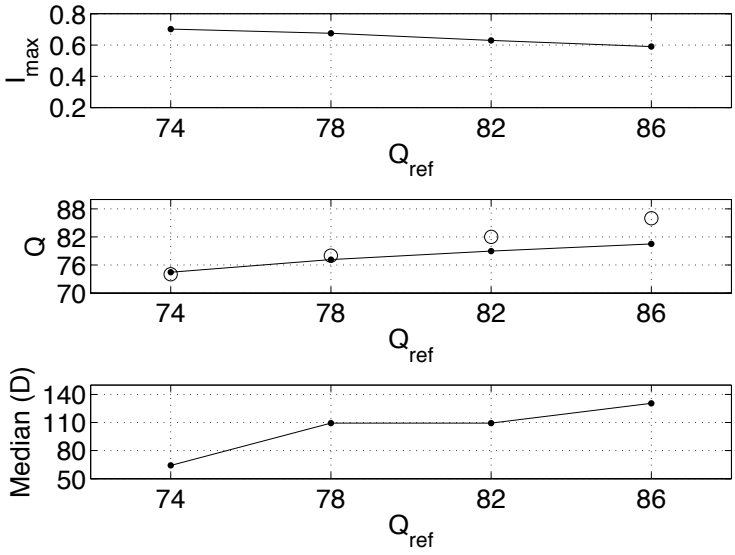


Figure 8.3: Control of budget (QALY). Budget reference levels of 74, 78, 82 and 86 were chosen to span the controllable range. Circles (○) indicate the reference levels and solid dots (●) indicate the resulting simulated data points. Q are the QALYs ranging between 0 and 100, I_{max} is the average maximum incidence and D is the median number of doses.

8.5.3 Control of budget and incidence

A single experiment was performed to assess the possibility of controlling incidence and budget simultaneously. A reference budget of $Q_{ref} = 86$ was chosen and the error in incidence and budget compared to each other across reference levels of 0.2, 0.3, 0.4 and 0.5. The result can be seen in Figure 8.4 and Table 8.2.

Table 8.2: Steady-state error for Q-I-control simulations.

Q_{ref}	Q	$Q_{sse}[\%]$	I_{ref}	I	$I_{sse}[\%]$	$Q_{csse}[\%]$
86	88.9	3.37	0.2	0.20076	0.38	0.11
86	87.3	1.51	0.3	0.295	1.7	0.23
86	84.2	2.09	0.4	0.454	13.5	0.24
86	80.9	5.93	0.5	0.5297	5.94	0.74
Avg	–	3.23	–	–	5.38	0.33

With increasing incidence levels, the average QALY decreases monotonically. The total optimised doses to ensure adherence to the reference level incidences were almost the same across all reference levels. On average, at the reference QALY level $Q_{ref} = 86$, both budget and incidence could be controlled to within 6% of the target reference levels. Greater percentage incidence errors I_{sse} were seen compared to budget errors Q_{sse}. Considering the characterised Q-I graph in Figure 8.2, budget levels more accurately followed the characterised QALY for a particular incidence level, compared to the required QALY reference Q_{ref}. This signifies that, considering simultaneous control of budget and incidence, budget would more likely follow the systemic relationship between Q and I than the control references.

An interesting observation here is that, when budget is controlled together with incidence, the average steady-state error for all incidence levels improves slightly over the case where only incidence is controlled. The improvement noted was 0.37%. This outcome suggests that, when budget (which is closely coupled to the network nodes' CD4+ T-cell counts) is controlled, better control of the incidence is possible.

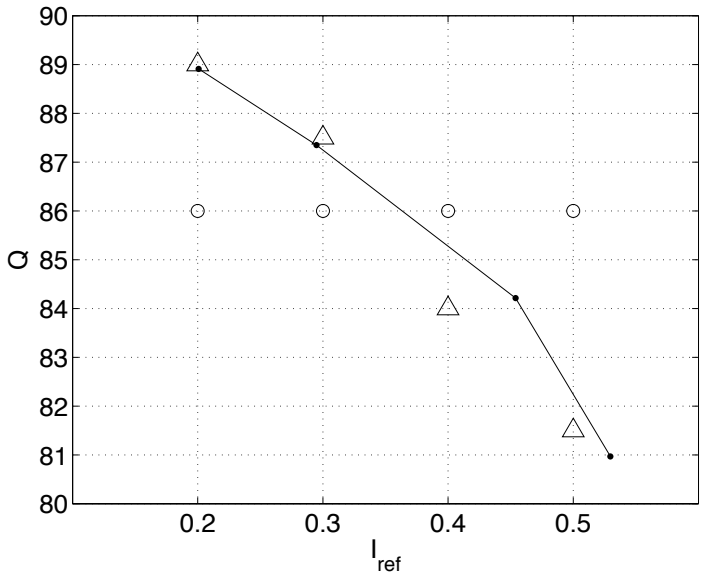


Figure 8.4: Simultaneous control of budget and incidence attempted for $Q_{ref} = 86$ and all reference values I_{ref} used in this thesis. Circles ($\circ$) indicate the reference budget in QALY on the Y-axis, as well as the reference incidence I_{ref} on the X-axis. Triangles ($\triangle$) signify the characterised QALYs for respective incidence levels seen in Figure 8.2. Solid dots ($\bullet$) are the simulated data points, each the average of 250 networks.

8.6 DISCUSSION AND CONCLUSIONS

NMPC control of the HIV disease networks in this chapter resulted in the following major conclusions after analysis:

1. NMPC control of the QALY budget in the 100-node networks in this thesis is possible, to within a maximum steady-state error of 5.94%. The QALY to be controlled can be selected by public health professionals, but the incidence in the network will then vary.

2. Simultaneous control of budget and incidence is possible, but the budget output is far more likely to follow the characterised relationship between budget and incidence than other reference values. When the budget reference was set to $Q_{ref} = 86$ during simultaneous control, the average error across all incidence reference values was $Q_{sse} = 3.23\%$. Comparatively, the average steady-state error with the characterised Q-I budget levels was $Q_{csse} = 0.33\%$.

3. When budget is controlled to a level close to the characterised Q-I relationship in a network, an improved accuracy in the control of incidence is noted. This improvement as noted as 0.37%.

8.6.1 QALY as incidence increases

On average, the QALY of complete networks decrease as the average incidence levels increase. This supports the causality that sicker individuals have less CD4+ T-cells and hence a poorer quality of life measure, even when connected to networks in which medicine doses are being administered.

8.6.2 The number of pinned nodes

The average number of pinned nodes for each set of 250 simulations per category is shown in Table 8.3 as $\overline{P}$, measured in %. The maximum ever number of network nodes pinned is given by Max P in the same table. The maximum ever number of nodes pinned during a single time step for the simulations performed is 4 nodes out of 100.

8.6.3 Cost-effectiveness

Cost-effectiveness is determined by the ratio of the costs of control (medicine) to the QALY saved [192]. The formula is given as:

$$CE = \frac{\text{Cost of intervention (Median of Doses)}}{\text{Health benefit (QALY saved)}} \tag{8.3}$$

The unit of cost-effectiveness is *doses per QALY saved*. The cost of each dose may be determined and an overall budget for the number of QALYs saved can be determined by simple multiplication. The measured values of cost-effectiveness for different combinations of reference incidence and reference budgets are shown in Table 8.3.

The cost-effectiveness values shown in the right-hand column of Table 8.3 indicate that, for all three main experiments performed, the most cost-effective (value-for-money) interventions were those where the doses per QALY saved were the lowest. The most cost-effective strategies per category of control, in order, were: (1) control to an incidence of 20%, (2) control of the budget to 86 QALY, and (3) the simultaneous control to 86 QALY and 20% incidence.

Table 8.3: Cost-effectiveness (CE) of each control strategy (C) tested: (1) Incidence control, (2) budget control and (3) incidence and budget control simultaneously. The average percentage of pinned nodes (in a 100-node network) over 250 simulations is given by $\overline{P}$ and the maximum ever percentage pinned nodes is given by Max P.

C	I_{ref}[%]	Q_{ref}	$\overline{I}_{max}$[%]	Q_{avg}	Q saved	$\overline{P}$[%]	Max P[%]	Median - D	CE
Incidence	–	–	72.33	72.07	–	–	–	–	–
	20	–	19.74	89.00	16.93	1.43	3.62	498	**29.4**
	30	–	30.60	87.27	15.2	1.39	2.92	505	33.2
	40	–	44.8	84.25	12.18	1.31	3.74	481	39.5
	50	–	54.23	80.81	8.74	1.22	2.88	434	49.7
Budget	–	74	70.22	74.47	2.4	0.19	0.44	64	26.8
	–	78	67.52	77.15	5.1	0.26	0.66	109	21.5
	–	82	62.96	78.98	6.9	0.3	0.76	109	15.8
	–	86	59.03	80.51	8.4	0.34	0.91	130	**15.5**
Incidence and budget	20	74	19.75	89.07	17	1.42	3.51	526	31
	20	86	20.08	88.91	16.8	1.44	3.02	520	**30.9**
	30	74	30.33	87.18	15.1	1.43	3.64	502	33.3
	30	86	29.49	87.35	15.3	1.46	3.14	523	34.2
	40	74	46.74	83.87	11.8	1.37	2.83	511	43.3
	40	86	45.40	84.21	12.1	1.38	3.05	507	41.8
	50	74	52.20	80.81	8.7	1.18	2.88	409	46.9
	50	86	52.97	80.97	8.9	1.23	2.89	450	50.6

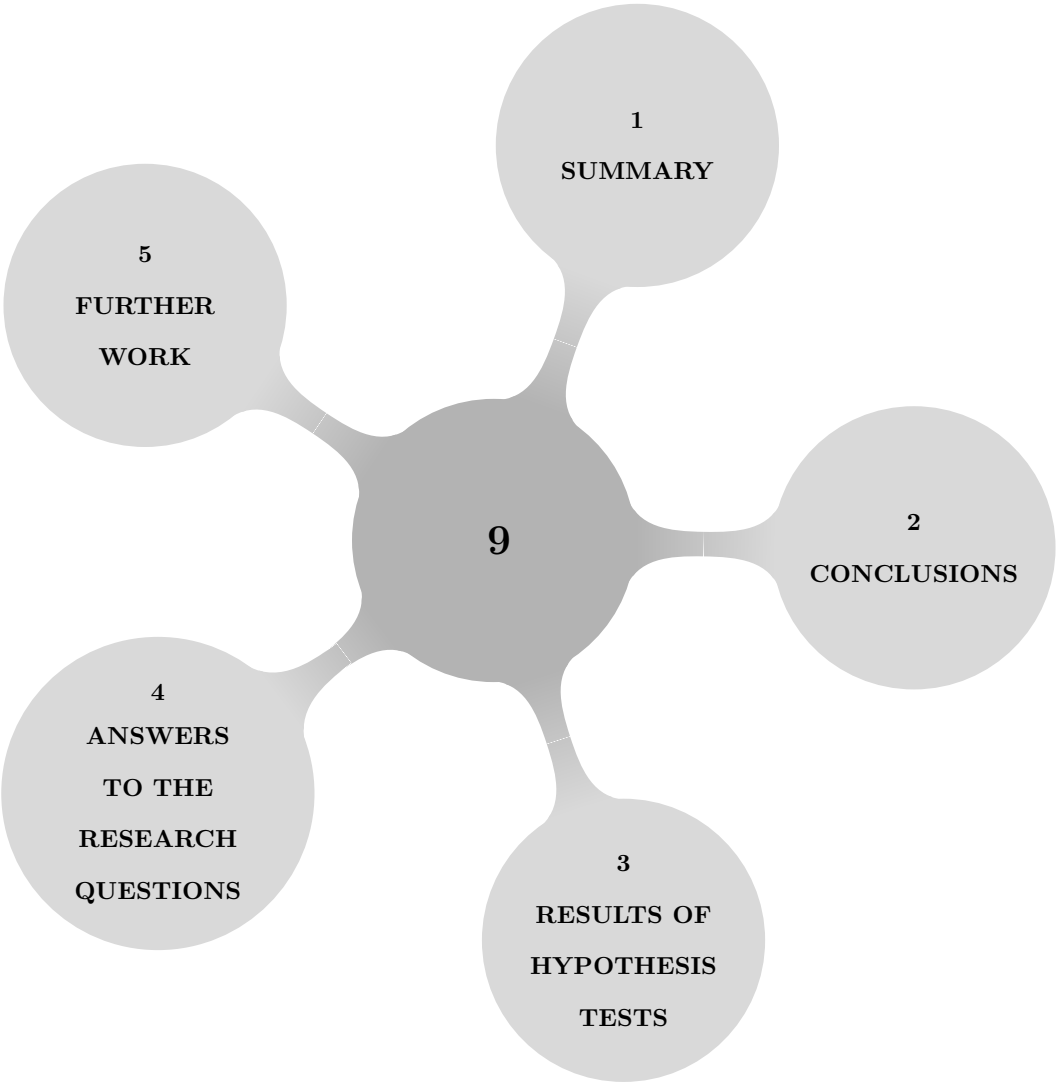
8.7 CHAPTER SUMMARY

This chapter focused on the control of networks in settings where budgets are limited. Pinning control was applied to selected nodes in contact networks for HIV. Budget was used both as a reference signal and as a measured outcome when incidence was controlled. Because budget is directly related to the average CD4+ T-cell count of nodes in the network, there is a very tight coupling between incidence and budget. A smooth utility function required by the NMPC algorithm to produce accurate results was devised from categorical QALY utility data for HIV. After characterisation of the relationship between incidence and budget,

simulation results showed that budget can indeed be controlled to various levels. Higher budget reference levels were more difficult to reach with the control system. Simultaneous control of budget and incidence did not yield very good results, although controlling both parameters on their characterised values yielded better results for the control of incidence. The most cost-effective control strategy was determined.

CHAPTER 9

CONCLUSIONS AND FURTHER WORK



9.1 SUMMARY

This thesis presented the contribution of a new methodology to control, analyse and compare different pinning control strategies for the spread of disease on networks. The methodology was tested using a node model of the immune response to HIV infection scaled and implemented on networks of up to $N = 10000$ nodes. Control of these HIV infection networks were varied between a selective proportional pinning strategy, a random pinning strategy and an optimal selective pinning control strategy using NMPC. The latter used more control action than the selective proportional strategy, but improved greatly on accuracy in reaching reference incidence levels. Budget could also be controlled in networks. Budget was measured in QALYs, which was modelled as a continuous function in order to provide suitable results with an NMPC controller. The frequency distribution of doses between all strategies were compared. Such a comparison may prove to be very useful to public health professionals seeking to implement particular interventions within environments with budgetary constraints.

Chapter 1 provided an introduction to this research and the thesis. The research questions were posed and the question on why this research should be performed was answered: It is important to break into areas of research where synergy between fields are sought, as this strategy advances new ways at addressing both old and new problems. As such, control systems, epidemiology and complex networks were proposed as the relevant fields to this study. The gap in the scientific body of knowledge was identified and the adaptability of a potentially useful method such as pinning control of disease networks was presented. The method may be used with varying control strategies, varying sizes of networks, various network topologies, different types of medicine with varied pharmacokinetic effects, various transmission functions, co-infected networks and more. The chapter highlighted the approach followed and objectives of this study.

Chapter 2 presented a literature study of the information available that addresses disease spread using multi-disciplinary knowledge. The current control systems literature on pinning control, the complex systems literature on spread of diseases on networks and the relevant epidemiological background were discussed. The challenges facing any researcher modelling disease spread on networks and then applying this in an epidemiological context were given.

Chapter 3 presented the models used in this work. A three-tiered modelling framework was given as the basis from which this research is formed. A node model representing the immune response of an individual to HIV was chosen and scaled to a network and population model for disease spread. Model parameters were chosen from literature. Possible simulation options using these models were also given.

Chapter 4 clearly presented the control systems method of pinning control. Different types and levels of pinning control were discussed, from open- and closed-loop pinning on a node level to random and selective pinning on a network level. The pinning options specifically available for disease spread were discussed.

Chapter 5 discussed bond percolation, a technique from statistical mechanics. This technique was shown to be useful for establishing the correct reference signal for transmissibility (the probability of transmission) of disease in a network in order to determine the eventual outcome of maximum incidence. Bond percolation formulae from literature were presented and integrated into a final outcome of I_{ref}, the incidence reference for the control systems applied in the rest of the thesis.

Chapter 6 presented a classical proportional control feedback loop applied to disease spread networks. Networks were placed into the loop as the "process" to be controlled. Various reference signals, each simulated 350 times and then averaged, were scrutinised. This chapter found that control of disease networks using feedback and pinning control in combination is feasible. Two main strategies were compared: random pinning of all nodes and selective pinning of the highest risk nodes in the networks.

Chapter 7 provided an application of NMPC to disease networks. HIV contact networks were controlled with a horizon of $H = 4$ and compared to the pinning control strategies from Chapter 6. NMPC used more control action but leads to much greater accuracy in steady-state error when compared to the other (random and proportional selective) strategies.

Chapter 8 showed how budget, measured in QALYs, could be controlled in networks. A decision can be made on the "QALY saved", after which simulations could be performed using the reference signal Q_{ref}. It was shown that an optimal outcome of budget could be seen when only budget was controlled. When both budget and incidence were controlled, the incidence target was prioritised.

9.2 CONCLUSIONS

The following main conclusions could be drawn from this work, in alignment with the identified research questions:

Applying pinning control to networks:

- Pinning control could be applied to disease networks for the spread of HIV.
- Different pinning control strategies may be applied to networks, and the outcomes compared.

Bond percolation as reference signal:

- The use of bond percolation as a reference signal for the control systems was successfully illustrated in this thesis.
- It is shown that bond percolation can be applied to HIV contact networks.

Control strategies and control action:

- Of all the control strategies used, the NMPC pinning control scheme for disease incidence was the most accurate (least steady-state error).
- Random pinning uses the most control action and is also the least accurate. Selective pinning with proportional feedback uses the least control action, but is also less accurate than NMPC selective pinning.
- NMPC selective pinning is on average about 6.26% more accurate than proportional selective pinning control in a proportional feedback loop.
- For networks with $N = 100$ simulated over 1 year, NMPC uses more control action than a proportional selective pinning control strategy and less control action than a random pinning control strategy. When NMPC is compared to a proportional selective pinning control strategy, there is a trade-off between accuracy and control action when 100-node networks are considered. Accurate NMPC simulations use more control action, whilst inaccurate proportional selective simulations use less control action.

- The NMPC control strategy could not be tested for networks greater than $N = 100$ due to the computational time complexity of the problem and the available computing hardware.

- A selective pinning control scheme applied within a proportional feedback control loop uses on average about 51.3% less control action when compared to a random pinning scheme medicating all nodes.

Control of budget as measured in QALYs:

- It is possible to control networks according to a reference budget, measured in QALYs.

- After characterisation of a network according to input control reference and output budget, suitable reference signals for budget control could be established. Not all networks are capable of reaching all predetermined QALY levels due to inherent structure and the nature of the infection process.

9.3 RESULTS OF THE HYPOTHESIS TESTS

9.3.1 Result of Hypothesis 1: Selective pinning significance

Hypothesis 1 consisted of the following statements:

> H_0: Control of specific nodes in a network (selective pinning control) is not using significantly less control action, on average, than pinning all infected nodes in order to achieve the same average maximum epidemic level, with a p value of less than 0.01.
>
> H_A: Control of specific nodes in a network (selective pinning control) is using significantly less control action, on average, than pinning all infected nodes in order to achieve the same average maximum epidemic level, with a p value of less than 0.01.

Result: The distribution of doses attributed to selective pinning control is taken from a different sampling population than that of random pinning control, as shown by the Kolmogorov-Smirnov (KS) test with a p value of less than 2×10^{-16}. The Mann-Whitney U-test indicated that the median applied doses difference of 51.3% less doses using the selective pinning strategy compared to the random pinning strategy was significant with a p value of less than 2×10^{16}. For this reason, H_0 is rejected.

9.3.2 Result of Hypothesis 2: Optimal pinning control significance

Hypothesis 2 consisted of the following statements:

> H_0: Control of specific nodes using optimal control techniques (NMPC) is not significantly more accurate to using conventional proportional feedback control techniques to achieve the same average maximum reference epidemic levels, with a p value of less than 0.01.
>
> H_A: Control of specific nodes using optimal control techniques (NMPC), provides a significant improvement in accuracy over conventional proportional feedback control techniques to achieve the same average maximum reference epidemic levels, with a p value of less than 0.01.

Result: The use of NMPC was shown to be 6.25% more accurate in achieving the reference average maximum epidemic levels in 100-node networks, compared to conventional selective proportional feedback techniques. The distribution of doses showed that the strategies differed significantly (Wilcoxon Rank sum test), with a p value of less than 1×10^{-6}. Note that the NMPC control strategy used a median of 69.5% more doses to reach the improvement in accuracy shown, compared to the selective proportional feedback strategy. For this reason, H_0 is rejected.

9.3.3 Result of Hypothesis 3: Budget control significance

Hypothesis 3 consisted of the following statements:

> H_0: The intervention budget, measured in QALY, cannot be specifically controlled in a complex static network, using pinning of selective nodes.
>
> H_A: The intervention budget, measured in QALY, can be controlled to specific reference levels in a complex static network.

Result: It was shown that budget, as measured in QALY, can be controlled to within an average maximum steady-state error of 6.4%. This value is statistically significant with a p value of less than 0.01. The result was obtained as the average of 250 networks per budget reference level, for references of 74, 78, 82 and 86 QALY. For this reason, H_0 is rejected.

9.4 ANSWERS TO THE RESEARCH QUESTIONS

Answers to the research questions

After the research performed in this thesis, the following **answers** can be provided to the research questions in Section 1.1:

1. Q: Could the control action (application of doses of medicine) be less or more optimal on such networks, while still providing the same outcomes?
   A: It was shown in this thesis that, considering networks over several years, the control action can be made significantly less by focusing on the highest-risk individuals.

2. Q: Could limited resources or eventual impact be defined as an input to the planned control action, and the system be driven to the desired steady-state? **A: Disease networks of the type researched in this thesis can be controlled to the maximum average incidence of the epidemic. The networks can also be controlled to the budget applied to reach a particular incidence. Simultaneous control of budget and incidence is only possible under certain circumstances.**

3. Q: Could a multi-disciplinary approach with a primary focus on control systems provide feasible solutions to this problem?
   A: A multi-disciplinary approach involving mainly control systems applied to complex networks and epidemiological outcomes can be successfully applied to provide solutions to the problem.

4. Q: Could public health specialists or funders use the researched information to supplement decision-making for interventions?
   A: Public health specialists and funders may use the proposed methodology to configure many particular network settings, and obtain simulated answers.

9.5 FURTHER WORK

The methodology proposed in this thesis for analysis of disease networks may be implemented with great variation and extension in order to address particular problems. Because this is the case, future work may include:

- Different network topologies, such as scale-free networks, may be compared to another and inference on the structure's effect on disease outcomes provided.
- The node model may be adjusted to incorporate any disease for which a feasible immune-response model can be provided. Possible diseases for immediate next study would be: EBOLA, tuberculosis, Hepatitis-B virus (HBV) and measles.
- The nodes may be given unique parameters. If enough data is available on CD4+ T-cell counts and viral loads, parameters can be estimated for each node and completely heterogenous networks simulated and analysed.
- If a suitable model for disease co-infections can be obtained and verified, the effect of co-infected individuals in network settings could be analysed.
- The impact of pinning control may be assessed on real-world network structures if this information can be obtained. One example is the availability of anonymous sexual-contact data from an island in the Malawi Lake. Because this type of network stays more or less static, a suitable network structure may be constructed and researched.
- The NMPC control strategy should be tested on networks from $N = 100$ to $N = 10000$. For this to be feasible, suitable computing hardware should be available.
- Over and above the proportional feedback and NMPC controllers used in this work, several other control configurations may be applied. The use of feed-forward control and the extension of the proportional controller to include integral and derivative action may be considered initially.
- The cost function may be adapted to target a different set of priorities. Other priorities may include minimising the viral load in each individual or adding a time factor within which medicine should be applied.

- The pharmacokinetics of the intervention may be adapted. Multiple drugs, as briefly discussed in Section 6.3.1.6 may be considered. The use of multiple stages or regimens of drugs is in line with current public health practices and would be a reasonable next portion of research to perform.

- A study could be done to ascertain the control effort needed to provide medicine to the largest number of nodes it would take to barely avert an epidemic. If the priorities of the users of this study are that medicine should be provided to as many persons as possible, but only so far as to avoid an epidemic, control could be done on β_c, the critical transmissibility.

- Epidemiological studies of population-based models could be used to calibrate network models and estimate network-model parameters. At least one such a study should be attempted.

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APPENDIX A

CONTROL SYSTEM PARAMETERS

Table A.1: Summary of all control system parameters used in this thesis.

Parm.	Description	Value / Range	Source
I_{ref}	Reference HIV incidence	[0.2, 0.3, 0.4, 0.5]	–
Q_{ref}	Reference QALYs	[74, ..., 86]	–
I_k	HIV incidence at time k	$0 - 100\%$	–
Q_k	QALYs at time k	$0 - 100$	–
$\hat{\beta}_{ref}$	Bond-percolation reference estimate of the average transmissibility	$0 - 1$	–
u_k^*	NMPC controller optimal output obtained from optimiser	$0 - 100\%$	–
$\hat{u}_k$	Estimated optimal output from optimiser for step k	$0 - 100\%$	–
w_u	Cost function weight for the control output	10e+5	–
w_x	Cost function weight for the disease incidence state	10e+5	–
w_q	Cost function weight for the budget	10e+5	–
J_w	Cost function output	–	–

APPENDIX B

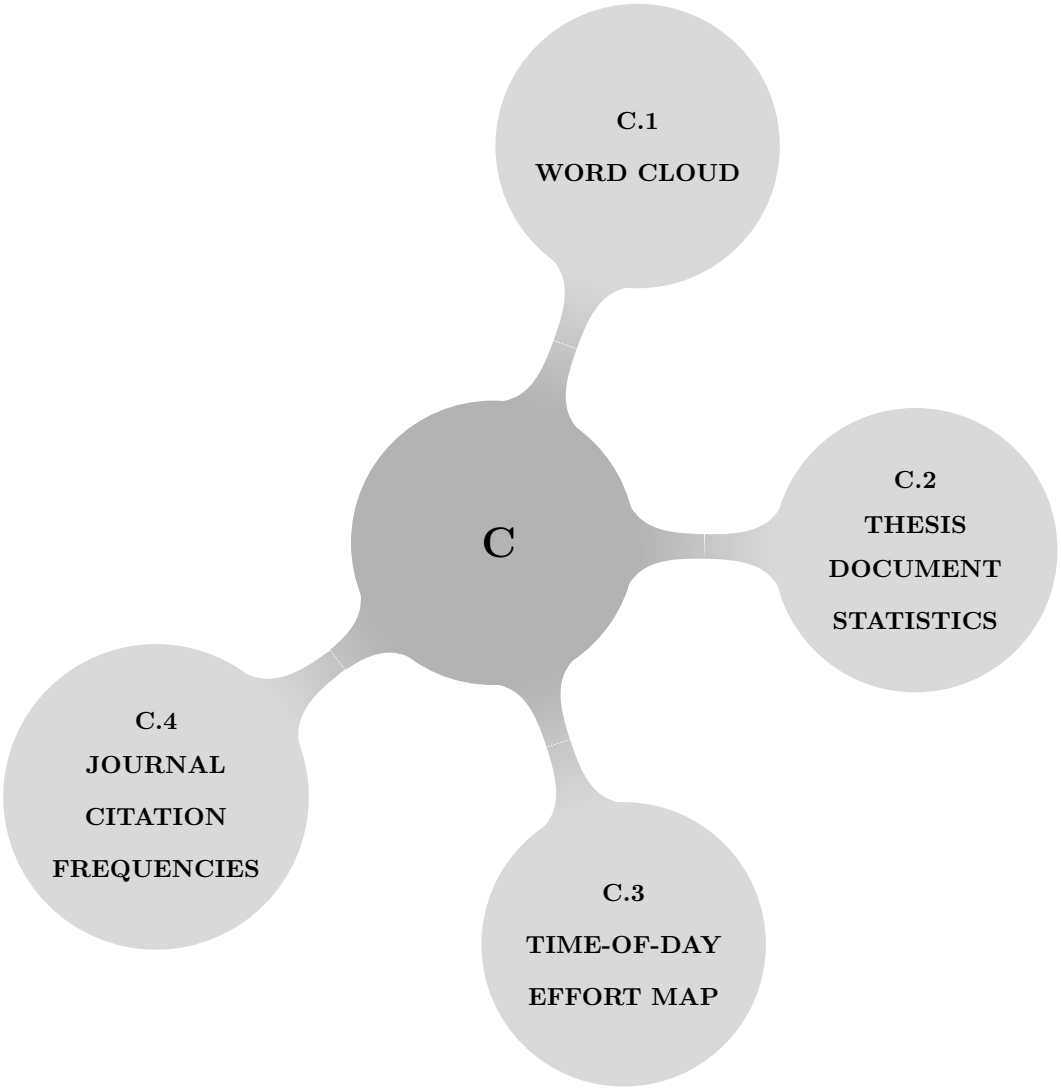
SOFTWARE TOOLS

Table B.1: Summary of the software tools used in this thesis.

No.	Description	Source
1	**Matlab R2014a** : Mac version	http://Mathworks.com/
2	**Matlab Complex Networks Package** : Toolbox for analysis of complex networks in Matlab.	Dr. Lev Muchnik, Hebrew University of Jerusalem, E-mail address: (levmuchnik@gmail.com)
3	**Homophily** : C++ software for large-scale networks simulation. The software was heavily modified by the author of this thesis to run and integrate node models, implement a variety of controllers and run NMPC algorithms.	Dr. Lev Muchnik, Hebrew University of Jerusalem, E-mail address: (levmuchnik@gmail.com)
4	**YANE Nonlinear MPC** : C++ software library that implements a variety of NMPC algorithms and controllers.	Prof. Dr. Jürgen Pannek, University of Bremen, E-mail address: (pan@biba.uni-bremen.de)
5	**BOOST Library** : C++ software library for numerical integration.	http://www.boost.org/
6	**R** : Open-source statistical analysis tool (The R Project for Statistical Computing)	http://www.r-project.org/
7	**Omnigraffle for Mac** : Diagrams in this thesis were drawn using Omnigraffle	http://www.omnigraffle.com

APPENDIX C

THESIS ANALYTICS



C.1 WORD CLOUD

Figure C.1: A word cloud graph of the frequency distribution of words in this thesis. Higher frequencies are indicated by darker, larger words.

C.2 THESIS DOCUMENT STATISTICS

Table C.1: Summary statistics of this thesis document.

Statistic	Value
Pages	146
Words	29431
Figures	30
Tables	18
Equations	61
References	192

C.3 TIME-OF-DAY EFFORT MAP

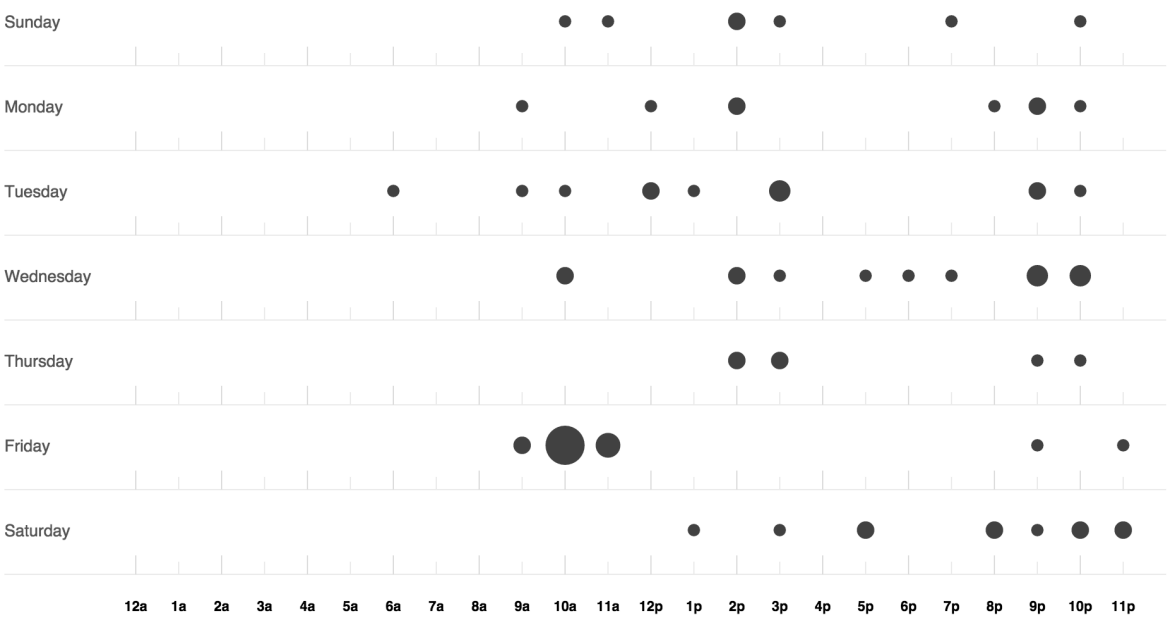


Figure C.2: An effort map indicating which days of the week and which hours of the day were spent working on this thesis. Larger dots indicate higher frequencies of time spent in a particular slot.

C.4 JOURNAL CITATION FREQUENCIES

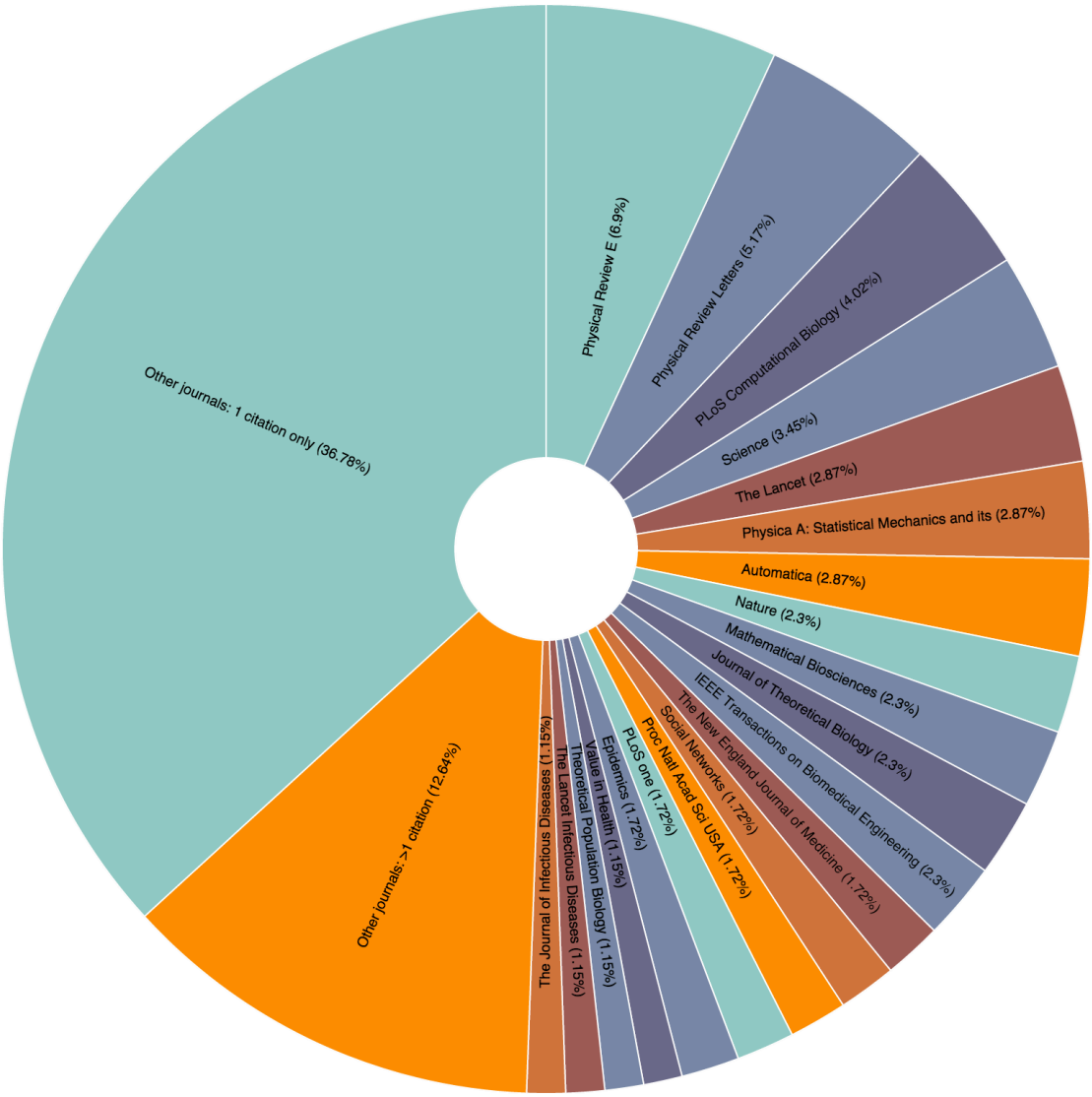


Figure C.3: A doughnut chart indicating the frequencies of citation for the referenced journals in this thesis. The most-cited journal is *Physical Review E*.

Table C.2: Summary statistics of the citations in this thesis.

Statistic	Value
Total citations	191
Total journal citations	174
Journals cited once	64
Citations in top 20 most cited journals	88

APPENDIX D

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