Model-based approaches to decision making in healthcare delivery

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Abstract

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Abstract

Healthcare systems worldwide face escalating pressures from aging populations, advancements in pharmaceuticals and technologies, strained services, and economic constraints. Hence, robust decision-making processes are imperative to maximise population health. Mathematical modelling has proven to be a valuable tool for addressing such healthcare challenges. Recent experiences, exemplified by the COVID-19 pandemic, have demonstrated the effectiveness of mathematical modelling in decision-making in healthcare delivery.

This thesis contributes to the advancement of model-based decision-making in healthcare with a focus on practical applicability. It leverages two healthcare domains, colorectal cancer screening and the blood supply chain, to illustrate the benefit of model-based approaches in improving cost-effectiveness and resource utilisation in public healthcare delivery. One avenue for informed decision-making aimed at achieving an equitable, efficient, and high-quality healthcare system is health technology assessment; a process that employs analytical methods to evaluate the value of healthcare technologies or interventions throughout their life cycle. In this thesis, the long-term evaluation of appropriate modal of colorectal cancer screening practices and resource allocation is considered through cost-effectiveness analyses.

Second, given that healthcare systems are inherently fraught with uncertainty, there exists a necessity for day-to-day decisions that remain robust in the face of the unknown. This thesis employs mathematical optimisation models to address decision-making under uncertainty, particularly within the management of blood inventories. Optimisation entails the selection of the decision alternatives to maximise a specified objective. Stochastic programming is utilised to incorporate uncertain blood demand into models that define optimal blood inventory policies. Optimisation is a powerful tool when decisions made today must remain valid into the future.

In conclusion, this thesis underscores the role of model-based approaches in healthcare decision-making. By applying these approaches in the contexts of colorectal cancer screening and the blood supply chain, this research contributes to enhancing the efficiency, cost-effectiveness, and overall quality of public healthcare delivery.

Keywords optimisation, stochastic programming, health economics, decision support


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My doctoral journey has not been smooth, there have been bumps, changes of direction, and potholes along the way, but when I separate those challenging experiences from the people I’ve had the honour of working alongside and getting to know over these years, I can’t help but smile and be grateful. And that is the feeling I would like to concentrate on and take forward into my post-doctoral life. Therefore, I’d like to offer my sincere and utter gratitude to all of the following people, without you there to guide and support me who knows where I’d be.

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My research career began in Melbourne when I was offered the opportunity to work at the Melbourne University School of Population and Global Health. Little did I know the impact this job would have on my life and career. Working at the University of Melbourne broadened my interests and knowledge, and I could finally say I worked at a place where I felt at home. I have no doubt this feeling of home was due to the diversity of people and skills in the department. So I would like offer my unending gratitude to Professor Mark Jenkins, Doctor Louisa Flander, and Doctor Driss Ait Ouakrim. I am truly honoured to be your colleague. On a separate note, I would like to thank Louisa for agreeing to be my thesis advisor.
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Next I would like to thank my co-authors. I had the pleasure of working with Professor Babak Abbasi on my first published paper, which began my work in the blood supply chain. Thank you Babak for giving me the opportunity to work with you and instilling your knowledge of the subject to me. This knowledge set me up to pursue research ideas within the blood supply chain and led me to supervising Ilmari Vauhkonen’s bachelor thesis on platelet inventories. The thesis was such a success that we ran with the idea and contacted Doctor Jarkko Ihalainen (MD) and Doctor Mikko Arvas from the Finnish Red Cross Blood Service to partner with. This collaboration resulted in a paper in this thesis, of which I am very proud. Therefore, I would like to thank Ilmari, Jarkko and Mikko for their contributions to this thesis. I’ve truly enjoyed working with you. The other subject in this thesis is cancer screening and I would like to thank all my co-authors in Australia for their expertise on this subject. In particular, I would like to thank Doctor Daniel Buchanan, Mark, Louisa and Driss. Finally, I would like to thank my co-authors Doctor Maija Jäntti and Doctor Sirpa Heinävaara from the Finnish Cancer Registry and my colleague Doctor Lauri Neuvonen. Although our paper didn’t make it into my thesis, I want to thank you for all the work we have done together during my doctorate. Lauri, it has been a pleasure working with you over these years, your forever optimism has been a light in the dark. I am extremely grateful to be able to call you a friend.

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Living in a country that isn’t your home country has it’s challenges, but the hardest is most definitely living thousands of kilometers away from
your family. I was reminded of this in the pandemic when the choice to see my family in person was not available for long periods of time. It was an isolating and difficult time for many, me included. I think I spent well over a year of my doctoral studies alone in my home office. I would not of been able to get through that without the love and support of my family. My sister, Amy, I cannot thank you enough, you are my confidante and never let me wriggle out of talking about the hard stuff. I love you. My mum, Barbara, thank you for all the long rambling messages that fill me in with the many many things going on back home. Because of these, when I visit I still feel a big part of your day-to-day life, and that means home is still home even after all these years away. My dad, Richard, I want to thank you for all the support over these years. I knew that I always had you there if I needed, and your at least weekly check in messages have been and continue to be a comfort for which I am extremely grateful. I also have to say how proud I am of you. Every time you come for a visit I see the excitement in you, you fit Finland and Finland fits you. It makes me so happy I was able to give you this. And finally to my family in Brazil. Muito obrigada por tudo. Eu adoro visitar vocês no Brasil e posso sentir seus amor e suporte todos os dias. Amy and Jon, mum and dad, sogra, Henrique, and Arthur, I love you all very much.

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This doctoral thesis consists of a summary and the following publications, which are referred to in the text by their Roman numerals.


Author’s Contribution

Publication I: “Family history-based colorectal cancer screening in Australia: A modelling study of the costs, benefits, and harms of different participation scenarios”

Dillon is the primary author. Ait Ouakrim, Jenkins, and Flander proposed the research topic. Dillon extended the model from Ait Ouakrim. Dillon and Ait Ouakrim performed the numerical analysis and analysed the results. Dillon and Ait Ouakrim wrote the paper under the guidance of Flander and Jenkins with expert discussions and comments from Buchanan, Macrae, Emery, Winship, Boussioutas, Giles, and Hopper.

Publication II: “Planning for the next pandemic: The Finnish colorectal cancer screening programme”

Dillon is the sole author. Dillon proposed the research topic, implemented the model, performed the numerical analysis, and analysed the results. Dillon wrote the paper.

Publication III: “A two-stage stochastic programming model for inventory management in the blood supply chain”

Dillon is the primary author. Abbasi and Oliveira proposed the research topic. Dillon worked on the problem formulation with the help of Oliveira and Abbasi. Dillon and Oliveira formulated the mathematical model. Dillon implemented the model, performed the analysis, and analysed the results for the case study. Dillon and Oliveira wrote the paper with comments from Abbasi. Oliveira and Abbasi helped Dillon in editing and revising the manuscript.
Publication IV: “Supporting platelet inventory management decisions: What is the effect of extending platelets’ shelf life”

Dillon is the primary author. Dillon and Oliveira proposed the research topic. Arvas and Ihalainen provided the data and ongoing expertise. Vauhkonen implemented the model. Dillon analysed the results. Oliveira wrote Section 4, and Dillon wrote the remaining sections of the paper under the guidance of Vilkkumaa with comments from Arvas and Ihalainen.
Abbreviations

2SSP  Two-Stage Stochastic Programming
CBA  Cost-benefit analysis
CEA  Cost-effectiveness analysis
CRC  Colorectal cancer
CUA  Cost-utility analysis
DALY  Disability-adjusted life year
EUT  Expected utility theory
HTA  Health technology assessment
HRQoL  Health-related quality of life
ICER  Incremental cost effectiveness ratio
MCDA  Multi-criteria decision analysis
MILP  Mixed-integer linear programming
MOO  Multi-objective optimisation
PT  Prospect theory
QALY  Quality-adjusted life year
1. Introduction

1.1 Background

Mathematical modelling of public health problems is not a new concept, despite the increased media attention during the COVID-19 pandemic. In fact, from as far back as the 1700s mathematical models have been applied to health problems. For example, in 1760, Daniel Bernoulli created a mathematical model of the spread of smallpox to evaluate the effectiveness of vaccination [8].

Mathematical modelling approaches lend themselves well to healthcare problems as many aspects of healthcare systems are quantitative [51]. This has been evident in recent years with the COVID-19 pandemic, where mathematical modelling has been used, for example, to predict infection spread and trends, explore intervention scenarios, and estimate resource needs [4, 32, 1]. In general, resources in health systems are limited, however, access to quality health services is an inclusive human right [48], thus the appropriate use of such resources is paramount. Additionally, ageing populations, rapidly emerging pharmaceuticals and technologies, strained services (that have worsened because of the pandemic, e.g., mental health services [17]), and economic issues, are all pressures facing current healthcare systems worldwide. Robust decision-making is essential in ensuring the right decisions are made at the right time to maximise the health of a population.

One area that is increasingly used to inform decision-making in order to promote an equitable, efficient, and high-quality health system is health technology assessment (HTA). HTA is a multidisciplinary process that uses explicit methods to determine the value of a health technology or intervention at different points in its lifecycle [39]. HTA typically includes an assessment of short-term affordability and long-term value for money by employing model-based approaches. Within the short-term assessment, budget impact models are utilised to estimate the likely change in expen-
diture resulting from a new healthcare decision. Within the long-term assessment, the effectiveness of the decision is included by the use of methods such as cost-effectiveness and cost-benefit modelling, comparative clinical effectiveness, and contextual considerations [24]. However, these modelling approaches are not the only way to support decision-making in healthcare. Outside of the HTA field, a variety of modelling methods have been and are being developed. Notably, methods within the discipline of decision-making under uncertainty.

In healthcare, uncertainty is ingrained, whereby, healthcare systems must provide reliable policy and day-to-day decisions that are robust to the unknown. For example, a hospital must have a good estimation of the demand in each department to allocate the appropriate staffing levels and other resources to adequately and equitably care for all patients. Mathematical optimisation model-based approach to decision making under uncertainty utilised in this thesis. Optimisation involves selecting the “best” alternative in regards to a specified objective. Uncertainty can be incorporated into the optimisation model via, for example, parametric uncertainty (the unknown demand in the hospital example above) or structural uncertainty (whether the mathematical structure of a model accurately represents the problem). Optimisation is a useful tool when critical decisions that need to be made in the present maintain their validity in the future.

Model-based approaches to healthcare problems, such as HTA methods and mathematical optimisation, can increase the transparency in the decision-making process and provide justifiable policy recommendations in situations of uncertainty.

1.2 Thesis Scope

This thesis furthers the development of model-based approaches to decision-making in healthcare. Papers in this thesis place particular emphasis on practical applicability. Two healthcare areas, colorectal cancer screening and the blood supply chain, are utilised to demonstrate the application of the chosen modelling approaches in aiding improved cost-effectiveness and resource use in public healthcare delivery.

Despite the distinct and obvious differences between colorectal cancer screening and the blood supply chain, four common themes are identified from the papers in this thesis, depicted in Figure 1.1.
Papers I and II focus on colorectal cancer screening, the economic and health evaluation of inappropriate screening practices, and the impact of resource utilisation. Colorectal cancer is the third most common cancer and the second most deadly cancer worldwide. The International Agency for Research on Cancer predicts that the burden of colorectal cancer will increase by 56% and the number of attributed deaths will increase by 69% between 2020 and 2040, equating to more than 3 million new cases and 1.6 million deaths globally per year [25]. The long lag time (from several years to a decade) between benign small adenoma and carcinoma [45], makes screening for colorectal cancer a crucial method to reduce incidence and mortality due to the disease. Many countries have implemented national bowel screening programmes for early detection and prevention of the disease. Such programmes require many resources from medical and logistical to funding, which need to be utilised to maximise the health of the targeted population. Papers I and II employ model-based approaches to assess and refine colorectal cancer screening policies.

Papers III and IV focus on resource utilisation and economic analyses in the blood supply chain. The blood supply chain is an essential part of any healthcare system, furthermore, effective management of blood product inventories within the chain is vital. Similar to managing other perishable inventories, managing blood products involves balancing storage and wastage based on demand needs. However, unlike other perishable inventories, blood products have an associated societal cost as they are donated by individuals within the population. In England, the National Health Service Blood and Transplant Service require around 400 new donors a day to meet demand and around 135,000 new donors a year to replace those who can no longer donate [34]. With the need for donors so...
high, one can imagine the deleterious impact on donors and recipients if the blood supply chain was interrupted due to inefficient inventory management. The importance of effective inventory control throughout the supply chain cannot be overstated. Papers III and IV employ methods from mathematical optimisation to define inventory policies to maximise resource utilisation while minimising operational costs.

1.3 Thesis Structure

The thesis is structured as follows. Section 2 presents the methodological foundations of the two disciplines applied in this thesis, with the intention of providing the reader with a basic understanding of the methods used. Section 3 describes the contribution of each paper, including research objectives and setting, main results, and key takeaways. The final section is a discussion on conclusions and implication, highlighting possible areas for future developments. The four research papers that make up the contributions to the literature follow.
2. Foundations

The papers in this thesis utilise two theoretical disciplines that aid healthcare delivery decision-makers: (i) health economic evaluation and (ii) mathematical optimisation, in particular stochastic programming. Health economic evaluation is well-established in the literature and in practice, and as such is applied in Papers I and II. Stochastic programming in contrast, although not a new discipline, is still emerging in the context of healthcare, especially in the areas covered in this thesis. Papers III and IV advance state-of-the-art stochastic programming approaches in the healthcare context by presenting new models and algorithms to real-world applications.

2.1 Health economic evaluation

Health economic evaluation involves the comparison of costs and health outcomes of alternative interventions such as pharmaceutical medications, technologies, and public health strategies. Health economic evaluations are often used in HTA and can assess a health intervention’s value for money and can support and improve decision-making in the allocation of the limited resources [50].

Cost-effectiveness analysis (CEA) [37], cost-utility analysis (CUA) [38], a specific type of CEA, and cost-benefit analysis (CBA) [18] are frequently applied in health economic evaluations. Each method evaluates the costs and effectiveness outcome (or health benefit) of two or more health intervention alternatives. Health benefits can be measured in a number of ways, such as clinical outcomes (as in CEA), monetary assigned values (as in CBA), or by health-related quality of life (as in CUA)\(^1\). Clinical outcomes could include, e.g., the number of true positive cancer cases detected or the number of life years gained by a given intervention. Monetary benefits can be assigned by a willingness to pay of a given intervention for a stated im-

\(^{1}\text{Note that CUA is sometimes referred to as CEA in literature (and in the papers in this thesis) and thus can also include health-related quality of life outcomes.}
Foundations

improvement in health. Neither clinical or monetary measurements include information regarding the quality of life. This is where more generic health measurements that incorporate health-related quality of life (HRQoL) are beneficial.

HRQoL is the self-perceived well-being of an individual specifically associated with health dimensions, and can include, but is not limited to, physical pain, mobility, and psychological well-being. HRQoL is often quantified by assigning health utilities representing an individual’s quality of life in a given health state. Health utilities are bounded on a scale from 0, representing death, to 1, representing perfect health. In CUA, these utilities are typically aggregated over a period of time and expressed as quality-adjusted life years (QALYs) that weigh the duration of time by health utilities. For example, one QALY can equate to one year in perfect health \((1 \text{ year } \times 1 \text{ utility } = 1 \text{ QALY})\) or two years with a health utility of 0.5 \((2 \text{ years } \times 0.5 \text{ utility } = 1 \text{ QALY})\). Other measurements of HRQoL include disability-adjusted life years (DALYs) that are based on the burden of disease in a population and expressed by the number of years lost due to ill health, disability or early death, so one DALY is equal to one year of healthy life lost.

The cost, utility, and health benefits of alternative interventions depend on decisions related to each intervention (e.g., decisions in a screening pathway, such as what test to use) and various chance events (e.g., disease progression, and adverse events from testing choice). By and large, decision analysis models are the foundations of many health economic evaluations, with Markov models frequently employed in CEA and CUA due to their ability to model complex disease progression and intervention pathways. Markov models can represent and analyse stochastic processes over time, making them well-suited to model, for example, cancer progression. A Markov model comprises a finite set of mutually exclusive states with transitional probabilities that permit movement between states over a given time period (known as a cycle). Figure 2.1 illustrates a simple Markov model with four health states and arrows (or arcs) depicting allowable transitions. There are three classifications of Markov states: transient, recurrent, and absorbing. In Figure 2.1, the ‘Well’ state is transient as there exists a way to leave the state and not return, the ‘Sick’ and ‘Recovered’ states are recurrent as an individual can both exit and return to the states, and the ‘Dead’ state is absorbing as once entered an individual cannot exit. Costs and utilities are assigned to the states and transitions in the model allowing for the estimation of long-term costs and effects when the model is run for a large number of cycles. Due to this, Markov models are

\(^2\)However, it can be argued, as health utilities are an individual’s preference between health states, that for some there are health states worse than death. It is also worth noting that perfect health is exactly that, meaning better than day-to-day health and by definition some may never experience it, but it cannot be exceeded.
particularly suited to the calculation of quality-adjusted life years (QALYs) [13].

![Markov state transition diagram]

**Figure 2.1.** Markov state transition diagram

Patient-level simulation (or microsimulation) can be used in conjunction with Markov models when memory and consequently many states are inherent to the model due to the need to circumvent the Markovian property [21]. A stochastic simulation method, often Monte Carlo sampling, moves individuals through the Markov model creating individual pathways. These pathways accumulate the individual’s history, including costs and HRQoL utilities. The procedure is repeated a large number of times, e.g., 100,000, and the sample mean of the costs and utilities present estimates for the expected costs and effectiveness associated with the modelled intervention. Based on the Law of Large Numbers, these expected values can be viewed as best estimates; the sample mean approaches the true expected value as the number of simulation runs increases. The two main disadvantages of patient-level simulation are (i) the computational burden of simulating a large number of individuals to obtain the best estimates of expected costs and effects and (ii) the high level of demand for data inputs.

A common and easy-to-interpret method of presenting health economic analysis results is the cost-effectiveness plane. This is a graphical interpretation of the results in which the costs (y-axis) are plotted against the effects/QALYs (x-axis). The incremental costs and effects between the alternative interventions are used to inform the incremental cost-effectiveness ratio (ICER). The ICER states the additional costs needed to result in one additional unit of effect (e.g., QALY) for each alternative. Incremental cost-effectiveness analysis implies that alternatives are not analysed in isolation but in comparison [16]. When analysing ICERs, two important concepts from the field of decision analysis arise: dominance and extended dominance. An intervention alternative is dominated if it is more costly and less effective than another. Extended dominance occurs when the ICER of one alternative is larger than the ICER of a more effective alter-
Figure 2.2. Reproduced from [21] with permission from copyright holders: Cost-effectiveness plane illustrating dominance and extended dominance between five mutually exclusive intervention alternatives.

native. By plotting all the non-dominated intervention alternatives on the cost-effectiveness plane, the efficiency frontier can be seen (Figure 2.2 reproduced with permission from [21], Fig. 2.4, page 16). However, it has been noted that the cost-effectiveness plane cannot represent correlation between alternatives and has limited use in representing uncertainty associated with the cost-effectiveness of an intervention alternative [6]. A willingness-to-pay threshold, a monetary threshold that decision-makers are willing to pay for an additional unit of effect, can also be drawn onto the cost-effectiveness plane. The ICER and its graphical representations are simplified decision rules that can aid policy recommendations. For example, the National Institute for Health and Care Excellence in England uses a willingness-to-pay threshold of £20,000 -£30,000 [35]. Not all HTA agencies use a threshold as a decision criterion, but most still require an ICER to be a part of the cost-effectiveness analyses submitted to them. The Finnish Medicines Agency for in-hospital drugs, FIMEA, is one such example.

2.2 Mathematical optimisation

This section will explore the basic ideas of mathematical optimisation and methods used in Papers III and IV.
Mathematical optimisation involves determining the optimal decision variables that maximise (minimise) an objective function subject to a defined set of constraints. There exist two main disciplines within optimisation: linear and nonlinear optimisation. This thesis concentrates on a linear form of optimisation, specifically mixed-integer linear programming (MILP). A representation of a MILP problem is presented in Equation 2.1.

\[
\text{maximise } z = c^\top x \\
\text{subject to } Ax = b \\
x \geq 0,
\]

where \( z \) is the linear objective function, with \( c \) as a vector of the objective function coefficients and \( x \) the vector of decision variables, being either integer or continuous. \( Ax = b \) and \( x \geq 0 \) are the constraints, in which matrix \( A \) and vector \( b \) represent known data from the problem. The overall aim is to identify the decision variable values \( (x) \) that maximise the linear objective function value \( (z) \) within the feasible region defined by the constraints. Please refer to [10] for a comprehensive introduction to linear optimisation.

The practical use of optimisation started in 1947 with the invention of the Simplex method to solve linear optimisation problems. Simply put the Simplex algorithm is as follows: The algorithm starts at an arbitrary vertex of the feasible region, then at every iteration, the algorithm moves to a neighbouring vertex with a better objective function value and terminates when no improving move can be made. During the first few decades, using the Simplex method enabled problems with tens of constraints and variables to be solved in single-digit hours. These problem sizes are regarded as small, limiting their applicability to real-world problems. Additionally, the Simplex algorithm is based on the fact that the feasible region of a linear optimisation problem (as in Equation 2.1) is convex. However, when modelling real-world problems, it is likely that some of the variables must be integer. The inclusion of integer variables increases the complexity of the problem as the feasible region is no longer convex. This led to the need for other solution algorithms that are efficient in solving mixed-integer problems.

Today, optimisation problems with millions of constraints and mixed-integer variables can be solved in seconds and minutes. This computational speedup is due to the advances in optimisation solvers such as CPLEX and Gurobi that employ a variety of solution algorithms (including the Simplex method), and to the improvement in computer hardware. It is estimated that the speedup is over 2 trillion times that of the early 1990s [9]. With the current computational power, large-scale optimisation problems can be used to model realistic problems and aid decision-makers within a
reasonable time. This has opened up the areas in which optimisation is applied, with healthcare as one of them.

Linear optimisation is extremely well-suited to areas such as resource planning, scheduling, inventory control, and systems design. In healthcare, there is a growing recognition of the applicability of optimisation methods in aiding decision-makers [19], with the use of resource constraints in public health and HTA modelling coming into focus [49]. In recent years optimisation has been applied to areas such as home health care [22], vaccine supply chains [46], and controlling infectious disease [44]. Noorain et al. (2022) provide an overview of optimisation literature in healthcare [36].

When modelling real-world problems such as scheduling appointments that may vary in length, it is vital that uncertainties are captured within the model as it is seldom, if ever, that everything in life is certain. In optimisation, there are a number of methods to include uncertainty in a model, for example, robust optimisation, and stochastic programming. Robust optimisation is a methodology for handling optimisation problems with uncertain data [7], it seeks to identify solutions that remain feasible to a measure of robustness against the uncertainty (see [7] for detailed explanation). Stochastic programming is a framework that includes uncertainty in optimisation problems [47] (see [11] for further details). The key difference between these two methodologies is that in stochastic programming the uncertainty is assumed to be random with the distribution at least partially known [7]. This thesis concentrates on stochastic programming, in particular, two-stage stochastic programming.

A stochastic program is an optimisation problem in which some or all problem parameters are uncertain. The overall aim of stochastic programming is to determine the decision variable values that optimise the objective function value while accounting for the uncertainty of the problem parameters. The uncertainty (or stochasticity) is represented as a random variable of either a known or well-estimated probability distribution or a given data set. Each random variable is typically represented as a set of possible scenarios of the uncertain event, for example, the demand for ICU beds on a given day is the random variable, with a realised bed occupancy being one scenario. The larger the scenario set, the better the representation of uncertainty within the model, as by the Law of Large Numbers the more scenarios used, the closer the average results are to the expected value. Two-stage stochastic programming (2SSP) models include a first-stage optimisation problem that must be solved before the uncertainty has occurred and a second-stage problem that is solved after the uncertainty has become apparent. The aim is to make first-stage decisions that, on average, perform well across all uncertainty scenarios in the second stage. A standard form of a 2SSP is presented in Equation 2.2 below.
Foundations

maximise \[ z = c^\top x + \mathbb{E}_\xi \mathcal{Q}(x, \xi) \]  \hspace{1cm} (2.2)

subject to \[ Ax = b \]
\[ x \geq 0. \]

In the above formulation, the objective function \((z)\) is split into two stages. The first stage is the same as the MILP standard form objective function (cf. Equation 2.1). The second stage represents the expected objective function value over all uncertainty scenarios. Specifically, \(c^\top x\), as in Equation 2.1, is the first-stage problem objective and \(\mathbb{E}_\xi \mathcal{Q}(x, \xi) = \max\{q^\top_\xi y_\xi | W_\xi y_\xi = h_\xi - T_\xi x, y_\xi \geq 0\}\) is the second-stage objective, in which the uncertainty is represented by scenarios \(\xi\). First-stage decision variables are \(x\) as in Equation 2.1 and the second-stage decision variables are represented by \(y\). Scenario-dependent (second-stage) objective function coefficients are represented by \(q^\top_\xi\), whereas the scenario-dependent constraint coefficients are shown by \(W_\xi, h^\top_\xi\) and \(T_\xi\).
3. Contributions of the Thesis

This thesis aims, with the use of model-based approaches, to aid decision-makers in making informed decisions to improve effectiveness and resource use in public health care delivery. As described in Section 2, two disciplines were chosen as the foundations upon which the health delivery problems were modelled. Papers I and II focus on colorectal cancer screening from a health economics perspective. Paper I quantifies the costs, benefits and harms of appropriate and inappropriate screening practices based on family history. Paper II investigates the implications of amending the screening test positivity threshold for alternative resource capacities. Papers III and IV take a different approach; these employ optimisation for inventory management and optimal resource utilisation of the blood supply chain. Paper III advances the field of red blood cell inventory management by using two-stage stochastic programming, a method not previously used in the blood supply chain. Paper IV further extends this model with the formulation of platelet inventories, and introduces the use of an algorithm to generate recommendations for inventory management policies that are robust across a large number of platelet demand scenarios.

Table 3.1 summarises the research objectives, methods, results, and key policy takeaways of the four papers presented in this thesis.
<table>
<thead>
<tr>
<th>Paper</th>
<th>Research Objectives</th>
<th>Method</th>
<th>Results</th>
<th>Key Policy Takeaways</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>Investigate CRC screening practices in Australia and characterise based on national guidelines. Model the long-term health and economic impact of the identified screening practices and different participation scenarios for the defined CRC family history risk categories.</td>
<td>Markov tree model with Monte Carlo simulation</td>
<td>Screening participation was low across all family risk categories. A fully implemented screening programme, for average risk, is the most cost-effective approach to reduce CRC mortality. Higher adherence to screening guidelines is highly cost-effective for those at moderate risk.</td>
<td>Investing in policies to increase adherence to appropriate CRC screening will save lives and deliver high value for money.</td>
</tr>
<tr>
<td>II</td>
<td>Investigate the health and economic implications of FIT positivity thresholds on resource capacities in the Finnish CRC screening programme for the next pandemic.</td>
<td>Monte Carlo simulation</td>
<td>Confirm the current FIT threshold for Finnish males is optimal choice for males and females. Reducing the current threshold for females will be better in detecting CRC and adenomas.</td>
<td>Provide a maximum colonoscopy capacity for the fully rolled out screening programme. Policy recommendations for alternative colonoscopy capacities are provided.</td>
</tr>
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### III

**Develop an optimisation model to define target levels and periodic review policies considering demand uncertainty for blood inventories. Apply model to real-world setting to evaluate performance.**

For single blood experiments, reducing the target inventory level reduces the total costs, while keeping average expiry and unmet demand near zero. Setting the review period to one day acts as a bias towards minimising expiry.

It is possible to revise inventory control policies by reducing current target levels to diminish wastage and total costs without compromising the service level. It is cost minimising to use a compatible blood type to fulfil low and sporadic demand, however this may lead to increased risks associated with transfusion reactions.

### IV

**Develop a methodological framework for modelling platelet inventories, resulting in robust managerial recommendations regarding extending shelf lives. Ensure model tractability by exploiting the problem structure to decompose it.**

Extending the shelf life of platelets reduces the expiry, unmet demand, and total costs of national hospitals. And decreases the target level inventory for the central blood bank, while keeping expiry and unmet demand low. The decomposition algorithm allows all models to be solved within 45 minutes, whereas the deterministic model could not reach an optimality gap of less than 8% for one model within 28 hours.

The results can be used to optimise the Finnish platelet supply chain and inform future cost-effectiveness analyses regarding shelf life extension.

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<td>III</td>
<td>Develop an optimisation model to define target levels and periodic review policies considering demand uncertainty for blood inventories. Apply model to real-world setting to evaluate performance.</td>
<td>Two-stage stochastic programming</td>
<td>For single blood experiments, reducing the target inventory level reduces the total costs, while keeping average expiry and unmet demand near zero. Setting the review period to one day acts as a bias towards minimising expiry.</td>
<td>It is possible to revise inventory control policies by reducing current target levels to diminish wastage and total costs without compromising the service level. It is cost minimising to use a compatible blood type to fulfil low and sporadic demand, however this may lead to increased risks associated with transfusion reactions.</td>
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<tr>
<td>IV</td>
<td>Develop a methodological framework for modelling platelet inventories, resulting in robust managerial recommendations regarding extending shelf lives. Ensure model tractability by exploiting the problem structure to decompose it.</td>
<td>Two-stage stochastic programming with decomposition algorithm</td>
<td>Extending the shelf life of platelets reduces the expiry, unmet demand, and total costs of national hospitals. And decreases the target level inventory for the central blood bank, while keeping expiry and unmet demand low. The decomposition algorithm allows all models to be solved within 45 minutes, whereas the deterministic model could not reach an optimality gap of less than 8% for one model within 28 hours.</td>
<td>The results can be used to optimise the Finnish platelet supply chain and inform future cost-effectiveness analyses regarding shelf life extension.</td>
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**Table 3.1. Summary of Papers I-IV**
### 3.1 Paper I

The Australian colorectal cancer screening programme has been in effect since 2006. The programme aims to reduce morbidity and mortality by screening the eligible target population, aged between 50 and 74, for early detection or prevention of the disease. Despite this, Australia as a world region ranks high in global age-standardised colorectal cancer (CRC) incidence and mortality statistics [33]. Low participation in the programme and non-adherence to national screening guidelines may be reflected in these statistics. In the 2017 screening programme monitoring report, which was utilised in Paper I, only 39% of those invited to screen returned the completed screening test. Since then, participation has improved, but only slightly to 40.9% [5].

Based on the high incidence and low participation in CRC screening in Australia, we aimed in Paper I to investigate screening practices within and outside of the national programme. These practices were characterised based on the national family-history screening guidelines at the time. The long-term health and economic impacts were reported. From these, we recommended more sustained efforts from governments to improve adherence to the CRC national screening guidelines, thus positively impacting screening outcomes.

A Markov decision tree was employed as the model framework, enabling the representation of the adenoma-carcinoma pathway. Monte Carlo simulation allowed a hypothetical population of 100,000 individuals (representing the Australian target population) to progress through the mutually exclusive Markov health states. Australian data were applied to the model; these included participation rates in the national screening programme, participation in screening outside of the programme from the Australasian Colorectal Cancer Family Registry, estimated prevalence, incidence, and mortality due to CRC, and costs. Health utilities based on Australian data could not be obtained; therefore, values from international literature were used.

In 2017, Cancer Council Australia published the updated national guidelines for the prevention, early detection and management of CRC [14]. These revised guidelines included changes in screening approaches based on risk according to age and family history. Professor Mark Jenkins is lead author in the renewed guidelines on screening strategies along with co-authors Dr. Driss Ait Quakrim, Dr. Alex Boussiotas, Professor Jon Emery, Professor Finlay Macrae, Professor John Hopper, and three other co-authors [15]. These named authors are co-contributors in Paper I and thus had knowledge of the paper’s results prior to publication. The 2017 CRC screening guidelines align with Paper I in two key findings: (1) Paper I found that a fully implemented screening programme to be the most cost-effective approach in the general population. The 2017 guidelines validate
this finding in recommending all people of average risk for colorectal cancer to use the screening programme [26]. (2) Paper I presents that the vast majority of people under age 50 in the high-risk group were under-screening (with either no screening, a lower frequency, or using an occult blood test instead of a colonoscopy). The paper found that a programmatic approach to colonoscopy-based screening for the high-risk group may provide further benefits in cost-effectiveness. The 2017 guidelines increased the starting age and decreased the frequency of colonoscopy screening in the high-risk group [26].

### 3.2 Paper II

During my doctoral studies, a pandemic disrupted day-to-day life around the world. We saw remote working and teaching, businesses close and services interrupted, health systems overrun, and millions of infections and deaths. COVID-19 impacted us all in some way or another, and cancer screening was not exempt from that. During the first wave of the pandemic, in early- to mid-2020, CRC screening programmes faced various challenges that led to the suspension of screening in a number of countries, for example Northern Ireland, England, the Netherlands, Catalonia, and Canada, all of whom paused CRC screening in the initial phases of the COVID-19 response. Later analysis found a decrease in advanced neoplasia detection and an increase in later stages of CRC compared to expected detection without a pandemic [29, 52]. Notable reasons for programme suspension include disruptions in supply chains, reserving health system capacity for COVID patients, allowing facilities time to establish infection-control measures, and the redeployment of clinical staff to support the COVID-19 response. The colonoscopy (the gold standard test in detecting CRC) capacity within screening programmes was affected by many of these reasons, especially the redeployment of clinical staff.

Resilient programmes are those with planned resources in place to minimise programme disruption and, thus, clinical impact. Screening programmes and governments must have policy decisions in place to limit the effect of future epidemics and other large-scale disruptions. This is the context in which Paper II was developed.

Specifically, Paper II investigates the impact of screening test positivity thresholds on the number of colonoscopies performed within a screening programme. One round of the Finnish CRC screening programme is modelled using a decision tree structure and Monte Carlo simulation. Clinical results, including total detected and missed CRC, average costs per individual and average effectiveness (health utility) per individual, are reported, alongside the total number of colonoscopies performed. From the results, screening policy recommendations that mitigate the clinical
impact of reduced colonoscopy resources are presented. To the best of my knowledge, no studies at the time of writing Paper II addressed varying screening test positivity thresholds for mediating colonoscopy resources with respect to planning for the next pandemic.

3.3 Paper III

As mentioned in Section 1.2, the blood supply chain is essential in the delivery of healthcare. Without a well-functioning supply of blood we would be risking the lives of many in our populations, but, ensuring the high-functioning level required can be complex. The perishable nature of blood products and the uncertainty in their supply and demand are a few of the key complexities encompassed in the operation of the blood supply chain. All blood products, red and white blood cells, platelets, and plasma, have different lengths of shelf life in which they can be transfused to a patient in need. The perishability of blood products enforces a time constraint in which the supply chain must operate. Additionally, as blood products are donated (and thus it is the decision of the person when they will donate their blood) the supply on any given day cannot be fully known beforehand. Similarly, the demand for blood products in health centres is based upon the patients’ needs at that time, and also cannot be fully known in advance. It is clear that uncertainty is inherent in the blood supply chain. At the same time, there exists the almost conflicting requirement to minimise both unmet demand (i.e., too few blood products to satisfy demand) and blood wastage (i.e., too many blood products supplied that then outdate).

Paper III investigates this opposing problem setup with the use of a novel two-stage stochastic programming approach. Unlike other inventory products, blood products such as red blood cells are perishable items, with different blood compatibility groups, and service levels that must be met not to risk lives. These challenges together with the uncertainty in supply and demand add to the complexity of the problem. Stochastic programming is perfectly suited for addressing the needs of inventory management of the blood supply chain. The two-stage stochastic programming model proposed in Paper III defines optimal inventory control policies for red blood cells in a hospital setting while considering the uncertain nature of the demand, minimising operational costs, unit shortage due to unmet demand, and unit expiry due to overstocking. The defined inventory policies are classified as $(R, S)$, a classical policy that determines the periodicity of review ($R$) in which orders are placed to return the stock position to the target level ($S$).

Discrete scenario sets based on negative binomial distributions are used to represent the demand uncertainty in the model. The larger the scenario sets, the more robust to uncertainty the policies will be. However, large scenario sets lead to a heavy computational burden. Therefore, a trade-off
between uncertainty representation and computational load exists. The formulation of the model in Paper III allows for 100 scenarios of each blood group with every scenario representing daily demand for three months. The computational time of CPLEX to solve a single blood group model was approximately 15 to 20 minutes, a reasonable length of time for planning inventory operations. The sizes of these scenario sets are regarded as large compared to other sets published in the literature at the time [42, 43].

A case study of a single hospital is used to demonstrate the performance of the proposed approach and illustrate how the model could be employed as a decision-support tool for defining optimal inventory control policies for red blood cells. The model can produce policies either separately, for single blood groups, or simultaneously, for multiple blood groups with the option of utilising a blood group substitution matrix. In all cases, minimum service level and maximum expiry level constraints are included in the model formulation to ensure that operational performance remains high. In addition to the optimal \((R, S)\) policies, the outputs of the model include total operating costs, average age at issue, average inventory level, average expiry, and average shortage for each blood group. Paper III indicates that it is possible to modify the case study’s current policy by reducing the target inventory level \((S)\) without compromising the service provided while minimising expiry, age of issue and holding costs. The consideration of multiple blood groups simultaneously with the possibility of substitution at the planning stage seems to further improve the performance of the inventory management system.

Paper III’s approach of using a novel two-stage stochastic programming model for defining optimal \((R, S)\) periodic review policies whilst considering demand uncertainty and multiple perishable products had not been applied elsewhere in the literature at the time of publication.

3.4 Paper IV

Paper IV is produced in collaboration with the Finnish Red Cross Blood Service and investigates the inventory management of platelets within the Finnish blood supply chain. Platelets, a product of whole blood, have a challenging inventory to manage due to their short shelf life, five days in most EU countries. Co-author Jarkko Ihalainen, Medical Director at the Finnish Blood Service, proposed an exploration into the costs and implications to the national blood supply chain of extending the shelf life of platelets from five to seven days.

Paper IV builds upon Paper III, but also extends it in several ways. For instance, whereas Paper III only considers one hospital, Paper IV considers all demand nodes within a blood supply chain. The demand nodes in the Finnish chain include the national blood service bank and
the national hospitals. To realistically represent the decentralised decision process between the central blood bank and the hospitals, Paper IV takes a two-levelled approach. The first level generates target inventory level policies ($S$ as in Paper III) and daily order quantities for each hospital individually. The second level uses the aggregated hospital order quantities to generate the demand for the central blood bank, and thus its optimal target inventory level. A two-stage stochastic programming based on the formulation in Paper III is used to model the Finnish problem.

Compared to red blood cells studied in Paper III, platelets have a more challenging inventory to manage due to both their short shelf life and their less frequent demand compared with other blood products. These added challenges increase the complexity of the problem to the point where the model could not be solved even by only including a single hospital within a reasonable time frame (less than 28 hours). Therefore, to circumvent the computational issues posed by the model, a progressive hedging algorithm is employed to decompose the problem into computationally manageable sub-problems and recover tractability. The use of the decomposition algorithm reduces the computing time by 50% to 72%, rendering the approach usable in a real-world setting.

The model developed in Paper IV helped identify optimal target-level policies for both shelf life lengths for the national hospitals and the central blood bank. In addition, the results of Paper IV suggest that an increase in platelet shelf life would decrease unmet demand, expiry, and operational costs for hospitals; and reduce the inventory target level at the central blood bank.

The novelty and contributions of Paper IV to the literature are the proposed decentralised two-levelled approach to platelet inventory management; the combining of the two-stage stochastic programming model with the progressive hedging algorithm, which allows for large scenario sets using real-world data to produce implementable policies; and, to the best of our knowledge, we are the first to assess real-world inventory control and cost implications of extending the shelf life of platelets in the Finnish setting.
4. Discussion

4.1 Conclusions and implications

With public funds and resources limited in many countries globally (exacerbated further in recent years by the COVID-19 pandemic and the war in Ukraine) available healthcare resources must be allocated in a cost-effective manner to secure the health maximisation of a population. Yet, to ensure accountability to various stakeholders, e.g., external regulatory bodies and patient advocate groups, highly complex black-box approaches should be avoided. Model-based approaches are beneficial in that they can handle the complexity of healthcare delivery decision-making, while simultaneously maintaining transparency and accountability.

This thesis consists of four papers applying model-based methods that can aid cancer screening recommendations and inventory control policies. Papers I and II employ mathematically accessible models, implemented in a point-and-click decision tree proprietary software. The main advantages of the software used are in the ease of use and visual representation of the model, thus allowing stakeholders and fellow decision-makers to scrutinise the model structure and the impacts of varying parameters without much prior expertise. The two main drawbacks of the software utilised in Papers I and II are (1) that it requires a paid-for licence to access full functionality, and (2) complex real-world problems with many states and decisions cannot be implemented elegantly (and doing so inelegantly increases the chance of error and computation time).

In contrast, Papers III and IV apply complex mathematical formulations, in which prior expertise in the field is needed to assess the decision problems modelled. Whereas Paper III employs proprietary software, Paper IV implements the mathematical model formulation using an open-source computer programming language. The advantages of open-source software, apart from the obvious lack of cost, include the absolute transparency of the programming language and packages, community-driven support,
Discussion

The utilisation of a programming language over point-and-click enabled the inclusion of advanced solution algorithms, which further increased the ability to model large real-world problems. The added mathematical complexity that underpins the solution algorithm requires high-level analytical capabilities to confidently and accurately amend model parameters to achieve optimal performance. This highlights the need and advantage of multidisciplinary teams. In healthcare, a broad range of expertise, from decision-makers to healthcare specialists to analysts and modellers, are needed to make the right decision at the right time.

In a world with perfect information and hence no uncertainty in the consequences of our decisions, model-based approaches to decision-making could be seen as using a hammer to crack a nut. Yet, in our world, where we are surrounded by uncertainty and limited information, important decisions still need to be made. This is where model-based approaches hold an advantage. They are not the only tool to be used, but an important one in the toolbox.

4.2 Future research

Health equity is an increasingly critical factor in the delivery and assessment of health care. The United States Institute for Clinical and Economic Review published a white paper titled ‘Advancing health technology assessment methods that support health equity’ in early 2023 [2]. The stated objective of the white paper is to ensure that HTA in the United States advances the goal of improving health equity for socially disadvantaged groups. Currently, limitations to equitable healthcare include, among others, the lack of racial and ethnically diverse representations in clinical trials, issues arising from prioritising one demographic over another to close gaps in health disparities, and the measurement of quality of life.

The presence of limited resources raises questions regarding equity in terms of resource allocation among different segments of the population. Indeed, one avenue of potential development is the inclusion of resource allocation in health economic evaluations, particularly in health technology assessment. Methods employed in such evaluations (as discussed in Chapter 2.1) assess the efficacy and relative affordability of health interventions but do not provide information on the feasibility of implementation [49]. Health services have limited resources and how to share these resources to ensure all those in need have access is a decision problem in itself. For example, a HTA into the cost-effectiveness of cancer screening for the over 50s in England may result in an ICER of £21,000/QALY, which is below the formal threshold and thus, can be deemed cost-effective to implement. Although resource costs, e.g., clinicians’ time or a hospital stay, may have been included in the model, the source and relevance of particular costs...
are rarely included. For example, what is the source for the required additional clinical time? If the health service is hiring additional clinicians for the screening programme there will be additional costs that may affect the ICER; this often occurs with limited resources. To achieve equity in any health service, consideration of how resources are allocated among demographics is vital.

For many years, there has been a discussion surrounding the QALY [41, 23, 28, 12, 40] and how health outcomes may impact other areas of society such as social care and the potential discrimination against people with disabilities when used to measure health gain in HTA. A concern with the standard QALY model is that utilities derived using the standard gamble or time trade-off methods may be inconsistent as they follow expected utility theory (EUT) and its axioms, and most often assume a linear relationship between HRQoL and duration of life. Prospect theory (PT; [27]) challenges the axioms of EUT in that it states that utility is experienced not in absolute terms (such as QALYs) but relative to some reference point that can be different for different individuals. Furthermore, PT suggests that individuals have a greater aversion to losses with respect to the reference point than desire for the same value in gains, resulting in non-linear utility functions. A potential future research direction is to apply PT to health utility and duration of life elicitation in order to reduce the bias in the QALY and, in turn, produce a more inclusive measure of health gains. Some work has already been published on PT and the QALY [30], however, it may be time for a renewed investigation and development in the context of increasing health equity.

A final area of potential future development in the context of this thesis is the possible inclusion of multidimensional aspects to model-based approaches to generate decision recommendations for equitable healthcare delivery. Methods of multi-criteria decision analysis (MCDA) can be used to structure various kinds of objectives in healthcare decision-making problems and make trade-offs between these objectives explicit. These objectives could include, but are not limited to, the cost-effectiveness, equity, and accessibility of different decision alternatives. For example, the results of cost-effectiveness analyses with the addition of resource use for each alternative could be employed to select a set of non-dominated alternatives and thus better assess the feasibility and fairness (equity) of implementation. HTA already employs straightforward methods of MCDA, as cost-per-QALY analysis can be viewed as a qualitative MCDA and cost-benefit analysis can be viewed as a quantitative MCDA. Encouraging evidence of the further the use of MCDA in the healthcare context has been presented by, e.g., [31, 20, 3]. However, it should be noted that potential issues could arise from MCDA, such as the use of CEA defined only by race, disability, or socioeconomic status included as a criterion within the MCDA. Additionally, MCDA can require analysts to elicit preferences from
various decision-makers and be time-intensive, perhaps limiting the use in practice.

In the context of mathematical programming, methods of multi-objective optimisation (MOO) could be examined. Instead of a single optimal solution, such methods produce a set of Pareto optimal solutions which cannot be improved with respect to any objective without impairing performance on some other objective. One example of how MOO is already used in healthcare, is the cost minimisation of given medicine or intervention and the maximisation of the resulting health gains, subject to a willingness-to-pay constraint. This fairly simple MOO model could be extended to include additional equity objectives, such as minimising the distance the majority of the intended population has to travel to make use of the intervention and maximising the service level for the intended population(s). Then, the final policy choice could be made in view of the decision-maker’s preferences to implementation fairness as well as cost-effectiveness.

Within any health policy decisions, various stakeholders such as patient advocacy groups, clinical expert opinions, and social values, among others, must always be included. Model-based approaches can be useful in providing stakeholders and decision-makers with structure and support in framing quantitative analyses. To conclude, there are many avenues to explore in applying model-based approaches to aid in making better decisions and increasing equity in healthcare delivery.
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