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MODEL BASED EVALUATION OF
INTEGRATED CARE AND HEALTH ECONOMIC
OUTCOME IN HEART FAILURE TREATMENT

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Abstract

Demographic changes, increased life expectancy and the associated rise in chronic diseases pose challenges to public health care systems. Optimized treatment methods and integrated concepts of care are potential solutions to overcome increasing financial burdens and improve overall quality of care. In this context modeling is a powerful tool to evaluate potential benefits of new treatment procedures on health economic outcomes. In this doctoral thesis a novel modeling approach for simulating different treatment procedures of heart failure patients is presented. Agent based and discrete event methodologies were used to build the hybrid heart failure treatment model which facilitates the incorporation of different therapeutic procedures for outpatient and inpatient care on patient individual level. The state of health is modeled with the functional classification of the New York Heart Association (NYHA), strongly affecting state transition probabilities alongside age and gender. Cooperation with Austrian health care and health insurance providers allowed the realization of a detailed model structure based on clinical data of more than 25,000 patients. Simulation results of conventional care and an exemplary telemonitoring program underline the unfavorable prognosis for heart failure and reveal the correlation of NYHA classes with health and economic outcomes. Average expenses for the treatment of NYHA class IV patients of €10,077 ± €165 were more than doubled compared to other classes. The selected use case of a telemonitoring program demonstrated cost savings within two years of application. NYHA classes II and III revealed most potential for additional treatment measures. The developed model allows performing extensive simulations of established treatment procedures for heart failure patients and evaluating new holistic methods of care and innovative study designs. This approach offers health care providers a unique, adaptable and comprehensive tool for decision making in the complex and socioeconomically challenging field of cardiovascular diseases.

Keywords: Agent Based, Discrete Event, Heart Failure Treatment Model, Health Economic Modeling, Integrated Care.

Kurzfassung

Demographische Entwicklungen, erhöhte Lebenserwartung sowie die damit verbundene Zunahme an chronischen Erkrankungen stellt Gesundheitssysteme vor große Herausforderungen. Optimierte Behandlungsmethoden und integrierte Versorgungssysteme sind mögliche Lösungsansätze um finanzielle Belastungen auszugleichen und auch die Behandlungsqualität zu verbessern. In diesem Kontext ist die Modellbildung ein mächtiges Werkzeug um gesundheitsökonomische Auswirkungen neuer Behandlungsmethoden zu evaluieren. In dieser Doktorarbeit wird eine neuartige Modellierungsmethodik zur Simulation der Versorgung von Herzinsuffizienzpatienten (HI) vorgestellt. Agenten- sowie ereignisorientierte Ansätze beschreiben ein hybrides Herzinsuffizienzmodell, welches die Einbindung von verschiedenen Behandlungskonzepten im extra- und intramuralen Bereich auf Patientenebene ermöglicht. Der Gesundheitszustand einzelner Patienten ist auf Basis der funktionellen Klassifikation der New York Heart Association (NYHA) modelliert, welche – neben dem Alter und dem Geschlecht – einen wesentlichen Einfluss auf modellbasierte Zustandsänderungen hat. Die Zusammenarbeit mit österreichischen Gesundheitseinrichtungen ermöglichte die Umsetzung einer detaillierten Modellstruktur auf Basis klinischer Daten von über 25.000 Patienten. Simulationsergebnisse der konventionellen Versorgung sowie eines telemedizinischen Systems unterstreichen die ungünstige Prognose für HI-Erkrankte und veranschaulichen die Korrelation von NYHA-Klassen mit gesundheitsökonomischen Auswirkungen. Durchschnittliche Behandlungsausgaben für NYHA-Klasse IV Patienten von €10,077 ± €165 waren doppelt so hoch wie für andere Klassen. Der gewählte Anwendungsfall eines Telemonitoring-Systems demonstrierte mögliche Kosteneinsparungen innerhalb von zwei Jahren. Dabei zeigten zusätzliche Behandlungsmethoden das größte Potenzial für NYHA-Klassen II und III auf. Das entwickelte Modell ermöglicht die Durchführung umfassender Simulationen von etablierten Behandlungsformen für HI-Patienten sowie die Evaluierung ganzheitlicher Versorgungsformen und innovativer Studiendesigns. Dieser Ansatz bietet Gesundheitsdienstleistern ein einzigartiges, adaptierbares und umfassendes Werkzeug zur Entscheidungsfindung im komplexen und sozioökonomisch bedeutsamen Feld kardiovaskulärer Erkrankungen.

Schlüsselwörter: Agentenbasiert, Ereignisorientiert, Modell der Therapie von Herzinsuffizienz, Gesundheitsökonomische Modellierung, Integrierte Versorgung.

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List of Abbreviations and Acronyms

AB	Agent Based
ACC	American College of Cardiology
ACE	Angiotensin-Converting Enzyme
AHA	American Heart Association
AICD	Automated Implantable Cardioverter Defibrillator
ARB	Angiotensin Receptor Blocker
AT ₁	Angiotensin II receptor type 1
CCD	Cardiac Contractility Modulation
CHF	Chronic Heart Failure
CLD	Causal Loop Diagram
CRT	Cardiac Resynchronization Therapy
DE	Discrete Event
DMP	Disease Management Program
DRG	Diagnosis-Related Groups System
EF	Ejection Fraction
ESC	European Society of Cardiology
FIFO	First-In First-Out
FP	Case Flat Rate (≡ FP...”Fallpauschale”)
HF	Heart Failure
HFpEF	Heart Failure with preserved Ejection Fraction
HF _r EF	Heart Failure with reduced Ejection Fraction
HIS	Health Information System
IBM	International Business Machines Corporation
IC	Intensive Care
ICD	International Statistical Classification of Diseases and Related Health Problems
ICER	Incremental Cost Effective Ratio
ICT	Information and Communication Technology
ICU	Intensive Care Unit
IHCE	Institute of Health Care Engineering with the European Testing Center of Medical Devices
IMC	Intermediate Care Unit
IMP	Individual Medical Procedure (≡ MEL...”Med. Einzelleistung”)
INTENSE-HF	Integrated Telemonitoring and Nurse Support Evaluation
KAGes	Steiermärkische Krankenanstaltengesellschaft GmbH
LOS	Length Of Stay
LVEF	Left-Ventricular Ejection Fraction

MIT	Massachusetts Institute of Technology
PDRG	Procedure and Diagnosis-related Groups System
PDG	Primary Diagnosis Group (≡ HDL...”Hauptdiagnosegruppe”)
PDCG	Procedure- and diagnosis-oriented case group (≡LDF...Leistungsorientierte Diagnosefallgruppe)
RAM	Random-Access Memory
SD	System Dynamic
SD	Standard Deviation
SHFM	Seattle Heart Failure Model
STS	Structured Telephone Support
TISS	Therapeutic Intervention Scoring System
TM	Telemonitoring

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1 INTRODUCTION

Demographic changes, emphasizing the population gap between young and old, increased life expectancy and the associated rise in chronic diseases challenge public health care systems. [1] Particularly, the proportion of people above the age of 65 years increased considerably over the last decades, with no decrease foreseen in the near future. Between 2001 and 2014, the number of elderly people (65 years and above) in the EU-28 rose by 21.8 %, while the overall population increased by only 3.8 %. [2] Similarly, the number of people turning 65 each year is expected to more than double between 2000 and 2025 in the United States as a result of the baby boom generation. [3] Prediction models of Statistics Austria reveal that due to decreasing fertility rates and the mentioned increase in life expectancy, in the year 2060 over a quarter of the Austrian population will be over 65 years. [4] The necessity for changes in health policies is evident since the increase of the ageing society correlates with a consequential rise in chronic illnesses, representing a not to be underestimated socioeconomic burden. [1,5]

Heart failure (HF), as a representative of cardiovascular diseases such as e.g. stroke, coronary artery disease and myocardial infarction is the leading cause for hospitalizations among elderly patients [6–8]. The incidence of HF approaches 21 per 1,000 people over 65, predictions show that from 2012 to 2030 prevalence will increase by roughly 46 % in the United States. [9,10] At the age of 45 to 55 years about 1 % of the European population suffers from heart failure, between 65 and 75 years this value varies from 2 to 5 % and rises to roughly 10 % at the age of 80 and above. [8,11,12] Overall the calculated lifetime risk of developing heart failure is about 20 %, with even higher risks for those with hypertension. [13] Treatment expenditures for HF account for 1-2 % of the total health care budget of western countries and are expected to

consequentially rise in the future. [14,15] For high-income countries the total costs for HF are even higher encompassing 2-3 % of the total expenditure of healthcare systems and are projected to increase by more than 200 % in the next 20 years. [9] Up to three quarters of the total treatment costs are associated with hospital admissions, in-hospital treatment and patient care in nursing homes. [16] In addition to the financial impact, heart failure is associated with an unfavorable prognosis. High mortality of up to 50 % within five years after the initial diagnosis underlines the severity of the disease. [17–20] One year case fatality rate after hospitalized heart failure is up to 30 %. [21–23] Additionally, a disease-related readmission rate of up to 50 % within the first year and likewise 30-day readmission rates of over 23 % in contrast to 12.6 % for all cause-readmissions after hospital discharge, indicate room for improvement in post-inpatient management. [24–27] Patients' poor adherence to medication and recognition of early signs of cardiac decompensation, as well as insufficient collaboration among health care providers, are exemplary limitations in therapy. [28] Estimations indicate that up to two thirds of HF readmissions are triggered by potentially preventable factors, including suboptimal discharge planning, non-adherence to HF medication, inadequate follow-up, insufficient social support as well as delays in seeking medical attention. [29–31] New solutions based on optimized and individualized treatment and integrated concepts of care are potential ways to manage future financial burdens. Commonly, they focus on the detection of symptoms at an earlier stage and thus on stabilizing the patient's health status and minimizing unnecessary admissions. [32] However, several studies analyzing the potential benefits of these novel approaches present controversial results and are often based on small study cohorts and short follow-up times. [33–35]

In this context, modeling is a powerful tool to evaluate potential benefits of different treatment procedures on health outcomes as well as health care budgets. This work presents a unique hybrid modeling approach for simulating different treatment procedures of HF patients based on extensive data sets from outpatient and inpatient care. A precise simulation of conventional care and the adaptability of the model allow the evaluation of integrated methods of care and associated study designs to support decision making in healthcare. [36]

1.1 Heart Failure

Heart failure (HF), also known as chronic heart failure (CHF) describes an insufficiency of the heart muscle, being unable to pump enough blood to meet the body's need for oxygen. As a clinical syndrome characterized by typical symptoms (e.g. breathlessness, fatigue, ankle swelling as well as anorexia, depression and confusion) it may be accompanied by signs (e.g. elevated jugular venous pressure, peripheral oedema, displaced apex beat or cardiac holosystolic murmur) that are caused by a structural and/or functional cardiac abnormality, resulting in elevated intracardiac pressures and/or reduced cardiac output at rest or during stress. Prior to clinical symptoms becoming apparent, patients can suffer from these asymptomatic structural or functional cardiac abnormalities (systolic or diastolic left ventricular (LV) dysfunction), which are known precursors of HF. The main terminology used to describe HF is based on the measurement of the left-ventricular ejection fraction (LVEF), ranging from normal LVEF (typically considered as $\geq 50\%$; HF with preserved EF (HFpEF)) to those with reduced LVEF (typically considered as $< 40\%$; HF with reduced EF (HFrEF)). HF patients without detectable LV myocardial disease may have other cardiovascular causes resulting in HF, such as pulmonary hypertension and valvular heart disease. [37,38]

To counteract physiological impairments due to HF, the heart can react in three ways: *By enlarging*, the heart stretches to contract stronger and keep up with the demand to pump more blood which, over time, causes the heart to enlarge; *By developing more muscle mass*, the heart can pump stronger, at least initially. The increase in muscle mass is mostly driven by contracting cells of the heart getting bigger; *By pumping faster*, the heart's output increases. Not only the heart but also the body tries to compensate symptoms. Blood vessels tend to narrow to keep the blood pressure up, to make up for the power deficiency of the heart. Also the body diverts blood away from less important tissues and organs (e.g. kidneys) as well as the heart and brain. All these temporary measures may succeed in masking the problem of heart failure, but are not solving it. The heart's impairment increases until compensating mechanisms work no longer. [39]

In general there are several ways to distinguish the affected region of the heart due to HF, superficially it can be divided into left-sided, right-sided and biventricular failure. To classify the severity of HF, most commonly the classification system of the New York Heart Association (NYHA) is used, describing four states of impairment (Table 1). [40] The NYHA classification system was introduced in 1928 and further developed and changed over time, to assess functional capabilities of the patients and assess response to treatment. [41]

Table 1: The New York Heart Association Classification System. Adapted from [40].

Class	New York Heart Association functional classification
I	Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain
II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain
III	Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain
IV	Patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased

Another classification scheme was introduced by the American College of Cardiology (ACC) in collaboration with the American Heart Association (AHA) in 2001. The ACC/AHA guidelines are an extension of the NYHA classification, describing four stages of HF (A, B, C and D). Next to functional criteria also cardiac reports are assessed (Table 2). Stage A describes “pre-heart failure”, a stage where intervention with treatment can presumably prevent progression to overt symptoms, and thus does not have a corresponding NYHA class. ACC Stage B corresponds to NYHA Class I, ACC Stage C to NYHA Class II and III, while ACC Stage D overlaps with NYHA Class IV. [9,42]

Table 2: ACC/AHA classification scheme. Adapted from [42].

Stage	ACC/AHA classification
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

There are further, more recent classification schemes such as the HLM (Heart – Lung – Malfunction of other organs) [43] or classification systems that are considering specific comorbidities, e.g. the cardiorenal syndrome classification system (CRS) [44], which won't be further addressed in this work due to lack of evidence and/or comparability with the NYHA classification system.

Since heart failure is a cardiovascular disease frequently associated with comorbidities, therapy is specific to the patient and encompasses life style modalities as well as clinical interventions with the aim to improve symptoms and prevent further progression of the disease. Behavioral modifications are mostly focusing on dietary guidelines regarding fluid and salt intake as well as an improvement in physical conditioning. [45,46]

The first-line therapy for HF patients is mostly based on medication therapy, which is then combined with other treatment approaches. There is a variety of potential drugs being used to treat heart failure; most commonly the following are used: [47–50]

- Angiotensin-converting enzyme (ACE) inhibitors
- Angiotensin receptor blockers (ARBs)
- Beta-adrenergic blocking agents (beta blockers)
- Diuretics

ACE inhibitors are primarily used for the treatment of hypertension and congestive heart failure and cause the relaxation of blood vessels as well as a decrease in blood volume and thus lower blood pressure and decreased oxygen demand from the heart by inhibiting the angiotensin-converting enzyme. [51] ARBs are, same as ACE inhibitors, indicated as first-line antihypertensives in patients developing hypertension

along the left-sided heart failure. Their main purpose is to modulate the renin-angiotensin system and selectively block the activation of AT₁ receptors (Angiotensin II receptor type 1), preventing the binding of angiotensin II and thus controlling blood pressure and volume in the cardiovascular system. [52,53] Beta blockers are predominantly used to manage abnormal heart rhythms and to prevent secondary heart attacks. Additionally they are widely utilized to reduce blood pressure. Their basic function as competitive antagonists is to block receptor sites for the endogenous catecholamines epinephrine (adrenaline) and norepinephrine (noradrenaline) on adrenergic beta receptors of the sympathetic nervous system, which mediates fight-or-flight response. [54–56] A diuretic is any substance that promotes diuresis, the increased production of urine. There are several subgroups of diuretics, in their basic principle they all increase the excretion of water from bodies, although in distinct ways. Subgroups are e.g. loop diuretics, thiazides, potassium-sparing diuretics, etc. Antidiuretics as alternative agents reduce the excretion of water in urine. Some diuretics, such as thiazides and loop diuretics specifically have antihypertensive actions and are commonly used to treat heart failure by preventing fluid retention and the resulting shortness of breath. [57,58]

Further medication therapies such as Angiotensin-Receptor Neprilysin Inhibitors (ARNIs), I_f channel blockers or inhibitors, hydralazine and isosorbide dinitrate, anticoagulants, cholesterol-lowering drugs (statins) [59], etc. are additionally used up-and-coming methods. Surgical therapies and implanted devices are further possible treatment methods, automatic implantable cardioverter defibrillators (AICDs), cardiac resynchronization therapy (CRT) and cardiac contractility modulation (CCM) are keywords in this field. [60–62] In selected cases also heart transplantation can be considered, although presenting substantial downsides, including the immunosuppressive regimen to prevent rejection. [63]

Due to the importance of changes in lifestyle modalities and preventive measures in the treatment of HF, newer therapeutic concepts start to include integrated approaches between outpatient and inpatient care, with home-based care on regular basis. These holistic measures and their relevance are further discussed in the subsequent chapters.

1.2 Disease Management

In general the goal of a disease management program (DMP) is to provide evidence-based diagnosis and therapy for patients as well as to educate patients and caregivers, resulting in improvement of symptoms and quality of life alongside a reduction of hospitalizations and mortality. The implementation of a successful DMP may include: [64]

- Integration of all sectors of care (integrated care)
- HF outpatient clinics
- Multidisciplinary involvement of specialized HF cardiologists and HF nurses
- Adherence to guidelines

Core parts of DMPs for HF comprise an established network between hospital and outpatient care structures, a seamlessly working system of care in the outpatient setting, patient education and improvements in adherence. An optimized HF therapy modification is another task tackled by a DMP, often supported by home nurses. The lack of information between hospitals and office-based physicians and nurses can be improved with effective information management. [64,65] Their effectiveness is emphasized by the European Society of Cardiology (ESC), which strongly recommends the provision of multidisciplinary programs for HF (recommendation class I, level of evidence A). [37]

There are many literature sources describing effects of DMPs in various scenarios for HF patients such as home visits combined with structured telephone support (STS), self-management approaches and also combinations with telemonitoring programs. Many show successful and significant reductions in rehospitalisation rates of up to 45 % within three to six months and also reduced overall admissions up to 37,5 % in the same time frame [33,35,66–70]. Reported decreases in overall mortality of up to 39 %, after follow-up of 6 months, are mostly not significant [35,66]. The incremental cost effective ratio (ICER) is generally positive for disease management programs over conventional care. [68,71,72] Due to the increasing availability of technological support and progress in data science, effects of methods of care including telemedical support are frequently discussed in literature.

1.3 Telemedicine

Telemedicine originates from the 1970s, literally meaning “healing at a distance” and signifies the use of information and communication technologies (ICTs) to improve patient outcomes by increasing access to care and medical information. [73] There is no definite definition of “telemedicine”, a study from 2007 found 104 peer-reviewed definitions of the word. [74] The world health organization (WHO) has adopted the following general description:

“The delivery of health care services, where distance is a critical factor, by all health care professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education of health care providers, all in the interests of advancing the health of individuals and their communities” [75]

The many definitions highlight that telemedicine is an open and constantly evolving science, incorporating new advancements and progressions in technology and responds and adapts to the changing health needs and contexts of society. Some distinguish telemedicine from telehealth, but they both are synonymous and used interchangeably. Four elements are pertinent to telemedicine: [76]

- Its purpose is to provide clinical support
- It is intended to overcome geographical barriers, connecting users who are not in the same physical location
- It involves the use of various types of ICT
- Its goal is to improve health outcomes

Telemedicine has great potential for reducing the variability of diagnoses as well as improving clinical management and delivery of health care services by enhancing access, quality, efficiency and cost-effectiveness. [77–79] However, despite its promise, telemedicine applications have achieved varying levels of success in both industrialized and developing countries. One challenge of many in the employment of telehealth applications is the resistance of health care providers, health care workers and patients to adopt new service models. [78–80] In industrialized countries telemedicine systems are not used to cover long distances, but to consistently monitor the patients’ state of

health. A typical telemonitoring system, as it may be used in heart failure therapy, is depicted in Figure 1.

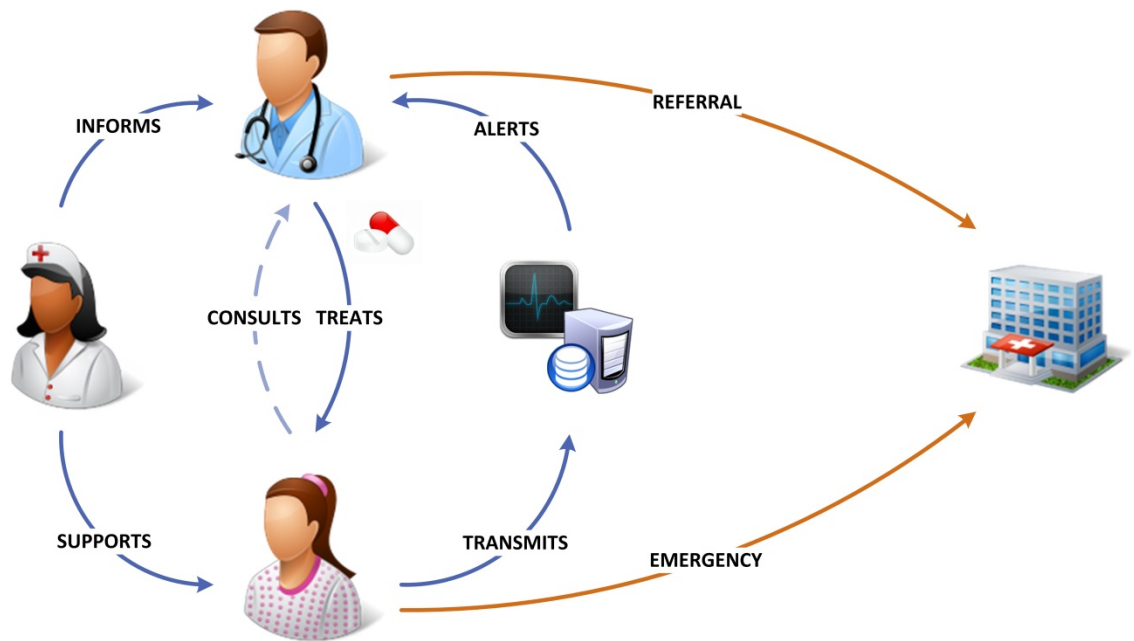


Figure 1: Typical concept for the use of telemedicine in integrated care.

Usually the patient receives a scale to measure body weight, a device to perform blood pressure measurement and a cellphone. The state of health is then monitored on a daily basis through data transfer to the data center. In case of conspicuous health parameter changes the general practitioner is alerted and timely approaches the patient to e.g. adapt the medication. A home nurse, as part of a DMP, can additionally support the patient by informing about heart failure, self-care, prevention and/or how to use the telemonitoring system, thus promoting health literacy. In case outpatient care is not sufficient to treat symptoms, the seamless transition to inpatient care covers further needs in therapy.

Many studies are published, investigating potential benefits of telemedicine programs for HF patients. However, results are inconsistent and often based on small study cohorts and short follow-up times. [33–35] Inglis et al. performed a systematic review and meta-analysis of the outcomes of structured telephone support and telemonitoring as a primary component of CHF management for over 8000 patients. Slight, non-significant reductions in mortality (up to 12 %) could be achieved as well as decreased admission numbers for HF of up to 23 %. [81] Some of the studies did not identify any change in clinical results. Cost efficiency is sparsely addressed in literature, Voigt et al. performed a meta-analysis, reporting costs savings of up to USD 17.400 per

patient for admissions within a year, although not significant. [82] Klersy et al. in 2011 investigated the economic impact of remote patient monitoring. A cost simulation model was constructed to compare telemedicine with usual care. Results show that direct costs for hospitalization are lower for telemonitoring systems with a range from 300 to 1,000 Euro per patient. It was concluded that the overall acceptance of remote patient monitoring was encouraged, but there is still a lack of prospectively and uniformly collected economic data. [83] Seto et al. in 2008 performed a systematic review regarding cost comparison between telemonitoring and usual care of heart failure. It was concluded that costs can be reduced between 1.6 to 68.3 % by using a telemonitoring system including a component of home physiological measurements. Although telemonitoring systems require an initial investment, they have the potential to substantially reduce costs in the long term. [84] In 2009 Scherr et al. performed a study in cooperation with the Medical University of Graz, where 54 patients were enrolled in a conventional care and a telemonitoring setting each for half a year, reporting considerable improvements in health with the usage of the telemonitoring system. [85] In a recent meta-analysis Lin et al. analyzed the effectiveness of telemedicine interventions. They reported that overall telemedicine was beneficial; especially home-based teletransmission was successful in reducing all-cause mortality and HF-related hospital admission, length of stay and mortality. [77] Another overview of systematic reviews on remote monitoring of HF patients was published by Bashni et al. in 2017, stating that telemonitoring and home telehealth appear to be generally effective in reducing heart failure rehospitalization and mortality. However, further investigations are required. [86]

There is still room in literature to further investigate the application of DMPs in combination with telemonitoring for specific patient collectives, addressing overall effects on quality of life, health and economic outcomes as well as patient adherence. There is no general consensus to which program would be the most beneficial for a specific patient collective, therefore one goal of this work is to present a framework that supports decision-making in this complex and socioeconomically challenging field of HF, to lastly provide valid predictions and analyses as a basis for the adaption of new approaches in health care.

1.4 Simulation Modeling

Modeling is one of the ways to solve real world problems, for which, in many cases, the finding of a proper solution would not be otherwise affordable. Experiments with real objects would be too time consuming, dangerous, costly or even impossible. Therefore models come into play as representations of a real system, a process, which assumes a certain abstraction. Redundant (presumably) details are neglected and the focus is set on what we consider as important. The resulting model will always be less complex than the original system. Figure 2 visualizes the difference between the real world and the world of modeling. Starting with a complex problem, crucial processes are analyzed and formulated as a model. With several iterations and trains of thought the program is optimized up to a level, which allows for realistic estimations. With the created model predictions of future events or influences of changes of sensitive parameters can be calculated, saving time and money, to draw out potential best solutions. [87]

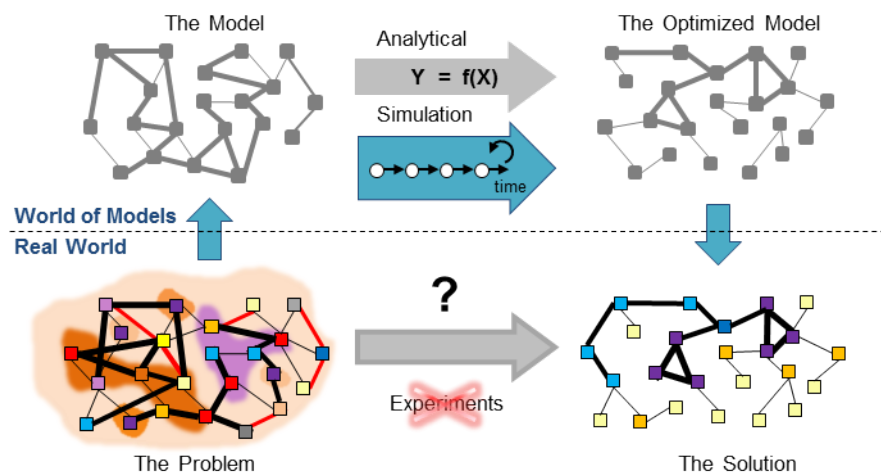


Figure 2: The world of modeling. Adapted from [87]

There is a magnitude of models that can be considered, such as mental models, pen and paper approaches, physical models and models in the virtual world. Basically they can be split into two large groups, analytical and simulation models. [87]

Analytic models are based on formulas and scripts. They can be found nearly everywhere in life, mainly because their implementation is rather simple. The formulation of equations in e.g. a Microsoft (MS) Excel™ spreadsheet would be an example. Input and output values are linked via chains of formulas and scripts, ranging from little requirements to complex parameter variations, Monte Carlo simulations or

optimization experiments. However, there are limitations to analytic (formula-based) models in finding solutions for dynamic systems, such as: [87]

- Non-linear behavior
- “Memory”
- Non-intuitive influences between variables
- Time and causal dependencies
- All above combined with uncertainty and large numbers of parameters

Simulation models though can describe static relationships and dynamic behavior. They are always executable models with distinct simulation runs that can be changed and adapted dynamically through input parameters. They typically require some training and learning and are able to depict complex relations with different degrees of abstraction, from small and precise control systems to supply chains and whole ecosystems. Figure 3 gives an overview of applications areas for simulation models with exemplary degrees of abstraction. [87]

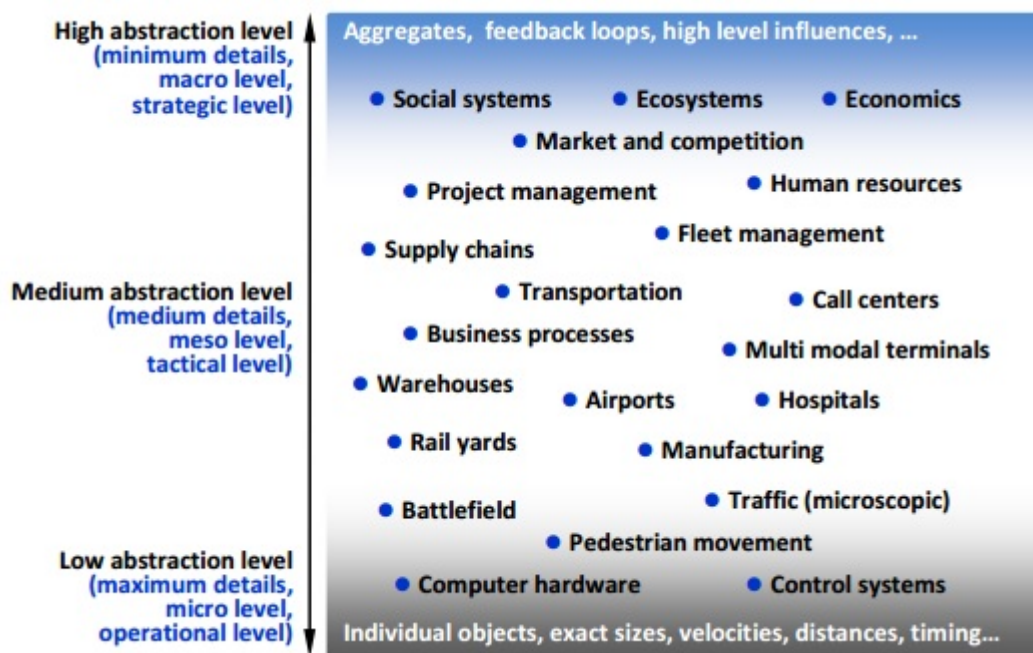


Figure 3: Applications of simulation and respective degrees of abstraction. Taken from [87].

A method in simulation modeling is a general framework for mapping a real world system to its model, suggesting a type of language or “terms and conditions” for model building. To date, three main methods exist: [87]

- System Dynamics (SD)
- Discrete Event Modeling (DE)
- Agent Based Modeling (AB)

These three methods serve a particular range of abstraction levels, which is depicted in Figure 4.

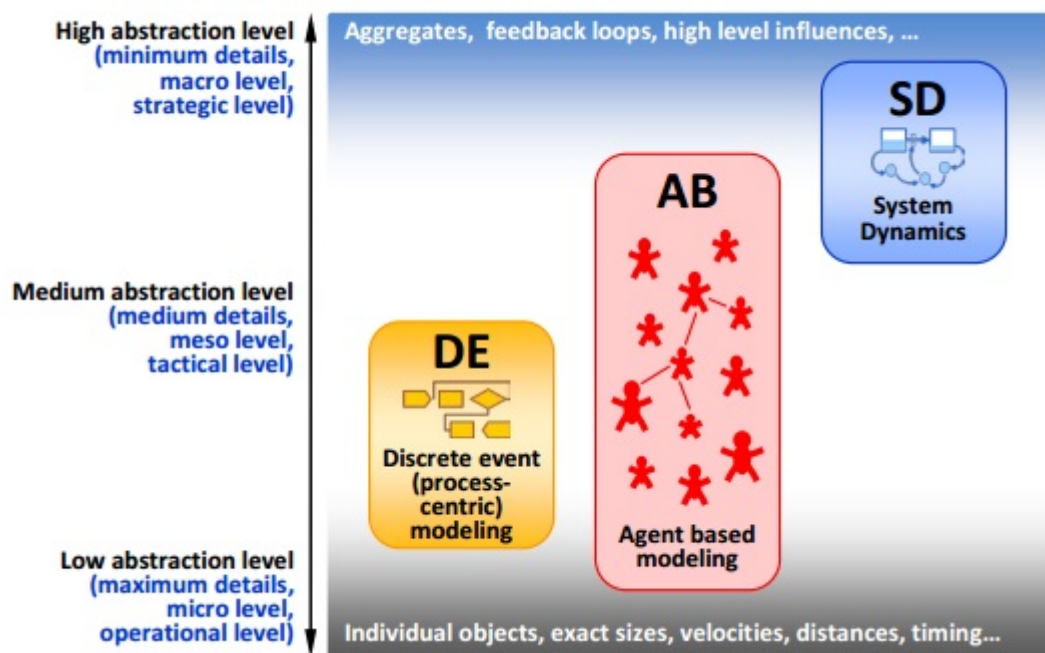


Figure 4: Methods in simulation modeling and their respective degree of abstraction. Taken from [87]

System dynamics modeling operates mostly at high abstraction level and is commonly used for strategic modeling, population growths and dynamic processes in nature. Discrete event modeling has a process-centric approach, which supports medium and medium-low levels of abstraction. Examples would be supply chains, health care processes and state machines. Agent based models have a huge variety in their application and can therefore vary from very detailed agent models of physical objects up to highly abstract applications where agents are competing companies or governments. [87–89] These three methods will be further described in the following chapters.

1.4.1 System Dynamics

System Dynamics (SD) was created in the mid-1950s by the Massachusetts Institute of Technology (MIT) by Professor Jay Forrester. [87] John Sterman described this method as follows:

“System dynamics is a perspective and set of conceptual tools that enable us to understand the structure and dynamics of complex systems. System dynamics is also a rigorous modeling method that enables us to build formal computer simulations of complex systems and use them to design more effective policies and organizations. Together, these tools allow us to create management flight simulators-microworlds where space and time can be compressed and slowed so we can experience the long-term side effects of decisions, speed learning, develop our understanding of complex systems, and design structures and strategies for greater success.” [90]

As the name indicates, system dynamics is a method of studying dynamic systems. It is mostly used for long-term, strategic models with a high degree of abstraction of simulated objects. People, products, events, organisms, etc. are represented in a quantity that makes individual behavior and dynamics negligible. SD models are often based on so-called causal loop diagrams (CLD), which describe variable interdependencies and feedbacks for an investigated system. Hereby stocks and flows are identified among other variables and internal feedback loops to describe the system. Differential equations then mathematically describe their interdependencies. [90]

1.4.2 Discrete Event Modeling

Discrete event modeling was introduced in October 1961 by IBM (International Business Machines Corporation) engineer Geoffrey Gordon, who presented the first version of a so-called GPSS (General Purpose Simulation System, originally Gordon's Programmable Simulation System). In DE modeling the system being modeled is seen as a process, i.e. a sequence of specific operations being performed across entities. Entities were originally called transactions in GPSS and may represent patients, clients, phone calls, vehicles, tasks, projects, etc. Those entities can then use resources that may represent e.g. doctors, various staff, operators, machines, servers, equipment or transport. Flow and process charts can be directly translated into computer language; typical objects used for their description would be delays, queues, decision elements, sources and sinks. They usually are, similar to a Markov model, described with discrete

steps alongside the model flow. Transitions are stochastic and mostly based on probability density functions. Therefore, models have to run for a certain simulation time or repeatedly, to have significant outputs. As illustrated in Figure 4, DE modeling can very precisely simulate specific tasks, activities or processes that are well defined. Their usage in process engineering, health care management and optimization problems is widely spread. [87,89]

1.4.3 Agent Based Modeling

Agent based modeling is the most recent method of aforementioned three. It was first introduced in the year 2002, until the early 2000s it was mostly an academic topic. Triggers for the development of this approach were the desire to get a deeper understanding of systems not being captured appropriately by existing modeling approaches as well as advances in modeling technology and CPU power and memory. For ABM you may not know how the system as a whole behaves and what are the key variables and dependencies, but you may have some insight into how objects (agents) in the modeled system behave individually. Therefore, ABM is mostly a bottom-up approach, where behavior is defined for chosen agents. Agents can also interact with the environment that may be modeled with discrete event modeling or system dynamics. An example would be the clinical pathway (patient flow) of patients (agents). The term agent is still discussed in literature, since it is not well defined which characteristics an object has to have to be called an agent. Intellect, the ability to learn, social interaction and reactivity would be examples of terms being discussed in this context. Agents may be smart, stupid and communicative within the model or rather passive elements that can learn or stay in chosen patterns. A few facts addressing this topic could be summarized the following: [87–89]

- Agents are not identical with cellular automata and they do not have to live in discrete space. Space may even be redundant in ABMs.
- ABM does not necessarily assume clock “steps” in which conditions are tested and decisions are made. Most well defined ABMs are asynchronous.
- Agents can be passive and do not necessarily have to be people.
- The number of agents is specific to the modeled context and does not have to be within a certain range.
- Agents do not have to interact.

Most of published ABMs work in discrete time, where decision-making, interactions and state changes are instant. The basic simulation engine often doesn't differ much from the one used for DE modeling. For higher level approaches the engine should support large numbers of concurrent activities, including dynamic creation and destruction, the correct handling of multiple instantaneous events (with deterministic and random execution) as well as space-related functionality, whether 2D, 3D or geographical space. [87]

2 METHODS

This section describes the fundamentals of the presented simulation model as well as the approach to this work in general. Starting with a take on the literature review that was conducted, expanded and updated manifold throughout the process of creation, ending with the detailed model description in chapter 2.5. Essential to this work was the contact to and cooperation with health care and health insurance providers in Austria. All the welcome coincidences that lead to new projects and cooperation are described. Measures taken to deal with big data, from data cleansing to automated extraction of information and statistical evaluation are further delineated in the chapters 2.3 and 2.4. The primary findings in data sets are represented and then the chapter 2.5 *Simulation Model* will guide through the modeling environment, the development of the up to date version of presented model, verification and validation as well as the starting point for the simulation results.

2.1 Literature Review

The basis for most scientific works is a comprehensive literature review, covering state of the art and visions in the selected field. The content of presented work was formulated over many years, ranging from lateral literature reviews to very precise isolations of scientific topics. Approaches and methods taken to gather information are described subsequently.

The literature reviews were all based on scientific search engines and data bases, most commonly used were:

- PubMed (<https://www.ncbi.nlm.nih.gov/pubmed/>)
- Cochrane Library (<https://www.cochranelibrary.com/>)
- Google Scholar (<https://scholar.google.at/>)

Of those three data bases mostly PubMed was used with specific filter settings. Search results were displayed in relevance-ranked order, meaning that when a user’s search exactly matches a MeSH (Medical Subject Headings) term, that term is displayed first. MeSH Databases are a vocabulary thesaurus used for indexing PubMed citations and include Subheadings, Publications Types, Supplementary Concepts and Pharmacological Actions, which are then translated into the PubMed search. The algorithm used for finding best matching citations was the standard best match order, where PubMed displays documents in order of decreasing relevance score. This score is calculated by comparing an input query to the document fields such as *text*, *author*, *journal*, etc. These document fields are indexed, for each literature source the terms and their frequencies are calculated. During retrieval of search results, the term *frequencies* is used in a weighted fashion to return a ranked list of PubMed citations matching the terms in the user query. There is a specific explanation of this algorithm in the “Help”-Library of PubMed. [91] For Cochrane Library and Google Scholar standard filter settings have been used.

For each query a minimum of the first 100 titles and abstracts have been read and assessed in terms of quality and relevance to this work. Each literature research was based on specific keywords and time frames to narrow down the number of resulting hits. Table 3 and Table 4 present keywords for different searches.

Table 3: Keywords for the review of heart failure models in literature

keywords – heart failure modeling

heart failure	model
agent based	discrete event
simulation	costs
prediction	NYHA
Monte Carlo	Markov

Table 4: Keywords for the review of heart failure therapy

keywords – heart failure therapy	
heart failure	comorbidity
classification	ICD
therapy	medication
telemedicine	disease management
telemonitoring	STS
inpatient	outpatient
integrated care	nursing
readmission	costs
mortality	ATC

To gather comprehensive information, meta-analyses and review papers were specifically addressed with additional keywords. An extensive search of secondary literature was a key aspect in gathering thorough knowledge of heart failure therapy and modeling. To classify each literature source, an individual rating system for papers was developed, consisting of quality criteria for study design, number of patients, overall quality and relevance to this work. Each publication was also commented in Citavi 6 to have an overview of the literature sources. For this work the most essential sources haven been included and meta-analyses are more often cited than singular research projects. The literature research was closed on the 11th of February 2019.

2.2 The Austrian DRG System

Until the year 1996, reimbursements for health care services in Austria were based on a per diem payment model in which every inpatient stay was reimbursed on the basis of the number of days of care, thus days spent in the hospital. For every day a fixed sum was charged to the payee, which in Austria usually is the relevant social insurance institution. The payment was made regardless of the procedures the patient underwent and also of the disease the patient was suffering from. Remaining hospital costs were borne by various payees and summarized with the term “operational losses”. Since 1997 though, Austrian hospitals have largely been financed under the Austrian Procedure and Diagnosis-related Groups System (PDRG), a DRG system adapted to

meet the Austrian framework conditions (in German: System der leistungsorientierten Krankenanstaltenfinanzierung – LKF). In this system, in addition to diagnoses, procedures provided are a primary criterion for the allocation of case groups. With the Austrian DRG system the introduction of a nationally standardized diagnosis documentation based on the WHO's International Classification of Diseases (ICD) and the development of a nationally standardized catalogue of procedures in the inpatient sector with detailed cost analysis of case flat rates has been build, financed from public resources. To determine specific costs, a total of 20 hospitals from all over Austria were recruited to calculate the costs of procedures on the basis of this new catalogue. These, so-called, reference hospitals were used to calculate the costs on the basis of roughly 500,000 inpatient stays to build the economic basis for the model. In this test period it became clear that the pathology (primary diagnosis) of the patient was the primary criterion for the allocation to a case flat rate in roughly under three fifths of all flat rates, with medical procedures being the primary criterion for the other two fifths. Terminologically this was reflected with the distinction between primary diagnosis group (PDG) (in German: "Hauptdiagnosegruppe" - HDG) and individual medical procedures groups (IMP) (in German: "Medizinische Einzelleistungsgruppen" - MEL). Since the introduction of this system in 1997, the model has been subjected to annual maintenance work, including further adaptations over the years. Importantly, in 1999 an overhauled system for the documentation and scoring for intensive care medicine and oncology was introduced. In 2001 a switch from the ICD-9 to the ICD-10 system followed, in 2002, due to the introduction of the Euro in Austria, further major changes were implemented. From 2002 onward the Austrian DRG system was also used for the distribution of social insurance resources in the hospitals of the private hospitals financing fund (PRIKRAF). Over the years further changes were implemented, keeping reimbursements up to date and handling difficulties in the use of the system as well as special cases. [92]

The basis for this work is the Austrian DRG model 2018, which includes 979 primary diagnosis groups. The DRG model 2018 uses the cost basis from the calculations in 2014. Each admission is allotted with a point score per procedure- and diagnosis-oriented case group (PDCG) (in German: "Leistungsorientierte Diagnosefallgruppe" – LDF). This score is defined as the mean value of calculated costs for inpatient days per LDF. Each LDF has a specific length of stay (LOS) (defined by a concrete minimum and maximum) allocated to it, during which a specific point score is

reimbursed to the hospital. Further, for each LDF a procedure component (in German: “Leistungskomponente” – LK) as well as a daily component (in German: “Tageskomponente” – TK) is defined. The daily component is used to reimburse expenses that are incurred daily within the framework of care for the patient. These can include e.g. medical and nursing care and any drug therapy. The procedure component is based on points, equivalent for selected medical procedures and is thus independent of the average length of stay of the patient in inpatient care. [92–94].

2.2.1 Admissions

The length of stay per LDF is crucial for cost calculations within the Austrian DRG system, since transgression above or below the minimum and maximum LOS is differently reimbursed. In case the LOS extends beyond the maximum length of stay set for the specific case group, supplementary points are added to the case flat rate for each additional day. This daily supplement is not constant and decreases with the number of days above the maximum LOS, ergo more points are awarded for the first day in excess than the second, more for the second than the thirds, etc. In case of extreme periods of hospitalization beyond the set LOS, the daily supplement is frozen once a set threshold value has been reached and this value is then added per day. For short stays reduced case flat rates are charged. In this case the procedure component is charged to the full amount, but the daily component is reduced linearly, thus the same number of points is subtracted for each day less than the minimum LOS. Equations (1) and (2) are used for the calculations of transgressions above the maximum and minimum length of stay respectively. [93]

$$surcharge(x) = \max \left[\frac{\frac{dailyComponent}{averageLOS} * maxLOS}{x} \text{ OR } \frac{\frac{dailyComponent}{averageLOS}}{x} \right] \quad (1)$$

$$points/case = procedureComponent + \frac{dailyComponent * x}{minLOS} \quad (2)$$

x...number of days in hospital

Since this work presents a model of the treatment of heart failure patients, specific primary diagnoses for HF haven been used for cost calculations within the Austrian DRG system. Based on the catalogue of the LKF model, four ICD-10 categories represent HF, which are listed in Table 5. These four categories are further structured in patient- and diagnosis-related characteristics (e.g. age or type of diagnosis), which are associated with individual case flat rates (in German: “Fallpauschale” – FP). Thus each primary diagnosis is associated with a case flat rate, containing information on the reimbursement of hospital stays. The average, minimum and maximum LOS is defined for every case flat rate, which is listed in Table 6.

Table 5: Primary diagnosis groups (HDG) for cost calculations of inpatient care. Taken from [93]

ICD-10	diagnosis	HDG	case flat rate	
			FP A	FP B
I11.0	hypertensive heart disease with (congestive) HF	HDG06.04	FP A	FP B
I50.0	congestive HF	HDG06.04	FP A	FP B
I50.1	left ventricular HF	HDG06.03		FP C
I50.9	HF, unspecified	HDG06.04	FP A	FP B

Table 6: Reimbursement parameters for HDG of HF. Node A is taken, if the age of the patient exceeds 64 years, otherwise node B is used for calculations. Taken from [93]

HDG	node	LDF-score	daily component	procedure component	minLOS	maxLOS	meanLOS
06.03	C	2,873	2,807	66	3	10	6.9
06.04	A	3,134	3,062	72	4	11	7.5
06.04	B	2,688	2,516	172	3	10	6.5

2.2.2 Intensive and Intermediate Care

For intensive and intermediate care the standard case flat rates for admissions are not enough to reimburse necessary procedures at high quality facilities. Therefore, special rules for the assessment of costs have been developed within the Austrian DRG System. First and foremost there is the differentiation of intensive care (ICU) and intermediate care units (IMC), whereby intensive care units are further split in three tiers. The classification of intensive care units is based on mean values of the Therapeutic Intervention Scoring System 28 (TISS) (see Table 7 and Table 8). The TISS system is a scoring system for the maintenance of care of seriously ill patients. TISS-28 includes a list of 28 procedures of care, which may be performed on a patient. The sum of performed procedures on a patient within 24 hours results in the TISS score. Thus, the higher the score, the higher the maintenance of care is. [93,95]

Table 7: Criteria for the classification of intensive and intermediate care units. Taken from [93]

Classification	IMC	ICU		
		Tier I	Tier II	Tier III
mean of TISS-28 points	none	≥22	≥27	≥32
specialized nursing staff per systemized bed	≥1.50:1	≥2.00:1	≥2.50:1	≥3.00:1
minimal number of systemized beds	4	6	6	6

Table 8: Criteria for the scoring of intensive and intermediate care units. Taken from [93]

scoring	IMC	ICU		
		Tier I	Tier II	Tier III
specialized nursing staff/systemized bed	$\geq 1.50:1 + 0.01$ per 0.1 TISS-28	$\geq 2.00:1 + 0.01$ per 0.1 TISS-28 above 22	$\geq 2.50:1 + 0.01$ per 0.1 TISS-28 above 27	$\geq 3.00:1 + 0.01$ per 0.1 TISS-28 above 32
additional points per day	480 + 3.0 per 0.1 TISS-28 over 16	748 + 3.4 per 0.1 TISS-28 over 22	1,134 + 4.2 per 0.1 TISS-28 over 27	1,664 + 5.2 per 0.1 TISS-28 over 32
	max. 657	max. 915	max. 1,340	max. 2,080

2.2.3 Individual Medical Procedures

In principle similar rules apply for individual medical procedures as for standard admissions. In total there are over 1,500 IMPs that each lead to one of over 200 IMP (MEL) groups. MEL groups also have associated case flat rates, minimum, maximum and average length of stay. One important differentiation is that in the case of multiple IMPs being simultaneously performed, only the one yielding the highest point score is reimbursed and consequently the procedure component of the most expensive procedure. Individual medical procedures can range from cataract operations and chemotherapies up to physiotherapeutic treatments and thus strongly vary in their respective costs. [93] In subchapter 2.4.4 the methodology of cost calculations of IMPs for the model is covered.

2.3 Data Acquisition and Data Sets

The backbone of stochastic approaches and statistical simulation methodologies is a comprehensive data basis. As described in the introduction section, for the discrete event method several or timewise longer simulation runs have to be performed to get reliant and statistically significant results. The bottleneck of most studies for alternative treatment methods for HF patients and published modeling approaches is the underlying data structure. Results from studies with follow-up times of mostly half a year and low recruitment numbers are strongly divergent and hamper the formulation of significant conclusions. One highlight of this work is the inclusion of huge data sets of health

insurance and health care providers as the basis for the model formulation. Through a collaboration with the Austrian regional health care provider Steiermärkische Krankenanstaltengesellschaft m.b.H (KAGes) in 2012, the conventional treatment of heart failure patients could be assessed and served as a basis for the conceptualization of the simulation model, resulting in the publication by Schroettner et al 2013 [94]. This teamwork got revitalized in 2018 and was vital to model the conventional care of HF patients in the publication by Lassnig et al in 2019 [36]. Through cooperation with one of the largest Styrian (region of Austria) health insurance provider, data on outpatient care for HF patients could be assessed in 2016. This would not have been possible without the partial employment at the health insurance provider's premises.

In October 2012 the, so far, largest clinical trial in Austria regarding telemonitoring of HF patients in combination with nurse support "Integrated Telemonitoring and Nurse Support Evaluation in Heart Failure" (INTENSE-HF) was started by the Medical University of Graz, the Ludwig Boltzmann Institute for translational heart failure research, the Austrian Institute of Technology and Graz University of Technology, aiming for an enrollment of roughly 350 participants in Graz. The task for Graz University of Technology was to perform statistical analyses and, if possible, to create a simulation model. However, this study didn't meet its recruitment goals and was prematurely closed. [96] Therefore the simulation of DMPs and telemonitoring applications could not be realized with the anticipated input data and had to be based on literature. With the health insurance provider and KAGes a sophisticated conventional model framework was developed. Each data set is detailed in subsequent chapters.

2.3.1 Data Set KAGes

The regional health care provider KAGes provided the Institute of Health Care Engineering with the European Testing Center of Medical Devices (IHCE) with a huge, anonymized and monocentric data set of conventional care of heart failure patients in Styria. This data set is intended for scientific purposes only and was derived from their Health Information System (HIS). Altogether 7.412 HF patients (50.39 % male, 49.61 % female) between 2006 and 2016 with 10,449 admissions in total were represented in the data. The criteria for patients to be included in the data set were hospital discharges based on the 10th Revision of the International Statistical

Classification of Diseases and Related Health Problems (ICD-10) for HF (I50.0x, I50.1x, I50.9 or I11.0x). Figure 5 presents the age distribution for both genders.

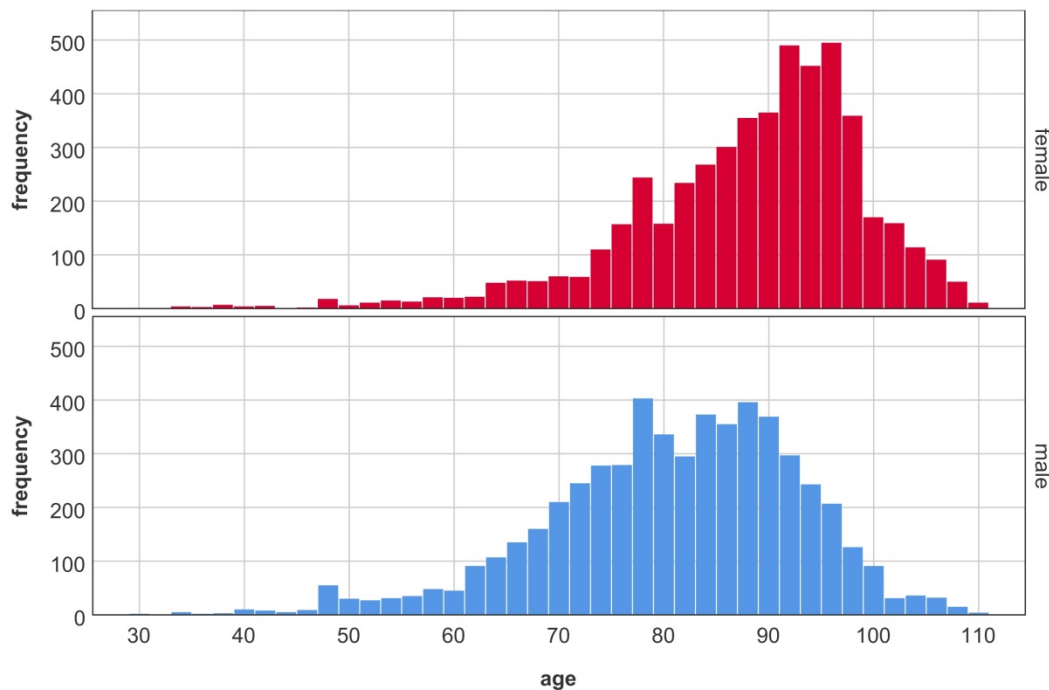


Figure 5: Histograms of heart failure patients in the data set for inpatient care

The data included medical reports for each hospital stay. NYHA classes based on medication, ICD-10 codes and medical procedures were derived for each patient. Based on guidelines on the treatment of HF patients [97,98], 62 % of the patients could be assigned to NYHA classes. KAGes also provided a data set with information on treatment in outpatient clinics for 14,234 patients (59.95 % male, 40.05 % female) with an overall of 25,939 visits. Median age for both genders was 69 years. 53.3 % of the patients could be classified in accordance to the NYHA classification system. [36]

2.3.2 Data Set Health Insurance Provider

Through cooperation with a Styrian health insurance provider, general anonymized data on outpatient care for heart failure patients could be assessed. This data set included records for 10,775 patients, collected between 2008 and 2013, covering information on admissions, treatment expenses for physicians/specialists and details on medication. Age distributions for both genders are visualized in Figure 6. Several million rows of data formed the basis to analyze and summarize medication. No information on outpatient death and overall mortality based on ICD-10 was included.

Derived costs for medication and the respective probability density functions are collected in Table 54 (see Appendix). [36]

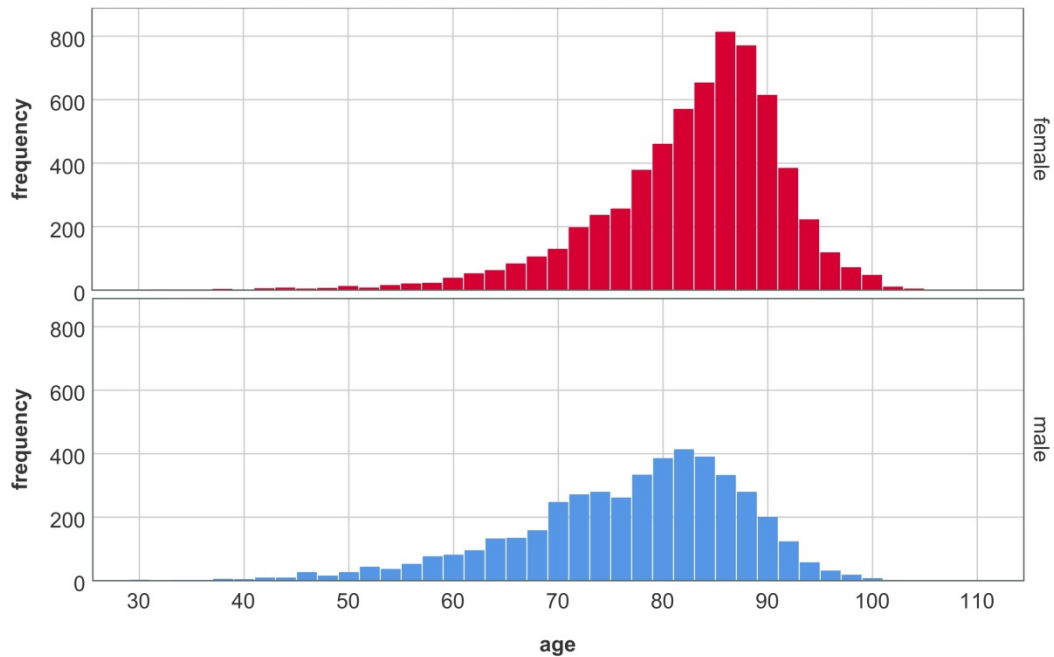


Figure 6: Histograms of heart failure patients for outpatient care based on the data set of the health insurance provider

2.4 Data processing and Analyses

To derive information out of the mentioned data sets it was necessary to analyze the data accordingly. In general the data quality was rather high for both data sets; only sparsely including missing values or multiple entries with the same information. To properly handle the data sets mostly IBM SPSS Statistics (Version 25) was used. Additional analyses were performed with R (Version 3.5.1). The basic process to assess best fitting probability density functions was to use the simulation function of SPSS after reducing outliers with the 95 % confidence interval and then analyze the goodness of fit based on Anderson-Darling and Kolmogorow-Smirnow. Due to the nature of HF and the source data, Weibull-, Gamma- and Lognormal functions were proper descriptions, which are commonly used to analyze health care data [99,100]. This was done for all density functions in chapter 2.5. In case the data disallowed significant predictions, median values were taken as the basis for simulation. Very specific algorithms had to be implemented to derive information for e.g. the classification of patients or the calculation of medication and hence will be covered in subsequent

chapters. Note that results of the data analysis won't be covered in this section, but will be further explained in the specific parts of the simulation model in chapter 2.5.

2.4.1 Age Groups

In general, for data analyses every patient in the data sets was considered except patients with LOS of less than one day. To deduce information and trends, the role of age and gender on treatment outcomes was of interest and thus explicitly investigated. By using statistical approaches to find the optimal class sizes, depending on the question in mind, different configurations would have been optimal. The decision was made to categorize patients into age groups based on literature to increase comparability of the model to other approaches, studies and models and lastly for model validation and generalizability of results. The age groups ≤ 55 , $56 - 65$, $66 - 75$, $75 - 85$ and ≥ 86 years were chosen as the best fit in terms of prevalence of HF and comparable approach to most research articles covered in meta analyses, such as [101]. As detailed in the introduction section, HF as a disease is mostly affecting people above the age of 65 years with a distinct difference between men and women in prevalence. This was supported by the data sets, where most patients were in higher age groups and specifically men suffered from heart failure at an earlier stage compared to women (see Figure 5 and Figure 6).

2.4.2 NYHA Classification

The KAGes data set had no direct information on the state of health of HF, thus the state of health had to be derived based on medication, individual medical procedures and anonymized clinical reports. An algorithm was deduced and implemented to classify patients to either one of the four NYHA classes. The algorithm consists of keywords for the categories NYHA class, implants, medication and text (see Table 9) that are being searched in the free texts of clinical reports and then evaluated with a ranking system that is based on clinical guidelines for heart failure therapy. [97,98,102–105]

Table 9: Keywords for the assessment of NYHA classes

NYHA class	implants	medication	text
I			NYHA I
I-II			NYHA I-II
II			NYHA II
II-III	ICD	ACE inhibitors beta blockers	NYHA II-III
III			NYHA III
III-IV	CRT ICD / CRT	diuretics ARBs	NYHA III-IV
IV	CRT		NYHA IV dyspnea at rest, lung edema, cardiac shock, cardiac decompensation, heart transplantation (HTX)

The keywords for the medication (Table 9) are generic terms for medication groups; the algorithm included names of specific drugs to assess the NYHA classes (see Table 10).

Table 10: Derivatives and representatives of drugs for heart failure therapy [37,59]

ACE inhibitors	beta blockers	diuretics /thiazides	loop diuretics	ARBs
Benazepril	Metoprololsuccinat	Hydrochlorothiazid	Furosemid	Candesartan
Captopril	Bisprolol	Chlortalidon	orasemid	Aprosartan
Lisinopril	Carvedilol	Indapamid	Piretanid	Irbesartan
Preindopril	Nebivolol	Xipamid	Traitmeren	Iosartan
Quinapril			Amilorid	Olmesartan
Rampril				Telmisartan
Trandolapril				Valsartan

Each admission or visit to the outpatient clinic in the data set was then categorized as “implants”, “medication” and “text”. E.g. a patient could have the classification “II-III” for implants, “III-IV” for medication and the “text” “NYHA IV”. This information was then ranked according to the sequence in Figure 7.

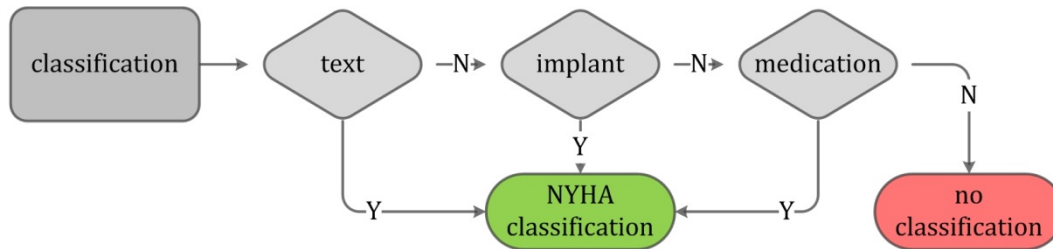


Figure 7: Ranking of clinical reports to assess NYHA classes

The direct classification by the physician had the highest priority, followed by implantable devices and then medication. Due to the likelihood of comorbidities of HF patients, there was no clear indication whether or not drugs were prescribed based on the principal diagnosis. To reduce classification errors due to misspellings, missing words, case sensitivity, etc., clinical records were first transformed into lower case, which was done with the *LOWER*-function of SPSS. The *INDEX*-function was then used to compare keywords within the clinical reports. Multiple combinations of keywords were used to reduce spelling mistakes, including abbreviations. An example for one (for the example shortened) search line would be:

DO IF (*INDEX(LOWER(LANGTEXTFELD1), nyha i-ii) > 0*) ***OR***
(INDEX(LOWER(LANGTEXTFELD1), nyha i - ii) > 0) ***OR***
(INDEX(LOWER(LANGTEXTFELD1), nyha i bis ii) > 0)

In general there is rarely the necessity of inpatient care for HF patients below NYHA class III, which is supported by the data. With the help of cardiologists from KAGes the additional keywords for symptoms in Table 9 for NYHA class IV patients were added to improve classification outcomes. Overall results of the classification for inpatient care can be seen in Figure 8.

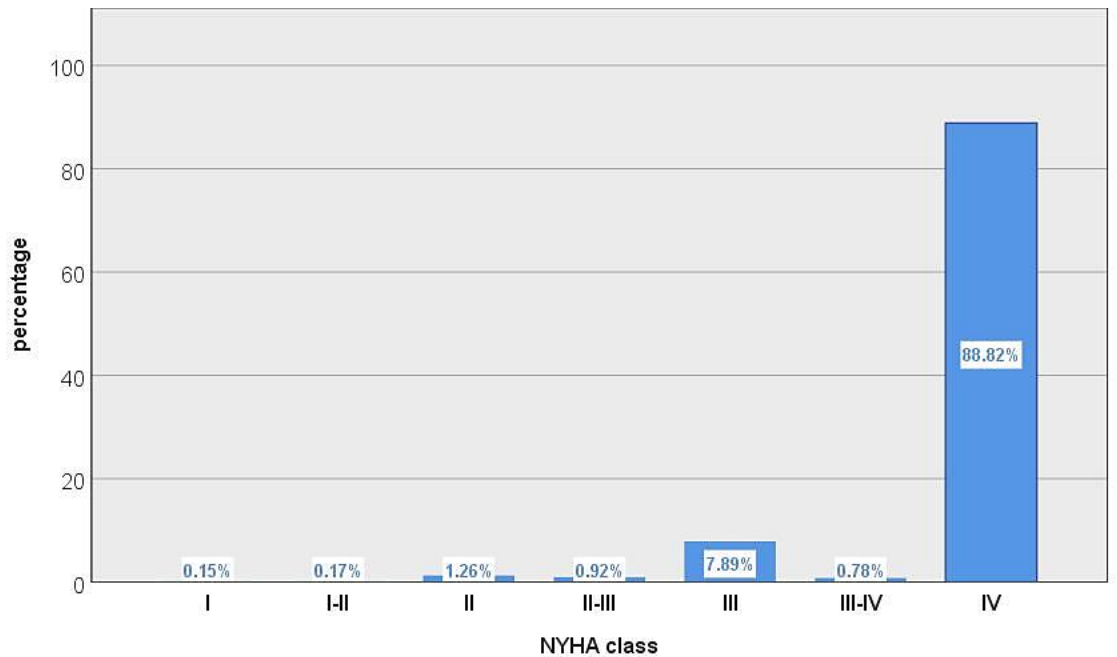


Figure 8: NYHA classification for admissions to inpatient care

Per admission there was a field in the data base of KAGes for the anonymized admission diagnosis as well as a discharge diagnosis. The free text at hospital discharge had a higher priority, since it usually is more specific. If there was no discharge classification at hand, the admission diagnosis was used for the classification. The classes I-II, II-III and III-IV represent patients who could not be clearly categorized into one NYHA class. For further calculations they were split half and half to the lower and higher NYHA class to analyze their course of treatment.

There is an obvious difference between the distribution of NYHA classes in outpatient and inpatient care, as can be seen by comparing Figure 8 and Figure 9. For the outpatient clinic the crux for the classification was that there were often multiple entries per visit to the clinic with the same identification number, since results from e.g. laboratory tests were also given a date and number. The work around was to use the most recent classification to the actual physical visit at the outpatient clinic as the reference.

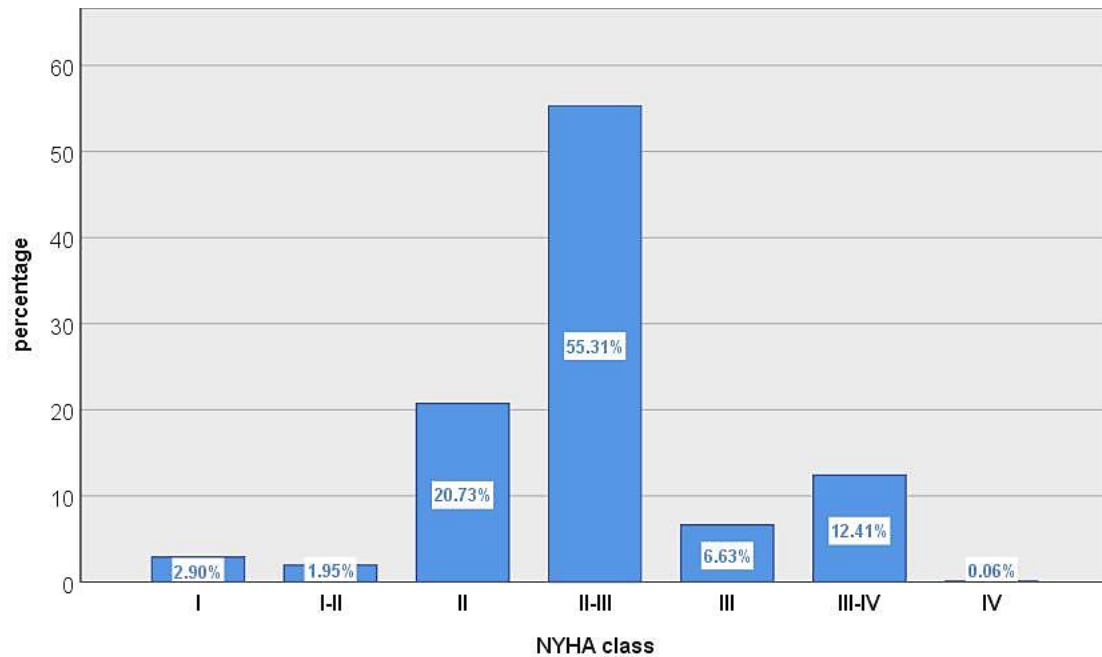


Figure 9: NYHA classification for visits to the outpatient clinic

Based on the classification scheme the NYHA classes II and III are predominant for patients visiting the outpatient clinic. Most of them could not be clearly identified as being either NYHA class II or III. NYHA classes I and IV are scarcely reported in outpatient care.

2.4.3 Medication

The data set of KAGes included medication in clinical reports, which greatly promoted the assignment of NYHA classes to patients or cases. The data set of the health insurance provider though offered information on expenses per patient, which was necessary for health economic analyses. In general costs for medication was given based on clearing items of the health insurance provider, more precisely the part they take over in covering costs for individual prescriptions. Several million data rows were available, forming large matrices that were further split and analyzed with SPSS.

Most importantly, medication was classified based on the Anatomical Therapeutic Chemical (ATC) Classification System, which classifies drugs according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. This system is controlled by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC) and was first published in 1976. Active substances are classified in a hierarchy with five different levels; the system has fourteen main anatomical/pharmacological groups (1st levels). Each ATC main group is

then further divided into 2nd levels which can be either pharmacological or therapeutic groups. The 3rd and 4th levels are pharmacological, chemical or therapeutic subgroups and the 5th level is the chemical substance. Table 11 gives an overview of the five levels. [106,107]

Table 11: ATC classification system, 5-level scheme

Level	Description
First level	Anatomical main group
Second level	Therapeutic subgroup
Third level	Pharmacological subgroup
Fourth level	Chemical subgroup
Fifth level	Chemical substance

In case of heart failure, the main ATC groups are C03 (diuretics), C07 (beta blocking-agents) and C09 (agents acting on the renin-angiotensin balance) and their subgroups. The data set of the health insurance provider does not distinguish between medications for HF or other diseases, therefore the three mentioned codes were used to finally assess costs for the medication of HF patients. The next step was then to cluster medication, visits to physicians, etc. for each patient and evaluate them in terms of age, gender and time distribution. Results were cost distributions of medication per age and gender for HF patients. This was done for the main groups of ATC-Codes and subgroups of medication. An overview with drugs classified with ATC codes can be taken from Figure 10, the number of prescriptions per patient is listed in Table 12 and the resulting costs are presented in Table 13.

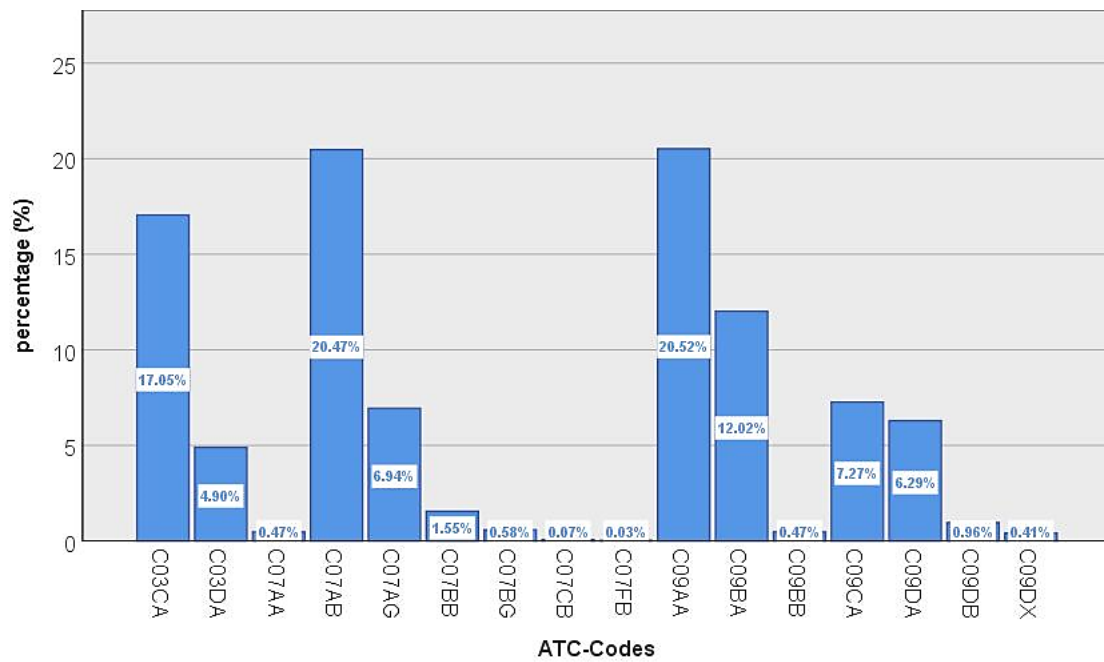


Figure 10: Frequency of prescribed medication based on ATC codes in the data set for the main groups ATC 03, 07 and 09.

Table 12: Overview of prescriptions per ATC main group, patient and year

ATC main group	Prescriptions				
	per patient				sum
	mean	median	minimum	maximum	
C03	18	11	1	347	145,214
C07	26	20	1	168	203,972
C09	41	34	1	247	359,598

Table 13: Overview of costs per ATC main group, patient and year

ATC main group	Costs				
	per patient				sum [€]
	mean [€]	median [€]	minimum [€]	maximum [€]	
C03	166.59	75.60	1.25	5410.60	335,255.90
C07	238.54	149.17	1.20	2611.50	1,871,607.45
C09	569.77	377.95	2.35	4714.45	5,051,563.40

Ultimately the goal was to derive probability density functions for each ATC main group considering age and gender. This was done with the simulation function of SPSS, best fits were mostly Weibull- and Gamma- functions. Detailed parameters can be taken from Table 54 in the Appendix.

2.4.4 Individual Medical Procedures

As the second most important aspect of reimbursement in inpatient care, individual medical procedures (IMPs) are also covered in the data set by KAGes. The number and type of IMPs per patient is highly divergent in the data set, therefore instead of the aforementioned cost calculation system for IMPs, a different approach has been taken. The method chosen for the further modeling of inpatient care was to calculate mean costs of all consumed IMPs per patient and NYHA class and multiplying them with the average number of use. In the data set IMPs were saved in one string, therefore firstly this string was divided and written into individual cells as new variables with the SPSS command *char.substring(string,pos,length)*. The maximum number of IMPs per stay was 8; therefore 8 variables have been created for each patient. For some patients the individual medical procedure was defined with “NA” for not available and thus not further considered. Altogether 332 different IMPs were classified for the HF patients. For the first analyses so-called “multiple response sets” in SPSS were used to define categorical variables. After the first assessment, Pareto-analyses were performed to identify most common IMPs for each patient class. IMPs that were less frequent than 1% were excluded from the analysis as an assumption to simplify further calculations. This one percent of IMPs was, on average, more expensive than the others, but not applicable for most patients. Costs for IMPs are based on the catalogues of the Austrian DRG system. A cost calculation table published by the Austrian Federal Ministry of Labor, Social Affairs, Health and Consumer Protection [108] was used to derive costs for each IMP. This table relates costs for each IMP to the costs of IMP HH040 (appendectomy open). Based on these relations and the information that an appendectomy on average is reimbursed with 3,959.33 LDF points, LDF point scores could be assessed per IMP and patient. Calculated values were multiplied by the performed procedures in the data set and divided by the total number of all consumed IMPs to get average costs per day and IMP. To better understand this process the following calculation example may be helpful:

total number of all IMPs in the investigated class of patients: 781

LDF-point score for HH040: 3,959.33

Exemplary consideration of IMP ZA010 (Computer Tomography – Head and Neck):

- Number of performed operations: 89
- Cost relation to HH040: 0.12711 (based on calculation table)

-
- i. $relative\ frequency(ZA010) = \frac{89}{781} = 11.39\%$
 - ii. $mean\ of\ LDF - points\ (ZA010) = 3,959.33 * 0.12711 = 503.27$
 $\rightarrow relative\ points\ in\ class = (i) * (ii) = 57.32$

These steps then have been done for all IMPs in each patient group; relative points were summed up and divided by the different kinds of IMPs to get the mean value of one singular IMP. Similar to LDF-groups of admissions, there are several nodes for IMPs with distinct scores for procedure and daily component that depend on age, type of disease, etc. and thus influence the final score. For the calculations in the model the mean value of IMP HH040 of LDF-scores was used to reduce complexity.

2.5 Simulation Model

The chapter Simulation Model explicitly describes the construction and use of the model with the input parameters derived from data analyses. Since the model was built over many years in various versions based on different data bases and to answer different scientific questions, a short history will be given to the modeling environment and the overhauled model features. Aspects of verification, validation and the presentation of results will be further explained, serving as the background to the results section. In general this chapter is based on the publication by Lassnig et al in 2019 in the *BMC Journal Medical Informatics and Decision Making*, which won't be continuously cited in this section [36]. To describe the model in more detail, also on how it mathematically works, for each subsequent section the specific AnyLogic® elements will be described with their inherent functionalities.

2.5.1 A Short History

The first simulation model built on the Institute of Health Care Engineering with AnyLogic® goes back to over 10 years ago. The system dynamic modeling of the Austrian population growth and a SD model on diabetes mellitus type 2 were the first topics covered. Besides logistic simulations of processes in emergency departments, the first heart failure model was created in the following years. This model was built with the discrete event methodology with the aim to precisely reflect a study design which investigated the effects of home-based telemonitoring using mobile phone technology on the outcome of heart failure patients (MOBITEL) [85]. This model was based on 54 patients for conventional and telemedical care and allowed further investigations and optimizations of methods of care, including specialists and physicians as well as inpatient care, expressing time transitions with triangular functions. This HF model was further developed and expanded between 2012 and 2013, key features were e.g. the vastly improved process flowchart of the discrete event model and its translation into programming language as well as the collaboration with KAGes, which delivered a vastly improved and more comprehensive data base. All this was summed up in the publication in 2013 [94]. Age and gender were though not regarded and parameters of individual agents could not be tracked. Effects of the telemonitoring system were still based on the MOBITEL study, which had a follow-up period of half a year. The investigation of effects of disease management programs was another topic covered in those years and was frequently discussed at international conferences. A few conference publications later and through the first collaboration with an Austrian health insurance provider and additional contributions of KAGes, new ideas came up and allowed for thinking outside the box. In this context the old, static model was not sufficient enough to describe the treatment of heart failure patients on a statistically significant level. Therefore further model progress had to be based on improved data sets and statistical analyses which led to the conclusion to leave the purely discrete event model behind and build a hybrid model, including agent based and discrete event modeling. This new approach led to further conference contributions as well as another paper in 2019 [36], on which basis this work was written. The subsequent chapters go into detail to precisely describe the presented model. The modeling of heart failure was not the only topic though which was investigated over the years, many models were created to find and overcome bottlenecks in the health care sector, e.g. time in stroke treatment, hip and

knee joint replacement (resulting in a publication in 2016 [109]), population forecasts with probabilistic approaches and the treatment of diabetes mellitus type 2.

2.5.2 Modeling Methodology and Overview

The presented model builds upon on a previously published HF treatment model [94], further advancing modeling methodology and complexity. The original discrete event model was complemented by an agent based approach to form a comprehensive hybrid model which combines advantages of both methodologies. Discrete event models offer middle to low degrees of abstraction. Discrete steps, implemented with their respective transition probabilities, directly match the flow chart nature of the clinical pathway.

The agent based modeling approach allows including patients with distinct features. Each entity in the model is represented as an agent of the class “Patient”. Parameters such as age, gender, state of health and the patient’s history through the course of treatment classify each individual and influence transition probabilities along the decision tree of the discrete model. Both methods align naturally thanks to the structure of the virtual flow chart (see Figure 11) with agents passing through it. The introduction of a patient collective (patient pool) to inpatient and outpatient care for heart failure patients, allows for more in-depth analyses of individual behavior through the agent based approach.

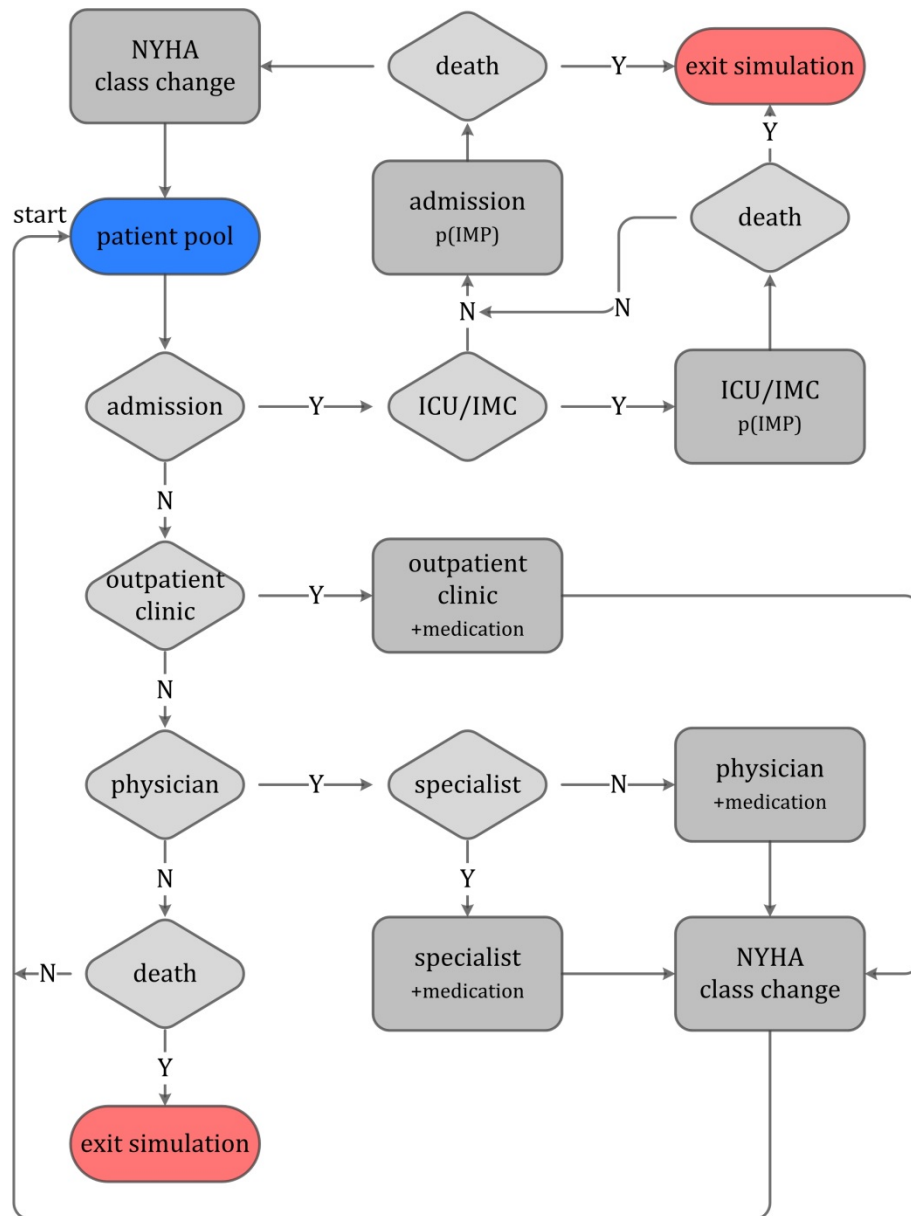


Figure 11: Flow chart of the clinical pathway implemented in the model.

Every simulation run begins with the starting point at the patient pool, where the cohort to be simulated is generated. The next step is to face transition probabilities for admissions, the outpatient clinic, the physician or potential death. In case of an admission to the hospital there may be the necessity for a stay at an intensive care unit (ICU) or intermediate care unit (IMC). Again, patients can then potentially improve their state of health, stay in their respective NYHA class or further deteriorate in health, which leads to either admissions to standard care or death. After the admission based on an HDG for HF, the treatment with individual medical procedures may be necessary (this is summarized within the block admission). After inpatient care the state of health of patients can further improve, maintain or deteriorate. If there is no death event, they

return to the patient pool. For outpatient clinics, physicians and specialists the same routines apply, after the treatment they may get medication and may change their state of health.

To evaluate the state of health, New York Heart Association (NYHA) classes are used to differentiate four groups by severity of HF, correlating with different frequencies, lengths and costs of the treatment procedures. The open model framework allows simulating different specific patient collectives and study cohorts by introducing adaptable parameters such as age and gender distribution and certain risk factors (e.g. comorbidities, obesity, smoking, etc.). Transitions between NYHA classes are implemented as a way to evaluate improvement or deterioration of the state of health. To give insight to exemplary model dependencies, Figure 12 visualizes the interactions between outpatient care, inpatient care and the patient pool. The agent symbol refers to information saved in the individual agent record. Several additional features can be implemented and adapted for each treatment area to simulate specific study designs.

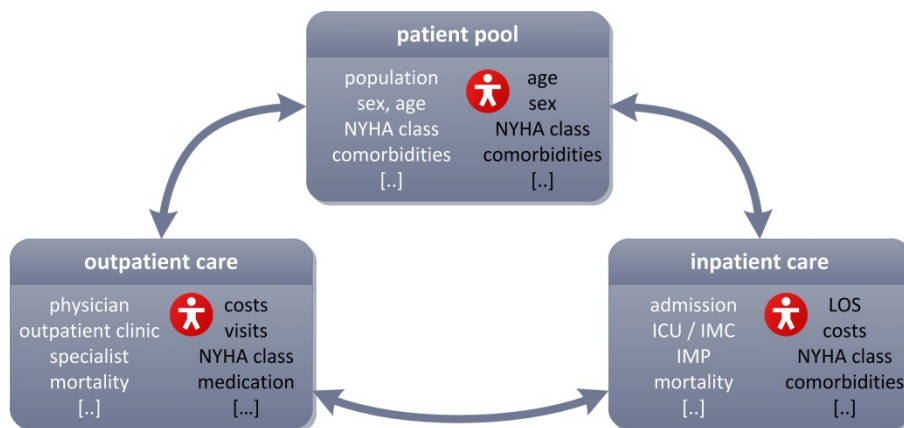


Figure 12: Simplified overview of interactions between patient pool, outpatient and inpatient care. Parameters describing the treatment procedures are illustrated in white font, interactions within the agent profile in black respectively.

For simulation, the Java based software AnyLogic® (Version 8.3) was used. Statistical analyses were performed with R (Version 3.5.1) and IBM SPSS Statistics (Version 25). The subsequent subchapters further detail the model structure of the hybrid model.

2.5.2.1 Discrete model

The discrete model is described as a Markov model with a set of distinct states q_i ($i = 1, \dots, M$) and transition probabilities p_{ij} , describing the probability for a transition from state q_i to state q_j (see Figure 13).

The transition probabilities are derived from rate constants per day (sampling size $\Delta t = 1$) taken from clinical data. Discrete states are the inactive state in the patient pool, the physician, the specialist, the outpatient clinic and the hospital, which is further divided into intensive and intermediate care. For the discrete system the probability P_i of being in state q_i at time $k+1$ can be derived from the probability P_i at time step k and the outgoing and incoming probabilities of state q_i in the following way [110]:

$$P_{i,k+1} = \left(\sum_{j=1}^N P_{j,k} p_{ji} - \sum_{j=1}^N P_{i,k} p_{ij} \right) \cdot \Delta t + P_{i,k} \quad (3)$$

where N is the total number of discrete states, p_{ij} describes the conditional probability of finding the system in a new state q_j , if it has recently been in state q_i . (p_{ij} corresponds to transitions out of state q_i and p_{ji} to transitions entering state q_i).

2.5.2.2 Extended hybrid model

In the presented hybrid model the discrete model is combined with an agent based approach. For the simulated scenarios in chapter 3 the probabilities for state transitions p_{ij} depended on the following inner states \vec{x}_v of the agent v :

$$\vec{x}_v = \begin{bmatrix} \text{age} \\ \text{sex} \\ \text{NYHA} \end{bmatrix}, v=1, \dots, n \quad (4)$$

...whereas n is the total number of patients

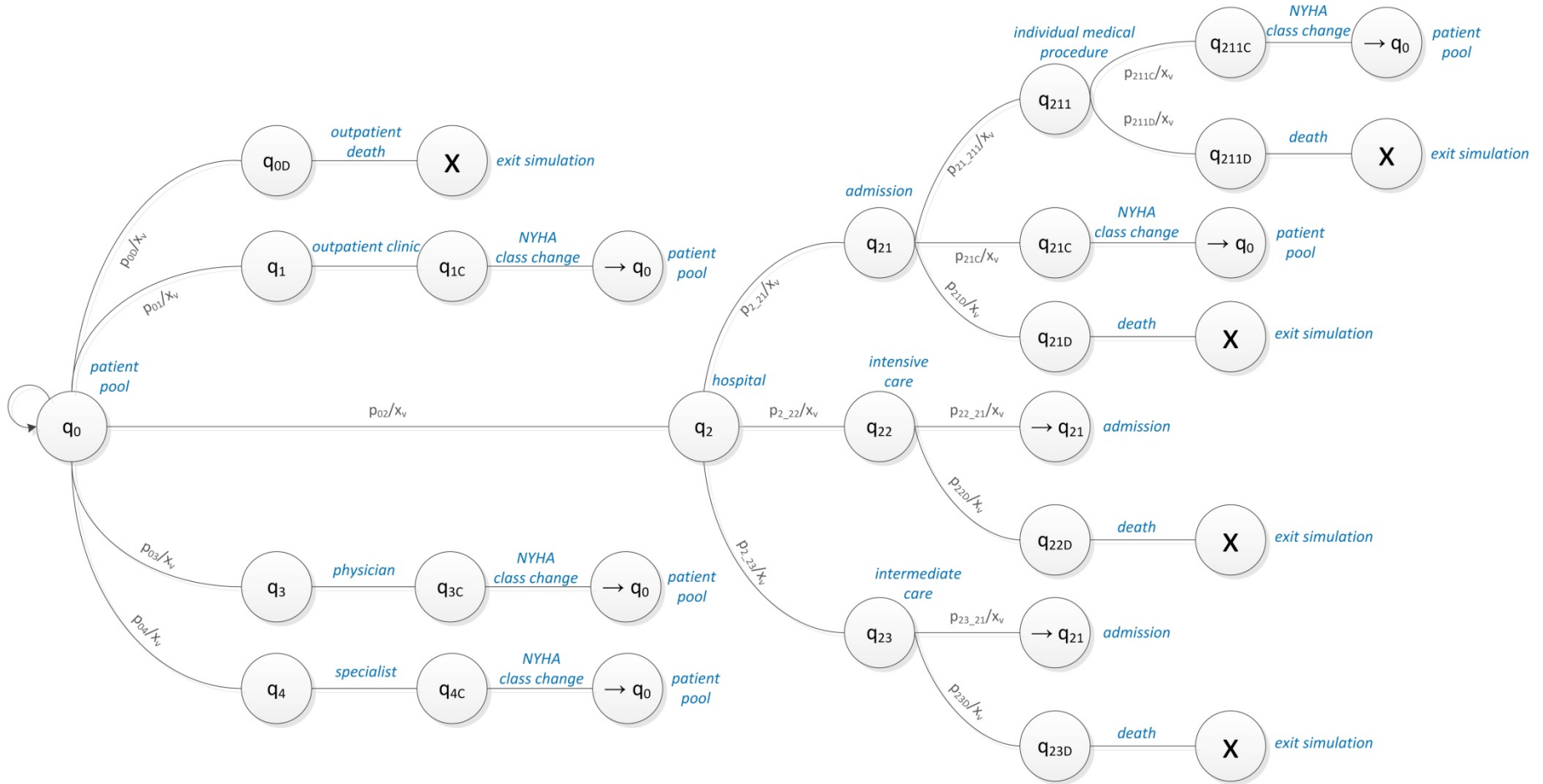


Figure 13: State transitions in the hybrid model, starting with the ground state q_0 of patients in the patient pool. x_v are the inner states of the patient and p_{ij} the transition probabilities from state q_i to state q_j

Based on comprehensive data these three inner states can be further expanded to e.g. also investigate effects of comorbidities or risk factors. Additionally each agent also contains a set of auxiliary variables \vec{a}_v logging necessary information per agent on the course of treatment. These variables comprise costs, frequencies of visits, lengths of stay and are further explained in sections 2.5.4 to 2.5.7. (ATC...Anatomical Therapeutic Chemical Classification System Codes, IMP...Individual Medical Procedures, DMP...Disease Management Program, LOS...Length Of Stay, IC...Intensive Care, IMC...Intermediate Care)

$$\vec{a}_v = \begin{bmatrix} \text{outpatientClinicCosts} \\ \text{physicianCosts} \\ \text{specialistCosts} \\ \text{ATC03} \\ \text{ATC07} \\ \text{ATC09} \\ \text{ATCxx} \\ \text{admissionCosts} \\ \text{intensiveCareCosts} \\ \text{intermediateCareCosts} \\ \text{IMPCosts} \\ \text{DMPCosts} \\ \text{LOS} \\ \text{LOSINT} \\ \text{LOSIMC} \\ \text{visitsPhysician} \\ \text{visitsSpecialist} \\ \text{visitsOutpatientClinic} \\ \text{visitsInpatientCare} \\ \text{visitsIntensiveCare} \\ \text{visitsIntermediateCare} \\ \text{visitsIMP} \\ \text{acquisitionDMP} \\ \text{fixedRateDMP} \\ \text{history} \end{bmatrix}, v=1, \dots, n \quad (5)$$

The initial inner states of the patients follow set values or probability distributions that can be defined at the beginning of the stimulation. In the presented use cases these probability distributions were defined mainly based on data sets of Austrian health insurance and health care providers (see chapters 2.3.1 and 2.3.2). After leaving a specific state q_i there are potential changes of the inner state x_v of the patient which in turn may alter the state transition probabilities. Investigating selective problems and scientific questions can be carried out by changing state transition probabilities. In case

of death, patients exit the simulation run and do not interact with the virtual environment anymore. Each individual simulation run is based on a random number generator initialized with random seeds.

The inner state changes of the agents are not fully independent. For example, the prescription of medication depends on age and gender as well as state of health (NYHA class) of the patient. Thus investigating selective problems and scientific questions can be carried out by changing state transition probabilities. In case of death, patients exit the simulation run and do not interact with the virtual environment anymore. Each individual simulation run is based on a random number generator initialized with random seeds as the starting condition.

2.5.3 Model Description in AnyLogic®

Chapter 2.5.2 gave an overview of the processes and elements of the model structure from a more generic perspective. This subchapter is focusing on the simulation model in the environment of AnyLogic®. AnyLogic® as a platform or framework strongly supports the building process of a model, since many important features are already pre-defined and usable per drag and drop system. These elements, such as functions or events, even 3D-objects and data sets are pre-programmed classes that can be adapted to serve the desired functionality. They are optimized to intuitively work together and allow very clean and comprehensible modeling methods. Code that is entered is Java-based, thus every function of generic Java libraries can be used, for specific applications additional libraries can easily be added. The different elements of AnyLogic® and thus Java source code used in this model will be explained at the stage they are firstly used to have a common thread across the description of the model.

From a top down perspective, the *.alp*-executable of the built model is called *HeartFailure* and consists of the classes *Main()* and *Patient()* as well as several *Experiments*. *Experiments* store a set of configuration parameters of a model and are often used as simulation experiments, so-called *Simulations*. There are different types of *Experiments*, for this model several *Simulations* and a *Parameter Variation* have been used. A *Parameter Variation* is a type of *Experiment* that allows to run a model with different model parameters and to analyze how some parameters affect model behavior. Thus complex model simulations can be configured that comprise several single model runs, varying one or more root object parameters. The importance hereby is that

Parameter Variations can be used with fixed parameters to assess the effects of random factors in stochastic models.

The HF model is a combination of discrete event and agent based modeling and thus based on *random seeds*. *Random seeds* are random values used as the starting condition for a pseudorandom number generator. Every result in this work is created through the iteration of millions of probability density functions and other stochastic elements in the decision tree. The standard random number generator of AnyLogic® was used for the general simulations, the option to have runs with fixed seeds (thus reproducible experiments) was only used for testing procedures. In every simulation simultaneous events are handled with the *First-In First-Out* (FIFO) principle in the order of scheduling. The initialization of the experiment *Parameter Variation* will be covered in section 2.5.8 of this work.

Next to the classes and the experiment setups also so called *Option Lists* are implemented for the different NYHA classes and the sex of patients being simulated. *Option Lists* are generally used as elements for defining agent attributes that have limited choice of alternative options. They can be used, similarly to global variables, in every class. The newer versions of AnyLogic® also automatically include a *Run Configuration* to export model results to a cloud as well as a *Database* which stores defined parameter values that were produced throughout a simulation run.

The presented model flow in Figure 11 is only the translation of the flow chart that has been implemented in AnyLogic®. Figure 14 shows the general structure of the main model flow in AnyLogic®.

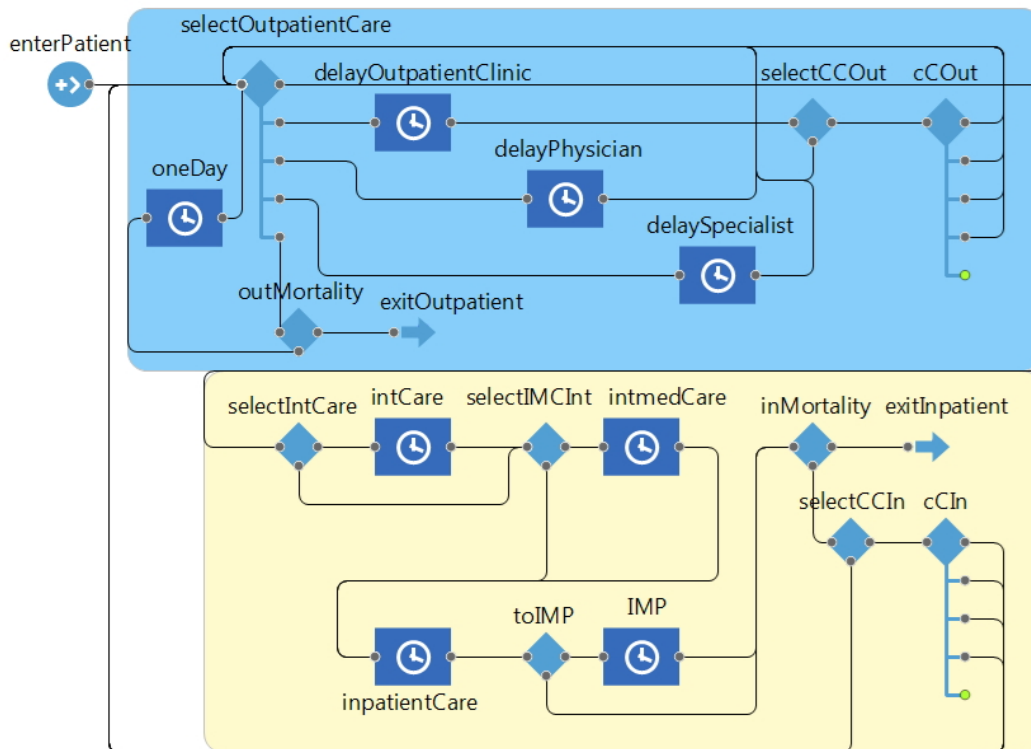


Figure 14: Model flow in AnyLogic®. Outpatient care is colored in blue and inpatient care in yellow

The source *enterPatient* can be seen at the start of each simulation run, which is connected to a patient pool. The *selectOutpatientCare* element is a multiple *selectOutput* function which, depending on in this case five different probability trees (which are further dependent on the NYHA class of the patient) selects one of them based on the random number generator and has the following structure:

- Probability 1: $\text{toHospital}(\text{agent.NYHA})/\text{timeFactor}$
- Probability 2: $\text{toOutpatientClinic}(\text{agent.NYHA})/\text{timeFactor}$
- Probability 3: $\text{toPhysician}(\text{agent.NYHA})/\text{timeFactor}$
- Probability 4: $\text{toSpecialist}(\text{agent.NYHA})/\text{timeFactor}$
- Probability 5: $1 - (\text{Probability 1} + \text{Probability 2} + \text{Probability 3} + \text{Probability 4})$

Thus this element triggers either admissions, visits to outpatient care or serves as a delay without any event. With the variable *timeFactor* the dependency of implemented probabilities on different time frames can be adjusted, in the standard case it is set for 365 days. In the unlikely case (wrong inputs) that the sum of probabilities 1 to 4 is higher than 1, probability 5 will not be executed and the simulation displays an error message due to invalid entry values for the individual probabilities.

Overall the model consists of hundreds of variables, parameters and functions that can be adjusted to meet specific simulation requirements or to adapt the model to study protocols. Each element that can be seen in Figure 14 has a defined set of functions that define their behavior or rather their effect on the patient if entered. Subsequent chapters detail the actual programming part alongside input values derived from the data sets for the patient collective, inpatient as well as outpatient care.

2.5.4 Patients

As mentioned before, patients are implemented as individual agents with distinct features such as age, the state of health (NYHA class) or the enrolment in a disease or telemonitoring program that are assigned at the start of the simulation. Additional attributes, such as comorbidities, quality of life and life style (e.g. smoking, drug abuse, alcohol), can be included in the model but were not considered for standard simulation runs. To verify model calculations and give insight into treatment effects on an individual level, a patient specific history file tracks all relevant parameters. The history file consists of timestamps of all events passed throughout the simulation run and may, for example, include: PH5 OC28 IC52 AD54 CC64. The example describes a visit to the physician on day 5 (PH5) and the outpatient clinic on day 28 (OC28), a stay for 2 days at an intensive care unit starting day 52 (IC52), followed by an admission for 10 days on day 54 (AD54) and, finally, a NYHA class change on day 64 (CC64) at hospital discharge.

In the simulation model itself the class *Patient* handles features of the constructed agents. They contain a defined set of variables and parameters as well as functions and events. Table 14, Table 15 and Table 16 give a short description of each element in the class *Patient*. Every agent thus inherits predefined parameters and then follows his own and individual path through the model.

Table 14: Parameters in the class *Patient* with type and description

parameters	type	description
sex	Sex (option list)	gender, either m or f
age	int	age of patient
NYHA	NYHA (option list)	NYHA1 to NYHA4
LOS	int	length of stay for standard admissions
LOSInt	int	length of stays for intensive care
LOSIntmC	int	length of stays for intermediate care
LOSSum	double	sum of LOS
LOSIntSum	double	sum of LOS intensive care
LOSIntmCSum	double	sum of LOS intermediate care
totalCosts	double	total costs per agent of class Patient
visitsPhysician	int	visits to the physician
visitsSpecialist	int	visits to the specialist
visitsOutpatientClinic	int	visits to the outpatient clinic
visitsInpatientCare	int	number of standard admissions
visitsIntensiveCare	int	number of admissions to intensive care
visitsIntermediateCare	int	number of admissions to intermediate care
visitsIMP	int	number of stays at hospital with individual medical procedures

Table 15: Variables in the class *Patient* with type and description

variables	type	description
outpatientCosts	double	costs outpatient care
outpatientClinicCosts	double	costs for visits to outpatient clinics
physicianCosts	double	costs for visits to physicians
specialistCosts	double	costs for visits to specialists
medicationCosts	double	costs due to medication
inpatientCosts	double	costs inpatient care
admissionCosts	double	costs for standard admissions

intensiveCareCosts	double	costs for intensive care
intermediateCareCosts	double	costs for intermediate care
IMPCosts	double	costs for IMPs
DMPCosts	double	costs for the DMP or telemonitoring
sumFixedRateDMP	double	costs of a fixed rate for the DMP
monthlyFixedRateDMP	double	costs of a monthly fixed rate for the DMP
acquisitionDMP	double	acquisitions costs for the equipment (DMP)
ATC03	double	costs ATC03
ATC07	double	costs ATC07
ATC09	double	costs ATC09
ATCxx	double	costs for the rest of the medication
history	String	initial value: ""
death	boolean	true or false

Table 16: Functions and events in the class *Patient* with type and description

functions/events	returns	description
costCalc()	void	<p>calculates overall costs through call from <i>Main()</i></p> <p>function body:</p> <pre> medicationCosts = ATC03 + ATC07 + ATC09 + ATCxx; outpatientCosts = outpatientClinicCosts + physicianCosts + specialistCosts + medicationCosts; inpatientCosts = admissionCosts + intensiveCareCosts + IMPCosts + intermediateCareCosts; DMPCosts = acquisitionDMP + sumFixedRateDMP; totalCosts = outpatientCosts + inpatientCosts + DMPCosts; </pre>
calcDMP()	void	<p>adds the monthly fixed rate of the DMP/TM to the sum of the fixed rate if the patient is still alive, otherwise does nothing</p> <pre> if (death==false) { sumFixedRateDMP += monthlyFixedRateDMP; } else {} </pre>
calcDMPEvent	function call	<p>event with trigger type 'timeout' in cyclic mode. Calls the function calcDMP() with a recurrence time of 30.42 days and first occurs at time (absolute) 0.</p>

The history file is a variable containing strings that are attached whilst patients pass elements in the class *Main* and grows throughout the simulation period until a patient dies. The function *costCalc()* is called in several elements of the class *Main* as well, to update and sum up all the arising costs and ultimately save them in specific data sets. This functionality is important to log and see values when the simulation is interrupted or closed abruptly. An event such as *calcDMPEvent*, is a possible way to schedule actions in the model. They are laid out to model delays and timeouts and thus work similar to timed transitions in statecharts, but may be more efficient. In general they can be timeout, condition or rate triggered. There are also dynamic variations of this element that are used to schedule any number of concurrent and independent events.

The class *Patient* is linked to the class *Main*. To construct a defined patient collective in the class *Main*, an agent block is integrated into the *Main* as a population of agents. In this case it is called *patient[.]* and includes the parameters previously defined in the class *Patient*. This population of agents is initially empty and then filled with agents at the start of the simulation run with attributes defined in the simulation screen. To load these agent parameters defined in the experiment into the class *Main*, the event *startModel* occurs once at the start of the simulation and has the following form:

event	description
startModel	<p>injects new patients into the population defined in <i>patient[.]</i> at the start of the simulation. It is triggered only once at the start of the simulation run and has the following actions:</p> <pre> calculateCostsOverLOS(minLOS, maxLOS); newPatientNYHA=NYHA1; enterPatient.inject(initialPopulationNYHA1); newPatientNYHA=NYHA2; enterPatient.inject(initialPopulationNYHA2); newPatientNYHA=NYHA3; enterPatient.inject(initialPopulationNYHA3); newPatientNYHA=NYHA4; enterPatient.inject(initialPopulationNYHA4); </pre>

The element *enterPatient* is the source defined in Figure 14, in which *patient[.]* is loaded as a population. The “manual” inject functions allow to have a numerically precise number of patients, with their respective starting NYHA class entering the simulation. The variables *initialPopulationNYHA#* (# is an abbreviation for the NYHA classes I to IV) can be defined at the start of the simulation run. The function *calculateCostsOverLOS()* has a specific use in calculating charges for the length of stay

per day based on the chosen input parameters. This is important to reduce computing efforts when a patient has an admission, because costs for specific LOS are calculated just once at the start of the simulation run and then saved into the array of the type `double costsLOS[]` (see Table 17 for further details).

Table 17: Calculation of costs per LOS for inpatient care at the start of the simulation run

element	returns	description
calculateCostsOverLOS(minLOS, maxLOS)	void	<p>function that calculates the costs for LOS based on input parameters for inpatient care. The arguments <i>minLOS</i> and <i>maxLOS</i> are of the type <i>double</i> and describe the minimum and maximum length of stay for the modeled primary diagnosis.</p> <p>function body:</p> <pre> double[] charge = new double[1825]; double RateLDF; for (int LOS = 0; LOS<1825; LOS++) { // LOS is shorter than min LOS if(LOS < minLOS){ RateLDF= procedureComponent + (dailyComponent*LOS) / minLOS; charge[LOS] = Math.round(RateLDF)*euroLKF; } //LOS is between min and max LOS if(minLOS <= LOS && maxLOS >= LOS){ charge[LOS] = fixedRateLDF * euroLKF; } //LOS is longer than max LOS if(LOS > maxLOS){ double surcharge = (dailyComponent/meanLOS)*(maxLOS/LOS); if (surcharge < (dailyComponent/meanLOS)/2){ surcharge = (dailyComponent/meanLOS)/2; } RateLDF = charge[LOS-1] + surcharge; charge[LOS] = Math.round(RateLDF)*euroLKF; } //traceln(charge[LOS]); } costsLOS = charge; </pre>
costsLOS	double[]	array displaying the costs per day of a hospital stay

Sections of code that are in blue with the double slashes “//” are comments. The `traceln(charge[LOS])` function is an inherent Java code that writes the index of the `charge` array in the console of AnyLogic® and therefore allows the verification of the calculations of costs per LOS. The function in Table 17 basically is the programmed solution of the formulae for transgressions of the maximum and minimum LOS defined in chapter 2.2.1.

The population of patients is further used for gathering statistics, which is directly implemented in the element `patient[..]` and saves results in so called *data sets*. A *data set* is capable of storing 2D (X, Y) data of type *double* and maintains the up-to-date minimum and maximum of the stored data for each dimension. A limited number of the latest data items is stored, in the case of this model every data point (thus every action per day) is logged and further computed, summing up e.g. 1825 data points for a simulation time span of 5 years. Data sets used in the class *Main* to access patient statistics are listed in Table 18.

Table 18: Data sets in the class *Main* assessing the statistics of the patient population. #...is a space holder for integers between 1 and 4

data set	accessing statistics of the patient population with the command:
totalCostsDS	patient.totalCostsPatients()
totalCostsNYHA#DS	patient.totalCostsNYHA#()
totalCostsOutpatientDS	patient.outpatientCostsTotal()
totalCostsOutpatientNYHA1DS	patient.outpatientCostsNYHA#()
totalCostsInpatientDS	patient.totalCostsInpatientCare()
totalCostsInpatientNYHA#DS	patient.costsInpatientCareNYHA#()
visitsPhysicianNYHA#DS	patient.countPhysicianNYHA#()
visitsOutpatientClinicNYHA1DS	patient.countOutpatientClinicNYHA1()
patientCountNYHADS	patient.countNYHA1()+patient.countNYHA2()+patient.countNYHA3()+patient.countNYHA4()-deathsNYHA1-deathsNYHA2-deathsNYHA3-deathsNYHA4
patientCountNYHA#DS	patient.countNYHA#()-deathsNYHA#
visitsIPNYHA#DS	patient.countInpatientCareNYHA#()
LOSNYHA#DS	patient.LOSNYHA#()
visitsICNYHA#DS	patient.countIntensiveCareNYHA#()

visitsIMCNYHA#DS	patient.countIntermediateCareNYHA#()
visitsIMPNYHA#DS	patient.countIMPNYHA#()
medicationCostsNYHA#DS	patient.medicationCostsNYHA#()
DMPCostsNYHA#DS	patient.DMPCostsNYHA#()

2.5.5 Outpatient Care

The patient flow through outpatient care is represented in Figure 11 (page 39). Key elements are the physician, the outpatient clinic as well as the specialist and medication, which are implemented as *delay* elements in the model. Expenses for visits to health care providers are implemented with a median value per visit. Data for visits to physicians was derived from a Styrian health insurance provider; standard rates for such treatments account for €544 (mean) per year and patient. [111]

Expenses for outpatient clinics are approximated from the Styrian benefits catalogue for standard procedures, with the first visit being reimbursed with €209 and later ones with €134. [112–115] As standard procedures 12-channel resting electrocardiography (ECG), exercise ECG, transthoracic ECG, 24-hour blood pressure measurement, 24-hour ECG and x-ray scan of the thorax haven been considered. The 24-hour ECG and the 24-hour blood pressure measurement are not performed routinely; therefore there is a difference between the first year and later years. [116]

As an important classification and treatment criteria, medication is based on the Anatomical Therapeutic Chemical Classification System Codes (ATC) with the main groups C03 (diuretics), C07 (beta-blocking agents) and C09 (agents acting on the renin-angiotensin balance) and their subgroups. Accounting data were used to derive costs and frequency of prescriptions. Table 19 shows probability density functions of medication with costs per year and patient based on gender and ATC group. Expenses for the aforementioned ATC groups account for roughly 30 % of overall costs for the medication for HF patients. [111] Thus, the sum of the density functions in Table 19 was multiplied by a factor of 3.33 in order to more realistically estimate medication costs. The state of health and the cause of outpatient death (in terms of ICD-10 codes) were not included as parameters in the data set from the health insurance provider and therefore disregarded.

Table 19: Probability density functions for medication in outpatient care, based on ATC-10 codes

ATC / sex	male	female
C03	Weibull(59.83, 0.78)	Weibull(43.27, 0.93)
	$p \leq 0.01^a$, N=3180	$p \leq 0.01^a$, N=4668
C07	Gamma(51.30, 1.33)	Gamma(56.67, 1.25)
	$p \leq 0.001^a$, N=3218	$p \leq 0.001^a$, N=4451
C09	Weibull(153.11, 1.12)	Weibull(165.84, 1.13)
	$p \leq 0.01^a$, N=3593	$p \leq 0.01^a$, N=5087

a... goodness-of-fit based on Anderson-Darling Test

As already mentioned delays are implemented to describe procedures in outpatient care (the blue section in Figure 14, page 46). Each “delay” element has a delay time of one day, thus there cannot be more than one visit to outpatient care per day. If there is no action after the *selectOutpatientCare* element, the delay *oneDay* adds a delay time of one day before patients go through *selectOutpatientCare* again on the next day. Actions of the delays in outpatient care are described in Table 20 and Table 21. The functions for the calculation of costs for medication based on Table 19 are detailed in Table 22.

Table 20: Description of the delay *delayOutpatientClinic* in AnyLogic®

action	description and code of <i>delayOutpatientClinic</i>
On enter	<p>adds the information “OC” (outpatient clinic) to the <i>history</i> variable of the agent with the actual time the patient had the visit to the outpatient clinic</p> <pre>agent.history = agent.history.concat("OC" + string.valueOf((int)time()) + " ");</pre>
On at exit	<p>when leaving the delay the visits to the outpatient clinic are incremented and the costs of the outpatient clinic of the patient updated with the call of the function <i>costCalc()</i></p> <pre>agent.visitsOutpatientClinic = agent.visitsOutpatientClinic + 1; agent.outpatientClinicCosts = agent.outpatientClinicCosts + calcOCCosts(agent); agent.costCalc();</pre>

Table 21: Description of the delay *delayPhysician* in AnyLogic®

action	description and code of <i>delayPhysician</i>
On enter	<p>adds the information "PH" (physician) to the <i>history</i> variable of the agent with the actual time the patient had the visit to the physician</p> <pre>agent.history = agent.history.concat("PH" + string.valueOf((int)time()+ " ");</pre>
On at exit	<p>when leaving the delay the variables for visits to the physician are incremented in the class <i>Patient</i> and the costs of the physician and the medication updated with the call of the function <i>costCalc()</i>. The calculation of costs in <i>ATCxx</i> is done with the mentioned multiplier of 3.3333</p> <pre>agent.physicianCosts = agent.physicianCosts + physicianCosts; agent.ATC03 = agent.ATC03 + costsC03(agent.sex)/12; agent.ATC07 = agent.ATC07 + costsC07(agent.sex)/12; agent.ATC09 = agent.ATC09 + costsC09(agent.sex)/12; agent.ATCxx = 3.3333*(agent.ATC03 + agent.ATC07 + agent.ATC09); agent.costCalc(); agent.visitsPhysician = agent.visitsPhysician + 1;</pre>

Table 22: Functions for the calculation of costs for medication

function	returns	description
<i>costsC03</i> (sex)	value of type <i>double</i>	<p>returns the probability density function for the calculation of medication costs based on the sex of the patient</p> <p>function body:</p> <pre>switch (sex) { case m: return weibull(59.83293592, 0.78187418); case f: return weibull(43.26708011, 0.92750740); default: return 1; }</pre>
<i>costsC07</i> (sex)	value of type <i>double</i>	<p>returns the probability density function for the calculation of medication costs of C07 based on the sex of the patient. The gamma-function in AnyLogic® has the form $\text{gamma}(\text{shape}, \text{scale})$, therefore the values are in different order</p>

		function body: <pre> switch (sex) { case m: return gamma(1.25236918,56.67309751); case f: return gamma(1.33370323, 51.30145953); default: return 1; } </pre>
costsC09(sex)	value of type <i>double</i>	returns the probability density function for the calculation of medication costs of C09 based on the sex of the patient function body: <pre> switch (sex) { case m: return weibull(153.10949860, 1.11973953); case f: return weibull(165.83859245, 1.12790871); default: return 1; } </pre>

The *delaySpecialist* has in principle the same code as *delayPhysician* with the difference of the expression “*SP*” instead of “*PH*” in the *history* variable. For the simulation runs the specialist was not considered separately and thus simulated together with the physician. It is important to note that the division of medication costs with the divisor 12 is due to the number of visits implemented for physicians. Basically, each patient visits the physician, on average, once a month. This is not realistic in terms of frequency, but it was more important to have a significant representation of costs for visits to the physician and the medication for the showcased scenarios. There was not enough data to support a narrower differentiation for this final model setup. Therefore also the probability to have visits to the physician in *selectOutpatientCare* is set to 12 for each NYHA class, thus 12 visits a year (for more information go to chapter 4). The standard procedure for outpatient clinics is to have a mandatory visit once a year, thus the element *toOutpatientClinic(agent.NYHA)* is set to one. The functions *toOutpatientClinic()*, *toSpecialist()* and *toPhysician()* have the same structure, which can be taken from Table 23.

Table 23: Description of the probabilities for events (visits) in outpatient care

function	returns	description
toOutpatientClinic()	value of type <i>double</i>	<p>returns the probability for a visit to the outpatient clinic: <i>probToOutpatientClinic#</i> is a variable containing the probability for a visit to the outpatient clinic that was defined in the simulation experiment</p> <p>function body:</p> <pre> switch (NYHA) { case NYHA1: return probToOutpatientClinic1; case NYHA2: return probToOutpatientClinic2; case NYHA3: return probToOutpatientClinic3; case NYHA4: return probToOutpatientClinic4; default: return 0; } </pre>
toPhysician()	value of type <i>double</i>	<p>returns the probability for a visit to the physician: <i>probToPhysician#</i> is a variable containing the probability for a visit to the physician that was defined in the simulation experiment. The code in the function body is the same as for the <i>toOutpatientClinic()</i>, instead of <i>probToOutpatientClinic#</i> the variable <i>probToPhysician#</i> is linked</p>
toSpecialist()	value of type <i>double</i>	<p>returns the probability for a visit to the specialist: <i>probToSpecialist#</i> is a variable containing the probability for a visit to the specialist that was defined in the simulation experiment. The code in the function body is the same as for the <i>toOutpatientClinic()</i>, instead of <i>probToOutpatientClinic#</i> the variable <i>probToSpecialist#</i> is linked</p>

The state of health is most commonly not documented in outpatient data. In this work, through cooperation with KAGes, the state of health could partially be classified for treatment in outpatient clinics. Medication, ICD-10 codes and procedures such as ICD (implantable cardioverter defibrillator) and CRT (cardiac resynchronization therapy) were used as classifiers for NYHA classes, as detailed in chapter 2.4.2. The course of treatment for individual patients was then analyzed, resulting in the following transition matrix (Table 24) for NYHA class changes in outpatient care. Some patients in the data set had outpatient visits with time delays of over 5 years in between. For the calculation of those transition probabilities only patients were included that had at least one visit to the outpatient clinic per year to reduce uncertainties and misinterpretations. In general, class changes in outpatient care are only triggered by visits to the outpatient

clinic, since no further information on patients' health after visits to the physician or the specialist were contained in the data set of the health insurance provider.

Table 24: NYHA class changes for outpatient care

NYHA class		follow-up				
		I	II	III	IV	N*
start	I	23.08 %	43.95 %	28.57 %	4.40 %	182
	II	4.26 %	52.41 %	38.29 %	5.04 %	2,301
	III	2.97 %	43.93 %	44.77 %	8.33 %	1,885
	IV	2.06 %	25.77 %	45.36 %	26.81 %	291

N*...number of patients for data assessment

In the model the realization of NYHA class changes is done with two steps for outpatient care. *selectCCOut* is a *selectOutput* element that decides whether or not class changes are considered for the simulation run. In case of activated class changes in outpatient care the *multi-selectOutput* element *cCOut* changes the NYHA class with the probabilities in Table 24. The implemented code for *cCOut* can be taken from Table 25.

Table 25: Description of the code in the *multi-select output* element *cCOut* for NYHA class changes in outpatient care

cCOut	description
Probability 1	probability for class change towards branch 1, thus change of the NYHA class to class I $\frac{\text{probCCOut1}(\text{agent.NYHA})}{\text{probCCOut1}(\text{agent.NYHA})+\text{probCCOut2}(\text{agent.NYHA})+\text{probCCOut3}(\text{agent.NYHA})+\text{probCCOut4}(\text{agent.NYHA})}$
Probability 2	probability for class change towards branch 2, thus change of the NYHA class to class II $\frac{\text{probCCOut2}(\text{agent.NYHA})}{\text{probCCOut1}(\text{agent.NYHA})+\text{probCCOut2}(\text{agent.NYHA})+\text{probCCOut3}(\text{agent.NYHA})+\text{probCCOut4}(\text{agent.NYHA})}$
Probability 3	probability for class change towards branch 3, thus change of the NYHA class to class III $\frac{\text{probCCOut3}(\text{agent.NYHA})}{\text{probCCOut1}(\text{agent.NYHA})+\text{probCCOut2}(\text{agent.NYHA})+\text{probCCOut3}(\text{agent.NYHA})+\text{probCCOut4}(\text{agent.NYHA})}$
Probability 4	probability for class change towards branch 4, thus change of the NYHA class to class IV $\frac{\text{probCCOut4}(\text{agent.NYHA})}{\text{probCCOut1}(\text{agent.NYHA})+\text{probCCOut2}(\text{agent.NYHA})+\text{probCCOut3}(\text{agent.NYHA})+\text{probCCOut4}(\text{agent.NYHA})}$
On exit #	depending on the branch taken, different codes are implemented for the action taken when leaving <i>cCOut</i> . # again stands for the different NYHA classes and has values between 1 and 4 <pre>agent.NYHA=NYHA#; agent.history = agent.history.concat("CC#" + String.valueOf((int)time())+ " ");</pre>

The *probCCOut#(agent.NYHA)* functions are four different functions that call the correct probability for the transition from the existing NYHA class to the new one. Each function returns a *double* value and consists of a *switch/case* loop iterating the different NYHA classes as cases and then returning the specific probability, which is always in the form *probCCOutNYHAxy*, whereby x equals the existing NYHA class and y the new NYHA class.

As mentioned before no information on outpatient death based on NYHA class, age and gender could be derived from the data set. Still the implementation of potential outpatient mortality was done with the *selectOutput* element *outMortality*, which serves as a placeholder that can be easily adjusted. If a patient dies they leave the simulation via an *Exit* element *exitOutpatient*, this will be detailed in the inpatient care section, where the full functionality of this element is explained.

2.5.6 Inpatient Care

Admissions are based on the clinical data set from the Styrian health care provider KAGes representing data on over 10,000 admissions between 2006 and 2016. Cost calculations follow the Austrian Diagnosis-Related Groups system (DRG) 2018, where hospital stays are grouped into procedure-oriented, diagnosis-related case flat rates associated with a defined length of stay and an allotted point score reimbursed to the hospital. This score depends on the size, equipment and services of individual clinics. For the model calculations 1 point was equated to €1, which was an assumption for the simulations and is further discussed in chapter 4. In the case of chronic HF, two different case flat rates are applied depending on the age of the patient. Above the age of 64 years, minimum and maximum lengths of stay are defined with 4 and 11 days respectively, with a case flat rate of 3,134 points. Below 64 years the standard treatment window is between 3 and 10 days with a case flat rate of 2,688 points per stay. If the length of stay exceeds the set treatment window, supplementary points are added to the case flat rate for each additional day. In case of a shorter stay than the minimum length of stay, a reduced flat rate is reimbursed (see also chapter 2.2.1). [32] The nature of this calculation system underlines the importance to include transgressions of set treatment windows to realistically estimate overall costs. In the model, probabilities for standard admissions correlating to the NYHA class of patients are implemented (Table 26), length of stay for visits is described via probability density functions.

Table 26: Admission characteristics based on NYHA class

NYHA class	admission rate/year ^a (p ₀₂)	length of stay (days)
I	0.0186	3b median, N=15
II	0.4287	gamma(10.66, 0.63) p≤0.05a, N=296
III	0.7643	gamma(8.84, 1.27) p≤0.01a, N=449
IV	1.6590	gamma(7.56, 1.83) p≤0.01a, N=5745

^a... goodness-of-fit based on Anderson-Darling Test

^b... number of patients too small for significant prediction

As can be seen in Figure 14 standard admissions are implemented as the delay *inpatientCare*. The admission rate of patients is based on the NYHA class and is realized as the function *toHospital(agent.NYHA)* in *selectOutpatientCare* (see Table 27). The structure of the delay *inpatientCare* can be taken from Table 28. The functions used in the delay *inpatientCare* are described in Table 29.

Table 27: Description of the function *toHospital(agent.NYHA)* which covers the probability of admissions

function	returns	description
<i>toHospital</i> (<i>agent.NYHA</i>)	value of type <i>double</i>	<p>returns the probability of an admission. <i>probToHospital#</i> is a variable containing the probability for an admission that was defined in the simulation experiment</p> <p>function body:</p> <pre> switch (NYHA){ case NYHA1: return probToHospital1; case NYHA2: return probToHospital2; case NYHA3: return probToHospital3; case NYHA4: return probToHospital4; default: return 0; } </pre>

Table 28: Description of the delay *inpatientCare* in AnyLogic®

action	description and code of the delay <i>inpatientCare</i>
Delay time	<p>the delay time is depending on the LOS of the individual patient, which is expressed with the function:</p> <pre>inpatientCareLOSCalc(agent.NYHA, agent)</pre>
On enter	<p>adds the information "IP" to the history variable of the agent with the actual time the patient had the admission</p> <pre>agent.history = agent.history.concat("PH" + string.valueOf((int)time())+ " ");</pre>
On at exit	<p>after the admission the function <i>costCalcAdmission(agent)</i> for the calculation of costs for the stay is called and the variable <i>visitsInpatientCare</i> is incremented by +1</p> <pre>costCalcAdmission(agent); agent.visitsInpatientCare = agent.visitsInpatientCare + 1;</pre>
On exit	<p>the last part is the call of the <i>costCalc()</i> function in the class <i>Patient</i></p> <pre>agent.costCalc();</pre>

Table 29: Description of the functions used in the delay *inpatientCare*

function	returns	description
inpatientCareLOSCalc (agent.NYHA, agent)	value of type <i>double</i>	<p>calculates the length of stay for the patient based on the NYHA class. If the checkbox <i>LOSPDF</i> in the input mask is set to the value <i>true</i>, probability density functions are used to calculate the length of stay. Calculations with mean or median values are also possible, therefore an <i>else</i>-loop is implemented</p> <p>function body:</p> <pre>if (LOSPDF == true){ switch (NYHA){ case NYHA1: pointerPatient.LOS+=LOSNYHA1; return pointerPatient.LOS; case NYHA2: pointerPatient.LOS+=Math.round(gamma(0.62952, 10.66,1)); if(pointerPatient.LOS <1){ pointerPatient.LOS = 1; } return pointerPatient.LOS; case NYHA3: pointerPatient.LOS+=Math.round(gamma(1.2724, 8.8448));</pre>

		<pre> if(pointerPatient.LOS <1){ pointerPatient.LOS = 1; } return pointerPatient.LOS; case NYHA4: pointerPatient.LOS+=Math.round(gamma(1.8295, 7.5598)); if(pointerPatient.LOS <1){ pointerPatient.LOS = 1; } return pointerPatient.LOS; default: return 0; } } else{ switch (NYHA){ case NYHA1: pointerPatient.LOS+=LOSNYHA1; return pointerPatient.LOS; case NYHA2: pointerPatient.LOS+=LOSNYHA2; return pointerPatient.LOS; case NYHA3: pointerPatient.LOS+=LOSNYHA3; return pointerPatient.LOS; case NYHA4: pointerPatient.LOS+=LOSNYHA4; return pointerPatient.LOS; default: return 0; } } </pre>
costCalcAdmission (agent)	void	calculates the costs of the admission based on the length of stay and the costs for the duration saved in the <i>costsLOS[]</i> array <pre> pointerPatient.admissionCosts = pointerPatient.admissionCosts + costsLOS[pointerPatient.LOS]; </pre>

It can be seen that probability density functions from Table 26 are part of the code of the delay for inpatient care. The decision whether or not probability density functions are used for the calculation of the length of stay is taken before the start of the simulation run in the simulation experiment.

Intensive care (ICU) and intermediate care (IMC) units are based on the Austrian Therapeutic Intervention Scoring System (TISS-28), associating per-day cost flat-rates (see chapter 2.2.2 for further explanation). There are several definitions for intermediate care, “high-dependency”, “step-up/down” or “progressive care” units are often synonymous. Intermediate care in this work is based on its use in KAGes and thus describes a concept to manage patients who need more care than a general ward can provide but do not really need the degree of monitoring, equipment and expertise that an ICU offers. [117] For simulation runs, a well-equipped ICU with a TISS score of 32 points was chosen, resulting in 1,664 points (ICU) and 480 points (IMC) per day of stay. [118] Table 30 summarizes implemented probabilities per admission for both ICUs and IMCs, length of stay (LOS) was expressed via median values.

Table 30: Likelihood for intensive and intermediate care admissions

age/ sex	ICU (p _{2,22})			IMC (p _{2,23})		
	male (N*=569)	female (N*=348)	LOS _a	male (N*=735)	female (N*=421)	LOS _a
0-55	16.10 %	15.50 %	4	27.78 %	21.05 %	3
56-65	16.10 %	14.40 %	4	21.83 %	15.35 %	3
66-75	11.60 %	10.00 %	4	17.96 %	13.54 %	2
76-85	8.60 %	7.10 %	3	12.22 %	9.30 %	2
86+	3.90 %	3.30 %	2	8.25 %	5.19 %	2

_a... median values for length of stay (LOS)

N*...number of patients in the data pool

The decision whether a stay at intensive or intermediate care is necessary is taken right after exiting the *selectOutpatientCare* element due to the function *toHospital(agent.NYHA)*. Table 31 and

Table 32 describe the elements of the decision tree in inpatient care and implemented functions.

Table 31: Description of select output elements for the implementation of intensive and intermediate care units

select output	description and code of select output elements for IMC/ICU
selectIntCare	<p>this select output element decides whether or not a stay at the intensive care unit is necessary with the function:</p> <pre>toIntensiveCare(agent.sex, agent)</pre>
selectIMCInt	<p>this select output element decides whether or not a stay at the intermediate care unit is necessary with the function:</p> <pre>toIntermediateCare(agent.sex, agent)</pre>

Table 32: Function bodies for the *switch/case* elements of intensive and intermediate care

function	returns	description
toIntensiveCare (agent.sex, agent)	value of type <i>double</i>	<p>function that describes the probability for treatment at an ICU based on age group and gender</p> <pre>double pIC = 0; switch (sex) { case m: if (pointerPatient.age <= 55) { pIC = 0.161; } else if (pointerPatient.age >= 56 && pointerPatient.age <= 65) { pIC = 0.161; } else if (pointerPatient.age >= 66 && pointerPatient.age <= 75) { pIC = 0.116; } else if (pointerPatient.age >= 76 && pointerPatient.age <= 85) { pIC = 0.086; } else if (pointerPatient.age > 85) { pIC = 0.039; } return pIC; case f: if (pointerPatient.age <= 55) { pIC = 0.155; } else if (pointerPatient.age >= 56 && pointerPatient.age <= 65) { pIC = 0.144; } else if (pointerPatient.age >= 66 && pointerPatient.age <= 75) { pIC = 0.100; } else if (pointerPatient.age >= 76 && pointerPatient.age <= 85) { pIC = 0.071; }</pre>

		<pre> else if(pointerPatient.age>85){ pIC = 0.033; } return pIC; default: return 0; } </pre>
<p>toIntermediateCare (agent.sex, agent)</p>	<p>value of type <i>double</i></p>	<p>function that describes the probability for treatment at an IMC unit based on age group and gender</p> <pre> double pIMC = 0; switch(sex){ case m: if(pointerPatient.age<=55){ pIMC = 0.2778; } else if(pointerPatient.age>=56 && pointerPatient.age<=65){ pIMC = 0.2183; } else if(pointerPatient.age>=66 && pointerPatient.age<=75){ pIMC = 0.1796; } else if(pointerPatient.age>=76 && pointerPatient.age<=85){ pIMC = 0.1222; } else if(pointerPatient.age>85){ pIMC = 0.0825; } return pIMC; case f: if(pointerPatient.age<=55){ pIMC = 0.2105; } else if(pointerPatient.age>=56 && pointerPatient.age<=65){ pIMC = 0.1535; } else if(pointerPatient.age>=66 && pointerPatient.age<=75){ pIMC = 0.1354; } else if(pointerPatient.age>=76 && pointerPatient.age<=85){ pIMC = 0.0930; } else if(pointerPatient.age>85){ pIMC = 0.0519; } return pIMC; default: return 0; } </pre>

For the intermediate and the intensive care each, the functions *intCareLOSCalc()* and *intmCareLOSCalc()* respectively are implemented to define the length of stay, which are then called in the delays *intCare* and *intmedCare*. These functions are structured in the same way as *toIntensiveCare()* and *toIntermediateCare()* with the

difference that instead of the probability of care the length of stay is defined with chosen values. Table 33 and

Table 34 show the attributes of the delay elements and Table 35 gives insight into the function parameters. Table 36 lists the functions used for the calculation of costs for the stays at the ICU or the IMC.

Table 33: Description of the delay *intCare*

action	description and code of the delay <i>intCare</i>
Delay time	the delay time is depending on the LOS of the individual patient, which is expressed with the function: <code>intCareLOSCalc(agent.sex, agent)</code>
On enter	adds the information "IC" to the <i>history</i> variable of the agent with the actual time the patient had at intensive care <code>agent.history = agent.history.concat("IC" + string.valueOf((int)time()) + " ");</code>
On at exit	after intensive care the function <i>costCalcInt(agent, agent)</i> for the calculation of costs for the stay is called and the variable <i>visitsIntensiveCare</i> is incremented by +1 <code>costCalcInt(agent, agent);</code> <code>agent.visitsIntensiveCare = agent.visitsIntensiveCare + 1;</code>
On exit	the last part is the call of the <i>costCalc()</i> function in the class <i>Patient</i> <code>agent.costCalc();</code>

Table 34: Description of the delay *intmedCare*

action	description and code of the delay <i>intmedCare</i>
Delay time	the delay time is depending on the LOS of the individual patient, which is expressed with the function: <code>intmCareLOSCalc(agent.sex, agent)</code>
On enter	adds the information "IMC" to the <i>history</i> variable of the agent with the actual time the patient was in intermediate care <code>agent.history = agent.history.concat("IMC" + string.valueOf((int)time()) + " ");</code>
On at exit	after the intermediate care the function <i>costCalcIntmed(agent, agent)</i> for the calculation of costs for the stay is called and the variable <i>visitsIntermediateCare</i> is incremented by +1 <code>costCalcIntmed(agent, agent);</code> <code>agent.visitsIntermediateCare = agent.visitsIntermediateCare + 1;</code>
On exit	the last part is the call of the <i>costCalc()</i> function in the class <i>Patient</i> <code>agent.costCalc();</code>

Table 35: Description of the functions used in intensive care and intermediate care to describe the length of stay

function	returns	description
<p><code>intCareLOSCalc</code> (agent.sex, agent)</p>	<p>value of type <i>double</i></p>	<p>function assigning the length of stay for intensive care based on sex and age of the patient</p> <pre> double pIC = 0; switch(sex){ case m: if(pointerPatient.age<=55){ pIC = 4; } else if(pointerPatient.age>=56 && pointerPatient.age<=65){ pIC = 4; } else if(pointerPatient.age>=66 && pointerPatient.age<=75){ pIC = 4; } else if(pointerPatient.age>=76 && pointerPatient.age<=85){ pIC = 3; } else if(pointerPatient.age>85){ pIC = 2; } pointerPatient.LOSInt+=pIC; return pIC; case f: if(pointerPatient.age<=55){ pIC = 4; } else if(pointerPatient.age>=56 && pointerPatient.age<=65){ pIC = 4; } else if(pointerPatient.age>=66 && pointerPatient.age<=75){ pIC = 4; } else if(pointerPatient.age>=76 && pointerPatient.age<=85){ pIC = 3; } else if(pointerPatient.age>85){ pIC = 2; } pointerPatient.LOSInt+=pIC; return pIC; default: return 0; } </pre>
<p><code>intmCareLOSCalc</code> (agent.sex, agent)</p>	<p>value of type <i>double</i></p>	<p>function assigning the length of stay for intermediate care based on sex and age of the patient. The function code is identical to the one in <code>intCareLOSCalc()</code>, only names of variables are changed to <i>IMC</i> instead of <i>Int</i></p>

Table 36: Cost calculation functions for intensive and intermediate care

function	returns	description
costCalcInt (agent, agent)	void	function calculating the costs for the stay at intensive care based on the defined tier costs for the ICU <pre>pointerIntCosts.intensiveCareCosts = pointerIntCosts.intensiveCareCosts + pointerLOSInt.LOSInt*LDFIC*euroLKF;</pre>
costCalcIntmed (agent, agent)	void	function calculating the costs for the stay at intermediate care based on the defined tier costs for IMC <pre>pointerIntmedCosts.intermediateCareCosts = pointerIntmedCosts.intermediateCareCosts + pointerLOSIntmed.LOSIntmC*LDFIMC*euroLKF;</pre>

Individual medical procedures (IMP) were also obtained from the data set of KAGes. Over 332 different IMPs were classified in the data set. Using Pareto-Analyses the most common interventions could be identified for patients based on age and gender. The average point scores were calculated for the sum and frequencies of procedures in the data sets, information on the actual points was taken from [118]. Table 37 gives an overview of implemented probabilities for IMPs and respective point scores.

Table 37: Likelihood and average point score of individual medical procedures

age/ sex	IMP (p _{21,211})		average points per IMP	
	male (N*=2939)	female (N*=2747)	male (N*=1423)	female (N*=1514)
0-55	57.21 %	54.76 %	236.43	181.37
56-65	54.50 %	55.93 %	242.60	155.00
66-75	56.11 %	51.09 %	205.60	178.68
76-85	47.61 %	43.34 %	179.55	136.16
86+	46.76 %	41.63 %	146.65	106.56

After an admission the decision in the select output element *toIMP* is taken whether or not an individual medical procedure is performed (see Table 38) with the probability *toIMPfunction(agent.sex, agent)*. As detailed in chapter 2.4.4 on individual medical

procedures, they are summed up and multiplied with the number of IMPs used. The delay IMP is described in Table 39 and its functions are detailed in Table 40.

Table 38: Implementation of the function *toIMPfunction()* describing the probability for individual medical procedures based on sex and gender

function	returns	description
toIMPfunction (agent.sex, agent)	agent value of type <i>double</i>	<p>function defining the probability for an individual medical procedure during or after an admission</p> <pre> double pMEL = 0; switch(sex){ case m: if(pointerPatient.age<=55){ pMEL = 0.572; } else if(pointerPatient.age>=56 && pointerPatient.age<=65){ pMEL = 0.545; } else if(pointerPatient.age>=66 && pointerPatient.age<=75){ pMEL = 0.561; } else if(pointerPatient.age>=76 && pointerPatient.age<=85){ pMEL = 0.476; } else if(pointerPatient.age>85){ pMEL = 0.468; } return pMEL; case f: if(pointerPatient.age<=55){ pMEL = 0.548; } else if(pointerPatient.age>=56 && pointerPatient.age<=65){ pMEL = 0.559; } else if(pointerPatient.age>=66 && pointerPatient.age<=75){ pMEL = 0.511; } else if(pointerPatient.age>=76 && pointerPatient.age<=85){ pMEL = 0.433; } else if(pointerPatient.age>85){ pMEL = 0.416; } return pMEL; default: return 0; } </pre>

Table 39: Description of the delay *IMP*

action	description and code of the delay <i>IMP</i>
Delay time	<p>the delay time is depending on the LOS for IMPs defined in the experiment setup. For results shown in this work no delay was chosen to model individual medical procedures, they were assumed to be performed during the stay for the primary diagnosis</p> <pre>LOSIMP</pre>
On enter	<p>adds the information "IM" to the <i>history</i> variable of the agent with the actual time the patient had the IMP</p> <pre>agent.history = agent.history.concat("IM" + string.valueOf((int)time())+ " ");</pre>
On at exit	<p>the calculation of costs for the IMP is defined by the number of IMPs and the costs per IMP. After the IMP is performed the counter for IMPs is incremented by +1</p> <pre>agent.IMPCosts = agent.IMPCosts + frequencyIMP(agent.sex, agent) * costsPerIMP(agent.sex); agent.visitsIMP = agent.visitsIMP + 1;</pre>
On exit	<p>the last part is the call of the <i>costCalc()</i> function in the class <i>Patient</i></p> <pre>agent.costCalc();</pre>

Table 40: Description of functions for the assessment of the number of IMP performed and respective costs

function	returns	description
frequencyIMP (agent.sex, agent)	value of type <i>double</i>	<p>function calculating the number of IMPs performed for each patient</p> <pre>double fIMP = 0; switch(sex){ case m: if(pointerPatient.age<=55){ fIMP = 3.45; } else if(pointerPatient.age>=56 && pointerPatient.age<=65){ fIMP = 3.54; } else if(pointerPatient.age>=66 && pointerPatient.age<=75){ fIMP = 3; } else if(pointerPatient.age>=76 && pointerPatient.age<=85){ fIMP = 2.62; } else if(pointerPatient.age>85){ fIMP = 2.14; } return fIMP;</pre>

		<pre> case f: if(pointerPatient.age<=55){ fIMP = 3.37; } else if(pointerPatient.age>=56 && pointerPatient.age<=65){ fIMP = 2.88; } else if(pointerPatient.age>=66 && pointerPatient.age<=75){ fIMP = 3.32; } else if(pointerPatient.age>=76 && pointerPatient.age<=85){ fIMP = 2.53; } else if(pointerPatient.age>85){ fIMP = 1.98; } return fIMP; default: return 0; } </pre>
costsPerIMP (agent.sex)	value of type <i>double</i>	<p>function defining the costs per IMP, as entered in the simulation experiment. <i>costsPerIMPm</i> and <i>costsPerIMPf</i> are the variables that are assigned with the respective values for men and women</p> <pre> switch(sex){ case m: return costsPerIMPm; case f: return costsPerIMPf; default: return 0; } </pre>

The point scores for individual medical procedures per day that are assigned by the function *costsPerIMP(agent.sex)* with the variables *costsPerIMPm* and *costsPerIMPf* are €8.53 for men and €3.82 for women, thus, on average, IMPs performed on men are more expensive in the data set.

After potential intermediate and intensive care stays, the admission and individual medical procedures, the delay *inMortality* describes potential inpatient death. Mortality rates per admission were derived from the data set of KAGes and based on patient age and gender (Table 41). A description of the select output element with its features can be taken from Table 42. The *exitInpatient* element defines the exit of the simulation for deceased patients and is described in Table 43; coded functions important for the implementation of the inpatient mortality can be seen in

Table 44.

Table 41: Mortality rates per admission (p_{21D})

Age / Sex	male	N*	female	N*
0-55	8.40 %	391	6.80 %	161
56-65	8.80 %	787	10.60 %	263
66-75	9.30 %	1,616	8.90 %	872
76-85	13.30 %	1,892	12.30 %	1,975
86+	18.20 %	748	15.60 %	1,744

N*...number of patients in the data pool

Table 42: Code within the select output element *inMortality*

attributes	description and code of the select output element <i>inMortality</i>
Probability	<p>this decision is based on the function call of <i>toInpatientMortality()</i> which again is based on sex and age of patients</p> <pre>toInpatientMortality(agent.sex, agent)</pre>
On enter	<p>when a patient dies some of the variables in the class <i>Patient</i> are still initialized and could falsely contribute to patient parameters. Therefore the total LOS for admission, intensive and intermediate care are summed up in the sum-functions and the singular auxiliary variables are then set to 0</p> <pre>agent.LOSSum = agent.LOSSum + agent.LOS; agent.LOSIntSum = agent.LOSIntSum + agent.LOSInt; agent.LOSIntmCSum = agent.LOSIntmCSum + agent.LOSIntmC; agent.LOS = 0; agent.LOSInt = 0; agent.LOSIntmC = 0;</pre>

Table 43: Description of the exit element *exitInpatient*

attributes	description and code of the exit element <i>exitInpatient</i>
On exit	<p>adds the information "RIP" to the history variable of the agent with the actual time the patient died in inpatient care. <i>mortalityPatientCalc(agent.NYHA)</i> is a simple function increasing the death counters for each NYHA class. At the end the variable <i>death</i> as the state of the patient is set to <i>true</i></p> <pre>agent.history = agent.history.concat("RIP" + String.valueOf((int)time())+ " "); mortalityPatientCalc(agent.NYHA); agent.death = true;</pre>

Table 44: Functions used to describe inpatient mortality

function	returns	description
toInpatientMortality (agent.sex, agent)	value of type <i>double</i>	<p>function calculating the probability for each patient based on sex and age to face death after or whilst inpatient care</p> <pre> double pInMort = 0; switch(sex){ case m: if(pointerPatient.age<=55){ pInMort = 0.084; } else if(pointerPatient.age>=56 && pointerPatient.age<=65){ pInMort = 0.088; } else if(pointerPatient.age>=66 && pointerPatient.age<=75){ pInMort = 0.093; } else if(pointerPatient.age>=76 && pointerPatient.age<=85){ pInMort = 0.133; } else if(pointerPatient.age>85){ pInMort = 0.182; } return pInMort; case f: if(pointerPatient.age<=55){ pInMort = 0.068; } else if(pointerPatient.age>=56 && pointerPatient.age<=65){ pInMort = 0.106; } else if(pointerPatient.age>=66 && pointerPatient.age<=75){ pInMort = 0.089; } else if(pointerPatient.age>=76 && pointerPatient.age<=85){ pInMort = 0.123; } else if(pointerPatient.age>85){ pInMort = 0.156; } return pInMort; default: return 0; } </pre>
mortalityPatientCalc (agent.NYHA)	value of type <i>double</i>	<p>function counting patients and their NYHA class who died after or whilst inpatient care and saving those values in the variables deathNYHA# (# is between 1 and 4)</p> <pre> switch(NYHA){ case NYHA#: return deathsNYHA#++; default: return 0;} </pre>

To assess the state of health of HF patients, the same method as for outpatient care was used, with *selectCCIn* and *cCIn* as select output elements. *selectCCIn* is active if the simulation includes NYHA class changes and *cCIn* is the actual implementation of NYHA class changes. In the case of inpatient care there was additional information on the state of health through medical reports per admission. Table 45 shows the transition matrix for NYHA class changes. Implemented probabilities for NYHA class changes in inpatient care can be seen in Table 46.

Table 45: NYHA class changes inpatient care

NYHA class		follow-up				
		I	II	III	IV	N*
start	I	16.22 %	35.14 %	27.03 %	21.62 %	37
	II	2.96 %	39.65 %	35.30 %	22.09 %	575
	III	2.17 %	31.83 %	40.00 %	26.00 %	600
	IV	2.16 %	27.88 %	34.86 %	35.10 %	416

N*...number of patients for data assessment

Table 46: Description of the code in the multi-select output element *cCIn* for NYHA class changes in inpatient care

cCIn	description
Probability 1	probability for class change towards branch 1, thus change of the NYHA class to class I $\text{probCCIn1}(\text{agent.NYHA}) / (\text{probCCIn1}(\text{agent.NYHA}) + \text{probCCIn2}(\text{agent.NYHA}) + \text{probCCIn3}(\text{agent.NYHA}) + \text{probCCIn4}(\text{agent.NYHA}))$
Probability 2	probability for class change towards branch 2, thus change of the NYHA class to class II $\text{probCCIn2}(\text{agent.NYHA}) / (\text{probCCIn1}(\text{agent.NYHA}) + \text{probCCIn2}(\text{agent.NYHA}) + \text{probCCIn3}(\text{agent.NYHA}) + \text{probCCIn4}(\text{agent.NYHA}))$
Probability 3	probability for class change towards branch 3, thus change of the NYHA class to class III $\text{probCCIn3}(\text{agent.NYHA}) / (\text{probCCIn1}(\text{agent.NYHA}) + \text{probCCIn2}(\text{agent.NYHA}) + \text{probCCIn3}(\text{agent.NYHA}) + \text{probCCIn4}(\text{agent.NYHA}))$
Probability 4	probability for class change towards branch 4, thus change of the NYHA class to class IV $\text{probCCIn4}(\text{agent.NYHA}) / (\text{probCCIn1}(\text{agent.NYHA}) + \text{probCCIn2}(\text{agent.NYHA}) + \text{probCCIn3}(\text{agent.NYHA}) + \text{probCCIn4}(\text{agent.NYHA}))$
On exit #	depending on the branch taken, different codes are implemented for the actions taken when leaving cCIn. # again is a placeholder for the different NYHA classes and has values between 1 and 4 <code>agent.NYHA=NYHA#;</code> <code>agent.history = agent.history.concat("CC#" + String.valueOf((int)time()) + " ");</code>

The code segments *probCCIn#(agent.NYHA)* are four different functions that call the correct probability for the transition from the existing NYHA class to the new one. Each function returns a *double* value and consists of a *switch/case* loop iterating the different NYHA classes as cases and then returning the corresponding probability, which is always in the form *probCCInNYHAxy*, whereby x equals the existing NYHA class and y the new NYHA class.

2.5.7 Disease Management / Telemonitoring Programs

To compare novel disease management and telemonitoring programs with conventional care, the model parameters can be adjusted accordingly to analyze potential outcomes. On the structural level this is mostly done by changing transition probabilities depending on the system of interest and implementing deviations of standard treatment routines by adapting the model flow. Additional expenses for simulated programs are implemented two-fold, as a one-time investment at the start of the simulation run and as reoccurring monthly fees. Extra expenses can be variably chosen based on the desired comparison between disease management, telemonitoring and conventional approaches. The foundation to simulate different treatment approaches was considered while programming the modular framework of the heart failure model, based on complexity and diverse characteristics of different intervention programs, no “standard” procedure was implemented. With the presented model already a broad range of different approaches can be simulated by just altering existing model parameters.

2.5.8 Parameter Variation and Handling of Simulation Results

As initially stated the simulation experiment *Parameter Variation* is used to perform multiple simulation runs. This is mostly important for having a significant predictive power. In the model itself after each simulation run data sets are filled with information on the patient population at each time step, which is one day in the default setting. Before each simulation run the information in the *Parameter Variation* is reset after being exported to a *.xlsx*-file via the *data_export* function and the function call of *writeData()*. After iterations information in data sets is deleted. The code of the simulation experiment *Parameter Variation* in the AnyLogic® model can be seen in Table 47.

Table 47: Description of the simulation *Parameter Variation* in the heart failure model

<i>Parameter Variation</i>	description and code of the <i>Parameter Variation</i> experiment
Maximum available memory	custom: 54,000 Mb
Parameters	parameters: freeform (model is run for the fixed number of runs specified and parameter values are calculated according to the defined expressions) number of runs: 100
Model time	start: 0 stop: 1825
Randomness	random seed (unique simulation runs)
Initial experiment setup	code executed on experiment setup <pre>totalCostsTimeDS.reset(); patientSum = 0; totalCostsNYHA#DS.reset(); totalCostsOutpatientDS.reset(); totalCostsOutpatientNYHA#DS.reset(); totalCostsInpatientDS.reset(); totalCostsInpatientNYHA#DS.reset(); patientCountNYHADS.reset(); patientCountNYHA#DS.reset(); visitsPhysicianNYHA#DS.reset(); visitsOutpatientClinicNYHA#DS.reset(); visitsIPNYHA#DS.reset(); LOSNYHA#DS.reset(); visitsIMCNYHA#DS.reset(); visitsIMPNYHA#DS.reset(); visitsICNYHA#DS.reset(); medicationCostsNYHA#DS.reset(); DMPCostsNYHA#.reset();</pre>
Before simulation run	<pre>onStartupMain();</pre>
After simulation run	after each simulation run, information of data sets in the class <code>Main()</code> is copied to the mirrored data sets in the <i>Parameter Variation</i> with the code <code>dataSet.fillFrom(root.dataSet)</code> . The function <code>fillFrom()</code> makes the data set an exact copy of the given original data set and the command <code>root</code> references to the class <code>Main()</code> . This is done for each data set, a few examples are listed subsequently: <pre>totalCostsTimeDS.fillFrom(root.totalCostsDS); totalCostsNYHA#DS.fillFrom(root.totalCostsNYHA#DS); LOSNYHA#DS.fillFrom(root.LOSNYHA#DS);</pre>

	[...]
After iteration	<p>in this field the command after each iteration run is implemented. In this case the function <code>writeData()</code> in the <i>Parameter Variation</i> is called, which writes the information in data sets in the <code>data_export</code> function. this is a keyword in Java and works as a reference to the current object.</p> <pre>this.writeData();</pre>

By opening the simulation experiment, graphical interfaces can be implemented showing simulation results in AnyLogic® graphs. This function is not used in the *Parameter Variation* to reduce the necessary random-access memory (RAM) for the simulation. Generally, since the simulation experiment for the class `Main()` is not used in the *Parameter Variation*, the information defined at the start of the simulation run has to be implemented in the *Parameter Variation* screen, thus each parameter and variable has to be initialized with the correct input parameters. A “copy” of the data sets used in `Main()` is listed there to have clean references between classes in the model. Table 48 lists the objects in the *Parameter Variation* which are used to transport the simulation data to the `.xlsx`-file.

Table 48: Description of objects and parameters in the experiment *Parameter Variation*

objects and functions in the experiment <i>Parameter Variation</i>	description
<code>writeData()</code>	<p>function that writes the entries in the data sets into an <code>.xlsx</code>-file. Exemplarily two entries are shown below; they are repeated for each data set. The function <code>setCellValue()</code> directly writes the specific information of the data set (y-value with iteration of the index <code>i</code>) into the predefined excel-sheet “CALL” and then iterates to the next column. So each individual simulation run is saved to one column.</p> <pre>for(int i=0; i< 1825; i++){ data_export.setCellValue(totalCostsTimeDS.getY(i), "TotalCosts", i+1, column); data_export.setCellValue(patientCountNYHADS.getY(i), "CALL", i+1, column); } column++;</pre>
<code>data_export</code>	<p>accesses the predefined <code>.xlsx</code>-file “<code>simData2018</code>” in the specified directory. This can be adapted to the directory of interest. This function is loaded on model startup and saves the data on model termination.</p> <pre>Y:/Anylogic_Telemedizinmodell/Modelle/HeartFailurePhD/HeartFailurePhD1.5/Data/simData2018.xlsx</pre>
data sets	as already mentioned every data set in the class <code>Main()</code> is copied due to hierarchical reasons into the <i>Parameter Variation</i>

2.5.9 Verification and Validation

100 simulation runs were performed to attain statistical coherent and significant values for outcomes presented in Results. Formula (4) states the maximum number of iterations per decision element for a simulation with *Parameter Variation*.

$$\text{iterations}_{\max} = n_{\text{patients}} \cdot n_{\text{days}} \cdot n_{\text{sim_runs}} \quad (6)$$

With 10.000 patients, 1,825 days within a simulation window of 5 years and 100 parallel simulation runs, overall a theoretical maximum number of $18.25 * 10^8$ iterations per decision element can be reached. The resulting deviation of results for the comparison of two simulations, each featuring 100 runs, in regard to overall costs and mortality rate is less than 0.5 % for each NYHA class. With the *history* file in every agent of the class *Patient* their respective course of treatment could be followed and recalculated to verify economic outcomes.

To validate statistical analyses and prove generalizability of the data sets, a 10-fold cross-validation was performed for the main input parameters. A 10-fold cross-validation is a method mostly known from machine-learning approaches that is used for assessing how the result of a statistical analysis will generalize to an independent data set. It therefore is mainly used in settings where the goal is prediction and one wants to estimate how accurately a predictive model will perform in practice. A model is usually given a data set of known data on which training is run (training data set) and a data set of unknown data which the model is tested against. In the case of this work this approach was used on the main input parameters of the data set to figure out, whether or not there are inconsistencies in the input data sets. [119,120] In the presented case the data sets were split into 10 folds, whereas mean values and standard deviation of mortalities and length of stay based on age and gender were calculated. 9 folds were used as training sequences to test against the one test fold (see Table 49 and

To evaluate the sensitivity of the model outcomes, a sensitivity analysis was carried out for the inner states of the model, namely age, gender and NYHA class (see Table 52 and Table 53 in the Results section).

Table 49: Comparison of test data and training data regarding age groups (mean values \pm standard deviation)

age groups (in years)	length of stay (in days)		mortality (in %)	
	training	test	training	test
< 56	12.52 \pm 0.20	12.49 \pm 1.84	8.04 \pm 0.57	8.36 \pm 5.15
56 – 65	13.39 \pm 0.12	13.38 \pm 1.11	9.31 \pm 0.33	9.28 \pm 3.05
66- 75	12.75 \pm 0.06	12.75 \pm 0.53	8.98 \pm 0.17	8.94 \pm 1.51
76-85	10.88 \pm 0.05	10.87 \pm 0.46	12.84 \pm 0.46	12.82 \pm 2.11
> 85	8.91 \pm 0.28	9.02 \pm 0.38	16.37 \pm 0.22	16.37 \pm 1.96

Table 50: Comparison of test data and training data regarding gender (mean values \pm standard deviation)

gender	length of stay (in days)		mortality (in %)	
	training	test	training	test
male	10.98 \pm 0.03	11.08 \pm 0.40	11.79 \pm 0.16	11.78 \pm 1.53
female	11.43 \pm 0.07	11.43 \pm 0.64	12.59 \pm 0.13	12.58 \pm 1.22

It can be seen that there is no significant difference between the folds and the test sequences. Obviously, the more detailed the split criteria get for the folds, the higher deviations can get. Another reason for the choice of mentioned age groups and not simulating every patient year was to increase validity of results. For more detail see chapter 4.4.

3 RESULTS

Several scenarios for the use cases of conventional care and a telemonitoring program were developed to represent exemplary potentials and capabilities of the developed model. If not stated otherwise, the basis for the simulations was the following: 10,000 patients were simulated over a time span of 5 years, with an even distribution between the four NYHA classes, consequently featuring 2,500 patients each. Probabilities describing the state transitions for the simulation runs are defined in Table 10 and match the pathways of the simulation model in Figure 3.

Table 51: Probabilities of state transitions for standard simulation runs

probability	description	value
p ₀₀	outpatient mortality	0
p ₀₁	outpatient clinic	1/365 ^a
p ₀₂	hospital	Table 3
p ₀₃	physician	12/365 ^a
p ₀₄	specialist	0
p _{2_21}	admission	1-(p _{2_22} + p _{2_23})
p _{21_211}	individual medical procedure	Table 5
p _{211C}	NYHA class change	1-(p _{211D}), Table 7
p _{211D}	inpatient death	equals p _{21D} , Table 6
p _{21C}	NYHA class change	1-(p _{21D}), Table 7
p _{21D}	inpatient mortality	Table 6
p _{2_22}	intensive care	Table 4
p _{22_21}	admission	1-p _{22D}
p _{22D}	death intensive care	0
p _{2_23}	intermediate care	Table 4
p _{23_21}	admission	1-p _{23D}
p _{23D}	death intermediate care	0

^a... assumed rates per day

Outpatient mortality was neglected for simulation runs due to missing information on the cause of death. Inpatient mortalities for standard admissions, intensive and intermediate care were combined into one parameter for treatment at wards. For outpatient care, NYHA class changes were only triggered by visits to the outpatient clinic with the average frequency of one visit per year. Physicians and specialists were simulated as one combined state with costs described in the Patients section. Since there was no clear indication on differences in outpatient costs for patients in different NYHA classes in the provided data sets, the same cost profile was implemented for each patient. 100 simulation runs were compared for each scenario in order to narrow statistical deviations and improve consistency of results, which were expressed with mean values plus standard deviations in the figures. All results are based on the data set described in the previous chapters and give insight on the treatment of heart failure patients for the use cases of conventional care and a telemonitoring program for an Austrian hospital, published by Lassnig et al [36].

3.1 Use Case 1 – Conventional Care

3.1.1 Scenario 1

In the first scenario, average costs per patient, year and NYHA class were simulated, disregarding mortality rates and NYHA class changes (Figure 15).

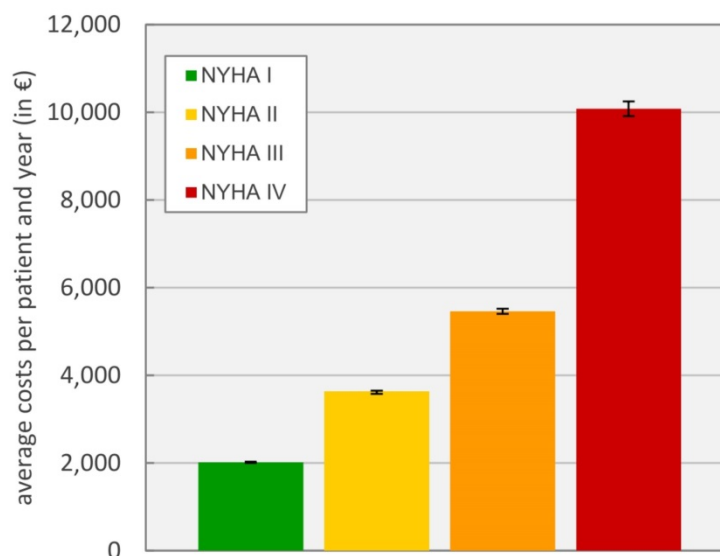


Figure 15: Average costs per patient and year, calculations without mortality and class changes.

Treatment efforts for NYHA class IV patients, with an average of €10,077 ± €165, more than doubled the corresponding values of other classes, mostly due to higher expenses for inpatient care and admission frequencies. As expected, costs increase consistently with higher classes. Figure 16 shows a breakdown of costs between outpatient (OP) and inpatient (IP) care per NYHA class.

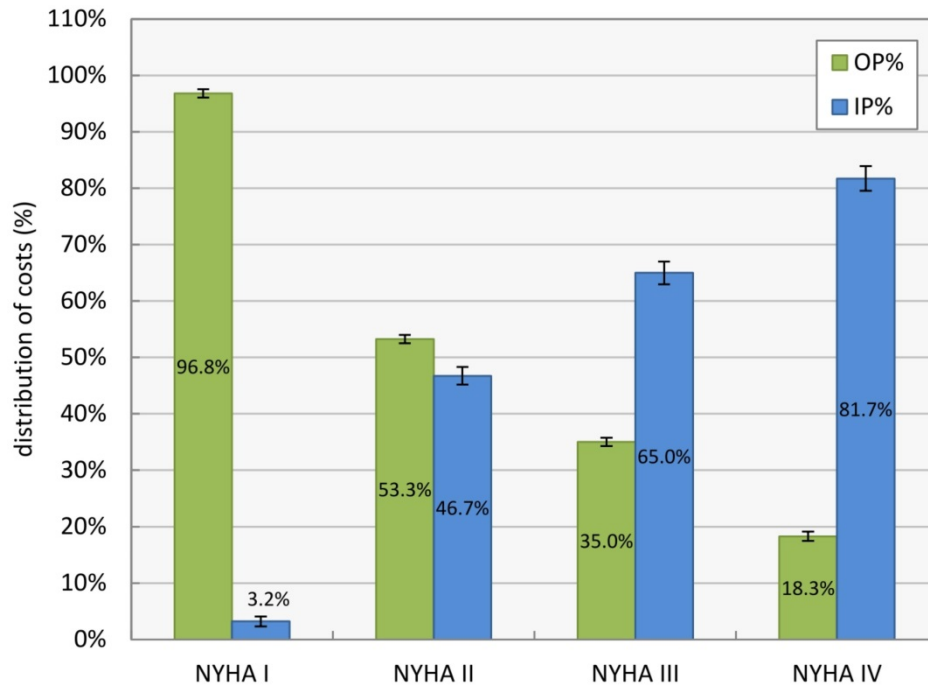


Figure 16: Costs distribution between outpatient (OP) and inpatient (IP) care for the four NYHA classes.

The distribution of treatment efforts in outpatient and inpatient care correlates with the severity of the heart failure condition. In the data set, NYHA class I patients were rarely treated in inpatient care, while for NYHA class IV patients, admissions amounted to over 80 % of the related expenses. Overall costs for outpatient care were divided into expenses (median values) for the physician (27.6 %), the outpatient clinic (9.4 %) and the prescribed medication (63.0 %).

3.1.2 Scenario 2

Scenario 2 represents calculations including inpatient mortality rates based on age and gender. Figure 17 depicts total costs for men, whereas costs for 50 year old patients are used as the baseline.

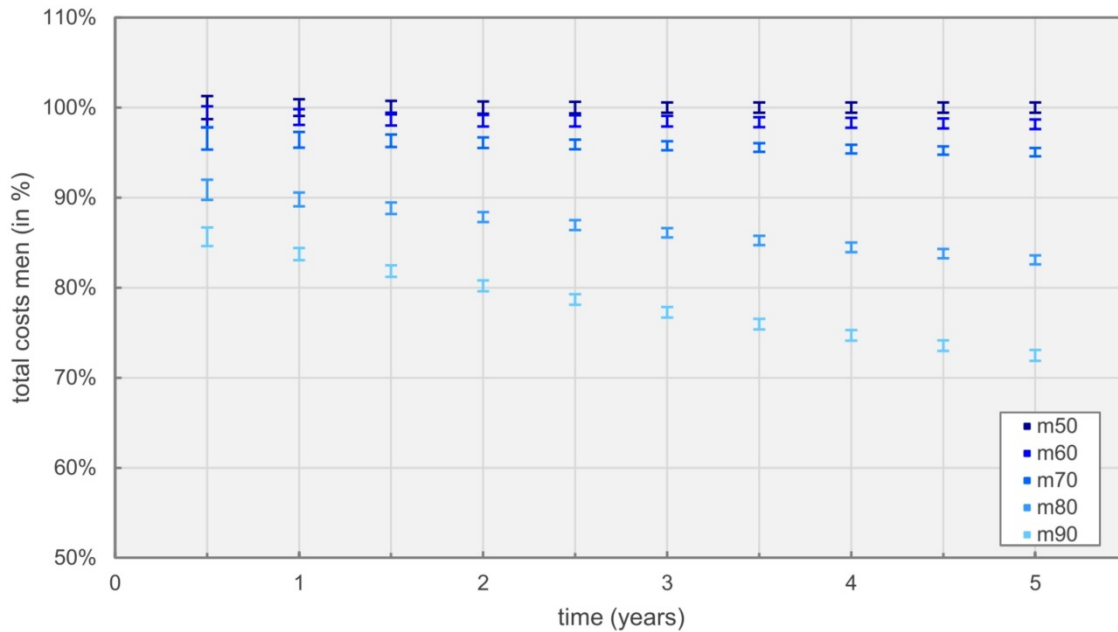


Figure 17: Total costs over time for male patients at different age

Total costs for men and women showed a general trend in which expenses declined with increasing age. This is mostly due to higher mortality rates for older patients, but was also affected by the significantly higher probabilities for intensive care admission and individual medical procedures experienced by younger patients (see Table 30). Overall, only minor cost deviations could be assessed between men and women in respect to their age when compared to the average 50 year old patient. For men, the difference in cost between 50 and 60 year old patients was minimal but started to increase significantly with higher age. As already mentioned, trends for women were similar with the exception of 60 and 70 year old patients, where trends in both age groups nearly coincided.

Figure 18 further underlines the progression of expenses as shown before, outlining survival rates for women based on age over the simulated time frame of 5 years.

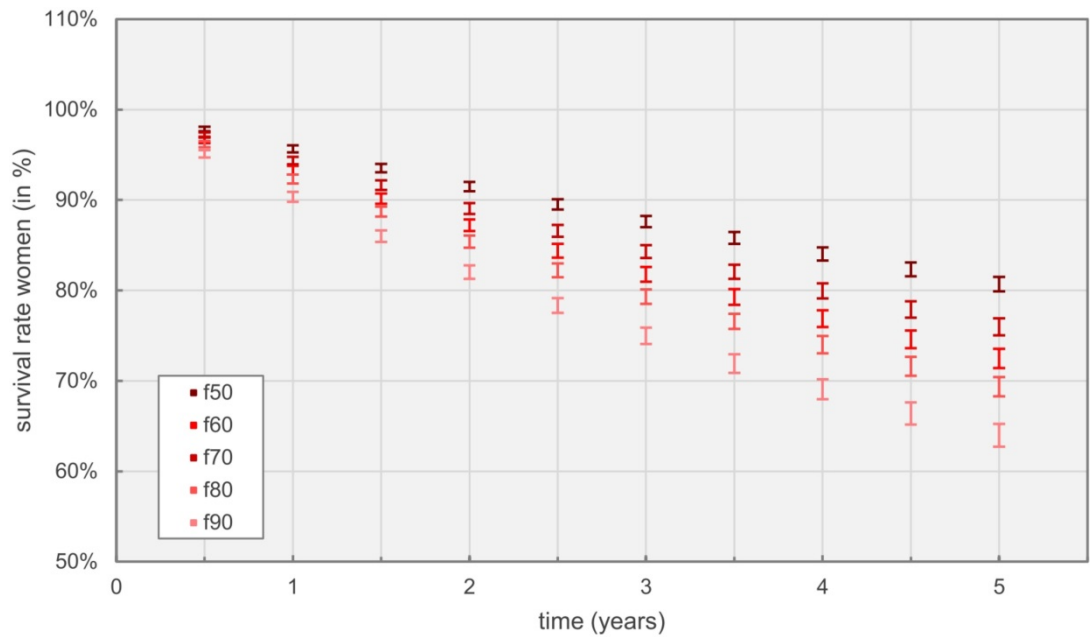


Figure 18: Survival rate for women at different age over time.

Naturally, mortality rates due to HF increased with age. However, distinct differences between men and women could be extracted; survival rates for women decreased evenly with increasing age (see Figure 18), whereas only minor differences in mortality for men between 50 and 70 years of age could be found, with distinctively increasing mortality rates afterwards. Generally, mortality rates were slightly higher for men compared to women, on average resulting in inpatient death rates across all age groups of roughly 29 % for men and 28 % for women within 5 years.

Figure 19 shows survival rates for 70 years old male patients based on their starting NYHA class, disregarding NYHA class changes.

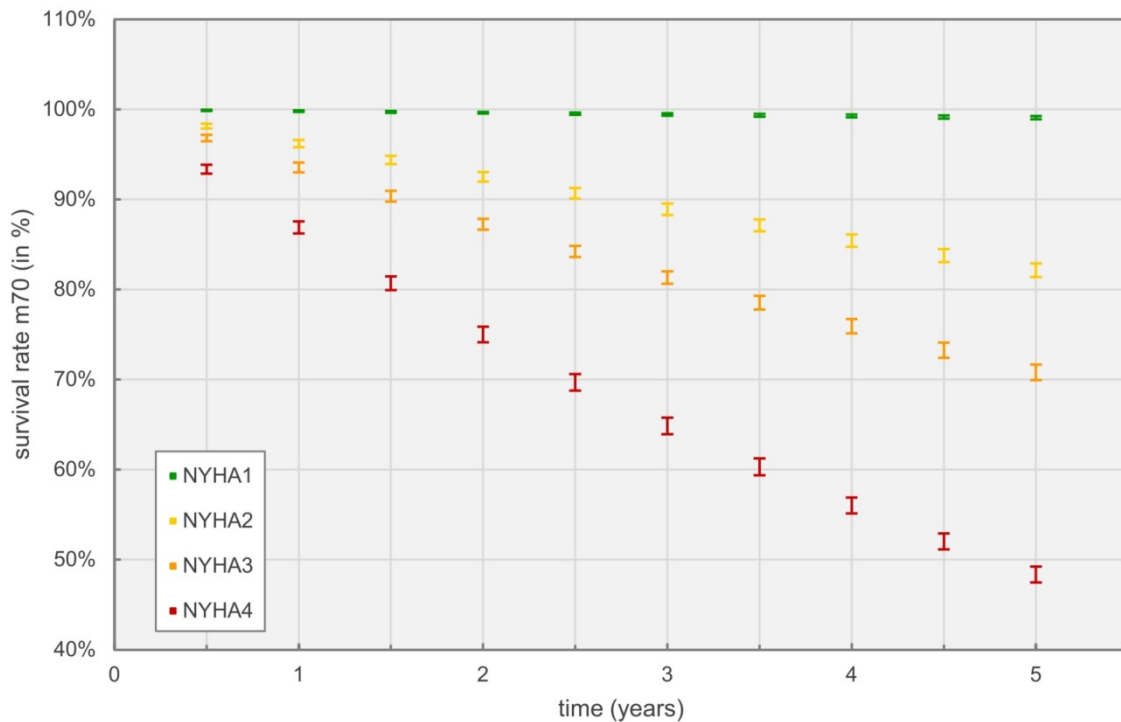


Figure 19: Comparison of survival rates for men at the age of 70 based on starting NYHA class.

While nearly no NYHA class I patient died due to heart failure in the modeled time frame, over 50 % of NYHA class IV patients suffered death.

3.1.3 Scenario 3

Scenario three investigated simulation results for 70 years old men, including NYHA class changes for outpatient and inpatient care as well as inpatient mortality rates. Figure 20 shows how NYHA classes change over time based on the implemented data sets. Overall, deaths are represented as black lines (mean values) with whiskers (standard deviation).

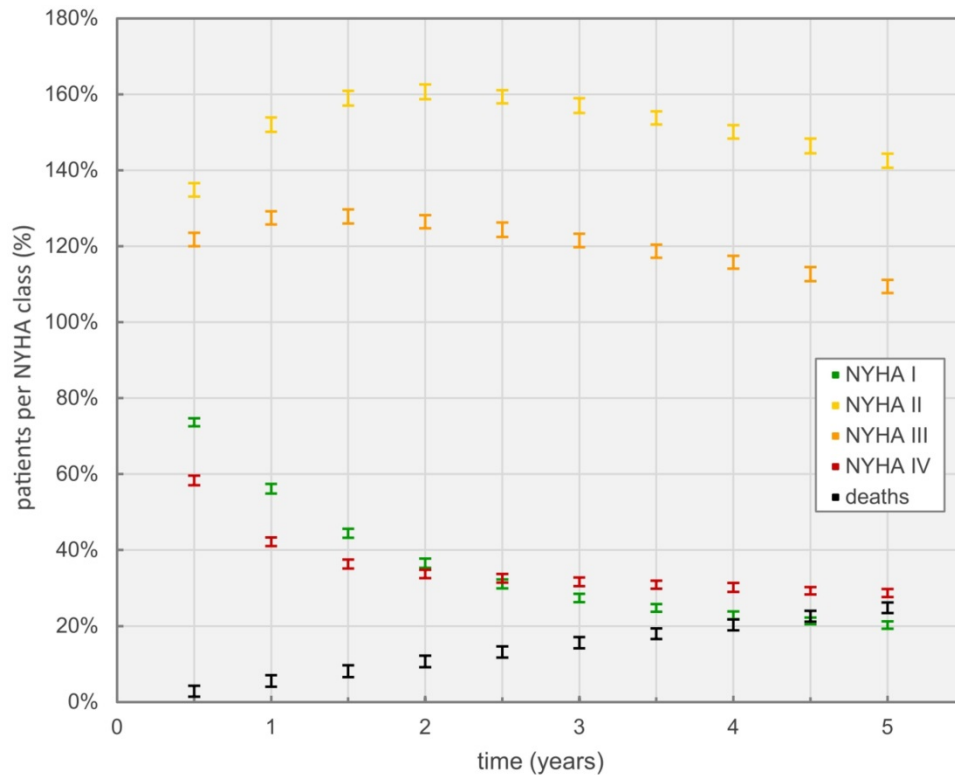


Figure 20: Development of the state of health for 70 year old male patients, expressed through NYHA class changes. Each NYHA class starts at 100 % with a pool of 2,500 patients each.

Out of the initial 2,500 patients in each NYHA class, most transitioned towards the NYHA classes II and III. The number of NYHA class I patients showed the most significant decline over time. On the other end, high mortality and hospital admission rates of NYHA class IV patients were the driving cause for the noticeable downward trend in Figure 20, which stabilized after the third year. Total deaths are increasing constantly over time, adding up to roughly 23 % of overall deaths after 5 years.

3.1.4 Sensitivity Analysis

To evaluate the range of model outcomes of presented simulation results, a sensitivity analysis (Table 52 and Table 53) was conducted to investigate the influence of age, gender and the NYHA class on economic outcomes and mortality. Results are presented as mean values of the 95 % confidence interval, standard deviations across all values are less than 1 % of the mean values and therefore neglected.

Table 52: Results of the sensitivity analysis for total costs/year in regard to age, gender and the NYHA class based on standard simulation settings, disregarding mortality and NYHA class changes (mean values of the 95 % confidence interval).

	age	NYHA I	NYHA II	NYHA III	NYHA IV
total costs/year compared to m70	m50	-0,73 %	-4,62 %	-3,71 %	-3,10 %
	m60	-0,70 %	-3,61 %	-2,69 %	-2,08 %
	m70	-	-	-	-
	m80	0,39 %	4,97 %	5,65 %	6,24 %
	m90	0,73 %	8,89 %	10,47 %	11,74 %
total costs/year compared to f70	f50	-0,91 %	-4,81 %	-3,76 %	-3,31 %
	f60	-0,67 %	-2,77 %	-1,56 %	-0,85 %
	f70	-	-	-	-
	f80	0,32 %	4,70 %	5,58 %	5,84 %
	f90	0,59 %	8,23 %	9,43 %	10,71 %
total costs/year men/women	50	3,35 %	3,56 %	3,40 %	3,03 %
	60	3,57 %	4,59 %	4,59 %	4,51 %
	70	3,53 %	3,74 %	3,45 %	3,25 %
	80	3,45 %	3,45 %	3,37 %	2,82 %
	90	3,38 %	3,00 %	2,25 %	2,05 %

Table 53: Results of the sensitivity analysis for the mortality after 5 years in regard to age, gender and the NYHA class based on standard simulation settings (mean values of the 95 % confidence interval)

	age	NYHA I	NYHA II	NYHA III	NYHA IV
mortality compared to m70	m50	-0,17 %	-1,89 %	-3,41 %	-7,36 %
	m60	-0,08 %	-1,01 %	-1,59 %	-4,05 %
	m70	-	-	-	-
	m80	0,32 %	8,18 %	14,16 %	26,86 %
	m90	0,78 %	17,08 %	28,43 %	50,58 %
mortality compared to f70	f50	-0,22 %	-4,46 %	-8,24 %	-18,01 %
	f60	0,15 %	3,74 %	6,20 %	12,69 %
	f70	-	-	-	-
	f80	0,33 %	7,01 %	12,05 %	23,46 %
	f90	0,67 %	13,33 %	22,22 %	40,70 %
mortality men/women	50	0,14 %	3,38 %	5,90 %	11,89 %
	60	-0,14 %	-3,95 %	-6,68 %	-15,41 %
	70	0,09 %	0,94 %	1,51 %	3,15 %
	80	0,08 %	2,18 %	3,87 %	7,44 %
	90	0,20 %	5,22 %	9,37 %	19,28 %

The sensitivity analysis showed that there is a clear distinction of the influence of age and gender per NYHA class for simulation outcomes. Total costs were simulated disregarding mortality to compare outcomes with Figure 15 and are more dependent on age than gender, especially with increasing NYHA class. The influence of gender on costs is rather evenly distributed across the NYHA classes, with men being slightly more expensive. Considering mortality, age is an even stronger influence, reaching values of up to 50.58 % for male NYHA class IV patients. Here the increased admission rates affect overall mortality; older patients have a significantly higher likelihood to suffer death than younger ones. Again, gender has a lower impact on outcomes, nevertheless varying results up to 19.28 % for NYHA class IV patients. In general men

have slightly increased mortality rates compared to women. The higher mortality for women at the age of 60 is based on the data set and can be taken from Table 41.

3.2 Use Case 2 – Telemonitoring Program

3.2.1 Scenario 4

Scenario four compares overall costs for two exemplary applications of a telemonitoring program. The simulated telemedical support is based on a recent program for HF patients at KAGes that was firstly introduced as additional HF treatment in Tyrol in Austria in 2014. Patients are equipped with a sphygmomanometer to assess blood rate and pulse, a scale to measure body weight and a cellphone to transmit data to a data center. An additional nurse complements the treatment as a communication interface between physician/specialist and patient and supports with individual training on HF and medication intake. [28] To simulate expenses based on the mentioned program, additional costs of the telemonitoring approach were calculated to €1,000 per patient for initial expenses for equipment purchase (acquisitionDMP) and an extra €45 per patient and month to cover additional efforts by the nurse/physician and for maintenance and service of the system (fixedRateDMP). The impact of additional efforts in outpatient care was extracted from [121] and amounted to 21 % decrease in overall admission rate, as well as a reduction of the average length of stay by 35 %. In Figure 21, expenses for conventional care are compared with the telemonitoring systems TM_1 (as described above) and TM_2 (no telemonitoring system for NYHA class I patients).

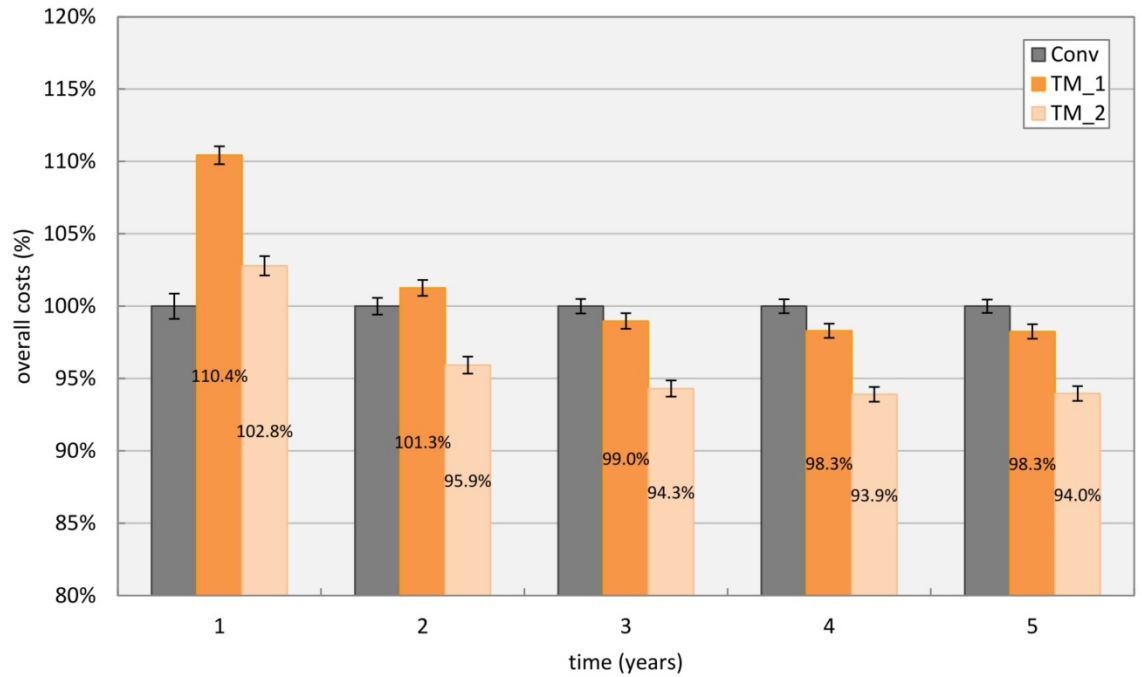


Figure 21: Overall costs for conventional care (Conv) and two different implementations of the same telemonitoring program. TM_1 was used on all patients, whereas TM_2 excluded NYHA class I patients.

Initial investments for the chosen telemonitoring system increased costs within the first year by up to 10 %. Depending on the telemonitoring approach, cost efficiency could be reached within the first two years, after three years both systems were cost efficient compared to conventional care.

4 DISCUSSION

This chapter discusses the build heart failure treatment model and its innovation and relevance to existing work in literature. A comprehensive and critical analysis of the simulation results and reasoning for the final model build are given. Advantages of the chosen modelling methodology as well as bottlenecks and rooms for improvements are further detailed to give a sense of the validity of the approach and open the discussion to possibilities of future extensions and considerations.

4.1 Simulation Model

Based on a published work by Schroettner and Lassnig in 2013 [94] a considerably advanced heart failure treatment model was built by Lassnig et al. in 2019 [36]. Improvements include a new, hybrid modeling methodology and conceptual approach, as well as two comprehensive data sources for outpatient and inpatient care as the underlying basis for the simulation of realistic outcomes for the treatment of heart failure. The model focuses on the detailed description of conventional care to create an adaptable basis for further simulations of integrated concepts of care. With the implementation of the mentioned data sets a completely revised and significantly refined model could be attained. The development of the model over the years was also further pushed through cooperation with Austrian health insurance and health care providers. Projects such as the INTENSE-HF study [96], even though having been prematurely closed, gave valuable insight into arising problems and difficulties with the implementation of alternative or more holistic treatment approaches. The health care system in Austria develops at its own pace, newer approaches have to legitimize their existence and benefits through either significant improvements of the state of health, cost efficiency or both. Covering needs of the public at large in terms of accessibility

and affordability is bound to the acceptance and funding of health insurance providers. Holistic methods of care, such as some disease management programs, consider the human being as a complex ecological system and recognize the need for adaptations of social, mental, biological and physical parameters to enhance awareness of one's life style and lastly, potentially, hone it.

The developed HF treatment model is not the only existing model to simulate HF treatment. Several decision-analytic modeling approaches are reported in literature estimating effects of health technologies for chronic heart failure patients. Goehler et al. [122] identified 34 modeling studies investigating different HF intervention programs. Markov models were the most common approach next to mathematical equation sets and discrete event simulations, with most models focusing on the effectiveness of new pharmacological or device-oriented interventions. A comprehensive analysis of overall survival in heart failure treatment has been published by Levy et al. through the Seattle Heart Failure Model (SHFM) [123], which is frequently discussed in literature and used in scientific studies. For example Li et al. in 2019 discussed the validity of the model after heart failure hospitalization [124], Ng Fat Hing investigated its utility for palliative care referral in advanced ambulatory heart failure. [125] The origin of the underlying data base is always crucial to the simulated outcomes, therefore Shiraishi et al. recalibrated and validated the SHFM for its use for Japanese acute heart failure patients. [126] Bilchick et al. used the SHFM and proportional risk models to predict benefits of ICDs [127], Sartipy et al. discussed the model's utility in patients with CRT and ICD referred for heart transplantation. [128] These studies are entries in an ongoing list of applications for predictive baseline models, such as the SHFM, which is not the only existing addressing chronic HF. Caro et al. developed discrete event simulations to compare the course of HF patients after the implantation of an ICD with additional amiodarone medication. [129,130] Klersy et al. investigated the economic impact of patient remote monitoring compared to usual care with a linear model based on an Excel platform, considering costs for hospitalizations. [83] Gasperoni et al. published two models in 2017, giving deeper insight into outcomes for overall admissions and death. Their models are based on risk factors and interventions, giving deeper insight into patterns of care for heart failure patients. [131]

In contrast to published modeling approaches, the detailed description of inpatient and outpatient care as delineated in the present work in regard to the NYHA classification system is unique and has high potential for future applications. The chosen modeling methodologies, discrete event and agent based, have so far not been used in combination to model heart failure treatment and offer several advantages in their interactions. First and foremost, the variable range of degree of abstraction allows the simulation on agent-individual and population level. Subgroups can be easily simulated and the effects of treatment outcomes on distinct parameters estimated. With the patient-specific history file, treatment processes can be individually followed and analyzed to assess trends and behaviour. The discrete model with distinct transition probabilities between states is highly adaptable to the clinical setting of interest and the inner states of patients can be adjusted to specific patient collectives. Therefore, study designs and clinical pathways in e.g. different regions or health care systems can be implemented with minor adaptations to the overall model. The multitude of potential applications is enormous and by far not limited to heart failure. The existing framework suits a multitude of treatment procedures for chronic diseases; new cooperation in different fields of health care research is a definite goal for further research.

4.2 Data Sets

To achieve reliable results with the chosen modeling methodologies, a significant depth of data is required. This was attained via the mentioned data sets for outpatient and inpatient care. One limiting factor concerning data quality was that the data sources were not structured based on a specific study design with defined health parameters; moreover inpatient data was derived from the extensive hospital information systems by KAGes, using ICD-10 codes for HF as the inclusion criteria for patients. Naturally, deviations in the quality of documentation regarding patient information occurred. For many patients, NYHA classes were not defined and information on left-ventricular ejection fraction (LVET) or N-terminal pro b-type Natriuretic Peptide (NT-proBNP) was not included in assessing the state of health, resulting in a certain bias of the final classification, since the state of health was not always assessed by a clinician. Out of the 10449 admissions, 57.7 % could be classified directly through the indication of the NYHA class in medical reports, roughly 5 % more were assessed based on medication or individual medical procedures. For outpatient care these numbers were 22.5 % versus 30.80 %, thus less patients were classified directly by physicians compared to inpatient

data, which may increase the likelihood of inadequate classifications. Criteria for assessing the NYHA class are regulated, but can be differently interpreted by physicians. The loss of information or misinformation through the classification algorithm had to be considered, as a basic approach the 95 % confidence interval was used to reduce outliers of derived parameters. Discussions with cardiologists led to conclusions that were supported by the used algorithm to classify the patients. Roughly 90 % of inpatient stays are due to NYHA class IV, for outpatient care most patients are in the classes II and III which are rather volatile and can improve or deteriorate rather quickly compared to the other classes. Therefore therapies mostly focus on these two classes, where most improvements in the state of health are possible. Additionally, NYHA class I patients are rarely classified, since the HF or rather its symptoms are not clearly perceived by the patient. On the contrary NYHA class IV patients are mostly stationary and treatment measures in outpatient care are insufficient to improve the severe state of health. The best practice in classifying HF patients is still frequently discussed in literature; the choice of using NYHA classes for this work was made due to its significance and frequency of mentioning in the field as well as its use at KAGes. A disadvantage of the monocentric data base was that follow-up times could not be consistently monitored for individual patients due to potential hospitalizations in surrounding centers of care; however, admission rates of 107 patients with precisely documented follow-up could be tracked across hospitals in Styria, as shown in Table 26 to derive frequencies of hospitalizations.

For outpatient care, detailed information on treatment in outpatient clinics was available for modeling based on the data set of KAGes. Medication, as well as visits and reimbursements of physicians were based on the data set of the health insurance provider, which included no information on the state of health. Therefore, distinct treatment profiles could not be consistently drawn for each patient. This is the main reason why no further differentiation in outpatient costs profiles for each NYHA class was achievable. Patients who experienced treatment in the outpatient clinic and the specific hospital could be matched due to the same data source. The health insurance provider used an anonymized national insurance number to identify patients; data restriction policies and the anonymization of both data sets disallowed the alignment with identification numbers used in the hospital association KAGes. The decision to increase the degree of abstraction by calculating with monthly visits to the physician and an annual visit to the outpatient clinic was based on the lack of cross-referenced

patients. As described in chapter 2.5.5, the annual costs for visits to the physician and the specialist were derived from accounting data and divided by the assumed number of visits. In terms of expenses for the medication, outcomes for each patient were addressed in the data set of the health insurance provider. Since there was no evidence, whether or not these costs arose due to the HF or other illnesses, only the medication specifically addressing symptoms of HF were considered. Disregarding all other drugs administered would have severely underestimated general costs for medication. The publication of the German health insurance provider [111] gave deeper insight into overall expenses and therefore was used to calculate overall costs based on the specific HF prescriptions.

The choice of using mentioned age groups for the statistical analyses was made due to their frequency of use in literature and to have a basis for comparisons with existing studies. Furthermore prevalence of heart failure starts to significantly increase after the age of 65 years and rarely occurs at younger ages, as published by [8–12]. Based on the used data sets, clear differences in outcomes for the chosen age groups could be drawn from the simulation results. Depending on demographics and setting of care different age considerations may be necessary to precisely represent HF treatment.

4.3 Simulation Results

The four presented scenarios give an overview of exemplary simulation results and model capabilities for the two use cases of conventional care and a telemonitoring program and can be further developed into a variety of potential scenarios and model applications. Assumptions for producing presented results are mentioned in chapter 3, calculations were disregarding outpatient mortality and visits to specialists. Every patient had the same cost profile for outpatient care, since the outpatient data set didn't include information on the state of health. Due to the disregard of differences between NYHA classes in outpatient care, outcomes and costs partially are under- and overestimated (see section 4.4). The missing information on outpatient mortality is obviously influencing overall outcomes. The clear assessment of this parameter outside a specific study design is challenging, since the cause of death is sometimes unknown and not based on a specific ICD-10 code. There was no indication whether or not death in the data set of the health insurance provider was due to HF or other diseases. Comorbidities were only addressed for the outpatient clinic. Therefore the decision was

made to neglect outpatient mortality and to compare results for age, gender and NYHA class considering inpatient mortality only.

An important aspect for assessing overall costs for the treatment of HF patient is how the allotted point score in inpatient care is equated to Euros. For the simulation runs one point was equated to €1. This may change based on each individual hospital and could be even €1.40 or less than one € which would strongly affect presented outcomes and thus stresses the importance of treatment-specific input values. The detailed description of inpatient care is essential to calculate costs of admissions. Especially modeling the length of stay with probability density functions instead of median or mean values is necessary to realistically predict expenses due to the nature of DRG systems with additional costs for transgressions of set treatment windows. No study in literature considering these transgressions could be found and the assumption can be made that concurring costs are severely underestimated in many reported cases.

In the first scenario costs for patients based on their NYHA class (Figure 15) were compared and divided into expenses for outpatient and inpatient care (Figure 16). The clear shift of costs from outpatient to inpatient care with worsening heart failure condition corresponds to clinical guidelines and findings in literature. However, costs in regard to NYHA classes are scarcely reported directly [101]. Berry et al. [14] compared costs per year and heart failure patient based on their respective NYHA class. Averages of €6,754 in France, €10,437 in the Netherlands and €24,790 in Belgium for NYHA class IV patients per year were approximated values, underlining huge divergence in inpatient expenses. In a systematic review of the economic burden caused by heart failure, Shafie et al. reported huge gaps of costs in literature, where annual expenses for the treatment of NYHA class IV patients ranged from Int\$4,147 to Int\$36,297 and from Int\$3,604 to Int\$20,871 for NYHA class III. Median annual inpatient costs per person summed up to Int\$10,141. [101] The simulated outcome of €10,077 ± €65 per NYHA class IV patient and year correlates with these findings. The definition of outpatient costs vary across literature; reported annual costs in literature range from Int\$64 to Int\$32,332 per patient, with a median of Int\$939 per year and patient [101]. Outpatients costs amounted to €1,912 ± €4 in scenario one.

Scenario two discussed overall costs and mortality of heart failure patients, based on age and gender as well as differences between the four NYHA classes. The high costs for 50 year old patients were not only explainable by the increase in admissions to intensive care and intermediate care units, but also by the nature of the DRG reimbursement system. Transgressions of the set windows for length of stay per NYHA class, as discussed in the methods section, are driving cost factors. Probability density functions for the length of stay are right-skewed and only slightly differ in their median values based on age. Differences in overall costs between the mentioned age groups were mostly influenced by the higher likelihood of intensive care and intermediate care admissions.

Survivability of patients is described in Table 41 and illustrated in Figure 18, showing an expected increase in mortality with age and an overall higher disease-related mortality for men compared to women. Both findings are supported by reports in literature, for example Goyal et al. investigated sex- and race-related differences in characteristics and outcomes of hospitalizations for heart failure patients with preserved ejection fraction [132], confirming significant differences in mortality based on age and gender. Outcomes for disease related survivability per NYHA class are depicted in Figure 19. Probabilities for admissions and inpatient deaths strongly correlate with the NYHA class as specified in Table 26.

The inclusion of NYHA class changes for outpatient and inpatient care in scenario three (Table 24 and Table 45) led to the results in Figure 20. The increase with time of the number of patients classified as NYHA class II and III is mostly based on transition probabilities in outpatient clinics (Table 24), where a significant trend towards both classes could be observed. Inpatient care probabilities for class changes favor transitions to higher NYHA classes, as described in Table 45. The simulated, even distribution between the four NYHA classes, doesn't reflect the actual distribution of heart failure patients in society and was chosen for the comparison of treatment effects. The trend towards NYHA classes II and III is supported by a publication by Poelzl et al., describing the Austrian heart insufficiency register, where most observed patients are either in NYHA classes II or III [12].

The influence of age, gender and NYHA class on economic and health outcomes was tested with a basic sensitivity analysis. As depicted in Table 52 and Table 53, all three parameters influence simulation outcomes, with age being a stronger parameter than gender, having distinct differences in outcomes based on inpatient characteristics.

The NYHA class strongly influences simulation outcomes, due to the limitations in addressing consistent NYHA classes for patients with longer follow-up times in the data sets; admission rates are not dependent on age or gender. The stronger deviations for NYHA class IV patients were expected due to overall higher probabilities for admissions.

Several publications address effects of outpatient and inpatient intervention programs for heart failure patients, with inconsistent positive effects [33–35,66]. The simulated telemonitoring setting for scenario four, based on findings by Dendale et al. [121], scores in the upper spectrum in terms of potential benefits, with a decrease in admission rates as well as length of stay. Primary investments for the implementation of the system increase costs at first, but can turn out to be costs efficient within 2 years due to the potential of an overall better outcome, as depicted in Figure 21. However, these effects are highly sensitive to the chosen patient collective in terms of age and overall state of health. Results indicate that highest potentials for the application of a telemonitoring system can be achieved for patients in the NYHA classes II and III, which are most susceptible to potential changes of the state of health. With the herein reported model, a variety of approaches can be modeled to estimate outcomes for highly specific patient collectives and to directly assess solution potential.

4.4 Validation

The model is based on a consistent and comprehensive data base. Data homogeneity was tested with a 10-fold cross validation for the main input parameters, which showed only minor deviations between test and training data sets. As already mentioned, study results vary distinctively in their outcomes for different intervention programs [33–35,66], therefore published models and studies in this field are subject to limitations in their generalizability. The specific patient collective, study design and region has a distinct influence on cost and health outcomes. Nevertheless, with the simulated scenarios, a first approach to results based on the parametrization with Austrian health insurance and clinical data could be achieved. Several findings in literature confirm the presented simulation results. Costs of inpatient care for NYHA class IV patients of roughly €10,100 per patient per year are within ~1 % of the median of the published review by Shafie et al. [101], who considered 35 publications addressing inpatient costs. Overall costs for inpatient care are mostly based on the length of stay, which is precisely modeled based on the Austrian DRG system.

Calculations with mean or median values of the length of stay do not representatively estimate cost outcomes, the inclusion of probability density functions allows realistic calculations. Reported costs in outpatient care strongly vary in literature and are heavily dependent on health care systems and treatment settings, requiring careful interpretation of estimations. Nevertheless, the expenses for heart failure medication based on ATC-codes derived from the data set of the health insurance provider matched findings published by a German health insurance provider [111], which is a comparable source to the Austrian health care system. Costs for physicians and specialists are based on actual accounting data of the Austrian health insurance provider. Overall, heart failure related mortality is naturally underestimated compared to [131] due to the exclusion of outpatient mortality and strongly correlates with age, NYHA class and comorbidities. [133] The presented mortality rates for inpatient care in the data set are higher compared to findings by Goyal et al. [132], who reported median in-hospital mortality rates per stay of 4.6 % across age and gender. The difference presumably is based on the rather ill and old patient collective in the data set, with nearly 90 % of hospitalized patients being classified to NYHA class IV. Based on the high number of patients in the included data sets, the derived mortality rates per admission were significant; their generalizability has yet to be proven. The heterogeneity of health care systems, study designs and regional outcomes of heart failure treatment and integrated methods of care hampers a cross-sectional validation. Huge divergence in cost predictions with highest costs reported in literature being approximately 45-fold higher as compared with lowest outcomes underline the difficulty to outline a standard costing methodology as reported by Shafie et al [101]. This supports the presented modeling approach by offering a framework that is highly adaptable to the context of interest. The matching of simulated results with literature reports and accounting data however underlines the validity of the presented model, exemplarily demonstrated for the use case of an Austrian hospital.

4.5 Model Limitations

Since no outpatient mortality could be extracted based on the ICD-10 codes for heart failure, it has been neglected for the simulations. Therefore and also based on the exclusion of outpatient deaths, mortality rates of up to 50 % within the first 5 years are not apparent in the mentioned scenarios except for NYHA class IV patients. In general, ethnicities as well as social status have been neglected in data analysis. Probabilities for admission per NYHA class were based on 107 patients with well documented follow-

up; no age correlation has been used for this parameter due to statistical insignificance. Several assumptions have been made to conclude results. The specialist and the physician could not be distinguished in the data set of the health insurance provider therefore they were simulated as one entity with on average 12 visits per year and costs per visit had to be generalized based on standard rates for Austria. This is not representing real frequencies of visits; however, the realistic estimation of costs had a higher priority. NYHA class changes in outpatient care were only possible after visits to the outpatient clinic, which could be drawn from the data set. Inpatient mortalities were implemented after admissions and disregarded for stays at intensive and intermediate care. Represented mortalities in Table 41 already include death rates for intensive and intermediate care. This was mostly done to have higher sample sizes to derive mortality rates per age and gender. NYHA class changes were triggered in inpatient care and after visits to outpatient clinics, but not after visits to physicians or specialists. It would be desirable to precisely model the prescription of medication and its influence on health outcomes, detailed studies on this subject would be necessary to derive more realistic estimations. Presented simulation results are based on Austrian data sets, their validity for other health care systems, especially outside of Central Europe, has to be investigated based on specific data sets for the selected use case of interest. The model offers the possibility to include individual treatment preferences and medication profiles for patients. For the simulated scenarios more generalized treatment profiles based on NYHA classes have been used. Data restrictions disallowed the conjunction of data from the health insurance provider and KAGes. Access to consistent and comprehensible patient profiles across all areas of care could improve model performance. The wide range of potential model applications and parameter adjustments is by far not fully explored yet; ongoing projects with health care providers may serve as a basis for the analysis of new treatment concepts for heart failure patients.

4.6 Outlook

The capabilities of the presented modeling approach are by far not exhausted. With the presented scenarios just a first view into this field is given and there are numerous possibilities of use for this unique and adaptable modeling approach. Especially in the context of the evaluation of new methods of care and their implementation into standard health care procedures, this tool could be of great use. Diametrical results in literature on the feasibility of intervention programs for HF

patients are partially based on the heterogeneity of patient collectives. With an a priori evaluation of the individual setting of care, including the health care system, the specific patient collective and treatment modalities, decision-making could be significantly improved to enhance the success of modernized treatment solutions. As for most decision-analytic simulation models, the data base is always significant for the predictive power. With the open model framework most studies could be simulated and outcomes predicted to tune the model even further and answer specific questions of interest. End of 2018 a positive vote of the Styrian ethics committee has been granted (30-525 ex 17/18) to initiate the cooperation with a renown German heart clinic to assess and analyze HF treatment with another huge clinical data set. The model will be extended with machine learning approaches and comorbidities will be integrated into the model structure. Together with the ongoing cooperation with KAGes the model can then be rigorously validated with an independent data base and further refined with the gathered information. The model based evaluation of ongoing studies in the field of integrated care for heart failure treatment is another set target; continued cooperation with Austrian health care providers has been established to sustainably improve care of heart failure patients.

5 CONCLUSIONS

In this work a unique, comprehensive and adaptable simulation model for the treatment of heart failure patients is presented, combining agent based and discrete event modeling based on extensive data sets for inpatient and outpatient care. Acquisition and statistical analyses of the input data are described including the algorithms used to deduce key aspects for the formulation of the model structure in AnyLogic®. Four presented simulation scenarios for two use cases, the conventional care and a telemonitoring program, demonstrate potential model applications and give insight into health and economic outcomes for heart failure patients based on age, gender and NYHA class. Results underline the unfavorable prognosis for heart failure and demonstrate costs savings within two years of using a more holistic treatment approach. Especially NYHA classes II and III reveal most potential for additional treatment measures. However, results strongly depend on the chosen patient profile and treatment setting. The validity of the modeling methodology and simulation results could partially be proven based on comparisons with literature and statistical procedures. The build model is unique in its field and showcases a novel approach and explicit depiction of care for heart failure patients. It is well known that sustaining present health care systems in the future is a rapidly growing challenge with increasing complexity in treatment procedures alongside economic feasibility. Comprehensive simulations of established treatment procedures provide the basis for the evaluation of new holistic methods of care and innovative study designs to improve health and economic outcomes. This work offers health care providers a novel tool for decision making in the complex and socioeconomically challenging field of cardiovascular diseases and may be a further piece in the sophisticated puzzle of refining health care systems.

6 REFERENCES

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7 APPENDIX

7.1 List of Scientific Papers

- *A novel hybrid modelling approach for the evaluation of integrated care and economic outcome in heart failure treatment [36](lead author)*
- *Simulation model for cost estimation of integrated care concepts of heart failure patients [94] (lead author; Schröttner and Lassnig contributed equally to this paper)*
- *Hip replacement in Austria - modelling the economic burden due to obesity [109](secondary author)*
- *A novel network-based approach for discovering dynamic metabolic biomarkers in cardiovascular disease [134](secondary author)*

7.2 List of Conference Contributions

- 1) *ESM' 2019: oral, Palma de Mallorca, Spain:*
Lassnig, A., Rienmueller, T., Baumgartner, C., Schroettner, J.
Model based evaluation of integrated care in heart failure treatment
- 2) *World Congress on Medical Physics and Biomedical Engineering 2018 - oral, Prague, Czech Republic:*
Lassnig, A., Bergmoser, K.M., Langthaler, S., Baumgartner, C., Schröttner, J.
Model-based evaluation of integrated care solutions in heart failure treatment
- 3) *World Congress on Medical Physics and Biomedical Engineering 2018 - poster, Prague, Czech Republic:*
Baumgartner, C., Lassnig, A., Buchhold, N.
A new optical, adaptable, high-resolution 3-axis sensor for medical device navigation

- 4) World Congress on Medical Physics and Biomedical Engineering 2018 - oral, Prague, Czech Republic:
Bergmoser, K.M., Langthaler, S., Lassnig, A., Horn, M., Baumgartner, C.
Estimating cardiac intensive care patients' responsiveness to late conservative fluid management using systems analysis

- 5) World Congress on Medical Physics and Biomedical Engineering 2018 - poster, Prague, Czech Republic:
Langthaler, S., Bergmoser, K.M., Lassnig, A., Baumgartner, C.
Temperature-induced modulation of voltage-gated ion channels in human lung cancer cell line A549 using automated patch clamp technology

- 6) ESM' 2017: oral, Lisbon, Portugal:
Lassnig, A., Baumgartner, C., Schroettner, J.
A modeling approach to heart failure treatment

- 7) BMT 2016: D-A-CH Dreilängertagung - poster, Basel, Switzerland:
Hinteregger, L.K., Lassnig, A., Rienmüller, T.M., Baumgartner, C., Schroettner, J.
Development of a simulation model to assess time in stroke treatment

- 8) BMT 2016: D-A-CH Dreilängertagung - poster, Basel, Switzerland:
Lassnig, A., Rienmüller, T.M., Baumgartner, C., Schroettner, J.
Development of a hybrid model to evaluate integrated care in heart failure treatment

- 9) BMT 2016: D-A-CH Dreilängertagung - oral, Basel, Switzerland:
Langthaler, S., Lassnig, A., Rienmüller, T.M., Baumgartner, C., Schroettner, J.
Usability evaluation of a locomotor therapy device considering different strategies

- 10) IHCM 2015 - oral, Gümüşhane, Turkey:
Siegl, W., Lassnig, A., Schroettner, J.
Hip replacement in Austria - Modelling the economic burden due to obesity

- 11) ÖGBMT 2014 - oral, Hall, Austria:
Lassnig, A., Siegl, W., Schroettner, J.
Integrated care in heart failure treatment - a modelling setup combining established concepts

- 12) ÖGBMT 2014 - oral, Hall, Austria:
Siegl, W., Lassnig, A., Schroettner, J.
Hybrid modelling – a new prospect for healthcare systems simulations
- 13) Global Conference on Healthcare Systems Engineering 2015 - oral, Istanbul, Turkey:
Siegl, W., Lassnig, A., Herzog, A., Schroettner, J.
A New National Model for Hip Replacement Costs Under Changing Demographics
- 14) BMT 2013: D-A-CH Dreilängertagung - poster, Graz, Austria:
Lassnig, A., Schroettner, J.
Comparison of telemedical and conventional treatment of heart failure patients considering different approaches to in-hospital stay
- 15) IWBBIO 2013: oral, Granada, Spain:
Schroettner, J., Lassnig, A.
Influence of NYHA Classification of Heart Failure Patients for Assessing Telemedical Applications and Services by Using a Discrete Event Model
- 16) Med-e-Tel 2012 - oral, Luxemburg, Luxemburg:
Schroettner, J., Harter, P.V., Lassnig, A., Kastner, P.
Heart Failure Model for Assessment of Different Intervention Programs
- 17) eHealth 2011 - oral, Vienna, Austria:
Schroettner, J., Lassnig, A., Liebmann, A., Kastner, P., Schreier, G.
Heart Failure Model for Assessment of Different Intervention Programs

7.3 Distribution Functions – Medication

Table 54: Distribution functions of expenses for set ATC group, based on age and gender (M...men, W...women)

Annual costs per patient (2008, 2009, 2010, 2011, 2012)									
Case Filter			PDF	PDF parameter	Goodness of fit		cases	mean [€]	SD [€]
ATC group	age group	gender	Weibull	a ... scale parameter, b ... form parameter	P ... probability of error				
			Gamma	1/scale ... scale parameter, shape ... form parameter	Anderson-Darling (A)	Kolmogorow-Smirnow (K)			
all	all	both	Weibull	a = 205.01336834 b = 1.11618805	A = 5.77 P = 0.01	K = 0.01 P = 0.01	38,701	196.75	180.31
all	all	W	Weibull	a = 200.79847804 b = 1.13685894	A = 4.02 P = 0.01	K = 0.01 P = 0.1	22,454	191.70	168.99
all	all	M	Gamma	1/scale = 170.50298380 shape = 1.1819640	A = 3.47 P = 0.001	K = 0.01 P = 0.09	15,375	201.54	193.08
all	1	W	Weibull	a = 222.47608883 b = 0.95062065	A = 0.4 P = 0.25	K = 0.04 P = 0.1	248	227.75	244.38
all	2	W	Gamma	1/scale = 153.49194167 shape = 1.3526290	A = 0.64 P = 0.1	K = 0.03 P = 0.25	867	207.61	183.96
all	3	W	Weibull	a = 248.06712376 b = 1.20962715	A = 0.64 P = 0.1	K = 0.01 P = 0.1	3,136	232.89	193.13
all	4	W	Weibull	a = 209.88991908 b = 1.16768456	A = 2.93 P = 0.01	K = 0.01 P = 0.1	9,261	198.90	169.48
all	5	W	Weibull	a = 174.01200468 b = 1.11179161	A = 2.23 P = 0.01	K = 0.01 P = 0.1	8,942	167.27	150.52
all	1	M	Weibull	a = 232.35661506 b = 0.98946285	A = 1.49 P = 0.01	K = 0.04 P = 0.1	670	233.49	252.71
all	2	M	Gamma	1/scale = 183.51991191 shape = 1.2077000	A = 0.87 P = 0.03	K = 0.02 P = 0.25	1,657	221.64	209.52
all	3	M	Gamma	1/scale = 178.92288424 shape = 1.2785670	A = 0.88 P = 0.03	K = 0.01 P = 0.1	4,154	228.78	209.17
all	4	M	Gamma	1/scale = 160.66838046 shape = 1.1874860	A = 1.72 P = 0.001	K = 0.01 P = 0.12	6,197	190.80	180.56
all	5	M	Weibull	a = 169.27592335 b = 1.08527565	A = 1.0 P = 0.01	K = 0.01 P = 0.1	2,697	163.97	155.33
C03	all	both	Weibull	a = 50.21469873 b = 0.83420658	A = 245.45 P = 0.01	K = 0.09 P = 0.01	20,775	56.66	101.15
C03	all	W	Weibull	a = 43.26708011 b = 0.92750740	A = 95.28 P = 0.01	K = 0.08 P = 0.01	12,255	45.05	61.03
C03	all	M	Weibull	a = 59.83293592 b = 0.78187418	A = 128.11 P = 0.01	K = 0.1 P = 0.01	8,010	71.86	138.13
C03	1	W	Weibull	a = 73.69476168 b = 0.79144096	A = 1.6 P = 0.01	K = 0.08 P = 0.1	155	86.69	150.06
C03	2	W	Weibull	a = 50.00191361 b = 0.85650063	A = 2.88 P = 0.01	K = 0.07 P = 0.05	394	54.77	77.84
C03	3	W	Weibull	a = 51.66191692 b = 0.89740276	A = 11.34 P = 0.01	K = 0.07 P = 0.01	1,623	54.78	69.73
C03	4	W	Weibull	a = 43.34473723 b = 0.93682098	A = 39.88 P = 0.01	K = 0.08 P = 0.01	5,078	44.88	61.33
C03	5	W	Weibull	a = 39.34804114 b = 0.96679688	A = 36.73 P = 0.01	K = 0.07 P = 0.01	5,005	40.02	49.43
C03	1	M	Weibull	a = 94.30039156 b = 0.70470476	A = 6.87 P = 0.01	K = 0.1 P = 0.01	304	126.08	234.60
C03	2	M	Weibull	a = 79.08749737 b = 0.77673769	A = 16.92 P = 0.01	K = 0.09 P = 0.01	855	95.37	171.61
C03	3	M	Weibull	a = 68.44689421 b = 0.77015257	A = 34.41 P = 0.01	K = 0.09 P = 0.01	2,121	83.19	153.33
C03	4	M	Weibull	a = 55.37902286 b = 0.80993366	A = 46.56 P = 0.01	K = 0.1 P = 0.01	3,308	64.28	121.69
C03	5	M	Weibull	a = 42.64128288 b = 0.86166954	A = 16.2 P = 0.01	K = 0.01 P = 0.01	1,422	46.85	81.55

Annual costs per patient (2008, 2009, 2010, 2011, 2012)										
PDF parameter			Goodness of fit	cases	mean [€]			cases	mean [€]	SD [€]
ATC group	age group	gender			a ... scale parameter, b ... form parameter	P ... probability of error				
			Weibull							
			Gamma							
C07	all	both	Gamma	1/scale = 54.13908254 shape = 1.29134924	A = 116.87 P = 0.001	K = 0.07 P = 0.001	24,737	69.91	71.18	
C07	all	W	Gamma	1/scale = 51.30145953 shape = 1.33370323	A = 72.37 P = 0.001	K = 0.07 P = 0.001	14,150	68.42	69.24	
C07	all	M	Gamma	1/scale = 56.67309751 shape = 1.25236918	A = 41.52 P = 0.001	K = 0.06 P = 0.001	9,990	70.98	72.32	
C07	1	W	Weibull	a = 91.65528265 b = 1.02487087	A = 2.55 P = 0.01	K = 0.13 P = 0.01	169	90.63	99.34	
C07	2	W	Gamma	1/scale = 57.07927926 shape = 1.38276076	A = 2.44 P = 0.001	K = 0.06 P = 0.001	654	78.93	75.89	
C07	3	W	Gamma	1/scale = 53.60158252 shape = 1.42537981	A = 18.58 P = 0.001	K = 0.08 P = 0.001	2,334	76.40	75.08	
C07	4	W	Gamma	1/scale = 49.60061927 shape = 1.35215852	A = 25.14 P = 0.001	K = 0.06 P = 0.001	6,028	67.07	67.47	
C07	5	W	Gamma	1/scale = 49.44732735 shape = 1.29778163	A = 28.95 P = 0.001	K = 0.07 P = 0.001	4,965	64.17	65.70	
C07	1	M	Gamma	1/scale = 57.04748929 shape = 1.31467459	A = 1.99 P = 0.001	K = 0.06 P = 0.001	538	75.00	71.05	
C07	2	M	Gamma	1/scale = 61.53882817 shape = 1.30206449	A = 5.82 P = 0.001	K = 0.07 P = 0.001	1,199	80.13	78.54	
C07	3	M	Gamma	1/scale = 63.14726380 shape = 1.24979402	A = 13.80 P = 0.001	K = 0.07 P = 0.01	2,928	78.92	79.96	
C07	4	M	Gamma	1/scale = 51.93415226 shape = 1.27480811	A = 15.87 P = 0.001	K = 0.06 P = 0.001	3,858	6.21	67.21	
C07	5	M	Gamma	1/scale = 47.18124578 shape = 1.24424677	A = 4.77 P = 0.001	K = 0.04 P = 0.001	1,467	58.71	60.71	
C09	all	both	Weibull	a = 160.67489036 b = 1.12208366	A = 13.82 P = 0.01	K = 0.02 P = 0.01	30,577	153.96	138.26	
C09	all	W	Weibull	a = 165.83859245 b = 1.12790871	A = 8.52 P = 0.01	K = 0.02 P = 0.01	17,546	158.68	141.17	
C09	all	M	Weibull	a = 153.10949860 b = 1.11973953	A = 5.64 P = 0.01	K = 0.01 P = 0.03	12,359	146.78	133.06	
C09	1	W	Weibull	a = 154.00185372 b = 1.03852558	A = 1.39 P = 0.01	K = 0.08 P = 0.10	183	151.53	151.88	
C09	2	W	Gamma	1/scale = 117.67474700 shape = 1.2587410	A = 0.93 P = 0.02	K = 0.04 P = 0.01	721	148.13	141.76	
C09	3	W	Gamma	1/scale = 142.34875445 shape = 1.2541910	A = 1.89 P = 0.001	K = 0.03 P = 0.001	2,594	178.53	156.90	
C09	4	W	Weibull	a = 173.74662523 b = 1.13721657	A = 5.0 P = 0.01	K = 0.02 P = 0.01	7,292	165.91	144.97	
C09	5	W	Weibull	a = 151.09309475 b = 1.12754726	A = 3.94 P = 0.01	K = 0.02 P = 0.03	6,756	144.58	128.23	
C09	1	M	Weibull	a = 146.50023874 b = 0.99679852	A = 1.52 P = 0.01	K = 0.05 P = 0.1	530	146.71	154.88	
C09	2	M	Gamma	1/scale = 102.50102501 shape = 1.3554220	A = 0.45 P = 0.25	K = 0.01 P = 0.25	1,365	138.94	119.99	
C09	3	M	Weibull	a = 163.80526153 b = 1.14669991	A = 1.39 P = 0.01	K = 0.01 P = 0.1	3,482	155.89	138.01	
C09	4	M	Weibull	a = 150.80510800 b = 1.10500431	A = 2.93 P = 0.01	K = 0.02 P = 0.1	4,919	145.21	132.38	
C09	5	M	Weibull	a = 146.05277617 b = 1.11284161	A = 1.35 P = 0.01	K = 0.02 P = 0.1	2,063	140.33	127.46	

