# Hybrid Simulation Approach for Prospective Assessment of Mobile Stroke Units*

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Abstract: Technology innovations in health care offer high potentials for all stakeholders (e.g., patients, healthcare providers and health industry), but the development phase of such innovations is often very expensive and the effects are hardly predictable without a systematic strategy. The new interdisciplinary approach Prospective Health Technology Assessment (ProHTA) uses simulation techniques to indicate the effects of new health technologies, early before the cost-intensive development process begins. Furthermore, ProHTA helps to detect gaps and bottlenecks in the health system to catch potentials for new innovations. The scope of ProHTA includes both a strategic aggregated level of analyses as well as an individual detailed level. This paper describes the use of hybrid simulation approaches, consisting of System Dynamics and Agent-Based Simulation, to analyze the effects of an innovative stroke technology. We discuss an example of the prospective assessment of Mobile Stroke Units within a Metropolitan Scenario. The project ProHTA is a part of the Centre of Excellence for Medical Technology - Medical Valley EMN - and is supported by the German Federal Ministry of Education and Research (BMBF), project grant No. 01EX1013B.

## 1 INTRODUCTION

The global market for medical technology products is growing rapidly due to an increasing demand of innovative healthcare technologies. Presumably, some reasons of this notice are the increasing life expectancy of the population, new technical opportunities and an increasing complexity of the healthcare delivery.

A significant consequence of this trend is that the healthcare industry has to handle even faster tradeoff decisions before developing new innovations in medicine. To be more profitable a new product must have a short development phase, low costs and it is also important that the expected revenue can be reached. In addition, health technologies are safety-critical, as the life quality can depend on the product's quality. Following this fact, proven evidence is necessary and regulatory barriers have to be overcome. Usually, such activities are time-consuming and their results are difficult to predict. Often there is also no proven evidence available, so the development of new innovations can degenerate into a risky, non-profitable project.

The main difference between the healthcare domain and other safety-critical areas is that many involved stakeholders with different interests have to be satisfied before a product can be placed on the market. Some examples of them are patients, healthcare providers such as hospitals and outpatient departments, manufacturers in healthcare, technology developers, insurance companies, governments, regulatory institutions and academia.

According to the described situation, assessments of health technologies are very complex and advanced assessment methods are crucial to prevent disinvestments and to make the product development more effective. All players must be considered for this pro-

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cess to reach an overall credibility of the product's quality and to detect all kinds of problems as early as possible.

Three assessment methodologies for healthcare technologies have been introduced until now. Health Technology Assessment, Early Health Technology Assessment and Horizon Scanning.

Health Technology Assessment (HTA) is an approach used after the market launch of a product when evidence is available from studies. In accordance with Goodman (Goodman, 2004), the main field of HTA is to inform, among others, regulatory agencies and lawmakers about permission decisions for a commercialization of a regarded innovation.

Early Health Technology Assessment (Early HTA) tends to be an appropriate tool in cases where the product is already in the development phase but only limited evidence is available. Some examples for such evidence levels are animal testing, early clinical experience, or data from previous technology generations (Pietzsch and Paté-Cornell, 2008).

The impact of Horizon Scanning (HS) is the comparative assessment of similar technologies to observe trends of possible disinvestments and impacts of new healthcare technologies. Horizon Scanning Systems focus on health technologies that are ready to enter the market, i.e. in early post-marketing phases (Geiger-Gritsch, 2008).

In many cases the technological progress is the key factor for new products and there is only a little consideration of possible future consequences. But new innovations must reach positive assessment results before their impact can be seen by all stakeholders as reasonable. Hence, an enormous number of disinvestments can be expected, as established assessment methods (HTA, Early HTA and HS) are just used for products that already have passed the expensive design and development process.

For that reason we call for advanced foresight healthcare assessment methods which are applicable early before high efforts and investments were made. This is where our approach ProHTA can take an important role, because simulation techniques can be applied to assess new innovations prospectively.

## 2 RELATED WORK

There are already a couple of publications which are presenting the use of simulation for the healthcare domain. Most of them are considering healthcare processes and are modeled by the Discrete Event Simulation approach. Brailsford (Brailsford, 2008) discussed System Dynamics (SD) as tool for healthcare modelers. The author presented several examples and depicted some reasons for the growth in SD popularity. Following this, some advantages of SD are lower data requirements, the sight of the big-picture and in particular very fast simulation runs.

In order to benefit from high-level abstractions as well as to allow more detailed modeling possibilities, hybrid simulation techniques are gaining acceptance. Heath et al. (Heath et al., 2011) discussed several challenges and successes of cross-paradigm modeling. In particular, Discrete Event Simulation, System Dynamics and Agent-Based Simulation approaches were considered in detail. Though hybrid simulation is not precisely defined yet, there are however software packages that allow multi-paradigm modeling.

## 3 PROSPECTIVE HEALTH TECHNOLOGY ASSESSMENT

Prospective Health Technology Assessment (ProHTA) is a new approach that extends the tool environment of healthcare assessment methodologies and fills the gap, mentioned previously. For this reason the project is located within the Medical Valley EMN (European Metropolitan Region Nuremberg) and is a part of the Centre of Excellence for Medical Technology.

The innovative intention of ProHTA is the assessment of health technologies from many perspectives, early before the development of a medical innovation begins. It helps to detect potentials for process optimization and allows learning about the influence of a new technology on the established health system structures. Innovation's cost-effectiveness has to be prospectively calculated as well as the impact on the patient's health.

Figure 1 summarizes the main prospective evaluation processes. In this respect, two questions are central to ProHTA:

- What are the changes that result from the launch of a new technology? - ProHTA will be able to simulate and assess the effects of changes to processes, which are introduced e.g. by a new technology. ProHTA will project the effects of innovative health technologies on the quality and costs of health care.
- What does a technology need to be like in order to have a specific effect? - If certain input requirements of a desired change are specified, the ProHTA tools will enable outcome related conclusions concerning the required changes to the process (hypothesis development). ProHTA will

envisage the effects of the potential efficiency enhancement on the health care system.

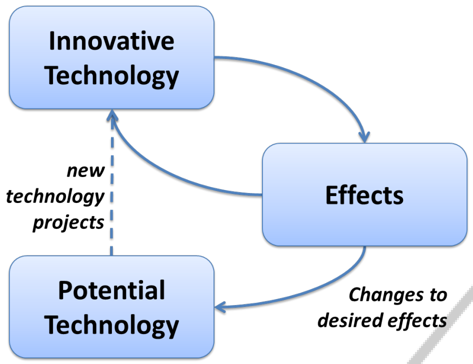


Figure 1: ProHTA overview.

Especially the second question allows ProHTA to examine the existing health system and to find bottlenecks and weaknesses of currently applied practices. This can lead to new ideas for health technologies that are particularly based on desired effects and not only on technical opportunities. In the course of the method creation of ProHTA a new scientific service platform has to be developed targeting on the scope of the just described project.

The regarded challenges and questions are handled together by an interdisciplinary team consisting of experts from the areas of Public Health, Health Technology Assessment, Clinical Medicine, Health Economics and Outcomes Research, Medical Informatics, Knowledge Management as well as Modeling and Simulation. Furthermore, two representatives of the healthcare industry also participate in the project.

In this paper we discuss the use of hybrid simulation approaches, consisting of System Dynamics (SD) and Agent-Based Simulation (ABS), for the new foresight assessment method ProHTA. As the complexity of the considered domain and the interdisciplinary co-working is enormous, a structured methodology towards a hybrid simulation model will be described within the next section as well. The current focus of the approach is the assessment of innovative technologies in management of acute stroke. We use Mobile Stroke Units (MSU) within a Metropolitan area as an innovative health technology to show exemplary how hybrid simulation techniques can be applied to the impact of ProHTA. Within the discussion section we look ahead to the future work, including the validation of our approach and its application to oncology diseases.

# 4 CONCEPTUAL MODELING

As already mentioned, many challenges have to be mastered during the project realization phase. To achieve an effective and intensive co-working of all experts with different backgrounds, a structured methodology is essential.

For that reason a dedicated *Conceptual Modeling Process (CMP)* for ProHTA was defined, classifying the main steps towards a hybrid simulation model, beginning at the domain experts' knowledge collection. It is largely based on current work of a research group from the University of Warwick and Loughborough University (Robinson, 2011; Kotiadis and Robinson, 2008).

As hybrid simulation builds the focus of this paper and the CMP will be the topic of another publication, we introduce in the following only some parts of it, as it is important for the simulation.

The CMP distinguishes in particular between *domain experts* and *technical experts* and defines fields of activity and intermediate interfaces for all of them. Furthermore, the reality is summarized within the *Domain World* and the abstraction of it is contained in the, so called, *Model World*. The significant artifact of the Domain World is the non-formal specification of the problem, represented by the *Conceptual Domain Model (CDM)*. This result is used by an iterative formalization process as input for the Model World, according to create the *Formal Conceptual Model (FCM)* which serves as a basis for the simulation model and knowledge base.

Figure 2 depicts by solid lines the main steps of the Conceptual Modeling Process towards a simulation model. Dashed arrows represent the feedback steps of iterative improvements.

# 5 USE-CASE: MOBILE STROKE UNITS WITHIN A METROPOLITAN REGION

Stroke is one of the leading causes of death and disability and absorbs a considerable proportion of healthcare budgets (Kjellström et al., 2007). In Germany an increase of 1.5 million stroke cases is estimated in the next decade (Kolominsky-Rabas et al., 2006). Due to an ageing population, increasing incidence values could be expected in the future, as stroke appears mainly at higher age groups. The costs for treatment and rehabilitation in Germany are estimated to be totally about 58 billion of euros in the period 2006-2015 (Kolominsky-Rabas et al., 2006).

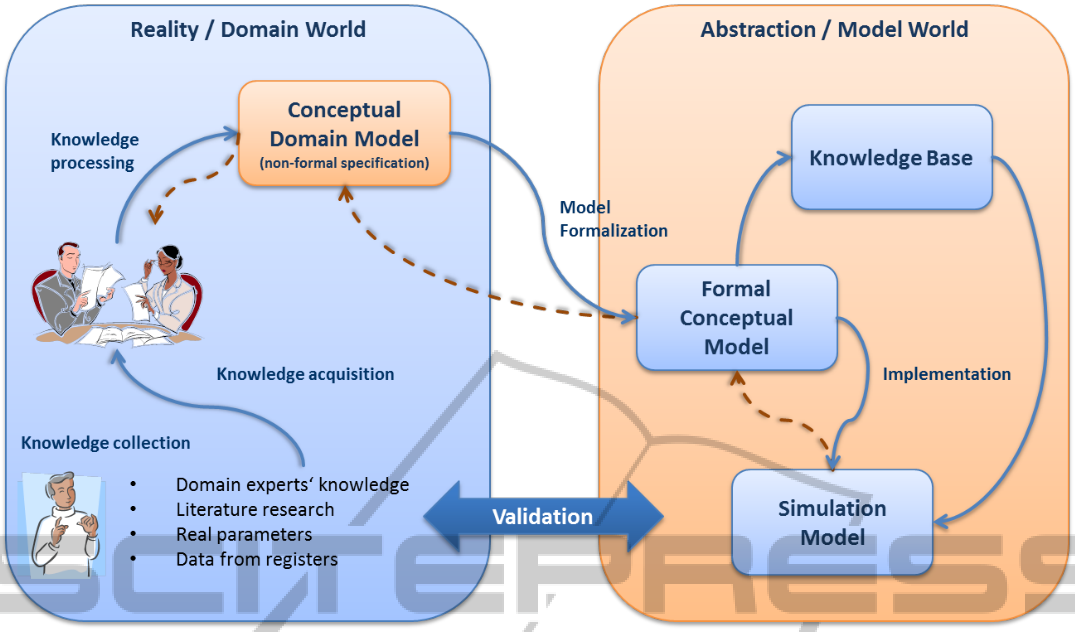


Figure 2: Conceptual modeling process of ProHTA.



One of the most frequent form of stroke is the *ischemic stroke*, caused by an oclusion of cerebral arteries. Currently, an approved method for the treatment is the *intravenous thrombolysis* by recombinant tissue plasminogen activator (rtPA) (Fassbender et al., 2003). However, even in specialized hospitals (Stroke Units), only 7 to 10 percent of patients are treated by this effective method (Heuschmann et al., 2010). The main reason for such a bad rate is the applicability of the thrombolysis only within 4.5 hours after the obstruction's occurrence and the time, elapsed during the transport to the hospital (Purrucker and Veltkamp, 2011). A significant increase of the rate from 3 percent to 7 percent had been observed after the extension of the recommended time window from 3 hours to 4.5 hours in 2008 (Purrucker and Veltkamp, 2011).

In case of an affection, nearly 1.9 million of neurons can die per minute (Kuehn and Grunwald, 2011). Hence, the "time is brain" concept has to be applied to the extremely time-critical treatment of stroke. Following this fact, particularly innovations in stroke treatment are necessary which are able to reduce the call-to-therapy-decision time.

Two German research groups from Saarland and Berlin (Walter et al., 2010; Ebinger et al., 2012) are working with their partners on methods targeting at the transfer of the thrombolytic inpatient treatment to the pretreatment phase. In that case the therapy can be applied before the time-intensive transfer to the hospital and an increase of the number of patients, treated by thrombolysis can be expected. The main problem of this idea is the important exclusion of an intracerebral haemorrhage, before applying rtPA. This can be done by laboratory analyses and Computer Tomography (CT), usually installed in hospitals. To prevent a loss of crucial time, both research groups developed similar prototypes, the *Mobile Stroke Unit (MSU)* and the *Stroke-Einsatz-Mobil (STEMO)*. Such a vehicle extends the standard emergency equipment by a CT and further tools for a rapid diagnostic decision onsite at stroke occurrence location.

In an early phase, first trials have shown that a shortened call-to-therapy-decision-time of approximately 35 minutes is not a vision (Kuehn and Grunwald, 2011). To inspect other relevant effects (e.g. long-term cost-effectiveness, application in other regions) more trials are necessary, so that further time and cost investments have to be made. This is where ProHTA can provide an early analysis by hybrid simulation.

## 6 HYBRID SIMULATION

For the purpose of the Prospective Health Technology Assessment simulation has been identified to be an appropriate tool. Customized large scale simulation models are crucial to handle complex questions in situations where an innovative technology possibly hasn't been developed yet. Depending on the point of view, ProHTA must be able to answer specialized questions (e.g. effectiveness of a new innovation) as well as to calculate global and long-term consequences. Hence, large scale models are necessary to fulfill these requirements. Furthermore, separate data management and data quality components are crucial to handle a couple of different input data formats in an efficient way (Baumgärtel and Lenz, 2012).

We need methods to create models on an abstract, macroscopic level (e.g. economic flows, population dynamics) where data about details is not available, or even is not necessary. In our approach System Dynamics (SD) (Forrester, 1999) was qualified as an appropriate tool for this kind of simulation. To model individual aspects of patient's workflows and its behavior, the Agent-Based Simulation (ABS) approach has been selected. New technological innovations can also be modeled by the ABS approach to allow behavioral changes, according to inspect their impacts on output values.

Each assessment scenario is individual. For this reason we propose to combine the SD and the ABS approach into a common hybrid simulation using an adequate ratio according to the desired simulation level and high simulation performance. This trade-off decision can be handled by following a top-down approach. In that case the problem environment can be modeled as deeply as needed by abstract methods and a special simulation part will be framed-out and realized by the ABS approach.

The idea of hybrid simulation is getting more and more popular in current research (Heath et al., 2011; Brailsford et al., 2010). There are many software packages that allow to create simulations by SD, Discrete Event Simulation (DES) or ABS models, but most of them support only one of the presented approaches. AnyLogic (XJ Technologies Company Ltd., 2012) offers the power to combine different simulation paradigms within a common simulation environment. This is why this tool is qualified to create models within the scope of ProHTA.

## 6.1 Modular Environment

In accordance to the Conceptual Modeling Process (Section 4), the CDM represents a non-formal description of the collected experts' knowledge. The FCM is central to develop simulation models within the context of ProHTA.

We have to deal with different, interacting simulation parts, such as money flows, healthcare structures, disease, and population development. To make models reusable for further assessment scenarios and to master the complexity, modularization is important.

Figure 3 depicts the identified modules within the scope of ProHTA.

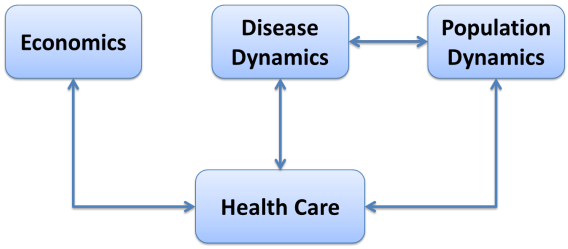


Figure 3: Overview of the modules.

*Population Dynamics* summarizes models and parameters that handle with the development of demographic structures, e.g. birth rate, mortality, immigration and emigration.

*Disease Dynamics* includes generic model parts that deal with illness parameters, e.g. incidence, prevalence, case fatality rate and remission.

*Economics* combines the dynamics of money flows of the health system. Statutory and private health insurance can be modeled there as well as the long-term care system.

*Health Care* is a module where especially workflows of prevention, pre-treatment, treatment and post-treatment of a regarded disease can be modeled.

Chahal and Eldabi (Chahal and Eldabi, 2008) proposed a *process environmental format* for hybrid simulations. In our hybrid simulation approach for ProHTA, SD models can be used to build the environment of a simulation. An important simulation part can be modeled by ABS approaches and used as core within the process environmental format.

## 6.2 Scenario Description

Before we set the focus on our model, the scenario with Mobile Stroke Units within a Metropolitan region will be shortly presented in the following:

- Stroke scenario with usage of a predefined number of 10 MSUs.
- A German Metropolitan region, represented by Berlin, with approximately 3.416.000 people is modeled using data from the statistical calculations of (Amt für Statistik Berlin-Brandenburg, 2010).
- The regional distribution of people is done by information about the district density.
- MSUs are randomly distributed within the region boundaries.
- People can get stroke and call the Rescue Service (RS).
- RS decides whether an MSU can be sent (e.g.

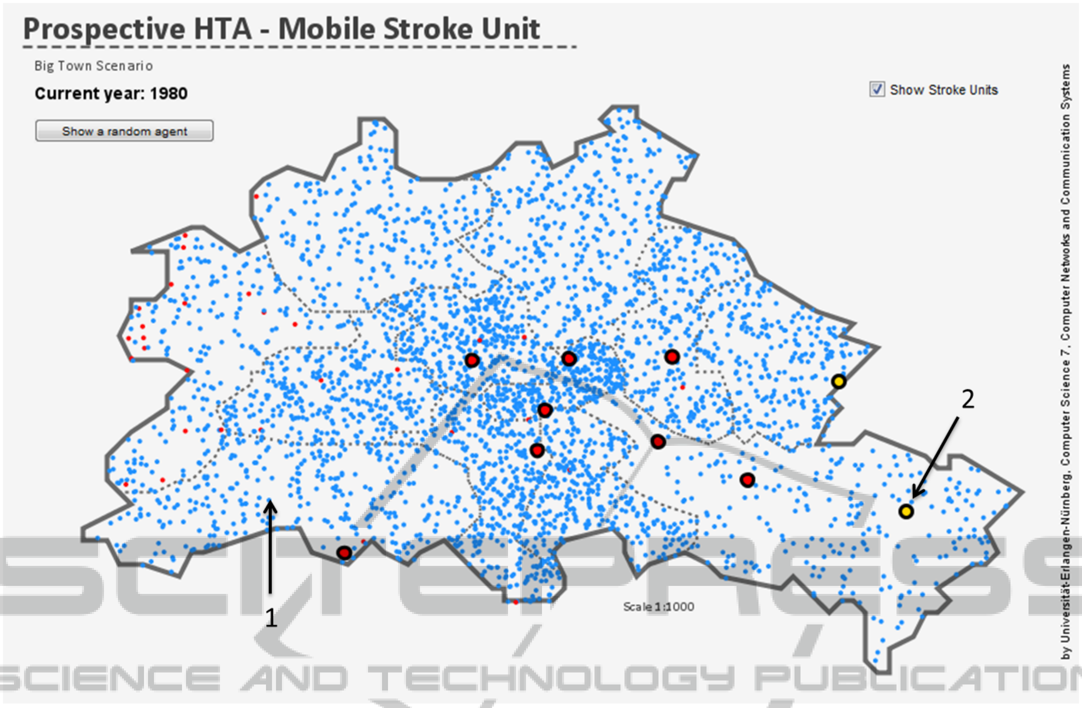




Figure 4: Mobile stroke units within a metropolitan scenario.

there are free MSUs available) to the affected patient.

- During the affection phase, people pass through diagnostic and therapy workflows and lose life quality according to a therapeutic effectiveness.
- In case of using an MSU, thrombolytic therapy can be started onsite at patient's location, after a mobile CT and laboratory diagnose were performed.
- Calculated costs are drawn from financial budgets.
- Demographical information is used to reproduce the population development.
- Prevalence is used to separate the population in affected and not-affected parts.
- Incidence is used as a dynamic affection rate.

For assessment purposes the same scenario without MSUs will be used afterwards. It allows to make the effects of a new intervention (MSUs) visible.

## 6.3 Simulation Model

### 6.3.1 Overview

The simulation is started within an initialization phase and proceeds with a forecasting phase after a couple of data has been produced.

There are two types of agents modeled within the hybrid simulation of our MSU scenario, the individual behavior of persons and Mobile Stroke Units. Demographic development is reproduced by a separate System Dynamics model (Population Dynamics) as well as money flows of the health system.

Figure 4 depicts a screenshot of a running simulation. Small points represent person agents (number 1). Changing the color from blue to red a patient becomes affected. Yellow bullets with black borders are a representation of MSU agents (number 2). During simulation runs they are colored in red, if an MSU is busy to see an overall utilization of the new technology. MSUs pick up patients and move them to the next hospital.

### 6.3.2 Agents

Age, risk factor (RF), gender and life quality (LQ) are important attributes of a person and are sampled initially. A normal risk is represented by $RF = 1$, high risk by $RF > 1$ and low risk is a value $RF < 1 \wedge RF > 0$. LQ is represented by a value between 0 and 100. Dependent on the therapy success, the patient loses more or less LQ points.

Time until the next occurrence of stroke symptoms is calculated by an appropriate function. An *annualEvent* is used to increase patient's current age and to run a death calculation function. The behavior is represented by the left hand state chart of Figure 5 with three states (*normal*, *symptoms*, *affected*).

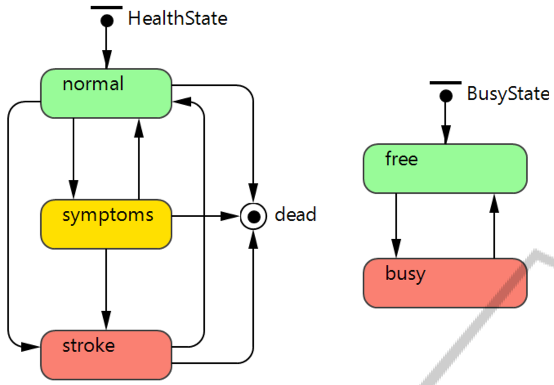


Figure 5: Behavior state charts of agent person (left) and MSU (right).

The state chart of the agent type MSU is depicted on the right hand of the Figure 5 and includes two states (*free*, *busy*). The variable *timeApprToScene* is used to simulate the delay of an MSU until arrival at patient's location. In a further step it can be used to reproduce traffic by an additional simulation part.

The health care structure is modeled within a separate state chart. At the beginning, each person is located in the state *noHealthCare*. After the occurrence of suitable events, a patient changes to an appropriate composite state, such as prevention, pre-treatment, treatment and post-treatment that are partially presented in the following.

Each step that produces costs (e.g. special treatments, materials, staff employment) collects them in a global variable within the economics System Dynamics model. The calculated number is pulled off from the corresponding budgets once-a-year.

#### 6.3.3 Prevention

As prevention interventions for stroke are not usual, a simple part of the model takes into account only weak preventive influences, e.g. healthy lifestyle. Preventive check-ups are simulated in undetermined cycles with a minimum of five years elapsed since the last prevention.

The time until next stroke symptoms occurrence is calculated by a multiplication of the remaining time and the individual risk factor (RF) of a person. The higher a RF, the higher the prevention effect and the earlier a prevention, the higher is the gain of time.

#### 6.3.4 Pre-treatment

After the expiration of the time until next symptoms, an event is fired and the concerned person enters the *symptoms* state and starts the workflow of the pre-treatment phase within the *HealthCare* state chart, figured in 6.

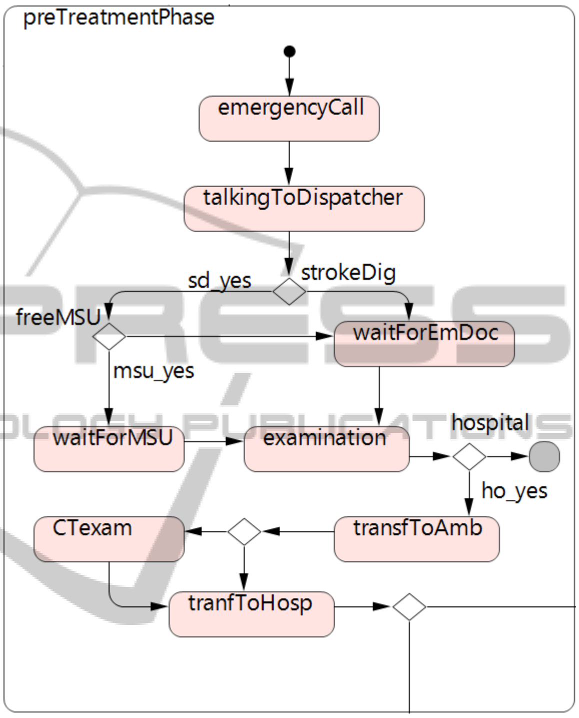


Figure 6: Agent-based model of the pre-treatment phase.

According to the workflow an emergency call is modeled first. After talking to the dispatcher a first diagnosis is made and a rescue service is alarmed to move to the patient. Due to the assessment of MSUs, the dispatcher searches for free Mobile Stroke Units. The more of them are initially available, the higher is the probability to get one free. Otherwise, a normal emergency doctor will be sent.

In case of MSU usage, a CT exam can be performed at the patient's location in the pre-treatment phase, as described in section 5.

Following our assessment scenario, the branches where MSU are involved are set to 0 during the comparative simulation runs.

#### 6.3.5 Treatment

Due to the arrival in the hospital the treatment phase starts by an invocation of the composite state *treatment*. Diagnosis and therapy steps which were already performed during the pre-treatment phase are

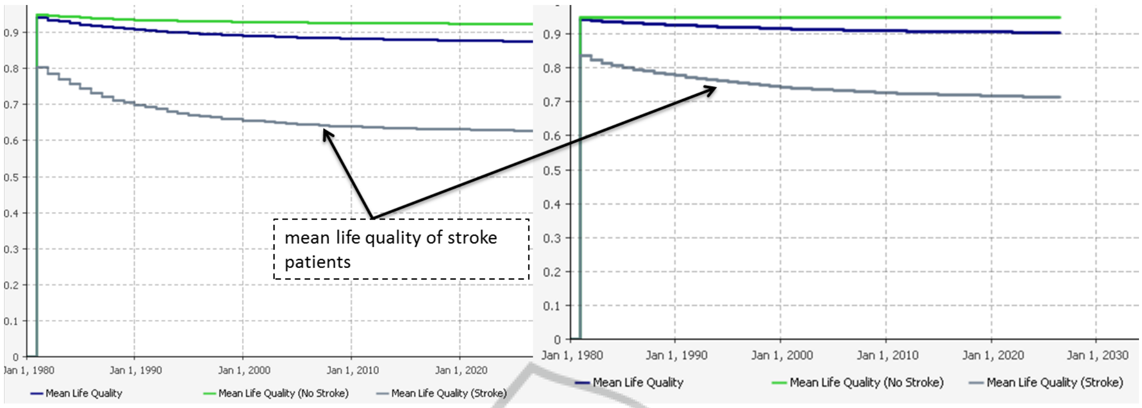


Figure 7: Mean estimated life quality without/with 10 MSUs.

skipped and a best-case workflow, modeled by our domain experts, is traversed by the patient.

### 6.4 Simulation Results

In our exemplary use-case of Mobile Stroke Units we noticed some trends due to the implementation of 10 MSUs in a metropolitan area. According to the used input parameters that were partially estimated by domain experts, we monitored some of the expected results.

Figure 7 shows two plots of the estimated mean life quality. On the left hand we can see graphs that were calculated by a simulation run without MSU usage; on the right hand a scenario with 10 Mobile Stroke Units was applied. According to the results we can notice that persons with stroke affection achieve a higher mean life quality after the launch of the regarded innovation. The main reason for this is the possibility to apply the thrombolytic therapy immediately at the stroke occurrence location and an intervention can be done within the important time-window of 4.5 hours.

In our model we also aggregated costs caused by MSU usage to show exemplary economic assessment calculations. To check if a new technology is reasonable, a Cost-Effectiveness-Analysis (CEA) was computed by the equation 1 during simulation runs.

$$CEA = \frac{K_{MSU} - K_{NoMSU}}{\Delta LQ_{NoMSU} - \Delta LQ_{MSU}} \quad (1)$$

We regarded life quality as effectiveness parameter to determine the effect of MSUs. Within the equation the following variables are defined as follows: $K_{MSU} - K_{NoMSU}$ (cost difference between MSU usage and conventional therapy workflows), $\Delta LQ_{NoMSU}$ and $\Delta LQ_{MSU}$ are mean life quality losses of stroke patients without/with MSU implementation.

Graph 8 shows an example result of a Cost-Effectiveness-Analysis. The plot suggests that an increase of the mean quality of life of the population of one point comes with a cost of approximately 12,000. It also shows the effects of the initialization phase which have been alleviated in the forecasting phase starting around the year 2010.

## 7 DISCUSSION

ProHTA is a new approach that uses simulation techniques to assess health technologies early before the cost-intensive development process starts. It allows to evaluate healthcare innovations within the context of the health system and to find gaps and bottlenecks that can lead to new ideas for innovations. We identified hybrid simulation, consisting of the System Dynamics and the Agent-Based Simulation, to be an appropriate modeling approach for large scale simulations. This method enables to solve problems on a macroscopic level, e.g. disease dynamics in a global context, as well as on a detailed, behavioral microscopic level. A further benefit of this approach within the scope of ProHTA is the possibility to build models top-down, beginning from high abstractions and going more in detail to frame-out individual workflows. To make models capable for reuse and to master com-

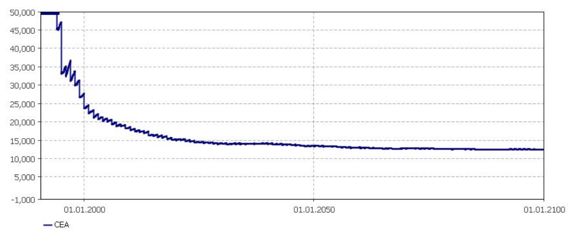


Figure 8: Example of a cost-effectiveness-analysis (CEA). [y-axis: costs per one life quality point, x-axis: time].

plexity, we designed a modular and generic environment that is also eligible for flexible model changes. As an effective co-working of interdisciplinary experts is crucial to get useful results, a conceptual modeling process was developed. The main benefits are in particular well-defined areas of activity for all experts and the capability to proceed in a structured way.

To evaluate our methods, an exemplary use-case scenario of an innovative stroke treatment approach, represented by Mobile Stroke Units within a Metropolitan Scenario, had been implemented, using the simulation software AnyLogic (XJ Technologies Company Ltd., 2012). This tool is predestinated for multi-method simulation paradigms. The project procedure strictly followed the CMP and an overall expert-credibility has been achieved.

There are still many challenges to master in the future. Real data from the Stroke Register of Erlangen (ESPro) will be used to validate the model using other stroke use-cases and to asses interventions whose effects are already attestable by evidence data. A further complex task will be the application of our hybrid simulation approach to other diseases, especially within the domain of personalized medicine. As the ProHTA research group includes oncology experts, cancer diseases will be the focus of further work. Some technical challenges are also still remaining. Some of them are simulation performance, scalability of models, requesting data (semi-)automated from the data management component and further hybrid simulation research for combination of SD and ABS models.

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