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HYBRID SIMULATION WITH LOOSELY COUPLED SYSTEM DYNAMICS AND AGENT-BASED MODELS FOR PROSPECTIVE HEALTH TECHNOLOGY ASSESSMENTS

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ABSTRACT

Due to the ageing of the world population, the demand for technology innovations in healthcare is growing rapidly. All stakeholders (e.g., patients, healthcare providers and health industry) can take profit of innovative products, but the development degenerates often into a time consuming and cost-intensive process. Prospective Health Technology Assessment (ProHTA) is a new approach that combines the knowledge of an interdisciplinary team and uses simulation techniques to indicate the effects of new innovations early before the expensive and risky development phase begins. In this paper, we describe an approach with loosely coupled system dynamics and agent-based models within a hybrid simulation environment for ProHTA as well as a use-case scenario with an innovative stroke technology. The project ProHTA is a part of the Centre of Excellence for Medical Technology and is supported by the German Federal Ministry of Education and Research (BMBF), project grant No. 01EX1013B.

1 INTRODUCTION

Innovative health technologies have the power to improve the life quality of populations and to make healthcare more effective (Garrido et al. 2008). For that reason an increasing demand for healthcare products can be observed worldwide. Especially in countries with a fast-growing economical standard (e.g., China and India), the market for new healthcare products plays an important role. The challenges coming with demographic changes in the future and new technological opportunities are further important reasons for this trend.

It should be noticed that not all innovations can generate profitable outputs for all stakeholders equally. Indeed, it is often important to consider the impact from different perspectives. Patients are interested in better quality of healthcare, insurance companies can benefit from cost-effectiveness, governments and lawmakers prefer innovations that have positive influences regarded from a global point of view and healthcare manufacturers are interested in yield maximization in particular.

The development of new healthcare technologies requires high investments and the effects are in most cases not predictable in advance. Thus, this process can become risky and non-profitable for many health industry companies. Before a new innovation can be adopted, it is strictly necessary to prove its effectiveness and to provide a transparent assessment process as early as possible. Furthermore, it is important to have reasonable costs to achieve an acceptable cost-effectiveness of a new innovation.

Health Technology Assessment, Early Health Technology Assessment and Horizon Scanning are three methodologies that enable one to evaluate healthcare products in light of cost-effectiveness and treatment impacts.

Health Technology Assessment (HTA) is a classical method within evidence-based medicine (EbM). Technology can be represented in this context by medical devices, pharmaceuticals, procedures, therapies, or systems (Wulsin Jr. and Dougherty 2008). Primarily, this method is used to inform regulatory agencies and other lawmakers about the effects of new interventions. The assessment process includes a systematic review of existing studies and trials. Thus, this approach can be applied when enough representative evidence data is available.

As the name Early Health Technology Assessment (Early HTA) already expresses, Early HTA can be deployed by using evidence from early bench, early clinical experience (Pietzsch and Paté-Cornell 2008) and before the classical HTA can be applied.

Horizon Scanning (HS) allows one to assess new developments in the healthcare technology field and to compare similar products. It is usually supported by Horizon Scanning Systems (HSS) which are used among others for early assessments and prioritization (Langer and Wild 2006).

All of the just introduced methodologies are applicable only to those innovations that already passed the market launch or that will do this in near future. In case of desired decrease of unprofitable investment numbers, foresight assessment approaches are necessary that can be used before high costs have been produced.

2 PROSPECTIVE HEALTH TECHNOLOGY ASSESSMENT (PROHTA)

Prospective Health Technology Assessment (ProHTA) is a methodology that aims to fill the gap within the healthcare assessment tool environment. This project is a part of Centre of Excellence for Medical Technology and is located within the Medical Valley EMN (European Metropolitan Region Nuremberg). The main goals and first ideas were already presented within the General Poster Session of the 2011 Winter Simulation Conference (Djanatliev and German 2011). The current scope of the project will be depicted in the following.

It is the approach of ProHTA that combines the knowledge of an interdisciplinary team in order to assess new healthcare innovations early before the expensive development phase has started. It allows to make the effects of a new innovation visible and to optimize a potential product in early phases. Particularly, two questions are considered by ProHTA:

- How can a new technology be optimized prospectively after the observation of simulated effects?
- What innovation is required to reach desired output values?

In order to answer these questions, hybrid simulation techniques can be applied using data from an appropriate data management component (Baumgärtel and Lenz 2012). Accordingly, to create large scale simulation models with a high complexity level, a structured process has been developed. The so called *Conceptual Modeling Process (CMP)* allows one to work in an efficient way with clearly defined fields of activity for each involved expert. Proceeding towards hybrid simulation models, the CMP distinguishes between two conceptual models. The main artifact of the *domain world* is the Conceptual Domain Model (CDM) that represents a non-formal specification of a simulation scenario. The CDM is used afterwards within the formalization process in order to enter the *model world* and to create the Formal Conceptual Model (FCM) which serves as basis for a runnable simulation.

The scope of ProHTA requires both, an aggregated level of simulation as well as a more detailed level with high granularity. In the following, we describe our approach with loosely coupled system dynamics and agent-based simulation models. An example use-case scenario with a stroke innovation has been defined as a proof-of-concept.

3 RELATED WORK

Currently, hybrid simulation techniques are the focus of many academic publications. The idea to combine different simulation paradigms into a common environment helps to make complex simulation architectures easily handled and to profit from the advantages of different modeling approaches.

Heath et al. (2011) presented a discussion focused on cross-paradigm simulation modeling, using Discrete-Event Simulation (DES), System Dynamics (SD) and the Agent-Based (ABS) approach. Advantages and problems had been worked out considering pairs of different paradigms and software packages had been evaluated in light of hybrid simulation modeling. There are tools that appear to be predestined for one paradigm simulation with extension possibilities and it seems that some packages offer hybrid modeling functionality, even though the hybrid methodology is not defined precisely yet, according to Heath et al. (2011).

Brailsford, Desai, and Viana (2010) published the use of hybrid simulation approaches in the healthcare domain by two case studies, Chlamydia Infection and Social Care in Hampshire. The main idea is to combine continuous and discrete simulation using SD and DES techniques on the way towards the “holy grail”. According to the authors, it is probably not possible to combine the approaches genuinely from a philosophical standpoint, however current research at the field of hybrid modeling is approaching the “holy grail” (as they refer to the ultimate goal of successful hybrid simulation in health care).

Chalal and Eldabi (2008) introduced three different formats for hybrid simulation. The authors proposed to use system dynamics and DES techniques to help policymaking for evaluating impacts from a strategic and operational point of view. The *Hierarchical Format* allows one to develop SD models at a strategic level and DES at an operational level. The output of the one is then used as input for the other and vice versa. The *Process Environment Format* allows one to model a specialized process in DES and SD is used to reproduce the environment that surrounds the process. Using the *Integrated Format,* there is no distinction when to use SD and when DES is a suitable approach.

4 HYBRID SIMULATION ENVIRONMENT

Within the scope of ProHTA, simulation was identified to be an appropriate tool. To answer the research questions it is important to cover both an aggregated level from a global perspective as well as a more detailed level to frame-out specialized workflows. For that reason we decided to use hybrid simulation techniques, consisting of system dynamics parts for more abstract contexts and agent-based models to focus on patient’s behavior and its traversing through healthcare workflows.

ProHTA aims to answer various questions within a simulation scenario, e.g., economic prognoses or impacts on patient’s health. Hence, it is essential to develop models that are able to handle the complexity of large scale simulations. Therefore, we call for generic, modularized and reusable model parts. It is reasonable to build up a toolbox that includes already predefined and validated building blocks in order to develop an environment for a dedicated scenario.

In the following we describe the modeling approach using the commercial simulation tool AnyLogic 6 (XJ Technologies Company Ltd. 2012) for realization purposes. As described by Heath et al. (2011) this software package has the power to combine multi-paradigm models in one common environment.

4.1 Model Modularization

Each simulation project poses its individual questions that are not known beforehand. For this reason our hybrid simulation environment should be prepared by providing a structured modeling methodology and generic, reusable model parts.

The vision of ProHTA is to create simulation models that include many influences, e.g., demographical, economical, geographical and even political ones. In order to go in the direction of this vision, we use a top-down approach, starting by highly abstracted top-level models and forward to more detailed parts if necessary. For that reason we defined modules that have their own fields of activity and which can be combined in a dedicated simulation scenario.

Currently, some ambitious domain areas are deferred, e.g., political influences. In our current scope we identified the following four modules as important ones:

- Population Dynamics
- Disease Dynamics
- Health Care
- Health Care Financing

Population Dynamics (PD) is a module that includes demographic flows, such as births, immigration and emigration of people as well as the mortality. This part of the simulation is mostly developed by the system dynamics method and statistical data from public registers has been used to reproduce a realistic population development. The main parameter which is important for other modules is the population number, but the rates (e.g., birth rate) can also be affected by other simulation parts. Such dependencies are included in an interface that is used by other modules. PD is generally independent of a considered disease, so it is possible to model and run this module independently from other simulation components.

Disease-specific, non-individual changes are incorporated within the Disease Dynamics (DD) module. Hence, the parameters incidence, prevalence, remission or the case fatality rate are playing an important role within this component. Prevalence is used to divide the population into an affected and a non-affected part initially. Incidence is a dynamic affection rate which is used during the runtime. In our case, this simulation module is modeled by the SD approach and can also be modeled independently.

Health Care Financing reproduces money flows within the healthcare system. There are different levels of granularity. A more abstract level differentiates between payers, service providers and consumers and includes continuous money flows. In a more detailed scenario we modeled the German statutory health insurance as well as the money flows within the long-term care system. In both cases the SD approach was an appropriate tool.

The Health Care module plays an important role within the scope of ProHTA. This part is developed by agent-based simulation. A person's behavior is reproduced by a state chart and events that trigger state changes. Further sub-modules have been created for each healthcare phase, e.g., prevention, pre-treatment, treatment (inpatient, outpatient) and post-treatment. To achieve a better performance, the sub-modules are used on demand when a patient traverses a certain workflow.

4.2 Module Arrangement

In our simulations we focus on a special part of the world's abstraction where a new health technology is implemented. The other parts are modeled in an aggregated way as detailed as necessary to learn about the impacts of the considered innovation. For that reason we separated the overall model into a core simulation and the environment which surrounds it. The arrangement is implemented by the Process Environment Format (PEF) that was published by Chahal and Eldabi (2008).

Figure 1 depicts the arrangement of different modules within the PEF. The environment consists of Population Dynamics, Disease Dynamics and the Health Care Financing modules. All of them are developed by system dynamics models on an abstract simulation level. The core simulation is modeled by the agent-based approach for the greater part and includes highly detailed models. Agents represent in most cases persons, but it is also possible to define agents types for new innovations with an individual behavior, e.g., Mobile Stroke Units as explained in Section 5.

Configuration parameters can be used as input for the system dynamics environment which affects the core simulation itself. For example, prevalence is incorporated within the Disease Dynamics model and the calculated numbers of affected/not affected persons are used to initialize the core simulation at a certain time. Alternatively, it is possible to define parameters for the agent-based simulation directly. Some examples can be time delays for states, costs of special workflow steps (e.g., laboratory analyses) or probability distributions for decision nodes.

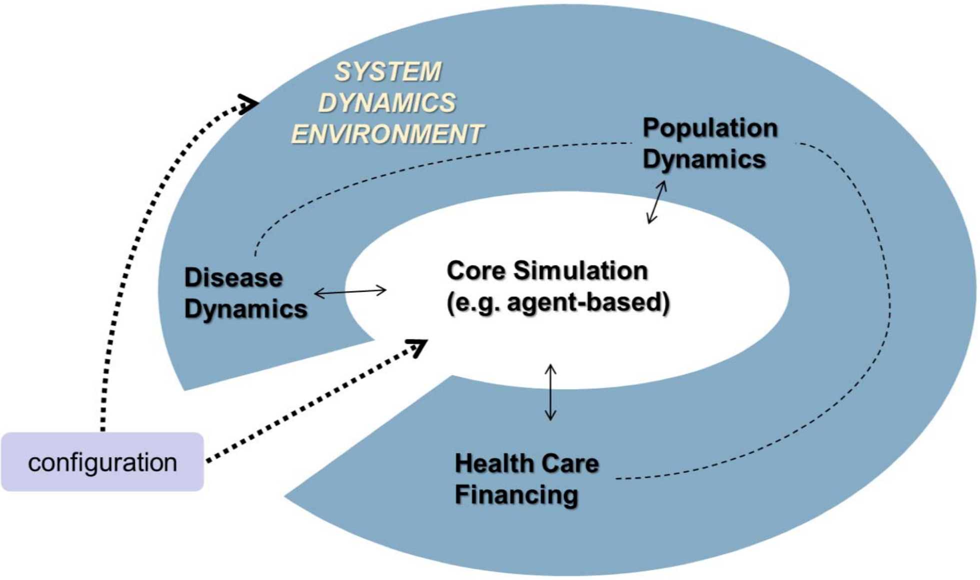

Figure 1: Arrangement of modularized system dynamics and agent-based models within the common hybrid simulation environment of ProHTA.

4.3 Module Coupling

In the modular environment each module is running independently and communicates with other simulation parts by well-defined interfaces. In order to create a dedicated simulation scenario it is possible to exclude unnecessary modules and to fit dependent components with statistical data. For example we can turn off Population Dynamics and use pre-calculated population data, if already available. But PD has to be turned on if a simulation scenario aims to show effects on population development, e.g., a new technology affects the mortality rate or the birth rate.

Continuous system dynamics modules that are included in the simulation environment are closely coupled. It means that current values from one component are used at the same time in the other ones. For example, population numbers (occurring in PD) are always synchronized with incidence and prevalence values (occurring in DD).

To synchronize continuous and discrete simulation parts, more advanced methods are needed. It is important to distinguish between different directions. As the continuous simulation is fine grained, variables from discrete simulation can be used to affect flow rates within a system dynamics simulation. The reverse direction requires a discretization of continuously changing values, e.g., population number or number of affected. Our first non-modularized hybrid simulation prototypes were closely coupled. Hence, we tried to always have a real population number within the discrete simulation component. This approach gave rise to bad simulation performance and was very inflexible and not transparent. To prevent such high interactions rates and to master the complexity, we disconnected the agent-based simulation parts from the environment. Following this, the agent-based core simulation is now running independently from the SD environment. To prevent a deviation of the values in the different modules, the core is loosely coupled with the SD models by annual synchronization.

Figure 2 depicts an exemplary development of the population. The black line reproduces a (artificial for explanation purposes) linear population growing in PD. The green line illustrates the simulated population within the agent-based module. As we can see, there are population number errors at certain discrete points, but in the long-term we can notice a linear increase also within the core module. It is necessary to remove persons, if there are too many, or to sample new ones in case of a low population number. To prevent removing wrong samples, this procedure has to be done in accordance with other simulation modules. Thus, further parallel synchronization, e.g., with Disease Dynamics is essential.

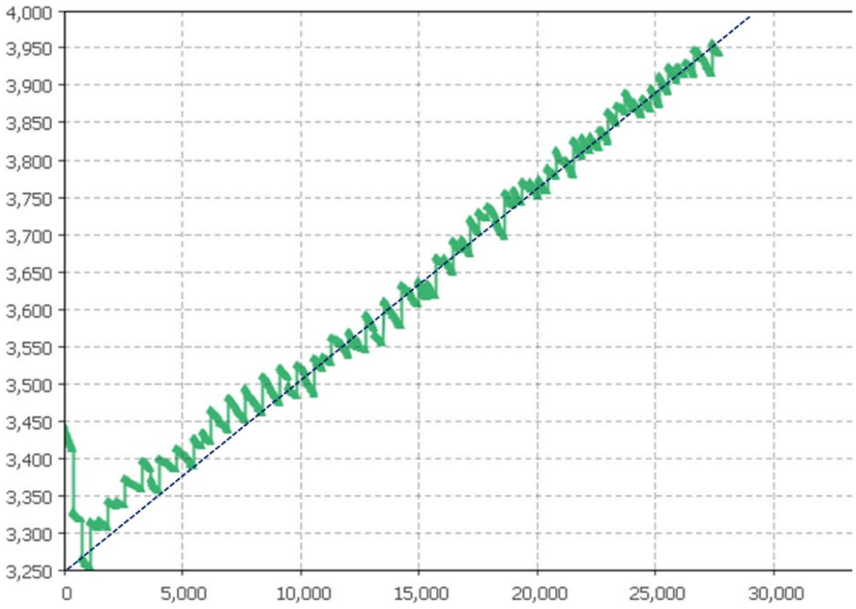

Figure 2: Black line shows an exemplary linear growing population within the Population Dynamics module. The green line reproduces the population development within the agent-based core simulation using the loose coupling mechanism.

5 USE-CASE

5.1 Stroke Treatment using Mobile Stroke Units

Stroke is the major reason for severe disability of people and the third greatest cause of mortality worldwide. Most people survive the first occurrence of stroke, but with a significant morbidity (NICE 2008). In England and Wales more than 56,000 deaths occurred in 1999 (NICE 2008) and costs of around £9 billion were estimated in 2009 by Saka, McGuire, and Wolfe (2009).

Stroke appears in most cases at higher age groups. Following this, a growing number of cases can be assumed due to the ageing of the world population. Kolominsky-Rabas et al. (2006) estimated for Germany an increase of 1.5 million stroke cases within the next decade and costs for the period 2006-2015 of about 58 billion of Euros.

Stroke can appear in different forms. Approximately in 80% of all cases the *ischemic stroke* can be observed. Treatment for this form of stroke can be done by the *intravenous thrombolysis* and *recombinant tissue plasminogen activator* (rtPA) (Fassbender et al. 2003) that represents an effective therapy and allows one to prevent severe disabilities. Heuschmann et al. (2010) estimated an increase from 8.5% to

12.1% of lysed patients, but it is still not a very high rate. Even though specialized hospitals for stroke treatment (Stroke Units) are well distributed in Germany, new stroke innovations are necessary.

Thrombolysis can be applied only within the first 4.5 hours after the occurrence of a stroke. In case of an affection, approximately 2 million brain cells die per second (Kuehn and Grunwald 2011). For these two reasons it is strongly necessary to begin with the therapy as early as possible and to reduce the call-to-therapy-decision time.

An idea to reduce the time until the thrombolytic therapy begins, is to apply it onsite at the stroke occurrence location. But it is strongly recommended to exclude an *intracerebral haemorrhage* (brain bleeding) before. Unfortunately, this is currently only possible by computer tomography (CT) and laboratory values in hospitals.

In Germany two groups focus their research onto transferring the thrombolysis to the pretreatment phase (Walter et al. 2012, Ebinger et al. 2012). In order to gain time, a standard emergency vehicle has been extended by a CT and mobile laboratory to allow an exclusion of brain bleeding at patient's location and to enable an immediate thrombolytic therapy. First trials of the prototypes *Mobile Stroke Unit (MSU)* and *Stroke-Einsatz-Mobil (STEMO)* have shown that 35 minutes can be saved using this new innovative technology.

As already mentioned a consequence of stroke is severe disability of people. The *Barthel scale* or *Barthel index* (BI) is a helpful metric for classifying the function of stroke patients (Wade and Hewer 1987). Usually it is possible to increase a BI 7 days after stroke by thrombolysis, or within 3 to 6 months after stroke by rehabilitation and care.

5.2 Scenario

In order to define a proof-of-concept scenario for ProHTA we selected Mobile Stroke Units as a new healthcare technology innovation that we want to assess prospectively in a metropolitan area. To make simulations more realistic, we used statistical data for Berlin. People are distributed by the district density and MSU distribution is done randomly. In a further assessment scenario it is possible to use other distribution methods for MSUs to find an optimal one.

Emergency calls are simulated after stroke occurrences. In case of stroke, the dispatcher sends a free MSU to the patient and the diagnosis and therapy can be done onsite, otherwise a standard rescue service is used and the therapy begins not until the hospital is reached. During the affection, the patient traverses through different workflows and produces costs. Furthermore, several time delays (e.g., cognition, transfer) are incorporated in our models. If a Mobile Stroke Unit is used the patient eliminates the transfer time to the hospital, because the thrombolytic therapy can be started directly at the stroke occurrence location.

For assessment purposes we run the model with MSUs and without MSUs in order to compare the outcomes. The most important metric in particular is represented by the ratio of lysed patients, as thrombolysis helps to prevent severe brain damage. Following this, we can assume that more people will have a high Barthel index after stroke.

5.3 Simulation Model

In this section we describe some important aspects of the simulation model that we developed for MSU assessment, according to the previously described scenario.

We started with an implementation of the modular hybrid simulation environment in AnyLogic 6 (XJ Technologies Company Ltd. 2012) without considering individual use-cases. As already mentioned the modules PD, DD and Health Care Financing have been created by system dynamics models and are independent from each other. In the second step we incorporated connections between modules within the SD environment, e.g., population number from PD is used as an external variable in DD and Health Care Financing. After completion of SD models, we proceeded with the core simulation by a definition of an agent type for persons. According to our Conceptual Modeling Process, we created together with domain experts that are participating in the ProHTA project several workflow diagrams and a person behavior state chart. Furthermore, different data sources have been used to define stochastic distributions for time delays and decisions.

During the development phase of the agent-based core, we were concerned with performance problems that were caused by complex structures. For that reason we separated our stroke workflows in many small snippets. It allows one to distinguish between “generic-like” (further use-cases have to show if they are really generic) parts and disease specific ones. Furthermore it is possible to reuse them and create instances dynamically, only when they are needed. The following example areas are modeled as atomic snippets:

- Prevention
- Pre-treatment Phase, e.g., rescue service
- Treatment Phase: differentiates between inpatient and outpatient treatment workflows. Further subdivision, e.g., initial treatment, diagnostics, therapy, follow-up care
- Post-Treatment: includes rehabilitation and long-term care workflows

Figure 3 depicts four example models of the simulation. The central-right state chart represents the behavior of an agent. Following this, three main states are available. A patient is *normal*, if no affection and no symptoms of a concerned disease are available, *affected* is used after a disease is diagnosed. *Symptoms* is a composite state with an underlying sub-diagram. After symptoms occurrence, the patient can ignore them or else he will traverse through pre-treatment workflows (e.g., emergency call) after a sampled cognition delay time has elapsed. If the *pretreatment* state is reached, a pre-treatment object will be instantiated dynamically and the workflow is continued in it. The topmost figure shows workflows of the pre-treatment active object. According to sampled probabilities the patient can use the emergency service, contact a general practitioner or it is possible to go directly into the hospital. In case of MSU usage standard time delays and costs are changed to MSU specific ones and the state *primaryMedCare* includes a CT examination and thrombolysis, if an ischemic stroke has been diagnosed.

In case of ignored symptoms a special function is called and the patient is affected with severe causes or turns back to state normal. The central-left figure depicts the inpatient part of the treatment phase workflow. Blue states are assumed to be generic with disease specific parameters, e.g., anamnesis delay time or laboratory analysis costs. Yellow states include further active objects that represent disease specific diagnose and therapy workflows. The lowermost picture shows an exemplary system dynamics model of the Health Care Financing module. Variables from the agent-based simulation are used to affect money flow rates. For example, direct payments from patients are filling budgets and calculated costs are used to increase the outgoing flows.

We extended the model to incorporate the MSU scenario that was described in Section 5.2. First of all a new agent type for Mobile Stroke Units was defined with a simple behavior state chart. Within the pre-treatment module the dispatcher currently searches for MSUs and sends a standard rescue service, if all of them are in busy state. Using an MSU the eliminated time is subtracted afterwards before the therapy decision node is reached. This leads to shortened call-to-therapy-decision times and a higher thrombolysis rate can be assumed.

5.4 Results

In this section we discuss some exemplary simulation results of our MSU scenario. As already described, the most important output is the rate of stroke patients that profit from thrombolysis therapy. Figure 4 depicts sample simulation plots. On the left side we can see that approximately 10.6% of patients with diagnosed stroke had been lysed. The right graph presents a possible increase to 18.2% with MSU usage.

A further interesting output is the number of persons with a high BI after stroke treatment. As MSU implementation leads to a higher thrombolysis ratio, we noticed a low increase of patients with a top BI after stroke. A consequence of this is savings of long-term costs for rehabilitation and care.

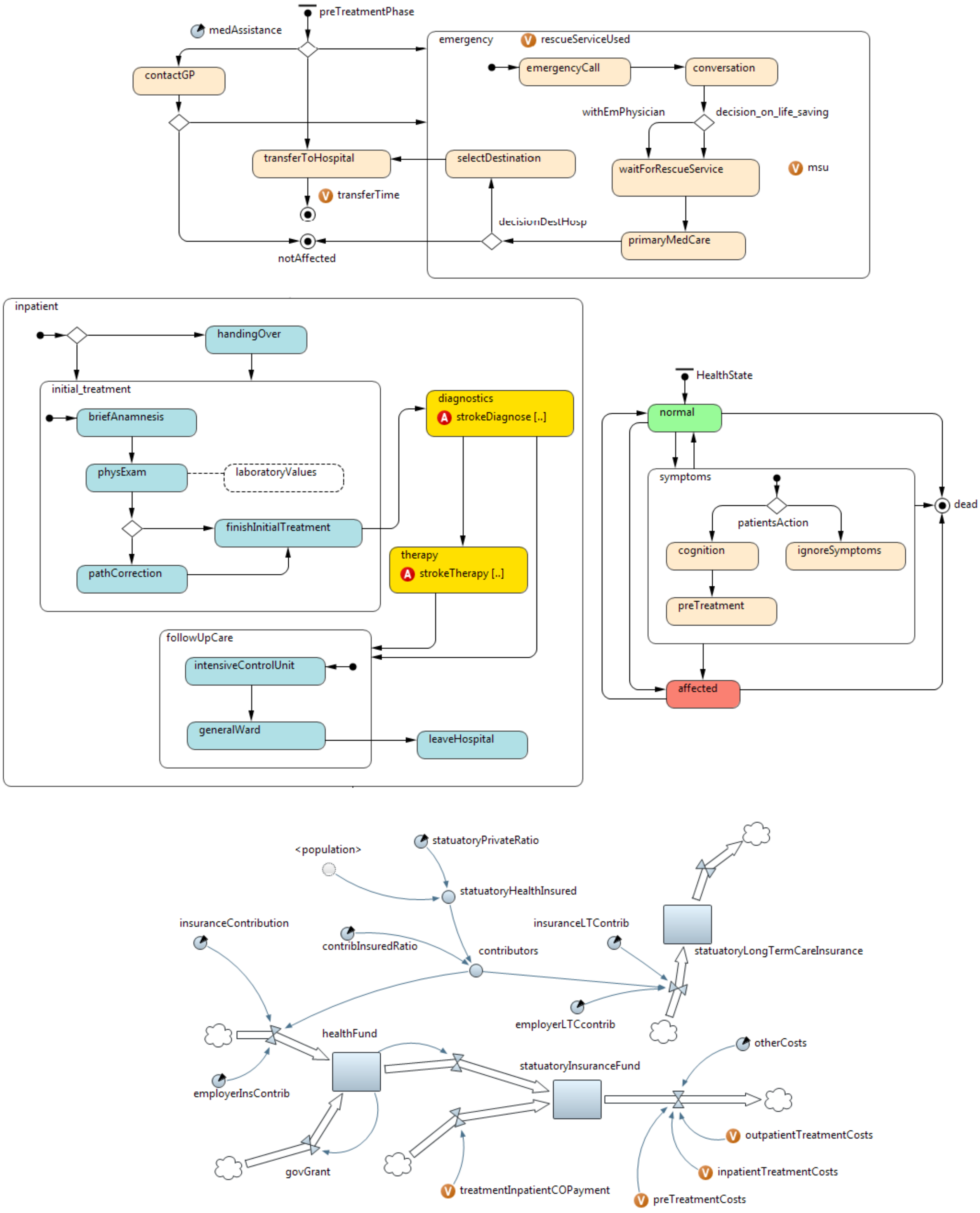

Figure 3: The central-right figure depicts a state chart of person's behavior, the lowermost one includes an example of an SD model. The central-left figure shows the inpatient workflow, the topmost one depicts the pre-treatment active object.

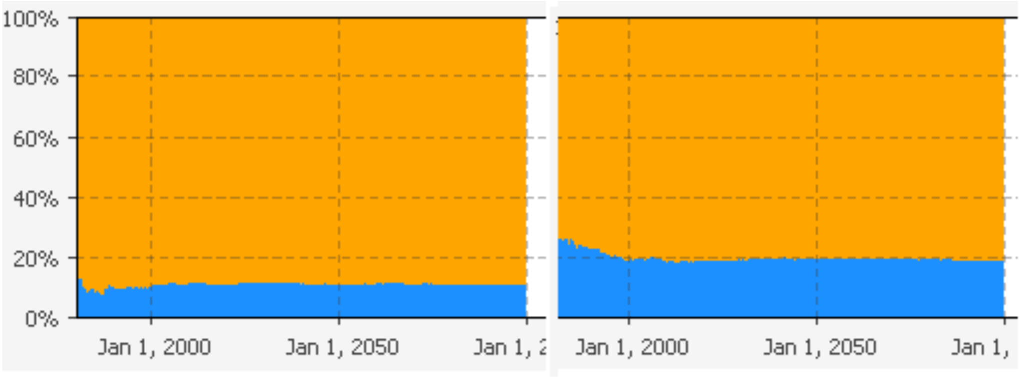

Figure 4: The left graph shows a possible thrombolysis rate of approximately 10.6% without Mobile Stroke Units. The right plot shows a possible increase to 18.2%, if MSUs are implemented.

Statistical significant output metrics can be produced by several replicated simulation runs, but we noticed equal output values already after few iterations. This effect is possibly caused by many independent agents that generate a high number of samples.

6 CONCLUSION

Prospective Health Technology Assessment (ProHTA) is a new approach that extends the tool environment for technology assessments in healthcare. In contrast to existing methods HTA, EarlyHTA and Horizon Scanning, ProHTA allows to evaluate a new technology early before the product has been developed or is still designed. The main idea is to use simulation techniques to learn about the effects of a new healthcare innovation.

In this paper we introduced a hybrid simulation environment for ProHTA by the application of the Process Environment Format (Chahal and Eldabi 2008). A sample implementation of our use-case is done by using the software tool AnyLogic 6 (XJ Technologies Company Ltd. 2012) which turned out to be suitable for this purpose.

The core simulation is developed by the agent-based approach and includes detailed workflows of patients behavior. The environment surrounding the core is modeled by continuous system dynamics models. The overall simulation model is divided in different modules. This enables one to master the complexity and to reuse model parts in different scenarios. Furthermore a separation between “generic-like” components and disease specific ones has been done.

As different modules within the SD environment and the core simulation are running independently, a loose coupling mechanism with annual synchronization has been introduced, in order to prevent a deviation of runtime values. In comparison to our first models which were completely closely coupled, loose coupling mechanism helped to run the simulation more liquidly. Another performance gain was achieved by dynamic instantiation of active objects in AnyLogic 6 (XJ Technologies Company Ltd. 2012) only when they are necessary, e.g., diagnostic and therapy workflows.

We applied the hybrid simulation approach to an exemplary assessment use-case. Mobile Stroke Units were used as a new healthcare innovation and a raise in the thrombolysis rate had been shown after MSU implementation. Our hybrid simulation environment with loosely coupled system dynamics and agent-based models enabled us to create a simulation scenario very fast and we could achieve overall credibility from all project experts (e.g. doctors, health economics, medical informatics and knowledge management experts).

There are still further challenges that have to be mastered. One of them is to prove that “generic-like” model parts are truly generic. This will be done by an application of our approach to other diseases. As our project team includes oncology experts, a new use-case scenario for oncological innovation assessment will be developed in future. Furthermore our industrial partners (e.g., Siemens AG, Healthcare Sector) will help to create assessment scenarios of real innovations. Another potential optimization can possibly be achieved by dynamic synchronization times for loosely coupled modules, e.g., synchronizing only if a threshold value has been exceeded.

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