Large Scale Healthcare Modeling by Hybrid Simulation Techniques using AnyLogic

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ABSTRACT

In contrast to already established tools for health technology assessments, Prospective Health Technology Assessment (ProHTA) uses hybrid simulation techniques to make early predictions about the effects of new healthcare innovations. In such studies, it is necessary to consider problems at high abstraction levels, as well as at detailed microscopic levels. According to the diversity of expected output metrics and the lack of medical evidence, the situation can be compared to other large scale and complex simulation problems. In such cases well-known modeling methods are often not sufficient to use. Therefore, advanced modeling and simulation techniques have to be developed and properly applied. This paper describes a methodical and practical approach of hybrid model creation using the simulation tool AnyLogic. We focus on general modeling aspects and on advanced techniques using a *Level-Based Architecture* that help to develop large scale hybrid simulation models. An implementation of a stroke therapy use-case and its simulation results will be discussed. Finally, some practical ideas for validation will be outlined, as we experienced during the stroke use-case development.

Categories and Subject Descriptors

I.6.5 [**Simulation and Modeling**]: Model Development—*Modeling methodologies*

General Terms

Design, Verification

Keywords

Modeling and simulation, hybrid simulation, multi-paradigm modeling, large scale modeling, healthcare, technology assessment, agent-based simulation, system dynamics

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1. INTRODUCTION

To prevent undesirable consequences to people, it is important to gain knowledge about the impacts of healthcare products. Health Technology Assessment (HTA) [4] is a common approach for collecting information about already established technologies. The idea is to perform literature research in order to learn about the impacts of a considered healthcare product. Primarily, this method is used to inform regulatory agencies and government players. Early HTA [14] and Horizon Scanning (HR) [11] are further techniques that help to learn about the medical effects of new innovations. However, all approaches share a common problem. They can only be applied when a product has been launched in the market or an expensive development process has already started.

Prospective Health Technology Assessment (ProHTA)[1] is a multidisciplinary research project within the Centre of Excellence for Medical Technology - Medical Valley EMN. The idea is to learn about the impacts of healthcare technologies at the same time when an innovative idea is born and a product is not developed yet. ProHTA uses advanced modeling and simulation techniques to predict medical and economic impacts of a new innovation [6]. It is a tool for different stakeholders (e.g., patients, doctors, health industry, insurance companies, governments) and enables the combination of available knowledge in a common simulation environment. One has to consider problems at high abstraction levels (e.g., population crowds) as well as ones at more detailed and individual levels (e.g., therapy steps within a hospital). A further difficulty in ProHTA evaluations is a lack of reliable medical evidence and low availability of appropriate data sources.

Due to the safety-critical property of healthcare products, real studies and trials with already developed products are preferred within Evidence-Based-Medicine. However, it is helpful to use simulation and modeling (SM) techniques as well, for instance in the design phase of new healthcare technologies. It allows to optimize products prospectively and to see preliminary effects before the installation of new processes or the development phase of real products begins. Using SM health industry gets a tool that allows to learn about the market for new healthcare products and to find weaknesses and bottlenecks in the system in order to develop new innovative ideas.

[1] http://www.prohta.de

The aims of ProHTA studies have to consider many different domain fields (e.g., medical, economic, demographic) that make simulation models complex and hard to handle. Following the just described aspects, the situation can be compared to other large-scale simulation problems. In such cases established modeling methods are not sufficient to use. Therefore, advanced modeling and simulation techniques have to be developed and properly applied. It is challenging to create rapidly reusable and powerful simulations within the context of ProHTA. Usually, one has to deal more with modeling than with simulation problems.

In our previous publications we already presented a *Conceptual Modeling Process* for interdisciplinary work and a hybrid simulation approach for ProHTA combining System Dynamics (SD) with Agent-Based Simulation (ABS) [7]. In Djanatliev et al. [8] a loose coupling mechanism between SD and ABS models has been published in particular.

This work focuses on further important aspects of large scale healthcare modeling using the software package AnyLogic [25]. We describe important modules and explain how they can be structured and used within the scope of ProHTA. General architectural aspects with *virtual connections* between the modules will be depicted and the *Level Based Architecture (LBA)* is introduced that helps to reduce the complexity of the overall model by information hiding and "black-box" modeling. An example implementation of a stroke therapy use case helps to depict the presented techniques from a practical point of view. Finally, some of our experiences will be outlined, how validation of large scale healthcare models can be done in practice.

2. RELATED WORK

ProHTA shares many common aspects with several domain fields: simulation and modeling in healthcare, hybrid and multi-paradigm simulation and health economic evaluations.

The use of simulation and modeling in healthcare is already frequently discussed and well covered in available literature. Kuljis et al. [16] published a work about benefits for healthcare from modeling and simulation. The publication compares the situation with business and manufacturing fields in particular. According to the authors, many well-known methods can be adapted in healthcare, "but their practical application is not straightforward", because healthcare simulations have often to deal with "tougher challenges". For example, connection of different layers (e.g., governmental, organizational, service, procedural, physical). A suggestion to be successful in healthcare modeling is to use the *seven axes of differentiation* that were presented by the authors in [17]. There are further examples available in literature that focus on modeling of hospital workflows for resource planning in particular (e.g., [26]).

Disease cost calculations and other economic considerations are mostly covered by the field of health economic evaluations. There are several techniques available to perform health economic studies. Most popular ones are decision tree analyses, Markov modeling and budget impact evaluations. Discrete-Event-Simulation (DES) is getting more attention in economic studies as well. Introductions to the field of health economic evaluations are presented by [2, 21].

Figure 1 depicts at the top an example decision tree, in order to decide between two alternatives for treatment of patients with symptoms: with or without an additional test.

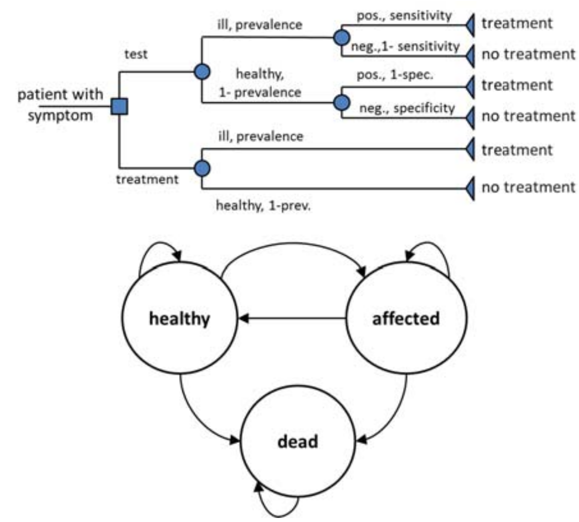

Figure 1: At the top: Decision tree - Comparing a new cheap test with an established therapy. At the bottom: Simple Markov model. The arrow from *affected* to *healthy* is omitted for chronic diseases.

The leaves are labeled with costs, multiplying them with branch probabilities and adding them leads to expected costs of both alternatives. On this base a decision can be taken. At the bottom of Figure 1 a simple Markov model can be found. Persons are located in different states (healthy, affected, dead) and change to other ones with a certain probability by traversing the transitions. When considering a chronic disease, the arrow from the state *affected* to *healthy* would be omitted, as it is not possible to heal a chronic disease. Costs can be associated with different states of the model, a solution leads to expected overall costs.

In healthcare one has to deal with structures at high abstraction levels (e.g., demographic patient flows) as well as at individual microscopic levels (e.g., individual treatment steps), so it is usually not easy to find an appropriate simulation technique. System Dynamics is well suited for continuous flows, however the DES and the Agent-Based-Simulation are appropriate for discrete and detailed models. In large scale models it is important to benefit from all approaches. Thus, hybrid simulation techniques are recently getting popular. The main idea is to combine continuous modeling techniques with discrete ones.

Heath et al. [12] presented an interesting discussion about cross-paradigm simulation modeling. The work focused on advantages and problems considering pairs of different simulation paradigms (e.g., SD-ABS, SD-DES, DES-ABS). A short evaluation of software packages in light of hybrid simulation modeling was outlined. The authors propose AnyLogic [25], as it allows to combine different simulation methods in one simulation environment. A further publication focusing on topics for hybrid simulation in healthcare is Chahal and Eldabi [5], presenting three different modes for SD and DES arrangements. Another one is Brailsford et al. [3] discussing hybrid simulation on the way towards the "holy grail", representing an ultimate goal of hybrid simulation from a theoretical point of view.

3. LARGE SCALE MODELING METHOD

As already mentioned, two characteristic properties of large scale models are high complexity and consideration of different domain fields that requires different experts and an efficient interdisciplinary co-working.

Before starting a ProHTA study, it is essential to define a simulation scenario with expected output metrics and to collect knowledge from involved domain experts and other stakeholders. According to a large interdisciplinarity it is challenging to proceed in a structured way. For that reason a proper Conceptual Modeling Process (CMP) with clearly defined steps towards a simulation model has been defined and is depicted in Gantner-Bär et al. [10].

To be more effective in similar use cases, complexity reduction and sustainability are further important requirements in large scale simulation studies. It is essential to benefit in future use cases from already done work by reuse of available and validated models in different contexts and one has to prevent large restructurings.

In order to meet these requirements, modularization and information hiding techniques have to be applied. Small module units help each other to execute their individual tasks in order to solve an overall problem. This method enables domain-focused modeling where experts are able to focus on such modules that are mostly covered by their knowledge. In healthcare it is particularly challenging to find well-defined boundaries for modules and it can be compared to a situation where "everything affects everything". Thus, an iterative optimization process has to be performed before optimal units can be identified.

3.1 Hybrid Healthcare Simulation Modeling

In our recent publications we already presented a hybrid simulation approach for ProHTA [7, 8]. SD is used to develop models on high abstraction levels with low data requirements and ABS helps to represent individual workflows of persons in particular. In the following further methodical extensions and implementation aspects for this approach will be depicted.

Figure 2 depicts an overview and an arrangement of identified modules within the scope of ProHTA. The core mainly contains individual workflows for agents, the SD environment summarizes high abstract level modules that affect the core and vice versa. The main modules will be discussed within the following implementation section. Information hiding helps to keep a general view on important things without considering details. Two appropriate methods therefore are hierarchical and nested modeling with distinctions between abstraction levels.

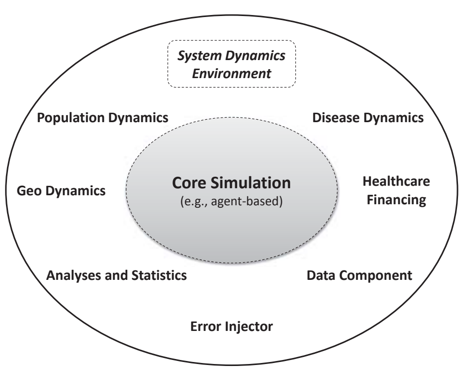

Figure 2: ProHTA module arrangement: The core includes ABS individual workflows. The System Dynamics environment contains high level models.

3.2 Implementation in AnyLogic

There are many software packages for simulation and modeling. Some of them are well suited to be used for continuous structures in SD (e.g., [15, 23]), other ones are often used for DES (e.g., [19, 22]). Hybrid simulation of large scale systems uses continuous SD as well as discrete ABS methods. For this reason we selected AnyLogic (AL) [25] to implement the ProHTA simulation framework, because the tool allows to combine both paradigms in one common modeling and simulation environment.

3.2.1 General Architectural Aspects

Figure 2 depicts main modules that were identified for ProHTA. For reusability we are aiming to build up a toolbox with already modeled and validated components that are mostly independent of each other. Each module has to solve a dedicated problem and requires a list of input parameters to transform them into output metrics (see Figure 3). To reduce complexity by information hiding, it is not relevant on the top-level how the transformation is done (black-box modeling).

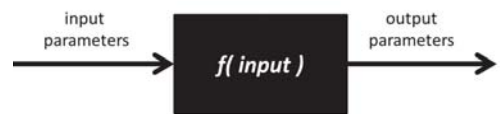

Figure 3: Module black-box. Input parameters are transformed to output metrics by algorithm *f* which is defined inside the component.

When modeling small scenarios it is possible to connect different modules directly to each other in order to receive expected input from connected components. In large models that are usually considered in ProHTA we experienced that it can be very difficult for the modeler to "think" about each connection between already available modules from the ProHTA toolbox. For that reason we propose a centralized inter-module architecture with `MainController` (MC) as central component (see Figure 4). In that case each module can be connected directly to the MC and defines a set of expected input data objects to start running.

On module startup an object reference is being sent to the output port that is connected to the MC which checks received instances and forwards them to all connected components. Each one catches only such objects that are necessary to instantiate itself and saves the reference. Using this technique *virtual connections* will be established automatically during the instantiation procedure and the inter-module communication can be done directly on runtime in order to prevent a bottleneck at the MC. Modules that are expecting input from other components extend the generic class `AbstractDataConsumer` that allows saving the received references in generic variables.

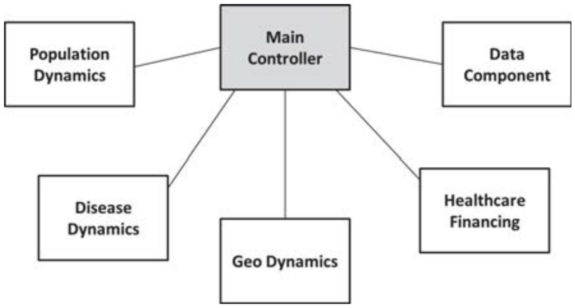

Figure 4: Centralized inter-module communication.

As modules (particularly SD ones) cannot be started before expected input parameters have been received, one needs module start and stop functionality. We defined therefore the interface `IModelRuntimeController`. Each module that implements this interface calls the method `startModel` after receiving all expected input values and sends automatically a reference of itself to the MC.

The ProHTA simulation framework uses a dedicated *Level-Based Architecture (LBA)* to allow hierarchical modeling and hide information in order to master the complexity. Following the LBA, there are four levels of abstraction possible for module definition:

- *Inter-module level*: Top-level of the simulation model. It is possible to build a ProHTA simulation from the toolbox and to define inter-module connections (e.g., by previously explained centralized approach). At this level modules are "black-boxes".

- *Configuration level*: Step inside a module. Contains a "black-box" representation of a model object and controls to define/modify input parameters. Implements the `IModelRuntimeController` interface to start/stop the containing model.

- *Model level*: Step inside the model. SD model or/and state charts with the corresponding model logic is visible at this level.

- *Calculations level*: Step inside a model element (e.g., SD stock or state of a state chart). Further calculations can be performed at this level. For example separation of the population number stock in dimensions (e.g., age-groups, gender), or a definition of a therapy workflow for a state "inTherapy".

Active objects (AOs) in AnyLogic [25] can be used to develop a common model. Each module on the *inter-module-level* is implemented within an own AO. Models and calculation objects are further AOs that are connected to the parent object or nested within the parent AO.

In the following we describe some important modules for ProHTA. We start with modules from the SD environment and present some ABS state charts afterwards.

3.2.2 Data Component

Data Component (DC) is responsible for loading, preparing, handling and distribution of input data. It helps to collect all required information at one location and to keep the overview when changing parameters and making transformations. Each module is expecting a data packet for initialization purposes that is inherited from the `IDataObject` interface. According to predefined and configured parameters (e.g., starting date) DC reads MS Excel tables, text files and other sources to load runtime data. The next step is to convert the data to model specific formats. In most cases values have to be transformed to the simulation time-unit in particular (e.g, incidence: persons per day instead of persons per year). After preparation steps have been finished, DC generates individual data objects for all connected modules and sends them to the output port which is usually connected to the MC. Global parameters can be accessed on runtime using the reference to the Data Component. Configurable parameters can be modified during simulation runs using predefined control elements of the DC.

3.2.3 Population Dynamics

In ProHTA evaluations demographic changes have to be considered. Population Dynamics (PD) is a module that uses birth rate and immigration rate to calculate a population increase. Mortality and emigration are parameters that decrease the number of the population. The values for this input parameters are loaded by DC from connected data sources and can be modified at the configuration-level on simulation runtime.

Figure 5 presents a screen shot of the PD configuration level active object. Slider controls are set to 0 (center), if unmodified rates are used. The user can increment and decrement the values during simulation runs. The *updateAuxillary* forwards the parameter changes to the nested model. Within the current state PD is modeled by SD (see Figure 6). Rates are modeled as flows affecting the population number which is represented by a stock.

PD Calculations represent a nested object to split the current population in dimensions. Currently, we are using age (in ten year steps) and gender as dimensions. We benefit from the hyper array dimension object provided by AL. It

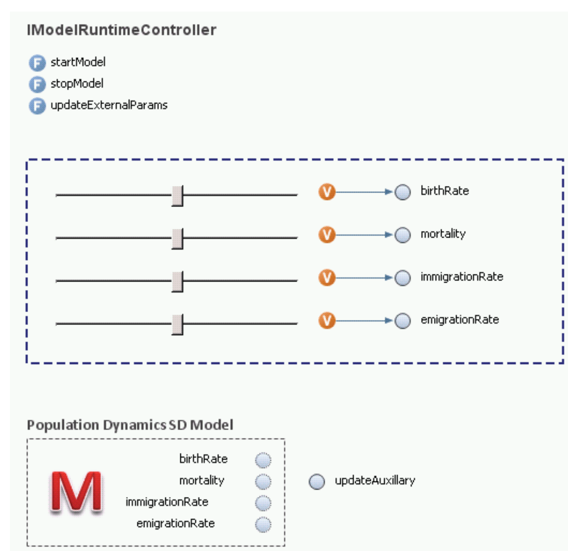

Figure 5: Configuration level example of the Population Dynamics module.

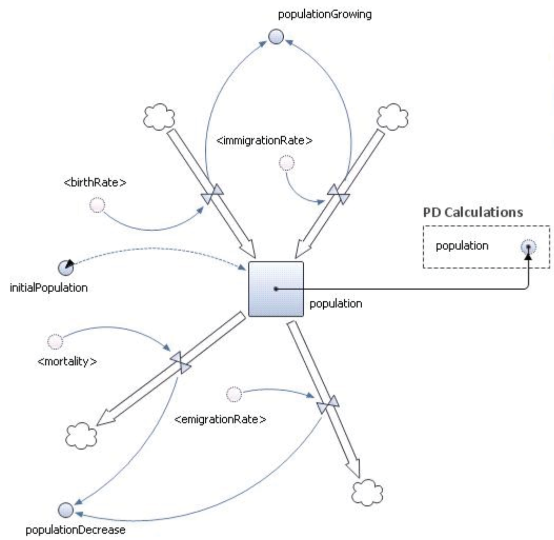

Figure 6: Population Dynamics SD model (model-level).

allows to combine several dimension types to create matrices with calculated values. To use dimensions in contexts different from SD, additional enumeration Java classes were implemented to map AnyLogic dimensions to enumeration values (e.g., age group `CHILD`).

The Data Component prepares also a dedicated data object for the *PD Calculations* module. This object is encapsulated within the PD data object and can only be accessed and forwarded to the calculations module by PD model-level object.

3.2.4 Disease Dynamics

In contrast to PD, Disease Dynamics (DD) contains flows that concern a considered disease. This component uses prevalence values to initialize the stocks *affected* and *not affected* and incidence values to calculate dynamically new affections. A remission rate can be used to represent the healing process (usually not available when considering chronic

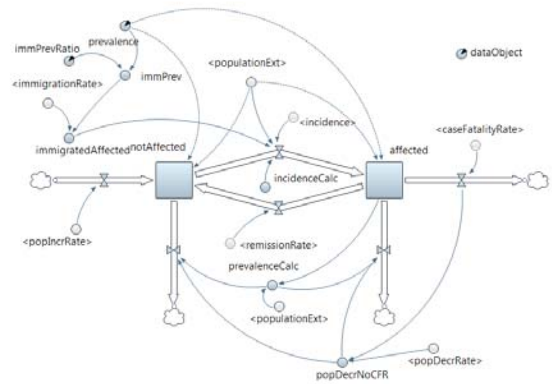

Figure 7: Overview of the Disease Dynamics SD model.

diseases). Case fatality rate includes disease specific deaths and decrements the affected stock. A further affected outflow ($affOut$) is calculated by the equation 1. We use the population decrease rate ($pDecr$) from population dynamics, the calculated case fatality rate (cFR) by DD and the model prevalence concerning affected (aff) and not affected ($notAff$) values.

$$affOut = aff * (pDecr - cFR)/(aff + notAff) \quad (1)$$

DD Calculations uses age specific incidence rates in order to calculate new affections in different age groups. The SD model of DD is depicted in Figure 7. This module is more complex than PD and took much time for modeling and validation in particular. DD does not depend on a special disease and is generic in principle, but the parameters used in this component on runtime are mostly disease specific.

3.2.5 Error Injector

In order to reflect erroneous situations, it is necessary to generate errors in large scale ProHTA simulation models. Error Injector (EI) is a component that is developed to consider treatment failures and wrong resource utilizations.

A four field table depicted in Figure 8 shows different possibilities of diagnosis. The columns represent a real condition. Positive means that a patient is truly affected, otherwise the condition is negative. The rows are diagnostic results which may not be correct. Sensitivity is the probability of correct disease cognition (true positive) and the specificity is a value for correct diagnosis of not affected persons. EI can be used to increase false positive cases (possible consequence: wrong patient treatment, resource wasting, costs) as well as to raise false negatives (e.g., a doctor does not diagnose an available affection).

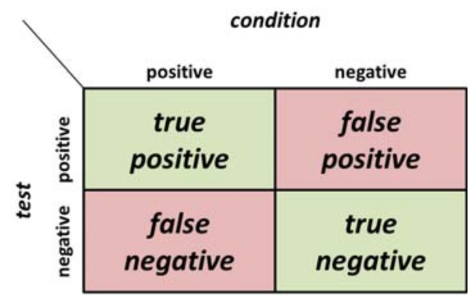

Figure 8: Sensitivity: true positives, specificity: true negatives.

In our current implementation the user is enabled to change the values on runtime to find new optimization possibilities (e.g., changing healthcare processes).

3.2.6 Geo Dynamics

GeoDynamics (GD) is a module that allows modeling diseases on a map (example for Berlin is depicted in Figure 9). Thus, we can define a region that has to be considered and it is possible to divide the region in smaller units, for example a city in districts. Each district can be modeled separately and uniquely (e.g., district age distribution, hospitals, traffic, infection processes). Using district densities one can distribute the calculated population by PD on the GD map within the configuration level.

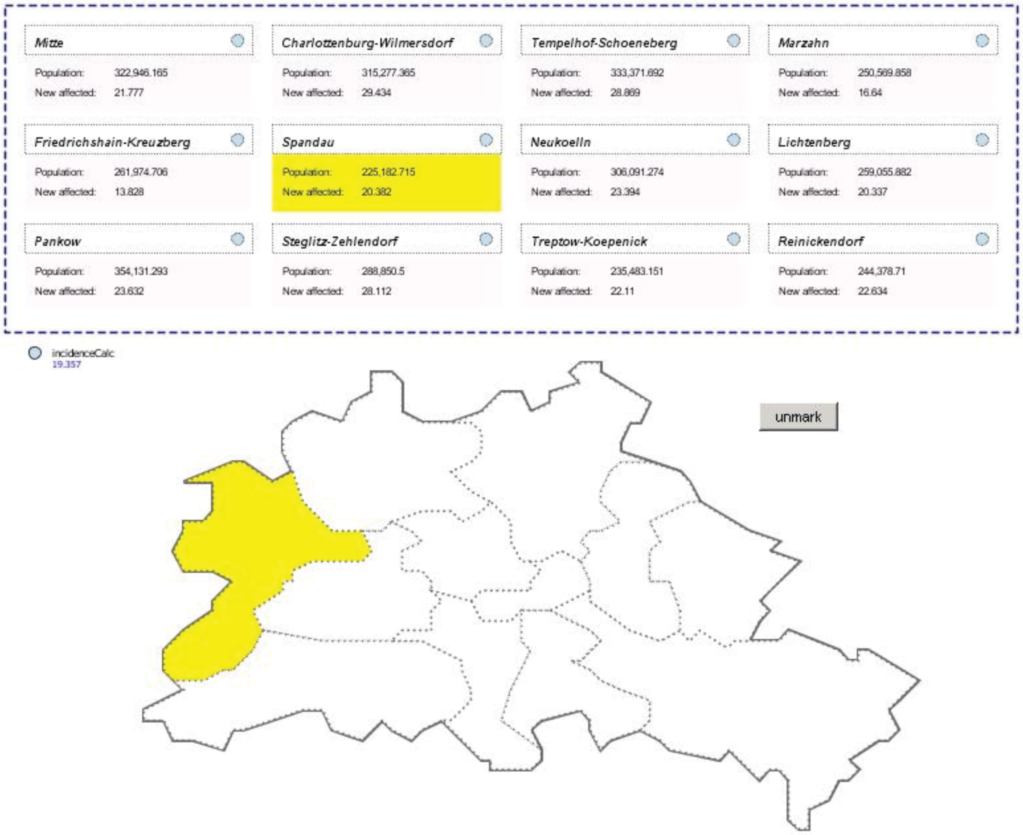

Figure 9: Configuration level of the GeoDynamics module.

A new active object instance of *PD Calculations* is used to get population numbers within the age and gender dimension. *DD Calculations* enables to calculate new affections in a district considering district specific dynamics (e.g., age distribution, traffic values).

3.2.7 Health Care

Once new affections have been calculated, new agents are generated by the simulation framework. According to an age group the agent samples a value and a life expectancy from statistical death tables. After an affection begins, the agent enters the cognition phase and traverses a modeled cognition process. In most cases a certain time is sampled dependent on daytime and other influencing aspects.

The Health Care (HC) module is located within the core of the simulation and combines diverse state charts and behavioral diagrams for prevention, pre-treatment phase (e.g., rescue service) and treatment phase (e.g., inpatient and outpatient workflows).

3.2.8 Post Disease Observer

After an agent traversed different diagnostic and therapy phases, a post disease routine is started. In many cases the agent traverses care and rehabilitation workflows and produces costs until a complete remission has been noticed. For consideration of chronic diseases the agent remains within the post disease observer until a death event is thrown and the agent leaves the simulation.

4. CASE-STUDY: STROKE THERAPY BY MOBILE STROKE UNITS (MSU)

The just described methods for large scale healthcare modeling by hybrid simulation techniques were applied to create a use case within the stroke therapy. In Djanatliev et al. [7] we already presented a first approach of the MSU scenario. In this work we focus particularly on the current state of the use case to provide a practical application for previously defined methods.

4.1 Introduction to Stroke and MSU

Stroke is a major cause for severe disability of people and for mortality. According to an increasing life expectancy and aging population one can estimate an increasing incidence in future, as it is a disease that occurs in higher age particularly.

There are different types of stroke. In approximately 80% of all stroke cases the *ischemic stroke* can be counted. This type is caused by an occlusion of brain arteries. Hence, approximately 2 mill. of neurons can die, as the brain is not sufficiently supplied with blood. Following the “time is brain” concept, stroke is a highly time-critical disease and it is important to act very fast.

There is an effective therapy for stroke treatment available that is called *thrombolysis*, which can only be applied within a 4.5 hour time window after the affection. The problem is that it is hard to recognize the symptoms fast. Often stroke occurs in the night and a patient can only detect the symptoms after getting up in the morning (wake-up stroke). The next problem is that a bleeding (haemorrhage) has to be excluded, before the thrombolytic therapy can be applied. This can only be done after Computer Tomography (CT) in hospitals and the patient loses a lot of time. Currently, only 8-10 percent are treated by this effective therapy [13].

Two research groups in Germany are working on an innovative technology which aims to transfer the thrombolytic therapy from inpatient treatment to the rescue service [24, 9]. The main idea is to use a specialized vehicle, Mobile Stroke Unit (MSU), with a CT and laboratory options on board. This allows to exclude a haemorrhagic stroke on-site at patients location and to begin with the thrombolysis immediately.

4.2 Scenario and Input Data

We defined a scenario with 10 MSUs in a metropolitan region that is represented by Berlin. Demographic structures of the city and its districts are modeled using statistical data from [1]. Disease specific parameters (e.g., incidence and prevalence, case fatality) have been prepared by domain experts using appropriate publications, register data and by new analyses. Time values of the MSUs are gained by further publications (e.g., [24]) in combination with expert opinions. Cost calculations, researches and data preparations are mostly done by health economic experts.

Patients are getting stroke and call the emergency service. After talking to the dispatcher a stroke can be assumed with the probability of a configurable sensitivity value. The dispatcher sends an MSU to the patient, if stroke symptoms are there and a free vehicle is available, otherwise a usual rescue service will be sent. Specificity is used to generate wrong calls by EI that are falsely determined as stroke cases. Before patients call the emergency service, a cognition phase has to be passed through. According to probabilities of four prominent time intervals (0-90 min. - Group A, 91-180 min. - Group B, 181-270 min. - Group C and > 270 min. - Group D), a time value is sampled which has to be elapsed, before contacting the rescue service.

4.3 Barthel Index considerations

The Barthel-Index (BI) represents self-reliance of people. A low value stands for disability, however a high BI reflects more independent persons. There are different ranges for BI available (further explanations about the Barthel-Index can be found in Quinn et al. [18]).

In the MSU scenario we have used the BI scale with values between 0 and 20. In that case a value 20-19 is used as Top-BI and between 18-0 as Low-BI. In order to sample a BI for agents after stroke we have used time dependent probabilities. Patients that have not undergone the thrombolysis will have a lower probability for a Top-Barthel than lysed ones. Persons that get the therapy in an earlier group have also a higher Top-BI probability. Using an MSU the patient is able to gain time in order to prevent severe disabilities.

4.4 Selected Examples

In contrast to SD-environment modules that were presented previously, Health Care and Post Disease Observer are two components that contain structural workflows for a specific disease. Therefore, we focus on this two examples in the following describing stroke specific modeling.

4.4.1 Health Care

The HC module is located within the simulation core and starts by a state chart of the agent *person* (see Figure 10), that represents its behavior.

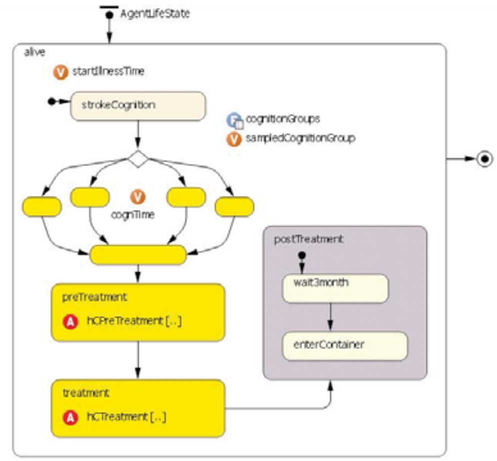

Figure 10: Behavioral state chart of the agent *person*

Initially, a cognition group is sampled according to the predefined frequency in a `CustomDistribution` object of AL. After the time elapsed the agent enters the pre-treatment phase by changing to the corresponding hierarchical state.

A new instance of the pre-treatment active object is created and the workflow (see Figure 11) is started. After talking to the dispatcher, an appropriate vehicle is sent to the patient. In case of stroke a free MSU will be sent and the patient traverses diagnostic and therapy workflows that are hierarchically encapsulated in composite states.

A patient leaves pre-treatment and enters the treatment phase by sending a `HCPreTreatment` object to the behavioral agent state chart. The Pre-Treatment active object will be deleted and the received message containing a health record object from pre-treatment is forwarded to the newly instantiated treatment active object.

4.4.2 Post Stroke Observer

Within the stroke therapy use-case the Post Disease Observer is called *Post Stroke Observer*, as it contains stroke specific workflows. We defined 10 containers representing the first 10 years after stroke. Each container is modeled uniquely and includes costs distributions for Top-BI and Low-BI persons.

The idea is to collect similar agents in one common container in order to perform set calculations instead of identical routines for each agent. This technique increases significantly the simulation performance. Initially, we used data from registers to define the number of Top-BI and Low-BI patients in each container.

New affections are represented by agents which have their individual shifting time and death event. After the agent reaches the second year after stroke, a shifting function is called and the agent changes from the first to the second container and generates costs that are specific on the agent's individual BI and the new container.

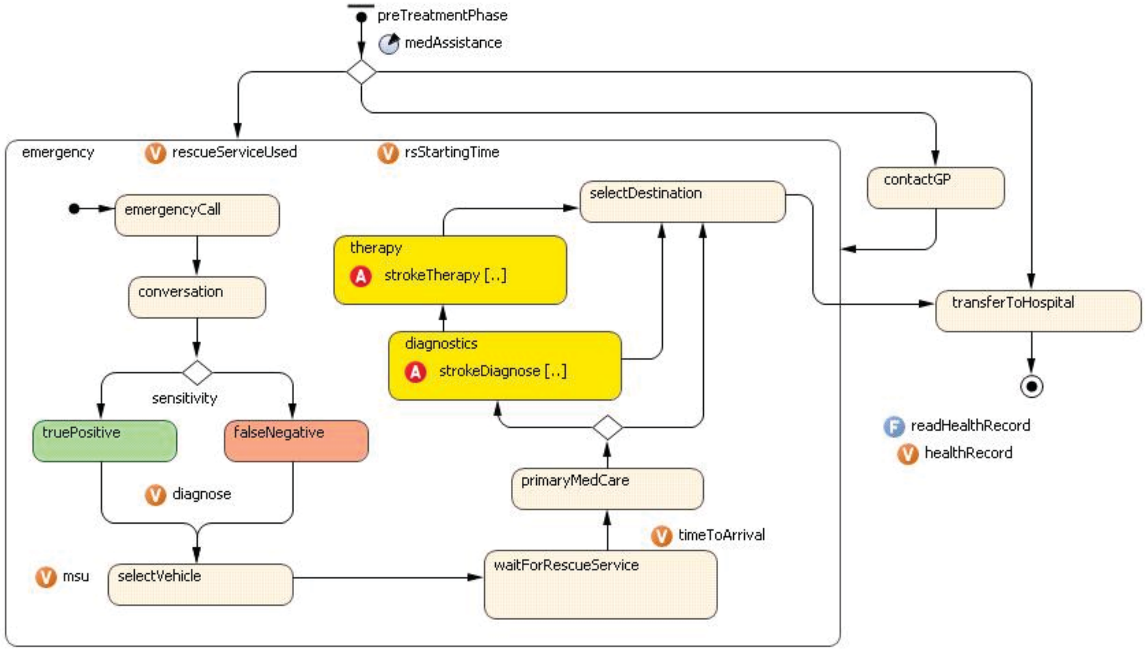

Figure 11: Simplified workflow state chart of the Pre-Treatment active object.

4.5 Model Validation

We validated our model together with our domain experts. We learned that it is highly challenging to perform structured validation steps. Although there are already validation approaches available (e.g., [20]), it remains a hard task in large scale modeling.

To perform successful validation it is important to gain domain experts' credibility and to make the simulation model transparent to them. Furthermore, sensitivity analyses have to be done comparing model reaction to realistic results from registers. Moreover, we did many model modifications and corrections until an overall trustworthiness has been reached. Our large scale modeling approach was based on module validations. It was chosen to validate modules first, before making large validation steps of the overall model.

4.6 Output Data Examples and Results

After we gained the credibility of our domain experts, a first analysis of simulation output has been started. Output metrics are presented and visualized on runtime by the *Statistics and Analyses* component. Additionally, a CSV file is generated annually that outputs yearly calculated costs values for further analyses.

Mean onset-to-therapy decision (OTD) time gained by MSU usage is depicted in Figure 12. The green line shows mean time for lysed patients that were not treated by MSU, however the blue line depicts the mean OTD time only for agents that were treated by MSUs. The difference between the values is depicted by the lower pink curve (Mean OTD time gained). Grey line depicts currently sampled values to show the variability of time values. The upper pink curve represents the overall mean time. Using the current state of the model, approximately 45 Minutes are gained on average when using MSUs. It is important to know that we parametrized the hospital with an internal process delay between 10 and 40 minutes by a uniform distribution. In further studies it is possible to change this sensitive value in order to represent a more or less effective hospital.

A further important output is the ratio of Top-BI agents after stroke and lysis. Figure 13 depicts an exemplary output considering only lysed patients. The blue line represents the mean Top-BI ratio of agents with MSU usage 3 months after stroke occurrence. The green one depicts the same for persons that were not treated by MSUs. Approximately up to 4-5 percent can be gained in mean.

Individual costs per patient are calculated individually in all 10 post stroke containers. The resulting values are higher for Low-BI patients than for Top-BI ones. A reason for this notice are the costs for care in particular. As MSU usage can raise the ratio of Top-BI patients one can estimate lower costs in long-term calculations.

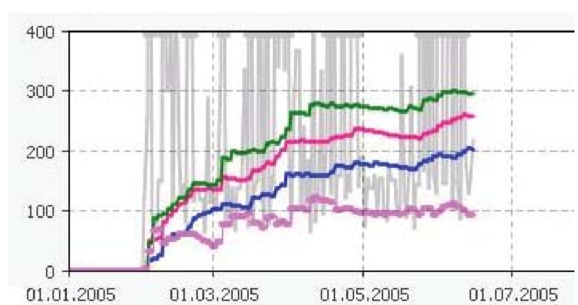

Figure 12: Example simulation output: Mean onset-to-therapy decision time. [x-axis: model date, y-axis: time in minutes]

Figure 13: Ratio of Top-BI patients (consideration of only lysed persons) [x-axis: model date, y-axis: ratio in %]

One more output example is the MSU utilization depicted in Figure 14. The graph values show the ratio of used MSU vehicles which is calculated on runtime by $100 - freeMSUs * 100/totalMSUnumber$.

A further important output metric shows the distribution of patients in different time groups (A,B,C,D). A main result is that many agents that previously were also lysed can be shifted to a better time group when using MSUs. In particular the group A (0-90 min.) gets a significant increase of approximately 9-11 %. That is the main reason for higher Top-BI ratios of lysed patients.

5. CONCLUSIONS

Large scale healthcare modeling is highly challenging according to many different domains that have to be considered. Furthermore, well-known modeling and simulation techniques are not sufficient to use, as one has to handle problems on high abstraction levels as well as such ones on low levels. Hence, structured scenario definition and advanced simulation techniques have to be applied.

We presented an approach of large scale healthcare simulation modeling for ProHTA [6] using hybrid simulation techniques in AnyLogic [25]. General architectural aspects were depicted and a *Level-Based-Architecture (LBA)* for ProHTA studies has been presented. LBA helps to reduce the complexity by hierarchical modeling and information hiding. The main modules of the ProHTA framework have been described. Data Component helps to handle all input data at one location and allows fast modifications to perform different simulation analyses by parameter variations.

This paper describes also a preliminary large scale ProHTA assessment case-study. A scenario within the stroke therapy was outlined in a metropolitan area represented by Berlin. We focused on model description and implementation of agent-based pre-treatment workflows and behavioral state charts.

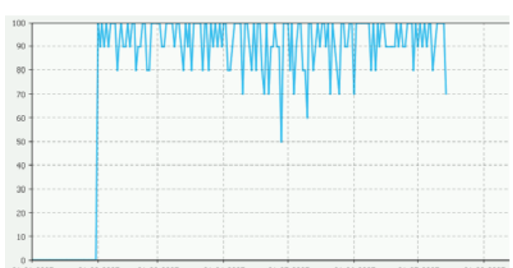

Figure 14: MSU utilization. Calculated by $100 - freeMSUs * 100/totalMSUnumber$

Moreover, our validation approach has been presented that is based on sensitivity analyses and gaining the credibility of domain experts. Furthermore, module based validation has been mentioned. It was much easier to validate modules first, before performing general validation steps of the overall model.

Finally, some important output data examples and results of the case-study model have been presented including the mean onset-to-therapy decision time gained when using MSUs, mean ratio of Top-BI patients and a time group distribution of persons.

Currently, the research of ProHTA particularly is focused on oncological scenarios and further MSU and stroke evaluations. In future, there are also some modeling and simulation challenges that have to be mastered. A main task will be to simulate large population numbers (e.g., nation population) by further methodical approaches.

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