MODULAR MODELING AND HYBRID COMBINATION IN HEALTH TECHNOLOGY ASSESSMENT MODELS – EXAMPLES AND TECHNOLOGY

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ABSTRACT

Simulation of communicable diseases is an important field of interest in HTA. As requirements of stakeholders in the field of HTA are getting higher there is a need for complex models using different approaches.

A concept to deal with the increasing effort and complexity is to split up models into single parts, so called modules, which enables easier development, more flexibility and reusability.

In this work we concentrate on two different modular approaches for simulation of epidemics:

The agent based approach, dealing with individual behavior of persons. A model for Influenza with different environments, a model for Streptococcus-Pneumoniae with complex infection rules and another influenza-model with social interaction deal as examples.

The top-down approach starts with the epidemiological part where, epidemiological outcomes are calculated in a more general way, following by the demographical part. It ends with the economical part that calculates costs and evaluates economic aspects. A model for human papillomavirus vaccination (HPV) serves as an example.

Keywords: modular, modeling, agent based, HTA, health technology assessment, epidemics, communicable diseases, sexual transmitted disease, STI.

1. INTRODUCTION

Modelling and simulation of communicable diseases is an important field of interest in HTA. The aims range from understanding epidemic dynamics to predictions of an outbreak and to economical assessments.

There are several ways of modelling the spread of an epidemic. The traditional ways are statistical calculations or Markov models, mathematicians prefer differential equations or System Dynamics. These approaches are well known and examined but due to their structure they have certain limitations. Due to increasing computational power, other methods like agent based modelling or cellular automata became popular in recent years.

However, the closer such models are to reality the more complex they become. They get harder to develop, to handle and to control. For that matter we try to split such models into single parts, also called modules. These parts are easier to develop and to maintain because they are smaller and, if they are split wisely, only refer to a single aspect of the model. Another benefit is that modules might be replaced without touching the rest of the model which increases reusability and even makes it possible to connect different modelling methods.

In this work we are going to provide two different modular approaches that both provide detailed calculations and allow flexible usage: An agent based approach and a top-down approach..

2. THE AGENT BASED APPROACH

An agent based model is a model that consists of single parts that act individually and independently. For an epidemic model it is simple: The agents are the persons. We propose a general structure that consists of four modules (see also Fig. 1).

This structure was further developed and improved within IFEDH (Innovative Framework for Evidence-Based Decision-Making in Healthcare), a project funded by FFG (FFG project number: 827347).
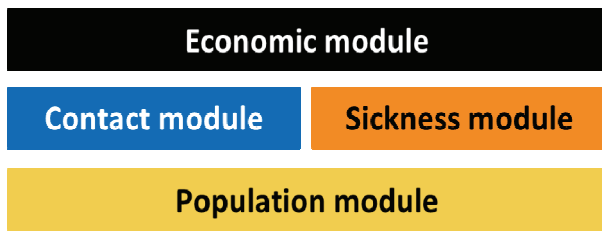
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Figure 1. The proposed modules of an agent based epidemic model.

The population module is in charge to construct the persons in the beginning of the simulation and equip them with correctly distributed parameters (i.e. gender, age), monitor them during the simulation and assure their progression (i.e. that they get older).

The contact module creates an environment in which the persons can move and can have contacts and assigns collective or individual rules to the persons concerning moving around in that environment and meeting other persons there.

The sickness module assigns collective or individual rules what happens to a susceptible person when he meets an infectious person.

It assigns rules that control the progression of a sickness after an infection and it performs preventive interventions like vaccinations at certain points in time and on certain persons.

The economic module keeps track of all costs caused by preventive interventions or sicknesses and performs statistical analyses on the population and on the costs.

3. EXAMPLES OF THE AGENT BASED APPROACH

In the following part three examples for modular modeling of infectious diseases using agent based technology are listed. The first example uses also hybrid coupling of another bottom-up technique: cellular automata for modeling of spatial dynamics of the agents.

3.1. Combination of cellular automata and agent based modeling techniques

The first example is a model to simulate an influenza epidemic. The population module constructs a population according to Austria's demographics where people have a gender but they do not have a specific age, they are assigned to an age group. The contact module is more complex. The environment consists of households, schools, workplaces and neighbourhoods that compose as a collection of households. People are assigned to those places according to data from Statistics Austria. They visit these places on a daily basis. Contacts within households are generated stochastically between all household members. All other places a are constructed like lattice gas cellular automata (LGCA) while people move around like particles according to LGCA-rules. Contacts are considered whenever two or more persons are together

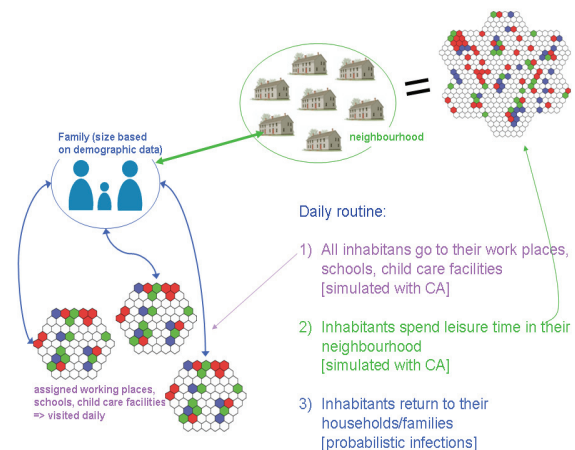in one cell. Fig. 2 shows a visualization of the contact module.

Figure 2. The contact module from the first agent based Influenza model (Emrich et al. 2008).

The sickness module has been modelled (according to available medical information) as follows: Individuals start out in the state susceptible in which they are vulnerable to infection. Upon infection individuals are in the state infected without symptoms in which they can pass on the infection but not yet be detected (e.g. cannot stay at home because they feel sick) eventually their status changes to infected and symptomatic, recovered (and immune) or dead. Alternatively individuals that are not symptomatic can become recovered (and immune) without going through the symptomatic state. These transitions are time-triggered trough with a normal distribution around the set time-period. Additionally recovered individual lose their immunity after a period of 75 days. (Emrich et al. (2008), Zauner et al. (2011)).

3.2. Streptococcus Pneumonia children vaccination model

The second example is a model for Streptococcus Pneumoniae. This bacteria can cause pneumonia, otitis media, meningitis, sepsis. The population module constructs persons according to Austria's demographics with gender and a specific age. Due to a simulation time of 20 years people get older, can die and babies (persons with age 0) are born. The contact module is relatively simple. It assumes a well-mixed population where people meet each other randomly on a weekly basis. The sickness module has to deal with several issues. There are more than 90 types of Streptococcus Pneumoniae pathogens, called serotypes. They are in a concurrent situation since a person can be infected by only one serotype at one time but never by two or more. The vaccination only works against some of these serotypes. The sickness module has to assure that the preconditions are preserved. It does not consider all serotypes in detail, instead it considers two serotypes: One stands for all serotypes that can be repelled by the vaccination and the other one for the rest. It provides these rules (see also Fig. 3):

Infected people recover after a while and can be infected again by any serotype.

Vaccinated persons can be infected only by the second serotype not included in the vaccine, simulating a hundred percent protection rate.

Infected people can either be blocked for or infected with the other serotype. If an infected person gets infected by another serotype he gets rid of the old one. The new serotype replaces the old serotype out of the person.
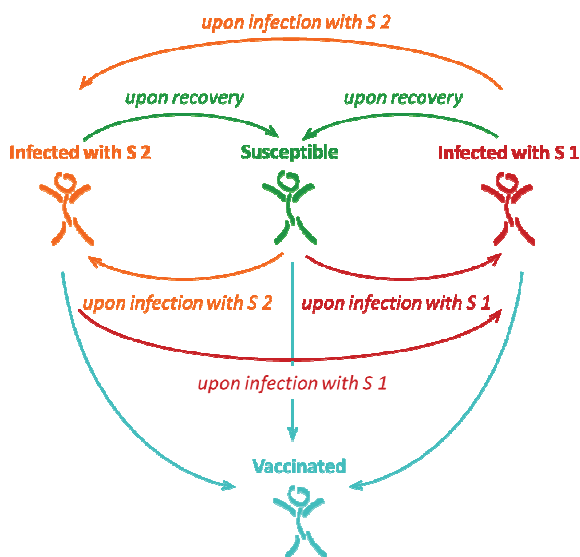

Figure 3. Sickness module of the agent based model for Streptococcus Pneumoniae (Zauner et al. 2010).

The economic module keeps track of all infections by the serotypes. Based on this data it estimates the number of sickness cases and furthermore costs due to treatment and vaccinations. It provides several outputs to analyse the spread of the pathogen as well as sicknesses as well as costs and cost-benefit analyses. (Zauner et al. (2010))

3.3. Modular real world influenza model

The third example is another model for Influenza. The population module is the same as the one used in the Streptococcus-Pneumoniae-model in the second example modelling realistic Austrian population (Brooks-Pollock et al.. (2010)). The main difference is that no aging of the population is implemented due to the fact that an Influenza season lasts only about 15 weeks and therefore no effects of changing demographic structure has to be implemented. The contact module is very detailed and complex. The environment consists of households, schools, work places and a leisure place. According to data provided by Statistics Austria people are assigned to these places. This means, households in the model are filled with persons, so that the number of inhabitants and their age distribution correspond with real world data.

The same conditions apply for schools that consider children and teachers classrooms. It assures that children of the same age are put together in a classroom so that they have more contacts with each other that with children of other age. The number of people in workplaces is also distributed accordingly to the situation in Austria. This sets the size of groups that can have contacts at work.

People know where they live, study and work so they are mainly always surrounded by the same potential contact persons in the different places. The leisure place can be visited by everybody and does not need assignments.

Based on an individual daily schedule people move around between those places and can meet other present people. Parameters are adjusted in a way that the sum of contacts in a certain place corresponds with current social studies that evaluate daily contacts that are relevant for airborne diseases. Fig. 4 shows a visual representation of this module, split into different parts explaining the logic development process.
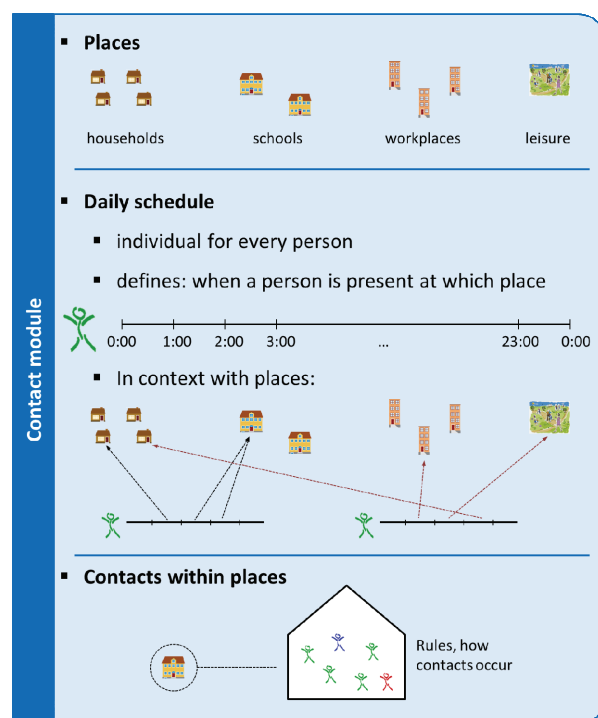

Figure 4. The contact module in the second agent based model for Influenza.

The sickness module is the same as used in the first Influenza model (see Fig. 5). The definition of interfaces between the different modules are defined in an interdisciplinary team, including specialists with health technology assessment (HTA) knowledge, modeler, and physicians. This guarantees the technical practicability as well as reusability and that the standardized HTA output measures can be calculated.

The economic module performs evaluations on the spread of Influenza and analyses in detail how many infections occur in the single places (Miksch et al. (2010).
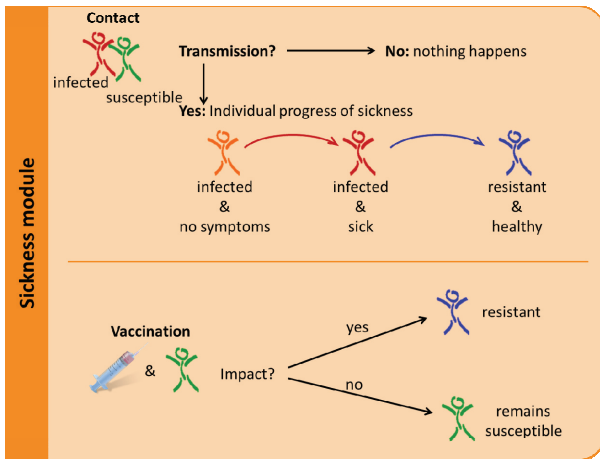
Figure 5. The sickness module of the second agent based model for Influenza.

Cost data are not parameterized in detail yet because of limited reliability of cost data for Influenza cases in Austria. Nevertheless the modular structure and the interfaces are implemented using object oriented programming techniques. The economic evaluation module calculates the costs per life years gained (€/LYG) without discounting the costs, but discounting the lost life years due to superinfections (pneumonia, etc.) caused by influenza Infection (module depiction see Fig. 6). The usage of costs without discounting is based on the fact that the costs occur at the actual time point whereas lost life years occur at a future time point.
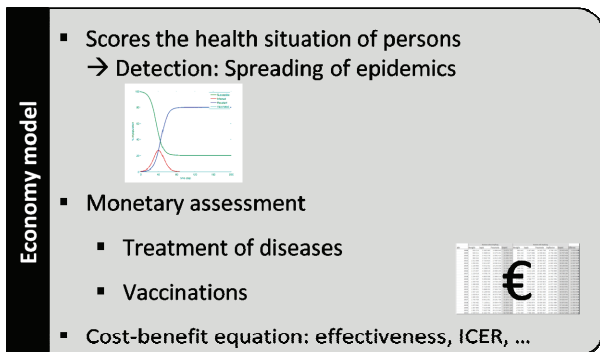

Figure 6. The economy module structure of the advanced agent based model for influenza

4.   THE TOP-DOWN APPROACH

Top-down models for epidemics are a quite different approach than agent based models. They do not consider single persons representing a bottom-up approach; instead they calculate the fractions of the population that are in certain states representing the persons of interest and their behaviour using a top-down point of view. Common techniques especially in health technology assessment applications are Markov models – mainly Markov chains, based on quite simple decision trees for each time step not taking into account a longer history - and ordinary differential equations (ODEs) realized using System Dynamics simulation tools without knowledge of the equations.

In the following discussion an ODE approach is the basis for all assumptions and findings. As in case of agent based techniques the model in general has to provide a structure for simulation of a real world population and its demographic change over time, the disease propagation and the resulting costs/benefits from a health care service provider point of view.

One possible approach splits the problem into three modules:

The **disease module** calculates clinical and epidemic outcome parameters, including the number of carriers, sicknesses and deaths for a research population/standardized population with homogeneous cohorts.

The **demographic module** takes the results of the disease module and matches it on the demographics of a given population. This means, it calculates the outcome parameters for a specific population.

The **economic module** calculates the costs and performances for the clinical and outcome parameters from the demographic module using predefined average cost data and statistical distributions.

4.1. ODE modeling example: HPV vaccination

The included example simulates the spread of human papillomavirus (HPV) in the Austrian population and is used for modeling of vaccination effects (Zechmeister et al. 2009).

As the effect of decreased cervix cancer incidence and mortality is highest for women age 50 years and older, however vaccination is done in the age of 12 years, long simulation time span (and thereby unsecure events) have to be focussed. The long term effects achieved by vaccination against the most common known virus strains and the concurrence behaviour changes by vaccination against these strains is not known and can therefore not be found in literature to get secure parameterization. Calibration techniques and comparison of the qualitative behaviour of other diseases have to be realized to get a reliable model structure.

As the HPV modelling question of interest is quite complex in the following bullet list the main boundary conditions are listed in non-graded form:

HPV is the main known reason for cervix cancer and genital warts (causing death due to severe illness) and therefore has to be modelled quite detailed to ensure to fit the model quality requirements.

HPV is a sexually transmitted infection (STI), which means that other distribution pathways are the basis for transmission as in case of airborne diseases (in comparison with the other examples given in this paper)

In case of HPV another prevention method of sever diseases than vaccination is under discussion: screening.

Although screening is not implemented in the realized model in the actual form, interfaces for additional screening application have to be discussed.

The realization of the disease module was implemented in C using a set of coupled ordinary differential equations modeling the sexual contacts of

population groups for a research population. The contact data are based on international studies and expert opinion, beyond that these data sets are identified as one of the most unsecure information integrated in the model. Additionally the model and system behaviour is quite sensitive regarding changes in the contact parameterization. That is why univariate and multivariate sensitivity analysis for sexual contact data is planned.

The ODE structure in this model part is based on simple SIR structures.

Using the calculated distribution of infected women (men can be carrier of the virus strains, but do not get ill), age dependent probabilities are used to estimate the number of cervix cancer cases and genital warts due to HPV infection. Additionally statistical methods are used to assess the number of deaths and lost life years (based on assumed remaining lifetime for each modelled population group) for the research population.

The demographic module matches the gathered results to the real Austrian population. Errors based on the different behaviour of research (simulation) population and real life population are tolerated due to the complexity and the bounded reliability of the used parameter sets. The weakness of the model is mainly based on parameterization questions and other structural boundaries not the conversion of the simulated population to the real life population.

But anyhow the problematic behind this strategy has to be focussed analyzed in each additional model extension.

The economic module as top level of the model – being the part of highest interest for decision maker in health technology assessment and evidence based medicine – calculates the discounted costs and benefits for the vaccination strategy. As costs the vaccination program costs and the treatment are taken into account; additionally the lost life years due to death by cervix cancer are analyzed in discounted form for each strategy realized in the model and the comparing scenario – in this case the state of the art without organized vaccination program.

The benefits are prevented illness cases and therefore reduced morbidity and mortality, leading to a cost reduction for treatment of severe illnesses.

The interface for implementation of screening technologies can be realized in the disease module; the transmission part is not directly influenced and can therefore be used as a basic model block. The resulting virus carrier (men and women) can be understood as population group of main interest, which should be detected by the screening program.

The result of screening as a new layer in the module hierarchy could be placed in between disease module and demographic module.

If model refinement would be done, taking into account that people detected as carrier or with prestage cervix cancer are handled quite special because this population group knows their carrier stage, structural

changes in the ODE system have to be realized. In general STI models are not realized that detailed.

5. CONCLUSIONS

The examples show in different simulation situations that it is possible to split up a disease model into single modules.

The agent based approach dealing with different circumstances fits into the four-module-concept. Even more, it is possible to share some modules while other modules needed to be developed newly to fit the situation accurately. This clearly points out the strength of the modular approach.

The two Influenza models show (in the first example) the possibility of hybrid coupling used in a modular model structure, realizing spatial dynamics by implementing neighbourhood strategies and (second Influenza example) explain the usage of a very detailed contact model for Austrian settings which can be used for a long list of communicable airborne diseases.

The top-down approach also depicts benefits of modular models and reusability: The problem is split into three tasks that can be solved independently. It even allows using and adopting one module that has been developed in Britain instead of developing it in Austria again.

In general we can conclude that modular modeling helps to structure modeling process and that reusability of tested and validated modules makes projects more efficient and reliable.

6. OUTLOOK

The presented modular and hybrid modeling techniques for infectious disease strategy evaluation presented in this paper are applications focused on in the IFEDH framework research program in Austria. Besides the development of standardized reusable modeling techniques, the set up of interdisciplinary processes for simulation model based decision support in HTA questions is realized.

One result of cooperation and immediately one of the future working tasks is the optimization of the model output quality by the following tasks:

- Integration of HTA experts and physicians in the model definition process; discussion of reusability of pre-developed, validated modeling modules;
- Constant cooperation of data quality assessment specialists and data experts during the model set up and parameterization phase;

The integration of these points into the model realization process, together with the consequent refinement and validation of the already realized modules will lead to faster implementation of future issues in HTA and the results will obtain higher acceptance by the decision maker because of higher reliability.

The definition and implementation of additional module interfaces will be one of the most important future tasks. This work will be done iteratively to secure

that external expert knowledge from HTA and statistics can be taken into account.

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