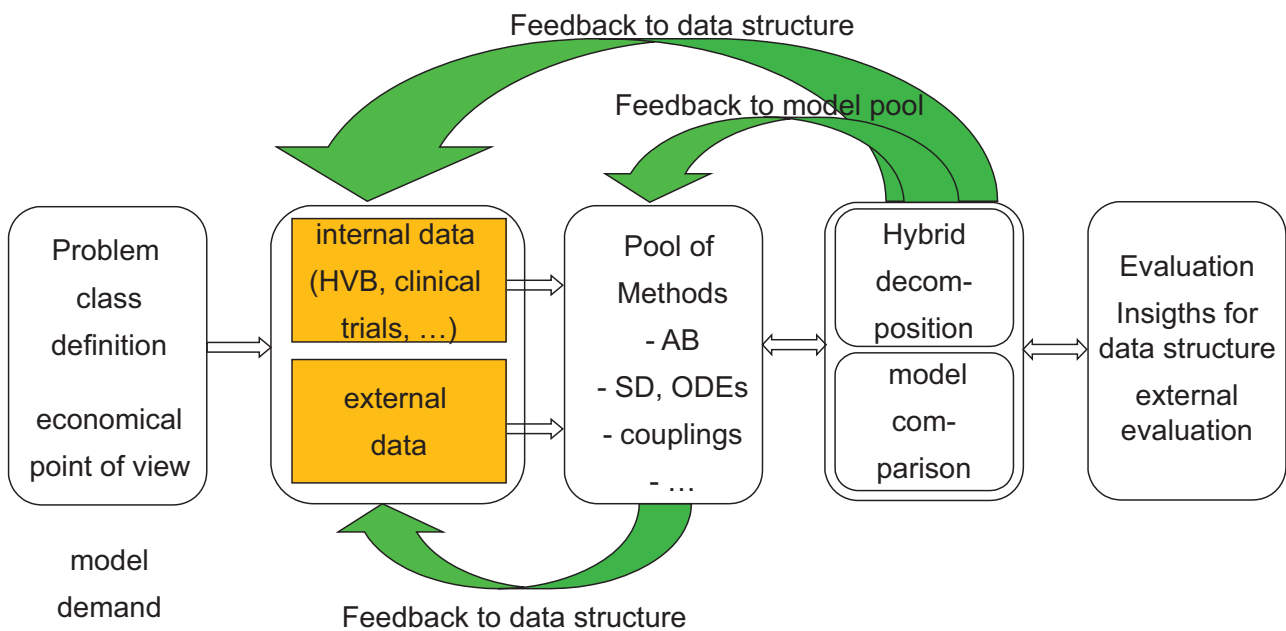


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Special Issue: Modelling & Simulation in Health Care Technology: Development - Implementation - Assessment



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Dear readers,

We are glad to continue the SNE Special Issue Series with this special issue SNE 20/2 on 'Modelling and Simulation in Health Care Technology – from Development via Implementation to Assessment'. The editorial policy of SNE Special Issues is to publish high quality scientific and technical papers concentrating on state-of-the-art and state-of-research in specific modelling and simulation oriented topics, and interesting papers from the world wide modelling and simulation community. The subject 'Health Care Technology – from Development via Implementation to Assessment' is a relatively new subject for classical modelling and simulation, and therefore very well suited for a special issue.

While modelling and simulation is already a must in biomedical engineering, for health care systems analysis and design, modelling and simulation is now supporting and partly replacing classical statistical methods. And very new is the use of modelling and simulation in development circles from design until spread and use of a new method or product for health care.

I would like to thank all authors and all people who helped in managing this SNE Special Issue, especially the guest editors of this special issue, Niki Popper from dwh Simulation Services Vienna (a research company dealing with health care systems), and Siegfried Wassertheurer from the Dept. Biomedical Systems of Austrian Institute of Technology

For SNE Volume 21 (2011), we are planning a special issue SNE 21/2 on 'Modelling and Simulation in and for Education'.

Felix Breitenecker, Editor-in-Chief SNE; Felix.Breitenecker@tuwien.ac.at

SNE Editorial Board

Simulation News Europe (SNE) is advised and supervised by an international editorial board. This board is taking care on peer reviewing and handling of *Technical Notes*, *Education Notes*, *Short Notes*, *Software Notes*, and of *Benchmark Notes* (definitions and solutions). Work of the board is supported by a new SNE Contribution. Management and Reviewing System via the new SNE website, and by the Society News Editors of the EUROSIM Societies. At present, the SNE Editorial Board is increasing:

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SNE Contact. SNE - Editors /ARGESIM
c/o Inst. f. Analysis and Scientific Computing
Vienna University of Technology
Wiedner Hauptstrasse 8-10, 1040 Vienna, AUSTRIA
Tel + 43 - 1- 58801-10115 or 11455, Fax – 42098
office@sne-journal.org; www.sne-journal.org

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Scope: Technical Notes and Short Notes on developments in modelling and simulation in various areas /application and theory) and on benchmarks for modelling and simulation, membership information for EUROSIM and Simulation Societies.

Editor-in-Chief: Felix Breitenecker, Inst. f. Analysis and Scientific Computing, Vienna University of Technology, Wiedner Hauptstrasse 8-10, 1040 Vienna, Austria; Felix.Breitenecker@tuwien.ac.at

Layout: Markus Wallerberger, markus.wallerberger@gmx.at

Administration, Web: Anna Mathe, anna.mathe@tuwien.ac.at

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Modeling and Simulation in Health Care Technology: Development - Dissemination - Assessment

Simulation is an important method which helps in development, dissemination and assessment of health care technology. While modelling and simulation is used at the level of development of health care products for a long time, the use in dissemination and especially in assessment is relatively new. This SNE special issue on 'Modeling and Simulation in Health Care Technology: Development - Dissemination - Assessment' presents the very broad variety of the area.

The first contribution 'Modelling and Simulation in Health Technology – from Development via Implementation to Assessment' by Niki Popper and Siegfried Wassertheurer gives an overview on the special issue's subject: from use of modelling and simulation in cardiovascular investigations for research and treatment until new areas like modelling and simulation for decision making in health technology.

The contribution 'Applying Hybrid Tokens to the Estimation of the Therapeutic Outcome of Psychiatric Treatments' by K. Dammasch, B. Rauch-Gebbensleben, and G. Horton describes a model that can provide a decision support for physicians and therapists

The third paper 'Novel Concept of Modelling Embryology for Structuring an Artificial Neural Network' by R. Thenius, T. Schmickl and K. Crai proposes a novel method to organise the nodes and links of an Artificial Neural Network in a biologically motivated manner using virtual embryology.

Esko Juuso presents a simulator which combines several models which are specific to the operating conditions in 'Intelligent Modelling of a Fluidised Bed Granulator used in Production of Pharmaceuticals'.

The contribution 'Modeling and Simulation of Patient Flow in Hospitals for Resource Utilization' by L. Zhao and B. Lie propose models to predict the future resident patient number in each department/ward.

The sixth contribution 'Analysis of the Aortic Influence on the Impedance Cardiography Signal by a Simple Model using Finite Integration Technique' by M. Ulbrich, A. Schauer- mann, and S. Leonhardt proves that the aorta indeed is the major contributor for the impedance cardiography signal

The paper 'Long Term Behaviour of Agent based Epidemic Simulation of Streptococcus Pneumoniae - A Mathematical Status Report' by F. Miksch, N. Popper, G. Zauner, I. Schiller-Frühwirth, and G. Endel introduce the agent-based modelling as alternative and efficient approach for modelling and simulation of epidemics.

The last contribution 'A System Dynamics Model of Health Insurance Financing in Austria' by P. Einzinger, G. Zauner, and A. Ganjezadeh-Rouhani presents a system dynamics

population model, which also simulates global income and expenses from medical attendance and prescribed drugs – with possibilities for studying different control strategies. system

The editors would like to express their gratitude to all authors for their co-operation and efforts, e.g. for sending revised versions. We hope that the selected papers present a good overview and state-of-the-art of modelling and simulation health care technology and health care system - by means of contributions to on the one side very different areas but on the other side areas which are In the future.

*Niki Popper, dwh Simulation Services, Vienna, Austria
niki.popper@dwh.at*

*Siegfried Wassertheurer, Austrian Institute of Technology,
Dept. Biomedical Systems, Vienna, Austria
siegfried.wassertheurer@ait.ac.at*

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REPORTS



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Modelling and Simulation in Health Care Technology – from Development via Implementation to Assessment

Nikolas Popper¹, Siegfried Wassertheurer²

¹dwh Simulation Services Vienna,

²Austrian Institute of Technology, Dept. Biomedical Systems, Vienna

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Modelling and Simulation (M&S) has found its way into many areas, almost in our daily life, so also into health technology (HT). Health technology and medical technology encompass a wide range of health care products and services – from vaccination strategies to heart circulation monitoring. And they are used to diagnose, monitor or treat every disease or condition that affects humans. M&S in HT is improving the quality of health care delivered and patient outcomes through earlier diagnosis, less invasive treatment and reductions of illness. This contribution investigates M&S in HT at different levels: (i) M&S for developing a HT product, (ii) M&S implemented in a HT product, and (iii) M&S for assessment of a HT product. While the step from model-based development of HT products to model-based operation of HT products is evident, the last step to model-based assessment of HT products is relatively new application of M&S – and necessary for the success of HT products. Interestingly, although the aims of M&S at these three levels differ significantly, the M&S techniques – from Markov models via ODEs/PDEs to Agent-based models stay the same.

Introduction

Experts in many application areas today use methods of modelling and simulation for developing new products and services. In many technical fields this is already well standardised and widespread in all areas from developing to implementation, and also for assessment of implemented solutions. In HT the usage of M&S has recently reached different stages of integration of the methodology in these areas. That means we can see different levels in the usage of modelling and simulation in development, implementation and assessment of HT. This situation gives us the possibility to focus on different aspects of M&S, to analyse different possibilities and problems and furthermore we can demonstrate the various requirements for M&S by reference to these areas of Health Technology Assessment.

Today development of new health technologies is assisted by many standardised models, like physical modelling, partial differential equations or compartment models. Also implementations can refer to many technical realisations over the last decades, which have led to standards or de-facto standards. Especially the usage of widely used platforms like MATLAB show a wide consensus in the community and lead to de facto standards, which – by the way – not always have to be the best possible solution.

Still methodical improvements on a market of highly competitive systems are important. New models are rated by how well the methodology can map and realise available data, the “state of the art” knowledge and established features – for example for mobile terminal devices. So - in the field of development and implementation of new Health Technologies - the discussions about detail-oriented improvements dominates the scientific discourse, sometimes losing the survey and the attendance for new, alternative approaches and solutions.

The situation in the area of the assessment of medical services is different. After the development of a new product or a new service these are assessed and their success is analysed and quantified. These assessments currently use M&S too, as e.g. the European Joint Actions (EUNetHTA) show; however the methodology is quite new and a lot of solved problems for technical areas remain open today. A main difference in the state of the art between M&S in development and implementation and M&S in assessment is that it is still under development which modelling method or which simulation implementation represents the best solution. So competition can here be found in a totally different area of model development. Missing standards lead to often not target-oriented discourse, which lacks a common language.

In the scientific discourse we have two opposite situations. The different “roles” of M&S in development, implementation on the one side and assessment on the other side are in the focus of considerations.

Are questions like the dominance of one modelling technique to be answered definitely at some point of development of M&S in an application area like HT? Continuous research clarifies the demands of M&S, so the choice of the M&S Technique should also be clarified. Or are demands and techniques in a constant change, also changing the demands and possibilities for M&S? What are the minimum standards for an effective scientific discussion between different M&S methodologies like PDEs and Cellular Automata? How can demands for the use of M&S be formalized to make the different techniques comparable.

Are there restrictions for the use of M&S in HT? What is the primary objective of M&S? Is it the construction of new things? Or is it the optimisation of implemented processes? Or is it the acquisition of a deeper understanding of a system? “Anything goes” one could say, but trust in a jack of all trades device has always been, and still is, subdued – and this is well justified. Models can and will be utilised for various – even opposing – aims. This constitutes an enormous potential, but on the contrary it involves the danger of “abuse”.

1 Models in Development of Health Technology Products

One example for the need of new HTs are cardiovascular events. Recently here has been a rapid increase, however there has only been moderate corresponding success in the implementation of actual treatment strategies, with an unfortunate simultaneous dramatic rise in treatment costs. Actual data provided by the WHO or the American Heart Association accordingly show that about 50 percent of all deaths in OECD countries are brought about by some form of cardiovascular dysfunction. Hypertension can actually be considered as the most important pathology in cardiovascular disease.

Due to these facts medical sciences indicate an urgent need to find further relevant indicators besides high blood pressure. The current treatment guidelines of the European Cardiology Society (ESC) and the European Society for Hypertension (ESH) point out the need to analyse the cardiovascular system using pulse wave analysis (PWA) and the synthesis of hemody-

namic parameters. However, the guidelines emphasize the lack of easy-to-use technologies. These, much needed technologies are, on the one hand non-invasive measuring devices and on the other hand models and tools for indirect measurement or model-based determination of cardiovascular parameters.

Today Hypertension is seen as a relevant risk factor, but reasons for cardiovascular dysfunction are manifold and complex. Since risk factors cluster in hypertensive individuals, risk stratification should be employed and decisions on the management should not be based on blood pressure alone, but also on to the presence or absence of other risk factors, target organ damage, diabetes, and cardiovascular or renal damage, as well as on other aspects of the patient’s personal, medical and social situation.

Due to the complexity and diverse coherence requirements of the cardiovascular system, a broad multidisciplinary knowledge is required to understand the biophysical as well as the medial causes. This has been reflected in the formation of interdisciplinary research groups to work on this problem over the last few years. So also virtual physiological modelling is seen as a powerful approach to improve the understanding of the complexity of the human physiology as a whole. Another problem caused by the intrinsic complexity mentioned above is that many results obtained in fundamental biomedical research (as with cardiovascular research) do not find their way into true clinical practice, mainly because the required bridges to show practical benefits are missing. This demands a new generation of multidisciplinary clinicians, educated by the means of integrative systems like provided by M&S.

Combining Models - Modelling arterial and left ventricular coupling for non-invasive measurements

Nowadays different “high-end” measurement devices exist for the determination of hemodynamic parameters such as cardiac output and peripheral resistance. On the one hand there are non-invasive methods, such as the Doppler method or impedance-cardiographs, whose drawbacks are the operator dependency and the costs. On the other hand there are invasive methods, such as the Gold Standard Thermodilution used also in combination with pulse contour analysis (PCA). The disadvantage of these methods is the invasiveness and the combined risks. Existing non-invasive pulse contour analysis methods are either dependent on personal data, such as age, height or weight or on an initial calibration.



In Figure 1 the functional principles of pulse contour analysis methods using a personal calibration factor obtained by Indicator- or Thermodilution are illustrated.

The basic idea behind PCA is that the cardiac stroke volume is proportional to the area of the pressure curve during systole. To consider physiological boundary conditions like vessel diameter or arterial compliance as well as the cardiovascular status, an external calibration is needed and has to be repeated periodically. Currently the non-invasive assessment of functional hemodynamic parameters using simple and affordable devices for widespread application in internal medicine or by general practitioners is not possible. The goal is the development of an algorithm for a non-invasive, portable, easy-to-use and affordable device for measuring functional cardiovascular parameters based on a common oscillometric measurement using an occlusive blood pressure cuff.

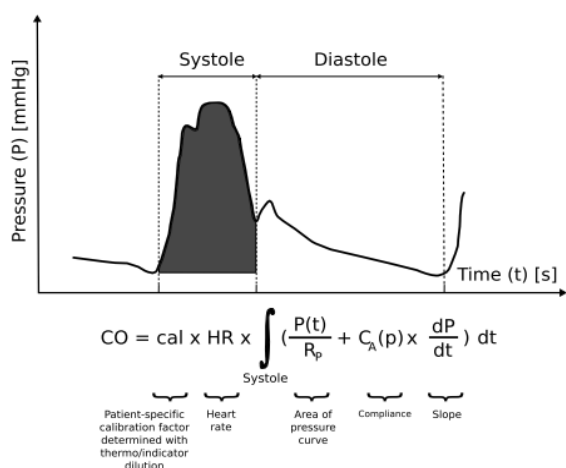


Figure 1. Example for cardiac output determination using pulse contour analysis.

An algorithm for a non-invasive, portable, easy-to-use, and affordable device for measuring systemic cardiovascular parameters such as cardiac output and peripheral resistance was to be developed. The data acquisition was based on a common oscillometric measurement using an occlusive blood pressure cuff with no additional calibration necessary. For results and detailed description see [1]

This novel algorithm combines several simulation techniques like neural networks or differential equations. The determination of the hemodynamical parameters is based on the idea that the ejection work of the left ventricle is subject to an optimization principle.

As one advantage this kind of model needs no additional external calibration and opens therefore good perspectives for non-expert use in cardiovascular risk stratification and hypertension therapy optimization. Combination of different M&S techniques so lead to a simpler and more efficient tool.

The project showed evidence that the proposed method provides clinically relevant and reliable hemodynamics. The measurements showed good agreement between the algorithm and the reference methods. Therefore the application presents itself as a suitable alternative to standard cardiac output determination methods as well as a supplementary investigation method for general practitioners or specialists in internal medicine. Future work will incorporate additional considerations, regarding pulse wave velocity and pulse transit times, in order to refine the calculations on arterial compliance and subsequently reduce scattering and standard deviation with regard to the Thermodilution method.

Models in Implementation – Pulse Wave Analysis

As we could see a demand (development of an easier algorithm with less calibration effort) could be satisfied combining different M&S techniques (see Fig. 2, Lattice-Boltzmann, Neural Networks, PDEs) to make non-invasive measurement more efficient. Another effort is to adapt measuring technology to new research results – new parameters have to be discussed – and to be modelled. The medical research regarding hypertension has fairly changed during the last two decades. Around the year 1990, the diastolic blood pressure was the most important value to look at, approximately 10 years later the focus was on the systolic blood pressure.

Today, we know that both systolic and diastolic blood pressures are prognostic ally important. But other vascular parameters seem to be of importance for evaluating the hypertensive patient with respect to his prognosis and potentially therapeutically options. With the beginning of the new millennium the topic of arterial stiffness of major vessels related to hypertension slowly arose in clinical practise. This issue was together with its indicators for the first time mentioned in the ESH–ESC (European Society of Hypertension– European Society of Cardiology) guidelines for hypertension treatment in the year 2003.

As parameters to measure arterial stiffness primary the methods of pulse wave analysis and pulse wave velocity have been suggested.

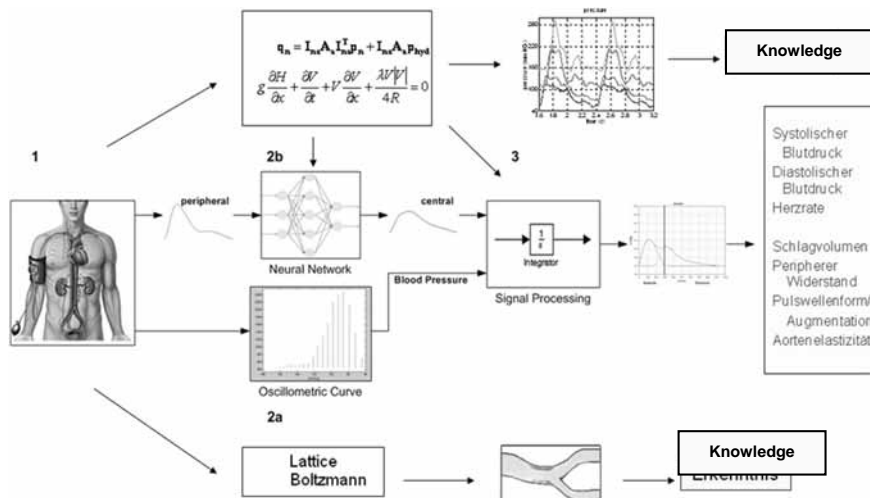


Figure 2 Structure of the strategy combining Techniques in developing process

Furthermore, it is reported that the AIx correlates with the left ventricular mass in normotensive men as well as in hypertensive ones. Moreover, the increase in cardiovascular risk can be estimated better from central than from brachial blood pressure measurements.

In the update of the ESH-ESC guidelines for hypertension treatment [2] in the year 2007, the consequences of arterial stiffness on cardiovascular mortality have a major role.

The pulse wave analysis evaluates shape and amplitude of the aortic pulse wave. The resulting parameters of relevance are the aortic systolic blood pressure (aSBP) and the so called augmentation index (AIx).

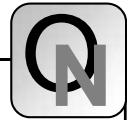
Owing to the differences in impedances between central and peripheral vessels and the moderate presence of wave reflection for healthy people, the systolic blood pressure at the aortic root is significantly lower than in the upper arm in such subjects. Diastolic and mean blood pressures do not differ significantly. 4 Different diameters and elasticities are responsible for the occurrence of these different wave impedances and the resulting differences in blood pressure. As a result of aging and pathological changes (for example, arteriosclerosis or subclinical organ damage) stiffening of vessels and therefore an increase of aSBP as well as an increased peripheral arterial resistance may occur. As a consequence of these changes, increased and premature pressure reflections emerge, which superimpose the generic pulse wave ejected by the heart earlier and more intensely. Their accumulation leads to an elevation of the aSBP and is called augmentation. The percent ratio of augmentation to the aortic pulse pressure is called AIx. The superposition may cause a pathological increase of the aSBP and subsequently an increase of the cardiovascular risk.

It has been shown that both elevated aSBP and AIx are independent predictors of mortality in patients with end-stage renal disease and coronary heart disease.

These guidelines additionally claim to provide widely suitable measuring devices for the measurement of arterial wall stiffness and its influence on aortic blood pressure. The increase of the aSBP is ad hoc not noticeable in the A. brachialis and therefore per se not to be measured by common oscillometric methods. Therefore, the aim was the validation of the novel method determining AIx and aSBP based on an oscillometric method using a common cuff (ARCSolver, Austrian Institute of Technology, Vienna, Austria) against a validated tonometric system (SphygmoCor, AtCor Medical Pty Ltd, West Ryde, Australia)).

The ARCSolver method aims to be a novel method for the determination of the aSBP and AIx based on oscillometric blood pressure measurement with a common cuff. The method is the implementation of the development described above and uses the pulse waves assessed at A. brachialis. The recordings are carried out at diastolic pressure level for approximately 10s using a conventional blood pressure cuff for adults available in two sizes (24–34 and 32–42 cm) and a high fidelity pressure sensor (MPX5050, Freescale Inc., Tempe, AZ, USA). The sensor is connected to a 12 bit A/D converter by means of an active analogue band pass filter (0 to 25 Hz)

After digitalization, the signal processing is performed using a three level algorithm. First, the single pressure waves are verified for their plausibility by testing the position of minima and the corresponding wavelengths. During the second stage, all single pressure waves are compared with each other to recognize artefacts.



Thereafter, an aortic pulse wave is generated by the means of a generalized transfer function. The idea behind a transfer function is the modification of a certain frequency range within the acquired pulse signal to get the aortic pressure wave.

Comparison with published data showed similar results. The first positive zero crossing of the fourth-order time derivative of the generated aortic pulse wave represents the desired inflection point. Finally, the coherence of the measured parameters was verified. Therefore, the inflection point of each single pulse wave was compared with the mean inflection point. The determination of aSBP and AIx was carried out in the same way as in the reference SphygmoCor.

The aim of this comparison was the analysis for clinical suitability of the ARCSolver algorithms compared with SphygmoCor, which served as a reference device because of its wide distribution and acceptance. The parameters under investigation were the aSBP and the AIx. Both are surrogates for increased cardiovascular risk caused by increased and premature arterial wave reflections. The trials showed satisfactory accordance of the two methods. Thus, the ARCSolver algorithms are suitable for the use in oscillometric cardiovascular measuring devices. This is emphasized by the fact that the measurements were taken by a representative sample of healthy volunteers and patients during clinical routine (error bandwidths and measurement procedures if applicable).

The reasons for this good accordance may be based on the fact that for the transformation to determine the aortic blood pressure, the lower frequency bands of the pulse wave are dominant. This frequency bands are very robust and stable during measurement. The mentioned dominance may also blur the effects of high-frequency impedance changes between brachial and radial artery and its influence on central pressure. The results of the analysis of the AIx comparison show sufficient accuracy. The variation values determined in our studies are in the same range as those published for SphygmoCor. The ARCSolver is based on an user-independent recording method. Considering this, the measured values of the mean difference and the s.d. show consistency.

Using M&S we were able to develop and implement new HT. Existing Technologies could be enhanced by combining different M&S techniques.

This was on one hand important for improving the HT itself, but on the other hand research showed new demands (as other and more parameters are important for physicians, which partly can only be measured indirect) that can only be satisfied with new approaches.

2 Modelling in Health Technology Assessment

Austrian health care system spends about 20 to 25 million Euros every year. The social insurances, the federal states and the federal government pay a large part (about 70%) of the costs. Because of new developments, which we described above – growing service portfolio and at the same time limited resources as well as an aging population lead to necessary decisions on supply of services. The assessment of new medical services that may or not may be paid by society – Health Technology Assessment – becomes more important every year.

Therefore the development of a comprehensible and problem-oriented assessment strategy for medical services both from a medical and economic viewpoint is necessary. Thus decision makers could better estimate costs and quality of medical services. In the long term a high level of medical service provision with optimal resource allocation will be ensured. The crucial factors for decision makers are flexibility, speed and replicability in the assessment – an ideal field of application for the application of models.

New studies show that between 4 and 8 percent of expenditures in the health care system are paid for administration, controlling, monitoring and decision support. For the small country of Austria alone this represents a market potential of (without expenditures for administration) 500 million Euros.

The application of models is most advanced in the area of development of new vaccination strategies. Vaccination is amongst the most effective prevention measures against infectious diseases. During the last years the use of vaccination has been discussed increasingly.

Each year many new vaccines are developed. Decision makers face the hard task of deciding on the reasonableness of each vaccination programme, primary with regard to cost-benefit efficiency. Comparison of competing vaccines in respect of costs and efficacy turns out to be especially difficult.



Demand of better decision foundations

Recently health care decision makers realize that for example clinical studies cannot describe the whole process from spreading of an illness in a social network to analysis of courses and economical evaluations. Medical interventions based on wrong decision foundations waste resources. Considering the background that resources are limited and the political brisance of decisions concerning health care, decision makers need rational basis of decision-making.

Systematic and quantitative evaluation of patient-relevant and economic long-term consequences is required [3, 4]. Therefore the demand for more and better evaluations rises. With the help of optimal chosen and realized decision models using valid data bases, these evaluations and their results should be presented in comprehensible ways. New price models of vendors (so-called Risk Sharing Invoicing) enhance their need. Overall the application of models strengthens the position of decision makers towards vendors of medical services.

State of the Art & methodical restrictions

Evaluation of vaccines is methodical particularly difficult. On the one hand modelling the spread of a disease needs to consider dynamic epidemiologic effects like herd-immunity, on the other hand social structures and costs must be considered appropriately. Evaluation of vaccination programs needs interdisciplinary assessment on the representation of the illness, whether the acute infectious aspect of the disease and therefore the epidemiological spread of the pathogen, which requires so-called dynamic models, or if the chronic aspect of the illness is in the foreground. Altogether it is necessary to choose suitable models and if it is required even connect several different models.

Apart from evaluations of databases and studies decision makers want progressively more systematic reviews of medical services and technologies with the help of Health Technology Assessment (HTA). HTA uses well-established and long proved methods to systematically evaluate medical services and assess the consequences of health care interventions. Independence of HTA-experts of medical vendors is essential. Recently developed HTA-principles [5] or guidelines of the German IQWiG to include Health Technology Assessment into the decision process emphasize this aspect.

Necessity of Modelling & Simulation

Combination of classical meta-analysis of clinical studies, statistical methods and HTA with a flexible choice of models and calculated scenarios leads to a modern evaluation tool for medical services.

On the European level the three-year Joint Action Project EUNetHTA started on the 1.1.2010 shows the demand. EUNetHTA standardizes methodical aspects of the evaluation of medical services and for the first time tries to include modelling and simulation sustainable into the evaluation process.

Concretely the realization of appropriate models poses some questions which could not be solved methodically in a sustained manner. On the one hand it is not clear which modelling approach is optimal for which area because the whole previously described process had to be reproduced. Even when only examining the example of the evaluation of vaccination strategies the following aspects have to be realized in the model:

- Social structures and interactions between affected people
- Modelling transmission of an infectious disease including Serotypes, Herd Immunity et al.
- Integration of statistics of given or comparable countries about occurring illnesses and complications caused by the pathogen.
- Economic evaluation of these effects including standardized values from HTA

Apparently choosing and combining the best possible modelling approaches and realizations of different implementation possibilities lead to various problems.

In the area of Health Technology Assessment only classical respectively non-dynamic modelling approaches are used nowadays. These methods include Decision Trees, Markovian Models and System Dynamics. All of them are thoroughly discussed in literature (for example System Dynamic Models [6]). These approaches often emphasize the use of data but comparison of different models rarely happens.

Regarding modelling there are far more advanced modelling approaches which often lack the connection to the complex data structures. Even simple prediction and evaluation models put interdisciplinary working research groups in front of serious problems [7].



For example just to mention the various standardized values like LYG (Live Years Gained) have to be expressed as a model result. The example of the development of a tool for evaluation of vaccination programs against pneumococci shows proposals for solutions and problems of the use of modelling and simulation in the evaluation of medical services.

Assessment of a Vaccination Strategy

In a cooperation of the independent institutions HVB (Main Association of Austrian Social Insurances), VUT (Vienna University of Technology) and dwh - simulation services the socio-economic influence of including Prevenar (PCV7) pneumococcus children vaccine into the Austrian children vaccination program was modelled and analysed [8].

Different Model Types were implemented - on one hand to match, compare and validate with given study results and on the other hand to introduce a new way of modelling of future scenarios: The models were compared to each other and to the studies and can integrate various different data types and sources to compute potential future scenarios.

This “modular” model realises the opportunity to compute different scenarios for different aspects of the vaccination with various assumptions to compare results and stability of results for each module separately. Effects of changes – in population structure or size, epidemiological assumptions like serotype changes or herd immunity, new data for diseases or costs can be implemented to compute the dynamic future scenarios and to compute the future economic data for different treatments.

White Box Modelling guarantees not only the computed results but also the possibility of improving the knowledge about the model system and to re-evaluate the assumptions after every scenario. White Box Modelling offers the possibility to get additional information which data and in which way this data is needed for future studies.

Analysis of the socio-economic influence of the introduction of the vaccination

Using the general available vaccination distribution assumptions in Austria and the saved data of regulatory authorities, information concerning pop data and costs of hospitalization for pneumococcal disease one can yield detailed estimations regarding the total costs: in the vaccination setup time the annual costs increase to approximately 14.2 Mio. € and then de-

crease due to the increasing number of avoidable cases per year to 12 Mio. €. This amount remains constant in the long run.

In spite of this deterrent high amount it is important to point out the accessible positive effects of the reduced burden of the disease: While in the first year after the introduction of the vaccination only about 15 critical pneumococcal illnesses can be avoided, after the first 10 years a positive effect of approximately 125 avoided meningitis-, sepsis-, and pneumococcal pneumonia cases can be expected. Especially, the possibility to prevent about 10 cases of meningitis a year has to be focused on.

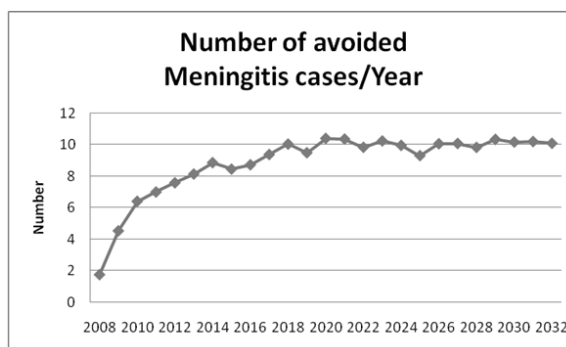


Figure 3 Number of avoided Meningitis Cases p.Y.

Another measure for the efficacy of vaccination programs is given by the abstract value CLYG, which are the costs per life-year gained. For the actually evaluated procedure the CLYG results in about 205.000€/LYG in the steady state.

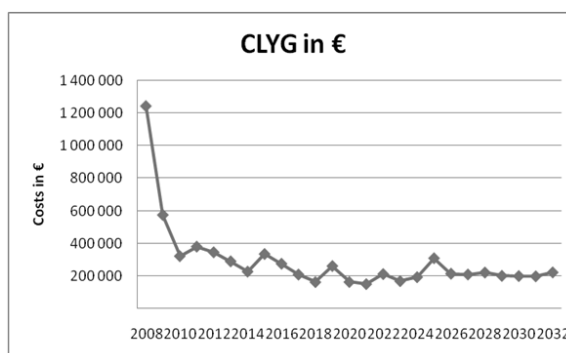


Figure 4 Costs per Life Year Gained in Euro

Combining the Methods for international comparable results

The results of this project are based on literature research, application of classical methods and on newly developed complex mathematical models,

which are calculated for the first time for the spread of pneumococcal bacteria and show the influence of population structures, social behaviour of individual persons and epidemiological detailed knowledge in a dynamical model. For epidemiological purposes the innovations of this simulation model are the consideration of the dynamical structures of the population for the following years and, especially, the research concerning the effects of herd-immunity, which are positive effects for the unvaccinated population based on the decreased number of carriers due to the vaccination, and the serotype-shift, which refers to the influence of the changing selection-impact on competing pneumococcal strains due to the vaccination.

To yield international comparable results and to classify possibilities and problems the first step was the implementation of the classical approach. Afterwards, assimilable dynamical methods were realized and modularly extended by further influencing factors. Other than in classical static methods the parameters for herd-immunity are not given but are modelled implicitly by the model structure and the possibility to comprise real social behaviour and, thus, age-dependent contact between individuals including the possible risk of infection. Thereby, it is ensured not to depend on abstract estimators, which are based on not evaluable assumptions instead of studies with persons due to the long action time.

Features

Because of the detailed highly parametrisable and objective model structure vaccines can be compared (which is most times not possible in clinical studies) in the model and different vaccination strategies and scenarios can be tested. Furthermore, the mapping of individual abstract persons enables an extendable implementation of social behaviour as well as the analysis of influences concerning demographical changes of the next decades. Immigration and emigration are already accounted for in the base model. Scenarios for vaccinations strategies can be computed.

Another important factor for the supplier and the epidemiological analysis which can only be analysed using dynamical models is the vaccination setup phase. Other than in any vaccination for the populace for introduction of a vaccination in the children immunisation schedule the complete herd-immunity-effect and the maximal immunisation protections appears with the aging of the children- in this case it lasts about ten years.

The present simulation model provides an objective independent support for decision makers due to its open comprehensible structure (White Box Modelling) and the broad range of implemented dynamical non-linear effects like Serotype Changes and Herd immunity. Because of the modular build up demography, epidemiology and economical key decision values can be analysed separately and additional understanding of the problem can be supported.

Summary of the benefits of this way of problem modelling and evaluation

Long term population dynamics: Long term effects like carrier behavior and strategies can be focused on in detail with a high resolution timescale.

Start-up phase simulation: In contrast with classical Markovian or Decision Tree based models, dynamic modelling represents also the start up phase of the vaccination program. This is of main interest for decision makers, because in this timespan full vaccination cost occur, but on the other hand not the ideal benefits can be reached.

Herd immunity effects are model generated and time dependent: Herd immunity is generated during simulation time and is based on the social interaction of the modelled agents. Using a sophisticated model for carrier and an extra part for illnesses guarantees the capability.

Selection pressure is model generated: As mentioned for herd immunity, this dynamic nonlinear effect is also generated during simulation time and uses the advanced simulation technique and its flexibility.

Different scenarios: Due to well defined parameter ports, different scenarios can be calculated easily without changing model structures. Furthermore simulation runs for other countries can be implemented easily.

Long term prognosis: Referring to population dynamics and other external long term effects parameter gateways are implemented in the model and thereby, flexible analysis timespans can be calculated.

Comparison of different vaccines: Because of modelling the carrier rates in detail, the influence of different vaccines (serotype coverage, vaccine efficiency, ...) can be evaluated. Beyond also mixing of different vaccination strategies and the global influence can be represented.



Adaptivity for different countries: Not only the poor parameter changes for foreign countries can be simulated, but also different assumption regarding social system structures.

White Box Modelling: One of the main benefits is that besides a complex high quality model used, the parametrization and used structure are dealing only with intuitive data and thereby the model can be used in interdisciplinary working groups.

In addition to the mentioned benefits of the implemented approach mainly fundamental open questions come up that need to be discussed in the following years.

For the evaluation of medical services, standardization of the used models is absolutely necessary. To that end consensus regarding the process of selection and the valid combination of appropriate modelling techniques have to be found in the scientific community. The European-wide acceptance of further development of models in the field of HTA in context of the EUnetHTA highly depends on this issue. Therefore a process has to commence that aims the comparability of different model approaches eventually.

The need for standardization becomes clear through consideration of the impact of such an assessment. Considering the economic impact the model described above leads to decision on cost in the range of 15 million Euros in the case of the use by decision-makers [9].

But besides the financial aspects the decision on the use of medical services further plays an important role in the aspect of the future question of coexistence in our society: "Who has got the right to receive which performances?" One's health is probably one of the most central aspects of personal life and the gap between newly developed facilities and their "no longer be financed"-aspect has the potential to lead to enormous social conflicts.

The model approaches in the field of health economics, HTA and Evidence Based Medicine are currently mostly data-driven approaches. In contrast method-driven approaches from the field of mathematics, computer science and physics cause a clash with the methods that are considered to be standard. The above-described method to compare models is only a very first small step of the necessary convergence of those different worlds.

3 Conclusion

HT touches some of the most important human needs: To keep a good health as long as possible, to anticipate future health problems or to cure illness. M&S helps HT to improve its "portfolio" in many ways. M&S extends the possibilities for example in computing values, which are not or only very complicate to measure. Or M&S helps comparing vaccines which were not tested against each other.

It is clear that still modelling systems and simulating scenarios is always only the second best solution. It is always some kind of placeholder, until the real tests can be made or the real data is available. But until that time it is simply the „best“ solution, and this shows that it is important to face the problems, which are raised by new and advanced modelling technologies.

New challenges for M&S can only be solved by using new approaches. In some areas we have reached the boundaries of the state of the art methods. The tasks described above show that new structural information or new data lead to new structures of the model and so there may be need for new modelling techniques to cover this demand. In progressing technologies like HT you never can give a final conclusion which modelling technique is best.

To compare "state of the art" M&S techniques and other approaches standards have to be developed. These strategies are followed by various scientific clusters and international efforts are made. Still it is to swim against the stream, as provider of modelling concepts and even more software developers have no interest to change a "winning team" – even if the game has changed.

New M&S strategies – and most notably the extension of the application areas in HT – induce an even higher responsibility for validation of the implemented models and simulations. Comparison of different models might be a promising strategy to cope with this problem.

Finally, let us point to a more philosophical aspect and to the dependency and the difference using M&S for the areas mentioned in the title. Only development of new technologies - enabled also through M&S - leads to the need of Assessment. For which – of course – M&S is very useful. So solution of problems induce new problems that are even more complex than the previously solved one. But it even gets worse.

Using M&S for development we expect the solution of a problem, otherwise the model is discarded. Not so using M&S for assessment. Here we must accept that the "non-decidability" of topics has to be accepted under certain circumstances. However neither the demand of the decision is waived nor is it compulsory to mistrust the quality of the model.

The traditional "Tertium non Datur" (Law of the Excluded Middle) does simply not apply. The first who introduced this well-known point against the universality of the law of excluded middle was already Aristotle [10]. He mentioned that the principle of the excluded middle does not apply to statements about the future (like the phrase "Tomorrow will be a sea battle") because the progress of the future is still open. And even if we try hard predicting the future using M&S, sometimes even modern life is like a sea battle. Why?

Using M&S we try to predict the future, but we do not succeed always. But decision makers have to decide – if they are not able to do this - even based on the best models and future forecasts - the discontent of the people might increase. In former times this led to the expulsion or even loss of life of decision makers, today fortunately probably only to the loss of personal power and influence.

Only one point can comfort us: Over time, the additional benefit of system knowledge and data, exclusion of errors and new evidence might ultimately lead to the decidability of the question [11]

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Corresponding author: Niki Popper
 dwh Simulation Services, Neustiftgasse 57-59
 1070 Vienna, Austria
 niki.popper@dwh.at

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Applying Hybrid Tokens to the Estimation of the Therapeutic Outcome of Psychiatric Treatments

K. Dammasch, B. Rauch-Gebbensleben, G. Horton, Otto von Guericke Univ. Magdeburg, Germany

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In mental health care clinical pathways determining the form of therapy that has to be administered are highly controversial and have not been officially established. However, surveys indicate that different treatments of the same mental disease can lead to different therapeutic outcomes. This has a direct influence on the number of future patients of the health care providers and thus on the system's input and output including treatment costs and quality of care.

In this paper we use computer simulation to examine the outcome of different treatments for mental disorders in a psychiatric hospital. The compliance of the patient, that is the motivation for taking part in the treatment, is crucial for the success of a therapy. In case of a discontinuation the probability of the mental disturbances occurring again is higher than in the case of a successful completion. As the in-patients' parameter compliance is changing continuously during the treatment we need a simulation technique allowing continuous attributes of entities in a discrete-event-driven system. We use the introduced concept of hybrid tokens in stochastic Petri nets for modelling the treated in-patients with both discretely and continuously changing attributes. For that purpose, a sufficient mathematical description of the in-patients' mental parameters and their development over time has to be derived. In doing so, a comprehensive statistical analysis has to be performed. The provision system and the resulting Petri net are comparatively simple. Instead, a high number of tokens that has to be created and the computation of their attributes during the simulation run are the challenges that we are facing. After building the simulation model of the therapy processes we were able to run experiments by variegating characteristics and treatments of the patients and observe the system's output.

We believe that the implemented model can provide a decision support for physicians and therapists. It will enable the estimation of the therapeutic outcome and thus the choice of the most promising treatment according to the patient's mental disturbances.

Introduction

The method of computer simulation finds use in a large number of application fields, but spread and acceptance are still very different. In the majority of cases, simulation is applied to rather technically oriented problems than non-technical application fields involving soft and qualitative aspects. This is often the case in the area of medicine and health care. Usually, difficulties do not occur when logistic chains such as patient flow or bed occupancy in a hospital are modelled, but they arise when processes where human parameters and behaviour are to be considered. This can especially be observed in the field of mental health care as mental disorders are very complex and difficult to examine. Psychological parameters can play a decisive role in an according model.

Nevertheless, computer-assisted planning is of great interest for decision makers and planners of psychiatric services.

The pressure to control health care spending requires a reliable method for improving the efficiency of a health care system and its quality. Computer simulation can be used to analyse and optimise existing structures and processes of a provision system [8] as well as evaluate effects of changes in parameters or processes. For each variation investment and treatment costs can be computed and compared. [1]

Furthermore, prognoses can be made about the future workload of health care providers depending on the expected number of patients and their different medical conditions. In every case the quality of care is of particular interest and is to be improved or, at least, has to be maintained independently of possible actions taken.

One example question is the estimation of the influence of a particular form of therapy on the therapeutic outcome.

In Germany somatic treatment follows strict clinical pathways determining the form of therapy that has to be administered. In mental health care clinical pathways are highly controversial and have not been officially established. The chosen therapy is within the sole discretion of the psychiatrist or psychotherapist and depends, for example, on the education of the attending physician or the focus and specialisation of the medical facility. However, surveys indicate that different treatments of the same disease can lead to different therapeutic outcomes. [6] This has an impact on the health care system including the number of patients and with it the workload of health care providers and overall costs.

Therefore, we would like to use the method of computer simulation to estimate the influence of different treatments of in-patients with mental disorders in a psychiatric hospital. This study requires a detailed model of the treated patients as the compliance, that is the motivation of the patient for taking part in the treatment, is crucial for the success of a therapy.

Each patient shows a different compliance to different kinds of treatments, based on parameters such as motivation or mood. As these parameters are changing continuously during the treatment we need a simulation technique allowing continuous attributes of entities in a discrete-event-driven system. For that reason we would like to apply the introduced concept of hybrid tokens in stochastic Petri nets to model the treated in-patients with both discretely and continuously changing attributes.

We believe a model like this might provide a decision support for physicians and therapists. It might enable the estimation of the therapeutic outcome and thus the choice of the most promising therapy according to the patient's mental disturbances. The collaboration with the holding company of a group of German psychiatric hospitals enables us to analyse the processes of psychiatric therapies in stationary care and to collect and interpret the necessary data for the simulation model.

In Section 1 of the paper we describe the course of psychiatric treatments as they could be observed in one of the cooperating hospitals. After a brief introduction on Petri nets, Section 2 explains the basic principles of hybrid tokens. Afterwards the derived simulation model and the collected input data and its analysis are described. It is followed by details on the implementation.

In Section 4 we describe several simulation runs for calibrating the model and finally present simulation results. The paper closes with an appraisal of the results.

1 Psychiatric treatments

1.1 Treatment of mental disorders in Germany

The treatment of mentally ill people can be carried out in many different ways depending on the kind and seriousness of the disturbances. Possible are ambulant treatments in out-patient departments and psychiatric or psychotherapeutic practices. In day hospitals patients stay for the day, availing different forms of therapy and are allowed to go home for the night. People with serious mental disturbances requiring a stationary treatment are admitted to hospitals. Reasons may be the need for a supervised drug therapy or if they endanger themselves or other people.

After admission, diagnoses are proposed including a leading diagnosis and, if necessary, one or more secondary diagnoses covering comorbidity. According to these diagnoses and the condition of the patient different treatments are possible. In a psychiatric hospital these include the prescription of drugs such as antidepressant or mood stabilizers and setting up a psychotherapeutic treatment. Possible treatments for addictive disorders are among others psychoanalysis, cognitive behavioural therapy or interpersonal therapy in individual and group sessions [6].

One important advantage of examining only hospital care is that the in-patients are under permanent medical observation. By contrast, during an ambulant treatment there are different happenings possible having an influence on the therapeutic outcome but cannot be observed and measured. Furthermore, the data acquisition and management in hospitals is usually clearly organised and is subject to certain standards.

Due to the complexity of mental disorders and the varying psychological conditions of patients we chose to focus on addictive disorders where cause and effect are slightly clearer and better explored. The group of addictive disorders covers among others the abuse of alcohol and tobacco as well as opioids or cocaine, whereas alcoholism is the most prevalent disorder. There a relapse is often associated with an acute withdrawal syndrome forcing the patient to go back into a stationary care where the return is recorded.

Other relapses, a depression relapse for example, cannot be diagnosed that easily as symptoms are usually not immediately visible or acute. The patient can also choose an ambulant type of care instead of being readmitted and thus does not appear in the data records of the hospital.

1.2 Influences on the Therapeutic Outcome

At the beginning of the treatment, physician and patient agree upon several therapy goals. Additionally, the patient's mental and physical state is rated by the physician on a defined numeric scale. During the discharge interview the current condition of the patient is compared to this numeric value and the achieving of the defined goals is evaluated. This results in the therapeutic outcome and is always only a subjective impression both of physician and in-patient.

In opposition to somatic medicine it is not possible to gain ambiguous, measurable and objective data and the actual outcome of a treatment can have diversified shapes. Especially difficult is the review of the therapy goals as it has a qualitative non-numeric result. For that reason, we simplify the therapeutic outcome being either the successful completion or the discontinuation of the treatment. This definition follows the idea of the remission being a marker of a patient's wellness. [5]

Besides different forms of therapy, there are additional factors influencing the therapeutic outcome. The most important one is the so-called compliance. It describes the motivation of the patient for taking an active part in the therapy and complying with the instructions of the medical personnel. This parameter plays a decisive role in psychiatric treatments. If the in-patient is not compliant the probability of discontinuing the therapy and leaving the psychiatric facility is high.

The level of compliance at the beginning of the therapy varies from patient to patient and changes continuously during the course of the treatment while different forms of therapy can cause different development courses. [3] The change can be completely independent of occurring events, although some can have an effect, for example happenings in therapy sessions or even the visit of relatives during the hospital stay. Additionally, the compliance depends on further mental attributes that may themselves have a continuous dynamic.

As a result, all these parameters and their discrete or continuous change over time have eventually an impact on the therapeutic outcome.

2 Modelling approach

2.1 Coloured Stochastic Petri Nets

Stochastic Petri nets are a common paradigm for modelling discrete-event systems [9] where the system state changes discretely at countable points in time. These points are determined by the occurrence of discrete events that may change the state of the approximated system. This state is described by all variables and attributes required for giving a complete image of the system at a particular time relative to the objectives of a simulation study. The time when each type of event will occur next has to be stored in an event list, called future event list. The simulation run is continued as long as there are scheduled events in the list.

In Petri nets the complete model is represented as a graph consisting of places (states) and transitions (state changes due to occurring events) that are connected by directed arcs. The places of the net can contain any number of mobile elements of the system, referred to as tokens. These tokens are moved from place to place by the "firing" of the transition representing an event occurring in the system. So-called immediate transitions fire instantaneously when becoming enabled, whereas timed transitions fire with a certain time delay.

Coloured stochastic Petri nets extend the concept by adding attributes to the tokens. [4] The firing of a transition not only changes the distribution of tokens but can also modify the attributes of the tokens. With coloured Petri nets, discrete-event systems can be modelled containing distinguishable mobile entities with specified attributes.

The most important advantage of Petri nets is the graphical representation that gives a clear and intuitive overview of the system. During the simulation run, the user is able to track the movement of tokens through the system. The whole definition of the system is revealed without hiding information or functionality. Furthermore, the net is easily extended by adding places and transitions – even for a user without expertise in modelling techniques. This is of interest to us, since the model we are developing is to be used by medical, rather than modelling, experts.

For that reason we decided to model the process of a psychiatric treatment with the aid of coloured stochastic Petri nets. However, the involved tokens, i.e. patients in the medical facility, are characterised not only by discrete but continuously changing parameters. Their development course is crucial for the output of the system. Therefore, we also had to enable the modelling of continuous token attributes in Petri nets.

2.2 Hybrid tokens

For modelling a discrete-event system with mobile entities described by hybrid attributes we introduced in [2] the concept of hybrid tokens in coloured stochastic Petri nets. As shown in Figure 1 the new token definition includes not only discrete but also continuous token attributes.

In addition, the new defined token contains functions describing the continuous change of these attributes, typically, implemented by differential equations describing the rate of change over time.

Therefore, a hybrid token has its own attribute dynamics which are independent of system events. Regarding that the continuous attributes are not to be precomputed, the integration steps have to be included in the global event list for proceeding the simulation run. That way, the introduced approach combines the idea of hybrid simulation with still distinguishable entities moving around in the system.

Considering the hybrid token extended by continuous attributes as well as dynamics, there are several interactions possible between different token attributes. They are no longer only influenced by events but by changing values of other token attributes. The following interdependencies are possible:

- A change in the value of either discrete or continuous attributes may cause a change in the value of a continuous attribute.
- A change in the value of either discrete or continuous attributes may cause the relationship governing a continuous attribute to change at a particular time.
- A continuous attribute achieving a threshold value may cause a change in the value of another continuous attribute.
- A continuous attribute achieving a threshold value may cause the relationship governing another continuous attribute to change at a particular time.

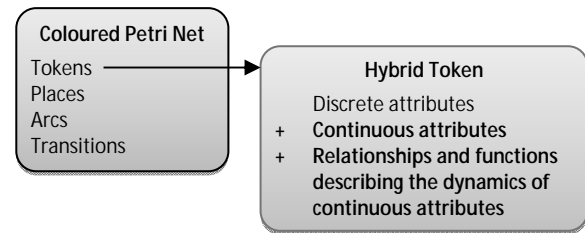


Figure 1. Components of coloured stochastic Petri net with hybrid tokens

All other components of the Petri net remain unmodified but their functionality has to take the attribute dynamics of the hybrid token into account. Transitions can be enabled either by values of discrete or continuous token attributes and in the same manner change all attribute values as well as attribute dynamics when they fire. There are also several types of possible interactions between system events and hybrid tokens:

- A discrete event may cause a discrete change in the values of discrete or continuous token attributes.
- A discrete event may cause the relationship governing a continuous token attribute to change at a particular time.
- A continuous token attribute achieving a threshold value may cause a discrete event to occur or to be scheduled.

The modelling approach of hybrid tokens adds attribute dynamics to the Petri net but keeps them separated from already existing dynamics due to the occurrence of system events. The graphical representation of the system is kept clear and easy to read.

3 The model

3.1 The derived Petri Net and hybrid tokens

Based upon the identified processes of the provision system briefly described in Section 2 the stochastic Petri net is small consisting of only a few places and transitions shown in Figure 2. Depending on the medical review the patient is admitted and after proposing the diagnoses, different treatments are administered. At every point in time it is possible that the patient's compliance falls below a certain threshold causing the patient to discontinue the therapy. Otherwise the patient leaves the facility after completing all treatments.

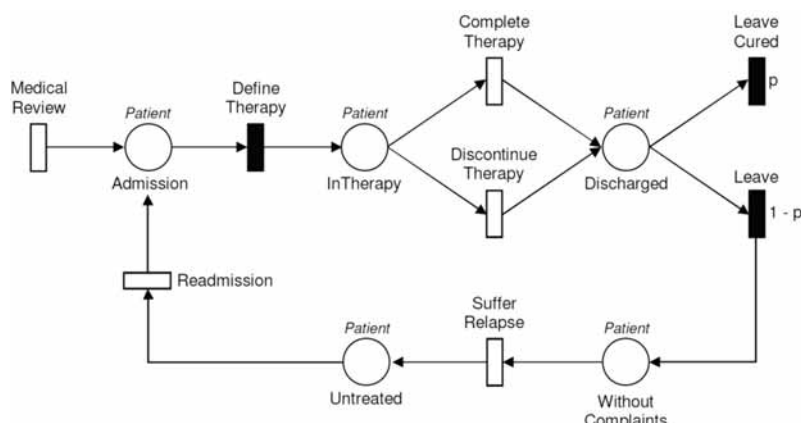


Figure 2. Petri net of health care service in psychiatric hospital

With some probability the mental disturbances occur again after a certain amount of time and the patient is readmitted. In case of a previous discontinuation this probability is higher.

All places of the net can contain tokens of the type *Patient*. A patient in this system is characterised by the following attributes:

- *nDiagnosis*: integer (discrete)
- *nCompliance*: double (continuous)
- *nThreshold*: double (discrete)
- *bDiscontinue*: boolean (discrete)

The variable *nDiagnosis* stores the leading diagnosis determining which therapies are to be administered. The previously mentioned compliance is modelled as continuous token attribute *nCompliance*, whose initial value is randomly distributed and, additionally, depends on *nDiagnosis* as different diseases and comorbidities result in higher or lower motivation.

The parameter *nThreshold* specifies the lowest value *nCompliance* is allowed to reach before the in-patient will discontinue the therapy. The logical attribute *bDiscontinue* marks this state and is set to TRUE whenever this case occurs.

| Substance | Rate of leading diagnosis | Rate of secondary diagnosis |
|----------------------|---------------------------|-----------------------------|
| Alcohol | 0.088 | 0.755 |
| Opioids | 0.011 | 0.037 |
| Cannabinoids | 0 | 0.037 |
| Other/multiple abuse | 0 | 0.072 |

Table 1. Frequencies of diagnoses of different addictive disorders.

For being able to build a computer model from this conceptual model, the according data for the described variables has to be collected and analysed. The mathematical relationships are derived from the data record of the psychiatric hospital.

3.2 Input and output data

The cooperating psychiatric hospital is a clinic for psychiatry and psychotherapy and provides psychiatric care for children, adolescents and adults. The set contains all patient records from November

2005 to October 2008. During that time 432 in-patients were treated. According to the question we would like to answer with the simulation and the process chain we have to analyse frequencies and mathematical relationships between several parameters.

Diagnoses. First, the number of in-patients with addictive disorders was examined: In 242 cases an addiction was set as leading or secondary diagnosis or both.

Table 1 shows frequencies of the abuse of the different psychotropic substances. It is noticeable that alcoholism is the predominant disorder but is usually set as secondary diagnosis.

In 79 percent of those cases the leading diagnosis is stated as personality and behavioural disorder as the abnormal consume of alcohol causes pathological changes in personality and behaviour.

Initial Compliance. Table 2 shows the initial motivation of the patient for taking part in the treatment. In the hospital's questionnaire this motivation can take only 5 qualitative values. For purposes of computation we declare the numeric equivalent as shown in the second column of Table 2. We let the given motivation be the mentioned parameter compliance.

Data analyses show that the motivation for the therapy of addictive disorders is exceptional high. One explanation might be that 92 percent of the patients came on their own free will and were not referred by another institution.

Furthermore, it has to be taken into account, that there is a certain inhibition threshold of telling the physician about being less or not motivated. Second the table shows the number of therapy discontinuations for each stated motivation. In the available data record the overall discontinuation rate is 0.3306. Thus nearly one third of 242 in-patients with an addictive disorder left the hospital before the therapy was completed.

As expected the rate is much higher if the patient is less motivated: About two thirds of the in-patients being less motivated discontinued the therapy.

Therapy forms. Finally, we analysed the combination of different treatments – resulting in the therapy form – and the according number of discontinued and completed therapies. Due to the high variety of possible treatments the combinations are manifold. Therefore, we only keep treatment combinations that were administered in at least 3 cases and grouped similar combinations for comparison. Some of the results are shown in extracts in Table 3.

For reasons of data security and simplification the treatments are named alphabetically and will mostly not be explained. In cases of D and E the appended number signifies either individual session (1) or group sessions (2). Treatments are among others behaviour or analytical orientated therapies as well as psychotherapeutic relaxation techniques and counselling interviews.

Additionally, somatic comorbidities can be treated (G) and patients can be medicated with psychotropic drugs (H).

| Motivation | Numeric equivalent | Rate of cases | Rate of discontinuation |
|----------------|--------------------|---------------|-------------------------|
| Very Motivated | 4 | 0.1529 | 0.2703 |
| Well Motivated | 3 | 0.6901 | 0.3353 |
| Motivated | 2 | 0.1281 | 0.3226 |
| Less Motivated | 1 | 0.0248 | 0.6667 |
| Not Motivated | 0 | 0 | 0 |

Table 2. Motivation at the beginning of the treatment and rate of discontinuation

| Motivation | Lower bound | Upper bound |
|----------------|-------------|-------------|
| Very Motivated | 3.0001 | 4.0000 |
| Well Motivated | 2.0001 | 3.0000 |
| Motivated | 1.0001 | 2.0000 |
| Less Motivated | 0.0001 | 1.0000 |
| Not Motivated | 0 | 0 |

Table 4. Numeric boundaries for non-numeric motivation values.

| The rapy | A | B | C | D 1 | D 2 | E 1 | E 2 | F | G | H | Cases | Discontinuation rate |
|----------|---|---|---|-----|-----|-----|-----|---|---|---|-------|----------------------|
| 1 | | • | | | • | | | | | • | 13 | 0.3846 |
| 2 | | • | | | • | | | | | • | 49 | 0.2857 |
| 3 | | • | | | | | • | | | • | 10 | 0.1000 |
| 4 | | • | | | | | • | | • | • | 28 | 0.0714 |
| 5 | | • | | | | • | • | | | • | 5 | 0.0000 |
| 6 | • | • | | • | • | | | | | • | 3 | 0.6667 |
| 7 | • | • | | • | | | | | | • | 3 | 0.3333 |
| 8 | • | • | | • | • | | | • | | | 17 | 0.5294 |
| 9 | • | • | • | • | • | | | | | • | 3 | 0.6667 |
| 10 | • | • | • | • | • | | | • | | | 5 | 0.4000 |

Table 3. Number of different administered therapy forms and rates of discontinuation

As the small number of cases for each therapy form shows is that the results can only provide an indication on the actual relationships but are not completely statistically reliable.

Therapies 1 to 5 show three different things: First, the additional treatment of somatic comorbidities (G) decreases the number of discontinuations as the rates are lower in therapy 2 and 4 compared to 1 and 3. Due to the improved state of health it is likely that the compliance of a patient increases. A further positive impact besides the mere treatment might have the additional attention that the patient appreciates.

Second, treatment E2 seems to be more successful than treatment D2 as the rates are lower in therapy 3 and 4 compared to 1 and 2. Third, for treatment E it might have a positive effect if the patient takes part in additional individual sessions. The last observation might also be shown by the differences between therapy 6 and 7 where additional group sessions seems to have no further positive effect.

Since nearly all in-patients in the hospital took part in individual sessions we were not able to retrieve the necessary mathematical relationships. But the positive effect on the remission of symptoms in individual sessions in comparison to group sessions could be observed in different surveys. [7]

Therapies 6, 8, 9 and 10 imply that treatment F has a larger positive effect on the patients' compliance than treatment H (psychotropic drugs). The patients' initial motivation cannot explain the result directly. For example, the mean motivation at the beginning of therapy 1 is about 2.8980 and at the beginning of therapy 2 about 2.8462. Thus the therapeutic outcome of therapy 1 is lower than the outcome of therapy 2 although the patients were better motivated.

3.3 Details of the implementation

This section describes how the derived statistical information is implemented in the simulation model and computed during the simulation run.

Initialisation of parameters. The discrete token attribute $nDiagnosis$ is distributed according to the frequencies listed in Table 1 and set to a discrete integer value between 1 and 4. The initial value of $nCompliance$ is set by random according to the frequencies of the motivation of the in-patients at the beginning of the therapy. Further analyses showed that there are no significant differences in the initial motivation between the four groups of addictive disorders listed above.

Therefore, we can handle the initial value for each diagnosis equally. For getting a certain variety between patients with the same motivation, the values are uniformly distributed within the boundaries shown in Table 4. The according threshold for the patients' minimal compliance is uniformly distributed between 0.0 and 0.1, because even a not motivated patient will not immediately leave the hospital.

Integration method. The most expensive routine is the computation of the differential equation governing the behaviour of the continuous token attribute over time. In our previous work we simply set a constant step size prior to the simulation run determining constant intervals at which the current values of continuous attributes are to be computed – for all tokens at the same time. After updating the value it is immediately checked if one of the termination conditions is fulfilled, in our example if $nCompliance$ is below $nThreshold$.

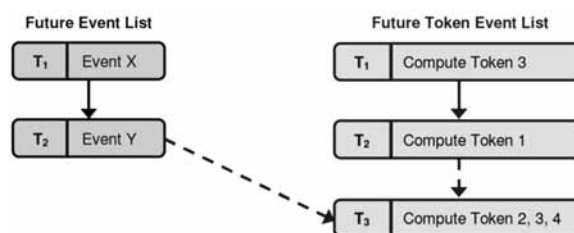


Figure 3. Structure of future event list and future token event list and connection between them

This approach was sufficient for developing the concept of hybrid tokens while working with fictional data, but it results in a large integration error.

As we are now interested in concrete simulation output we implemented an iterative integration method that chooses the largest possible step size with respect to the error and the termination condition. The method decreases the step size iteratively until the error of the computed compliance value is below a certain limit of tolerance. For our purpose the integration procedure is extended by a second step: If the error is acceptable at step size h the method checks if the termination condition would be fulfilled by the value of the continuous attribute, i.e. if $nCompliance$ is smaller than $nThreshold$. If that is not the case, the value of the attribute can be updated and the point in time when it has to be computed next is determined by the current simulation time plus the step size.

For that purpose it is helpful to store the point in time when each token has to be updated in a separate list structured similarly to the future event list of the simulator. We call this list the future token event list illustrated in Figure 3. Due to the previously described interactions between different token attributes it is necessary to update all other dependent attributes after computing the new value of the continuous one.

As the occurrence of discrete events in the system may cause a change in the token's attributes or relationships it is necessary to start the computation of the continuous attribute of the affected tokens at the time of the event. Therefore, an additional event has to be scheduled in the future token event list, illustrated in Figure 3 with Event Y causing a third event to be scheduled in the token list. Time T_2 of Event Y corresponds to time T_3 of the token event. Summarised, the future token event list stores points in time when the next value of a continuous attribute has to be computed. The simulation run is continued as long as there are scheduled events in either the future event list or the future token event list.

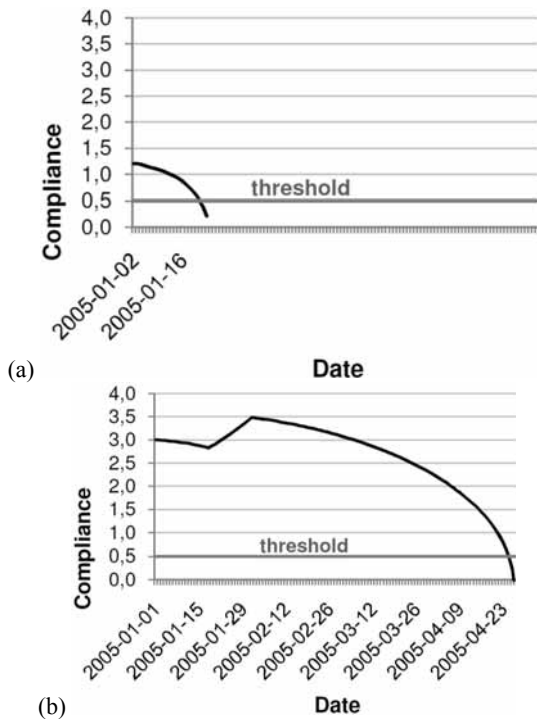


Figure 4. Example course of the compliance for two different tokens.

4 Simulation experiments

4.1 Deriving the development of the compliance over time

As the change of the compliance of the patient is regarded as continuous we have to find a suitable differential equation for the rate of change in time of the compliance. Considering the high number of patients not completing their therapy the compliance is expected to decrease fast during the therapy depending on different forms of therapy.

As we were not able to derive the differential equation directly from the data set we let it be simple (1) modelling a steady increase or decrease and run several simulations testing different variations and coefficients estimated from the data set. Thus the model is successively improved by calibration.

$$\frac{dx}{dt} = c \frac{t}{x} \quad (1)$$

Although it is more likely that the compliance is a complex variable depending among others on the mood of the patient we are only able to consider the given motivation of the in-patients as compliance without being influenced by other continuous parameters as they are not available.

Different behaviours of the compliance. At the beginning of the therapy the parameter compliance decreases fast as withdrawal symptoms lower the mood and thus the motivation of a patient. If the initial motivation for taking part in a therapy was low the probability that the value falls below the defined threshold is high.

Therefore, patients with low motivation discontinuing the therapy stay fewer days in hospital than leaving patients with a higher motivation. The data set slightly suggests this correlation. For that reason, the coefficient c in the differential equation is set to $-6E^{-03}$ following the information that was derived from the samples. Usually, after three days the worst withdrawal symptoms are gone and between seven to ten days most of the symptoms disappear. This has a positive effect on the sense of wellbeing as somatic symptoms cease weakening the patient. Therefore, we set c to $-3E^{-03}$ and after another 5 days to $-2E^{-03}$. If the motivation is below 1.0 after that, i.e. the patient is less motivated, we leave the equation and coefficient unmodified. As a result the value will decrease further and, eventually, fall below the threshold. If the patient is still motivated after the withdrawal we assign the coefficient c a positive value, for example $6E^{-03}$ modelling a fast increase in the motivation.

We assume that the compliance starts to decrease slowly after the first elevated mood as long as the therapy continues. The negative coefficient c is set depending on the administered treatment combination, described in Section 3.2. Again, we performed simulation runs for retrieving suitable values for c . Figure 4 shows two examples for possible developments of the compliance over time. The value for the first token was below 1 after eight days of withdrawal. Therefore, the value continues to decrease. The compliance of the second token was still high and the coefficient was set to a positive value causing an increase. After another week c is set to $-1E^{-03}$ and the compliance starts to decrease again.

The third possible course of compliance is equal to the course of the second token in Figure 4. But at a certain point in time the therapy is completed successfully while compliance is still above the threshold. The planned length of the hospital stay is, as derived from the data set, normally distributed with different parameters depending on the form of therapy.

| The rapy | A | B | C | D 1 | D 2 | E 1 | E 2 | F | G | H | Cases | Discon- tinuation rate |
|-------------|---|---|---|--------|--------|--------|--------|---|---|---|-------|------------------------------|
| 1 | | • | | | • | | | | ○ | • | 13 | 0.2942 |
| 2 | | • | | | • | | | | • | • | 49 | 0.2857 |
| 3 | | • | | | | | • | | ○ | • | 10 | 0.0693 |
| 4 | | • | | | | | • | | • | • | 28 | 0.0714 |

Table 5. Rate of discontinuation with changed forms of therapy

Validation. Data resulting from the system's behaviour can be used for checking the simulation output and comparing it to observed data. For our purpose, the ratio of completed and discontinued therapies is of interest as well as the length of the hospital stay in case of discontinuation. Unfortunately, we only have a few data samples as the date when the patient left is not always documented in the available data set.

After calibration of the model we chose to compute a scenario of one year length and only five replications, considering the immense computational effort caused by the integration for each token in the model. We then compared the computed rates of completed and discontinued therapies with the observed rates. Although the widths of the confidence intervals are expectedly large the computed rates approximate the observed values.

Also the length of stay in case of discontinuation is approximated. But as we used some parts of the data for calibrating the model this result only reveals that there are no influences in the model having an unintended effect on the output.

For a complete validation we would need an additional independent set of samples. Another way of testing the simulation output could be to compare the cases of discontinuation from the experiment with those patients being readmitted to the hospital. But due to the sample size covering a too short time period for that purpose such a comparison was not possible as only a few patients had relapses within four years.

4.2 Example scenario

As mentioned above, we are not able to make reliable statements on the basis of the available data set and its limitations. But since we intend to test the hybrid token approach we performed several simulation experiments. One is presented in this section.

The performed analysis of the available data implies that the treatment of somatic comorbidities has a positive effect on the therapeutic outcome, presumably due to the patient's improved state of health. In a simulation experiment we now increase the number of in-patients who are administered a somatic treatment. We did this for those cases where treatment combinations are equal except for the somatic treatment. Using the examples from Table 3, we added a somatic treatment (G) to therapy forms number 1 and 3. It results in a slower decrease of the compliance caused by the different coefficients c and has a positive effect on the number of discontinuations as shown in Table 5.

Further scenarios might be increasing the number of patients being administered therapy form F instead of additional pharmaceutical treatments. In order to do that, it has to be clarified under which circumstances pharmaceuticals have to be used, for example if patients endanger themselves. According to past surveys a possible scenario will be examining the differences between individual and group therapies as soon as the according data will be available.

5 Conclusions

In this paper we described the efforts made to apply the previously introduced concept of hybrid tokens in coloured stochastic Petri nets to the modelling of in-patients in psychiatric treatments. For that purpose, we not only had to improve the methods for the computation of the tokens' continuous attributes, but also had to collect and analyse the according data describing the system, i.e. the in-patients' characteristics and administered treatments. After building a simulation model of the therapy processes we were able to run different simulation experiments by varying characteristics and treatments and observe the system's output. As we are now using an iterative integration method the computational expense is increased whereas the error of the method is decreased.

Caused by the limited sample data we had to make several assumptions and were not able to retrieve all desired information. Due to the length of hospital stays, the sample size covering nearly four years of therapies is, with respect to the limited number of patients during a year, too small for comprehensive and statistically reliable analyses. Another reason is that the variety between different patients is very high and thus they are hard to compare.

Unfortunately, data from earlier years are not completely digitised and are also existent in a different form as the data acquisition tool was changed in 2004. Furthermore, as the results form more detailed questionnaires, filled by the in-patients themselves at several points in time during their treatment, were not available yet, we were not able to evaluate the actual course of the compliance. These questionnaires are part of a new concept for evaluating the quality of care and are not completely installed yet.

However, the currently available data shows that it is possible to retrieve the desired information from the data set. When the required amount of data will be available, comprehensive analyses will be performed to ensure the detected mathematical relationships. The next steps include gathering data from other hospitals and comparing the administered treatments depending on the kind of addictive disorders. Second, other disorders could be examined, for verifying the coherences and discovering more interrelationships.

One of the challenges in implementation is the suitable quantification of subjective data. Probably, the most obvious example in our simulation model is the initial motivation of the patient stated at the beginning of the therapy. There are five discrete values having different meanings for different patients. Due to that it is possible that the actual motivation is higher or more likely lower than stated. Therefore, it has to be reconsidered to integrate a certain error for the initial motivation values. We solved this problem by distributing the motivation randomly within numeric boundaries. Another solution might be the definition of a fuzzy set for modelling the initial motivation.

By way of conclusion it should be pointed out again that due to that subjectivity and the limited sample size, some of the results can only provide a vague indication on the underlying interrelationships. Nevertheless, this simulation study gave us the opportunity for successfully testing and improving hybrid tokens and the associated computational methods. More detailed data might also enable us to model more than one continuous attribute in the hybrid token influencing each other, e.g. the mood of a patient having an influence on the compliance, as well as discrete events occurring during the therapy. Only those complex interrelationships will be able to take real advantage of the hybrid token approach.

Eventually, all results have to be reviewed again and above all have to be discussed with physicians and psychotherapist for explaining the observed effects. When a suitable amount of proper data is available, the study will be resumed, especially focussing on the course of the compliance during the therapy and the sequence of treatments. In the face of restrictions and simplifications, we believe that a model like this enables the estimation of the therapeutic outcome and, after a comprehensive data analysis, might provide a decision support for physicians and psychotherapists.

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Corresponding author: K. Dammasch,
Otto von Guericke University Magdeburg
Department of Simulation and Graphics
Universitätsplatz 2, 39106 Magdeburg, Germany;
kristina@sim-md.de

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Novel Concept of Modelling Embryology for Structuring an Artificial Neural Network

Ronald Thenius, Thomas Schmickl, Karl Crailsheim

“Artificial Life Labs” of the Department of Zoology, Graz, Austria

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The organisation of an Artificial Neural Network (e.g., the organisation in layers, the number of cells per layer, the degree of connectivity between the cells) has a big influence on its abilities (e.g., learning ability). In our work we present a novel method to organise the nodes and links of an Artificial Neural Network in a biologically motivated manner using virtual embryology. For this purpose we developed a virtual embryogenesis, which mimics processes observable in biology. In our system a virtual embryo consists of individual cells, controlled by a genome. These cells can develop to nodes in the ANN during the embryogenetic process. The embryo is implemented as a spatially discrete and temporally discrete multi-agent model. The cells in our model interact with each other via virtual physics and via virtual chemistry. With the work at hand, we show that patterns developing in our virtual embryogenesis are comparable to patterns found during natural embryogenesis. We plan to combine the described virtual embryology with Evolutionary Algorithms to optimise the genome of the embryo. We expect the described model of virtual embryology (in combination with Evolutionary Algorithms) to lead to novel, evolutionary shaped net structures of Artificial Neural Networks.

SNE 20/2, August 2010

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Introduction

The morphological structure of an Artificial Neural Network (ANN) is very important for its functionality. Basic structural features of ANNs can determine the basic capabilities of the network [9] [4]. Several approaches to tune ANNs were published recently: One common approach is to fully link a network of cells, and then use a Genetic Algorithm to find optimal values for weighting these connections [12]. ANN controlled agents (e.g., autonomous robots) using such systems do not learn during runtime, but are customised for their environment by Artificial Evolution.

Such concepts are very effective but become more and more time consuming with increasing numbers of cells due to the quadratic scaling of the number of connections.

In other approaches the structure of ANNs is manually predefined [4]. This allows to rely on a set of well-defined and hand-designed networks with well-known features. A learning algorithm (e.g., reinforcement learning) tunes these weights of the connections during runtime. The advantage of such systems is the easy combination of several well defined network-structures for finding solutions to one given problem.

The disadvantage of such systems is the low ability of the network to adapt to unknown situations or problems that were not taken into account during the network design. This ability of networks is especially needed in adaptive controllers for real-world robotics or for comparison with biological systems. In nature we find that structures of neural nets develop during embryogenesis. The outcome of this developmental process is shaped by natural selection. During lifetime the connections between cells are tuned by learning [11].

Biologically inspired controllers are able to adapt to new situations in an evolutionary way by changing its network structure and by learning processes. The organisational mechanisms working in embryos are easy to evolve and enable a fast and effective artificial evolutionary development of controllers (e.g., for the purpose of robot control) [5].

In the work at hand, we present a novel method to organise the nodes and links of an ANN in a biological motivated manner using a novel method of virtual embryology. Our concept of virtual embryogenesis, which we present here, is mimicking processes observable in biology during the developmental phase of most multicellular life-forms, like *Drosophila m.* [8] or other species [14][6][1].

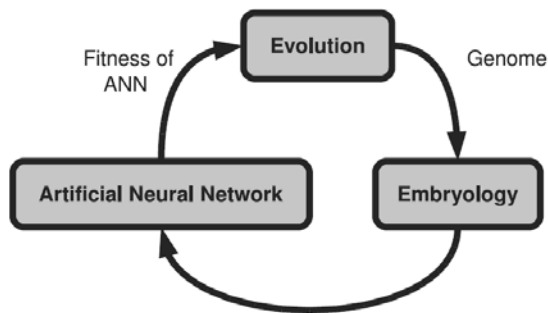


Figure 1. Process of optimisation of an ANN using artificial embryology and artificial evolutionary processes. For details please see 5

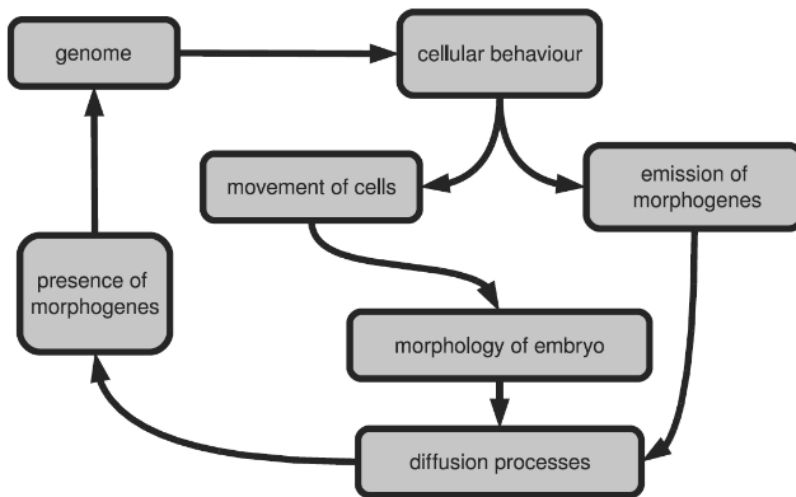


Figure 2. Network of feedbacks within the developing embryo. Boxes indicate subunits of the system controlling the growth of the embryo. Arrows indicate influences of one subunit on another.

1 Concept

Our virtual embryo consists of individual cells. These cells can develop to nodes in the ANN during the embryologic process. In our model, cells can duplicate, die, specialise, emit chemical substances (morphogenes), or build links to other cells. These links represent the connections between the nodes of the resulting ANN. Due to growth processes (duplication processes of other cells), which is an important aspect that we implemented in our model, a cell can be “pushed around” in space. A cell has no ability for active movement.

The cells’ actions are defined by the genome of a cell, which consists of a collection of genes, which can be triggered by virtual morphogenes. One possible effect of gene-activation can be the production of another morphogene. This way a network of feedbacks emerges (see Figure 2).

The resulting selforganised process governs the growth of the embryo. When the embryologic process is finished, the developed network is analysed and translated into a datastructure, which is compatible to a standard ANN-interpreter.

Our approach also synthesises general concepts of biological embryogenesis and of artificial embryogenesis [21][2]. These very complex processes are strongly abstracted in our virtual embryogenesis. These simplifications are important, to enable a later optimisation of the resulting ANN, by using artificial evolutionary processes (see figure 1).

Due to this requirement, the fast calculation of single embryologic processes is necessary. Especially for projects dealing with evolution in autonomous robotic systems (e.g., see [19][18]) the fast simulation of embryologic processes on systems with limited hardware resources is required.

2 Implementation

2.1 Diffusion processes

In our model, the embryo is implemented as a multi-agent model, in which a single cell is represented by an agent.

The space in our model is discrete. Each spatial unit (patch) can be occupied by a cell. These cells interact with each other via virtual physics and via virtual chemistry.

Morphogenes are emitted by cells and diffuse throughout the embryo [3].

The concentration $c_{m,x,y,t}$ of a morphogene m at the position x, y at time step t is calculated according to

$$c_{m,x,y,t} = \min(c_{\max,m}, cn_{m,x,y,t-1} - d_m) \quad (1)$$

whereby $c_{\max,m}$ is the maximum concentration of a morphogene m , $cn_{m,x,y,t}$ is the maximum concentration of the morphogene m in the cell at the position x, y and in all neighbouring cells (“Von Neumann” neighbourhood), at the time step t .

The amount of the decrease of the morphogene concentration when diffusing from one cell to another is d_m . When a cell at position x, y emits a morphogene, its value for $c_{m,x,y,t}$ is set according to

$$c_{m,x,y,t} = c_{\max,m} \quad (2)$$

Please note, that no conservation of mass is implemented in our model. This simplification of real physical diffusion processes is necessary to achieve the required computational speed (mentioned in the introduction).

The results of this abstract diffusion model suffices for our needs to achieve the desired embryogenesis.

2.2 Genetics and cellular behaviour

In our model, a cell measures the concentrations of morphogenes every time step and reacts in a preprogrammed way. The concentration of a morphogene needed to trigger a reaction as well as the triggered type of reaction is specified in the genome of the cell.

The genome N is a set of n genes G (see equation 3). Each gene is a tuple of numeric values (see equation 4). These values determine which cell-reaction r is triggered, if a defined morphogene s is present with a concentration higher than c_{\min} and lower than c_{\max} at the position of the cell in the embryo.

All cells share the same genome, which does not change during the embryogenetic process.

$$N = \{G_1, \dots, G_n\} \quad (3)$$

$$G_n = (s, c_{\min}, c_{\max}, r) \quad (4)$$

The reactions r of cells can be as follows: emission of a morphogene, cell duplication and cell death. They are described in detail in table 1.

Table 1. Possible reactions of a virtual cell in our model.

| Cell reaction | Description |
|----------------------------|---|
| Emission of morphogene | A cell emits a morphogene into the embryo |
| Cell duplication | The cell duplicates, which leads to a change of the embryo, due to virtual physics. For details see subsection 3.3. |
| Cell death | The cell dies, which leads to a change of the embryo, due to virtual physics. For details see subsection 3.3. |
| Changes in responsiveness | Changes the cells responsiveness towards a certain morphogene. By changing this values the cell is able to differentiate. |
| Changes of internal values | Internal values represent the predisposition for certain functions. |
| Linking to neighbours | Builds a neural connection (dendrite) to a neighbouring cell. |

The fact that our “genes” are triggered by morphogenes is comparable to the mechanisms of gene expression and protein synthesis found in nature. Especially the concepts of second-messenger mechanisms [7] and transcriptioncoregulator mechanisms found in biological cells [17] were used in a very simplified way for our concept of virtual embryology.

2.3 Simulated physics

In case of cell duplication or cell death the positions of cells within the embryo have to be reorganised. We implemented this process by assuming that cells interact with each other physically via pushing. No other complex interactions (e.g., cellular cohesion) are simulated. If a cell (mother cell) duplicates, it determines the numbers of cells in the directions up, down, left and right.

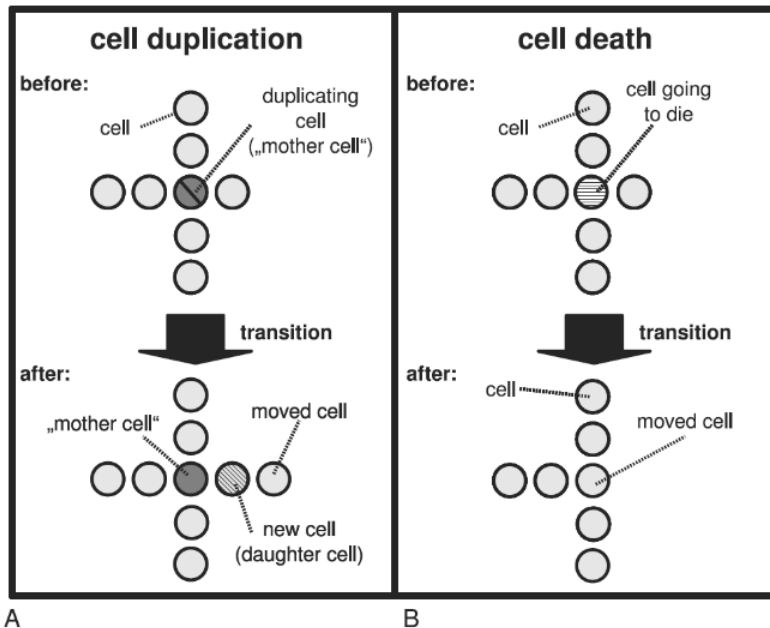


Figure 3. Movement of cells in the embryo during cell duplication and cell death processes. A: Modelling cell duplication: The daughter cell is placed in the direction where the number of other cells is lowest. B: Modelling cell death: Neighbouring cells are moved in from that direction where the number of cells is minimal.

The cells have to be in a continuous row to be counted. In the direction where the number of cells is the smallest, the whole continuous row of cells is shifted by one position in the according direction. The new cell (daughter cell) is then placed on the new free position next to the mother cell (see figure 3A). This process simulates the movement of cells during the growth process.

In case of a cell's death, analogously to cell duplication, the free patch of the died cell is filled by shifting the whole row of cells towards the empty space (see figure 3A). In both, the movement of cells after cell duplication and the movement of cells after cell death, always the smallest possible number of cells is moved.

This simulates the physical situation in a loose group of cells, where the physical inertia of subgroups of cells determines which cells have to move.

As well as there are morphogenes that can induce growth, other morphogenes can reduce growth. The balance between these two groups of morphogenes during the embryogenesis determines the size of the embryo (see figure 4).

A big variety of shapes can emerge from this system, because growth factors can be emitted in different locations and in different timephases during embryology.

2.4 Cell specialisation

Morphogenes can not only influence the growth of the embryo by inducing cell duplication or cell death, but they can also change internal status variables of cells (see figure 5)

These values can code for the receptivity for another morphogene, the probability quality of linking to other cells (mentioned below), or for properties that are necessary for the function of the resulting neural net (e.g., net (e.g., if a cell is an input cell or an output cell).

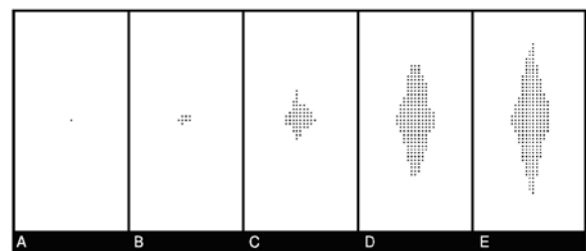


Figure 4. Screenshots of the growing embryo. The cells of the embryo are indicated by boxes.
 A: Starting condition with one single cell.
 B: Status of the embryo after 5 time steps.
 C: Status of the embryo after 10 time steps.
 D: Status of the embryo after 20 time steps.
 E: Final shape of the embryo.

2.5 Cell specialisation

Morphogenes can not only influence the growth of the embryo by inducing cell duplication or cell death, but they can also change internal status variables of cells (see figure 5). These values can code for the receptivity for another morphogene, the probability quality of linking to other cells (mentioned below), or for properties that are necessary for the function of the resulting neural net (e.g., if a cell is an input cell or an output cell).

Usually, the processes of cell specialisation take longer than the development of the shape of the embryo during embryogenesis. Especially the shape of the embryo has a big influence on the interactions of different morphogenes, what goes along with results found in nature [16]. Some of the emerging processes can be interpreted as being a sort of “Turing processes” [20].

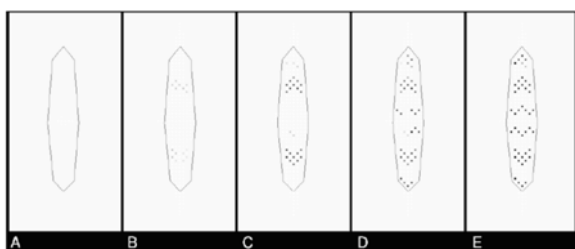


Figure 5. Screenshot of a virtual embryo during cell specialisation process. Specialised cells (high value of a given internal status variable) are indicated as gray dots, not specialised cells are not drawn. Lines indicate the boundaries of the virtual embryo.

- A: Starting condition,
- B: Status of the embryo after 25 time steps.
- C: Status after 30 time steps.
- D: Status after 40 time steps.
- E: Final status of the embryo.

2.6 Linkage

During our simulated embryogenesis, all cells can link with other cells (see figure 6). As mentioned above, those links represent the connections between the nodes of the neural network.

The amount of links built by a cell, as well as the distance to the linked cells, depends on the interplay between the morphogenes and the genome (see figure 7). This way the degree of connectivity within a certain area of the embryo is determined by the embryologic process.

If the cell is moved after linking, it stays still linked. This can lead to long-distance connections and enables a structuring of the resulting neural network (see figure 8). If a cell dies during the embryological process its links are deleted. Not all cells within the embryo have to be linked to other cells.

Cells, that are not linked, are not without function, they can operate as morphological structuring cells in our model. These cells are needed for shaping the embryo due to growth or dying, as well as for shaping the gradients of morphogenes.

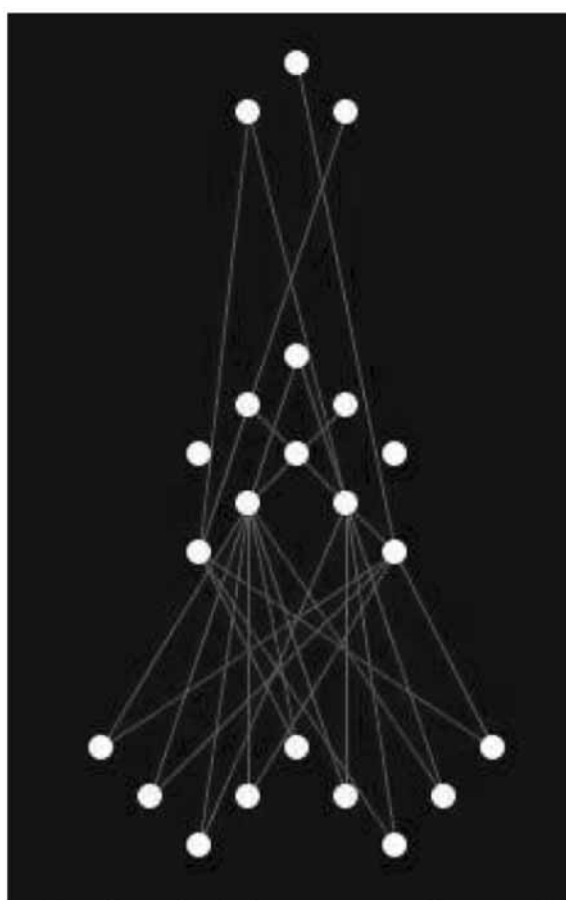


Figure 6. Example of links between cells. For depicting reasons lines indicating intercellular links are drawn into the embryo. The area of linked cells is depicted enlarged. Cells are indicated by white circles.

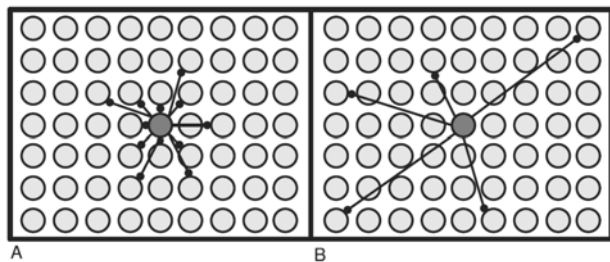


Figure 7. The process of linking cells: The degree of connectivity and the distance of cells selected for connection is determined by the genome, by the morphogene level and by the internal state of the cell.
 A: A focal cell links with its closest neighbours with a high density.
 B: A focal cell builds up a few long distance connections with cells further away.

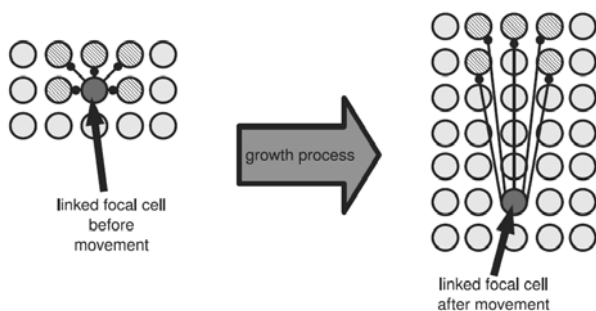


Figure 8. Scheme for the movement of linked cells. Once the focal cell is linked, the connections to other cells persist for the rest of the embryologic process, even if the cell is moved within the embryo.

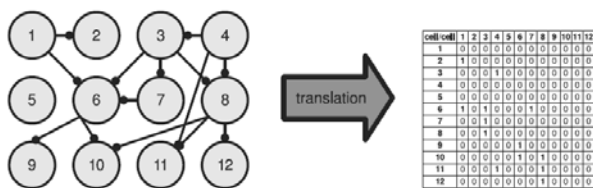


Figure 9. Scheme for the translation of a cellular pattern into a tabular representation which is easily readable by a standard neural network interpreter. Please note that not all cells in the embryo have to be translated into the neural net. Cell number 5, for example, has no connection to other cells, for it had a purely morphological structuring function during embryogenesis. For details see subsection 2.5.

2.7 End of growth process

For the work at hand, the modelled embryo was allowed to grow and differentiate, until all growth and celldifferentiation had finished. That means that no more cell duplication events, cell death events, or cell linking events occurred. Also the distribution of growth factors within the embryo had to stay stable. If an embryo reaches this stable point of a complex equilibrium of development, it is defined as “finished”.

If the growth processes are not regulated well by the genome, the embryo can grow infinitely. In our simulation, the embryological process is stopped, if the number of cells reaches a certain point, to deal with such “pathologic” forms of embryos that grow infinitely. The resulted embryo is then rejected from further analysis.

2.8 Extracting ANNs from our virtual embryos

After the embryogenesis is finished, the embryo is analysed and the network topology is transferred into a structure, that is readable for a standard neural network interpreter. Cells that had only a morphological structuring function during the embryogenesis and have not linked during the embryogenetic process are excluded from the translation process to save computational time. These cells have no influence on the shape or function of the ANN after the embryogenesis has finished.

3 Results

Using our model of virtual embryogenesis we can simulate the development of an embryo from a simple hardcoded genome for the purpose of structuring an Artificial Neural Network (see figure 10). The final shape of the embryo, the connectedness of the embryos’ cells, as well as the internal specialisation of cells (see figure 10 D) are controlled by a system of feedbacks.

These feedbacks arise from the ruleset described above (section 3), from the genome, from the spatial distribution of the cells within the embryo (see figure 10 A) and from the diffusion abilities of the morphogenes (see figure 10 B,C). The specialisation of cells within the embryo allows the development of different tissues, neural cells or structure cells, which have no neural function but morphological function.

The resulting patterns found in simulations of our model are comparable with patterns found in nature during embryological development. In figure 10, we compare the self-organised segmentation processes in our virtual embryo (figure 10A-D) with images from natural embryogenesis in *Drosophila m.* (figure 10E). Similar segmentation patterns are described also by Kalthoff [10].

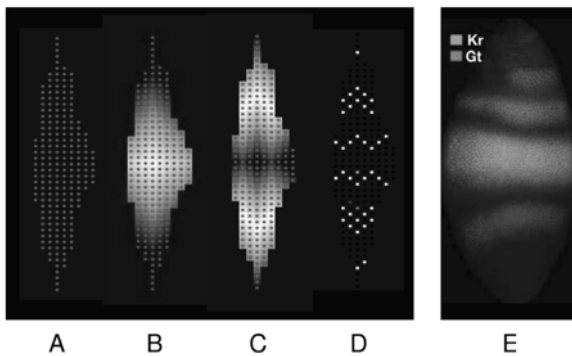


Figure 10. Comparison of virtual embryogenesis in our model and real-world embryogenesis:

- A: Virtual embryo, consisting of cells (dots);
- B: Morphogene gradient in embryo;
- C: Gradient of another morphogene, inducing cell differentiation.
- D: Embryo consisting of differentiated cells (white dots) and non-differentiated cells (invisible);
- E: Natural examples of gene expression: Activity domains of gap genes in larva (lateral view) of *Drosophila m.* (from [8]; 'Kr' and 'Gt' indicate gap genes.)

4 Related work

First ideas about possible self-organisation processes shaping or structuring a living creature can be found in [20], where the authors describe the interaction of different antagonistic chemical substances diffusing through a medium.

Early models of shape-giving processes are described in [6] [1]. In recent years many studies about mechanisms that are structuring an embryo have been published, dealing with the topics of genetic control mechanisms of embryogenesis as well as with physical mechanisms spatially organising an embryo (for a review please see [16]).

The topic of organising ANNs using genetic optimisation methods have been investigated recently in [13] which describes the coding of network topologies in a genome.

Another study [15] shows the technique to arrange groups of cells to solve a "french flag test", using evolutionary methods. Such tests have become a common benchmark in the field of virtual embryogenesis [22].

5 Conclusion and Outlook

Our model of embryogenesis for the purpose of structuring artificial neural nets uses ideas from evolutionary developmental biology. Our approach produces results that are comparable with the products of natural developmental processes.

The virtual embryogenetic processes described in this article have the potential to structure groups of cells, on the level of body shape, as well as at the level of microstructure.

We plan to combine our virtual embryology with Artificial Evolution. The network of (neural) cells that develops during the embryologic process will be tested in a standard neural network interpreter. The fitness of a genome will be determined by the quality (e.g., learning ability) of the resulting "grown" neural net. This way we plan to evolve novel and efficient Artificial Neuronal Network structures (see figure 1). Additionally, we think we can learn more about the properties of basic processes that act during the biological evolution of brain structures (e.g., evolution of hierarchical brain-structures).

Acknowledgements

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Corresponding author: Ronald Thenius
 “Artificial Life Labs” of the
 Department of Zoology,
 8010 Graz, Universitätsplatz 2 – Austria
ronald.thenius@uni-graz.at

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Intelligent Modelling of a Fluidised Bed Granulator used in Production of Pharmaceuticals

Esko K. Juuso. Control Engineering Laboratory, Department of Process and Environmental Engineering, University of Oulu, Finland

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The aim of dynamic modelling and simulation is to improve the control of the fluidised bed granulator. Modelling and simulation was done on the basis of data collected from several test campaigns. Several modelling methodologies have been compared in Matlab-Simulink environment. A solution based on dynamic linguistic equation models was chosen. The main input variables are humidity difference between incoming and outgoing air, temperature difference between inflowing air and granule and the rate of inflowing air. The final output is the estimated granule size but the overall models contains also dynamic models for temperature and humidity. The simulator combines several models which are specific to the operating conditions. According to the results, the spraying and drying processes included short-duration periods. Extension to fuzzy LE models provides useful information about uncertainties of the forecasted granulation results. The complexity of the models is increased only slightly with the new system based on the extension principle and fuzzy interval analysis.

Introduction

Powder particles are agglomerated through granulation processes due to interparticle bonds caused by the addition of a granulation liquid. The handling of the starting materials is facilitated and further processing (e.g. tableting) becomes more secure [1]. Granulation usually refers to processes whereby aggregates with sizes ranging from approximately 0.1 to 2.0 mm are produced by agitation of moistened powder. Compression characteristics are improved, and handling of powders become easier because of less dust, less adhesion with hydroscopic materials. [2]

During the granulation process a three-phase system of solid, liquid and gas is established. The system will reduce its free energy by formation of liquid bridges between the particles. By the liquid bridges cohesive forces are established which may cause agglomeration and consolidation of the agglomerates in so far as they can resist the disruptive forces. The outcome depends on the interactions between apparatus, process and compositional variables and the properties of the powder. [3, 4, 5]

Airflow rate, temperature and humidity of the inlet air and the addition rate and droplet size of the granulating liquid are critical input variables. Temperature and humidity measurements of the process air are the most important parameters for monitoring heat and mass transfer. However, the inlet air humidity cannot usually be specified accurately because the seasonal variations in the process air humidity are difficult to control entirely.

The actual effect of different humidity levels of the inlet air on the various fluid bed process parameters have been studied in [6]. Properties of the particles are also important. Effects of primary particle surface wettability by a binder solution on the rate of agglomeration were investigated in [7].

A physically-based mathematical model for the description of particle wetting and of temperature and concentration distribution in fluidized bed spraygranulation is presented in [8]. The bed mass and particle diameter growth in discontinuous granulation are taken into account and the two-dimensional calculation of the temperature and concentration distributions were carried out for the steady, continuous fluidized bed spray-granulation.

The physical changes in the beginning of spraying process are fast, because the weight of granules increases rapidly, which requires also that the amount of the inlet air has to be increased significantly so that fluidising would continue. This part of the process was the most difficult part to model. Correspondingly during the first few minutes of drying, the surface drying proceeds quickly until the balance is found. According to samples, the size of granules continued to grow for a while even the drying phase was started.

The aim of dynamic modelling and simulation is to improve the control of the fluidised bed granulator. Modelling is based on linguistic equation (LE) approach introduced in [9]. LE approach has been used in various applications [10, 11].

Dynamic LE models have provided accurate prediction and good performance in continuous processes, e.g. a lime kiln and a solar collector field [10]. A set of interactive intelligent systems can be combined with other modelling and simulation methodologies to build practical simulators for industrial processes [12].

For granulation process, dynamic modelling and simulation is necessary. Dynamic LE modelling was started in 2000 in cooperation with Helsinki University and Orion [13]. Dynamic models are well suited for forecasting the granulation result [13, 14]. The research equipment used in this project was a bench-scale fluidized bed granulator (Glatt WSG 5) shown in Figure 1. Modelling and simulation was done on the basis of data collected from test campaigns based on experimental design.

This paper presents more details of the solution and extends the models to uncertain environment.

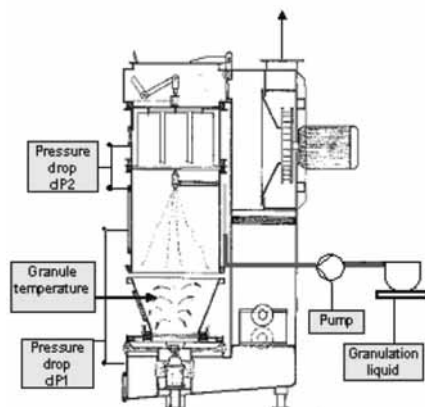


Figure 1. A bench-scale fluidised bed granulator.

1 Measurements

The granulation process shown in Figure 1 has three main phases:

- mixing to get granules homogeneous,
- spraying with PVP granulation liquid, and
- drying with warm air.

The model formulation (batch size 3500 g) consisting of verapamil hydrochloride, microcrystalline cellulose and lactose monohydrate was applied. Polyvinylpyrrolidone was used as a binder. The temperature of the drying air was 60 °C.

To eliminate the granules escape from granulator, filters were needed to shake every 100 seconds. The shaking takes 10 seconds, and meanwhile the process flows are off. For proper modelling it was essential to eliminate the effect of shaking as well as possible.

More stable data and better modelling was achieved by median and moving average method.

Testing data was collected from 38 batches, 27 batches were used to training and the rest of the 11 to testing. The design of experiments for the test batches R1-11 presented in Table 1 includes three levels (high, normal and low) for the feed rate and the pressure of the granulation liquid. To confirm the functionality there were three repeated batches in the normal conditions.

Table 1. The design of experiments for the batches.

| Test | Feed rate of granulation liquid [l/min] | Feed pressure of granulation liquid [bar] |
|------|---|---|
| R1 | 100 | 1.5 |
| R2 | 125 | 1.5 |
| R3 | 100 | 2 |
| R4 | 125 | 2.5 |
| R5 | 100 | 2 |
| R6 | 125 | 2 |
| R7 | 112.5 | 1.5 |
| R8 | 112.5 | 2.5 |
| R9 | 112.5 | 2 |
| R10 | 112.5 | 2 |
| R11 | 112.5 | 2 |

Numerous variables are known to affect the fluid bed process and the final granules. During the test campaigns, on-line measurements of more than 40 variables were collected with sampling time of one second. Air flow rate, temperature and humidity of the inlet air and the addition rate of the granulation are important variables. The instrumentation is described in [15].

Particle size analyses of intermediate and product granules and bulk factor were done off-line. Particle size analysis introduces two challenges: (1) it is based on samples, and there cannot be too many of them, and (2) particle size has always a distribution. The data driven modelling was based on the average particle size, and interpolation based on nonlinear regression was used to obtain additional points required for the dynamic modelling.

Seasonal variation in humidity is considerable and that will cause the changes in the water amount of the incoming air. The incoming air humidity should be included to the input variables or another possibility is to make a pre-moistening to a constant moisture value in the beginning of granulation.

2 Nonlinear modelling

Nonlinear models are needed in modelling of the granulation process. Various statistical and intelligent methodologies have been compared in this project.

2.1 Statistical modelling

Response surface methodology combines linear terms with interaction and quadratic terms to calculate one output variable y from multiple input variables x_j :

$$y = b_0 + b_1x_1 + b_2x_2 + b_3x_3 + \dots + b_{12}x_1x_2 + b_{13}x_1x_3 + b_{23}x_2x_3 + \dots + b_{11}x_1^2 + b_{22}x_2^2 + b_{33}x_3^2 + \dots \quad (1)$$

The number of parameters increases very fast with the number of variables.

Statistical models have been used for interpolating the granule size to obtain data for dynamic modelling. There are considerable differences between the batches (Figure 6).

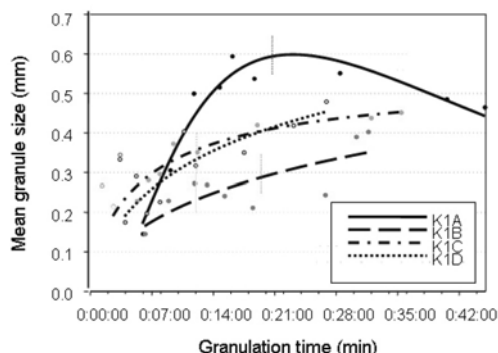


Figure 2. Interpolation of the granule size from 8 samples, starting point presumed to be 0.05 mm.

Dynamic statistical modelling is widely used in system identification. For parametric models, the output at time t is computed as a linear combination of past inputs and past outputs in such a way that the output at time t can depend on the signals at many previous time instants chosen according to appropriate time delays [16]. The number of delayed inputs and outputs is usually referred as the model order(s). The simplest model, ARX model, is usually written

$$y(t) + A_1y(t - 1) = A_2u(t - n_k) + e(t) \quad (2)$$

where A_1 and A_2 are model coefficients, $y(t)$ and $y(t - 1)$ state variables and $u(t - n_k)$ input variable delayed with n_k time steps. State-space models are widely used for combining effects of several input variables.

Various structures based on ARMAX, output error and Box Jenkins with different orders of the respective polynomials have been compared. Nonlinear models are needed, i.e. higher orders were needed in the parametric models, and the state-space models were insufficient.

2.2 Fuzzy modelling

Fuzzy set theory was first presented by Zadeh [17] to form a conceptual framework for linguistically represented knowledge. Extension principle is the basis generalisation of the arithmetic operations if the inductive mapping $F(x)$ is a monotonously increasing function, e.g. $F(x) = x_2$ in Figure 3. These results can be combined by applying fuzzy interval analysis in fuzzy arithmetic [18].

Linguistic fuzzy models [19], where both the antecedent and consequent are fuzzy propositions, suit very well to qualitative description of the process as they can be interpreted by using natural language, heuristics and common sense knowledge. The key idea is to use membership functions for both the inputs x and the outputs y . These functions can be defined by expert knowledge or by experimentation. The input-output mapping is realized by the fuzzy inference mechanism equipped with conversion interfaces, fuzzification and defuzzification. The approximate reasoning is based on T-norms and T-conorms [19].

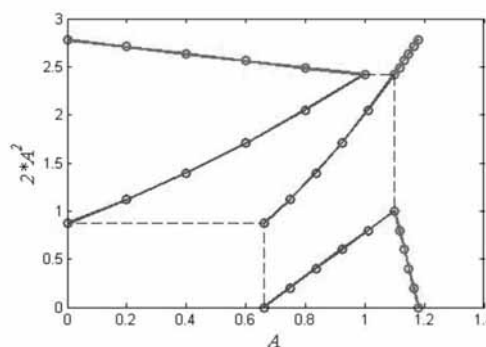


Figure 3. Fuzzy extension of a power function.

The Takagi-Sugeno (TS) fuzzy modelling method was proposed by Takagi and Sugeno as a framework for generating fuzzy if-then rules from numerical data [20]. A TS fuzzy model consists of a set of fuzzy rules, each describing a local linear input-output relationship:

$$\text{If } x_1 \text{ is } A_{i1} \text{ and } \dots \text{ and } x_n \text{ is } A_{in} \text{ then } y_i = a_i x + b_i, i = 1, 2, \dots, K \quad (3)$$

where A_{i1}, \dots, A_{in} are fuzzy sets defined in the antecedent space and y_i is the rule output of the model. K denotes the number of rules. The results of the rules are usually combined as a weighted average where the weights are obtained from the fulfilment of the rules.

Fuzzy relational models [21], which allow one particular antecedent proposition to be associated with several different consequent propositions, can be regarded as generalizations of the linguistic fuzzy models. Each element of the relation represents the degree of association between the individual reference fuzzy sets defined in the input and output domains, i.e. all the antecedents are tied to all the consequents with different weights.

Dynamic fuzzy models can be constructed on the basis of state-space models, input-output models or semimechanistic models [22]. In the state-space models, fuzzy antecedent propositions are combined with a deterministic mathematical presentation of the consequent. The most common structure for the input-output models is the NARX (Nonlinear AutoRegressive with exogenous input) model, in which the input and output values are chosen as in the ARX model according to appropriate system orders. The regressor vector consists of a finite number of past inputs and outputs [23]. This structure is directly used for multiple input, single output (MISO) systems. Multiple input, multiple output (MIMO) systems can be built as a set of coupled MISO models.

2.3 Neural modelling

Artificial neural networks consist of neurons

$$y_i = F\left(\sum_{j=1}^m w_{ij}p_j + B_i\right) \quad (4)$$

where w_{ij} is the weight factor of the element p_j in the input vector of the neuron i , and B_i a scalar bias. For the input layer, the elements are usually normalized values of the variables $x_j, j = 1, 2, \dots, m$.

Neurofuzzy systems use fuzzy neurons to combine the weight factors and the inputs. The activation function is handles as a function in the extension principle.

Dynamic ANN models are based on similar structures as the dynamic fuzzy models: simple structures, e.g. NARX structures, can be constructed by taking delays into account in the input vector p in (2). A dynamic ANN model can be realised by a static feedforward network and an external feedback connection [23].

Another possibility is to use recurrent networks, e.g. Elman networks} are two-layer feedforward networks, with the addition of a feedback connection from the output of the hidden layer to its input [24]. This feedback path allows Elman networks to learn to recognize and generate temporal patterns, as well as spatial patterns. The weight factors w_{ij} can also depend on time.

3 LE modelling

Data-driven steady state modelling is normally used in linguistic equation (LE) modelling [11]. Dynamic structures extend the models to dynamic simulation, and in this paper uncertainty of the results is handled with fuzzy arithmetics.

3.1 Steady state LE modelling

Linguistic equation models consist of two parts: interactions are handled with linear equations, and nonlinearities are taken into account by (membership definitions) [10]. The output is obtained by

$$x_{out} = f_{out}\left(-\frac{\sum_{j=1, j \neq out}^m A_{ij}f_j^{-1}(x_j) + B_i}{A_{iout}}\right) \quad (5)$$

Where parameters $A_{ij}, j = 1, \dots, m$, and B_i are the interaction coefficients of the linguistic equation i . Nonlinear scaling is based on membership definitions f_j and corresponding inverse functions f_j^{-1} . This model corresponds to the neural model (4) if the normalization is replaced by the nonlinear scaling.

In the LE models, the nonlinear scaling is performed twice: first scaling from real values to the interval $[-2, 2]$ before applying linguistic equations and then scaling from the interval $[-2, 2]$ to real values after applying linguistic equations (Figure 4). The linguistic level of the input variable j is calculated the inverse functions of the polynomials [11].

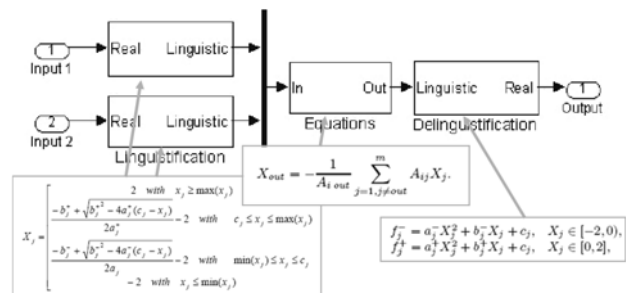


Figure 4. A steady state LE model for two inputs and one output.

3.2 Dynamic LE modelling

The basic form of the linguistic equation (LE) model is a static mapping in the same way as fuzzy set systems and neural networks, and therefore dynamic models will include several inputs and outputs originating from a single variable. External dynamic models provide the dynamic behaviour. The models are developed for a defined sampling interval in the same way as in various identification approaches [16]. However, the LE simulators normally use variable time step integrators.

Rather simple input-output LE models, where the old value of the simulated variable and the current value of the control variable as inputs and the new value of the simulated variable as an output, can be used since nonlinearities are taken into account by membership definitions. To use integration methods available in the simulation software, a difference of the output is calculated (Figure 5).

Nonlinear scaling reduces the order of the model, i.e. the number of input and output signals needed for modelling of nonlinear systems. Need for higher order models can be tested by applying classical identification with different polynomial degrees to the data after scaling with membership definitions. For the default LE model, all the degrees of the polynomials in parametric models become very low, i.e. all the parametric models become the same, ARX model shown in (2).

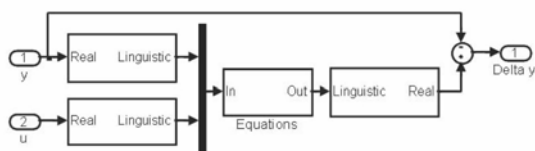


Figure 5. Dynamic LE model of Δy .

Several artificial neural networks have been compared for expanding the linear models, but these more complex model structures do not provide any considerable improvement to the results obtained by the basic LE models, i.e. a linear activation function can be chosen in (4) if the nonlinear scaling described above is used for the input variables.

Changing operating conditions can be taken into account by modifying membership definitions and/or interaction coefficients of the LE models. Linguistic fuzzy models can be used for selecting submodels. This approach is used for selecting the appropriate submodels for spraying and drying.

Also structures used Takagi-Sugeno type fuzzy models can be used if the interaction coefficients depend clearly on the input variables.

3.3 Fuzzy LE modelling

Universal approximators for fuzzy functions can be constructed as extension principle extensions of continuous real-valued functions which continuously map fuzzy numbers into fuzzy numbers [18, 25]. LE models can be extended to fuzzy inputs with this approach if the membership definitions and the corresponding inverse functions, are replaced by corresponding extension principle extensions of these functions presented in Figure 4.

The argument of the function f_{out} in (1) is obtained by fuzzy arithmetics. Here the calculations are based on interval analysis which has been widely used in physics for handling measurement errors. In this methodology, measurement values are assumed to be on intervals whose lengths depend on the accuracy of the measurements. The interval analysis is used for estimating the intervals of calculated variables [26]:

$$\begin{aligned}
 [a, b] + [c, d] &= [a + c, b + d], \\
 [a, b] - [c, d] &= [a - c, b - d], \\
 [a, b] \cdot [c, d] &= [\min(ac, ad, bc, bd), \max(ac, ad, bc, bd)], \\
 [a, b] / [c, d] &= [a, b] \cdot \left[\frac{1}{d}, \frac{1}{c} \right] \text{ if } 0 \notin [c, d]
 \end{aligned}
 \tag{6}$$

where intervals $[a, b]$ and $[c, d]$ are arbitrary real intervals.

The original interval analysis does not include any gradual approach, but the methodology can be generalized to horizontal membership functions (Figures 3 and 6) by applying interval analysis on each α -cut separately. The number of α levels should be increased when the fuzziness of the input increases.

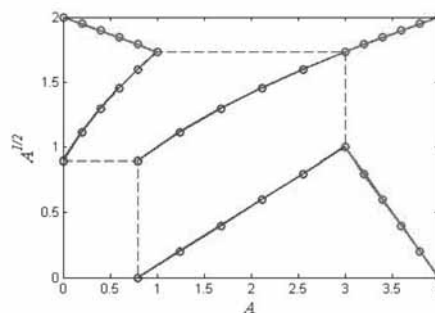


Figure 6. Fuzzy extension for a square root function.

Only addition and subtraction are needed if the interaction coefficients are crisp. The only fuzzy part in the linguistification function is the term which includes the input x_j (Figure 4). The extension principle is used to obtain a square root of the fuzzy number (Figure 6). The width and location of the input fuzzy number are modified by the parameters of the scaling functions. The output fuzzy numbers of these blocks are limited to the range $[-2, 2]$.

In the equation block presented by (2), the state variable $y(t-1)$ and the input variable $u(t-n_k)$, which are both fuzzy numbers, are multiplied by crisp numbers $-A_1$ and A_2 , respectively, if the model is crisp. The sum of the resulting fuzzy numbers is the new state variable $y(t)$ in the range $[-2, 2]$.

In the delinguistification block, the terms X_j^2 can be obtained by the extension principle (Figure 3) or by multiplication $X_j \cdot X_j$ with fuzzy interval analysis. The resulting fuzzy number and the original fuzzy number X_j multiplied by crisp numbers shown in Figure 4 are then added to the crisp number c_j to obtain the fuzzy output.

Fuzzy LE models with fuzzy inputs can be constructed by using fuzzy multiplication and division as well since the parameters $a_j^-, b_j^-, a_j^+, b_j^+$ and c_j are all fuzzy numbers. Fuzzy extension of the classical interval analysis suits very well also to these calculations. However, the result becomes naturally more uncertain when fuzzy models are used.

Results of the fuzzy interval analysis have always maximal uncertainty as it takes the worst case. A negative associations between the input variables reduces the uncertainty considerably. In the calculations, this can be taken into account by using own membership functions for the upper and lower parts of the value range.

4 Dynamic simulator

Data was separated to three main processes: mixing, spraying and drying. Modelling for mixing area has not done so far because of insignificant changes in the humidity and the airflow. Thus physical knowledge of mixing process is not well known. The aim of mixing step is to make a homogeneous batch.

In the beginning of spraying the physical changes were very rapid and that part of process has been the most difficult area to model. The weight of granules increase rapidly, i.e. the inlet air has to be increased

significantly to maintain fluidising. Correspondingly during the first few minutes of the drying, the surface drying proceeds quickly until the balance is founded. The granule growth may still continue for some time in the beginning of the drying phase.

The overall model for the spraying and drying phases consists of three models:

- temperature,
- humidity, and
- granule size.

Output variables were the temporary value of the granule temperature, the new value of humidity difference and the new estimated value of the granule size, correspondingly. The dynamic submodels have similar structures as shown in Figure 5 and model specific variables:

- The new granule size depends on the current granule size and two other variables, temperature difference and humidity difference.
- The granule temperature depends on airflow (F_{in}), humidity difference between inlet and outlet air (U_{diff}) and temperature between granule and inlet air (T_{diff}).
- The humidity depends on T_{diff} , U_{diff} and granule temperature.

The distribution of the particle size is based on the fuzzy extension principle, i.e. the membership function of the particle size is computed in each time step from the uncertain input values by using the dynamic LE model as a function. In this way the uncertainty of the model is not forgotten in the analysis. The system is able to select automatically the best submodel during the granulation process and move gradually from one submodel to another when the process proceeds by fuzzy methods.

The LE models have been developed and tuned in the FuzzEqu Toolbox: the LE model in Figure 7 is a model of the granule size. Membership definitions have been developed from the data: a batch specific example is shown in Figure 8.

5 Results and discussion

Testing data was collected from 38 batches, 27 batches were used to training and the rest of the 11 to testing. Stable data for modelling was obtained by filtering. The modelled and simulated results were compared with experimental data.

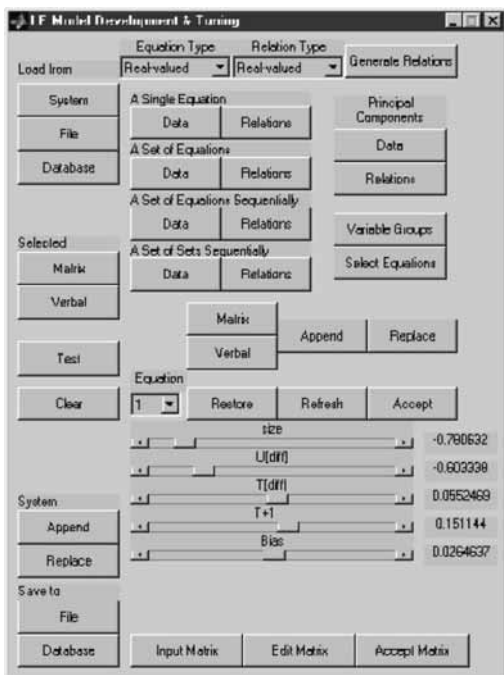


Figure 7. Model development and tuning in FuzzEquToolbox.

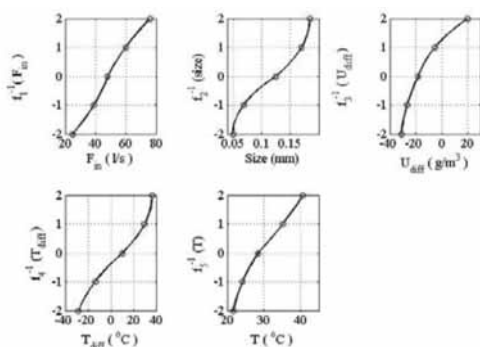


Figure 8. Membership definitions.

According to the modeling and simulation results, the most representative input variables were airflow in (F_{in}), humidity difference between inlet and outlet air (U_{diff}) and temperature between granule and inlet air (T_{diff}). In Simulink model, also other input variables were used but the interaction coefficients of these variables are rather small.

Modelling is aimed to help in estimating the granule size while processing since the analysis result of samples is not available on line. The granulation goes through considerably different routes depending on the operating conditions. By controlling the interaction coefficients of the variables the model worked well also in rapidly changing areas.

The temperature of granules varied mainly from 20 to 60 °C. The data of the batches were shared to several subperiods, and the membership definitions were made for every area. In the linguistic equation model, the variables are scaled between -2 and +2. The value range of the variables must be wide enough to guarantee the applicability to the modelling.

Fuzzy modelling is a reasonable extension as also the granule size has always a distribution rather than a single value. This distribution changes with time, and the result becomes more and more uncertain when the prediction horizon increases. Negative associations between T_{diff} and U_{diff} alleviate this problem slightly.

The first results show that the complexity of the models is increased only slightly with the new system based on the extension principle and fuzzy interval analysis. This study will be extended to the complete data set as it provides a lot of useful additional information about the granulation process. In future, the results will be compared to the measured distributions of the granule size. The goal is to develop more general models, i.e. the membership definitions will be developed from the complete data set related to the batches of the verapamil granulations.

Partly the uncertainty is caused by uncontrolled process conditions, e.g. seasonal variation in humidity is considerable and that will cause the changes in the water amount of the incoming air. The incoming air humidity should be included to the input variables or another possibility is to make a pre-moistening to a constant moisture value in the beginning of granulation. Later a humidifying system has been included, and this enables high and fluctuating humidity of the process air.

6 Conclusions

The data based modelling succeeded well after the main process stages were divided into sub stages corresponding to shorter time periods. The interaction of the main variables was improved by using fuzzy modelling. Extension to fuzzy LE models provides useful information about uncertainties of the forecasted granulating results. The complexity of the models is increased only slightly with the new system based on the extension principle and fuzzy interval analysis. Associations between input variables were useful in reducing the uncertainty of the final result.

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Corresponding author: Esko K. Juuso
Control Engineering Laboratory, Dept. of Process and Environmental Engineering, P.O.Box 4300, FI-90014 University of Oulu, Finland
esko.juuso@oulu.fi

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Modeling and Simulation of Patient Flow in Hospitals for Resource Utilization

Lei Zhao, Bernt Lie, Telemark University College, Porsgrunn, Norway

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Hospital costs play a significant role in national budgets. To some degree, patients are suffering from lack of vacant beds and caretakers. Emergency Department (ED) crowding causes a series of negative effects, e.g. medical errors, poor patient treatment and general patient dissatisfaction. One road to improve the typical clinical system is to describe the patient flow in a model of the system and how the system is constrained by available equipment, beds and personnel.

This paper focuses on modeling and simulation of the capacity of utilities and how using advanced control techniques can enable intelligent scheduling, leading to smooth patient flow to reduce emergency department crowding. By comparing different models, the most efficient ones will be identified for implementation. The idea is that hospitals can use the proposed models to predict the future resident patient number in each department/ward. The caretakers can use the predicted results with other information to make decisions of admission of the intake patients, find the optimal pathway for the patients to minimize the residence time, and make intelligent scheduling to reduce the queueing length in the hospital.

Introduction

Hospital cost plays a significant role in national budgets. To some degree, patients are suffering from lack of vacant beds and caretakers. Bottlenecks and congestion are everyday business. The probability of unacceptable refused admission is around 14% [1].

Emergency Department (ED) crowding causes a series of negative effects e.g. medical errors, poor patient outcomes and patient dissatisfaction. Patient satisfaction, staff satisfaction, and hospital revenue are all negatively impacted when patients, information, and materials do not move through hospitals in a timely and efficient way [2].

The hospital crowding is primarily regarded as the consequence of inadequate medical resources. However, recent research has shown that the highly stochastic process of incoming patients causes the violation of resources, which would lead to such crowding.

Hence, to simply expand medical care capacity may do little to relieve the emergency department crisis. The situation can be potentially improved by optimizing the utilization of medical resources, e.g. bed, equipment and personnel

To be able to improve the typical clinical system, it is necessary to develop the patient flow model through the system and describe how the system is constrained by available equipment, beds and personnel. Queuing Theory with Markov Chain (QTMC), and Discrete Event Simulation (DES), are the methods that are used to describe the system.

The first model (QTMC) is only able to consider limited scenarios that can occur. One published QTMC model of the orthopedic department of the Middelheim hospital focuses on the impact of outages of the personnel (preemptive and non-preemptive outages), on the effective utilization of resources, and on the flow time of patients [3]. Several queuing network solution procedures are developed such as the decomposition and Brownian motion approaches.

On the other hand, DES has been well recognized in healthcare. These models are broadly used for the validation of other models. The DES models offer a valuable tool to study the trade-off between the capacity structure, sources of variability and patient flow times [4].

This paper is organized as follows:

- In section 1, the definition of patient flow in the hospital is introduced. Diagnosis and treatment of patients and uncertainty in the system is discussed.
- In section 2, several modeling techniques will be described. Two modeling process, the Queueing Theory and Markov Chain (QTMC) model, and Discrete Event Simulation (DES), are applied to describe the patient flow.
- In section 3, possibilities of using Model Predictive Control (MPC) optimize the patient flow is discussed.
- In Section 4, conclusions are drawn.

1 Patient Flow

The patient flow can be considered as the movement of patients through a set of locations in a healthcare facility. There are six characteristics of patient flow. These characteristics are the basic elements and assumptions in the patient flow model [5].:

- Long waiting lists with respect to complex operations
- Uncertainty and apparent chaos are common
- Every patient is unique
- Relative large variation in Length of Stay (LoS)
- The incidence of complications
- Emergency admissions

The patient flow can be considered as a combination of physical flow, information flow and decision flow:

Physical flow

In this view, the flow of all the existing materials e.g. patients, test/treatment materials, or caretakers is considered. Some examples are patient pathway, transport of the blood, or the flow of caretakers.

Information flow

Include information about the patients and the states in different departments, such as the test results, the occupancy of beds, waiting lists of operation departments, numbers of doctors and nurses who are available, etc.

Decision flow

The decision of a different pathway of physical flow or information flow is the decision flow. The decision flow depends on the diagnosis of the patient and the state in the hospital. Sometimes, decision flow can be a part of information flow.

The components of intake emergency patients are patients from their home, other institutions, private care, other wards, site of the incident or born in hospital. The different sources have different inter-arrival rate; the combination of different intake patients presents a certain distribution. This distribution is able to be predicted by analyzing the history data.

All the intake patients at hospitals can be classified into two modes based on the sick level:

- emergency patients and
- planned patients.

The queueing policy will be different based on the illness level, such as without other factors, a patient with an open wound has a higher priority over a patient with a stomach pain. As a consequence, patients with lower priority have to wait longer. Arrival patients follow a process as depicted in Figure 1.

The arriving patient received by the registration clerk who records patient arrival time and the symptoms. The nurse checks the records and determines the acuity of the illness. If patients arrive in an ambulance, they begin their process at the ER bed area, with the registration paralleling with emergency care service.

In general, after the acuity of the illness has been determined, the patient either goes to the bed area or queues for a bed with a priority queue discipline. Once the patient gets an available bed, the medical treatment begins.

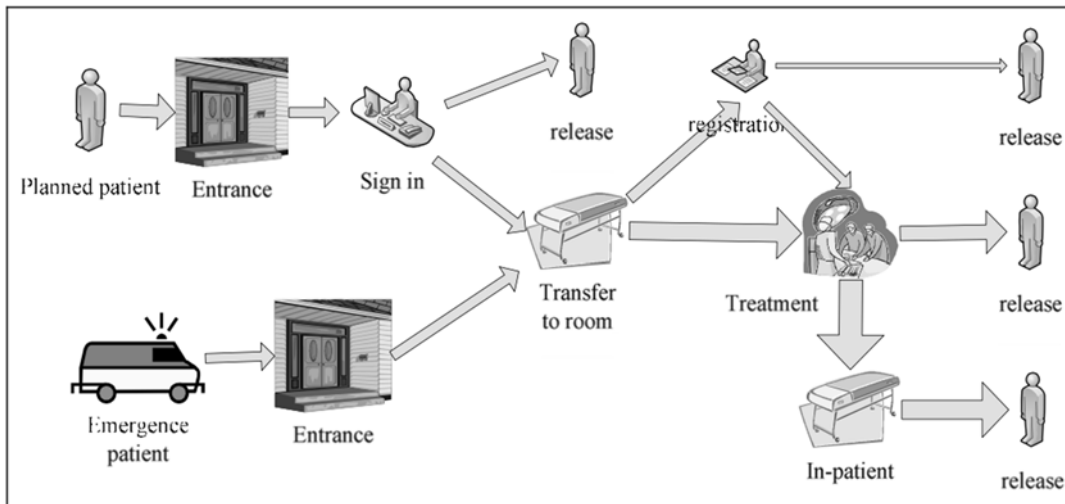


Figure 1. Patient flow of the emergency department

First, the necessary tests are ordered. After the results are obtained from the laboratory, the caretakers will decide whether the patient needs to be admitted or not. The admitted patients will continue treatment and are distributed to another care unit. The records and all the test results will follow the patients to the other units. Other patients will receive necessary therapeutic care and are sent home. The records will cease to exist.

Being admitted to the hospital, being discharged from the ED, leaving the emergency department before treatment, and deceased are the four ways a patient may exit the ED.

The following factors influence the results of diagnosis and selection of treatment [6, 7, 8]:

- Priority of patients
- Quantity of physicians and nurses
- Beds in the wards
- Treatment equipment
- Location of different hospital departments.

Some real data from Ringerike sykehus (Norway) are provided by IMATIS AS [19]. These data include 513 samples. Each sample records the patient ID, the arrival time, departure time, the ward to enter, next ward to enter after treatment.

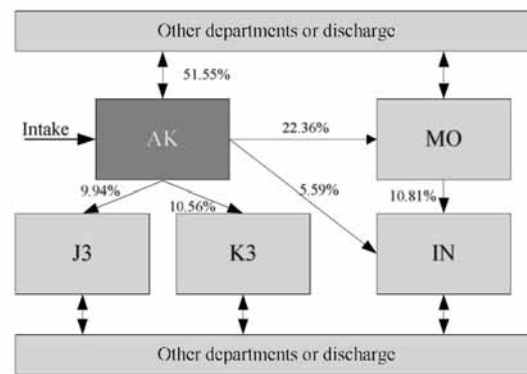


Figure 2. Selected patient flow at Ringerike hospital

In Ringerike sykehus, different departments share the same wards, and the wards are classified by the location and facilities. The wards include AK, MO, K2,3,4, J2,3,4, L2,3,4, IN, I3, 4, and so on [9]. Each ward has a capacity of 9 beds.

One typical pathway is shown in Figure 2. Figure 2 also indicates the frequency of patients going from the AK ward to one of the other ward. Figure 3 shows the number of patients in AK ward at a given time.

The residence time, is the time when the patients arrival at the hospital until they come out of the hospital. The residence time in the hospital includes the residence time at each department and the transfer time. For a department, the residence time includes the waiting time, and the processing time (service time).

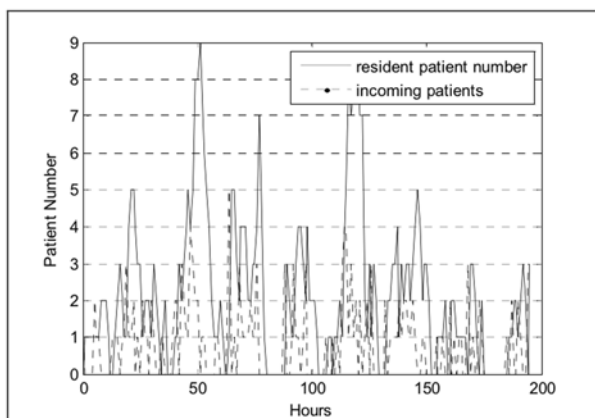


Figure 3. Resident patient number in AK at Ringerike hospital

The residence time in a process following is considered as an Exponential distribution. In actual processes, the distribution can be studied from the history data.

The mean value of arrival rate is influenced by many factors. There is a big difference between weekdays and weekends, working time and resting time, and so on. Big events may also increase the number of patients, e.g. anniversary, sports event, traffic accidents etc. In a day more patients arrive at the hospital during the day and evening than the morning.

The planned patients make an appointment with the hospital. The patients will come to the hospital based on a schedule, which also means this variable can be controlled.

To analyse stochastic variables, the corresponding distributions of interarrival rate and residence time should be found. Herein, Exponential distribution, Weibull distribution, and Poisson distribution are investigated.

- The Weibull distribution has a flexible shape. This distribution has been used successfully in many applications as a purely empirical model [17].
- The Exponential distribution has only one unknown parameter. This distribution has a memoryless property, which means previous states don't influence the future states [18].

- If the variable in the Exponential distribution is integer, the variable can be expressed by Poisson distribution. Poisson distribution has the same properties with Exponential distribution.

For Matlab, functions e.g.

`'wblfit', 'expfit', 'poissfit', etc.`

in the Statistical Toolbox can be used to estimate the parameters of different distributions. One example to obtain the parameters of Exponential distribution is as follows:

Given the data X,

$$\lambda = \text{poissfit}(X)$$

returns the maximum likelihood estimate of the parameter corresponding to 95% (default) confidence intervals of the Poisson distribution, λ [18].

The AK ward mainly processes primary care of the emergency patients. Comparing different distributions with the real data, the Weibull distribution fits the real data the best (mean and variance values in Figure 4, Tab. 1). The Weibull distribution is suitable to demonstrate the properties of the residence time in the AK ward.

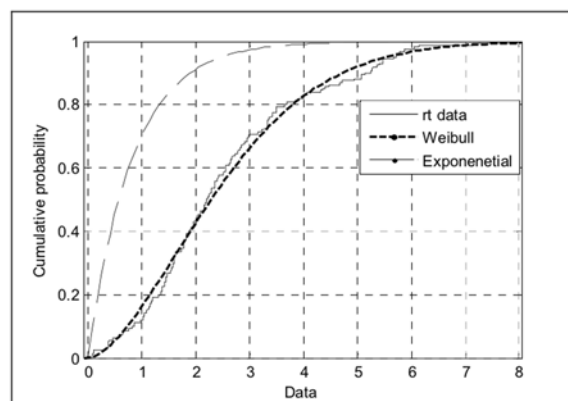


Figure 4. Residence time distribution in AK at Ringerike hospital

| Distribution: | Mean: | Variance: | Parameters: |
|---------------|-------|-----------|------------------|
| Weibull | 2.54 | 2.49 | a 2.85 b 1.65 |
| Exponential | 0.82 | 0.68 | μ 0.83 |

Table 1. Residence time distribution in AK at Ringerike hospital

The resident patient number from the data is always less than the capacity of 9 beds (Figure 3). Thus, it is seldom that patients have to queue for beds in the samples. In this situation, the residence time can be treated as the service time. The parameters in Tab. 1 are estimated using the Matlab Statistical Toolbox.

| Wards | Distribution | Parameters |
|-------|--------------|------------------|
| AK | Weibull | a 2.85 b 1.65 |
| MO | Exponential | μ 15.56 |
| K3 | Exponential | μ 52.02 |
| IN | Exponential | μ 34.37 |

Table 2. Selected residence time distributions in each ward

| Distribution (Poisson) | AK | MO | FO | K3 | IN |
|------------------------|------|------|------|-------|-------|
| Parameter λ | 0.82 | 0.17 | 0.23 | 0.087 | 0.095 |

Table 3. Incoming patient number distribution

The wards (MO, K3, IN) mainly process treatment after primary care, they have different functions and are mainly classified by their location in the hospital. The residence time in these wards are much longer than that of the AK wards (Tab. 2). By analyzing the real data, all the distributions of the residence time of these wards can be treated as an Exponential distribution. In the wards MO, FO, K3, and IN, the resident patient number of selected data is less than the capacity of each ward. The residence time can be taken as the service time.

The incoming patient number is a discrete stochastic variable (see dotted line in Figure 3). The Poisson distribution fits the discrete stochastic variables well. The parameters of all these 5 wards are shown in Tab. 3. The AK ward has the highest arrival frequency of about 0.8 patients per hour. The high arrival rate and the short service time (high throughput) lead to a big variation in performance during one day. On the other hand, the average time of one patient arrival at the other departments is more than 4 hours. The patient number has less variance during one day.

2 Simulation of the patient flow

2.1 Discrete Event Simulation

In DES, the operation of a system is represented as a chronological sequence of events. Each event occurs at an instance in time and marks a change of state in the system [10].

The modeled system is dynamic and stochastic. DES includes Clock, Events List, Random Number Generators, Statistics, Ending Condition [11].

For example, in the process that patients wait for a bed in the ward, the system states are queueing length or number of vacant beds. The system events are patients-arrival and patients-departure. The system states, like vacant beds are changed by these events. The random variables that need to be characterized to model this system stochastically are patient arrival time and residence time.

To simulate such system, first generate a series of random entities based on the distribution.

Let (n, t) be n patients coming into the station at the time t . Then all the incoming patients during

$$(t_1, t_2 = t_1 + dt, t_3 = t_2 + dt, \dots, t_k)$$

can be expressed as

$$\{(n_1, t_1), (n_2, t_2), \dots, (n_k, t_k)\}.$$

Here n_1, n_2, \dots, n_k are random numbers. dt is constant. The simulator generates service rate for each patient, l_1, l_2, \dots, l_k which are random numbers. All the random numbers obey a certain distribution. The patients leave the ward when the residence time is over. The simulator stores all the data. The patient number and other results can be obtained by analyzing the saved data. Such as to compute the resident patient number at time t_i , the simulator find out the patients that time t_i is between this patients' arrival and departure time. The number of these patients is the resident patient number (Figure 5).

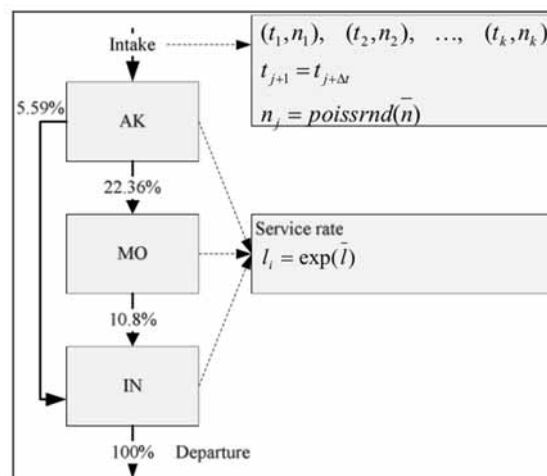


Figure 5. DES of patient flow at Ringerike hospital

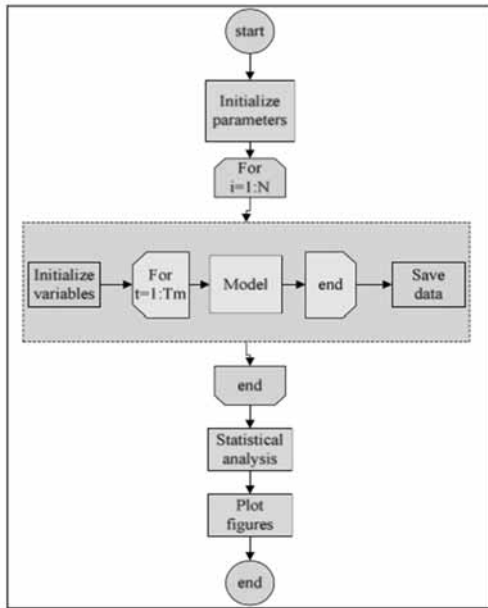


Figure 6. DES programming logic

The simulation logic of DES is shown in Figure 6. Here in order to get the mean value of the results at each time point, DES is repeated (first loop).

There are advantages to build such models [12]:

- Detailed system behavior can be modeled;
- Possibility to model performance, dependability
- Less matrices computing.

Also there are some drawbacks compared with other models [12].

- Long execution time;
- Simulation results are difficult to interpret;
- It is quite likely that some rare events or states are never encountered by the simulation runs.

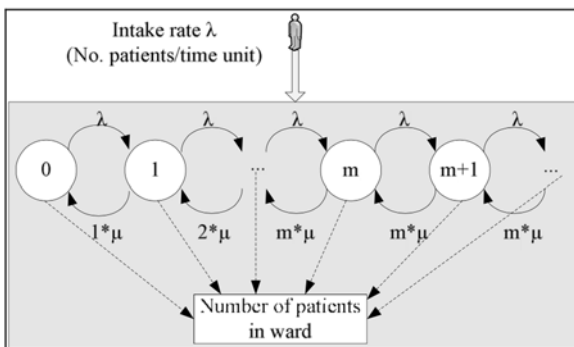


Figure 7. QTMC model of one ward

2.2 Queuing Theory and Markov Process

If a queueing system has m beds, a Poisson distributed incoming rate and an Exponential distributed service rate, this queueing system can be denoted by $M/M/m$ [17]. In Figure 7 μ the service rate in a station, the average time a doctor spent on a patient. λ the inter arrival rate, is the input.

Define $\pi_k(t)$ as the transient state probability vector is the state. An $M/M/m$ queueing system can be described by the model (Figure 7) [10].

$$1 \leq k \leq m:$$

$$\frac{d\pi_k(t)}{dt} = -(\lambda + k\mu)\pi_k(t) + \lambda\pi_{k-1}(t) +$$

$$k\mu\pi_{k+1}(t), k > m:$$

$$\frac{d\pi_k(t)}{dt} = -(\lambda + m\mu)\pi_k(t) + \lambda\pi_{k-1}(t) + m\mu\pi_{k+1}(t)$$

Boundary model $k = 0$:

$$\frac{d\pi_k(t)}{dt} = -\lambda\pi_{k0}(t) + \mu\pi_1(t)$$

This system of ODEs (Ordinary Differential Equation) can be written in Matrix form as:

$$\frac{d\pi(t)}{dt} = Q\pi(t), \pi(0) = (\pi_0(t0), \pi_1(0), \dots) \quad (1)$$

where: $\pi(t) = (\pi_0(t), \pi_1(t), \dots, \pi_m(t))^T$, m is the number of states. $\pi_0(t)$ is the boundary. Since $\pi(t)$ is a probability vector, the sum of the states equals to 1.

$$1^T_{m+1}\pi = 1 \quad (2)$$

The rank of Q is $m - 1$. Q is not a singular matrix.

In order to compute the value of $\pi(t)$, substitute Eq. (2) into Eq. (1), then the differential equation becomes:

$$\frac{dx}{dt} = Q_q x + B_1 u'$$

where $u' = \lambda$ the intake rate can be varied. Here x is the state, $x = \pi_{0:m-1}$, $dim(x) = m$.

$$\frac{d}{dt}(1^T \pi) = 1^T Q \pi \xrightarrow{1^T \pi = 1} 1^T Q \pi = 0;$$

Q_q can be written as a function with inputs u' :

$$Q_q = A_1 u_3 + A_2;$$

$$A_1, A_2 \in \mathbb{R}^{(m-1)(m-1)}.$$

$$A_1 = \begin{bmatrix} -1 & 0 & \dots & & & 0 \\ 1 & -1 & \ddots & & & \vdots \\ 0 & 1 & \ddots & & & \\ \vdots & \ddots & \ddots & & & \\ 0 & \dots & 0 & 1 & -1 & 0 \\ -1 & -1 & \dots & -1 & 1 & -2 \end{bmatrix}$$

$$A_2 = \begin{bmatrix} 0 & 0 & \dots & & & 0 \\ 0 & -2\mu & 2\mu & & & \vdots \\ \vdots & -3\mu & 3\mu & & & \\ & & \ddots & \ddots & & \\ & & & -S\mu & S\mu & \\ & & & & \ddots & \ddots \\ 0 & & & & 0 & S\mu \\ & & & & 0 & S\mu & S\mu \end{bmatrix}$$

u' can be separated into two categories; which are generated by emergency patients and planned intake patients. The Emergency patients are uncontrollable and can be regarded as disturbance v ; the planned intake patients can be scheduled, and can be taken as the control variable u in this model.

$$u' = u + v$$

$$\frac{dx}{dt} = Q_q x + B_1(u + v)$$

$$= (A_1(u + v) + A_1)x + B_1(u + v)$$

The patient number y can be approximately computed by:

$$y = Dx, D = [0, 1, 2, \dots, m - 1]$$

To obtain the solution for queuing networks (Figure 5), first introduce one property of Poisson streams.

Different streams of patients may come into one department. If the streams obey the Poisson distribution, then joining these Poisson streams produces a single Poisson stream. Patients will distribute to different departments after one treatment.

If the patient number obeys the Poisson distribution, probabilistically splitting this stream gives rise to two or more Poisson streams [12]. These two properties guaranteed the patients number coming out from AK ward to IN or MO ward, and the combination of patients from AK and MO wards to IN ward also obeys Poisson distribution.

The outputs of each station $(\lambda_{0,1}, \lambda_{0,2}, \lambda_{0,3})$ is computed by solving the 2nd order equation. This is an approximate value obtained from the steady state solution of a queuing system (M/M/m). The output of the queuing system is only dependent on the current input.

Here if the resident patient number has not reached the steady state, the current input is treated as it has reached the steady state with another input λ_0 . This value is only used to compute the departure patient number [10].

$$L = \frac{\lambda_0}{S} + \lambda_0 * \frac{C1}{S} * \mu$$

$$1 - \frac{\lambda_0}{S * \mu}$$

$$\Rightarrow \lambda_0 = \frac{1}{2} \mu (S + C1 + L$$

$$- \sqrt{S^2 + 2SC1 - 2SL + C1^2 * 2C1L + L^2})$$

Here, The current patient number, the number of servers, and current intake patient rate μ are known. $C1$, which equals to the probabilities that the patients must queue for a bed (including full beds occupied situation), can be computed in real time.

The inputs of each station are the output streams from other stations multiply the probabilities of patients from other stations flowing into this station.

The model in a three station queuing network (Figure 5) can be written as

$$\frac{dx'}{dt} = (A_1'(u' + v') + A_2')x + B_1'(u' + v')$$

$$\frac{dx''}{dt} = (A_1''(u'' + v'') + A_2'')x'' + B_1''(u'' + v'')$$

$$\frac{dx'''}{dt} = (A_1'''(u''' + v''') + A_2''')x'''$$

$$+ B_1'''(u''' + v''')$$

$$y' = D'x', y'' = D''x'', y''' = D'''x'''$$

$$\text{Here } v' = \lambda_1$$

$$v'' = \lambda_2 = p_{12} * \lambda_{0,1} + p_{32} * \lambda_{0,3}$$

$$v''' = \lambda_3 = p_{13} * \lambda_{0,1} + p_{23} * \lambda_{0,2}$$

$$\lambda_{0,1}$$

$$= \frac{1}{2} \mu_1 \left[S_1 + C1' + y' \right.$$

$$\left. - \sqrt{(S_1^2 + 2S_1C1' - 2S_1y' + C1'^2 + 2C1'y' + y'^2)} \right]$$

$$\lambda_{0,2}$$

$$= \frac{1}{2} \mu_2 \left[S_1 + C1'' + y'' \right.$$

$$\left. - \sqrt{(S_2^2 + 2S_2C1'' - 2S_2y'' + C1''^2 + 2C1''y'' + y''^2)} \right]$$

$$\lambda_{0,3} \frac{1}{2} \mu_3 \left[S_3 + C1''' + y''' \right]$$

$$- \sqrt{(S_3^2 + 2S_3C1''' - 2S_3y''' + C1'''^2 + 2C1'''y''' + y'''^2)}$$

$$C1' = E'x', C1'' = E''x'', C1''' = E'''x'''$$

The simulation logic is shown in Figure 8. Figure 9 is the simulation results of patient number and Figure 10 is the intake patient number in AK, MO, and IN wards.

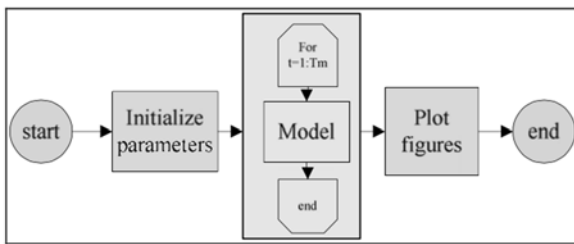


Figure 8. Queuing theory programming logic

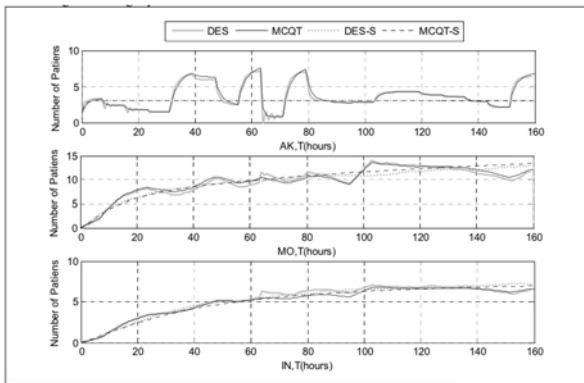


Figure 9. Patient number (AK, MO, IN)

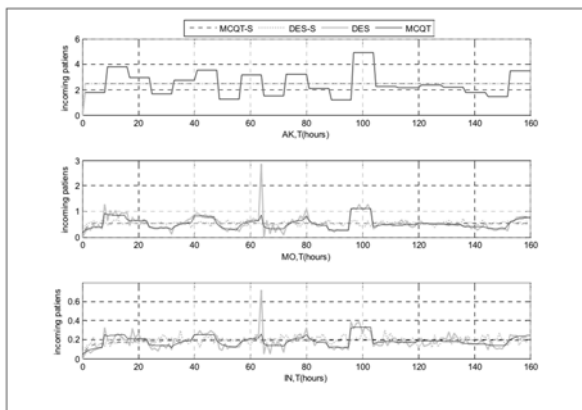


Figure 10. Intake patient number (AK, MO, IN)

The plots of DES and MCQT are the results simulated by the two models (DES, and MC + QT). The intake patient number has the circle time of eight hours. From Figure 3, we can see the intake patient number have cyclical changes, and the cycle time is around 8 hours. The selection of 8 hours circle time fits the actual situation and previous studies [2].

The MCQT model is less sensitive than the DES model, the fluctuation of MCQT model is less than the DES model, when the inputs have great changes.

The two plots DES-S and MCQT-S show the patient number of two models when the intake patient number and service time is constant. The relationship of AK, MO, and IN wards is shown in Figure 5. The plots show that both models can simulate the patient number and they have similar results.

The state space of MCQT is 100 and the ensemble size of DES is 200 (first loop in Figure 6). The larger the dimension of the state space the better results can be obtained. But a large state space requires more computation memory and time to simulate. The results show that the largest average patient number is less than 15.

The number of state space with 100 is possible to get a very accurate result.

The DES plots have more fluctuation between each simulation plots. These unstable properties can be improved by increasing ensemble size, but a large ensemble size of simulations will lead to a higher computation cost.

3 Optimal control of patient flow

In order to perform the function of the emergency department and the other departments optimally, we can control some variables, e.g. the work schedule of caretakers, the available beds, and the incoming patients. The control variable here is chosen as the planned incoming patients.

Many algorithms have been studied to control the queuing systems, e.g. dynamic programming [14], and Lagrange approach of adaptive control based on Markov Chain model [15]. In this chapter, the use of Model Predictive Control is discussed.

The model predictive controller uses the model and current measurements to calculate future inputs that will fulfill the objects and variable constraints. Model predictive controllers rely on dynamic models of the process. The models are used to predict the future unknown variables.

The dynamic system can be modeled as or be transformed to a linear state space model. Then the effect of changes in unknown variables can be added together to predict the response. This approach leads the control problem to a series of matrix algebra calculations that are fast and robust [16].

In the queuing system here, the predictive model is based on queuing theory and the Markov Chain model. The inputs are either planned or emergency patient inter-arrival rate. The object is to reduce the queuing length in a certain time horizon. The measurements are the current patient number in the system.

A control objective J_k (or cost function) is a measure of the process behavior over the prediction horizon L . This function can be the difference between future outputs and some specified future reference, and sometimes recognizing that the control is also costly.

This objective is minimized with respect to the future control inputs and only the first control input is actually used for control.

This optimization process is solved again at the next time instance. The advantage of MPC is that constraints of the process variables can be treated in a simply way. In order to optimize the patient number and minimize the transport of patients, both the deviation between outputs and references, and the variation of the control variable should be considered. The intake patient number should be positive.

These algorithms implemented real-time is shown in Figure 11.

The states are the probabilities x which cannot be measured. The inputs are patient arrival rate which is estimated. Current patient number y can be measured. In order to use MPC algorithm, the states should be estimated. One simply way is to set the current state $x_t(i) = 1, x_t(n \neq i) = 0$, when there are $i-1$ patients in the wards. A state estimator (e.g. Kalman Filter) can also be used to estimate the state.

The patient number has a daily and weekly cycle of change. When the throughput of the ward is high, the prediction horizon can be 1 day. Otherwise, the horizon can be 1 week. A smaller time step requires larger memory. The time step T could be selected as 1 hour. This selection can present nature of the system, and also be easy to compute and control.

Other selections with 6 or 8 hours time step are preferred for high throughput systems or long prediction horizon. The data from Ringerike sykhus shows that the throughputs of the wards are low and the data varies per day significantly. The MPC algorithm with 1 hour Time step and 24 hours horizon can be selected.

The states number combined with the unknown variables and horizon may cause large matrix and complex matrix computing. This algorithm is time consuming. Compared with the time step, the long computing time is tolerable.

4 Conclusion and further work

Health care resources and patient treatment have become increasingly important and expensive. The task of balancing the delivery of quality health care and the facilities in the hospitals is becoming a hot topic.

Patient flow is the transport of the patients through the health care system, including three different phases: the physical flow, information flow and decision flow. In order to find some possible solutions for improving the patient flow and predicting the number of the patient in different departments, models based on different theories, e.g. the Queuing Theory and Markov Chain model, the DES are introduced and compared.

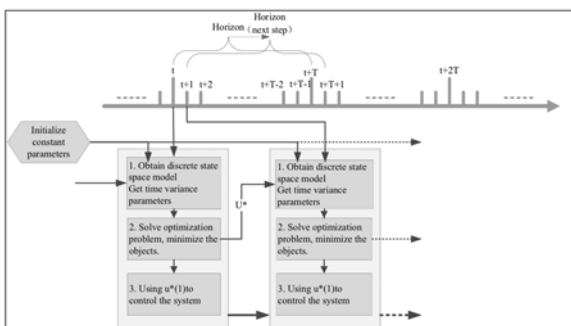


Figure 11. MPC for periodic variance system

The simulation based on Queuing Theory and Markov Chain can be a good approach for implementation in the real hospital. This model provides a quite good method to handle the randomness and uncertainty in the patient flow, but it is not easy to find a proper mathematical model when the process is complex. The DES models are commonly used in checking the other models. The approach of using this model in patient flow also gives a quite realizable result.

The patient flow can be controlled by a host of different methods. The MPC methods described here are adapted from its use in process control. And because of the limitation of the control variable, improved algorithms, e.g. more efficiently handling the integral variables and the constraints, should be further developed. The future work can be considered in the following aspects:

- Modeling systems with more complex properties. The real process is more complex than the case studies in this thesis. Problems like processes with different service disciplines, and process which includes the effect of caretakers can be modeled in the future.
- Optimal control of the queuing system Section 4 demonstrated the possibilities of using MPC to control the queueing systems. More research should be done to get the theory to practice.
- Reduce and optimize the matrices computing. Simulator generates plant of matrices during simulation. These matrices are time consuming and will take up lots of resources. Methods to reduce and optimize the matrices computing can be investigated in the future.
- Implementation in the real hospital.

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- [19] IMATIS AS, Vipeveien 51, N-3917 Porsgrunn

Corresponding author: Bernt Lie,
Telemark University College, Porsgrunn, Norway
Berndt.Lie@hit.no

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Analysis of the Aortic Influence on the Impedance Cardiography Signal by a Simple Model using Finite Integration Technique

Mark Ulbrich, Alexander Schauer mann, Steffen Leonhardt

Philips Chair for Medical Information Technology, RWTH Aachen University, Germany

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Chronic heart failure is a serious disease in our society which can potentially be diagnosed by impedance cardiography (ICG). However, there is a strong debate about using this technology. In this work, the capability of a simple model to generate the ICG signal by taking the aorta as major signal source has been analyzed. Therefore, a simulation with a high temporal resolution has been conducted using the finite integration technique (FIT). It has been shown that although neglecting other physiologic signal sources, the results obtained from the simulations produce an ICG signal which correlates very well with measured ICG signals.

Introduction

Since the beginning of the 20th century, a demographic change is observable in Europe which leads to a steadily aging society. Hence, society will have to face more and more geriatric patients and diseases, which leads to increasing costs and burdens on medical personnel. Thus, it is reasonable to establish methods to treat elderly people more cost-effectively and more easily by improving diagnostics and monitoring for certain diseases that prevalently occur among elderly people.

Cardiovascular diseases are the most common cause of death in Western Europe. One of these diseases is chronic heart failure (CHF) from which 2 million people are suffering and this number increases every year by half a million. The basic definition of CHF is a state in which the heart is not able to pump enough blood into the periphery to supply it with oxygen. Reasons for that can be dysfunctions concerning filling, contractility or emptying of the ventricle. Measures for these dysfunctions are hemodynamic parameters such as cardiac output (CO) or stroke volume (SV).

Until now, the gold standard for measuring these parameters is the thermodilution technique which utilizes a pulmonary artery catheter [1]. However, risks of estimating CO via catheters include infections, sepsis, and arrhythmias, as well as increased morbidity and mortality. A technology to acquire SV or CO non-invasively is echocardiography. Here ultrasound images are used to calculate these parameters by a physician.

A very promising technology to measure cardiac output and other hemodynamic parameters easily and non-invasively is impedance cardiography (ICG). Although this technology is known since the 1960s, it is not used in clinical practice today. One reason is that processes in the human body during ICG measurements are widely unknown, which means e.g. that the composition of physiological processes as contributors to the ICG signal is very complex. Another reason is that impedance cardiography is considered to provide unreliable results [2]. One way to analyze where the current paths run, and which tissue contributes significantly to the measurement result, is to use computer simulations employing FIT.

Other researchers have already examined multiple sources of the impedance cardiography signal, using different approaches. Some works are based on simple geometries [3], others on real anatomical data, such as MRI data [4, 5]. The examined sources comprise heart volume and position, diameter of large vessels, changes in conductivity of the lungs as they fill with blood, and shear rate dependent changes in conductivity of the blood in large vessels. Besides identifying sources, it is important to know to which extent the various sources contribute to the resulting signal. A recent study suggests, that the genesis of the impedance cardiogram is attributed primarily to volumetric expansion of the aorta [6].

Since controversial results have been obtained before, a simple model shall be analysed within this work to clarify if it is sufficient to explain the origin of the ICG signal. Therefore, physiologic signals with a high temporal resolution shall be used.

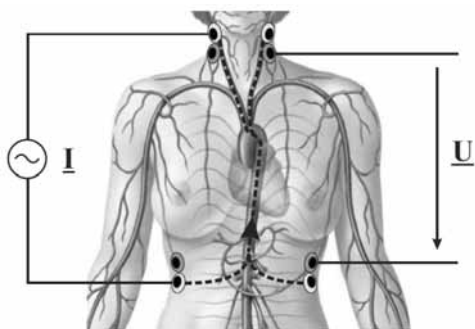


Figure 1. ICG measurement

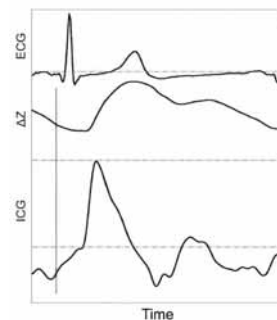


Figure 2. ECG, ΔZ and ICG waves

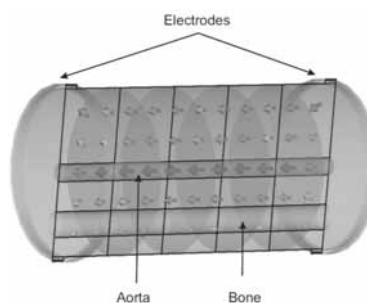


Figure 3. Simulation model.

1 Impedance Cardiography

ICG is a method for measuring hemodynamic parameters at one fixed frequency between 20 and 100 kHz. Similar to a bioimpedance analysis, tetrapolar electrodes are used to measure the complex bioimpedance. Therefore, one electrode pair is used to inject the current and the other to measure the voltage of the thorax so that four electrodes have to be used for one measurement (cf. Figure 1). In practice, 8 electrodes are used, because the pairs of current injecting electrodes act as one current source and the voltage sensing electrodes lie on the same equipotential lines.

The complex impedance is dependent on electrode position and quality, skin thickness, sweat and pathologies. In contrast to bioimpedance analysis, the thoracic impedance has to be acquired continuously because its temporal derivation contributes to the stroke volume.

The measured stroke volume according to Bernstein and Sramek can be described by the following equation:

$$SV = \delta \cdot \frac{(0.17)^3}{4.2} \cdot \left| \frac{dZ}{dt} \right|_{\max} \cdot \frac{t_e}{Z_0} \quad (1)$$

Here the factor δ is the actual weight divided by the ideal weight, t_e the left ventricular ejection time (LVET) and Z_0 the thoracic base impedance [7]. Two local minima of the ICG signal are used to calculate the LVET [8]. Figure 2 shows a typical impedance signal and its temporal derivation.

2 Methods

Classical impedance cardiography analyzes the thoracic impedance assuming the thorax to be composed of two cylinders: one inner cylinder representing the aorta and outer cylinder with one conductivity for all other tissues.

This is of course an assumption which leads to modelling errors [10]. Hence, new models with different approaches have been created.

In this work, the accuracy of the classical ICG model shall be analyzed using FIT simulations with a high temporal resolution and an anatomical data set of a male human to create an improved model. Other works mostly concentrate on systolic and diastolic events only [11]. The simulation program used for this is CST EM Studio[®] from Computer Simulation Technology in Darmstadt, Germany.

The simulation setup is based on the original model of Kubicek et al. and contains three cylinders [10]. The diameter of the outer cylinder (260 mm) is based on the size of the visible male's thorax, the diameters of the inner cylinders on the size of his aorta (25 mm) and spine (40 mm). The male data set is based on the Visible Human Data Set from the National Library of Medicine in Maryland [12]. The model used for the simulation results is shown in Figure 3. It consists of the materials bone, blood and tissue with the conductivities:

$$\sigma_{\text{bone}} = 0.05 \frac{\text{S}}{\text{m}} \sigma_{\text{blood}} = 0.7 \frac{\text{S}}{\text{m}}$$

$$\sigma_{\text{tissue}} = 0.25 \text{ S/m.}$$

These values are based on empirically assessed values by Gabriel et al. at 70 kHz [13]. For the value for the bone tissue, it has been taken into account that bone consists of bone marrow, cancellous and cortical bone tissue.

For every expansion step a new model has been created using an aortic diameter increase of 20% as the maximum [14]. In addition, the expansion of the surrounding tissue has been taken into account by increasing its radius by the following equation:

$$r_{\text{tissue}} = \sqrt{(130 \text{ mm})^2 - (12.5 \text{ mm})^2 + r_{\text{aorta}}^2} \quad (2)$$

To facilitate the creation of the different models, a script has been written using WinWrap Basic included in CST Studio, so that all 103 points in time could be simulated automatically. Every model had a mesh density of approx. 980000 tetrahedrons.

Since the expansion of the aorta is proportional to the aortic blood pressure (cf. eq. 3), real measured data from PhysioNet [15] has been used as basis for the aortic expansion [16].

$$\Delta R = \frac{\Delta P \cdot R_0 \cdot \text{extensibility}}{100} \quad (3)$$

Here R_0 is the diastolic radius of the aorta. The aortic blood pressure has then been scaled to fit the requirement for the maximum aortic expansion so that the diameter of the aorta varies between 25 and 30 mm. For every point in time, the impedance of the whole setup has been calculated so that the impedance depends on the expansion of the aorta only.

3 Results

For every point in time, the complex impedance of the simulation model has been calculated. To get correct impedances, a correction factor has to be considered resulting from an increase in simulated impedances due to the size of electrodes [17]. In addition, the resulting curve for the real values of the impedances has been derivated to get the impedance cardiogram. Both curves are shown in Fig. 4. The magnitudes of impedances were found to be in the range of physiological values ($37.3 < Z [\Omega] < 37.8$).

The last curve comprises three heart cycles and one cycle has been used for a cross correlation analysis with ICG raw data from a measured male subject (cf. Fig. 5). The thoracic impedance was acquired using a "niccomo" patient monitor [18].

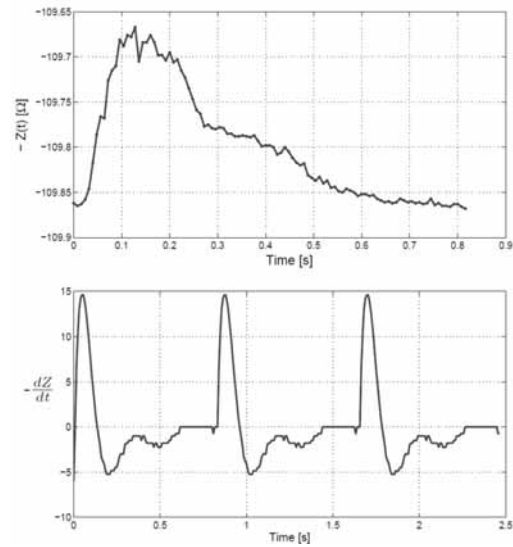


Figure 4. Simulated resistance and ICG

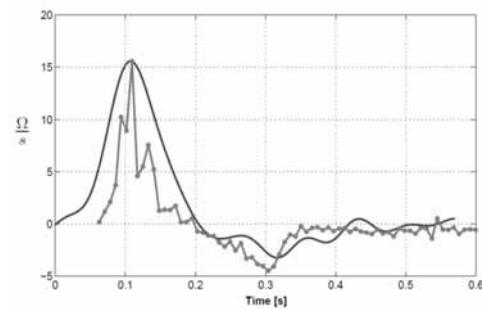


Figure 5. Comparison between simulated (red) and measured ICG (blue)

For the analysis, the height of the simulated curve has been scaled to fit the height of the measured curve. This must not be considered as a source of error because it is only taken into account that hemodynamic parameters vary interindividually. Comparing the two time signals, the correlation coefficient without lag is 0.88, proving what Fig. 5 suggests visually.

4 Discussion

The task of this work was to find out whether the assumption to take the aorta as the major contributor for the impedance cardiography signal is correct or not.

A simple dynamic simulation model has been created to simulate the aortic expansion during a heartbeat using a high temporal resolution. The dynamics of this model is based on measured data of a subject.

Despite the very simple model of the human thorax, comprising only a cylindrical aorta and an outer cylinder representing all other tissues, it could be shown that the aorta plays indeed a very important role in the physiological ICG signal generation as the major contributor, which corresponds to a recent study in which the impedance change of a dog's aorta has been measured in vivo [6]. This is an astonishing result because other works have shown that only about 0.7 % of the measured impedance change of the thorax are caused by the aorta [5].

5 Outlook

Models being created to overcome the inaccuracy of today's ICGs should take into account that the aorta is the major contributor of the ICG signal. In addition, future works shall show to which extent other dynamic signals influence the ICG signal (e.g. volume changes of heart and lung) and which static values contribute to the non-dynamic part of the signal. What is more, changes in the ICG signal caused by pathologies such as lung edema and the possibility of the simulated signal to reflect the characteristic points should be analyzed.

Acknowledgements

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Corresponding author: Mark Ulbrich

Philips Chair for Medical Information Technology
RWTH Aachen University
ulbrich@hia.rwth-aachen.de

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Long Term Behaviour of Agent based Epidemic Simulation of Streptococcus Pneumoniae - A Mathematical Status Report

Florian Miksch¹, Nikolas Popper², Günther Zauner², Irmgard Schiller-Frühwirth³, Gottfried Endel³

¹Vienna University of Technology, Institute for Analysis and Scientific Computing, Vienna, Austria;

²dwh Simulation Services, Vienna, Austria;

³Evidence Based Economic Healthcare, Hauptverband der Öst. Sozialversicherungsträger

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Streptococcus Pneumoniae is a bacterium that causes several infections like pneumonia, otitis media, meningitis and sepsis. Today, due to vaccination against many other epidemics, these are one of the most common and dangerous illnesses for small children in developed countries. The purpose of this work is to develop an agent based model that is able to simulate a pathogen like Streptococcus Pneumoniae and to understand the long term effects of different vaccination strategies. The main part of the work is to explain the model structure in detail, understand the benefits and problems of such an agent based epidemic model and find out how the model behaves in different situations. Also profound data search has to be done to understand the whole system and identify the model parameters as accurately as possible. It is important to realize how to cope with restrictions in data quality and different results of different studies. Agent based models are only one approach to simulation of epidemics so other people of the research group are simulating the same problem with different model types. In the end the results of the different models should be compared and benefits of the different approaches have to be discussed.

SNE 20/2, August 2010

1 Introduction

1.1 Streptococcus Pneumoniae

Streptococcus Pneumoniae is a bacterium that causes several infections like pneumonia, otitis media, meningitis and sepsis. Today, due to vaccination against many other epidemics, these are one of the most common and dangerous illnesses for small children in developed countries. The standard therapy against Streptococcus Pneumoniae is Penicillin but due to wide spread of the pathogen and its combat Penicillin resistance grew especially in North America [2].

In the early eighties a vaccination against Streptococcus Pneumoniae was invented. The problem with this vaccination is that it provides no protection for children younger than 24 months because it does not produce an immune reaction at them. But there are two reasons why it is quite important to protect young children: First, young children (as well as old people) have the by far highest disease rate because their immune system is quite weak compared to adults. And second, young children are suspected to be responsible for most of the transmissions of Streptococcus Pneumoniae.

The real world system seems to be very complex; additionally many different medical studies report different results.

Fact is that a significant part of the population is infected with Streptococcus Pneumoniae and can infect other people while only a small part falls ill with it. All the other people get rid of it after a while and do not even realize that they have been infected. All together there are more than 90 serotypes of Streptococcus Pneumoniae. It seems to be clear that the prevalent serotypes and the percentage of infected individuals in a population is regional different and changes over time.

The PCV-7 vaccination provides protection from 7 frequent serotypes, in North America it covers about 90% and in Europe about 70% of the prevalent serotypes [2].

1.2 Hospital data

Comprehensive hospital data from Austrian hospitals about pneumonia, meningitis and sepsis is available. This data can be normalized using population data, and then some statements can be made about the probability that a random person with a certain age falls ill with one of these illnesses. Therefore the number of infected people is a black box because there are no corresponding studies available for Austria.

The important result from this data research is that the probability to fall ill is very high for babies, then it gets lower for children, it stays on a very low level for adults and starts to increase dramatically again from age 65 onwards.

It is obviously that pneumonia is by far the most common illness caused by Streptococcus Pneumonia. Meningitis and sepsis are only occasional instances all over Austria.

1.3 Epidemiological phenomena

This model aims to examine two considerable epidemiological phenomena in detail.

Serotype replacement. One problem is that there are many uncommon serotypes that are not covered by the vaccine. Some studies presume that vaccinated people get infected with uncommon serotypes instead so other serotypes could become more common. So the real long term effect of the vaccination could be much lower than expected. There is even one clinical study that reports serotype replacement [3]. But usually serotype replacement cannot be observed because at the moment only a too small part of the population is vaccinated and therefore random effects cannot be separated. The few vaccinated people really benefit in many studies because they just do not get in touch with uncommon serotypes and compared to the rest of the population they are not many enough to make uncommon serotypes more common. This model should be able to give some more information if such a phenomenon can be expected and how strong it might be.

Herd immunity. Another presumption is that there exist substantial effects for the whole population if only children are vaccinated. The explanation is on the one hand a much higher percentage of children than adults are infected, on the other hand in some studies it is presumed that most transmissions of this pathogens are between infants and adults because their physical contact is often much closer than between two adults.

Missing Parameters. First, there are many studies with controversial results about the percentage of the children infected with Streptococcus Pneumoniae.

But no data about the part of infected adults, especially old people, can be found. In Austria only the reported cases of disease outbreaks with admission are reported. Second, clinical studies do not provide data about what part of infected people fall ill within a defined period or, at least, how many infected people are ill at a certain time.

2 The Model

The model is an agent based model with some special functionality. Requirements are:

- Simulate over a long period (approximately two decades) to find out long term effects
- Consider a changing population structure for of long term simulation
- Implement a social model to simulate contacts between individuals
- Simulate more than one pathogen to differentiate between covered and non-covered serotypes by the vaccination

The model consists of three parts: The population part, the social part and the epidemics part.

The population part. Single persons have the following attributes: Age, Gender, Infection State and Pregnancy (women only). Additionally the auxiliary attributes unique ID-Number for identifying a single person, Age Class and Infection Protocol is stored. Changing population is realized so that people are getting older, they can die and women can give birth to babies. The parameters can be easily identified with real population data of Austria provided by "Statistik Austria" [4].

The social part. Epidemics can be spread only through direct contacts between two persons. Contacts can happen in a household, at work, while meeting friends and randomly. It is not possible to simulate such a detailed system efficiently so it is modelled in a simplified way based on a suggestion in a US-American paper [1]: Consider a connection between two persons only without mentioning how and where they meet. A connection between two persons means that these persons meet each other in that time step. Two people are called friends as long as a

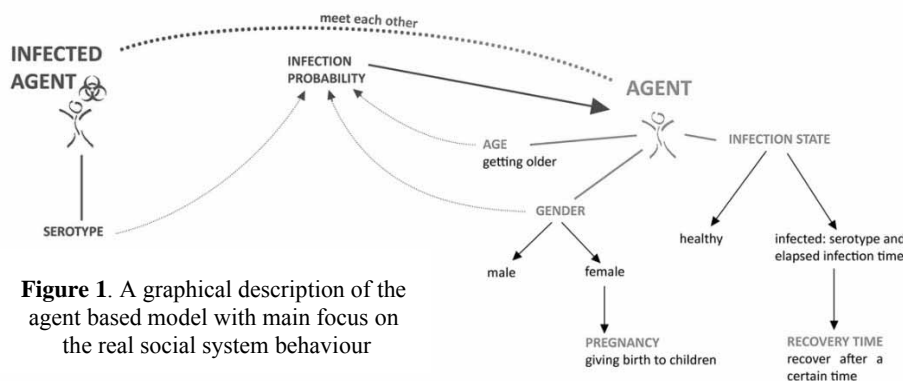


Figure 1. A graphical description of the agent based model with main focus on the real social system behaviour



connection between them exists. The social net is never constant so it has to change from time to time. At first, constants have to be defined: The average number of connections per person, the break-up rate and the connection rates. Every time step some of the connections depending on the break-up rate are deleted and new connections, depending on connection rates, are added until the average number of connections per person is reached. The new connections are, depending on the connection rates rate, partly completely random, partly two people of the same age group and partly two random “friends” of a person who are not connected yet.

The epidemics part. For the epidemics part two constants have to be defined: The infection probability and the recovery time. The procedure of the epidemics part is three steps: At first process all connections between an infected and a healthy person one by one and let the healthy person become infected with the infection probability which is dependent on the age and gender of the susceptible person and the serotype. In the second step increase the infection time by one of all infected persons. This value is stored in the Infection State attribute of a person and means how long an infected person has been infected already. At the end let all infected persons recover that have reached recovery time which means to set their Infection State the healthy state.

Additional functionality:

- Simulating two or more pathogens where a single person cannot be infected with more than one pathogen at one time.
- Individual infection probabilities and recovery time depending on the age and gender of the person and on the pathogen.

3 Simulating the model

3.1 Simulating one serotype

While simulating one pathogen only the model behaves very predictable. Depending on infection probability and recovery time the number of infected and healthy persons reaches, independent of the start values, a constant level. A higher infection rate, a longer recovery time and a lower number of connections per person cause a higher level of infected people. Additionally a correlation between two parameters can be observed: doubling (or halving) the infection rate has the same effect as halving (or doubling) the number of

connections per person. Correlations between the recovery rate and other parameters cannot be found but it has another effect: A higher recovery rate causes a more inert system which means that overshooting occurs for long recovery times but not for shorter ones.

The results seem to be really good and useable because the model is predictable and the parameters can be adjusted easily and efficiently. The prevalence of overshooting shows that the model does not correspond with the first-order differential equations of the simplest SIS-model. So differential equations of order two or higher have to be considered if the model should be identified with a differential equation model.

3.2 Simulating two serotypes

Things become more difficult when simulating two serotypes. If both serotypes are equally strong (that means that they have the same parameters) the behavior will be completely randomly until one of the serotypes becomes extinct. Then, the system continues in the stable one-serotype system.

If one serotype is stronger (higher infection probability or recovery time) the weaker serotype will become extinct very fast. Such behavior does not correspond with reality at all. There are over 90 different serotypes and all of them survive even if they only occupy a very small part of all infected people. At least all the time the numbers of healthy people and infected people altogether stays on a constant level. The level is the same as the level of the one-serotype model. If the two serotypes have different parameters the number of healthy people in the two-serotype model is the same as in the one-serotype model with the parameters of the stronger serotype (the stronger serotype is the one that will survive).

3.3 The updated model

Because of the strange behaviour another approach for the infection part is developed. In the original model only healthy persons are susceptible. This means that an infected person can only be infected with another serotype after he or she has recovered from the current infection.

Clinical studies report that sometimes infected persons get infected with another serotype without being recovered meanwhile. So the next try is to allow infected persons to get infected with another serotype and loose the old serotype simultaneously before the end of the recovery time.

Including this rule into the model structure it is now possible to simulate two different serotypes within a more stable system. First simulations show that it is not as predictable as the one-serotype system but if the parameters are chosen properly serotypes do not become extinct any more. Also a tendency of how strong the single serotypes are can be observed very well. This makes it possible to give proper statements about the behaviour of two or more serotypes in one system now and additional results about serotype replacement can be acquired.

4 Results

Results are very controversial. On the one hand we have predictable results – the number of infected people together. On the other we have a partly chaotic and non-predictable system. Things got better with the updated model which is not completely tested yet. Anyway the results of our simulation runs show the same problem than in real life. Different studies in different countries report completely different results, so it seems that the real system is not stable in a local area at all.

Simulation of vaccination strategies. Extensive testing with different parameters of vaccination strategies has not been done yet. First results show a good protection from vaccinated serotypes even if only a part of the population is vaccinated. But a very strong serotype replacement can be observed too.

Simulation runs based on real data. The problem is that many different clinical studies from Europe and the USA show completely different results. At first it has to be specified which real datasets we consider as our reality for the model, then it is possible to determine the model parameters and simulate it.

Simulation of herd immunity. No data about infection rates for different ages, especially for adults, could

be found yet for Austria, so the model has not been tested on herd immunity so far. Once we simulate the model with parameters based on real data we will get results for herd immunity automatically.

5 Outlook

Finish testing of the updated model. When finished, simulate the model with different parameters corresponding with clinical studies and find out effects of vaccination of small children.

Up to now all runs are done with same parameters for all age groups regarding infection rates. As there is no data about infection rates of adults and old people available, these parameters could be estimated using illness probabilities for different ages that are calculated from hospital data.

With consensus for Austrian data about infection, transmission and illness rates, vaccination effects on individuals for different age groups can be simulated and we will receive stable and reliable results for serotype replacement and herd immunity with the updated infection model.

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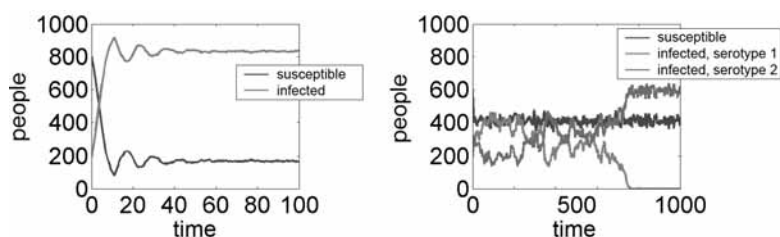


Figure 2. Representative results of the model. On the left side a result of a ‘single serotype run where overshooting can be observed and on the right side a result of a run with two simulated serotypes.

Corresponding author:

Florian Miksch
dwh Simulation Services, Neustift-
gasse 57-59, 1070, Vienna, Austria
florian.miksch@dwh.at

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A System Dynamics Model of Health Insurance Financing in Austria

Patrick Einzinger¹, Günther Zauner^{1,2}, A. Ganjeizadeh-Rouhani³

¹Vienna University of Technology, Institute for Analysis and Scientific Computing, Vienna, Austria;

²“Die Drahtwarenhandlung”-Simulation Services, Vienna, Austria;

³Evidence Based Economic Healthcare, Hauptverband der Öst. Sozialversicherungsträger

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ABSTRACT As the financial situation of the health care system in Austria is an important issue, a dynamic model of receipts and expenditures of public health insurance can give important insights on possible future behaviour and outcome of various policies. Therefore a model is developed using the method System Dynamics (as defined by Jay W. Forrester) and for implementation the software Vensim. Based on a dynamic population model, global income and expenses are simulated, where the income results mainly from contributions and expenses come from medical attendance and prescribed drugs, which are calculated from occurring illnesses. After introducing the structure of the underlying social insurance system in Austria, the model structure in detail and the implementation of the demographic population part are explained. Policy and scenario testing can be done very easily with such a model structure.

1 Motivation

In Austria, health care is organized primarily in public health insurances (see for example [4]). Most of them have been under great financial pressure during the last few years, so decisions have to be made in order to reform their structure. However, the health system is apparently complex, and impacts of new policies cannot be predicted easily as the system has various dynamic feedback loops with different delays — for example if one considers the long-term effects of disease prevention programs, which might be costly for the short term, but pay off later. Thus a dynamic cost model of a public health insurance is useful for getting better insight into resulting problems and the suitability of possible solutions. Furthermore it is feasible to simulate various scenarios and get qualitative insights.

2 Background on public health insurances

Public health insurance represents its insured persons when dealing with providers of medical care. It negotiates contracts with them and pays for treatments and prescribed drugs. On the other hand the insurance gets contributions which in Austria depend on the income of the insured. The objective of public health insurances is not to draw profit, but to achieve a balance between receipts and expenses. Even more important is public health in general; insured persons should receive at least all health services which make a substantial contribution to their well-being.

Contrary to private health insurances, public health insurances in Austria are not allowed to demand higher contributions from persons at higher risk for diseases, and therefore people with low income and high risk benefit from the system, which is desirable in a social state. However this can lead to disadvantages for health insurances with a bad risk structure. In Austria there is an equalization fund for compensation of such insurances. For more information on risk structure and risk selection, see [2]. All financial flows of an insurance can be seen from its closing of accounts (for example [5]). It is a promising approach to let the model replicate this structure. System Dynamics seems to be a natural approach for it, as it makes use of stock and flow diagrams and feedback loops. Moreover, System Dynamics models can be simulated quickly and allow mathematical analysis as they are essentially systems of ordinary differential equations. This approach has been used already by Groesser [3] for modelling the German health insurance fund. However, apart from various differences to the Austrian health system, that work does not go into much detail when it comes to the kind of health services provided or the structure of health care.

3 The chosen approach

The relations of main components of the model are represented in Figure 1. The central element is the “Health Insurance Fund”, which is a level that stands for the financial situation of the health insurance. It is modified by “Income” and “Expenses”.

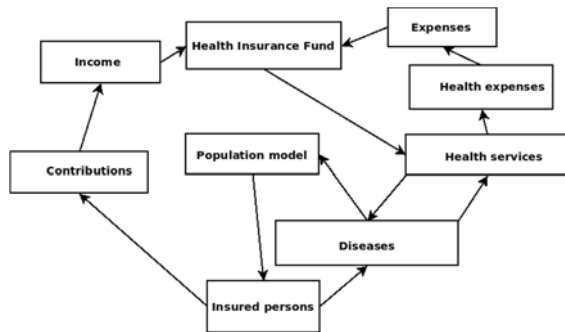


Figure 1. Overview of main components of the model, arrows signify influences between them

“Contributions” are by far the most important source of income, as “Health expenses” are the main source of expenses. To make it not too complex, other parts (like income from financial speculations and expenses from write-off) are not included in the figure. Contributions are paid by the “Insured persons”, who are themselves generated by a “Population model”, as described later. On the other hand the insured persons develop “Diseases”, which generate a need for “Health services” that produce health expenses. Furthermore, diseases can lead to changes in population through mortality, and it depends on the financial situation of the health insurance, which health services it is willing to pay. One of the most important determinants for the situation and further development of a health insurance is the structure of its insured persons — the distribution of age, sex, education, income, morbidity and other factors among them (see [1] for a theoretical model of these factors).

3.1 The population model

To cover the demographic influences, a dynamic population model is integrated into the whole model of the health insurance. It consists of 5-year age compartments for both sexes and the flows between them. Births, migration and deaths are also considered. The importance of this part of the model follows from the predicted change of demographic structure during the next decades.

Each compartment is changed by four flows. If three consecutive compartments are called A, B, and C (for example A... “women 20-25”, B... “women 25-30”, C... “women 30-35”) as in Figure 2, these flows are:

1. People come from A to B when they exceed the lower age limit of B.

2. People come from B to C when they exceed the lower age limit of C.
3. People who die while they are in B are collected in the flow “deaths” from B.
4. People who migrate or immigrate while they are in the age of B build the flow “migration” to B.

For calculating survival probabilities of persons in various compartments, the distribution function — which is given by $F(t) = 1 - \exp\left(-\left(\frac{t}{a}\right)^b\right)$ — of a Weibull distribution was fitted to data from mortality tables, but just for a cohort which starts at one year of age, because mortality during the first year of life is an outlier and cannot be fitted with the distribution.

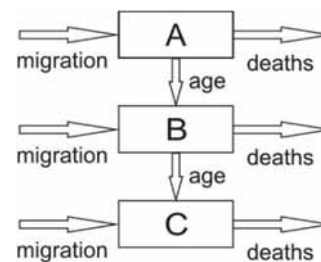


Figure 2. Scheme of age compartments, each compartment is changed through flows of migration and deaths, and people

Life expectancies are predetermined reasonably for the future, and the parameter a of the Weibull distribution should be changed according to get the same life expectancies for persons in the model (infant mortality during the first year of life is held constant). If X stands for the time someone survives in his first year of life, and Y for the time he survives after his first year of life, then $X+Y$ is the age he reaches (of course Y can only be unequal to 0 if X is 1).

Let p be the probability of dying in the first year of life and life expectancy for someone who actually dies before his first birthday be $1/8$ of a year (which is a reasonable value because mortality of newborns is especially high in the first days of life). Then the life expectancy $E(X+Y)$ in the model can be calculated to

$$E(X + Y) = \frac{p}{8} + (1 - p) \cdot (1 + E(Y_1))$$

if $E(Y_1)$ is the remaining life expectancy of somebody who already survived the first year.

As this is modelled by a Weibull distribution with the expected value $E(Y_1) = a \cdot \Gamma\left(\frac{1}{b} + 1\right)$ with given $E(X+Y)$, p and b (the parameter b is held constant and calculated from the fit with present life tables) the parameter a is obtained at each time. From this calculated Weibull distribution the model gets the probabilities of survival for each compartment. If U and O are the lower and upper age limit of a certain compartment, then the probability W is:

$$W(U, O) = 1 - \frac{(1 - F(U)) - (1 - F(O))}{1 - F(U)} \\ = \exp\left(\frac{U^b}{a} + \frac{O^b}{a}\right)$$

Concerning migration and births, the total number of migrants and general fertility rates are given over time, furthermore the age distribution of migration and fertility is held constant at present values. From this, actual migrants and births (the latter are equal to the flows into the first male and female age-compartments) are calculated.

3.2 Insured persons

The “population” - subsystem generates the insured persons of the health insurance. It was chosen to model a regional insurance because there is exactly one in every federal state and most people are covered in them. Aside from this, only special occupational groups are insured in other insurances.

In the population model the development of the population of the observed federal state is simulated. From present ratios of employees, retirees, unemployed persons, co-insured persons and others, which are held constant (but could be varied over time for further investigations and scenarios), these groups are calculated. They differ in their contributions and other important characteristics. Most co-insured persons for example do not pay any contributions, and retirees do not have to pay the fixed annual payment for the so called E-card (€10 at present). The contributions of each group are calculated. For employees and retirees, contributions depend on their income, therefore pension adjustments and pay increases over time are also considered.

3.3 Illnesses and medical services

On the one hand, contributions of the various insured persons are a large part of the insurances income. On the other hand, the most important matters of expense

are ambulatory and stationary medical attendance as well as prescribed drugs [5]. Therefore these parts are modelled in detail.

Central for the expenses is the generation of illnesses (the insured persons develop a certain amount of illnesses per year, according to their demographic structure and other influencing variables), which are separated in “light acute”, “heavy acute” and “chronic” diseases, because these types have to be treated differently in the model. Whereas acute illnesses last only a relatively short amount of time, chronic illnesses are often lifelong. The difference between light and heavy acute diseases is that the latter need stationary treatment. As seen in Figure 3, each of them is modelled in various levels (or stocks) which accumulate new illnesses.

People from each compartment of the population model have expected values for the number of new diseases of each type which they get in one year, so there is a flow into the levels “light acute diseases untreated”, “chronic diseases unrecognized” and “heavy acute diseases”. It is assumed that heavy acute diseases are always recognized and treated (this is clear when one takes for example a heart attack), light acute illnesses are recognized (here a good example would be a common cold), but the person has to decide whether he or she wants to consult a doctor and get treatment (which results in the flow into the level “light acute general practitioner” for illnesses treated by a general practitioner), and chronic diseases need to be recognized (flow into “chronic diseases recognized”) and a decision if they should be treated has to be made (flow into “chronic diseases treated”).

In Figure 3 only general practitioners are considered for simplification, but in the model there is also a level for cases of medical specialists.

Untreated or unrecognized chronic diseases generate additional new acute illnesses (complications), therefore the health insurance may save money in the short term but have to spend more in the long term.

Note that when somebody is released from hospital (where he or she is “with a heavy acute disease”) then there is a certain chance that he or she has to be treated ambulatory for a certain time (or gets a “light acute disease” in the language of the model) and a chance that a chronic disease is developed. The first case leads automatically to a contact with a physician.

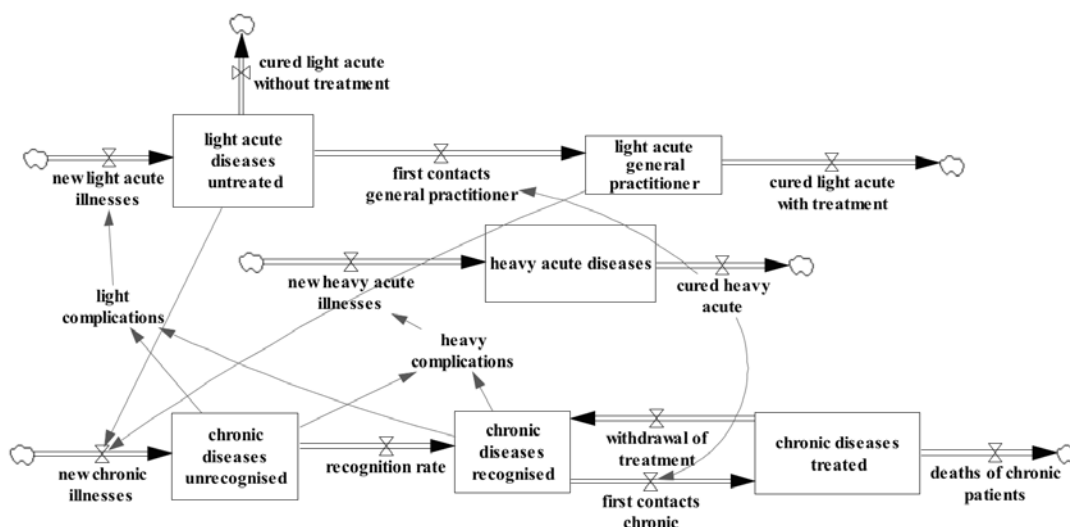


Figure 3. Modelling of diseases (simplified). Diseases are divided into three different types, and each type is further separated into one to three different stages (depending on if they are recognized and if they are treated)

As diseases get treated (which also includes the prescription of drugs), they generate costs for the health insurance. Doctors become a flat charge for each patient who has visited them in a quarter, no matter how often this was. Additionally there are certain services for whom they get paid extra. Accumulated data about how much was paid to doctors (separately for general practitioners and different medical specialists) and how many cases per quarter they treated was available from the Main Association of Austrian Social Security Institutions for the last few years. Even better data was available concerning medical prescriptions (also from the Main Association), because here costs and prescriptions were broken down by active ingredient of the drug and age of the patient. Therefore not only the average rate of prescriptions per case can be found and used in the model, but there would be even the possibility to model at least for one group of drugs and a few associated illnesses in more detail.

4 Summary

Various other financial flows are less important and therefore modelled in less detail. The whole model is implemented with the simulation software Vensim. Financial development of the public health insurances during the last years is known and thus the model can be validated. Many parameters, like fertility rates, life expectancies, expected values for new illnesses, compliance etc. lend themselves to be varied over reasonable ranges in order to test model sensitivity. Furthermore a stability analysis is performed numerically as the model is far too complex for an analytical analysis.

Altogether the model gives a comprehensive image of where costs are accumulated and which unintentional behaviour might occur from its structure and different policies. Particularly, easy testing and simulating of scenarios and policies which could be important in future health care makes this System Dynamics approach of a health insurance model so promising.

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Corresponding author: Günther Zauner

Vienna Univ. of technology, Inst. F. Analysis and Scientific Computing, Wiedner Hauptstrasse 8-10, 1040 Vienna, Austria
guenther.zauner@tuwien.ac.at

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Simulation News Europe is the official journal of EUROSIM and sent to most members of the EUROSIM Societies as part of the membership benefits. Furthermore **SNE** is distributed to other societies and to individuals active in the area of modelling and simulation. **SNE** is registered with ISSN 1015-8685. Circulation of printed version is 3000 copies.

eSNE - SNE at Web SNE issues are also available at www.argesim.org as eSNE – *Electronic SNE*. Web-resolution eSNEs are free for download. Subscribers, e.g. members of EUROSIM Societies have access to SNE Archive with high-resolution eSNE copies and with sources of ARGESIM Benchmarks.

This *EUROSIM Data & Quick Info* compiles data from EUROSIM and EUROSIM societies: addresses, weblinks, officers of societies with function and email, to be published regularly in SNE issues – independent of individual reports of the societies.

SNE Reports Editorial Board

EUROSIM

Mikuláš Alexík, alexik@frtk.utc.sk
Borut Zupančič, borut.zupancic@fe.uni-lj.si
Felix Breitenecker, Felix.Breitenecker@tuwien.ac.at

ASIM: Thorsten Pawletta, pawel@mb.hs-wismar.de
CROSSIM: Vesna Dušak, vdusak@foi.hr
CSSS: Mikuláš Alexík, alexik@frtk.utc.sk
DBSS: A. Heemink, a.w.heemink@its.tudelft.nl
FRANCOSIM: Y. Hamam, y.hamam@esiee.fr
HSS: András Jávör, javor@eik.bme.hu
ISCS: M. Savastano, mario.savastano@unina.it
PSCS: Zenon Sosnowski, zenon@ii.pb.bialystok.pl
SIMS: Esko Juuso, esko.juuso@oulu.fi
SLOSIM: Rihard Karba, rihard.karba@fe.uni-lj.si
UKSIM: Richard Zobel, r.zobel@ntlworld.com
CAE-SMSG: Emilio Jiminez, emilio.jiminez@unirioja.es
LSS: Yuri Merkurjev, merkur@itl.rtu.lv
ROMSIM: Florin Stanculescu, sflorin@ici.ro

ARGESIM

Felix Breitenecker, Felix.Breitenecker@tuwien.ac.at
Anna Mathe, Anna.Mathe@tuwien.ac.at
Nikolas Popper, Niki.Popper@drahtwarenhandlung.at

INFO:

- www.sne-journal.org
- ✉ office@sne-journal.org
- www.eurosim.info

If you have any information, announcement, etc. you want to see published, please contact a member of the editorial board in your country or sne@argesim.org.

Editorial Information/Impressum - see front cover



Information EUROSIM



EUROSIM Federation of European Simulation Societies

General Information. *EUROSIM*, the Federation of European Simulation Societies, was set up in 1989. The purpose of EUROSIM is to provide a European forum for regional and national simulation societies to promote the advancement of modelling and simulation in industry, research, and development.

→ www.eurosim.info

Member Societies. EUROSIM members may be national simulation societies and regional or international societies and groups dealing with modelling and simulation. At present EUROSIM has thirteen full members and one observer member:

| | |
|-----------|---|
| ASIM | Arbeitsgemeinschaft Simulation <i>Austria, Germany, Switzerland</i> |
| CEA-SMSG | Spanish Modelling and Simulation Group <i>Spain</i> |
| CROSSIM | Croatian Society for Simulation Modeling <i>Croatia</i> |
| CSSS | Czech and Slovak Simulation Society <i>Czech Republic, Slovak Republic</i> |
| DBSS | Dutch Benelux Simulation Society <i>Belgium, Netherlands</i> |
| FRANCOSIM | Société Francophone de Simulation <i>Belgium, France</i> |
| HSS | Hungarian Simulation Society <i>Hungary</i> |
| ISCS | Italian Society for Computer Simulation <i>Italy</i> |
| LSS | Latvian Simulation Society <i>Latvia</i> |
| PSCS | Polish Society for Computer Simulation <i>Poland</i> |
| SIMS | Simulation Society of Scandinavia <i>Denmark, Finland, Norway, Sweden</i> |
| SLOSIM | Slovenian Simulation Society <i>Slovenia</i> |
| UKSIM | United Kingdom Simulation Society <i>UK, Ireland</i> |
| ROMSIM | Romanian Society for Modelling and Simulation, <i>Romania, Observer Member</i> |

Contact addresses, weblinks and officers of the societies may be found in the information part of the societies.

EUROSIM board/EUROSIM officers. EUROSIM is governed by a board consisting of one representative of each member society, president and past president, and representatives for SNE and SIMPRA. The President is nominated by the society organising the next EUROSIM Congress. Secretary and Treasurer are elected out of members of the Board.

| | |
|----------------|---|
| President | Mikuláš Alexík (CSSS), <i>alexik@frtk.fri.utc.sk</i> |
| Past president | Borut Zupančič (SLOSIM) <i>borut.zupancic@fe.uni-lj.si</i> |
| Secretary | Peter Fritzon (SIMS) <i>petfr@ida.liu.se</i> |
| Treasurer | Felix Breitenecker (ASIM) <i>felix.breitenecker@tuwien.ac.at</i> |
| SNE Repres. | Felix Breitenecker <i>felix.breitenecker@tuwien.ac.at</i> |

SNE – Simulation News Europe. SNE is a scientific journal with reviewed contributions in the *Notes Section* as well as a membership newsletter for EUROSIM with information from the societies in the *News Section*. EUROSIM societies are offered to distribute to their members the journal *Simulation News Europe* (SNE) as official membership journal. SNE Publisher are EUROSIM, ARGESIM and ASIM.

Editor-in-chief Felix Breitenecker
felix.breitenecker@tuwien.ac.at

→ www.sne-journal.org, menu SNE

✉ office@sne-journal.org

EUROSIM Congress. EUROSIM is running the triennial conference series EUROSIM Congress. The congress is organised by one of the EUROSIM societies. EUROSIM 2010 will be organised by CSSS in Prague, September 5-10, 2010.

Chairs EUROSIM Miroslav Šnorek (CSSS)
2010 *snorek@fel.cvut.cz*
Mikulas Alexik (CSSS)
alexik@frtk.utc.sk

Organisation *chairs@eurosim2010.org*
EUROSIM 2010 *info@eurosim2010.org*
actionm@action-m.com

Information Mikulas Alexik (CSSS)
CSSS *alexik@frtk.utc.sk*

→ www.eurosim2010.org



ASIM German Simulation Society Arbeitsgemeinschaft Simulation

ASIM (Arbeitsgemeinschaft Simulation) is the association for simulation in the German speaking area, servicing mainly Germany, Switzerland and Austria. ASIM was founded in 1981 and has now about 700 individual members, and 30 institutional or industrial members. Furthermore, ASIM counts about 300 affiliated members.

→ www.asim-gi.org with members' area

✉ info@asim-gi.org, admin@asim-gi.org

✉ ASIM – Inst. f. Analysis and Scientific Computing
Vienna University of Technology
Wiedner Hauptstraße 8-10, 1040 Vienna, Austria

ASIM Officers

| | |
|-------------------------------|---|
| President | Felix Breiteneker felix.breiteneker@tuwien.ac.at |
| Vice presidents | Sigrid Wenzel, s.wenzel@uni-kassel.de T. Pawletta, pawel@mb.hs-wismar.de |
| Secretary | Anna Mathe, anna.mathe@tuwien.ac.at |
| Treasurer | I. Bausch-Gall, Ingrid@Bausch-Gall.de |
| Membership affairs | S. Wenzel, s.wenzel@uni-kassel.de W. Maurer, werner.maurer@zhwin.ch I. Bausch-Gall, Ingrid@Bausch-Gall.de F. Breiteneker, felix.breiteneker@tuwien.ac.at |
| Universities / Research Inst. | S. Wenzel, s.wenzel@uni-kassel.de W. Wiechert, W.Wiechert@fz-juelich.de J. Haase, Joachim.Haase@eas.iis.fraunhofer.de Katharina Nöh, k.noeh@fz-juelich.de |
| Industry | S. Wenzel, s.wenzel@uni-kassel.de K. Panreck, Klaus.Panreck@hella.com |
| Conferences | Klaus Panreck Klaus.Panreck@hella.com A. Gnauck, albrecht.gnauck@tu-cottbus.de |
| Publications | Th. Pawletta, pawel@mb.hs-wismar.de Christina Deatcu, christina.deatcu@hs-wismar.de F. Breiteneker, felix.breiteneker@tuwien.ac.at |
| Repr. EUROSIM | F. Breiteneker, felix.breiteneker@tuwien.ac.at N. Popper, niki.popper@drahtwarenhandlung.at |
| Education / Teaching | Ch. Deatcu, christina.deatcu@hs-wismar.de N. Popper, niki.popper@drahtwarenhandlung.at Katharina Nöh, k.noeh@fz-juelich.de |
| International Affairs | H. Szczerbicka, hsz@sim.uni-hannover.de O. Rose, Oliver.Rose@tu-dresden.de |
| Editorial Board SNE | T. Pawletta, pawel@mb.hs-wismar.de Ch. Deatcu, christina.deatcu@hs-wismar.de |
| Web EUROSIM | Anna Mathe, anna.mathe@tuwien.ac.at |

Last data update December 2009

ASIM Working Groups. ASIM, part of GI - Gesellschaft für Informatik, is organised in Working Groups, dealing with applications and comprehensive subjects:

ASIM Working Groups

| | |
|------|---|
| GMMS | Methods in Modelling and Simulation Peter Schwarz, schwarz@eas.iis.fhg.de |
| SUG | Simulation in Environmental Systems Wittmann, wittmann@informatik.uni-hamburg.de |
| STS | Simulation of Technical Systems H.T.Mammen, Heinz-Theo.Mammen@hella.com |
| SPL | Simulation in Production and Logistics Sigrid Wenzel, s.wenzel@uni-kassel.de |
| SVS | Simulation of Transport Systems U. Brannolte, Brannolte@bauing.uni-weimar.de |
| SBW | Simulation in OR C. Böhnlein, boehnlein@wiinf.uni-wuerzburg.de |
| EDU | Simulation in Education/Education in Simulation Katharina Nöh, k.noeh@fz-juelich.de |

CROSSIM – Croatian Society for Simulation Modelling

CROSSIM-Croatian Society for Simulation Modelling was founded in 1992 as a non-profit society with the goal to promote knowledge and use of simulation methods and techniques and development of education. CROSSIM is a full member of EUROSIM since 1997.

→ www.eurosim.info

✉ vdusak@foi.hr

✉ CROSSIM / Vesna Dušak
Faculty of Organization and Informatics Varaždin, University of Zagreb
Pavlinska 2, HR-42000 Varaždin, Croatia

CROSSIM Officers

| | |
|-------------------------|--|
| President | Vesna Dušak, vdusak@foi.hr |
| Vice president | Jadranka Božikov, jbozikov@snz.hr |
| Secretary | Vesna Bosilj-Vukšić, vbosilj@efzg.hr |
| Executive board members | Vlatko Čerić, vceric@efzg.hr Tarzan Legović, legovic@irb.hr |
| Repr. EUROSIM | Vesna Dušak, vdusak@foi.hr |
| Edit. Board SNE | Vesna Dušak, vdusak@foi.hr |
| Web EUROSIM | Jadranka Božikov, jbozikov@snz.hr |

Last data update March 2009



CSSS – Czech and Slovak Simulation Society



CSSS -The *Czech and Slovak Simulation Society* has about 150 members working in Czech and Slovak national scientific and technical societies (*Czech Society for Applied Cybernetics and Informatics, Slovak Society for Applied Cybernetics and Informatics*). The main objectives of the society are: development of education and training in the field of modelling and simulation, organising professional workshops and conferences, disseminating information about modelling and simulation activities in Europe. Since 1992, CSSS is full member of EUROSIM.

→ www.fit.vutbr.cz/CSSS

✉ snorek@fel.cvut.cz

✉ CSSS / Miroslav Šnorek, CTU Prague
FEE, Dept. Computer Science and Engineering,
Karlovo nám. 13, 121 35 Praha 2, Czech Republic

CSSS Officers

| | |
|------------------|--|
| President | Miroslav Šnorek, snorek@fel.cvut.cz |
| Vice president | Mikuláš Alexík, alexik@frtk.fri.utc.sk |
| Treasurer | Evžen Kindler, ekindler@centrum.cz |
| Scientific Secr. | A. Kavička, Antonin.Kavicka@upce.cz |
| Repr. EUROSIM | Miroslav Šnorek, snorek@fel.cvut.cz |
| Deputy | Mikuláš Alexík, alexik@frtk.fri.utc.sk |
| Edit. Board SNE | Mikuláš Alexík, alexik@frtk.fri.utc.sk |
| Web EUROSIM | Petr Peringer, peringer@fit.vutbr.cz |

Last data update December 2008

FRANCOSIM – Société Francophone de Simulation

FRANCOSIM was founded in 1991 and aims to the promotion of simulation and research, in industry and academic fields. Francosim operates two poles.

- Pole Modelling and simulation of discrete event systems. Pole Contact: *Henri Pierreal, pierre-va@imfa.fr*
- Pole Modelling and simulation of continuous systems. Pole Contact: *Yskandar Hamam, y.hamam@esiee.fr*

→ www.eurosim.info

✉ y.hamam@esiee.fr

✉ FRANCOSIM / Yskandar Hamam
Groupe ESIEE, Cité Descartes,
BP 99, 2 Bd. Blaise Pascal,
93162 Noisy le Grand CEDEX, France

FRANCOSIM Officers

| | |
|-----------------|---|
| President | Yskandar Hamam, y.hamam@esiee.fr |
| Treasurer | François Rocaries, f.rocaries@esiee.fr |
| Repr. EUROSIM | Yskandar Hamam, y.hamam@esiee.fr |
| Edit. Board SNE | Yskandar Hamam, y.hamam@esiee.fr |

Last data update April 2006

DBSS – Dutch Benelux Simulation Society

The Dutch Benelux Simulation Society (DBSS) was founded in July 1986 in order to create an organisation of simulation professionals within the Dutch language area. DBSS has actively promoted creation of similar organisations in other language areas. DBSS is a member of EUROSIM and works in close cooperation with its members and with affiliated societies.

→ www.eurosim.info

✉ a.w.heemink@its.tudelft.nl

✉ DBSS / A. W. Heemink
Delft University of Technology, ITS - twi,
Mekelweg 4, 2628 CD Delft, The Netherlands

DBSS Officers

| | |
|-----------------|--|
| President | A. Heemink, a.w.heemink@its.tudelft.nl |
| Vice president | W. Smit, smitnet@wxs.nl |
| Treasurer | W. Smit, smitnet@wxs.nl |
| Secretary | W. Smit, smitnet@wxs.nl |
| Repr. EUROSIM | A. Heemink, a.w.heemink@its.tudelft.nl |
| Deputy | W. Smit, smitnet@wxs.nl |
| Edit. Board SNE | A. Heemink, a.w.heemink@its.tudelft.nl |

Last data update April 2006

HSS – Hungarian Simulation Society

The Hungarian Member Society of EUROSIM was established in 1981 as an association promoting the exchange of information within the community of people involved in research, development, application and education of simulation in Hungary and also contributing to the enhancement of exchanging information between the Hungarian simulation community and the simulation communities abroad. HSS deals with the organization of lectures, exhibitions, demonstrations, and conferences.

→ www.eurosim.info

✉ javor@eik.bme.hu

✉ HSS / András Jávör,
Budapest Univ. of Technology and Economics,
Sztoczek u. 4, 1111 Budapest, Hungary



HSS Officers

| | |
|-----------------|--|
| President | András Jávör, javor@eik.bme.hu |
| Vice president | Gábor Szűcs, szucs@itm.bme.hu |
| Secretary | Ágnes Vigh, vigh@itm.bme.hu |
| Repr. EUROSIM | András Jávör, javor@eik.bme.hu |
| Deputy | Gábor Szűcs, szucs@itm.bme.hu |
| Edit. Board SNE | András Jávör, javor@eik.bme.hu |
| Web EUROSIM | Gábor Szűcs, szucs@itm.bme.hu |

Last data update March 2008

PSCS – Polish Society for Computer Simulation - update

PSCS was founded in 1993 in Warsaw. PSCS is a scientific, non-profit association of members from universities, research institutes and industry in Poland with common interests in variety of methods of computer simulations and its applications. At present PSCS counts 257 members.

→ www.ptsk.man.bialystok.pl

✉ leon@ibib.waw.pl

✉ PSCS / Leon Bobrowski, c/o IBIB PAN,
ul. Trojdena 4 (p.416), 02-109 Warszawa, Poland

PSCS Officers

| | |
|--------------------|---|
| President | Leon Bobrowski, leon@ibib.waw.pl |
| Vice president | Andrzej Grzyb, Tadeusz Nowicki |
| Treasurer | Z. Sosnowski, zenon@ii.pb.bialystok.pl |
| Secretary | Zdzislaw Galkowski, Zdzislaw.Galkowski@simr.pw.edu.pl |
| Repr. EUROSIM | Leon Bobrowski, leon@ibib.waw.pl |
| Deputy | A.Chudzikiewicz, ach@it.pw.edu.pl |
| Edit. Board SNE | Z.Sosnowski, zenon@ii.pb.bialystok.pl |
| PSCS Board Members | R. Bogacz, Z. Strzyzakowski Andrzej Tylikowski |

Last data update March 2009

ISCS – Italian Society for Computer Simulation

The Italian Society for Computer Simulation (ISCS) is a scientific non-profit association of members from industry, university, education and several public and research institutions with common interest in all fields of computer simulation.

→ www.eurosims.info

✉ Mario.savastano@uniina.it

✉ ISCS / Mario Savastano,
c/o CNR - IRSIP,
Via Claudio 21, 80125 Napoli, Italy

ISCS Officers

| | |
|-----------------|--|
| President | M. Savastano, mario.savastano@uniina.it |
| Vice president | F. Maceri, Franco.Maceri@uniroma2.it |
| Repr. EUROSIM | F. Maceri, Franco.Maceri@uniroma2.it |
| Edit. Board SNE | M. Savastano, mario.savastano@uniina.it |

Last data update April 2005

SIMS – Scandinavian Simulation Society

SIMS is the *Scandinavian Simulation Society* with members from the four Nordic countries Denmark, Finland, Norway and Sweden. The SIMS history goes back to 1959. SIMS practical matters are taken care of by the SIMS board consisting of two representatives from each Nordic country. Iceland will be represented by one board member.

SIMS Structure. SIMS is organised as federation of regional societies. There are FinSim (Finnish Simulation Forum), DKSIM (Dansk Simuleringsforening) and NFA (Norsk Forening for Automatisering).

→ www.scansims.org

✉ esko.juuso@oulu.fi

✉ SIMS / SIMS/Esko Juuso, Department of Process and Environmental Engineering, 90014 Univ.Oulu, Finland

SIMS Officers

| | |
|-----------------|---|
| President | Esko Juuso, esko.juuso@oulu.fi |
| Treasurer | Vadim Engelson, vaden@ida.liu.se |
| Repr. EUROSIM | Esko Juuso, esko.juuso@oulu.fi Erik Dahlquist erik.dahlquist@mdh.se |
| Edit. Board SNE | Esko Juuso, esko.juuso@oulu.fi |
| Web EUROSIM | Vadim Engelson, vaden@ida.liu.se |

Last data update December 2009

SLOSIM – Slovenian Society for Simulation and Modelling



SLOSIM - Slovenian Society for Simulation and Modelling was established in 1994 and became the full member of EUROSIM in 1996. Currently it has 69 members from both slovenian universities, institutes, and industry. It promotes modelling and simulation approaches to problem solving in industrial as well as in academic environments by establishing communication and cooperation among corresponding teams.

→ www.slosim.si

✉ slosim@fe.uni-lj.si

✉ SLOSIM / Rihard Karba, Faculty of Electrical Engineering, University of Ljubljana,
Tržaška 25, 1000 Ljubljana, Slovenia

**SLOSIM Officers**

| | |
|-----------------|---|
| President | Rihard Karba, rihard.karba@fe.uni-lj.si |
| Vice president | Leon Žlajpah, leon.zlajpah@ijs.si |
| Secretary | Aleš Belič, ales.belic@fe.uni-lj.si |
| Treasurer | Milan Simčič, milan.simcic@fe.uni-lj.si |
| Repr. EUROSIM | Rihard Karba, rihard.karba@fe.uni-lj.si |
| Deputy | B. Zupančič, borut.zupancic@fe.uni-lj.si |
| Edit. Board SNE | Rihard Karba, rihard.karba@fe.uni-lj.si |
| Web EUROSIM | Milan Simcic, milan.simcic@fe.uni-lj.si |

Last data update December 2009

UKSIM – United Kingdom Simulation Society

UKSIM has more than 100 members throughout the UK from universities and industry. It is active in all areas of simulation and it holds a biennial conference as well as regular meetings and workshops.

→ www.uksim.org.uk✉ david.al-dabass@ntu.ac.uk

- ✉ UKSIM / Prof. David Al-Dabass
Computing & Informatics,
Nottingham Trent University
Clifton lane, Nottingham, NG11 8NS
United Kingdom

UKSIM Officers

| | |
|---------------------|--|
| President | David Al-Dabass, david.al-dabass@ntu.ac.uk |
| Secretary | A. Orsoni, A.Orsoni@kingston.ac.uk |
| Treasurer | B. Thompson, barry@bjtcon.ndo.co.uk |
| Membership chair | K. Al-Begain, kbegain@glam.ac.uk |
| Univ. liaison chair | R. Cheng, rhc@maths.soton.ac.uk |
| Repr. EUROSIM | Richard Zobel, r.zobel@ntlworld.com |
| Edit. Board SNE | Richard Zobel, r.zobel@ntlworld.com |

Last data update March 2009 (partially)

CEA-SMSG – Spanish Modelling and Simulation Group

CEA is the Spanish Society on Automation and Control. In order to improve the efficiency and to deep into the different fields of automation, the association is divided into thematic groups, one of them is named 'Modelling and Simulation', constituting the group.

→ www.cea-ifac.es/wwwgrupos/simulacion→ simulacion@cea-ifac.es

- ✉ CEA-SMSG / María Jesús de la Fuente,
System Engineering and Automatic Control department,
University of Valladolid,
Real de Burgos s/n., 47011 Valladolid, SPAIN

CAE - SMSG Officers

| | |
|-----------------|--|
| President | María J. la Fuente, maria@autom.uva.es |
| Repr. EUROSIM | Emilio Jimenez, emilio.jimenez@unirioja.es |
| Edit. Board SNE | Emilio Jimenez, emilio.jimenez@unirioja.es |

Last data update March 2009

LSS – Latvian Simulation Society

The Latvian Simulation Society (LSS) has been founded in 1990 as the first professional simulation organisation in the field of Modelling and simulation in the post-Soviet area. Its members represent the main simulation centres in Latvia, including both academic and industrial sectors.

→ briedis.itl.rtu.lv/imb/✉ merkur@itl.rtu.lv

- ✉ LSS / Yuri Merkuryev, Dept. of Modelling and Simulation Riga Technical University
Kalku street 1, Riga, LV-1658, LATVIA

LSS Officers

| | |
|-----------------|--|
| President | Yuri Merkuryev, merkur@itl.rtu.lv |
| Repr. EUROSIM | Yuri Merkuryev, merkur@itl.rtu.lv |
| Edit. Board SNE | Yuri Merkuryev, merkur@itl.rtu.lv |

Last data update December 2008

ROMSIM – Romanian Modelling and Simulation Society

ROMSIM has been founded in 1990 as a non-profit society, devoted to both theoretical and applied aspects of modelling and simulation of systems. ROMSIM currently has about 100 members from both Romania and Republic of Moldavia.

→ www.ici.ro/romsim/✉ sflorin@ici.ro

- ✉ ROMSIM / Florin Stanculescu,
National Institute for Research in Informatics, Aversescu
Av. 8 – 10, 71316 Bucharest, Romania

ROMSIM Officers

| | |
|-----------------|---|
| President | Florin Stanculescu, sflorin@ici.ro |
| Vice president | Florin Hartescu, flory@ici.ro Marius Radulescu, mradulescu@ici.ro |
| Secretary | Zoe Radulescu, radulescu@ici.ro |
| Repr. EUROSIM | Florin Stanculescu, sflorin@ici.ro |
| Deputy | Florin Hartescu, flory@ici.ro |
| Edit. Board SNE | Florin Stanculescu, sflorin@ici.ro |

Last data update March 2009

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EUROSIM 2010

organised by CSSS



September 2010, Prague, Czech Republic

EUROSIM 2010

7th EUROSIM Congress on Modelling and Simulation

Eurosim Congress the most important modelling and simulation event in Europe

September 5-10, 2010, Prague, Czech Republic

Congress Venue

The Congress will take place in Prague, the capital city of Czech Republic, at the Congress Center of Masaryk College, part of Czech Technical University, in cooperation with the Faculty of Electrical Engineering of CTU.

About Czech Technical University in Prague

Czech Technical University celebrates 300 years of its history in 2007. Under the name Estate Engineering Teaching Institute in Prague was founded by the rescript of the Emperor Josef I of 18 January 1707 on the basis of a petition of Christian Josef Willenberg (1676-1731). This school was reorganized in 1806 as the Prague Polytechnic, and, after the disintegration of the former AustroHungarian Empire in 1918, transformed in to the Czech Technical University in Prague.

About EUROSIM

EUROSIM, the federation of European simulation societies, was set up in 1989. Its purpose is to promote, especially through local simulation societies, the idea of modelling and simulation in different fields, industry, research and development. At present, EUROSIM has 14 full members and 4 observer members.

Congress Scope and Topics

The Congress scope includes all aspects of continuous, discrete (event) and hybrid modelling, simulation, identification and optimisation approaches. Contributions from both technical and non-technical areas are welcome. Two basic tracks will be organized: M&S Methods and Technologies and M&S Applications.

Czech Republic - EUROSIM 2010 Host Country

The Czech Republic is a country in the centre of Europe. It is interesting for its 1,000-year-long history, rich culture and diverse nature. The country is open to new influences and opportunities thanks to a high level of industrial infrastructure, safety measures and plural media. The location of the Czech Republic in the very heart of Europe contributes to the fact that one can get there easily and fast. Usually all it takes to enter the country is a valid passport. The Czech Republic belongs to the Schengen zone. The need for a visas to enter the Czech Republic is very exceptional.

Prague - EUROSIM 2010 Host City

Prague is a magical city of bridges, cathedrals, gold-tipped towers and church spires, whose image has been mirrored in the surface of the Vltava River for more than a millennium. Walking through the city, you will quickly discover that the entire history of European architecture has left splendid representatives of various periods and styles. There are Romanesque, Gothic, Renaissance, Baroque and Classicist buildings, as well as more modern styles, such as Art Nouveau and Cubist. A poet once characterized Prague as a symphony of stones.

About CSSS

CSSS (The Czech and Slovak Simulation Society) has about 150 members in 2 groups connected to the Czech and Slovak national scientific and technical societies (Czech Society for Applied Cybernetics and Informatics, Slovak Society for Applied Cybernetics and Informatics). Since 1992 CSSS is a full member of EUROSIM.

Invitation

Czech and Slovak Simulation Society is greatly honored with the congress organisation and will do the best to organise an event with a high quality scientific programme with some other accompanied actions but also with some unforgettable social events.

Mikuláš Alexík, EUROSIM president,

Miroslav Šnorek, president of CSSS, EUROSIM 2010 Chair

