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Petri Nets in Biology, Chemistry, and Medicine
- Bibliography -

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CONTENTS

A PRELIMINARY REMARKS

This bibliography has been gathered by Jürgen Will, graduate in chemistry, during a practical training period with the research group for “Data Structures and Software Dependability” at the Brandenburg University of Technology at Cottbus, from August 5th to October 29th, 2002.

Special emphasis has been laid on Petri nets applications in biochemistry for modelling, analysis, and simulation. All the other entries given below may be considered as just a by-product of the mainstream search, which seemed to be too interesting for throwing them right away.

A.1 OVERVIEW

To the best of our knowledge, it was 1993 that Reddy et al. introduced Petri nets for the qualitative modelling of biochemical networks. Since that time, just a few papers appeared every year with similar approaches in order to model and/or analyse biochemical pathways, dealing with metabolism, gene regulation, or signal transduction, respectively. Only recently, there seems to be an increasing interest in that research topic, at least as far we can tell from the total number of published papers.

A quick search through the papers found reveals a quite large variety of Petri net extension, for qualitative modelling:

- hierarchies,
- colour

as well as for quantitative modelling and simulation:

- time dependency: discrete, continuous, hybrid,
- stochastics,
- self-modification, in different variations, and
- fuzzy Petri nets.

All these kinds of Petri nets are used on all levels of biological abstraction, for example for the modelling of the relationships between biochemical substances, cell components, cells, organs, individuals, species, organism classes, and population.

In chemistry, applications seem to be restricted to the control and regulation of process technologies and installations. Just Kuroda et al. used Petri nets for modelling more complex reaction dynamics.

Also, many applications are conceivable in the field of stuff and energy flows, ecological systems, population dynamics and evolution. Suzuki introduces spatial hybrid Petri nets for that purpose.

In medicine, the majority of the published applications come from the field of management processes, for instance the passing on of patients, diagnosis preparation, display preparation, and therapy. But, there are also a few applications, modelling the development of some diseases.

A central topic of almost all investigated publications is the demonstration of a methodology how to use Petri nets for the chosen application area, often associated with the presentation of related software tools. Accordingly, almost all published applications seem to rely on demon-

stration examples only. Therefore, a major break-through of a Petri net based technology for modelling and analysis in applications related to biology, chemistry, or medicine can't be reported yet.

Summarizing the following chapters, our search through the literature revealed the following special applications.

Chemical Reactions

- Oscillations in non-linear chemical reaction systems; non-linear waves in a sheared liquid with an exothermic diffusion reaction

Cell cycle

- Cell cycle (Drosophila fly, mammals)
- Cell division - Mitosis, Meiosis

Cell communication

- Embryonic evolution of nematode Caenorhabditis elegans

Diseases

- Heart rhythm
- Human seeing-channel - glaucoma formation
- Infection of erythrocytes by malaria pathogens (Plasmodium falciparum)
- Insulin kinetics

Gene-Regulation

- Day rhythmics (Drosophila fruit fly {melanogaster})
- DNA mutation and DNA translation
- EGFR-Pathway (Epidermal Growth Factor Receptor)
- Genetic switch mechanism λ-phage
- lac Operon regulation (bacterium Escherichia coli)
- Protein production, protein synthesis
- Replication of plasmides
- Sigma-B regulation

Metabolisms

- Citric acid cycle (cancer cycle)
- Glycolysis and pentose phosphate metabolism (bacterium Escherichia coli, red blood corpuscles)
- Metabolisms Mycoplasma pneumoniae
- Tricarboxylic acid metabolism
- Urea cycle

Morphology

- Excitement of saliva flow reflex at dog through an electrical bell

Population dynamics

- Grain growth
- Larva infestation of oak trees
- Migration of species at the Galapagos archipelago
- Robber-booty systems - hare-fox

Signal transduction

- Cell signalling system bacterium Escherichia coli
- Delta-Notch signal path (Drosophila fruit fly {melanogaster})
- Fas-induced apoptosis signal path
- Sigma-32 stress cycle bacterium Escherichia coli
- Two states of the mucoidity (slimyness) of the pathogenic bacterium Pseudomonas aeruginosa

Stuff and energy flux nets

- Sewage plant

Altogether, this compilation supplies

74 entries in biochemistry,
1 entry in chemistry,
58 entries in medicine,
13 entries in ecology and environment.

A.2 SOURCES

Research period

August 5th - October 29th, 2002

Internet search machines

Google (http://www.google.de),
Metager (http://www.metager.de)

CiteSeer

http://citeseer.nj.nec.com/cs

Petri net bibliography

http://www.daimi.au.dk/PetriNets/bibliographies/

DBI

http://dbix01.dbi-berlin.de:6100/DBI/login.html

Petri Net Newsletter

http://www.informatik.uni-Hamburg.de/TGI/pnbib/

PubMed MedLine

http://www.ncbi.nlm.nih.gov/PubMed/

Web of Science

http://elib.tu-intestine cities.de/WoS/

Open

Science Citation Index (state library Berlin).

Search keys

(petri & !boite & !dish* & !plate*, "petri net*") & (biochemi*, biolog*, chemi*, ecolog*, kinetic*, medic*, metabol*, molecul*, react*, "signal transduc*")

Search languages

German, English

Additionally, a CD-ROM with supplementing or related internet pages has been created. The internet addresses of the sources are usually given in the head of the HTML text of the respective internet page. The internet pages have been saved with the Microsoft Internet Explorer.

A.3 DISCLAIMER

This survey is very likely to be not complete, because basically only papers or references to papers available over the internet have been inspected. Therefore, the search result comprises also preprint and software announcements, or descriptions of research projects, respectively. For a great number of entries, summary and/or sources were not searchable. These entries might be lectures or unpublished papers. The abstracts given below originate from the respective original article, or - if it was unavailable - from the review (mostly PubMed or Web of Science). Under Keywords stand our own comments, concerning especially the applied class of Petri nets.

This report is complemented by a CD-ROM, containing a literature collection concerning modelling and analyzing biological networks.

B BIOCHEMISTRY

B1 Ambrosiano, J.; Oliviera, J. S.: A Biosystems Network Ontology Based on Petri Nets. 3rd Georgia Tech-Emory International Conference on Bioinformatics, Atlanta, USA, November 2001.

Abstract Complex biological systems on many levels, from genetic regulatory networks to communities of cells and organisms, can be viewed conceptually as self-regulating control networks. Unfortunately in biology, the diversity of interpretations that must be applied to this simple concept is enormous. This introduces substantial practical difficulties in designing ontologies for biological networks because we want them to be general enough to accommodate a broad range of interpretations, and yet still support data structures that can be customized to specific bioinformatics applications. While there are many good efforts underway to define knowledge ontologies for systems biology [1], we believe that the key to eventual success, that is a truly generic conceptual framework for biosystems networks, remains a challenge.

We will describe a conceptual framework under development for biosystems ontologies based on Petri nets. In the past, Petri nets have been applied successfully in the analysis of complex networks occurring in a number of settings such as parallel computing and manufacturing-distribution systems. Recently, Petri net models have also been applied to biomolecular networks [2,3].

The formal Petri net model has a number of features that appear ideal for capturing fundamental relationships in control systems; and models of biosystems ranging from reaction kinetics to logic circuits seem to map onto them well. Earlier work in "event nets", as these systems were once called, suggests that category theory may provide the formal basis on which to build useful mappings for ontology interchange. This can in turn provide a solid foundation for generic, object-oriented implementations of bioinformatics software that would be capable of handling the complex and diverse data sets expected to emerge from rapidly expanding research in systems biology.

Keywords describes a conceptual scheme for biosystem ontologies based on Petri nets

B2 Amer-Yahia, C.; Zerhouni, N.; Ferney. M.; El Moudni, A.: Modelling of Biological Systems by Continuous Petri Net. Proc. 3rd IFAC Symposium Modelling and Control in Biomedical Systems, Warwick, UK, March 1997, 383-388.

Keywords continuous PN

B3 Barjis, J.; Barjis, I.: Formalization of the Protein Production by Means of Petri Nets. Proc. IEEE International Conference on Information, Intelligence and Systems, Washington, USA, October - November 1999, 4-9.

Keywords protein production; formalization

B4 Barjis, I.; Barjis, I.; Barjis, J.: Simulation of Molecular Processes Using Petri Nets: Comparison of Mitosis and Meiosis. Proc. 2000 Summer Computer Simulation Conference (SCSC), Vancouver, Canada, July 16 - 20, 2000, 181-184.

Keywords cell division: mitosis, Meiosis; comparsion of mitosis and meiosis

B5 Barjis, I.; Barjis, I.; Barjis, J.: Modeling of a Chimeric Protein Construction by Means of Petri Nets. Proc. IASTED International Conference "Applied Simulation and Modeling" (ASM), Banff, Canada, July 2000, 87-90.

Keywords protein synthesis defect

B6 Barjis, I.; Barjis, I.; Barjis, J.: Analysis and Simulation Modeling of Glycolitic Pathway Using Petri Net. Proc. 4th International EUROSIM Congress, Delft, The Netherlands, June 2001.

Keywords metabolisms; glycolysis

B7 Chen, M.: Modelling the Glycolysis Metabolism Using Hybrid Petri Nets. DFG-Workshop im Rahmen des DFG-Schwerpunktes Informatikmethoden zur Analyse und genomischer Datenmengen, Magdeburg, Germany, May 2000, 25-26.
Keywords metabolisms; glycolysis; hybrid PN; quantitative analysis; methodics

B8 Chen, M.; Hofestädt, R.; Freier, A.: A Workable Approach for Modeling and Simulation of Biochemical Processes with a Hybrid Petri Nets System. 1st International MTBio Workshop on Function and Regulation of Cellular Systems: Experiments and Models, Dresden, Germany, June 2001.
Keywords metabolisms; hybrid PN; quantitative analysis; methodics

B9 Chen, M.; Freier, A.: Petri Net Based Modelling and Simulation of Metabolic Networks in the Cell; Bioinformatics Research and Education Workshop, EMBL-EBI, Hinxton, UK, 2002.
http://www.techfak.uni-bielefeld.de/GK635/publikationen/download/Chen2002-PNB.pdf
Abstract In this paper, an application of the Petri net methodology to simulation of metabolic networks is presented. A software system called IIUDB is developed to integrate the access to several biological databases and to offer a possibility to model and simulate gene regulated metabolic networks based on the Petri net modelling. A Petri net model of urea cycle and its simulation results are presented to show that Petri nets make possible a quantitative analysis of the metabolic networks as well as simulation of the dynamic behaviour of the networks.
Keywords metabolisms; urea cycle; hybrid PN; quantitative analysis, simulation of the dynamic behavior; methodics, software

B10 Chen, M.: Biochemical Reaction Pathways Modeling & Simulation: A Quantitative Modeling System Based on Petri Nets Approach.
http://wwwiti.cs.uni-magdeburg.de/~chen/research/abstract.htm
Abstract A quantitative model of metabolic network system based on Petri nets is outlined. A detailed model of urea cycle which includes gene regulatory network, metabolic pathways and signal transduction is developed. An explanation of the observed behavior of urea cycle is proposed based on the Petri net model. Some new observations indicate a highlight hint on metabolic engineering and medical care or gene therapy. The methodology of model can be used to all other metabolic networks or the virtual cell metabolism. All pathways within a cell or from various organisms are constructed to determine the alternative pathways, presented in this research work the alternative pathways related to urea cycle is to be picked up. The motivation of that is to investigate the possible alternative pathways to overcome the defect of urea cycle orientated diseases. Considering the choices of the best alternative pathways, or taking the biology evolution on metabolism level into account, pathway alignment is required. A new pathway alignment algorithm is to be given by scoring the similarity of pathways.
Keywords metabolisms; urea cycle; hybrid PN; quantitative analysis; methodics

B11 Chen, M.: Modeling Biological Systems with Petri Nets.
http://wwwiti.cs.uni-magdeburg.de/~chen/chenming.htm
Keywords glycolysis, sigma-B regulation; hybrid PN; quantitative analysis; methodics

B12 Chen, M.: Petri Nets and XML in Bioinformatics.
http://wwwiti.cs.uni-magdeburg.de/~chen/bio-petri-xml/seite_1.htm
Keywords metabolisms; hybrid PN; methodics XML

B13 Clark, L.: Information Processing Perspectives Of Cellular Communication.
Abstract The biological cell signalling system very clearly resembles some sort of information processing unit. Tasks are divided between different cells which are specialised for particular processes: eg. regulation, integration, coordination, and oscillation. In this report we ascertain whether

an information processing system can be used to model cellular communication. Such a model would have many benefits; eg. help in understand the computational power and structural organisation of the cell better, and suggest new systems for distributed, parallel information processing. The report begins with an examination of the biological cellular signalling system. Then various modelling strategies are discussed, including parallel distributed systems, cellular automata, distributed / decentralised artificial intelligence, algebraic machines, Petri Nets, and other net / graph schemes. It concludes by detailing further work to be carried out. This will involve implementing a cellular signalling system using some of the computational tools discussed, focusing on signalling / information processing in the bacterium Escherichia coli.

Keywords cell signal system; modelling the cell signal system in general

B14 Compte-Rendu de la Septième Réunion de l'Atelier "De la Simulation en Génomique vers L'Épigenese", June 2001.

Abstract A la suite de ses discussions avec Janine Guespin, Patrick Amar a proposé une nouvelle application potentielle aux réseaux de Petri, en biologie : la modélisation de la bistabilité de l'état de mucoïdie chez P. aeruginosa. La discussion a ensuite porté sur les extensions existantes et à envisager pour adapter le réseau de Petri à cette nouvelle problématique.

Translation As a result of his discussion with Janine Guespin, Patrick Amar proposed a new potential application of Petri nets in biology: the modelling of the bi-stable state of mucoidity of P. aeruginosa. After that the discussion referred to the existing extensions, taken into consideration to adapt Petri Nets to this new problem.

Keywords modelling the bi-stable state of mucoidity (slimyness) of the pathogenic bakterium Pseudomonas aeruginosa and extensions (The genome of this bakterium ist alrerady cleared up. - Will)

B15 Craemer, D.: A Net Representation of Old China's Eight Seasons Followed by a Hint to the Genetic Code and again to Quantum Mechanics.

Keywords eight season system; cyclic process; genetic code; quantum mechanics;

B16 CSM Computational Sciences & Mathematics: EGFR Network.

Figure: http://csm.pnl.gov/mathematics/biology.stm

Abstract We develop the mathematical machinery for the construction of an algebraic-combinatorial model using Petri nets to construct an oriented matroid representation of biochemical pathways. For demonstration purposes, we use a model metabolic pathway example from the literature to derive a general biochemical reaction network model. The biomolecular networks define a connectivity matrix that identifies a linear representation of a Petri net. The subcircuits that span a reaction network are subject to flux conservation laws. The conservation laws correspond to algebraic-combinatorial dual invariants, called S- (state) and T- (transition) invariants. Each invariant has an associated minimum support. We show that every minimum support of a Petri net invariant defines a unique signed subcircuit representation. We prove that the family of signed subcircuits have an implicit order that defines an oriented matroid. The oriented matroid is then used to identify the feasible subcircuit pathways than span the biochemical network as the positive cycles in a hyperdigraph.

Keywords biochemical networks; metabolisms; EGFR network; methodics of the use of Petri Nets to the construction of an oriented matroid representation of the network

B17 CSM Computational Sciences & Mathematics: Krebs Cycle Network.

Figure: http://csm.pnl.gov/mathematics/biology.stm

Abstract We have developed a computational model of biochemical reaction sequences that accurately renders pathways of enzyme-catalyzed reactions as directed hypergraphs, known as Petri nets. Application of the model to the citric acid cycle, or Krebs cycle, is presented. The Krebs cy-

cle, which oxidizes the acetyl group of Acetyl CoA to CO_2 and reduces NAD and FAD to NADH and FADH2, is a complex set of nine reactions. The utility of the algebraic-combinatorial model for identifying the complete set of biochemical subcircuits as a data set is demonstrated.

Keywords biochemical reaction networks; enzyme reactions; citric acid cycle; determining of the complete set of biochemical sub-circles

B18 Dixon, D. A.; Romine, M.; Oliveira, J. S.; Miller, J.; Landvoy, R.: Enabling the Silicon Cell: Development of Models of Cell-Signaling Pathways and Networks.

http://www.emsl.pnl.gov:2080/docs/tms/annual_report1999/1619b-4q.html

Abstract A critical need exists to understand cell-signaling processes to determine how a cell functions given an either natural or anthropogenic external signal. This is especially true when low signal/insult levels are present when trying to predict the biological outcome of an initial molecular interaction. We have focused on developing a variety of methods to analyze cellular pathways and networks. These methods include a variety of traditional approaches based on coupled-rate equations, as well as new methods based on new mathematical techniques such as Petri nets. Such models are inherently complex because significant variations exist in time and space in the various cellular processes. ...

Some of our research efforts this year focused on developing a Petri network model of cell signaling. The Petri net model transforms the molecular signal into a linear algebra representation of a systems process model. The linear algebra representation defines the stoichiometric system of energy-mass-balanced chemical equations. The Petri network model provides us with a representation of the molecular signal that enables us to mathematically predict the behavior of a molecular communications pathway when it is no longer in an equilibrium state. This model will direct us to the construction of the molecular information analog of Shannon's laws of information and communication. We will also have an opportunity to examine the orders of both physical and computational complexity associated with reliable molecular communications within and between cells. This year we

showed that place-transition Petri nets and stochastic Petri nets can be used to model molecular communications within a cell constructed a linear algebra-based, time-dependent, place-transition Petri net model of the EGFR biosignaling network of subnetworks shown in (Figure 4.21).

showed that S and T algebraic invariants can be used to establish the existence of self-regulating, bistable reaction states that imply the EGFR network has an adaptive feedback mechanism that acts to maintain a 3-D memory trace of molecular information as it passes through the network channel

employed path algebras to the linear null space associated with state paths to determine the existence of hidden and emergent, nonequilibrium state reaction paths

employed both abductive inference (reverse Bayesian) and hidden Markov methods to uncover hidden and emergent nonequilibrium state reaction paths

defined the computational complexity bounds of unbounded place-transition Petri net models of cell communication pathways.

Keywords signal transduction; EGFR pathway (Epidermal Growth Factor Receptor) of the MAPK-signalling network; time-dependent and stochastic PN; S- and T-invariants, methodics

B19 Doi, A.; Drath, R.; Nagasak, M.; Matsuno, H.; Miyano, S.: Protein Dynamics Observations of Lambda-Phage by Hybrid Petri Net. Genome Informatics (1999) 217-218.

http://www.jsbi.org/journal/GIW99/GIW99D08.pdf

Abstract We will demonstrate how we can effectively observe the dynamics of concentrations of proteins of λ-phage by using a hybrid Petri net (HPN) tool called Visual Object Net ++ [2]. The HPN has continuous and discrete elements. It is an extension of Petri nets which have been used to represent many kinds of systems including stochastic ones in the _eld of computer sciences and engineerings [1]. Then, it is possible to translate biological facts into HPNs and to observe continuous factors behavior such as mRNA or protein concentrations in a natural manner. We show some

computational results of the protein dynamics of the λ-phage mechanism that is simulated and observed by implementing the HPN on Visual Object Net ++.

Keywords gene regulation; protein dynamics of λ-phage; hybrid PN; methodics, software

B20 Doi, A.; Matsuno, H.; Miyano, S.: Induction Mechanism Description of Lambda-Phage by Hybrid Petri Net. 4th International Conference on Computational Molecular Biology (RECOMB), Tokyo, Japan, April 2000. Miyano, S.; Shamir, R.; Takagi, T.: Currents in Computational Molecular Biology, 2000, 26-27.

Keywords gene regulation; λ-phage; hybrid PN

B21 Doi, A.; Matsuno, H.; Matsui, M.; Hirata, Y.; Miyano, S.: Simulation of Biological Systems by Hybrid Petri Net with an Enhancement. Proc. International Conference on Fundamentals of Electronics, Communications and Computer Science (ICFS), Tokyo, Japan, March 2002, S5, 13-18.

Keywords hybrid PN

B22 Doi, A.; Matsuno, H.; Miyano, S.: Induction Mechanism Description of λ-Phage by Hybrid Petri Net.

http://bonsai.ims.u-tokyo.ac.jp/people/ miyano/systemsbiology/phage.ppt

Keywords gene regulation; λ-phage; hybrid PN

B23 Fuss, H.: Simulation of Biological Systems with Petri Nets - Introduction to Modeling of Distributed Systems; Moller, D. P. F. (ed): Advances in System Analysis. 1987, 1-12.

B24 Genrich, H.; Küffner, R.; Voss, K.: Executable Petri Net Models for the Analysis of Metabolic Pathways. 21st International Conference on Application and Theory of Petri Nets, Aarhus, Denmark, June 2000, International Journal on Software Tools for Technology Transfer 3(4) (2001) 394-404.

http://www.daimi.au.dk/pn2000/proceedings/pn2000_hlpnworkshop.pdf

Abstract Computer simulation of biochemical processes is a means to augment the knowledge about the control mechanisms of such processes in particular organisms. This knowledge can be helpful for the goal oriented design of drugs. Normally, continuous models (differential equations) are chosen for modelling such processes. The application of discrete event systems like Petri nets has been restricted in the past to low-level modelling and qualitative analysis. To demonstrate that Petri nets are indeed suitable for simulating metabolic pathways, the glycolysis and citric acid cycle are selected as well understood examples of enzymatic reaction chains (metabolic pathways). The paper discusses the steps that lead from gaining necessary knowledge about the involved enzymes and substances, to establishing and tuning high-level net models, to performing a series of simulations, and finally to analysing the results. We show that the consistent application of the Petri net view to these tasks has considerable advantages, and - using advanced net tools - reasonable simulation times can be achieved.

Keywords metabolisms; glycolysis, citric acid cycle; hybrid, time-dependent PN

methodic to find usable metabolisms from daten bases: 1.) consider only such ways, which include all educts, intermediate products and products; end of a path only at source, sink or complementary substances. 2.) limit length and width of the network.

simulation time, auantitative analysis; methodics

B25 Goss, P: Stochastic Petri Nets; 1997.

Abstract An integrated understanding of molecular and developmental biology must consider the low concentrations of many species in vivo and the large number of molecular species involved. Quantitative stochastic models of molecular interaction networks can be expressed as Stochastic Petri Nets, a mathematical formalism developed in Computer Science. Existing software can be used to define and solve Stochastic Petri Nets, allowing biologists to concentrate on modeling rath-

er than implementation, and to exchange models via a standardized format. Results are computed numerically or by simulation for several models as an illustration of the approach and the broad applicability of detailed stochastic models in biology.

Keywords quantitative stochastic models of molecular interaction networks; stochastic PN; methodics

B26 Goss, P. J.; Peccoud, J.: Quantitative Modeling of Stochastic Systems in Molecular Biology by Using Stochastic Petri Nets. Proc. Natl. Acad. Sci. USA, June 1998, 95(12) (1998) 6750-6755.

Abstract An integrated understanding of molecular and developmental biology must consider the large number of molecular species involved and the low concentrations of many species in vivo. Quantitative stochastic models of molecular interaction networks can be expressed as stochastic Petri nets (SPNs), a mathematical formalism developed in computer science. Existing software can be used to define molecular interaction networks as SPNs and solve such models for the probability distributions of molecular species. This approach allows biologists to focus on the content of models and their interpretation, rather than their implementation. The standardized format of SPNs also facilitates the replication, extension, and transfer of models between researchers. A simple chemical system is presented to demonstrate the link between stochastic models of molecular interactions and SPNs. The approach is illustrated with examples of models of genetic and biochemical phenomena where the ULTRASAN package is used to present results from numerical analysis and the outcome of simulations.

Keywords quantitative stochastic models of molecular interaction networks; stochastic PN; methodics

B27 Goss, P. J.; Peccoud, J.: Analysis of the Stabilizing Effect of Rom on the Genetic Network Controlling ColE1 Plasmid Replication. Pac. Symp. Biocomput. (1999) 65-76.

Abstract A stochastic model of ColE1 plasmid replication is presented. It is implemented by using UltraSAN, a simulation tool based on an extension of stochastic Petri nets (SPNs). It allows an exploration of the variation in plasmid number per bacterium, which is not possible using a deterministic model. In particular, the rate at which plasmid-free bacteria arise during bacterial division is explored in some detail since spontaneous plasmid loss is a widely observed empirical phenomenon. The rate of spontaneous plasmid loss provides an evolutionary explanation for the maintainance of Rom protein. The presence of Rom acts to reduce variance in plasmid copy number, thereby reducing the rate of plasmid loss at bacterial division. The ability of stochastic models to link biochemical function with evolutionary considerations is discussed.

Keywords replication of plasmides; stochastic PN

B28 Gull, D.; Oliveira, J.: Petri Net Representation of the Kreb Cycle.

Abstract We have developed a computational model which accurately depicts sequences of enzyme-catalyzed reactions as specialized directed graphs. We hypothesize that creation of network models for biochemical systems will allow elucidation and quantification of the system response to a given perturbation. Our model is a first step toward a goal of facilitating manipulation and study of a complete biochemical system. Graphical network models provide a computational framework for identifying key circuits, oscillatory behaviors, and response to biochemical perturbation. The model presented here represents a first approximation of the set of all mass-flux balance conserving pathways or circuits for a given biochemical reaction sequence. The size and complexity of the problem of identifying all such paths and combinations of paths requires enormous computational resources. We have extended previous approaches to this problem by formulating a combinatorial geometric model referred to as an oriented matroid. The interested reader is referred to our previous work and to the Mathematics section of this paper.

Keywords metabolisms; citric acid cycle; methodics

B29 Heiner, M.; Koch, I.; Schuster, S.: Using Time-dependent Petri Nets for the Analysis of Metabolic Networks. DFG-Workshop Informatikmethoden zur Analyse und Interpretation großer genomsicher Datenmengen, Magdeburg, Germany, May 2000, Univ. Magdeburg, Fakultät für Informatik, Preprint Nr.10/2000, pp. 15-21.

Abstract Petri net theory is a powerful tool for describing and analyzing information and control data flows. Hitherto this theory has been applied basically to technical networks. The application of Petri nets to metabolic pathways offers a lot of new possibilities for simulating and even analyzing them. We discuss the modeling of the extended combined glycolytic pathway and pentose phosphate pathway. Using time-dependent Petri nets we model one possible mode of the pathway and analyze the net in detail. We discuss the simulation of fluxes by moving tokens as well as the resulting structural and behavioral net properties. Results show that the time behavior of reversible reactions can be simulated using time-dependent Petri nets.

Keywords metabolisms; glycolysis und pentose phosphate metabolism combined; time-dependent PN; S- and T-invariants; steady states, elementary modes; methodics

B30 Heiner, M.; Koch, I.; Voss, K.: Analysis and Simulation of Steady States in Metabolic Pathways with Petri Nets, Proc. CPN Workshop, Univ. of Aarhus, August 2001, ISSN 0105-8517, 15 - 34.

http://www.daimi.au.dk/CPnets/workshop01/cpnpapers/Paper04.pdf

Abstract Computer assisted analysis and simulation of biochemical pathways can improve the understanding of the structure and the dynamics of these systems considerably. The construction and quantitative analysis of kinetic models is often impeded by the lack of reliable data. However, as the topological structure of biochemical systems can be regarded to remain constant in time, a qualitative analysis of a pathway model was shown to be quite promising as it can render a lot of useful knowledge, e.g., about its structural invariants. This paper deals with pathways whose substances have reached a dynamic concentration equilibrium (steady state). It is argued that appreciated tools from biochemistry and also low-level Petri nets can yield only part of the desired results, whereas executable high-level net models lead to a number of valuable additional insights by combining symbolic analysis and simulation.

Keywords metabolisms; glycolysis and pentose phosphate metabolism combined; time-dependent PN, hierarchical PN; S- and T-invariants; steady states, elementary modes; methodics

B31 Hirata, Y.; Matsuno, H.; Sasaki, M.; Miyano, S.: Genomic Object Net: Petri Net Enhancement for Multi-Cellular Processes. Genome Informatics 12 (2001) 292–293.

http://www.jsbi.org/journal/GIW01/GIW01P025.pdf

Abstract Recent study of cell lineage of multi-cellular organism such as C. elegans shows us that cell-cell interaction and localization of gene products take very important role in the development of early embryo [3]. In order to describe such multi-cellular processes, we extend the software tool Genomic Object Net [2, 4] in which we enhanced the hybrid parametrized functional Petri net (HPFPN) model to extend the parameter space of elements of Petri net and carry out the dynamical change of Petri net.

We are planning to simulate a realistic multi-cellular process such as the development of C. elegans embryo with this framework of HPFPN.

Keywords The article is only a summary. Extension of Genomic Object Net and hybrid functional Petri nets to hybrid parameterized functional Petri nets by defining the range of the parameter values; dynamic modification of the network structure; planned application to the communication between cells at the example of the embryonic evolution of nematode Caenorhabditis elegans. (The worm consists only of less than 2000 cells. Its genome is cleared up already. - Will)

B32 Hofestädt, R.: A Petri Net Application of Metabolic Processes. Journal of System Analysis, Modelling and Simulation 16 (1994) 113-122.

B33 Hofestädt, R.; Thelen, S.: Quantitative Modeling of Biochemical Networks. In Silico Biology 1 (1998).

http://www.bioinfo.de/isb/1998/01/0006/main.html

Abstract Today different database systems for molecular structures (genes and proteins) and metabolic pathways are available. All these systems are characterized by the static data representation. For progress in biotechnology, the dynamic representation of this data is important. The metabolism can be characterized as a complex biochemical network. Different models for the quantitative simulation of biochemical networks are discussed, but no useful formalization is available. This paper shows that the theory of Petrinets is useful for the quantitative modeling of biochemical networks.

Keywords biochemical networks; example glycolysis; (discrete) functional PN; introducing of self-modifying nets and functional Petri nets for biochemical networks; short discussion of the application of Petri nets for modelling biocatalytical reactions, gene regulation, cell communication and for the representation of biochemical networks; methodics

B34 Koch, I.; Schuster, S.; Heiner, M.: Simulation and Analysis of Metabolic Networks by Time-Dependent Petri Nets; Computer Science and Biology; GCB '99, Proceedings of the German Conference on Bioinformatics, Hannover, 4. - 6. Oktober 1999, ISBN 3-00-005121-X, pp. 208 - 209.

http://www.bioinfo.de/isb/gcb99/poster/koch/

Keywords metabolisms; glycolysis and pentose phosphate metabolism combinedt; time-dependent PN; methodics

B35 König, R.; Weismüller, M.; Eils, R.: Generating Petri Nets for Metabolic Network Modelling. Proc. 10th International Conference on Intelligent Systems for Molecular Biology (ISMB), Edmonton, Canada, August 2002.

Abstract Biological systems process physical substrates and information, e.g. by metabolic reactions for building cell structures or gain of energy, or by signal transduction pathways. Modelling metabolic reactions in networks provide insight into responses of the cell to drug treatments or/and mutations in a system view. However, constructing such metabolic nets for simulations, e.g. as Petri nets, is impeded by a lack of availability of cell and compartment-specific data. In our approach, we compile a metabolic net by combining two major database systems. Enzymatic reactions and classifications of metabolic subnets, e.g. glycolysis, PPP, are taken from the metabolic network database KEGG. Enzyme locations and organism specific abundancies are taken from the sequence based databases Swissprot and Embl/Genbank. Here, we present a concept to define organism-specific detailed metabolic Petri nets. These nets provide a robust starting point for modelling and simulation studies. Furthermore, we are developing a scheme for restricting certain metabolites and compare the net's connectivity with scale free networks.

Keywords metabolisms; glycolysis and pentose phosphate metabolism; methodics

B36 Koga, S.-I.; Matsuno, H.; Murakami, R.: A Simulation Tool for Regulatory Network of Gene Expressions in the Patterning of Multicellular Organisms. Genome Informatics Workshop, December 2000, Tokyo, Japan. Dunker, A. K.; Konagaya, A.; Miyano, S.; Takagi, T. (eds.): Genome Informatics, Universal Academy Press, Tokyo, 2000. Genome Informatics 11 (2000) 227-228.

http://www.jsbi.org/journal/GIW00/GIW00D04.pdf

Abstract Detailed knowledge has rapidly been accumulating on the regulatory network of gene expression in patterning of multicellular animals. With the expansion of knowledge, it is getting more and more difficult to understand and predict the working of gene regulatory networks. Usage of some simulation tool would be inevitable to improve thinking of researchers of gene regulatory networks, though only a few simulation methods have been proposed for multicellular systems [1]. We constructed a simulation tool for gene regulatory network in developing multicellular animals. Intracellular regulatory network was constructed by the Petri net [2]. Working of the network in

individual cells of multicellular systems coordinated by a modeling system for extracellular signalings, with visual interface whose operation and presentation are designed to be familiar and easy to biologists.

Keywords gene regulation; delta-notch signalling pathway; methodics, software

B37 Küffner, R.; Zimmer, R.; Lengauer, T.: Pathway Analysis in Metabolic Databases via Differential Metabolic Display (DMD). Bioinformatics 16(9) (2000) 825-836.

http://www.bioinfo.de/isb/gcb99/talks/kueffner/main.html

Abstract A number of metabolic databases are available electronically, some with features for querying and visualizing metabolic pathways and regulatory networks. We present a unifying, systematic approach based on PETRI nets for storing, displaying, comparing, searching and simulating such nets from a number of different sources. RESULTS: Information from each data source is extracted and compiled into a PETRI net. Such PETRI nets then allow to investigate the (differential) content in metabolic databases, to map and integrate genomic information and functional annotations, to compare sequence and metabolic databases with respect to their functional annotations, and to define, generate and search paths and pathways in nets. We present an algorithm to systematically generate all pathways satisfying additional constraints in such PETRI nets. Finally, based on the set of valid pathways, so-called differential metabolic displays (DMDs) are introduced to exhibit specific differences between biological systems, i.e. different developmental states, disease states, or different organisms, on the level of paths and pathways. DMDs will be useful for target finding and function prediction, especially in the context of the interpretation of expression data.

Keywords metabolisms; example glycolysis; classical PN; comparison of metabolism data bases, extraction of metabolisms from data bases; methodics

B38 Doheon Lee; Kwang-Hyung Lee; Yonggwan Won: Distributed Agent-Based Software Architectures for Bio-Pathway Simulation. Poster 10th International Conference on Intelligent Systems for Molecular Biology (ISMB), Edmonton, Canada, August 2002.

Abstract This paper proposes software architectures for bio-pathway simulation based on distributed agent technology. The fundamental advantages of distributed agents are their effectiveness in handling heterogeneous pathway information and efficiency in scalability. They also utilize XML to represent semi-structured data such as quantitative reaction rules, and adopt Petri nets to model concurrent pathway executions.

Keywords distributed agents

B39 Matsuno, H.; Doi, A.; Nagasaki, M.; Miyano, S.: Hybrid Petri Net Representation of Gene Regulatory Network. Proc. 5th Pacific Symposium on Biocomputing; World Scientific Press, 2000, 341-352.

http://www.smi.stanford.edu/projects/helix/psb00/matsuno.pdf

Abstract It is important to provide a representation method of gene regulatory networks which realizes the intuitions of biologists while keeping the universality in its computational ability. In this paper, we propose a method to exploit hybrid Petri net (HPN) for representing gene regulatory networks. The HPN is an extension of Petri nets which have been used to represent many kinds of systems including stochastic ones in the field of computer sciences and engineerings. Since the HPN has continuous and discrete elements, it can easily handle biological factors such as protein and mRNA concentrations. We demonstrate that, by using HPNs, it is possible to translate biological facts into HPNs in a natural manner. It should be also emphasized that a hierarchical approach is taken for our construction of the genetic switch mechanism of lambda phage which is realized by using HPNs. This hierarchical approach with HPNs makes easier the arrangement of the components in the gene regulatory network based on the biological facts and provides us a prospective view of the network.

We also show some computational results of the protein dynamics of the lambda phage mechanism that is simulated and observed by implementing the HPN on a currently available tool.

Keywords gene regulation; genetic switch mechanism of λ-phage; hybrid PN; methodics, software

B40 Matsuno, H.; Doi, A.; Drath, R.; Miyano, S.: Genomic Object Net: Object Oriented Representation of Biological Systems. Genome Informatics Workshop, December 2000, Tokyo, Japan. Dunker, A. K.; Konagaya, A.; Miyano, S.; Takagi, T. (eds.): Genome Informatics 2000, Universal Academy Press, Tokyo, 2000. Genome Informatics 11 (2000) 229-230.

http://www.jsbi.org/journal/GIW00/GIW00D05.pdf

Abstract One of the most important and interesting topic in the field of bioinformatics is to develop the tool simulating biological phenomenon such as gene expressions and biochemical reactions. The required conditions for realizing the effective simulation tool are

1) Acceptable technical expression of the tool to biologists,

2) Easy to describe biological facts and biological phenomenon on computers,

3) Easy to get the tool through Internet, and

4) Easy to simulate the biological phenomenon on the tool.

Our solution to the problems is “exploiting hybrid Petri net (HPN) technique for describing biological systems”. In [1], we showed that, by using HPN, the genetic switch mechanism of λ-phage can be realized on computer in a natural manner, and protein and mRNA concentrations of the mechanism can be successfully simulated by using Visual Object Net++ (Figure 1) [2] which is a general purpose system description tool based on HPN technique. The evaluation version of Visual Object Net++ can be downloaded from the site [2].

In this software demonstration, we will show the following examples of biological systems describing and simulating on Visual Object Net++; 1) Circadian rhythms in Drosophila, 2) Delta-Notch lateral inhibitory, and 3) Apoptosis induced by protein Fas. We then introduce our next strategy “Genomic Object Net Project” which may lead us to the development of new efficient bio-simulation tools.

Keywords gene regulation, signal transduction; circadian rhythmics of drosophila fly; lateral inhibition of delta-notch signalling patway, Fas-induced apoptosis, genetic switch-mechanism of λ-phage; hybrid PN; methodics, software

B41 Matsuno, H.; Doi, A.; Hirata, Y.; Miyano, S.: XML Documentation of Biopathways and their Simulations in Genomic Object Net. Genome Informatics 12 (2001) 54–62.

http://bonsai.ims.u-tokyo.ac.jp/people/miyano/ systemsbiology/GIW01F06.pdf

Abstract Genomic Object Net is a software tool for modeling and simulating biopathways which employs the notion of hybrid functional net as its basic architechture. This paper shows how to integrate this basic architecture with XML documents for biopathway representations, simulations, and visualizations for creating a tailor-made simulation environment.

Keywords methodics, software

B42 Matsuno, H.; Doi, A.; Drath, R.; Miyano, S.; Genomic Object Net: Hybrid Petri Net for Describing Biological Systems. Currents in Computational Molecular Biology (2001) 233-234.

Keywords hybrid PN; methodics, software

B43 Matsuno, H.: Genomic Object Net: Biopathway Modeling and Simulation System Based on Hybrid Functional Petri Net and XML Technology. Proc. 1st International Symposium on Biosystems, Daejeon, Korea, February 2002, 5-22.

Keywords hybrid functional PN; methodics, software

B44 Matsuno, H.: Genomic Object Net: On-Going Report on Biopathway Modeling and Simulation. Proc. 1st International Symposium on BioSystems, Daejeon, Korea, February 2002, 5-22.

Keywords methodics, software

B45 Matsuno, H.; Yamane, Rie; Fujita, S.; Yamasaki, N.: Modeling and Visualization of the Pattern Formation in Drosophila melanogaster by Genomic Object Net. Proc. 10th International Conference on Intelligent Systems for Molecular Biology (ISMB), Edmonton, Canada, August 2002.

Abstract Genomic Object Net (GON) is a powerful biosimulation system which consists of two tools, GON Assembler and GON Visualizer. GON Assembler can model any kind of biopathways based on hybrid functional Petri net architecture. With GON Visualizer, which is constructed on XML Technology, we can observe simulation results exported from GON Assembler.

In this poster, we present the modeling and visualization of two pattern formations of the neural precursor cells in embryos and the border cells at large intestine of Drosophila melanogaster by Delta-Notch signaling pathway which acts as follows. Delta protein is a transmembrane protein and works as a ligand for Notch receptor of adjacent cells. Binding of Delta ligand to the Notch receptor activates Notch signaling cascade, resulting in repression of Delta in the Notch-active cells. Conversely, Notch cascade is suppressed in Delta-expressing by Delta protein.

Keywords signal transduction; delta-notch signalling pathway of drosophila melanogaster fly; methodics, software

B46 Matsuno, H.; Hirata, Y.; Doi, A.; Miyano, S.: Genomic Object Net: On-Going Report on Biopathway Modeling and Simulation. Currents in Computational Molecular Biology 2002, 132-133.

Keywords methodics, software

B47 Matsuno, H.; Fujita, S.; Doi, A.; Hirata, Y.; Miyano, S.: Genomic Object Net: Hybrid Functional Petri Net Architecture for Representing and Simulating Biopathways.

http://bonsai.ims.u-tokyo.ac.jp/people/miyano/systemsbiology/GON2002.pdf

Abstract Motivation: In order for simulation tools to be widely accepted and used by biologists, two issues must be addressed. First, properties of the simulation irrelevant to biology should be removed from the representation and second, biologists should be able to intuitively and easily manage the details of the representation. Based on these criteria, we have implemented a novel notion of a Petri net called hybrid functional Petri nets (HFPN). We introduce a software tool, Genomic Object Net, for representing and simulating biopathways, which we have developed by employing the architecture of HFPN.

Results: In order to show the effectiveness of Genomic Object Net for representing and simulating biopathways, we demonstrate how biopathways can be modeled with HFPN through the example of lac operon regulatory mechanism and glycolytic pathway of E. coli. Moreover, simulation results of the model obtained from Genomic Object Net are evaluated.

Keywords metabolisms, gene regulation; glycolysis of bakterium escherichia coli, lac-operon regulation mechanism; hybrid functional PN; methodics, software

B48 Matsuno, H.; Murakami, R.; Yamane, R.; Yamasaki, N.; Fujita, S.; Yoshimori, H.: Boundary Formation by Notch Signaling in Drosophila Multicellular Systems: Experimental Observations and Gene Network Modeling by Genomic Object Net. Proc. Pacific Symposium on Biocomputing (PSB), Hawaii, January 2003.

Abstract The Delta-Notch signaling system plays an essential role in various morphogenetic systems of multicellular animal development. Here we analyzed the mechanism of Notch-dependent boundary formation in the Drosophila large intestine, by experimental manipulation of Delta expression and computational modeling and simulation by Genomic Object Net. Boundary formation representing the situation in normal large intestine was shown by the simulation. By manipulating Delta expression in the large intestine, a few types of disorder in boundary cell differentiation were observed, and similar abnormal patterns were generated by the simulation. Simulation results suggest that parameter values representing the strength of cell-autonomous suppression of Notch sig-

naling by Delta are essential for generating two different modes of patterning: lateral inhibition and boundary formation, which could explain how a common gene regulatory network results in two different patterning modes in vivo. Genomic Object Net proved to be a useful and flexible biosimulation system that is suitable for analyzing complex biological phenomena such as patternings of multicellular systems as well as intracellular changes in cell states including metabolic activities, gene regulation, and enzyme reactions.

Keywords signal transduction; embryonic development, cell differentiation; delta-notch signalling pathway of drosophila fly; hybrid functional PN; methodics, software

B49 Matsuno, H.; Doi, A.; Tanaka, Y.; Aoshima, H.; Hirata, Y.; Miyano, S.: Genomic Object Net: Basic Architecture for Representing and Simulating Biopathways.

http://www.genomicobject.net/public/tutorial/BasicArchitecture.pdf

Abstract Motivation: The following two matters should be resolved in order for biosimulation tools to be accepted by users in biology/medicine; (1) Remove issues which are irrelevant to biological importance, and (2) Allow users to represent biopathways intuitively and understand/manage easily the details of representatio and simulatiomechanism. From these criteria, we firstly define a novel notion of Petri net called hybrid functional Petri net (HFPN). Then, we introduce a software tool, Genomic Object Net, for representing and simulating biopathways, which we have developed by employing the architecture of HFPN.

Results: I order to show the effectiveness of Genomic Object Net for representing and simulating biopathways, we show some typical biopathway modelings related to gene regulation (switching mechanism of λ-phage, circadian rhythm of Drosophila, lac operon regulatory mechanism of E. coli), metabolic pathway (glycolitic pathway), and signal transduction (Fas ligand induced apoptosis), which cover the basic aspects in biopathways.

Keywords gene regulation: circadian rhythmics of drosophila fly, genetic switch-mechanism of λ-phage, lac-operon regulation mechanism of bakterium escherischia coli; metabolisms: glycolysis; signal transduction: Fas-ligand-induced apoptosis; hybrid functional PN; methodics, software

B50 Matsuno, H.; Doi, A.; Fujita, S.; Sasaki, M.; Hirata, Y.; Miyano S: Genomic Object Net: XML Visualization of Simulation Results from Biological Modeling on Hybrid Functional Petri Net.

http://www.jsbi.org/journal/GIW01/GIW01D06.pdf

Abstract In [2], we showed that hybrid Petri net (HPN) provides the promising basic architecture for representing biological processes with an example of description and simulation of λ-phage genetic switch mechanism. We launched the project “Genomic Object Net Project” whose aim is to develop the software tool which can be used by biologist easily and intuitively. As a first step, in [3], we introduced the new mathematical expression enhanced from HPN “hybrid functional Petri net (HFPN)” for realizing biopathways naturally and intuitively. Furthermore, by using Genomic Object Net Assembler [3], we showed how the concept of HFPN is suitable for describing and simulating biological processes through the realizations of circadian rhythms in Drosophila melanogaster, glycolytic pathway of Escherichia coli with the lac operon gene regulatory mechanism, and apoptosis induced by the protein Fas.

Recently, we developed a tool “Genomic Object Net Visualizer” based on XML technology which enables us to visualize simulation results produced by Genomic Object Net Assembler. By using this tool, users in biology/medicine can view simulation results on their own aspects.

In this software demonstration, we will present several visualization examples of simulation results including lac operon gene regulatory network, circadian rhythms in Drosophila, and Delta-Notch lateral inhibition mechanism.

Keywords metabolisms, gene regulation, signal transduction; circadian rhythmics of drosophila melanogaster fly, lateral inhibition of delta-notch signalling pathway in drosophila fly, Fas-induced apoptosis, glycolysis of bakterium escherichia coli, lac-operon gene regulation mechanism; hybride functional PN; methodics, software

B51 Meric, P. A.; Wise, M. J.: Quantitative, Scalable Discrete-Event Simulation of Metabolic Pathways. Ralf Zimmer (eds.): Proc. 7th International Conference on Intelligent Systems for Molecular Biology (ISMB), Heidelberg, Germany, August 1999, AAAI (1999) 187-194.

http://www.bio.cam.ac.uk/~mw263/ftp/doc/ISMB99.ps

Abstract DMSS (Discrete Metabolic Simulation System) is a framework for modelling and simulating metabolic pathways. Quantitative simulation of metabolic pathways is achieved using discrete-event techniques. The approach differs from most quantitative simulators of metabolism which employ either time-differentiated functions or methematical modelling techniques. Instead, models are constructed from biochemical data and biological knowledge, with accessibility and relevance to biologists serving as key features of the system.

Keywords metabolisms; glycolysis, tricarbonic acid metabolism; quantititative simulation of metabolic networks through discrete time steps and discrete values of the token set similiar to Petri nets; software, paramterfree

B52 Miyano, S.: Knowledge Discovery System for Biological Data and Biopathway Simulation.

Institute of Biomedical Sciences, Academia Sinica, 2001

Abstract The talk consists of three parts: (1) Gene Expression Profile Data Analysis: Algorithms for analyzing gene expression profile data are getting more important especially due to the invent of cDNA microarray and oligonuleotide chips. For the analysis of these data, we have been investigating strategies for inferring Boolean model-based genetic network with these data, where the expression level of mRNA. The first part of this talk presents our strategy for analyzing gene expression profiles based on the Boolean network model and othe models. (2) Principles of Knowledge Discovery Systems: We have been developing a software library, HypothesisCreator (HC), for assisting experts in knowledge discovery from genomic databases. It is said that a key to the successful discovery process is a creation of a new "view" on data which describes a way of interpreting a data set. For this purpose, we defined a concept of "view" mathematically so that software development based on this concept can be carried out. HC allows the seamless integration of various knowledge in databases, newly created attributes, and even experts' intuitions. HypothesisCreator facilitates a rapid development of application programs for knowledge discovery and the computational experiments, especially for genomic data. We are currently conducting a series computational experiments on demand of various laboratories for several different kinds of genomic data by scripting HC application programs. In this talk, we report an HC computational knowledge discovery experiment for protein localization problem where we identified important knowledge on Mitochondrial targeting peptides (mTP), chloroplast targeting peptides (cTP), and signal peptides. HypothesisCreator is free software distributed under the GNU General Public License. It will be available from the HypothesisCreator web site http://www.HypothesisCreator.net/. (3) Biopathway Simulation - Genomic Object Net: Genomic Object Net is a software tool for describing and simulating structurally complex dynamic causal interactions and processes such as metabolic pathways, signal transduction cascades, gene regulations. The notion of hybrid object net is employed as its basic architechture and visualization technique is developed for intuitive understanding of the representation and simulation. Along with the completion of many genome sequencing projects, a new interest of research is emerging for elucidating how the living systems function in terms of all levels of biological information, and then to develop information technology for applying such systemic information to medicine and biology. Among many issues related to this matter, a vital necessity is to develop information technology with which we can easily represent and simulate the structurally complex dynamic causal interactions and processes of various biological objects such as genomic DNA, mRNA, proteins, functional proteins, molecular transactions and processes such as metabolic pathways, signal transduction cascades, genetic networks, etc. In order for software tools to be accepted by users in biology/medicine for biopathway representation and simulation, the following two matters should be resolved, at least: (1) Remove issues which are irrelevant to biological importance; (2) Allow users to represent biopathways intuitively and understand/man-

age easily the details of representation and simulation mechanism. We have developed a software tool Genomic Object Net (http://www.GenomicObject.Net/) for representing and simulating biopathways based on [1,2] together with visualization strategy that would satisfy (1) and (2). Its employs the notion of hybrid object net [2] as its basic simulation architechure. Usually, a biopathway information is conceputually described as a figure together with the explanation about the relations between biological objects of concern and the measured/observed data proving their qualitative/ quantitative relations. These information can be easily described and simulated with Genomic Object Net. We show some representation and simulation examples of typical biopathways related to gene regulation, metabolic pathway, and signal transduction, which cover the basic ascpects in biopathways. [1] Matsuno, H., Doi, A., Nagasaki, M., and Miyano, S. 2000. Hybrid Petri net representation of gene regulatory network. Proc. Pacific Symposium on Biocomputing 2000, pp. 338-349. [2] Drath, R. 1998. Hybrid Object Nets: An object oriented concept for modeling complex hybrid systems. Proc. Hybrid Dynamical Systems. 3rd International Conference on Automation of Mixed Processes, ADPM'98, pp. 437-442.

Keywords metabolisms, gene regulation, signal transduction; methodics, software

B53 Miyano, S.: Modeling and Simulating Biopathways. Journées Ouvertes Biologie Informatique Mathématiques (Jobim), Saint Malo, France, June 2002.

http://bonsai.ims.u-tokyo.ac.jp/people/miyano/jobim/ModelingSimulating.ppt

B54 Miyano, S.: – Genomic Object Net. Towards Biopathway Simulation.

http://www.iis.sinica.edu.tw/~hil/summer/miyano3.pdf

Keywords metabolisms, gene regulation, signal transduction; circadian rhythmics, Fas-induced apoptosis, genetic switch-mechanism of λ-phage, glycolysis, lac-operon gene regulation mechanism; hybrid functional PN; methodics, software

B55 Mounts, W. M.; Liebman, M. N.: Analysis of Enzyme Pathways with Petri Nets and Stochastic Activity Nets. International Journal of Computer Simulation (1996).

Keywords metabolisms; stochastic PN

B56 Oliveira, J. S.; Bailey, C. G.; Jones-Oliveira, J. B.; Dixon, D. A.: An Algebraic-combinatorial Model for the Identification and Mapping of Biochemical Pathways. Bull. Math. Biol. 63(6) (2001) 1163-1196.

Abstract We develop the mathematical machinery for the construction of an algebraic-combinatorial model using Petri nets to construct an oriented matroid representation of biochemical pathways. For demonstration purposes, we use a model metabolic pathway example from the literature to derive a general biochemical reaction network model. The biomolecular networks define a connectivity matrix that identifies a linear representation of a Petri net. The sub-circuits that span a reaction network are subject to flux conservation laws. The conservation laws correspond to algebraic-combinatorial dual invariants, that are called S- (state) and T- (transition) invariants. Each invariant has an associated minimum support. We show that every minimum support of a Petri net invariant defines a unique signed sub-circuit representation. We prove that the family of signed sub-circuits has an implicit order that defines an oriented matroid. The oriented matroid is then used to identify the feasible sub-circuit pathways that span the biochemical network as the positive cycles in a hyper-digraph.

Keywords metabolisms; S- and T-invariants; methodics

B57 Peccoud, J.: Stochastic Petri Nets for Genetic Networks. M S-Medecine Sciences 14 (1998) 991-993.

Keywords stochastic PN

B58 Peleg, M.; Gabashvil, I. S.; Altman, R. B.: Modeling Mutations, Abnormal Processes, and Disease Phenotypes Using a Workflow/Petri Net Model. Proc. 10th International Conference on Intelligent Systems for Molecular Biology (ISMB), Edmonton, Canada, August 2002.

Abstract Predicting the molecular- and cellular- level effects of genetic mutations is a challenging task. It calls for models that integrate different data sets, and represent the interactions of mutated gene products with other cellular components, in order to understand their effects on molecular, cellular, and organism- level processes. We have developed a graphical knowledge model for representing molecular functional information as a first step towards modeling the relationship between molecular structure and disease phenotypes. Our model is based on a Workflow model that can be mapped to Petri Nets, and is implemented as a frame-based knowledge base using the Protégé-2000 tool. We use TAMBIS and the UMLS as to describe biological and medical concepts that can be mapped to the participants, roles, and processes in the workflow model. The formal nature of our model allows us to write queries about structural and functional aspects of biological systems – such as relationships between defective processes and the clinical phenotype of the mutation that is causing it. To illustrate the power of this model, we have used it to represent mutations in tRNA and their affects on the process of translation. Mapping the workflow model to Petri Nets enabled us to verify the soundness of some dynamic aspects of tRNA biology and to simulate system behavior in the presence of different mutations. Our model is available at http://www.smi.stanford.edu/people/peleg/Process_Model.htm.

Keywords gene regulation; DNA mutation and DNA translation; PN from workflow model; methodics

B59 Peleg, M.; Yeh, I.; Altman, R. B.: Modelling Biological Processes Using Workflow and Petri Net Models. Bioinformatics 18(6) (2002) 825-837.

http://smi-web.stanford.edu/people/peleg/ModelingBiologicalProcesses_paper_RBA.pdf

http://www.sbc.su.se/~per/Peleg_2002.pdf

Abstract I combined the best aspects of two of the models: (1) Transparent Access To Multiple Biological Information Sources (TAMBIS) - a biological concept model, and (2) a workflow model that can represent the ordering of processes, the structural components that participate in them, and the roles that they play. The Workflow model maps to Petri Nets, allowing verification of properties (correctness – Will) such as boundedness and soundness, and determination of reachability. I composed queries that can aid discovering relationships among processes and structural components. I used reachability analysis to answer queries that relate to dynamic aspects of the model.

Biological processes can be considered at many levels of detail, ranging from atomic mechanism to general processes such as cell division, cell adhesion or cell invasion. The experimental study of protein function and gene regulation typically provides information at many levels. The representation of hierarchical process knowledge in biology is therefore a major challenge for bioinformatics. To represent high-level processes in the context of their component functions, we have developed a graphical knowledge model for biological processes that supports methods for qualitative reasoning. Based on this assessment, we combined the best aspects of two models: Workflow/Petri Net and a biological concept model. The Workflow model can represent nesting and ordering of processes, the structural components that participate in the processes, and the roles that they play. It also maps to Petri Nets, which allow verification of formal properties and qualitative simulation. The biological concept model, TAMBIS, provides a framework for describing biological entities that can be mapped to the workflow model. We tested our model by representing malaria parasites invading host erythrocytes, and composed queries, in five general classes, to discover relationships among processes and structural components. We used reachability analysis to answer queries about the dynamic aspects of the model.

Keywords biological systems in general; modelling of processes of the infection of erythrocytes by malaria-pathogens (plasmodium falciparum); comparison of different modelling concepts of computer science with the destination to find methods for description of complex biological systems.

Result: workflow model in connection with a semantic net of biological terms (TAMBIS). Workflow models maps to Petri nets. Petri nets are used for the verification of correctness and for determination of interesting properties of biological systems; methodics

B60 Peleg, M.; Gabashvili, I. S.; Altman, R. B.: Integrating Bio-ontologies with a Workflow/Petri Net Model to Qualitatively Represent and Simulate Biological Systems.

http://www.cs.man.ac.uk/~stevensr/meeting02/abstracts/pelig.doc

Abstract The volume of data contained in biological literature is increasingly growing.The diversity of data is very large, and includes information such as genetic sequence polymorphism, molecular function, clinical phenotypes, and cellular location. Data exists in many levels of detail, ranging from atomic mechanisms to cellular-level processes. A challenge facing researchers is the ability to piece together the wealth of dispersed data relating to their domain of interest. Thus, our goal is to develop technology for representing qualitative, noisy, and sparse biological results in support of the eventual goal of fully accurate quantitative models. We developed data structures for storing data related to a biological domain in a way that allows the knowledge to be systematically evaluated and examined by scientists as well as computer algorithms. In an earlier work [1], we concentrated on representation of structural, functional, and dynamic aspects of biological systems and querying the system to discover relationships among processes and structural components (e.g., biopolymers that have the same set of roles and are not inhibited by the same inhibitor). We have extended this work by representing the interactions of mutated gene products with other cellular components. This representation and its querying tools may aid scientists to gain insights into the effects of specific mutations on molecular, cellular, and organism-level processes.

Keywords mutations; PN from workflow model; methodics

B61 Peleg, M.: Biological Processes Ontology.

http://smi-web.stanford.edu/projects/helix/pubs/process-model

Abstract We developed a formal yet intuitive knowledge model of biological processes and functions that is graphical, for human comprehension, and machine-interpretable, to allow reasoning. The model enables verification of safety and soundness, and querying information that can assist in discovering relationships among processes and structural components that participate in them.

Our framework for modeling biological processes is based on the Workflow model of the Workflow Management Coalition and incorporates the TAMBIS ontology as a biological controlled vocabulary. We added other elements that are relevant to biological systems: cellular location information for process participants and the types of evidence that support facts in the knowledge base. We augmented the Workflow model with elements taken from Object-Process Methodology, to create a graphical representation of four relationship types that occur between a process and the structural components that participate in it (i.e., catalysts, substrates, products, and inhibitors).

We implemented our framework using the Protege-2000 tool and tested it by representing Malaria parasites invading host erythrocytes. Using Protege's axiom language, we composed queries that can

aid discovering relationships among processes and structural components. We used reachability analysis on Petri Nets that were manually converted from the Workflow model to answer queries that relate to dynamic aspects.

Keywords modelling of processes of infection of erythrocytes by malaria pathogens (plasmodium falciparum); PN from workflow model; methodics

B62 Reddy, V. N.; Mavrovouniotis, M. L.; Liebman, M. N.: Petri Net Representations in Metabolic Pathways. Hunter, L. et al. (eds.): Proc. 1st International Conference on Intelligent Systems for Molecular Biology (ISMB), 1993, AAAI Press, Menlo Park, 328-336.

Abstract The present methods for representing metabolic pathways are limited in their ability to handle complex systems, incorporate new information, and to provide for drawing qualitative con-

clusions from the structure of pathways. The theory of Petri nets is introduced as a tool for computer-implementable representation of pathways. Petri nets have the potential to overcome the present limitations, and through a multitude of properties, enable the preliminary qualitative analysis of pathways.

Keywords metabolisms; introducing of PN for modelling of metabolisms; methodics

B63 Reddy, V. N.: Modeling Biological Pathways: A Discrete Event Systems Approach. Master Thesis, University of Maryland, 1994.

http://bellatrix.isr.umd.edu/TechReports/ISR/1994/MS_94-4/MS_94-4.pdf

Abstract A discrete-event systems approach is proposed for the modeling of biochemical reaction systems. The approach is based on Petri nets, which are particularly suited to modeling stoichiometric transformations, i.e., the interconversion of metabolites in fixed proportions. Properties of Petri nets and methods for their analysis are presented, along with their interpretation for biological systems. An example of the human erythrocyte metabolism is presented to illustrate the concepts of the methodology.

Keywords metabolisms; glycolysis in red blood corpuscles; methodics

B64 Reddy, V. N.; Mavrovouniotis, M. L.; Liebman, M. N.: Modeling Biological Pathways. A Discrete-event Systems Approach. Inst. Syst. Res., Univ. Maryland, College Park, USA. ACS Symp. Ser. 576 (Molecular Modeling) (1994) 221-34.

B65 Reddy, V. N.; Liebman, M. N.; Mavrovouniotis, M. L.: Qualitative Analysis of Biochemical Reaction Systems. Comput. Biol. Med. 26(1) (1996) 9-24.

BTU Cottbus

Abstract The qualitative analysis of biochemical reaction systems is presented. A discrete event systems approach is used to represent and analyze bioreaction pathways. The approach is based on Petri nets, which are particularly suited to modeling stoichiometric transformations, i.e. the interconversion of metabolites in fixed proportions. The properties and methods for the analysis of Petri nets, along with their interpretation for biochemical systems, are presented. As an example, the combined glycolytic and pentose phosphate pathway of the erythrocyte cell is presented to illustrate the concepts of the methodology.

Keywords metabolisms; glycolysis und pentose phosphate metabolism combined in redd blood corpuscles; methodics

B66 Schuster, S.; Pfeiffer, T.; Moldenhauer, F.; Koch, I.; Dandekar, T.: Structural Analysis of Metabolic Networks: Elementary Flux Modes, Analogy to Petri Nets, and Application to Mycoplasma pneumoniae. Bornberg-Bauer, E.; Rost, U.; Stoye, J.; Vingron, M. (eds.): Proc. German Conference on Bioinformatics, Berlin, Germany, 2000, Logos Verlag, Berlin, 2000, 115-120.

B67 Schuster, S.; Pfeiffer, T.; Moldenhauer, F.; Koch, I.; Dandekar, T.: Exploring the Pathway Structure of Metabolism: Decomposition into Subnetworks and Application to Mycoplasma pneumoniae. Bioinformatics 18(2) (2002) 351-61.

Abstract Motivation: Reconstructing and analyzing the metabolic map of microorganisms is an important challenge in bioinformatics. Pathway analysis of large metabolic networks meets with the problem of combinatorial explosion of pathways. Therefore, appropriate algorithms for an automated decomposition of these networks into smaller subsystems are needed.

Results: A decomposition algorithm for metabolic networks based on the local connectivity of metabolites is presented. Interrelations of this algorithm with alternative methods proposed in the literature and the theory of small world networks are discussed. The applicability of our method is illustrated by an analysis of the metabolism of Mycoplasma pneumoniae, which is an organism of considerable medical interest. The decomposition gives rise to 19 subnetworks. Three of these are here discussed in biochemical terms: arginine degradation, the tetrahydrofolate system, and nucle-

otide metabolism. The interrelations of pathway analysis of biochemical networks with Petri net theory are outlined.

Keywords metabolisms; mycoplasma pneumoniae; methodics

B68 Schuster, S.: Topologische Analyse metabolischer und regulatorischer Netzwerke.

Abstract: http://www.biologie.hu-berlin.de/~gk/studies/content.html

Abstract Aufbauend auf modernen Methoden der strukturellen Analyse sollen größere realistische Systeme modelliert werden, die biochemisch gut charakterisiert sind, z. B. Teile des Metabolismus in verschiedenen Zellen des Menschen, Bacillus subtilis, Escherichia coli u.a. Dabei sollen anhand der Elementarmoden optimale stöchiometrische Effizienzen ermittelt werden, insbesondere für technisch genutzte Biosynthesen wie z.B. die Aminosäuresynthese in E. coli und Hefe. Im nächsten Schritt ist geplant, biochemisch weniger gut untersuchte Systeme wie den Sekundärstoffwechsel zu untersuchen. Ein zentrales Forschungsobjekt werden die Mikroorganismen sein, deren Genom vollständig sequenziert vorliegt (z.B. Mycobacterium tuberculosis, Mycoplasma genitalium, Helicobacter pylori). Das Ziel dabei ist, die Lücken in der Zuordnung der Informationen über das Genom zur topologischen Struktur des Metabolismus schließen zu helfen (sog. Rekonstruktion von metabolisms).

Als medizinisch relevante Anwendung sollen Enzymdefekte (vererbte geringe oder fehlende Aktivität einzelner Enzyme) durch Ermittlung der verbleibenden bzw. alternativen metabolischen Routen charakterisiert werden. Anknüpfend an die Vorarbeiten zur Optimierung von Enzymsystemen soll die Frage untersucht werden, nach welchen Kriterien die biochemischen Wege während der Evolution aus der Vielzahl der stöchiometrisch und thermodynamisch zulässigen Routen ausgewählt wurden. Das wiederum kann helfen, evolutionäre Stammbäume von Mikroorganismen zu vervollständigen.

Es ist beabsichtigt, die bisher erarbeiteten Methoden so zu erweitern, daß sie auch auf die Wege der signal transduction (z.B. Enzymkaskaden) anwendbar sind. Die Schwierigkeit besteht dabei darin, daß diese Systeme häufig keinen stationären Zustand erreichen und es weniger auf den Stoff - als auf den Informationsfluß ankommt. Dabei könnten Methoden aus der Theorie der Petri-Netze Anwendung finden.

Eine wichtige Aufgabe wird die Erstellung und Adaptation spezifischer Software sein; z.B. soll ein Computeralgorithmus entwickelt werden, der alle mit den genetischen Daten und den Bilanzgleichungen konsistenten Topologien entwirft und dem Nutzer mittels eines Dialogprogramms erlaubt, die plausibelsten Möglichkeiten auszuwählen. Es ist geplant, Routinen einzufügen, die ein automatisches Einlesen von Reaktionsgleichungen größerer metabolischer Systeme aus Datenbanken wie PUMA und WIT erlauben. Sowohl die überarbeiteten als auch die neuen Programme können dann in Form von Services im WWW angeboten werden.

Translation Founded on modern methods of structural analysis bigger realistic systems that are biochemically good characterized are supposed to be modelled, for example parts of the metabolism in different cells of human, bacillus subtilis, escherichia coli and other. Thereby optimal stoichiometric efficiencies are supposed to be determined by means of the elementary modes, in particular for technically used biosyntheses as for example the amino acid synthesis in E. coli and yeast. In the next step it is planned to investigate biochemically less well examined systems as the secondary metabolism. The microorganisms whose genome is available completely sequenced will be a central investigation object (for example Mycobacterium tuberculosis, Mycoplasma genitalium, Helicobacter pylori). The destination in this case is, to help to fill the gaps in the assignment of the information about the genome to the topological structure of the metabolism (so-called reconstruction of metabolisms).

As a medically relevant application enzyme defects (inherited small or missing activity of individual enzymes) are supposed to be characterized by determination of the residual, respectively alternative metabolic routes. Establishing onto the preparatory works for the optimisation of enzyme systems the question is supposed to be examined, according to which criteria the biochemical ways

during evolution were selected from the multitude of stoichiometric and thermodynamic permissible routes. That again can help to complete evolutionary pedigrees of microorganisms.

It is intended to expand the up to now elaborated methods so, that they also are available to pathways of signal transduction (for example enzyme cascades). The difficulty thereby is, that these systems do not frequently achieve a steady state and that it depends less on the substance than the information flow. Thereby methods from Petri net theory could be applicated.

An important task will be the preparation and adaptation of specific software. For example a computer algorithm is supposed to be developed that works out all topologies consistent with the genetic data and balance equations, and that allows the user to choose the plausiblest possibilities by means of a dialog program. It is planned to insert routines which make possible an automatic input of reaction equations of bigger metabolic systems from databases as PUMA and WIT. Both the reworked ones and the new programmes can be offered then in the form of services in the WWW.

Keywords In German. description research prject; metabolisms, gene regulation, signal transduction; methodics

B69 Srivastava, R.; Bentley, W. E.: Kinetic Modeling of the Sigma-32 Response in Escherichia coli Using a Stochastic Petri Net. Abstracts of Papers of the American Chemical Society 217 (1999) 141 - Biot Part 1 Mar 21.

Keywords sigma-32 response in bakterium escherichia coli; stochastic PN

B70 Srivastava, R.; Peterson, M. S.; Bentley, W. E.: Stochastic Kinetic Analysis of the Escherichia coli Stress Circuit Using Sigma(32)-targeted Antisense. Biotechnol. Bioeng. 75(1) (2001) 120-129.

Abstract A stochastic Petri net model was developed for simulating the sigma(32) stress circuit in E. coli. Transcription factor sigma(32) is the principal regulator of the response of E. coli to heat shock. Stochastic Petri net (SPN) models are well suited for kinetics characterization of fluxes in biochemical pathways. Notably, there exists a one-to-one mapping of model tokens and places to molecules of particular species. Our model was validated against experiments in which ethanol (inducer of heat shock response) and sigma(32)-targeted antisense (downward regulator) were used to perturb the sigma(32) regulatory pathway. The model was also extended to simulate the effects of recombinant protein production. Results show that the stress response depends heavily on the partitioning of sigma(32) within the cell; that is, sigma(32) becomes immediately available to mediate a stress response because it exists primarily in a sequestered, inactive form, complexed with chaperones DnaK, DnaJ, and GrpE. Recombinant proteins, however, also compete for chaperone proteins, particularly when folded improperly. Our simulations indicate that when the expression of recombinant protein has a low requirement for DnaK, DnaJ, and GrpE, the overall sigma(32) levels may drop, but the level of heat shock proteins will increase. Conversely, when the overexpressed recombinant protein has a strong requirement for the chaperones, a severe response is predicted. Interestingly, both cases were observed experimentally.

Keywords sigma-32 stress circle in bakterium escherichia coli; stochastic PN

B71 Suzuki, R.: A Petri Net System Applied to Biochemical Reaction Networks. Master Thesis, 2002.

Abstract: http://www.jaist.ac.jp/library/thesis/ks-master2002/abstract/ryuuji-s/abstract.pdf

Abstract Information about genes and proteins is gathered in large amounts due to the quick increase in computer power and the development of improved analytic techniques and experiments. This information should not be considered in isolation, but rather as part of a larger system. Hence, a synthetic approach is required to verify whether or not the whole system can be reconstructed from the combination of those parts.

In this context, recent researches investigate the application of graph theory to describe the parts and their interaction. The theory thus developed provides a common methodological framework that can be applied at various abstraction levels (e.g. from a molecular reaction pathway to a full

ecosystem represented as a network of individulas). This makes it possible to understand the life phenomenon at various levels.

In this dissertation, we use Petri nets to model these networks. More specifically, we present models built using an extension of Petri nets adapted to the situation, and simulations based on those models.

The variant of Petri nets used in this research is based on “hybrid Petri net”, which allows both discrete and continuous values for tokens as well as arc weights. It extends hybrid Petri nets to allow the amount of token moved to parameterized by external values, such as general chemical reaction kinetics or enzyme reaction kinetics. It further extends hybrid Petri nets to allow the simulation of a system with spatial information. We call the resulting Petri net a „positional hybrid Petri net“.

In this dissertation, we use positional hybrid Petri nets to model and simulate the cell cycle control system, which is one of the well-known biochemical reaction pathways. Since this pathway involves no positional information, we repeat the process with the pattern formation in drosophila embryogenesis, another pathway which does.

Keywords In Japanese. embryonic development/cell cyclus of drosophila fly; hybrid PN, introducing parameterizable hybrid PN, introducing spatial PN; methodics

B72 Yoshioka, T.; Kotani, S.; Konagaya, A.: Computational Model of the Mammalian Cell Cycle using Hybrid Petri Net. Proc. 10th International Conference on Intelligent Systems for Molecular Biology (ISMB), Edmonton, Canada, August 2002.

Abstract Mammalian cells reproduce by passing through the cell cycle. To describe the molecular mechanism of the mammalian cell cycle in a correct manner, we developed a new computational model that makes use of hybrid Petri nets. The model shows the status of a given cell, such as the concentration of various proteins working in each stage, and the activity level of enzymes. This describes dynamic changes in each cell cycle controling molecule and the topology of the activity of Cdc2-cyclin B kinase (MPF), one of the core networks of cell cycle engines. We also confirmed that the model reproduces some previously- reported biological abnormalities in cell cycle fields. When the level of phosphatase(Cdc25B) is increased in the model, the speed of progression through the cell cycle is accelerated. This is a phenomenon actually seen in cells extracted from patients suffering from carcinoma of the colon and rectum. The model can also easily reproduce ”knockout” or overexpression of specific gene products related to cell cycle control in living cells. Therefore, this model is a potentially useful means of exploring relations between gene functions and diseases.

Keywords cell cycle mammalians; hybrid PN

B73 Voss, K.; Heiner, M.; Koch, I.: Steady State Analysis of Metabolic Pathways Using Petri Nets. Aarhus University, Aarhus, Denmark, 2001.

Abstract Computer assisted analysis and simulation of biochemical pathways can improve the understanding of the structure and the dynamics of cell processes considerably. The construction and quantitative analysis of kinetic models is often impeded by the lack of reliable data. However, as the topological structure of biochemical systems can be regarded to remain constant in time, a qualitative analysis of a pathway model was shown to be quite promising as it can render a lot of useful knowledge, e.g., about its structural invariants. The topic of this paper are pathways whose substances have reached a dynamic concentration equilibrium (steady state). It is argued that appreciated tools from biochemistry and also low-level Petri nets can yield only part of the desired results, whereas executable high-level net models lead to a number of valuable additional insights by combining symbolic analysis and simulation.

Keywords metabolsims; glycolysis and pentose phosphate metabolsim combined; time-dependent PN, hierarchical PN; S- and T-invariants; steady states, elementary modes; methodics

B74 Zevedei-Oancea, I.; Schuster, S.: Topological Analysis of Metabolic Networks Based on Petri Net Theory.

Abstract In the present paper, we shall focus on the topological analysis of biochemical networks by using Petri nets rather than on the analysis of the dynamic behaviour. In particular, we shall deal with various invariants and other features in these nets such as boundedness and liveness and reveal their biochemical meaning. Moreover, we shall discuss the appropriate treatment of source and sink metabolites.

Keywords metabolisms; invariants; source and sink transitions

C CHEMISTRY

C1 Kuroda, C.; Ogawa, K.: Nonlinear-Waves in a Shear-flow with a Diffusive Exothermic Reaction and its Qualitative Reasoning. Chemical Engineering Science 49(16) (1994) 2699-2708.

Abstract In nonlinear chemical reaction systems, the occurrence of the macroscopic structure is well known as the oscillatory pattern formation, the solitary wave, the chaotic behavior and so on. In this paper, the occurrence of nonlinear waves in a liquid shear flow with a diffusive exothermic reaction is reported and its qualitative reasoning using a timed Petri net is investigated. It is considered that the viscosity is a direct effective factor on the occurrence of waves. Such viscous nonlinear waves induced by a diffusive exothermic reaction are experimentally shown and qualitatively analyzed. The waves with the almost constant frequency, about 1.7 Hz, can be detected by visual observation, temperature measurements, and velocity measurements. A qualitative model on the mechanism of oscillation is proposed based on the interaction among concurrent events, i.e., reaction, molecular mass transfer, molecular heat transfer, molecular momentum transfer and forced-convective transfer. It is confirmed by Petri net simulations that the relationship of $Sc > Pr > 1$ in the liquid phase is closely connected with the continuation of the oscillatory phenomena. Moreover, it is expected that an increase of entire fluid viscosity induces an increase of the frequency, and it can be experimentally confirmed.

Keywords oszillations in non-linear chemical reaktion systems; non-linear waves in a sheared liquid with an exothermic diffusion reaction

D MEDICINE

M1 Atanassov, K. T.; Shannon, A. G.; Wong, C.; Owens, D.: A Generalized Net for Endogenous and Exogenous Insulin Kinetics. 1995.

M2 Atanassov, K. T.; Georgiev, P. R.; Shannon, A. G.; Wong, C.; Owens, D.: A Generalized Net for Insulin Flow. 1995.

M3 Atanassov, K. T.; Cekov, N.; Christov, R.; Georgiev, P. R.; Karagyozov, I.; Momchilov, P.; Sorsich, J. G.: Project: Generalized Net Model of Health Activities, Advances in Modelling & Analysis. 1994.

M4 Atanassov, K. T.; Bustince, H.; Daskalov, M.; Sorsich, J. G.: Generalized Net Models in Neurology (Introduction). 1995.

M5 Atanassov, K. T.; Bustince, H.; Daskalov, M.; Kim, S. K.; Shannon, A.; Sorsich, J. G.: Generalized Net Models in Neurology (Introduction, Second Part). 1995.

M6 Atanassov, K. T.; Bustince, H.; Daskalov, M.; Georgiev, P.; Sorsich, J. G.: Generalized Net Models in Neurology (NGN17: Clumsiness and Incoordination (Ataxia) Suspected). 1995.

M7 Atanassov, K. T.; Bustince, H.; Daskalov, M.; Kim, S. K.; Shannon, A. G.; Sorsich, J. G.: Generalized Net Models in Neurology (NGN84: Guillain-Barre Syndrome Suspected). Preprint MRL-MFAIS-2-95, Sofia, Oct. 6. 1995.

M8 Atanassov, K. T.; Bustince, H.; Daskalov, M.; Kim, S. K.; Shannon, A. G.; Sorsich, J. G.: Generalized Net Models in Neurology (NGN100: Findings of Chorea and Athetoid Movements). 1995.

M9 Atanassov, K.T; Daskalov, M.; Georgiev, P. R.; Kim, S. K.; Kim, Y.; Nikolov, N.N.; Shannon, A. G.; Sorsich J. G.: Generalized Nets in Neurology. 1997.

M10 Balk, E. W. M.: Einführung in Petri-Netze. Teil 2. Grundlagen von Petri-Netzen. 1998.
http://www.smolensk.ru/user/sgma/MMORPH/N-4-html/5.htm

Abstract Wir präsentieren grundlegende Vorstellungen über Modellierungsmethoden. Die zweite Arbeit dieses Zyklus ist grundlegenden Vorstellungen und Problemen gewidmet, die wir im Rahmen einer speziellen Art Graphen, nämlich Petri-Netzen, lösen. Wir betrachten Möglichkeiten und Verwendung dieses mathematischen Instruments in der medizinischen Morphologie.

Translation We present basic ideas about modelling methods. The second treatise of this cycle is dedicated to basic ideas and problems, which we solve within the framework of a specific graph kind, namely Petri nets. We consider possibilities and use of this mathematical instrument in medical morphology.

Keywords In Russian. medical morphology; excitement of saliva flow reflex at dog through an electrical bell

M11 Baresi, L.; Consorti, F.; Di Paola, M.; Gargiulo, A.; Pezze, M.: LEMMA: a Language for Easy Medical Models Analysis. J. Med. Syst. 21(6) (1997) 369-388.

Abstract The quality of health care systems and processes is becoming a prominent problem and more and more efforts are devoted to define methodologies and tools to measure and assure quality of care. New methods are required to optimize health care processes to guarantee high quality standards within (limited) available resources. Resource optimizations able to preserve the quality of treatments require good models of medical processes. This paper presents LEMMA, a new notation to model medical processes. LEMMA provides physicians with intuitive graphical elements to design their models. At the same time a high level timed Petri net corresponding to the designed model is built automatically. In this way, LEMMA models are ascribed formal semantics and can be executed and analyzed automatically. The dual language approach followed in this paper allows physicians to gain all the benefits of formal methods without being proficient in them. Medical users manage simple graphical elements, while Petri nets ensure formality and validation capabilities. In this way LEMMA mixes formal and informal notations, overcoming the problems of both the approaches. The definition of the notation has been supported by the development of an environment to design LEMMA models. The environment, besides letting us experiment with the notation, has been employed to define and analyze real case studies.

KeywordssSoftware

M12 Bjankova, B.; Sorsich, J. G.; Kim, S.-K.; Atanassov, K. T.: Application of the Generalized Net in Nephrology (Approach to Patient with Recurrent Urinary Symptoms). 1995.

M13 Blom JA: Temporal Logics and Real Time Expert Systems. Computer Methods and Programs in Biomedicine 51(1-2) (1996) 35-49.

Abstract This paper introduces temporal logics. Due to the eternal compromise between expressive adequacy and reasoning efficiency that must decided upon in any application, full (first order logic

or modal logic based) temporal logics are frequently not suitable. This is especially true in real time expert systems, where a fixed (and usually small) response time must be guaranteed. One such expert system, Fagan's VM, is reviewed, and a delineation is given of how to formally describe and reason with time in medical protocols. It is shown that Petri net theory is a useful tool to check the correctness of formalised protocols.

M14 Chin, T. M.; Willsky, A. S.: Stochastic Petri Net Modeling of Wave Sequences in Cardiac Arrhythmias. Comput. Biomed. Res. 22(2) (1989) 136-159.

Abstract We describe a methodology for modeling heart rhythms observed in electrocardiograms. In particular, we present a procedure to derive simple dynamic models that capture the cardiac mechanisms which control the particular timing sequences of P and R waves characteristic of different arrhythmias. By treating the cardiac electrophysiology at an aggregate level, simple network models of the wave generating system under a variety of diseased conditions can be developed. These network models are then systematically converted to stochastic Petri nets which offer a compact mathematical framework to express the dynamics and statistical variability of the wave generating mechanisms. Models of several arrhythmias are included in order to illustrate the methodology.

Keywords heart rhythm troubles; stochastic PN

M15 Ciccarese, P.; Kumar, A.; Quaglini, S.: NEW-GUIDE: A New Approach to Representing Clinical Practice Guidelines. Advances in Clinical Knowledge Management 5, London, UK, April 2002.

http://www.openclinical.orgcommunity/workshops/ackm5/ackm5.pdf

http://www.openclinical.org/docs/ext/workshops/ackm5/absciccarese.pdf

M16 Daskalov, M.; Bustince, H.; Atanassov, K. T.: Generalized Net Models in Neurology (Chronic Headache). 1995.

M17 Daskalov, M.; Atanassov, K. T.; Bustince, H.: Generalized Net Models in Neurology (Coma). 1995.

M18 Daskalov, M.; Bustince, H.; Atanassov, K. T.: Generalized Net Models in Neurology (First Headache). 1995.

M19 Daskalov, M.; Atanassov, K. T.: Generalized Net Models in Neurology (NGN33: Tinnitus). 1996.

M20 Dazzi, L.; Fassino, C.; Saracco, R.; Quaglini, S.; Stefanelli, M.: A Patient Workflow Management System Built on Guidelines. Proc. AMIA Annu. Fall Symp. (1997) 146-150.

Abstract To provide high quality, shared, and distributed medical care, clinical and organizational issues need to be integrated. This work describes a methodology for developing a Patient Workflow Management System, based on a detailed model of both the medical work process and the organizational structure. We assume that the medical work process is represented through clinical practice guidelines, and that an ontological description of the organization is available. Thus, we developed tools 1) for acquiring the medical knowledge contained into a guideline, 2) to translate the derived formalized guideline into a computational formalism, precisely a Petri Net, 3) to maintain different representation levels. The high level representation guarantees that the Patient Workflow follows the guideline prescriptions, while the low level takes into account the specific organization characteristics and allow allocating resources for managing a specific patient in daily practice.

M21 De Rosis, F.; Pizzutilo, S.; De Carolis, B.: Formal Description and Evaluation of User-adapted Interfaces. International Journal of Human-Computer Studies 49 (2) (1998) 95-120.

Abstract This paper describes a visual formalism and a tool to support design and evaluation of human-computer interaction in context-customized systems. The formalism is called XDM (for "con-

text-sensitive dialogue modelling") and combines extended Petri nets with Card, Moran and Newell's KLM operators theory to describe static and dynamic aspects of interaction in every context in which the system should operate, and to make evaluations of interface correctness and usability easier or automatic. The method was developed in the scope of a European Community Project to iteratively prototype a knowledge-based medical system. It has been subsequently employed in several research projects and in teaching activities. (C) 1998 Academic Press

M22 Doerschuk, P. C.; Chin, T. M.; Willsky, A. S.: Modeling of Cardiac Rhythms. A Signal-processing Perspective. J. Electrocardiol. 23(Suppl.) (1990) 102-110.

Abstract The authors describe their perspective on the modeling of cardiac rhythms as a component of cardiac arrhythmia signal-processing algorithms. They emphasize that these models are for a specific end purpose and that the aspects of cardiac behavior that are captured by the models are only those relevant for the development of the signal-processing algorithms. The approach is to use statistics to describe ranges of cardiac behavior that share some common feature with respect to the purpose of the signal processing. The statistical approach has the advantage that, coupled with a statistical performance criterion, it specifies an optimal signal-processing algorithm. These optimal algorithms are often computationally intractable, however, especially for real-time use in instruments. Approximations are therefore crucial. The mathematical form of the model is then important since, even if two forms generate identical statistics, the approximations that are natural in different forms can be quite different. Two different mathematical formulations are described - stochastic Petri nets and interacting Markov chains - and the different types of approximately optimal signal-processing algorithms that are natural in these two frameworks are discussed.

Keywords signal processing; heart rhythms; methodics

M23 Gerhard, E.; Wippich, K.: Structural Description of the Human Eye Using Petri Nets. Biomed. Tech. (Berl) 36(4) (1991) 66-9.

Abstract Petri nets are a tool for analysing and modelling processes and systems. Here they are used to describe the human visual canal for the first time. A dynamic net describes the formation of a glaucoma.

Keywords human seeing-channel - glaucoma formation

M24 Gyurov, P.; Georgiev, P.: On the Application of the Petri Nets in Medicine, Biology and Expert Systems. Proc. Int. Symp. Bioprocess Systems '95, Sofia, VI (1997) 103-106 (Bulgarian).

M25 Hughes, M.; Carson, E. R.; Makhlouf, M.; Morgan, C. J.; Summers, R. A.: Petri Net Based Model of Patient Flows in a Progressive Patient Care System. Proc. 20th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Piscataway, NJ: IEEE, 1998.

M26 Kimura, H.; Akatsuka, T.: Modeling and Performance Analysis of Image Transfer in PACS. Medinfo 9(Pt 2) (1998) 1080-1084.

Abstract Performance simulation plays an important role in the design of picture archiving and communication systems (PACS). This paper presents simulation models of a PACS in a context of outpatient clinical workflow. Models, which are discussed focusing on shared facilities are resources of the system, consist of two levels. One is the workflow level and the other is the physical level. Patients medical staffs and images are picked up as the important system resources in the workflow level. A network, hard disks and network interface buffers of PACS components are mainly described in the physical level. Models are described with Petri Nets in both levels. Two examples of performance evaluation are also presented. Both of them estimate transfer time of computed radiology images for outpatient consultation. In the first example, both the data transfer rate of hard disks and network speed are varied under fixed system loads. While in the second example, system loads are varied against given system components. From the simulation results, following points are summarized. If physicians want to get a set of images in 5 seconds, both high

performance hard disks or disk arrays and high speed network such as 100 Mbps networks are required. And it is effective for high speed network to be used in the acquisition phase. If we have to use the Ethernet and ordinary workstations, the PACS should be used in a single clinic. In conclusion this modeling method makes models simple and is quite useful for the performance evaluation of PACS in the early design phase.

M27 Marraro, G.; Mereu, M.; Ambroso, C.: Therapeutic Process Formalization in the Treatment of Respiratory Failure in Infants. Int. J. Clin. Monit. Comput. 10(3) (1993) 167-173.
Abstract The model described formalizes the therapeutic process developed in the Pediatric Intensive Care Unit (PICU) of Merate's Hospital as a support of medical decisions and as a continuous control of the adequacy of the ventilatory therapy. Causal and temporal structure of the keypoints of the treatment are represented by Petri Nets. The model could be utilised in different pathologies and for different clinical approach giving a meaningful organizational impact.

M28 Mateva, N.; Ouzounov, N.; Stefanov, R.: Assistance with Generalized Net Models to the Differential Diagnosis of Some Pathologic Somatic Muscular and Neurologic Conditions in Stomatology. Folia Med (Plovdiv) 40(3B Suppl 3) (1998) 81-87.
Abstract Some somatic pathologic muscular and neurologic conditions in stomatology are difficult to differentiate. For example, the myofascial pain dysfunction syndrome, trigger point muscle pains and a number of temporomandibular joint related pathoses often cause diagnostic difficulties. With the purpose to assist general clinicians and students to understand and differentiate more easily these difficult occasions, the authors try to offer a model simulating the decision-making process in some of the aforementioned pathoses. The model is based on the Generalized Nets Models which represent extensions of Petri's nets and their modifications.
Keywords generalized PN; methodics

M29 Mounts, W. M.; Liebman, M. N.: Qualitative Modeling of Normal Blood Coagulation and its Pathological States Using Stochastic Activity Networks. Int. J. Biol. Macromol. 20(4) (1997) 265-281.
Abstract We have developed a method for representing biological pathways and simulating their behavior based on the use of stochastic activity networks (SANs). SANs, an extension of the original Petri net, have been used traditionally to model flow systems including data-communications networks and manufacturing processes. We apply the methodology to the blood coagulation cascade, a biological flow system, and present the representation method as well as results of simulation studies based on published experimental data. In addition to describing the dynamic model, we also present the results of its utilization to perform simulations of clinical states including hemophilia's A and B as well as sensitivity analysis of individual factors and their impact on thrombin production.
Keywords blood cagulation; stochastic activity nets

M30 Müller, R.; Heller, B.: A Petri Net-based Model for Knowledge-based Workflows in Distributed Cancer Therapy. Proc. International Conference on Extending Database Technology (EDBT) Workshop on Workflow Management Systems, Valencia, Spain, March 1998, 91-99.

M31 Nicolosi, A.; Attolini, M.; Varesco, P.; Sicurello, F.; Pizzi, R.; Antoni, G.D.: An Integrated Workstation for Research on the Acquired Immunodeficiency Syndrome. Barber, B., et al.: MEDINFO 89. Proc. 6th Conference on Medical Informatics, Beijing, China and Singapore, 1989. North-Holland, Amsterdam, The Netherlands, 1989, 577-581.
Abstract A workstation oriented to AIDS research is described. The formalism used to represent the knowledge network was the Petri net. The knowledge base contains clinical, epidemiologic, immunologic, virologic, bibliographic data and text (articles, documents). The workstation utilizes advanced methods (semantic nets, hypertext), in order to allow the user to explore available knowledge and to produce advances in knowledge through inference and information interaction.

M32 Ouchi, Y., Tazaki, E.: Medical Diagnostic System Using Fuzzy Coloured Petri Nets under Uncertainty. Medinfo 9(Pt 1) (1998) 675-679.

Abstract We propose a medical diagnostic system using Fuzzy Coloured Petri Nets (FCPN) in this paper. For complex real-world knowledge Fuzzy Petri Net (FPN) models have been proposed to perform fuzzy reasoning automatically. However, in the Petri Net we have to represent all kinds of processes by separate subnets even though the process has the same behavior of other one. Real-world knowledge often contains many parts which are similar, but not identical. This means that the total PTN becomes very large. The kind of problems may be annoying for a small system, and it may be catastrophic for the description of large-scale system. To avoid this kind of problems we propose a learning and reasoning method using FCPNs under uncertainty. On the other hand to correct the rules of knowledge-based system hand-built classifier and empirical learning method both based on domain theory have been proposed as machine learning methods, where there is a significant gap between the knowledge-intensive approach in the former and the virtually knowledge-free approach in the later. To resolve such problems simultaneously we propose a hybrid learning method which is built on the top of knowledge-based FCPN and Genetic Algorithms (GA). To verify the validity and the effectiveness of the proposed system, we have successfully applied it to the diagnosis of intervertebral diseases.

Keywords colored Fuzzy-PN; methodics

M33 Padberg, J.: Categorical Approach to Horizontal Structuring and Refinement of High-level Replacement Systems. Applied Categorial Structures 7(4) (1999) 371-403.

Abstract Based on the well-known theory of high-level replacement systems - a categorical formulation of graph grammars - we present new results concerning refinement of high-level replacement systems. Motivated by Petri nets, where refinement is often given by morphisms, we give a categorical notion of refinement. This concept is called Q-transformations and is established within the framework of high-level replacement systems. The main idea is to supply rules with an additional morphism, which belongs to a specific class Q of morphisms. This leads to the new notions of Q-rules and Q-transformations. Moreover, several concepts and results of high-level replacement systems are extended to Q-transformations. These are sequential and parallel transformations, union, and fusion, based on different colimit constructions. The main results concern the compatibility of these constructions with Q-transformations that is the corresponding theorems for usual transformations are extended to Q-transformations. Finally, we demonstrate the application of these techniques for the special case of Petri nets to a case study concerning the requirements engineering of a medical information system.

M34 Peimann, C. J.: Modeling Hospital Information Systems with Petri Nets. Methods Inf. Med. 27(1) (1988) 17-22.

M35 Pizzi, R.; DeGaetano, A.; Guadalupi, P.; Chiara, O.; Columbano, C.; Sicurello, F.: Prediction of MSOF Evolution by Means of Nine Vital Systems Trajectories. MEDINFO 89. Proc. 6th Conference on Medical Informatics, Beijing, China and Singapore, 1989. Barber, B., et al. (eds.), North-Holland, Amsterdam, The Netherlands (1989) 577-581.

Abstract Multiple System Organ Failure (MSOF) remains a principal cause of death after major operative procedures. In a retrospective analysis of 132 emergency surgical patients, MSOF developed in 21. 240 integrated monitorings were derived from these patients. The records have yielded the first knowledge base for an original procedure developed to study this severe syndrome. The procedure includes a statistical algorithm and a method of knowledge representation and extraction by means of a Petri net system.

M36 Quaglini, S.; Mossa, C.; Fassino, C.; Stefanelli, M.; Cavallini, A.; Micieli, G.: Guidelines-based Workflow Systems. Artificial Intelligence in Medicine, Lecture Notes in Artificial Intelligence 1620 (1999) 65-75.

Abstract This paper describes a methodology for achieving an efficient allocation of resources while using clinical practice guidelines. The resulting system can be classified as a "guideline-based patient workflow management system". Both medical and organisational knowledge are represented through computational formalisms, from relational tables to Petri net, Human and technological resources, necessary to guideline-based activities, are represented within an organisational model. This allows running the Petri net for simulating the implementation of the guideline in the clinical setting, in such a way to validate the model and to suggest an optimal resource allocation, before the workflow system is installed. Finally, we are experimenting the real setting implementation. For illustrating the methodology, an application concerning the management of acute ischemic stroke is presented.

M37 Quaglini, S.; Stefanelli, M.; Cavallini, A.; Micieli, G.; Fassino, C.; Mossa, C.: Guideline-based Careflow Systems. Artif. Intell. Med. 20(1) (2000) 5-22.

Abstract This paper describes a methodology for achieving an efficient implementation of clinical practice guidelines. Three main steps are illustrated: knowledge representation, model simulation and implementation within a health care organisation. The resulting system can be classified as a 'guideline-based careflow management system'. It is based on computational formalisms representing both medical and health care organisational knowledge. This aggregation allows the implementation of a guideline, not only as a simple reminder, but also as an 'organiser' that facilitates health care processes. As a matter of fact, the system not only suggests the tasks to be performed, but also the resource allocation. The methodology initially comprehends a graphical editor, that allows an unambiguous representation of the guideline. Then the guideline is translated into a high-level Petri net. The resources, both human and technological necessary for performing guideline-based activities, are also represented by means of an organisational model. This allows the running of the Petri net for simulating the implementation of the guideline in the clinical setting. The purpose of the simulation is to validate the careflow model and to suggest the optimal resource allocation before the careflow system is installed. The final step is the careflow implementation. In this phase, we show that the 'workflow management' technology, widely used in business process automation, may be transferred to the health care setting. This requires augmenting the typical workflow management systems with the flexibility and the uncertainty management, typical of the health care processes. For illustrating the proposed methodology, we consider a guideline for the management of patients with acute ischemic stroke.

M38 Quaglini, S.; Caffi, E.; Cavallini, A.; Micieli, G.; Stefanelli, M.: Simulation of a Stroke Unit Careflow. Medinfo 10(Pt 2) (2001) 1190-1191.

Abstract This paper describes the development and use of a simulation model representing part of the medical practice within a Stroke Unit. In particular, we modelled the medical activities as described in a guideline for the ischemic stroke treatment, adopted by the Stroke Unit of our hospital. The Petri net formalism has been chosen for the model representation. The numerical parameters have been estimated both using a database of about 100 patients collected during the last two years, and eliciting knowledge from the neurologists. A commercial tool was used for performing simulations, while ad-hoc routines were written for tailoring the result presentation to the specific context. We consider simulation a very useful preliminary step for the subsequent implementation of a patient workflow (careflow) management system. In fact, simulation is based on the process model (the clinical practice guideline) and on the organisation model (human and technological resources), so allowing to detect bottlenecks in the care delivery organisation and to find the optimal resource allocation. For example, we show that simulation has been able to find some of the causes of the delay in the patients treatment, and accordingly, to suggest changes in the organisation.

M39 Shannon, A.; Sorsich, J. G.; Atanassov, K. T.: Application of the Generalized Net in Nephrology (Remark on the Global Generalized Net). 1995.

M40 Shannon, A.; Atanassov, K. T.: Applications of Generalized Nets in the Modelling of Biomedical Processes. 1995.

M41 Shannon, A. G.; Sorsich, J. G.; Atanassov, K. T.: Generalized Nets in Medicine. 1996.

M42 Shannon, A. J.; Sorsich, K.; Atanassov, N. N.; Georgiev, P.: Generalized Nets in General and Internal Medicine Vol. 1, 1998, Sofia

Abstract Generalized Nets (GNs) are extensions of Petri nets and their modifications. The purpose of this book is to apply the theory of GNs to general and internal medicine. Two volumes of the book are planned: the first (present) one, containing 106 diagnostic GN-models of the basic diseases in the areas of general medicine, cardiology, dermatology, endocrinology, gastroenterology and haematology/oncology, and a second volume with more than 100 other GN models from the areas of infectious diseases, nephrology, neurology, pulmonary diseases, rheumatology, emergency medicine, gynaecology, urology, behaviour medicine, and pharmacology.

M43 Shannon, A. J.; Sorsich, K.; Atanassov, N. N.; Georgiev, P.: Generalized Nets in General and Internal Medicine Vol. 2, 1999, Sofia.

Abstract Generalized Nets (GNs) are extensions of Petri nets and their modifications. The purpose of this book is to apply the theory of GNs to general and internal medicine. Two volumes of the book are planned: the first (present) one, containing 106 diagnostic GN-models of the basic diseases in the areas of general medicine, cardiology, dermatology, endocrinology, gastroenterology and haematology/oncology, and a second volume with more than 100 other GN models from the areas of infectious diseases, nephrology, neurology, pulmonary diseases, rheumatology, emergency medicine, gynaecology, urology, behaviour medicine, and pharmacology.

M44 Shannon, A.; Atanassov, K.; Sorsich, J.; Radeva, V.: Generalized Net Interpretations of Ivan Dimitrov's Informational Theory of Diseases. 2001.

Abstract Generalized Nets (GNs) are extensions of the Petri nets and their modifications. They are tools for modeling parallel processes. Elements of their theory are given in chapter 2. In chapter 3 the GNs are used for interpreting the basic elements of the informational theory of diseases introduced by Ivan Dimitrov (1940-1998), described shortly in chapter 1. Ideas for GN-modeling of the human body are discussed in chapter 4.

M45 Sorsich, J. G.; Atanassov, K. T.: Application of Generalized Nets in Medicine (Diagnostics of Arterial Hypertension of Renal Origin). 1984.

M46 Sorsich, J. G.; Atanassov, K. T.: The Application of Generalized Nets in Medicine (Renal Colic). 1984.

M47 Sorsich, J. G.; Atanassov, K. T.: Application of Generalized Nets in Medicine (Haemuturia). 1985.

M48 Sorsich, J. G.; Atanassov, K. T.: Application of Generalized Nets in Medicine (Permanent Proteinuria). 1985.

M49 Sorsich, J. G.; Atanassov, K. T.: Application of Generalized Nets in Medicine (Renovascular Hypertension). 1985.

M50 Sorsich, J. G.; Atanassov, K. T.: Application of Generalized Nets in Medicine (Acute Attack of Gouty Arthritis). 1987.

M51 Sorsich, J. G.; Atanassov, K. T.: Application of Generalized Nets in Medicine (Dysuria). 1987.

M52 Sorsich, J. G.; Atanassov, K. T.: Applications of the Generalized Nets in Nephrology. 1993.

M53 Sorsich, J. G.; Shannon A. G.; Atanassov, K. T.: Application of the Generalized Net in Medicine (Modelling of the Management of Blood Cholesterol in the Adult General Population). 1996.

M54 Sorsich, J. G.; Atanassov, K. T.: Application of the Generalized Net in Medicine (Polyuria). 1996.

M55 Sorsich, J. G.; Atanassov, K. T.: Application of Generalized Nets in Medicine (renal mass lesions). 1997.

M56 Srinivasan, P.; Vignes, G.; Venable, C.; Hazelwood, A.; Cade, T.: From Chart Tracking to Workflow Management. Proc. Annu. Symp. Comput. Appl. Med. Care (1994) 884-887.

Abstract The current interest in system-wide integration appears to be based on the assumption that an organization, by digitizing information and accepting a common standard for the exchange of such information, will improve the accessibility of this information and automatically experience benefits resulting from its more productive use. We do not dispute this reasoning, but assert that an organization's capacity for effective change is proportional to the understanding of the current structure among its personnel. Our workflow manager is based on the use of a Parameterized Petri Net (PPN) model which can be configured to represent an arbitrarily detailed picture of an organization. The PPN model can be animated to observe the model organization in action, and the results of the animation analyzed. This simulation is a dynamic ongoing process which changes with the system and allows members of the organization to pose "what if" questions as a means of exploring opportunities for change. We present, the "workflow management system" as the natural successor to the tracking program, incorporating modeling, scheduling, reactive planning, performance evaluation, and simulation. This workflow management system is more than adequate for meeting the needs of a paper chart tracking system, and, as the patient record is computerized, will serve as a planning and evaluation tool in converting the paper-based health information system into a computer-based system.

M57 Tetev, M.; Sorsich, J. G.; Atanassov, K. T.: Generalized Net Model of Hospital Activities. 1993.

M58 van der Maas, A. A. F.; ter Hofstede, A. H. M.; ten Hoopen, A. J.: Requirements for Medical Modeling Languages. Journal of the American Medical Informatics Association 8(2) (2001) 146-162.

Abstract Objective: The development of tailor-made domain-specific modeling languages is sometimes desirable in medical informatics. Naturally, the development of such languages should be guided. The purpose of this article is to introduce a set of requirements for such languages and show their application in analyzing and comparing existing modeling languages.

Design: The requirements arise from the practical experience of the authors and others in the development of modeling languages in both general informatics and medical informatics. The requirements initially emerged from the analysis of information modeling techniques. The requirements are designed to be orthogonal, i.e., one requirement can be violated without violation of the others.

Results: The proposed requirements for any modeling language are that it be "formal" with regard to syntax and semantics, "conceptual," "expressive," "comprehensible," "suitable," and "executable." The requirements are illustrated using both the medical logic modules of the Arden Syntax as a running example and selected examples from other modeling languages.

Conclusion: Activity diagrams of the Unified Modeling Language, task structures for work flows, and Petri nets are discussed with regard to the list of requirements, and various tradeoffs are thus made explicit. It is concluded that this set of requirements has the potential to play a vital role in both the evaluation of existing domain-specific languages and the development of new ones.

E ECOLOGY UND ENVIRONMENT

E1 Gnauck, A.: Modeling of Ecological Processes by Means of Petri Nets. BTU Cottbus 1995.

E2 Gnauck, A.: Analysis and Modelling of Ecosystems by Means of Petri Nets. Eco Summit ´96.

E3 Gnauck, A.: Modellierung von Ökosystemen mit Petrinetzen. Reader Pre-Meeting Workshop AK Theorie in der Ökologie. 1997, 1-10.

E4 Gnauck, A.: Modellierung von Ökosystemen mit Petrinetzen. Jahrestagung Gesellschaft für Ökologie, 1997.

E5 Gnauck, A.: The Use of Petri Nets for Ecosystems Modelling. Conference on Statistical and Mathematical Modelling, TU Berlin, Germany, 1997.

E6 Gnauck, A.: Automaten und Petri-Netze – Werkzeuge der Ökosystemtheorie. Workshop, 1999.

E7 Gnauck, A.: Automaten und Petri-Netze: Werkzeuge zur Ökosystemmodellierung. Jahrestreffen des Arbeitskreises Theorie der Gesellschaft für Ökologie, 2000.

E8 Gronewold, A.; Sonnenschein, M.: Event-based Modelling of Ecological Systems with Asynchronous Cellular Automata. Ecological Modelling 108(1-3) (1998) 37-52.

http://citeseer.nj.nec.com/gronewold97eventbased.html

Abstract In this article, we give an example for the modelling of ecological systems with cellular automata based on the description of cell's behaviour by Petri nets. Petri nets offer a formal modelling technique with event-based, concurrent, asynchronous state changes where graphical symbols are used for the description of states with respect to stale changes. This allows the formal description of cellular automata with asynchronous cells' behaviour within one synchronous time phase of the automaton, i.e. within one time phase of the whole automaton, many asynchronous mini-steps of cells can appear. This can be, e.g. used to model moving individuals that cross an arbitrary number of cells within one time phase. By this attempt, a large class of individual-oriented models can be defined in a more abstract and formal manner than can be done by computer simulation programs. Since Petri nets allow a graphical representation of the modelled cells' behaviour, interactions, dependencies or cause effect chains can be visualized in the representation of the model.

Keywords Larva infestation of oak trees; stochastic PN; methodics

E9 Seppelt, R.; Temme, M.-M.: Hybrid Low Level Petri Nets in Environmental Modelling – Development Platform and Case Studies. Integrative Systems Approaches to Natural and Social Sciences. Springer, 2002, 181-202.

http://www.tu-bs.de/institute/igg/ag-ans/pers/ralf/chapter.zip

http://citeseer.nj.nec.com/492919.html

Abstract In this contribution, a prototypical development platform is presented, which supports model development of standard and hybrid low level Petri nets with respect to the requirements of environmental modelling. The basic theory of hybrid Petri nets with important extensions for ecological modelling are summarised, and the development platform is shortly described. Two examples are chosen for detailed study: Petri net as integrating framework for a hybrid crop growth model based on ordinary differential equation systems, and a population/migration model for the Galapagos archipelago.

Keywords grain growth, population dynamics migration Galapagos archipelago; hybrid PN, methodics, software

E10 Seppelt, R.: Avenues of Spatially Explicit Population Dynamics Modeling — A par Excellence Example for Mathematical Heterogeneity in Ecological Models? Proc.Integrated Assessment and Decision Support (IEMS), Lugano, Switzerland, June 2002, Vol. 1, 269.

http://www.iemss.org/iemss2002/proceedings/pdf/volume%20uno/52_seppelt.pdf

Abstract This contribution discusses different approaches to spatially explicit modeling of population dynamics of the intrusion of non-endemic species into patched habitats. Different modeling approaches such as cellular automata, partial differential equations and hybrid Petri nets are summarized. An application of a meta–population model for the Galapagos archipelago is described using a partial differential equation and a Petri net model. A detailed comparison of both models in terms of simulation results and methodology shows how different building blocks of ecological models can be. And the question is raised, how far the integration of models is at all possible and should be aimed at. Results of the investigation give a detailed insight into the problem of scaling ecological models and the core question of what processes should be considered in which scale in terms of space, time or complexity.

Keywords population dynamics; spatial modelling of population dynamics of intrusion of non-endemic species into small habitates; meta-population model for the Galapagos archipelago; methodics

E11 Sharov, A. A.; Kull, K.: Definition and Elementary Properties of Self-Reproducing Systems. Zhurnal Obshchei Biologii 51(6) (1990) 723-730.

Abstract Formal analysis of self-reproducing systems allows to consider joint properties of chemical autocatalytic systems, biological populations, ecosystems, technical, social, and cultural systems. Potential self-reproducing system can be defined using Petri net language as a non-empty subset Q of positions with a sequence of internal transitions, in which at least one initial and one final position belongs to Q, and it increases the number of objects in all positions of subset Q. Minimal potential self-reproducing systems consist of one or several interconnected transition cycles. Real self-reproducing system can be defined on the basis of its stable existence at constant efflux of its components. It is simultaneously a potential self-reproducing system. At certain conditions, any potential self-reproducing system may become real. One can introduce a trophic structure similar to that in ecosystems in any Petri net. Abstract population is a minimal unit of trophic structure. It is a potentially self-reproducing system. Abstract populations can be divided into autotrophic and heterotrophic, and the latter, into phagotrophic and saprotrophic ones.

Keywords methodics

E12 Sharov, A. A.: Self-Reproducing Systems – Structure, Niche Relations and Evolution. Biosystems 25(4) (1991) 237-249.

http://www.gypsymoth.ento.vt.edu/~sharov/biosem/petri/petri.html

http://www.gypsymoth.ento.vt.edu/~sharov/pdf/selfrep.pdf

Abstract A formal definition of a self-reproducing system is proposed using Petri nets. A potential self-reproducing system is a set of places in the Petri net such that the number of tokens in each place increases due to some sequence of internal transitions (a transition is called internal to the marked subset of places if at least one of its starting places and one of its terminating places belongs to that subset). An actual self-reproducing system is a system that compensates the outflow of its components by reproduction. In a suitable environment every potential self-reproducing system becomes an actual one. Each Petri net can be considered as an ecosystem with the web of ecological niches bound together with trophic and other relations. The stationary dynamics of the ecosystem is characterized by the set of filled niches. The process of evolution is described in terms of niche composition change. Perspectives of the theory of self-reproducing systems in biology are discussed.

Keywords methodics

E13 Sonnenschein, M.; Gronewold, A.: Diskrete Petrinetze für individuenbasierte Modelle.
http://www-ui.informatik.uni-oldenburg.de/ai/forschung/projekte/EcoTools/berichte/Braunschweig95/paper.ps

Abstract Um die Möglichkeit der Verwendung von Petrinetzmodellen in der Ökologie und Biologie darzustellen, erfolgt die Entwicklung eines Petrinetzmodells für ein einfaches Räuber/Beute-System.

Translation In order to represent the possibility of application of Petri net models in ecology and biology, the development of a Petri net model for a simple robber/booty system follows.

Keywords In German. robber-booty systems; example fox-hare; place variable and arc weight is number of individuals; S-invariants, test arcs, inhibitor arcs, time-dependent PN, colored PN, hierarchical PN, (continuous PN); methodics

E14 Wursthorn, H.: Projektbericht Stoff- und Energieflußanalyse. Simulation der Kläranlage Osnabrück mit Umberto. Anwendung auf das Abwasser der Universität Osnabrück. Universität Osnabrück, Institut für Umweltsystemforschung, 1998.
http://www.usf.uos.de/projects/sue/Zubehoer/Zub_download/abwasser.pdf

Keywords stuff and energy flux nets; sewage plant; methodics, software

Cottbus, November, 24th 2002