09091 Abstracts Collection
Formal Methods in Molecular Biology
— Dagstuhl Seminar —

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Abstract. From 23. February to 27. February 2009, the Dagstuhl Seminar 09091 "Formal Methods in Molecular Biology " was held in Schloss Dagstuhl – Leibniz Center for Informatics. During the seminar, several participants presented their current research, and ongoing work and open problems were discussed. Abstracts of the presentations given during the seminar as well as abstracts of seminar results and ideas are put together in this paper. The first section describes the seminar topics and goals in general. Links to extended abstracts or full papers are provided, if available.

Keywords. Formal models, systems biology, biological processes.

09091 Executive Summary – Formal Methods in Molecular Biology

Formal logical models play an increasing role in the newly emerging field of Systems Biology. Compared to the classical, well-established approach of modeling biological processes using continuous and stochastic differential equations, formal logical models offer a number of important advantages.

Many different formal modeling paradigms have been applied to molecular biology, each with its own community, formalisms and tools. In this seminar we brought together modelers from various backgrounds to stimulate closer interaction within the field and to create a common platform for discussion.

A central feature of the seminar was a modeling competition (with a highly collaborative flavor) of various modeling paradigms.

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Formal Methods in Molecular Biology
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Keywords: Formal models, systems biology, biological processes

Joint work of: Breitling, Rainer; Gilbert, David Roger; Heiner, Monika; Priami, Corrado

Extended Abstract: http://drops.dagstuhl.de/opus/volltexte/2009/1996

Developing a projective Brane Calculus based on Activate, Bud and Mate primitive Actions

Johnrob Y. Bantang (LMU München, DE)

Hierarchy is one of the most striking features of biological systems. Inspired by this fact, a number of modeling approaches have been successful in capturing the dynamics of some biological systems. As a process calculus, Brane Calculus has been proposed to effectively capture the hierarchical nature of the system under study through the use of communicating compartments, as well as the dynamic properties of the membranes surrounding them. However, finding a more direct correspondence between biological reality and model elements is still challenging. With this in mind, we modify and extend Cardelli's Brane Calculus and Danos and Pradalier's Projective Brane Calculus (PBC). The resulting extension is proposed as a Projective Activate-Bud-Mate (PABM) calculus, a possible alternative to the Phago-Exo-Pino (PEP) basic calculus of L. Cardelli. PABM uses a generalized formalism for Action activation with receptor-ligand type channel construction that incorporates multiple association and affinity similar to Priami's beta binders. Here, we present its applicability in modeling Influenza A virus infection dynamics. We highlight the ability of PABM to represent membrane processes from three basic actions. We also wish to discuss the advantages and disadvantages of this approach, together with other possible applications and further challenges.

Keywords: Brane calculus, projective Brane calculus, model, pi calculus, process calculus

Joint work of: David, Maria Pamela; Youssef, Simon; Bantang, Johnrob Y.; Mendoza, Eduardo

Constraint-based analysis of regulatory networks

Alexander Bockmayr (FU Berlin, DE)

After recalling the basic principles of constraint-based modeling in systems biology, we focus on the constraint-based analysis of regulatory networks.

Starting from the logical formalism developed by R. Thomas, we obtain a refined qualitative description of the dynamical behavior by exploiting not only information on ratios of kinetic parameters related to synthesis and decay, but also constraints on the time delays associated with the operations of the system. We develop a formal framework for handling such temporal constraints using timed automata, and illustrate the potential of the approach by analyzing a gene regulatory network of bacteriophage.

Keywords: Regulatory networks, constraint-based modelling, timed automata

Executing multi-cellular development: Petri net model of AC/VU differentiation in C. elegans

Nicola Bonzanni (VU University Amsterdam, NL)

In our earlier work we used maximally parallel Petri nets to model C.elegans vulval development process.

Now, using the same method and organism, we built a network of AC/VU differentiation. We aim to combine the two networks in a single model of spatially and temporarily contiguous processes.

Keywords: Petri nets, C.elegans, maximal parallelism

Joint work of: Bonzanni, Nicola; Krepska, Elzbieta; Wan, Fokkink

Molecules as Automata

Luca Cardelli (Microsoft Research UK - Cambridge, GB)

Chemical and biochemical systems are described as collectives of interacting stochastic automata: each automaton represents a molecule that undergoes state transitions. This framework constitutes an artificial biochemistry, where automata interact by the equivalent of the law of mass action. We analyze systems and networks by discrete and continuous methods, and relate the two approaches.

Keywords: Stochastic automata, discrete and continuous analysis

Modelling the NF-κB pathway in Bio-PEPA

Federica Ciocchetta (University of Edinburgh, GB)

In this talk we present the models we have developed in response to the Dagstuhl modelling competition.

Using Bio-PEPA we have constructed two models of the dynamic response of NF-κB to external stimuli, focussing on the translocation of the NF-κB between the cytoplasm and the nucleus. The first model was developed in collaboration between a modeller and a biologist and our objective was to demonstrate the ease of model construction using Bio-PEPA and the use of stochastic model checking to analyse the system. A high level of abstraction was chosen, focusing on the experimental data which was available (in the literature) to validate against. Using stochastic simulation the model behaviour was shown to be preserved across different scales (in terms of numbers of molecules) and model checking was applied to find the probability that all NF-κB has moved into the nucleus within the first hour, and a number of other properties. The second model was derived from a previously published model by Lipniacki et al. Here the objective was to subject the model to sensitivity analysis, looking in particular at which rate parameters have most impact on the behaviours of interest. We were also able show that some species showed much more variability than others in their behaviour over a number of simulation runs. In both cases the models were validated against experimental results in the literature.

Keywords: Process algebras, NF-κB pathway, modelling, analysis

Joint work of: Ciocchetta, Federica; Degasperi, Andrea; Heath, John; Hillston, Jane

Modelling and analysis of the NF-κB pathway in Bio-PEPA

Federica Ciocchetta (University of Edinburgh, GB)

In this work we present a Bio-PEPA model describing the Nuclear Factor κB (NF-κB) signalling pathway. In particular our model focuses on the dynamic response of NF-κB to an external stimulus. Each biochemical species in the pathway is represented by a specific Bio-PEPA component and the external stimulus is abstracted by Bio-PEPA events.

The Bio-PEPA model is a formal intermediate representation of the pathway on which various kinds of analysis can be performed. Both stochastic and deterministic simulations are carried out to validate our model against the experimental data in the literature and to verify some properties, such as the impact of the stimulus duration and of the NF-κB initial amount on the behaviour of some species. Finally, sensitivity analysis is considered to investigate the most influential parameters of the model.

Keywords: Process algebras, NF-κB pathway, modelling, analysis

Joint work of: Ciocchetta, Federica; Degasperi, Andrea; Heath, John; Hillston, Jane

Full Paper: http://drops.dagstuhl.de/opus/volltexte/2009/1991

Analysing eukaryote gene regulation: in vivo, in vitro, in silico, and back again

Finn Drabløs (Univ. of Science & Technology - Trondheim, NO)

Expression of genes and gene products in eukaryotes is extensively regulated at several levels, through complementary mechanisms acting at different time scales. The most important mechanisms are transcription factors, microRNAs, histone modification and DNA methylation, but also factors like nucleosome positioning, nuclear lamina attachment and genome organisation is known to affect gene expression. This leads to a very complex system where it is difficult to get reliable experimental data. This makes modelling essential, as a way of testing and verifying our understanding of the system, and for the design of new experiments. However, it is challenging to make good models of complex systems when the experimental basis is incomplete or even partly wrong. This presentation will discuss some of the challenges associated with data generation for modelling of regulatory systems in eukaryotes, with focus on transcription factors and microRNAs and the interaction between these two systems.

Keywords: Gene regulation, transcription factor, microRNA

JAK/STAT pathway activation mechanism model selection via sensitivity analysis

Anna Gambin (University of Warsaw, PL)

We have identified four main mechanisms, capturing known differences in receptor activation steps between computational and biological models of JAK/STAT signalling pathway.

Based on them we have defined ODE models, for which the comparative analysis was performed.

We investigated noise robustness of the JAK-STAT pathway variants in local and global setting focusing on biologically significant notions like signal strength, signalling time and duration.

Workflows used in our study (e.g. Multi-Parameter Sensitivity Analysis method) have been implemented as the Web Services in the Taverna workbench. The main advantages of this approach are: standardization (common SBML models), integration, accessibility and transparency.

Keywords: Signalling pathway, ODE, sensitivity analysis

Joint work of: Gambin, Anna; Rybiński, Mikołaj

BioModel Engineering: Its role in Systems Biology and Synthetic Biology

David Roger Gilbert (Brunel University, GB)

BioModel Engineering takes place at the interface of computing science, mathematics, engineering and biology, and provides a systematic approach for designing, constructing and analyzing computational models of biological systems. Some of its central concepts are inspired by efficient software engineering strategies. BioModel Engineering does not aim at engineering biological systems per se, but rather aims at describing their structure and behavior, in particular at the level of intracellular molecular processes, using computational tools and techniques in a principled way.

The two major application areas of BioModel Engineering are systems biology and synthetic biology. In the former, the aim is the design and construction of models of existing biological systems, which explain observed properties and predict the response to experimental interventions; in the latter, BioModel Engineering is used as part of a general strategy for designing and constructing synthetic biological systems with novel functionalities.

The overall steps in building computational models in a BioModel Engineering framework are: Problem Identification, Model Construction, Static and Dynamic Analysis, Simulation, and Model management and development.

A major theme in BioModel Engineering is the construction of (qualitative) models, including the following common steps:

1. finding the structure,
2. obtaining an initial state, and
3. determining the kinetics by parameter fitting.

In an approach that we have taken, the structure is obtained by piecewise construction of models from modular parts, the initial state which describes concentrations of species or numbers of molecules is obtained by analysis of the structure, and parameter fitting comprises determining the rate parameters of the kinetic equations by reference to trusted data.

Model checking can play a key role in BioModel Engineering – for example in recent work we have shown how parameter estimation can be achieved by characterising the desired behaviour of a model with a temporal logic property and altering the model to make it conform to the property as determined through model checking.

Keywords: Biochemical systems, models, design, construction, systems biology, synthetic biology, model checking

Joint work of: Gilbert, David Roger; Breitling, Rainer; Heiner, Monika

Extended Abstract: http://drops.dagstuhl.de/opus/volltexte/2009/1992

Analysis of Signal Propagation and Crosstalk within Signaling Networks Using Animated Graph Representations of Dynamical Systems

Simon Hardy (Mount Sinai Medical School - New York, US)

Theoretical analyses of computational models can help us understanding how a cellular system changes in response to the information flow initiated by extracellular stimuli and routed through its signaling pathways. To figure out the cell's information-processing capability a combination of computational and experimental studies aim at identifying and characterizing the regulatory motifs of the cell's signaling network, such as positive and negative feedback and feed-forward loops. This investigation necessitates the analysis of the network's topology, but also an exploration of the temporal activity of its regulatory components.

Traditional theoretical approaches like graph theory and differential equations are well suited to perform either the topological analysis or the temporal dynamic analysis, but none can combine both types of analysis. In this study, we use a formal method from computer science named Petri nets to get insights into complex network dynamics and decompose the model into signaling components. With Petri nets, we create the interaction network representation of an ODE model and then animate it with concentration and flux values to interpret the model simulation data. Contrary to existing analysis tools of numerical simulation data, our method draws attention to the dynamic of regulatory motifs. We demonstrate this method with an ongoing project combining experiments and simulations to investigate the signaling pathway from beta-adrenergic receptor to the transcription factor CREB. We highlight the dynamic of the nested regulatory motifs of these pathways.

Keywords: Signaling networks, regulatory motifs, Petri nets, animation

Joint work of: Hardy, Simon; Iyengar, Ravi

On the Use of NF-kB Pathway Petri Net Model

Sampsa Hautaniemi (University of Helsinki, FI)

The nuclear factor-kappaB (NF-kB) comprises a family of proteins that are major regulators of programmed cell death (apoptosis) and proliferation. Here, we implemented a Petri net model for TNF induced NF-kB activation based on literature and leukemia cell line data. We then identified all genetic mutations (SNPs - Single Nucleic Polymorphisms) for the proteins in the pathway. We used a frameshift mutation to lead absence of a protein in the model and simulated the effect of this genetic mutation to proliferation and programmed cell suicide decisions mediated by NF-kB. We also identified signaling pathways that most likely cross-talk with NF-kB pathway, and proteins that most likely mediate the cross-talk signaling. Our preliminary results are encouraging and open many new directions for further work.

Keywords: Systems biology, bioinformatics, cancer genetics, Petri net, simulation.

Joint work of: Nousiainen, Kari; Asaoka, Tomoko; Karinen, Sirkku; Lahesmaa-Korpinen Anna-Maria; Eriksson, John; Hautaniemi, Sampsa

Data Integration in Systems Biology

Sampsa Hautaniemi (University of Helsinki, FI)

We have developed a component-based open source framework (Anduril) for data analysis. Each component of the framework implements a well-defined part of the analysis. The components communicate via text-files and Anduril creates automatically a LaTeX-based report that contains the experimental set-up, methods and their parameters, and resulting figures and tables. Anduril is an open-source software and is available at http://csbi.ltdk.helsinki.fi/anduril/.

Keywords: Bioinformatics, data integration, software engineering

Full Paper:
http://csbi.ltdk.helsinki.fi/anduril/index.html

Composing and Decomposing Biological Models

John K. Heath (University of Birmingham, GB)

Descriptions of biological processes found in the biological literature (or curated in databases) are fraught with problems of interpretation for the non-biologist. They treat all statements has having equal validity; encode hidden assumptions or community consensus and can be highly idealised or selective. When articulated as formal or informal diagrams it is easy to eliminate biologically important features such as temporal evolution or spatial confinement. I describe an approach in which biological processes are described as a Narrative which aims to enforce precision, identify ambiguity and be readily modified. Narrative approaches should be intuitive to the biologist and conform to formal methods for computational execution. I will discuss an approach which aims to link verifiable biological data to formal statements in computer science.

Keywords: Signalling, Formal methods, process calculus, Beta-binders

Joint work of: Heath, John K; Priami, Corrado; Ballarini, Paolo; Guerriero, Maria Luisa

Dynamic model of FSH signalling pathways in Sertoli cells adapted to two stages

Domitille Heitzler (INRIA - Le Chesnay, FR)

The FSHR-mediated signalling network comprises multiple transduction mechanisms, amongst which PIP3- and cAMP-dependent pathways converging to ribosomal S6 protein (rpS6), a component which plays a role in the ribosome cohesion and in its recruitment to the mRNAs. The information circulating in this network is likely to be tightly regulated by cross-talks, feedback, amount of total proteins and initial conditions. Our biological model consists in proliferating (5 dpp) and differentiating (19 dpp) rat Sertoli cells.

We modelized the differences that occur in FSH-induced rpS6 phosphorylation at both stages. We decided to construct the computational model as simple as possible by describing interactions between molecules as mass action laws for both stages. Then, we used conservation laws to make reversible simplifications. To render the model biologically relevant, we have expressed quantities in moles by gram of proteins. We found a relationship between the nM and the nmoles.g-1 of protein. We applied this conversion to the amount of hormone, receptor and to the Kd values. Then, thanks to a quantitative radioimmunoassay, we found the real concentration of cAMP. Furthermore, we referred to the values of p70 activity in response to Insulin, as provided by the literature, and considered these values to normalize PIP3, P-S6K and PrpS6 quantities in our model. With all those normalized data, we calculated dissociation rate thanks to values at the equilibrium for the ma jority of constituents of the model. As [Schoeberl], we estimated the kinetic parameters that were not available in the literature not by the data extraction. We used Scilab (http://www.scilab.org/), an open source platforms from INRIA for numerical computation, in order to estimate parameters from the data.

We have jointly fitted the simulation outputs of the model to experimental data at both cell stages. Our study give a 2-cell-stage model with almost the same ODE set and keep a maximum of the parameters identical between both stages. Furthermore, perturbations in the biological setting were performed and tested them in silico successfully. Fist, our model shows that only subtle differences can account for developmental changes in the regulation of rpS6 by FSH. Secondly it give explanation for behaviors of p70S6 kinase sum (experimental observations) by distinguish p70S6K phosphorylated form.

Keywords: ODEs, Intracellular signaling

Joint work of: Heitzler, Domitille; Musnier, A.; Boulo, T.; Tesseraud, S.; Durand, G.; Lécureuil, C.; Guillou, H.; Reiter, E.; Crépieux, P.

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The Bio-PEPA project

Jane Hillston (University of Edinburgh, GB)

Bio-PEPA is a stochastic process algebra that supports modelling of biochemical reaction networks which can then be analysed in a number of ways. In this talk I will explain the motivations for the design of Bio-PEPA including the benefits which can be gained from supporting a suite of analysis techniques, and describe the reagent- centric modelling style which it supports. In addition to the language definition and previous case studies, I will outline areas of on-going work.

Keywords: Stochastic process algebra, SSA, ODE, model checking, equivalence relations

Joint work of: Hillston, Jane; Ciocchetta, Federica; Duguid, Adam; Galpin, Vashti; Gilmore, Stephen; Guerriero, Maria Luisa; Loewe, Laurence

Full Paper:
http://homepages.inf.ed.ac.uk/jeh/Bio-PEPA/biopepa.html

See also: http://homepages.inf.ed.ac.uk/jeh/Bio-PEPA/TCS_CH.pdf

Constraint based modelling of eukaryotic cell cycle dynamics.

Andrzej M. Kierzek (University of Surrey, GB)

The limited knowledge of kinetic parameters is a major bottleneck in using computer simulations of biochemical reaction networks to make predictions useful in medicine and biotechnology. This motivates development of constraint based methods which use available quantitative information to constrain the solution space of the model and increase its predictive power but still make useful qualitative predictions even if the full set of quantitative parameters is not available. The constraint-based approach is very successful in analysis of genome scale metabolic reaction networks. For example, in our recent paper we applied the genome scale metabolic reaction network model for gene essentiality predictions in Mycobacterium tuberculosis. However, the constraint based modelling

of metabolic networks is limited to analysis of linear models of metabolic flux distribution at steady state.

This contribution will demonstrate that stochastic Petri net (SPN) formalism is very well suited for the constraint based dynamic simulations of molecular interaction networks in eukaryotic cells. The yeast cell cycle will be used as a benchmark. Detailed, quantitative and experimentally validated SPN model will be used as a starting point. Subsequently, quantitative parameters will be replaced by constraints. Predictive power of the models using constraints of varying accuracy will be evaluated by comparison with mutant phenotypes and results of detailed dynamic model. Results of the benchmark will be used to discuss feasibility of the constraint based dynamic modelling of the large scale molecular interaction networks governing mammalian cell cycle and morphogenesis.

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Keywords: Stochastic modelling, Petri nets and Rule-/Constraint-based Modeling

Searching for New Therapies for Duchenne Muscular Dystrophy through Modeling of Gene Regulation - a Petri Net Approach

Ina Koch (MPI for Molecular Genetics / TU Berlin, DE)

DMD is one of the most frequently inherited neuromuscular diseases in children. It is an X-linked recessive disease with a birth prevalence of 1 in 3500 live born males.

The disease is caused by mutation(s) in the dystrophin gene that result in a loss of the protein dystrophin. This loss is followed by the primary structural dysfunction and in addition it also influences several downstream processes. An efficient therapy is not available. Experimental data suggest signal transduction pathways downstream dystrophin that could compensate the dystrophin defect partially. In order to get new insights and, thus, new ideas for therapeutic possibilities mathematical modeling has been incorporated into research.

Because of the lack of kinetic data a discrete approach using Petri nets has been chosen. Petri nets have been successfully applied to model biochemical systems, including approaches to medically related questions. This contribution describes modeling and analysis of the first theoretical model downstream the dystrophin gene connecting two main signal transduction pathways encompassing dystrophin and gene regulation of participating proteins, such as transcription factors and utrophin A. The model has been developed on the basis of own experimental data, mainly Real-Time PCR data. Model validation applies invariant analysis, using MCTS, T-clusters, and Mauritius maps. Analyses of the model resulted in experimental modulation of selected members of the network using human skeletal muscle cells in cell culture whose consequences were studied on mRNA and protein level. The experiments show surprising results, which led to a new iteration of model extension and analysis.

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Keywords: Petri nets, Duchenne Muscular Dystrophy, gene regulation, sugnal transduction, T-invariants, MCT-sets, Mauritius maps.

Joint work of: Koch, Ina; Grunwald, Stefanie; Speer, Astrid; Ackermann, Jörg

See also: Stefanie Grunwald, Astrid Speer, Jörg Ackermann, Ina Koch. Petri net modelling of gene regulation of the Duchenne muscular dystrophy, BioSystems 92: 189-205 (2008)

Executing multi-cellular development: Petri Nets Model of the C.elegans Vulva

Elzbieta Krepska (Vrije Universiteit Amsterdam, NL)

Understanding the processes involved in multi-cellular pattern formation is a central problem of developmental biology.

We present a modelling technique based on discrete Petri nets, equipped with a notion of (maximal) parallelism. We created a large (hundreds of nodes) model of a developing vulva of the C.elegans worm.

We recorded statistical accurracy of the results and agreement between simulated protein levels and biological evidence.

Keywords: Petri nets, C.elegans, maximal parallelism

Joint work of: Krepska, Elzbieta; Bonzanni, Nicola; Wan, Fokkink

Rule-based Modeling of Transcriptional Attenuation at the Tryptophan Operon

Céline Kuttler (University of Lille, FR)

Transcriptional attenuation at E.coli's tryptophan operon is a prime example of RNA-mediated gene regulation. In this paper, we present a discrete stochastic model for this phenomenon based on chemical reactions. Our model is compact and intelligible, due to n-ary reactions (which preclude object-centric approaches) and to rule schemas that define finite sets of chemical reactions. Stochastic simulations with our model confirm results that were previously obtained by master equations or differential equations.

In addition, our approach permits to reflect mutation experiments by simple model modifications, and to re-use model components for transcriptional attenuation in other genes and organisms.

Keywords: Systems biology, rule-based modeling languages, stochastic simulation, kappa

Joint work of: Kuttler, Céline; Lhoussaine, Cédric; Nebut, Mirabelle

Full Paper: http://drops.dagstuhl.de/opus/volltexte/2009/1993

The Continuous pi-Calculus

Marek Kwiatkowski (University of Edinburgh, GB)

We present The Continuous pi-Calculus, a process algebra for molecular modelling in the context of Darwinian evolution. The two defining properties of the calculus are: flexible interaction structure of agents, and innovative semantics in terms of a continuous process space. We will conclude the presentation with a simple analysis of an actual molecular system.

Keywords: Systems biology, process algebra, evolution

Joint work of: Kwiatkowski, Marek; Stark, Ian

The Attributed Pi-Calculus

Cédric Lhoussaine (University of Lille, FR)

The attributed pi-calculus pi(L) forms an extension of the pi-calculus with attributed processes and attribute dependent synchronization. To ensure flexibility, the calculus is parametrized with the language L which defines possible values of attributes. pi(L) can express polyadic synchronization as in pi@ and thus, to some extent, diverse compartment organizations. A non-deterministic and a stochastic semantics, where rates may depend on attribute values, is introduced. The stochastic semantics is based on continuous time Markov chains. An example underlines the applicability of pi(L) to systems biology: Euglena's movement in phototaxis. We motivate an extension of the attributed pi-calculus with mutable attributes allowing for modeling of compartment dynamics.

Keywords: Pi-calculus, compartments, systems biology

Joint work of: Mathias John; Lhoussaine, Cédric; Niehren, Joachim; Uhrmacher, Adelinde

Full Paper:
http://www.springerlink.com:80/content/k51052170j04x166/

The molecular basis of behavioural plasticity: phototaxis of Halobacterium as case study for extended stochastic Petri nets

Wolfgang Marwan (MPI - Magdeburg, DE)

Halobacterium senses light and other stimuli to find the best available conditions for living and survival. Light stimuli are sensed by sensory rhodopsins, specific photoreceptor proteins that modulate the activity of a small network of interacting proteins. The output of the network, phosphorylation of the CheY protein determines the probability of a cell to continue or to reverse its current swimming path, respectively. The resulting phenomenon is called phototaxis. Some protein components of the network operate as information processing nodes.

The case study of phototaxis in Halobacterium shows how extended stochastic Petri nets (xSPN's) can be used to represent a fine-tuned information processing protein interaction network. Although the described biological phenomenon is special, the underlying molecular processes are typical for signal processing and regulatory control in living cells, to which the new features of the extended stochastic Petri net framework can be applied accordingly.

Keywords: Extended stochastic Petri nets, signal transduction

Joint work of: Marwan, Wolfgang; Heiner, Monika

Full Paper:
http://wasb.urz.uni-magdeburg.de/ag-marwan/

Simulation analysis for the effect of light-dark cycle on the entrainment in circadian rhythm

Hiroshi Matsuno (Yamaguchi University, JP)

Circadian rhythms of the living organisms are 24hr oscillations found in behavior, biochemistry and physiology. Under constant conditions, the rhythms continue with their intrinsic period length, which are rarely exact 24hr.

In this paper, we examine the effects of light on the phase of the gene expression rhythms derived from the interacting feedback network of a few clock genes, taking advantage of a computer simulation with hybrid functional Petri net. The simulation results suggested that the interacting circadian feedback network at the molecular level is essential for phase dependence of the light effects, observed in mammalian behavior. Furthermore, the simulation reproduced the biological observations that the range of entrainment to shorter or longer than 24hr light-dark cycles is limited, centering around 24hr.

Application of our model to inter-time zone flight successfully demonstrated that 6 to 7 days are required to recover from jet lag when traveling from Tokyo to New York.

Keywords: circadian rhythm, light-dark cycle, entrainment, simulation, hybrid functional Petri net

Joint work of: Mitou, Natsumi; Ikegami, Yuto; Matsuno, Hiroshi; Miyano, Satoru; Inouye, Shin-Ichi

Full Paper:
http://www.jsbi.org/modules/journal1/index.php/GIW08/GIW08018.pdf

See also: Mitou, N., Ikegami, Y., Matsuno, H., Miyano, S., Inouye, S.T., Simulation analysis for the effect of light-dark cycle on the entrainment in circadian rhythm, Genome Informatics, Vol.21, pp.212-223, 2008.

Algorithmic vs. Equation-based, executable vs. mathematical - is there a middle ground for modelers?

Eduardo Mendoza (LMU München, DE)

There is an exploding number of approaches to modeling biological systems which can be classified into two extreme groups [Fisher, 2007]. On the one hand, deterministic mathematical models offer convenience for analysis and the possibility of finding solutions by utilizing the computing power of modern computers. Although highly quantitative, such models require a high degree of abstraction of the biology making them difficult to create. On the other hand, algorithmic models offer easy model development comparable to creating cartoons of static biological models. Algorithmic models mark the convergence of computer

science and biology into a new discipline [Priami, to appear]. While for both approaches, stochasticity and concurrency can be achieved, there are other major aspects which still need to be considered such as hierarchy and space.

While fond of either case, modelers could look for a middle ground where significant challenges remain. We wish to talk about the specific advantages of these approaches and invoke discussions on the feasibility and advantages of having a spectrum of approaches. If this spectrum exists, what constitutes the middle ground? If space and hierarchy are taken into account how does the spectrum look like? Once clarified, better communications with between physicists and engineers on the one and computer scientists on the other side regarding these new approaches should be established.

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Keywords: Algorithmic systems biology, executable biology, modelling, membrane informatics

Joint work of: Mendoza, Eduardo; Bantang, Johnrob; Youssef, Simon

In Silico Pipeline for Extracting Dynamic Transcriptional Networks

Satoru Miyano (University of Tokyo, JP)

We developed an *in silico* pipeline for extracting and utilizing dynamic transcriptional regulatory networks estimated from large-scale data, including time-course transcriptome data and static protein-protein interaction data. In this pipeline, two computational methods for extracting transcriptional network structures are developed. One is our state space model combined with dimension reduction techniques. This dynamic model is used for investigating the systems behaviors responding an anti-cancer drug (gefitinib) and we predicted differentially regulated genes that were proven very powerful to prediction of survival in small cell lung cancer. The other is based on dynamic Bayesian network with nonparametric regression with which we can further refine these networks by statistical methods combining multiple-source information, e.g. protein-protein interaction data. With this model, we unraveled dynamic activities of autocrine pathways controlling drug-response transcriptional networks for a drug for hyperlipidemia (fenofibrate). The pipeline is equipped with a "data assimilation" function that can estimate parameters in dynamic pathway models by using time-course data. As GUI's for this pipe line, we developed a platform CSMLpipeline based on Cell System Markup Language (http://www.cmsl.org/), and Cell Illustrator Online 4.0 (http://cio.hgc.jp/) is employed for visualization, simulation and pathway

database management system (CSMLDB). This CSMLDB contains, for example, 100 dynamic pathways models based on macrophage LPS and PMA stimula by literature curation so that they can be utilized on Cell Illustrator for further modeling and analysis.

Keywords: Transcriptional network, state space model, dynamic Bayesian network, data assimilation, Cell Illustrator, CSML

Biological models based on experimental observations

Haluk Resat (Pacific Northwest National Lab., US)

This talk will highlight various aspects of dealing with real biological data in the construction of mechanical models for signal transduction pathways. Estimation of kinetic information from experimental data is non-trivial because of several factors:

First, the signal flow intensity is often a combined function of several factors whose simultaneous measurements are not possible. Second, not every form of biological species is amenable to experimental observations. This leads to the lack of proper sampling along the pathways and the resulting gaps in the network attributes are often filled using existing knowledge or personal preferences, which bias thinking. Third, often there is a disparity between measurement sampling periods and the time scales associated with involved reactions. Fourth, biological systems are inherently noisy, which makes parameter estimation an underdetermined problem. Last and not least, altering the conditions of biological systems in a controlled manner in experimental studies is very difficult.

This talk will first use the interactions among the human epidermal growth factor family of receptors as example to discuss the difficulties encountered in estimating the reaction rates from experimental data. It will then discuss why knowing the right parameters matter. For the latter the MAPK cascade will be used as the example to demonstrate that different parameter sets for the same network can lead to different dynamical behavior. Validations of theoretical predictions with experiments will be emphasized.

Keywords: Reaction rate, parameter estimation, EGFR, HER, signaling pathway, biological network

Joint work of: Resat, Haluk; Shankaran, Harish; Zhang, Yi; Opresko, Lee; Wiley, H. Steven; Chrisler, William B.

Analyzing various models of Circadian Clock and Cell Cycle coupling

Alessandro Romanel (Microsoft Research - University Trento, IT)

The daily rhythm can influence the proliferation rate of many cell types. In the mammalian system the transcription of the cell cycle regulatory protein Wee1 is controlled by the circadian clock.

Zamborszky et al. (2007) present a computational model coupling the cell cycle and circadian rhythm, showing that this coupling can lead to multimodal cell cycle time distributions. Biological data points to additional couplings, including a link back from the cell cycle to the circadian clock. Proper modelling of this coupling requires a more detailed description of both parts of the model. Hence, we aim at further extending and analysing earlier models using a combination of modelling techniques and computer software, including CoSBI lab, BIOCHAM, and GINsim.

Keywords: Cell cycle, circadian clock, computational modelling

Joint work of: Ballarini, Paolo; Csikász-Nagy, Attila; Faure, Adrien; Larcher, Roberto; Lecca, Paola; Mazza, Tommaso; Mura, Ivan; Jordan, Ferenc; Palmisano, Alida; Romanel, Alessandro; Sedwards, Sean; Siebert, Heike; Soliman, Sylvain; Thieffry, Denis; Zámborszky Judit

Extended Abstract: http://drops.dagstuhl.de/opus/volltexte/2009/1994

On Model-checking a class of ODE models with BioDiVinE

David Šafránek (Masaryk University, CZ)

This presentation deals with continuous deterministic approach to modeling and analysis of biochemical reactions. In particular, we briefly introduce two special classes of ODE models - multi-affine systems and piece-wise affine systems. For each of the classes we show which kinds of particular qualitative properties can be encoded in terms of Linear Temporal Logic and how they can be model-checked using the tool (Bio)DiVinE. The presented work is taken under the project EC-MOAN (Escherichia Coli - Modeling and Analysis, http://www.ec-moan.org).

Keywords: Multi-affine models, piece-wise affine models, linear temporal logic, model checking

Joint work of: Šafránek, David; Barnat, Jiří; Brim, Luboš; Černá, Ivana; Dražan, Sven; Fabriková, Jana

Detecting Inconsistencies in Large Biological Networks with Answer Set Programming

Torsten Schaub (Universität Potsdam, DE)

We introduce an approach to detecting inconsistencies in large biological networks by using Answer Set Programming.

To this end, we build upon a recently proposed notion of consistency between biochemical/genetic reactions and high-throughput profiles of cell activity. We then present an approach based on Answer Set Programming to check the consistency of large-scale data sets. Moreover, we extend this methodology to provide explanations for inconsistencies in the data by determining minimal representations of conflicts.

In practice, this can be used to identify unreliable data or to indicate missing reactions.

Keywords: Answer Set Programming, consistency, data set evaluation

Joint work of: Gebser, Martin; Schaub, Torsten; Thiele, Sven; Usadel, Björn; Veber, Philippe

Symbolic Steady States and Dinamically Essential Subnetworks of Discrete Regulatory Networks

Heike Siebert (FU Berlin, DE)

Analyzing complex networks is a difficult task, regardless of the chosen modeling framework. For a discrete regulatory network, even if the number of components is in some sense manageable, we have to deal with the problem of analyzing the dynamics in an exponentially large state space. A well known idea to approach this difficulty is to identify smaller building blocks of the system the study of which in isolation still renders information on the dynamics of the whole network. In this talk, we introduce the notion of symbolic steady state which allows us to identify such building blocks. We state explicit rules how to derive attractors of the network from subnetwork attractors valid for synchronous as well as asynchronous dynamics. Illustrating those rules, we derive general conditions for circuits embedded in the network to transfer their behavioral characteristics pertaining number and size of attractors observed in isolation to the complex network.

Keywords: Discrete networks, logical analysis, symbolic steady states

Extended Abstract: http://drops.dagstuhl.de/opus/volltexte/2009/1995

Approximating Bio-Pathways Dynamics

P.S. Thiagarajan (National University of Singapore, SG)

A standard formalism used to model signaling pathways (and other bio-pathways) is a system of Ordinary Differential Equations (ODEs). Signaling pathways usually involve a large number of molecular species and bio-chemical reactions. Hence the corresponding ODEs will not yield closed form solutions and in fact are difficult to study even via numerical solutions. We propose a probabilistic

approximation technique which consists of first sampling a representative set of trajectories and then exploiting the structure of the pathway to encode these trajectories compactly as a Bayesian network (BN). As a result, many interesting dynamic properties can be analyzed efficiently through standard Bayesian inference techniques, instead of resorting to a large scale ODE simulations. Our preliminary results are promising in terms of both accuracy and efficiency.

Keywords: Pathway dynamics, ODEs, sampling, Markov chains, Bayesian networks, probabilistic inferencing

Joint work of: Liu Bing, David Hsu, P.S. Thiagarajan

Compositional logical modelling of molecular regulatory networks

Denis Thieffry (Université de la Méditerrannée - Marseille, FR)

Systems biologists are facing the difficult challenge of modelling and analysing regulatory networks encompassing numerous and diverse components and interactions.

Furthermore, available data sets are often qualitative, which complicates the definition of quantitative computational models. Logical modelling constitutes a flexible framework to build qualitative predictive models, which can be readily analysed or simulated as such, and potentially used as scaffolds to build more quantitative (continuous or stochastic) models. We use Multi-valued Decision Diagrams to implement (multi-level) logical updating rules in the modelling software GINsim. This representation enabled the development of efficient algorithms for the identification of stable states, or yet to relate specific (positive or negative) regulatory circuits with specific dynamical properties (e.g., multiple attractors or sustained oscillations). Furthermore, to cope with ever larger networks, we have implemented a flexible reduction method conserving the attractors of the original model. Finally, we have delineated an incremental, compositional strategy to build large models by combining logical models for simpler regulatory modules.

These novel methodological developments are illustrated through applications dealing with (i) the segment-polarity network setting initial segmental borders in the fly embryo, and (ii) a comprehensive network controlling cell cycle in budding yeast.

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Keywords: Regulatory networks, logical modelling, decision diagrams, regulatory circuits

Elucidating Regulatory Mechanisms Downstream of a Signaling Pathway Using Informative Experiments

Jerzy Tiuryn (University of Warsaw, PL)

Signaling cascades are triggered by extra-cellular stimulation and propagate the signal to regulate transcription. Systematic reconstruction of this regulation requires pathway-targeted, informative experimental data. However, experimental design is difficult since even highly informative experiments might be redundant with other experiments. In addition, experimental outcomes vary not only between different genetic perturbations but also between the combinations of environmental stimuli.

We have developed a practical algorithmic framework that iterates design of experiments and reconstruction of regulatory relationships downstream of a given pathway. The experimental design component of the framework, called MEED, proposes a set of experiments that can be performed in the lab and given as input to the reconstruction component. Both components take advantage of expert knowledge about the signaling system under study, formalized in a

predictive logical model. The reconstruction component reconciles the model predictions with the data from the designed experiments to provide a set of identified target genes, their regulators in the pathway and their regulatory mechanisms. Reconstruction based on uninformative data may lead to ambiguous conclusions about the regulation. To avoid ambiguous reconstruction, MEED designs experiments so as to maximize diversity between the predicted expression profiles of genes regulated through different mechanisms.

MEED has several important benefits and advantages over extant experimental design approaches: First, it considers potential dependencies between the suggested experiments, making it possible to design and perform in parallel a set of informative, non-redundant experiments. Second, MEED optimizes not only the required genetic perturbations, but also the combination of environmental stimuli that should trigger the system. Finally, by using only the model predictions, MEED has the ability to choose experiments without access to high-throughput experimental data.

Our framework was extensively analyzed and applied on random models as well as the model of interconnected osmotic stress and pheromone pathways in Saccharomyces cerevisiae. In comparison to other approaches, MEED allowed to provide significantly less ambiguous conclusions about the regulation in this system.

Keywords: Signaling pathway, experiment design, regulatory mechanisms

Joint work of: Tiuryn, Jerzy; Szczurek, Ewa; Gat-Viks, Irit; Vingron, Martin

Stochastic modelling of cellular growth and division by means of the π@ calculus

Cristian Versari (University of Bologna, IT)

The application of Concurrency Theory to Systems Biology is in its earliest stage of progress. The metaphor of cells as computing systems by Regev and Shapiro opened the employment of concurrent languages for the modelling of biological systems. Their peculiar characteristics led to the design of many bio-inspired formalisms which achieve higher faithfulness and specificity.

In this paper we discuss the application to the biological modelling of π@, a core calculus for the representation of biological systems.

The π@ language represents a keystone in this respect, thanks to its expressiveness capabilities which allow the modelling of a wide variety of phenomena (e.g. simple chemical reactions, but also formation of molecular or protein complexes, organisation of complex system in dynamical compartment hierarchies) despite of its simplicity and conservativeness.

Here we analyse a biological case study involving cellular growth and division, modelled in the stochastic variant of π@: the case study is formalised and stochastically simulated according to a multi-compartment extension of Gillespie's stochastic simulation algorithm.

The results underline the usefulness of the modelling approach adopted in $\pi@$ for the correct handling of systems with variable volume.

Keywords: Process algebra, pi-calculus, simulation, stochastic

Full Paper: http://drops.dagstuhl.de/opus/volltexte/2009/1990

Finite state linear model (FSLM) and analysis of dynamics of gene regulatory networks

Juris Viksna (University of Latvia, LV)

Various mathematical models describing gene regulatory networks as well as algorithms for network reconstruction from experimental data have been a subject of intense studies, largely motivated by the current availability of high-throughput experimental data. Boolean network models currently are among the best studied. Also models based on differential equations are sufficiently common, especially in simulation of biological networks. From the viewpoint of biology even more interesting model class is models that unite both discrete and continuous components.

We consider finite state linear model (FSLM) introduced by Brazma in 2003. The model incorporates biologically intuitive gene regulatory mechanism similar to that in Boolean networks, and describes also the continuous changes in regulatory protein concentrations.

We study several properties of FSLM network dynamics. Previously we have shown that the problem whether a concrete gene will reach an active state in general is algorithmically unsolvable [2]. However, concrete biological networks often exhibit certain regularity and therefore could allow for automated methods to study their behaviour.

Usually slight changes in initial conditions do not shift behaviour of biological system radically. We try to capture these stability properties by providing tools for identification of stable regions and attractors within a network. The method of analysis of network behaviour translates continuous state space of FSLM to finite number of discrete states. Translation is performed in such a way that any stability properties discovered in the symbolic model will necessarily hold for the corresponding continuous FSLM model. Due to algorithmic unsolvability the method is not guaranteed to provide any results, but experiments suggest that it can be quite useful for real networks of reasonable size. The analysis experiments done on phage l network demonstrates that it has only two possible attractors. These attractors correspond to characteristic phage l behaviours – lysis and lysogeny.

Keywords: Gene regulatory networks, analysis of network dynamics

Joint work of: Viksna, Juris; Brazma, Alvis; Cerans, Karlis; Ruklisa, Dace

On the Turing (in)completeness of Chemical Kinetics

Gianluigi Zavattaro (University of Bologna, IT)

In 1997 Magnasco claimed that Chemical Kinetics is Turing Universal. Only more recently Soloveichik and others showed that Finite Stochastic Chemical Reaction Networks (FSCRN) are not Turing complete but are expressive enough to approximately model Turing powerful formalisms with any degree of precision. We present results by Zavattaro and Cardelli who extended those by Soloveichik giving a precise classification of the decidability/undecidability of termination/reachability problems in FSCRN.

Keywords: Process calculi for chemistry, Chemical kinetics, Turing completeness

Full Paper:
http://lucacardelli.name/Papers/On%20the%20Computational%20Power%20of%20Biochemistry.pdf

See also: Luca Cardelli, Gianluigi Zavattaro: On the Computational Power of Biochemistry. AB 2008: 65-80