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Contents

I  GERMAN PARTICIPANTS  
1  Mary-Ann Blätke  
2  Thomas Buder  
3  Fiete Haack  
4  Monika Heiner  
5  Stefan Höhme  
6  Christian Klukas  
7  Heinz Koeppel  
8  Benjamin Kormeier  
9  Jens Krüger  
10 Xin Lai  
11 Adelinde M. Uhrmacher

II  CHINESE PARTICIPANTS  
12 Ming Chen  
13 Gang Guo  
14 Rui Jiang  
15 Taijiao Jiang  

i
Contents

16 Chen Li 35
17 Fangting Li 37
18 Fei Liu 39
19 Zujian Wu 41
20 Dechang Xu 43
21 Ziding Zhang 45

III THIRD COUNTRY PARTICIPANTS 47
22 David Gilbert 49
23 Mostafa Herajy 51
24 Björn Sommer 53
Part I

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talk

A Framework for Modular Biomodel Engineering

abstract. The biomodelkit framework allows to modular compose multi-scale biomodels from a set of modules. A module is defined as a Petri net describing the functionality of a single genetic component (gene, mRNA, protein) and its interactions with other components. Next to the Petri net, each module encloses rich annotations to be compliment with MIRIAM (Minimum Information Required in the Annotation of Models) standards. Both, the Petri net and the annotations are explicitly stored in a MySQL-Database with a public web-interface. Using the web-interface of the biomodelkit framework the user can submit and curate modules, browse through the modules and their structure, compose modular models and generate alternative models by applying model mutation algorithms. A new feature addressing the spatial aspects of multi-scale biomodel engineering allows to extend a modular composed model with spatial properties. The spatial transformation includes the conversion of the flat Petri net model to a coloured Petri net, to represent an arbitrary number of instances for each component in the modular composed model. Furthermore, the spatial transformation equips each component with a local position, which can be changed to represent its movement on a defined grid. The grid itself is scalable and can either be of discrete or continuous character in 1-, 2- or 3-dimensions. The formation of complexes, respectively the interactions among components, are restricted by their local positions. To move components forming a complex, the local positions of the involved components
have to be updated simultaneously. By using this spatial transformation approach the mechanisms and components in the composed models can be mapped to different cellular arrangement, as well as different cell geometries. Thus, the biomodelkit framework based on modular concept using Petri nets and supported by a web-accessible database offers a powerful tool for multi-scale biomodel engineering.

research interests

Petri nets, systems biology, system medicine, personalised medicine, computational biology, modelling standards, model ontology

publications

• F Liu, MA Blätke, M Heiner and M Yang: Modelling and simulating reaction-diffusion systems using coloured Petri nets; Computers in Biology and Medicine, 53:297-308, October 2014 (online July 2014).
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talk

Mathematical model for pilocytic astrocytoma growth and progression provides clinical decision support

abstract. Pilocytic astrocytoma (PA) is the most common brain tumor in children and often only partial resection is possible due to the location of the tumor. In that case, spontaneous regression, regrowth, or progression to a more aggressive form have been observed. We developed a stochastic mathematical model for pilocytic astrocytoma growth and progression that allows to quantitatively predict the regression probability after partial resection based on epidemiological and volumetric data.

research interests

stochastic models of cancer progression; stochastic models of field cancerization; modeling and simulation environment Morpheus

publications

revision (Cancer Research)

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talk

Exploring the spatio- temporal dynamics of WNT/Beta-Catenin Signaling in-silico and in-vitro

research interests

cellular signal transduction pathways, specifically cell surface receptor dynamics and membrane organization with current focus on lipid rafts and intracellular signal mediators in canonical WNT signaling during early neural differentiation

publications


- F Haack, K Burrage, R Redmer, AM Uhrmacher (2013): Studying the role of lipid rafts on protein receptor bindings with Cellular Automata. - IEEE/ACM
Transactions on computational biology and bioinformatics, 10(3):760–770.


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talk

From Petri Nets to Partial Differential Equations

abstract. Petri nets offer a graphical and intuitive notation for biochemical networks, which can be immediately executed and interpreted in different modelling paradigms. Our unifying Petri net framework developed over the last 15 years comprises the traditional time-free Petri nets (PN) as well as quantitative, i.e. time-dependent Petri nets such as stochastic Petri nets (SPN), continuous Petri nets (CPN), and hybrid Petri nets (HPN), as well as their their coloured counterparts.

Coloured Petri nets permit, among others, the convenient and flexible encoding of spatial attributes, and thus the modelling of processes evolving in time and space, which are usually considered as stochastic or deterministic reaction-diffusion systems by help of stochastic or deterministic partial differential equations (PDE). In our approach, the discretisation of space already happens on the modelling level, while traditionally the discretisation is left for the PDE integration method (FEM, FDM, FVM).

Our framework is supported by a related Petri net toolkit consisting of Snoopy, Charlie and Marcie. It has been applied to a couple of case studies; some of them will be sketched in this talk.
research interests

design and application of computational modelling and analysis techniques for systems and synthetic biology, with focus on spatial and temporal multiscale systems, efficient analysis and simulation techniques deploying (coloured qualitative, stochastic, continuous, hybrid) Petri nets, tool development (Snoopy, Marcie, Charlie);

publications

- F Liu, MA Blätke, M Heiner and M Yang: Modelling and simulating reaction-diffusion systems using coloured Petri nets; Computers in Biology and Medicine, 53:297-308, October 2014 (online July 2014).

tools:

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talk

Multiscale modeling of liver regeneration

abstract. During the last years, modeling of different physiological and pathological aspects of the liver advanced significantly with the development of increasingly realistic models on molecular, cellular, tissue and whole organ scale. Nevertheless, model driven liver research is still hampered by a lack of techniques that allow robust integration of these different scales into unifying frameworks. We here present a novel multiscale spatio-temporal 3D model of liver tissue that is based on in-vivo 3D imaging and that may serve as such unifying framework. We use this model to study liver regeneration upon damage or tissue loss which depends on intracellular and tissue scale processes, which interplay with tissue mechanics. In order to capture all these processes at their respective scales, the presented multiscale modelling framework integrates sub-models at all relevant scales from intracellular signalling to body level. It thereby allows predictions on a wide range of possible regeneration scenarios and helps to identify on one hand particularly informative experiments permitting to distinguish between alternative mechanisms, on the other hand impossible scenarios that should not be pursued experimentally. In this way, the model predictions can guide the experimental strategy. The multiscale tissue model is able to simultaneously reproduce all experimental observations including the regeneration process kinetics on the tissue scale. The presented study is an example for how the tight systems-biological integration of experimentation and modelling, both covering multiple scales, can facilitate understanding of complex
5 Stefan Höhme

multi-scale processes as liver regeneration.

Collaborative work with D’Alessandro L.A.\(^2\), Hammad S.\(^4,7\), Schwen L.O.\(^5\), Raue A.\(^6,8\), Friebel A.\(^1\), Mueller S.\(^2\), Pinna F.\(^9\), Albrecht U.\(^10\), Breitkopf-Heinlein K.\(^11\), Schildberg F.\(^12\), Safferling K.\(^13\), Waldow K.\(^2\), Lucarelli P.\(^2\), Manthey S.\(^2\), Godoy P.\(^4\), Ilkavets I.\(^11\), Schirmacher P.\(^9\), Ernst C.\(^13\), Grabe N.\(^13\), Dirsch O.\(^14\), Dahmen U.\(^14\), Knolle P.\(^12\), Meyer C.\(^11\), Dooley S.\(^11\), Bode J.\(^10\), Breuhahn K.\(^9\), Timmer J.\(^6,8\), Kuepfer L.\(^15\), Preusser T.\(^5,16\), Hengstler J.\(^4\), Klingmueller U.\(^2\), and Drasdo D.\(^1,3\).

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research interests

multiscale and agent-based modeling, tissue models, systems medicine, image analysis;

publications

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talk

New approaches for analyzing multi-channel image data and post-processing of phenotypic data

research interests

information system for the storage and analysis of high-throughput image data; infrastructure for the automated movement and imaging of plants; investigate developmental changes and differences in the phenotype of plants

publications

- D Chen, ..., C Klukas: Dissecting the Phenotypic Components of Crop Plant Growth and Drought Responses Based on High-Throughput Image Analysis. Plant Cell tpc.114.129601 (2014)
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talk

Stochastic multi-scale models of biomolecular networks

abstract. Cellular reaction networks are often multi-scale in nature due to wide variation in the species abundance and reaction time scales. Traditional deterministic or stochastic modeling of such systems do not exploit this multi-scale feature and will either be inaccurate or computationally expensive for simulation or inference purposes. This necessitates developing simplified hybrid models combining both stochastic and deterministic approaches that can substantially speed up simulation of such reaction networks. In the talk I will present a layered partitioning approach which splits the reaction set into a fast and a slow group. We lay out a mathematical framework for objectively identifying these groups and performs a rigorous error analysis for the approximation proposed. We furthermore discuss a further partitioning of fast reactions into fast and super fast, where the latter is modelled according to ordinary differential equations. Coupling signal transduction with gene expression and metabolism is an important application domain for such multi-scale approximations.

research interests

systems biology, synthetic biology, statistical inference, Markovian population models, spatial models, single cell analysis, cell-to-cell variability, stochastic and hybrid
simulation algorithms;

publications

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talk

Visualization of biological networks based on a data warehouse

abstract. The progress in the area of biological research in recent years leads to a multiplicity of different databases and information systems. For this purpose the BioDWH data warehouse integration infrastructure was developed. Information must be visualized in a clear and understandable way. With the help of DAWIS-M.D. (Data Warehouse Information System for Metabolic Data) it is possible for the scientist to search quickly and efficiently in large data sets. In addition, we present a software framework for visualizing and modeling biological networks VANESA. Moreover based on the database integration we present a web-based decision support system GraphSAW which analyzes and evaluates drug interactions and side effects.

research interests

data warehouse, database integration, information system, network modelling, network visualization, drug interactions, drug side effects;
publications


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talk

Molecular Simulations using Workflows and Science Gateways

abstract. Research in structural bioinformatics and computational chemistry relies on a tremendous amount of different tools, applications and software suites. Their correct and reproducible usage represents a considerable hurdle for scientific users. The talk will highlight, how simulation protocols can be represented as scientific workflows, improving transparency and reproducibility just in the sense of good lab practice. Furthermore the benefits of science gateways for hosting these workflows such as the MoSGrid portal will be presented, including aspects like data handling and user management. Finally the positive impact of science gateways on teaching bioinformatics and related courses will be demonstrated.

research interests

molecular simulations, ion channels, membrane proteins, allosteric modulation, science gateways, simulation protocols as workflows, high performance computing;


Mathematical modelling of the communication between alveolar macrophages and epithelial cells during Legionella pneumophila infection

abstract. Pneumonia is an acute inflammatory lung disease provoked by infection with different pathogens, including Legionella pneumophila (L. pneumophila). The invading of L. pneumophila into the lung triggers the response of resident alveolar macrophages, which produce pro-inflammatory cytokines, such as IL-1β. However, the mechanism by which the macrophages communicate with surrounding epithelial cells in the lung to keep a tight control of the local inflammatory response remains to be further elucidated. In this study, we combined experimental data with mathematical modelling to dissect the features of the NF-κB signalling mediated process underlying this mechanism. We found that alveolar macrophages can cause the tolerance of lung epithelial cells via IL-1β. After recognising IL-1β, quick degradation of IRAK1 protein happens within the epithelial cells and blocks further stimulation by bacterial factors, such as flagellin. Moreover, we used the data-driven model to assess the influence of clinically relevant factors, such as single nucleotide polymorphisms (SNPs) within the IRAK1 gene altering its protein stability, on the lung inflammatory response induced by L. pneumophila.
research interests

Dynamic system, ODE models, Parameter estimation, Parameter identifiability, Network biology, Microarray data analysis, MicroRNA, Cellular signal transduction pathways & decisions, Melanoma

publications

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talk

The role of languages in spatial, multi-level modeling and simulation, Institute of Computer Science

research interests

Developing modeling and simulation methods and their applications. Among the applications, cell biology has played a central role for more than a decade. Her methodological research aims at developing modeling formalisms and languages for multi-level modeling, efficient execution algorithms and intelligent support for executing simulation experiments.

publications


Part II

CHINESE PARTICIPANTS
12 Ming Chen

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talk

Genome-wide multilevel spatial interactome model of rice

abstract. Multi-omics data brings us a challenge to develop appropriate computational systems biology approaches to model complex biological systems at spatial and temporal scales. In this talk, we will describe multi-omics data available for rice cellular interactome modeling. Biological networks on multiple levels such as gene regulations, protein interactions, noncoding RNA regulations and metabolic reactions are reconstructed. A systematic identification and quantification of rice proteins in various tissues and organs are introduced. To better understand the interactions of proteins in rice, we developed PRIN, a predicted rice interactome network. We presented a novel integrative approach (PSI) that derives the wisdom of multiple specialized predictors via a joint-approach of group decision making strategy and machine learning methods to achieve better prediction results of protein subcellular localization. A genome-wide multiple level of interactome model of rice is integratively built. Furthermore, a database RiceNetDB is developed for systematically storing and retrieving the genome-scale multi-level network of rice to facilitate biomolecular regulatory analysis and gene-metabolite mapping. A virtual rice cell model in three dimensions will be developed via international collaborations.

research interests

systems biology, computational and functional analysis of transcriptomics, and bioinformatics research and application for plant sciences
publications


Monte Carlo simulation of anomalous diffusion and its accuracy analysis

abstract. Anomalous diffusion observed in numerous physical, chemical and biological systems in recent years turns out to be quite ubiquitous which is characterized by a nonlinear behavior for the mean square displacement as a function of time. For anomalous diffusion described by fractional partial differential equation, lattice Monte Carlo (LMC) simulation is an important and effective method when it is difficult to get analytical solutions or necessary to track the trajectory of particles. We discuss some typical anomalous diffusions which are widely used in real applications, i.e., the Galilei-invariant fractional diffusion-drift equation, the Galilei-variant fractional diffusion-drift equation, and the modified fractional diffusion equation with two time scales. The first task is to derive the analytical solutions with different initial and boundary conditions, the first passage time distributions (FPT) and the corresponding Laplace transforms. The LMC simulation algorithms can be designed and developed based on the theory of continuous time random walk (CTRW). The study attempts to determine if there exists a separable CTRW model with a fixed lattice step in its structure function that is equivalent to the anomalous diffusion distribution in the sense of finite order moments or discrete integral transformations. Both the macroscopic and the microscopic accuracy of the LMC simulation algorithm will be analyzed and verified quantitatively by means of the difference between the higher order moments and the distribution functions respectively with the help of stochastic simulation and numerical calculation. The goal is to reveal partly the microscopic mathematical and physical mechanism and the
very nature of the typical anomalous diffusion as well as to provide rigorous mathematical theory and core algorithm for the application of stochastic simulation with high accuracy.

**research interests**

**publications**

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talk

Identification of disease-causing single nucleotide variants in exome sequencing studies

research interests

publications

• Rui Jiang, Walking on multiple disease-gene networks to prioritise candidate genes, Journal of Molecular Cell Biology, advance access online, 2015

• Shining Ma, Tao Jiang, Rui Jiang, Differential regulation enrichment analysis via the integration of transcriptional regulatory network and gene expression data, Bioinformatics, 31(4): 563-571, 2015

• Jiaxin Wu, Yanda Li, Rui Jiang, Integrating multiple genomic data to predict disease-causing nonsynonymous single nucleotide variants in exome sequencing studies, PLoS Genetics, in press, 2014
Modeling influenza virus evolution in big data era

abstract. The advancement of high throughput sequencing technology coupled with internet technology has enabled us to acquire massive genomic data for in-depth understanding of disease mechanisms, facilitating more effective strategies for disease prevention and treatment. In our lab, by focusing influenza viruses, we have developed a series of methods [1-5] to model influenza evolution from the massive gene data collected during influenza surveillance carried out by Chinese Center for Disease Control and Prevention (China CDC). Furthermore, we have proposed network-based approaches for effective seasonal influenza vaccine strain selection [4], and found the genetic pathways towards the generation of the novel H7N9 viruses occurred in East China of 2013. No doubt, the effective mining of the big genomic data related to diseases will not only greatly facilitate the prevention and control of infectious diseases but also advance the precision medicine for complex diseases like malignant tumors.

research interests

studying gene and protein networks involved in infectious diseases by network analysis and structural modeling; modeling of protein structures and complex biological systems, including novel computational methods to model the genetic and antigenic evolution of seasonal influenza virus;
publications

- Aiping Wu, Chunhu Su, Dayan Wang, Yousong Peng, Mi Liu, Sha Hua, Tianxian Li, George F Gao, Hong Tang, Jianzhu Chen, Xiufan Liu, Yuelong Shu, Daxin Peng, Taijiao Jiang. Sequential Reassortments Underlie Diverse Influenza H7N9 Genotypes in China. Cell Host & Microbe 2013, DOI: 10.1016/j.chom.2013.09.001


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talk

Study on kinetic parameter estimation of biological pathways with high speed and high accuracy

research interests

publications

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talk

The cell cycle model in budding yeast

research interests

Quantitative biology of the cell cycle process in yeast; Quantitative biology of the DNA replication checkpoint in yeast; Modeling the immune system response

publications

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talk

Colored Petri nets for multiscale systems biology

abstract. Systems biology aims to understand the behavior of a biological system at the system level by means of investigating the behavior and interactions of all the components in the system. Due to the ability to produce data of one and the same phenomenon at different scales, the modeling of biological systems is moving from single scales to multiple scales, e.g., from the molecular scale to the cell, tissue, and even the whole organism level. In this report, we will present a colored Petri net approach to modeling and analyzing multiscale systems biology. Specifically, in this report you will see what are colored Petri nets, what challenges of multiscale systems biology can be tackled by colored Petri nets, a colored Petri net framework for multiscale systems biology, and a couple of case studies.

research interests

Modeling and simulation for (multi-scale) Systems Biology and Synthetic Biology; Colored qualitative, stochastic, continuous, and hybrid Petri nets; Stochastic/PDE/ODE/hybrid simulation algorithms
publications

- F Liu, M Heiner and M Yang: Representing Network Reconstruction Solutions with Colored Petri Nets; Neurocomputing, 2015.
- F Liu, MA Blätke, M Heiner and M Yang: Modelling and simulating reaction-diffusion systems using coloured Petri nets; Computers in Biology and Medicine, 53:297-308, October 2014 (online July 2014).
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talk

An integrated qualitative and quantitative biochemical model learning framework using evolutionary methodologies

abstract. Both qualitative and quantitative model learning frameworks for biochemical systems have been studied in computational systems biology. In this talk, after illustrating two forms of pre-defined component patterns to represent biochemical models, I will introduce an integrative qualitative and quantitative modelling framework for inferring biochemical systems. Interactions between reactants in the candidate models for a target biochemical system can be evolved and eventually identified by the application of a qualitative model learning approach with an evolution strategy. Kinetic rates of the models generated from qualitative model learning are then further optimised by employing a quantitative approach with simulated annealing. Experimental results indicate that our proposed integrative framework is feasible to learn the relationships between biochemical reactants qualitatively and to make the model replicate the behaviours of the target system by optimising the kinetic rates quantitatively. Moreover, potential reactants of a target biochemical system can be discovered by hypothesising complex reactants in the synthetic models. Based on the biochemical models learned from the framework, biologists can further perform experimental study in wet laboratory. In this way, natural biochemical systems can be better understood.
research interests

publications


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talk

Design & Simulation of Synthetic BioSensor for Dioxion

research interests

Food Biotechnology, Bioinformatics

publications

- Dechang Xu, Jianzhong Li: An experimental research for automatic classification of unbalanced single-channel protein sub-cellular location fluorescence image set. BIBM 2013: 68-70
- Xiyuan Lu, Cuihong Dai, Aiju Hou, Jie Cui, Dayou Cheng, Dechang Xu: Dysregulated microRNA Profile in HeLa Cell Lines Induced by Lupeol. ISBRA 2014: 71-80
Understanding Plant Immunity through Integrative Network Analysis

**abstract.** Plants have evolved a sophisticated immune system that enables each cell to monitor every possible destructive invasion by microbe and to mount an appropriate defense response when necessary. Pattern-triggered immunity (PTI) and effector-triggered immunity (ETI) are two primary immune defense modes in plants. Up to now, genome-wide gene network organizing principles leading to quantitative differences between PTI and ETI have remained elusive. With the increasing availability of genome, proteome, and interactome data, network biology is becoming an important approach to decipher the molecular mechanism of plant immunity. Recently, we developed an advanced machine learning method and modular network analysis to systematically characterize the organization principles of Arabidopsis PTI and ETI. In this talk, we report our major findings from three network resolutions. At a single network node/edge level, we ranked important genes and gene interactions for immune response and successfully identified many known immune regulators for PTI and ETI, respectively. Topological analysis showed that important gene interactions tend to link network modules. At a subnetwork level, we identified a subnetwork shared by PTI and ETI, which covers 1159 genes and 1289 interactions. In addition to being enriched with interactions linking network modules, it is also a hotspot attacked by pathogen effectors. The subnetwork likely represents a core component to coordinate multiple biological processes in the transition from development to defense. Finally, we constructed modular network models for PTI and ETI to explain the quantitative differences from...
the global network architecture. Our results show defense modules appeared to be interdependently connected in PTI, but independently connected in ETI, providing an explanation for the robustness of ETI to genetic mutations and effector attacks. Taken together, the multiscale comparisons between PTI and ETI provide a systems biology point of view to understand plant immunity, and highlight the coordination among network modules to establish a robust immune response.

research interests

plant, pattern-triggered immunity, effector-triggered immunity, network, machine learning, systems biology

publications

Part III

THIRD COUNTRY PARTICIPANTS
Model checking for multiscale biological systems

abstract. I will present recent work from our group on the development of a model checking methodology and associated software for multiscale biological systems. These techniques are derived from extensions of standard model checking using temporal logic combined with a form of multidimensional spatial logic and a tree-based architectural description of multilevel biological systems. The method is implemented using simulative model checking, and can be applied to checking the behaviour of not only models but of multiscale biological systems themselves, and thus can be employed as part of the design-implementation process of complex synthetic biological systems. The approach is generic in that it can easily be applied to model checking other non-biological systems.

I will briefly illustrate this approach with the application of our techniques to some case studies.

research interests

model checking, temporal logic, systems biology, synthetic biology, computational design, multidimensional, multilevel.
publications

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talk

Efficient Simulation of Hybrid Petri Nets

abstract. Petri nets are promising tools for modelling and analyzing biological systems. They can help with the understanding of complex biological pathways by graphically depicting the underlying reaction networks. Nevertheless, with the increasing interest in modelling complex biological systems, basic place/transition nets tend to be inefficient to tackle emergent issues due to challenges coming with the modelling of multiscale reaction networks. Thus new classes of Petri nets are devised with a special aim to aid systems biologists in studying intricate reaction networks. Among these classes are Hybrid Petri nets (HPN) and Coloured Hybrid Petri nets (HPN\textsuperscript{C}). HPN permit the representation and simulation as well as the interplay of discrete stochastic and continuous deterministic components in one and the same model, while HPN\textsuperscript{C} allow for the efficient modelling of spatiotemporal systems exposing multiple time-scales.

During this talk, an overview of modelling multi-scale biological systems using (coloured) Hybrid Petri nets is presented. Moreover, the different simulation algorithms used to execute hybrid models are discussed highlighting the various issues that hamper the efficient simulation of (coloured) Hybrid Petri nets and how to work at them.
research interests

Hybrid Modelling; (Coloured) Hybrid Petri Nets; Multi-timescale modelling, Stochastic and continuous simulation

publications

- M Herajy, M Heiner: Modeling and Simulation of Multi-scale Environmental Systems with Generalized Hybrid Petri Nets; Frontiers in Environmental Science, 3(53), 2015 (accepted for publication: 13 July 2015).
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talk

Immersive Cell Exploration and Membrane Modeling

abstract The CELLmicrocosmos project provides different approaches to model biological cells at the mesoscopic level and membranes at the molecular level. It is possible to create different cell models, associate them with protein-related networks based on different localization databases, as well as to generate membrane patches or vesicles. Whereas in the recent years the modeling process was in the focus of our research, recently the visualization and especially exploration was improved. For this purpose, 3D interaction was integrated, as well as optional large-scale visualization capabilities compatible to, e.g., CAVE2.

research interests

to support Bioinformatics-related research by interdisciplinary visualization and modeling approaches; CELLmicrocosmos project (http://www.cellmicrocosmos.org) which provides different tools supporting the visualization and modeling of cells, cell compartments and cell membranes.
publications


