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Advances in Biological processes and Petri nets (BioPPN)

Preface

This special issue on ”Advances in Biological processes and Petri nets (BioPPN)” is based on best papers first presented at the BioPPN workshop series in the years 2013-2016, held in conjunction with the annual International Conference on Application and Theory of Petri Nets and Concurrency (PETRI NETS). All journal papers substantially improve and extend their previous versions published in the CEUR workshop proceedings at CEUR-WS.org (see volumes 988/2013, 1159/2014, 1373/2015, 1591/2016). All papers passed a regular journal peer-reviewing process, involving several rounds for most of the papers. On this occasion, we would like to thank all reviewers for spending their precious time to help with their careful and thoughtful work. There is no doubt that all reviews with their insightful and invaluable comments appreciably contributed to the overall high standard reached.

The BioPPN workshops have been organised to provide a platform for researchers aiming at fundamental research and real life applications of Petri nets and other concurrency models in Systems and Synthetic Biology. The research fields of Systems and Synthetic Biology are full of challenges and open issues, with adequate modelling and analysis techniques being some of them. The need for appropriate mathematical and computational modelling tools is widely acknowledged. Petri nets offer a family of related models, which may serve as a kind of umbrella formalism – models may share the network structure, but vary in their kinetic details (quantitative information). This unquestionably contributes to bridging the gap between different formalisms, and helps to unify diversity.

Looking back on the brief history behind us, Petri nets have proven their usefulness for the modelling, analysis, and simulation of a diversity of biological networks, covering qualitative, stochastic, continuous and hybrid models. The reader will find use cases for all these model classes in this special issue. Actually, the special strength of some papers comes by building on a well-chosen combination of different net classes and the sophisticated interplay of related net class-specific analysis methods.

For example, the paper by Simon V. Hardy et al. on ‘*A hybrid Petri net model of the Akt-Wnt-mTOR-p70S6K signalling network in neurons*’ exploits a structural analysis technique, known in the Petri net community as place and transition invariants, to generate dynamic graphs, which provide a more abstract system view of the signalling network dynamics modelled in detail as hybrid Petri net. The fruit on hand of this synergy is a novel model of the Akt-Wnt-mTOR-p70S6K network, based on which two new predictions are made, seeking now for experimental evidence.

Transition invariants are also crucial for the paper by Marta Simeoni et al. on ‘*Petri Nets for Modelling and Analysing Trophic Networks*’, which help here to systematically derive the transition rates required to turn a merely structural model represented as qualitative Petri net into a quantitative model represented as continuous Petri net, which in turn is known to be nothing else than a structural description of a system of ordinary differential equations (ODEs). The approach is demonstrated for a trophic network representing the feeding interactions in the Venice lagoon.

Let us recall - Continuous Petri nets can be considered as a graphical alternative to the traditional ODEs representation of biological models, which is still the most popular modelling approach in Systems and Synthetic Biology. Consequently, the synergy between '*Biological Processes and Petri nets*' has also motivated basic research aiming at formal foundations of existing net classes; a corresponding example is the paper by Mostafa Herajy et al. on '*Adaptive and Bio-semantics of Continuous Petri Nets: Choosing the Appropriate Interpretation*', which compares two widely used semantics of Continuous Petri Nets: one semantics is popular in the Petri net ccommunity, and the other one, called bio-semantics, is popular in Systems and Synthetic Biology.

The reader will also notice the advent of new modelling approaches, designed to address specific modelling needs. For example, two papers combine Petri nets with fuzzy logics to deal with unknown or imprecise kinetic data, see the paper by Jure Bordon et al. on '*Semi-quantitative modelling of gene regulatory processes with unknown parameter values using Fuzzy logic and Petri nets*' and the paper by Fei Liu et al. on '*Coloured Fuzzy Petri Nets for Dealing with Genetic Regulatory Networks*'.

A novel discrete concurrency framework called ANDy is presented by Cinzia Di Giusto et al. in their paper on '*Activity Networks with Delays; An application to toxicity analysis*'. ANDy aims at the qualitative modelling of time-dependent activities, its semantics is formally defined in terms of (traditional) high-level Petri nets, and the approach is illustrated by a case study modelling glucose regulation in the human blood.

The deployment of Petri nets to study biological applications has generated over the years numerous original models, and some of them can even be found in this special issue; for further examples, besides the already mentioned case studies, see the papers by Piotr Formanowicz et al. on '*Factors influencing essential hypertension and cardiovascular disease modelled and analysed using stochastic Petri nets*' and by Rza Bashirov et al. on '*Stochastic simulation-based prediction of the behaviour of p16-mediated signalling pathway*'. The former paper turns a previously published qualitative model into a stochastic model by applying simple heuristics to define appropriate rate parameters, the latter paper builds on a model previously published as hybrid functional Petri net, which is now discussed as a hybrid Petri net model, which involves (contrary to hybrid functional Petri nets) continuous and (standard) stochastic transitions. Both papers perform stochastic simulations to investigate and validate the consistency of their models.

Two papers in our special issue have their focus on new analysis methods and tools.

Stochastic simulation is often closer to the biological truth than deterministic simulation, but known to get rather expensive and this rather fast. Thus, much research has been devoted to improve the efficiency of stochastic simulation. In our special issue, the reader finds a related paper by Christian Rohr on '*Discrete-Time Leap Method For Stochastic Simulation*', proposing an approximative simulation algorithm, outperforming for large and dense biochemical reaction networks all state-of-the-art stochastic simulation algorithms known so far. The algorithm is supported by the Petri net tools Snoopy and Marcie.

The paper by Jacek Sroka et al. on '*Verification of dynamic behaviour in qualitative molecular networks describing gene regulation, signalling and whole-cell metabolism*' combines two modelling formalisms and related modelling-specific analysis techniques: Flux Balance Analysis (FBA) of a constraint-based model representing metabolic pathways and state space analysis of a qualitative Petri net representing related gene regulation. Both formalisms are interconnected; the gene regulation controls the metabolism, and vice versa the current metabolic steady state controls the gene regulation. The result is called Quasi-Steady State Petri Net (QSSPN) and can even be applied to genome scale modelling.

How to master complexity is one of the big and urgent challenges in Systems Biology; it is also the subject of the paper by Mary-Ann Blätke et al. on '*BioModelKit: Spatial Modelling of Complex Multiscale Molecular Biosystems based on Modular Models*', which proposes the use of coloured Petri nets to construct spatial and multiscale molecular biosystems by a modular modelling approach. The spatial model specifies the locality and movement of the individual biomolecular components by help of component-specific coordinate pointers on a defined, possibly infinite grid.

Most papers included in this special issue are the result of multi-disciplinary long-term collaborations of professionals with rather diverse background, involving biologists, mathematicians and computing scientists alike; some papers are the result of international collaborations. We wish all readers an enjoyable journey through this special issue contributing to an exciting field of research, full of many open questions seeking our attention.

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