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Preface

Petri Net Applications in Molecular Biology

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At the time when "classical" bioinformatics developed further towards modern systems biology, the idea of a holistic view of a biological system was not completely new: the aim to provide a comprehensive picture, e.g. about the genes and their regulatory features encoded in a genome, was inherent in bioinformatics research from the very beginning. Also the attempt to come up with an integrative view across the different levels of organisation was at least conceptually implicit in the numerous approaches to integrate the rapidly growing information about biological objects into comprehensive knowledge bases. However, to transcend the research focus on static objects and to step forward to the computer-aided investigation of biological processes was significantly pushed ahead by the emerging field of systems biology. The new paradigm to formally represent the processes that make up a biological system is now the "network".

The term "process" implies dynamic events, changes, that we may wish to simulate with the aid of a computer in order to predict the behavior of a biological system under certain circumstances. Biochemistry provides the formal instruments to do so for defined (bio)chemical reactions, usually resulting in a set of ordinary differential equations (ODEs). Solving the large number of ODEs that are required to exactly describe the behavior of a complex biological system may be cumbersome, but computationally feasible as soon as we have at hand all necessary parameters such as the corresponding kinetic constants for all reactions involved. Even in those cases where these kinetics have been studied *in vitro*, it is still questionable whether the insights we gained from these experiments are applicable on specific *in vivo* conditions. Nevertheless, this approach has been proven to work for (parts of) the metabolic network of living cells, but regulatory events that depend on just a very low number of individual molecules per cell may require different approaches. Moreover, applying ODEs onto a large complex system may be mere overkill, and a (presumably) less exact approach might be of even more appropriate granularity, at least for the larger part of the network under consideration.

Several years ago, Petri nets have been suggested to be well suited for modeling metabolic networks by overcoming some of the limitations outlined above [Reddy *et al.*, 1993]. Since then, a lot of further conceptual work, technical tool implementations and applications onto biological problems have been reported and demonstrated the usefulness of this concept for what we know today as systems biology. Being intuitively understandable to scientists trained in life sciences, they also have a robust mathematical foundation and provide the required flexibility with regard to the models' granularity. As a result, Petri net technology appears to be a very promising approach to modeling biological systems.

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A significant part of the progress in this field has been published by In Silico Biology since its beginning in 1998. Four articles constituted the first Petri Net Special in 2003 ("Petri Nets for Metabolic Networks"; http://www.bioinfo.de/isb/toc_vol_03.html#Petri_nets). R. Hofestädt's introduction to that Special summarized the most essential topics as well as some of the basic requirements and constraints relevant for applying Petri net technology, and is therefore following this preface [Hofestädt, 2003].

The early publication of Hofestädt and Thelen, 1998, demonstrated how the Petri net concept can be extended to a more quantitative modeling of metabolic networks, and expanded these ideas also to gene regulatory and cell-cell communication processes. In a subsequent work, Chen and Hofestädt could demonstrate how the Petri net approach can deal with an integrated process comprising gene regulatory and metabolic events, making use of the concept of hybrid Petri nets (HPN) [Chen and Hofestädt, 2003]. Having analyzed the requirements of the biochemical particularities of metabolic networks, Zevedei-Oancea and Schuster, 2003, have studied the resulting topological properties of the corresponding Petri net models. Takai-Igarashi suggested a consistent definition of Petri net units that are required for modeling signal transduction pathways; it was based on a specific ontology, the Cell Signaling Networks Ontology (CSNO) [Takai-Igarashi, 2005]. Voss *et al.*, 2003, have complemented these efforts by studying the Petri net models of metabolic steady states including all relevant reverse reactions. Similarly, Gambin *et al.* made an attempt to model the stationary state of a gene regulatory network in a Petri net [Gambin *et al.*, 2006]. A big step ahead towards dynamic simulation with the aid of Petri net models was undertaken by Matsuno *et al.*, 2003, by extending the underlying approach further to the concept of hybrid functional Petri nets (HFPN). This was proven to be applicable to simulate the dynamics of two regulatory pathways, and it was demonstrated how such a Petri net model can be constructed [Matsuno *et al.*, 2003; Doi *et al.*, 2004]. More recently, the concept of firing delay times was introduced into the HFPN approach and applied to a signaling process [Miwa *et al.*, 2010].

The conceptualization phase was also accompanied by the active development of a number of tools assisting in the creation and manipulation of biological Petri nets. While the early efforts used a platform that was originally developed for technical purposes (Visual Object Net ++, VON++) [Chen and Hofestädt, 2003], soon after a tool specifically developed for modeling biological processes with Petri nets was published: Genome Object Net, GON [Matsuno *et al.*, 2003; Doi *et al.*, 2004]. GON evolved subsequently into Cell Illustrator (CI), a platform that is suitable for easy modeling and simulating the dynamics of cellular processes [Nagasaki *et al.*, 2010]. A specialized tool (STEPP) for searching in a Petri net those paths that connect, e.g., two metabolites and thus generating hypotheses about the interconversion of these two compounds has been introduced by Koch *et al.*, 2004; the program is still available for download (http://www1.beuth-hochschule.de/bi/stepp). Janowski *et al.* have developed a powerful network editor, VANESA, that is able to work with Cell Illustrator as simulation engine [Janowski *et al.*, 2010].

A number of applications of Petri net-based modeling and simulation were published in recent years. While the early works were usually focussing on certain parts of the metabolic network such as glycolysis and pentose phosphate pathway [Voss *et al.*, 2003; Zevedei-Oancea and Schuster, 2003; Doi *et al.*, 2004], nucleotide metabolism [Zevedei-Oancea and Schuster, 2003], urea cycle [Chen and Hofestädt, 2003], or the conversion of sucrose into starch in potato [Koch *et al.*, 2004], different kinds of regulatory networks attracted attention of late. Thus, several signal transduction networks have been studied in great detail: the Fas ligand-induced cascade leading to apoptosis [Matsuno *et al.*, 2003], the TGF-beta pathway [Takai-Igarashi, 2005], and the p53 network [Doi *et al.*, 2006]. This year, the IL-1 pathway has been added [Miwa *et al.*, 2010].

Gene regulatory events were also studied, such as the control of circadian rhythm in *Drosophila* [Matsuno *et al.*, 2003], the regulation of glycolysis by the lac operon [Doi *et al.*, 2004], the flower

morphogenesis of *Arabidopsis* [Gambin *et al.*, 2006]. The latter topic has been resumed now by Kaufmann *et al.*, with the aid of Cell Illustrator [Kaufmann *et al.*, 2010]. The mRNA turnover for a number of components relevant for cell-cycle regulation has been studied with a stochastic Petri net by Csikász-Nagy and Mura, 2010. The assembly of the splicesosome has been modeled by Bortfeldt *et al.*, 2010, analyzing the modular nature of this regulatory network.

How intercellular communication processes can be linked with intracellular regulatory events and simulated has been shown in the contributions of Janowski *et al.*, taking the bacterial quorum sensing as an example [Janowski *et al.*, 2010]. The impact of delays and noise on the dopamine signal transmission has been investigated by E. Voit and colleagues [Wu *et al.*, 2010], and both studies made use of the HFPN-base simulation engine of Cell Illustrator [Nagasaki *et al.*, 2010].

This recent overview has been published as Special Issue on Petri Net Applications in Molecular Biology of ISB volume 10, whereas the whole collection now constitutes this First ISB Book on Biological Petri Nets. We are confident that the reader will benefit from this unique compilation of articles, and hope that it helps to illustrate the value of the Petri Net approach to modern life sciences.

While this book was in its last stages of editing, Prof. Dr. Carl Adam Petri passed away on the 2nd of July, 2010. We mourn the loss of a great scientist. His work has inspired researchers from a broad range of disciplines, which clearly indicates his perspicacious mindset. We wish to honor his outstanding scientific merits by dedicating this book to his memory.

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