# Interdisciplinary insights

Systems biology is an inherently complex discipline which requires researchers from a range of disciplines to work together. Here, **Professor Monika Heiner** describes how she has spent her career applying computing skills to biological questions and what she sees as the future of the discipline

**Can you define the term 'systems biology'?**

Systems biology aims at understanding living entities such as cells, tissues and organisms by considering them as a system, with internal regulatory processes to keep that system running and control how it reacts to external stimuli.

**How would you describe your professional background? What led you to working in this area?**

I'm a software engineer by training, and have always been interested in formal methods to improve the quality of the artefacts which we construct. Formal methods play a crucial role in software engineering, such as for software validation and verification, or reliability assessment.

As I gradually moved to the fascinating area of systems biology, I was able to reuse many of the techniques previously applied in software engineering – but now to validate a dry lab model against its wet lab reality, or to verify a blueprint from which the synthetic brick is built. At the same time I quickly realised that I had to substantially extend my toolkit in order to address all the questions at hand. Challenges are the spice of research, and over the years I learnt a lot about mathematics and related algorithms, and also a bit about genes, proteins and their regulatory processes.

**The Petri net framework comprises a group of closely related models; what are these models and how do they differ in their structure and application?**

A distinct characteristic of systems biology is that the same model can and often has to be interpreted in different modelling paradigms. Each perspective brings its own contribution to the understanding of the system. Depending on the phenomenon under investigation, these perspectives can either be complementary or competitive – delivering contradictory results that may finally lead to uncovering the underlying mechanism. Changing the paradigm sometimes has counterintuitive effects on system behaviour, which are currently not well understood. But there is a lot of research going on in the community to shed light on the subject.

**How will the NoPain (nociceptor pain model) Project apply the predictive power of these models to establish 'mechanism-based' pain therapies for humans?**

Our NoPain consortium is the first to approach this field from a systems biology perspective, which is understandable considering how little is known about pain phenomena. Nevertheless, modelling means collecting and systematising knowledge, which is typically spread widely over numerous research articles or hidden in the brains of professionals. Bringing such knowledge into a consistent representation already makes a big leap in the right direction. Modelling also means abstracting away some details which are supposed to be of less importance for the questions of interest. The consortium has made some progress in its ambitious aim, although it is far too early to speak of results.

**What do you see as being the future for Petri nets and computational methods as a whole in systems biology?**

Petri nets have a special charm from the modelling perspective, and also offer some specific contributions to the analysis. However, in my opinion, what really matters in the end is the total outcome of applying computational methods in biochemical and medical research, and in real life applications onwards.

# The power of Petri nets

The interdisciplinary nature of systems biology can provide challenges when researchers from very different backgrounds begin to talk past each other. Researchers from the **Brandenburg University of Technology**, Germany, are developing powerful graphical tools called Petri nets that model a variety of biological systems in a readily understandable way

**LIVING CELLS CONSIST** of many thousands of different biomolecules that functionally interact by forming interwoven systems termed molecular networks. Teasing out the relevant mechanisms to understand and solve a particular scientific or medical problem is a mammoth task. Modern biology has reached the point where the answers to our questions lie within the non-obvious interplay of genes, proteins and other biomolecules. Simply listing and understanding each element on its own, however, is not enough. An analogy for this would be a component list for a car. While having a full list is a reasonable start to a full understanding of the car's mechanism, it would certainly not be enough to simply consult the component sheet when the car breaks down in order to fix it. The vital missing ingredient is a description of how all the components interact.

This is the perspective from which systems biology has arisen. The functional interaction of the molecular components of living cells display the emergent (dynamic) behaviour of a complex system – the whole acts according to rules that none of the parts obey individually and that cannot be predicted from the part list alone. This outlook marks a fundamental change in how science is executed. Traditionally, science explores basic phenomena, aiming to understand large processes through the sum of their parts – this is known as reductionism. Systems biology, on the other hand, represents a shift to a more holistic perspective; it aims to understand the behaviour of systems by examining and modelling their overall structure. In order to analyse these complex molecular systems and their emerging dynamic behaviour, researchers in this field combine experimental work with simulation; data are collected experimentally and modellers use these to simulate the system. The model then makes testable predictions for pending experiments, which can either confirm that the model is sufficient to explain the experimental observations, or generate unexpected data that can be used to dismiss the model or to further refine it. This dialogue should finally converge on highly accurate models with a great deal of predictive and explanatory power. This is not straightforward, however, as a huge amount of data on the substructure of the systems still need to be built into the models in order for them to accurately mimic the overall behaviour of the system. Only now is this becoming possible in the life sciences as huge high-throughput screening techniques are generating vast quantities of data on gene expression and protein behaviour. The difficulty then becomes how to properly use these data to build models that are both sufficiently predictive and well constrained to run quickly.

## DECEPTIVE SIMPLICITY

Work being undertaken at the Brandenburg University of Technology, Germany, by Professor Monika Heiner aims to develop an assemblage of techniques that seem ideal to this situation. Petri nets were purportedly created by a 13-year-old Carl Adam Petri for visualising chemical reactions, and have a long history in computing science. The nets are a simple graphical interface that can model complex non-deterministic processes, like the ones found in biology. Petri nets take the form of simple graphs, consisting of collections of arcs that join places and transitions. Places are usually seen to represent certain conditions within the system being modelled, and transitions are events that happen to the system. Arcs show the connections between these elements, but only ever mark a connection between a place and a transition or vice versa, as conditions may only change through events. Arcs can also be weighted according to the conditions required for the changes of the system states. Tokens flow through the network, and can be seen as an abstract representation of resources, such as biomolecules. In a simple Petri graph showing the reaction $2H_2 + O_2 \rightarrow 2H_2O$, for

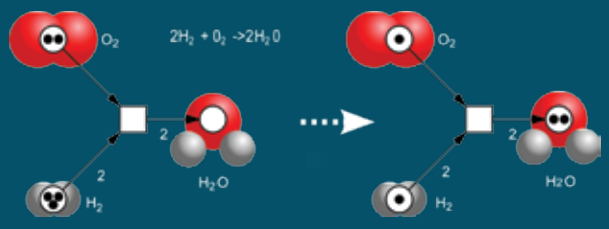


**Figure 1**: A simple Petri net in two states for the reaction $2H_2 + O_2 \rightarrow 2H_2O$.

The long-term goal is to apply this research for personalised model-based preventive and therapeutic medicine. For example, to derive lifestyle recommendations, to select from therapy alternatives the most suitable treatment or to guide drug prescription.

**The life sciences have not traditionally exhibited as much of a gender divide as has often been the case in other disciplines such as computational science and mathematics. As someone whose work covers all of these disciplines, what are your views on gender disparities in science?**

Gender equality has many facets. Before the life science wave, there was quite a gender divide in biology, in that life sciences researchers were almost all women. Wet labs are still packed with women, although they are becoming rare in higher positions. By contrast, dry labs are known to be male dominated. However, Italy, for example, is famous for having many women in mathematics and computer science, and they are well represented in the Italian academia. From a mathematical point of view, multidisciplinarity helps to overcome the gender gap by bringing wet lab and dry lab researchers together.

*Interview conducted March 2014.*

## INTELLIGENCE

### BIOMODEL ENGINEERING FOR MULTISCALE SYSTEMS BIOLOGY

#### OBJECTIVES

- To pioneer BioModel Engineering for reproducible computational research by the development of reliable and trustworthy modelling and analysis techniques and related tools
- To foster the application of computational methods in biochemical and medical applications. The long-term goal is to apply this research for personalised medicine

#### KEY COLLABORATORS

**Professor David Gilbert**, Department of Computer Science and Centre for Systems and Synthetic Biology, Brunel University London, UK

**Professor Wolfgang Marwan**, Regulatory Biology and Magdeburg Centre for Systems Biology (MaCS), Otto von Guericke University, Germany

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MONIKA HEINER is Professor of Data Structures and Software Dependability at the Brandenburg University of Technology in Cottbus, Germany, and Visiting Professor at the Department of Computer Science, Brunel University London, UK. She has a long history of expertise in Petri nets.

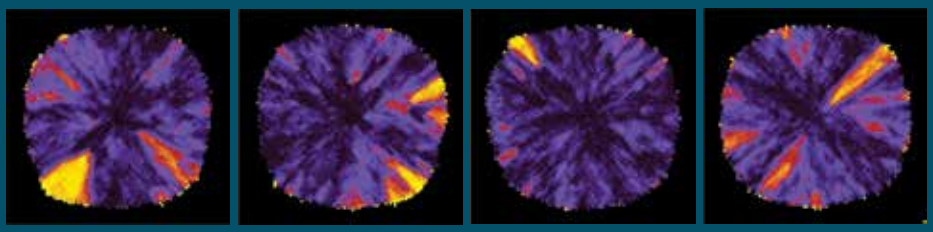

**Figure 2**: Stochastic simulation results of phase variation in bacterial colonies.

example, the presence of two tokens in the $H_2$ place and one token in the $O_2$ place enables the tokens to flow through the weighted arcs and into the $H_2O$ place (see Figure 1).

This is the fundamental aspect of Petri nets; but with other constraints, and appropriate modelling, they become incredibly powerful tools to visualise extremely complex systems in simple graphical form. This means that experimentalists can easily jump straight in and begin expressing the systems they are working with in the Petri net formalism, placing their ideas immediately into a language that is easily translated to simulation. This works the other way as well, with modellers being able to easily express their models to experimentalists, enabling them to design studies that properly test the models. The capacity for researchers from disparate backgrounds to communicate easily is vital in a research programme as interdisciplinary as systems biology.

#### NET APPLICATIONS

An example of Petri nets in action comes from the work of Heiner's collaborator Professor David Gilbert and his team, who used them to model a stochastic microbial gene-switching process called phase variation (see Figure 2). This process enables bacteria to make use of reversible mutations to vary their phenotype and adapt to rapidly changing environments, allowing them to survive in locations which would wipe out bacteria relying on conventional mutation. The random variation in this process can be easily captured in the Petri net models of the type that Gilbert has developed. A second application of these nets comes from a consortium that Heiner is set to be part of called NoPain (nociceptor pain model), which aims to model the mechanisms behind pain in order to develop intervention techniques. NoPain builds upon a previous three year project which helped to build a common language between the different groups of researchers involved. The consortium is therefore in an ideal position to begin tackling the pain mechanism.

Further collaboration comes from Professor Wolfgang Marwan and his team, who have modelled the JAK-STAT signalling pathway, which transmits signals throughout the entirety of the cell – from its exterior all the way to the DNA in its nucleus. This research models each biomolecule and its interactions with a Petri net. The varied nature of this work – which uses the software developed by Heiner's team – demonstrates the incredible flexibility of the state-based approach embodied in Petri nets. The software consists of a hierarchical Petri net editor and animator called Snoopy, a Petri net analysis tool called Charlie, and a model checker called Marcie. All have proved highly successful, with Snoopy being cited in over 70 papers by authors completely independent from the development team, and Marcie winning either gold or silver awards in 11 out of 12 examinations of surprise (unrevealed) Petri net models at Petri Nets 2013.

#### MELDING PERSPECTIVE

Science as a whole is becoming more interdisciplinary, but with this comes strains inherited from an old system of more rigidly defined research programmes where biologists talked to other biologists and modellers talked to other modellers. This structural deficiency is unlikely to disappear quickly, as undergraduate courses must be relatively focused in order to be completed within reasonable time. Given this situation, it is vital that researchers do not merely forge links, but develop shared languages. Heiner's work on Petri nets provides an ideal set of tools to enable easy communication between modellers and experimentalists, with an intuitive interface that belies its complexity.

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