ERCIM "Alain Bensoussan"
Fellowship Scientific Report

Fellow: Cristina Costa Santini
Visited Location : NTNU from 9/01/2008 to 8/01/2009
Duration of Visit: 1 year

I - Scientific activity

The project I am working on as an ERCIM fellow is currently a collaboration between the CRAB lab, from the Department of Computer and Information Science and the Gastrin Systems Biology (GSB) group, from the Department of Cancer Research and Molecular Medicine, NTNU. The CRAB lab is led by assoc. Prof. Pauline Haddow, who is my scientific contact; it is investigating a new computational technique, artificial development, and with regard to this project aims to refine the technique to achieve a modelling technique which can exploit the parallelism available on a hardware technology platform so as to model cellular signaling pathways.

Considering my work on this project, the important initial realisation was that living cells can be treated as networks [bray03]. These cellular networks are historically divided into metabolism, regulation and signalling. However, it is currently known that the same molecules participate in more than one of these networks. Therefore one must think of a genome-scale network [palsson06]. The gastrin regulatory system being investigated by the collaborating group can be seen as a genetic regulatory network.

Thus the possible representation techniques for such regulatory networks were investigated and their suitability for 'an artificial development modelling technique in hardware' was identified. Several representations or computational models for regulatory networks can be found in the literature [fisher07]. I proposed Boolean networks (BNs) [kauffman69] as a representation that would suit the project's aims and constraints. This representation has positive as well as negative aspects. In brief, BNs are synchronous and represent only two levels, on or off; and in general, the suitability of this representation depends on the system being modelled. There are examples in the literature that provide evidence that this representation, even though abstract and simplistic, captures the essential aspects of regulatory networks [huang00,li04,helikar08]. It is important to mention that the GSB group confirmed that the gastrin regulatory system could also, in principle, be represented by BNs, once, at an abstract level, it seems to be sequential and the main events can be considered within the same time scale.

Having chosen the representation, the issue of modelling had to be addressed. Reverse engineering is an important first step in the modelling of biological regulatory networks. In general, in this first step, even though microarray data is available, there is no mechanistic understanding of the regulatory processes that are triggered by a certain stimulus.

Working in collaboration with my colleagues from the CRAB lab, in particular Gunnar Tufte, I proposed a method for the reverse engineering of regulatory networks based on the Artificial Development technique. This method was investigated through *in-silico* reverse engineering experiments of the yeast cell-cycle network [li04]. Results show that the method that we refer to

as 'Artificial Development reverse engineering method' could successfully infer the network. Details about this method are presented in [santini08].

In-silico experiments applying this 'Artificial Development reverse engineering method' to the gastrin regulatory system have also been conducted. The binary time series data of a few classes of genes, in two different initial conditions, has been provided by the GSB group for this experiment. The aim of conducting the *in-silico* experiments was firstly, to investigate if the reverse engineering method would be able to determine, based only on the two given time series data, the network behind the biological regulation; and secondly, to compare the network found with the literature [amit07]. Results show that the method proposed can find the network and that the network found is indeed similar to the one proposed in the literature. Future work would include validation of the abstraction method applied to the biological time series data and further *in-silico* experiments considering more genes in the regulatory network.

[bray03] Dennis Bray. Molecular Networks: The Top-Down View. Science 301, 1864 (2003).
[palsson06] Bernhard O. Palsson. Systems Biology: Properties of Reconstructed Networks. Cambridge University Press, 2006.
[fisher07] Jasmin Fisher and Thomas A Henzinger. Executable cell biology. Nature Biotechnology, 25(11):1239–1249, 2007.
[kauffman69] S. A. Kauffman, "Metabolic stability and epigenesis in randomlyconstructed nets," Journal of Theoretical Biology, vol. 22, pp. 437–467, 1969.
[huang00] S. Huang and D. E. Ingber, "Shape-dependent control of cell growth, differentiation, and apoptosis: Switching between attractors in cell regulatory networks," Experimental Cell Research, vol. 261, pp. 91–103, 2000.
[li04] F. Li, T. Long, Y. Lu, Q. Ouyang, and C. Tang, "The yeast cell-cycle network is robustly designed," PNAS, vol. 101, no. 14, pp. 4781–4786, 2004.
[helikar08] T. Helikar, J. Konvalina, J. Heidel, and J. A. Rogers, "Emergent decision-making in biological signal transduction networks," PNAS, vol. 105, no. 6, pp. 1913–1918, 2008.
[santini08] Cristina Costa Santini, Gunnar Tufte and Pauline Haddow. Bio-inspired Reverse Engineering of Regulatory Networks. Submitted to 2009 IEEE Congress on Evolutionary Computation.
[amit07] Amit et. al. A module of negative feedback regulators defines growth factor signaling. Nature Genetics, 39, 503-512, 2007.

II- Publication(s) during your fellowship

Bio-inspired Reverse Engineering of Regulatory Networks
Cristina Costa Santini, Gunnar Tufte and Pauline Haddow

Regulatory networks are complex networks. In this paper the challenge of modelling these complex networks is addressed. A modelling architecture based on bio-inspired techniques applied to the search for Boolean network representations of sought regulatory networks is presented. Two bio-inspired techniques are investigated when applied to the reverse engineering of a Boolean network model: a Genetic Algorithm and an indirect reverse engineering method. The latter is proposed as a means of addressing the challenge of modelling large and complex networks.

Submitted to 2009 IEEE Congress on Evolutionary Computation (IEEE CEC 2009)
http://www.cec-2009.org/

III -Attended Seminars, Workshops, and Conferences

Biological Complexity: From Molecules to Systems
Thursday June 12, 2008 - Friday June 13, 2008
University College London

ICSB-2008
The 9th International Conference on Systems Biology
Dates: August 22-28
(Tutorials: 22-23, Conference: 23-27, Workshops: 27 & 28)
Venue: Göteborg Convention Centre

IV – Research Exchange Programme (12 month scheme)

Prof. de Jong's group at INRIA Rhône-Alpes
(http://www-helix.inrialpes.fr/article165.html)
September 29 - October 1.

Prof. Hidde de Jong's group is well known for their work in the modelling of genetic regulatory networks. During the visit, which was very well organized and therefore very profitable, I had the opportunity to first present my work in this project, then to talk to many members of his group about their specific roles on their current interdisciplinary aim of modelling the *E. coli*. It was very interesting to see their research structure. Specifically, I had a long very interesting meeting with Delphine Ropers. She told me about the research both behind and beyond the model building and simulation of the carbon starvation response of the E. coli. She pointed out the biological details that I would otherwise have missed and the interdisciplinary aspects of the research.

Prof. de Jong gave me several suggestions on how to tackle different issues on the project I am working on. He pointed out, for example, what are, in his view, the limitations of the chosen representation, BNs. That made me confirm if BNs would indeed be a suitable representation for the gastrin regulatory system as well, i.e. not only for the proof of principle model of the yeast cell-cycle network.