ERCIM "Alain Bensoussan" Fellowship Scientific Report

Fellow: De Maria Elisabetta
Scientific coordinator: Fages François
Visited Location: INRIA Paris-Rocquencourt, France
Duration of Visit: April 15, 2009 – April 14, 2010

I - Scientific activity

During my stay at INRIA I focused on a challenging issue for Systems Biology, that is, coupling models of biological processes. Coupling biological models is necessary to study how they interact together and to make predictions on the global behavior of the system under particular conditions. Model coupling is also a method to better understand and improve the original models. The knowledge acquired from the global view provided by a coupled model can indeed lead to modify the single model components in order to satisfy some observed property of the global system.

I concentrated myself on coupling existing biochemical models of the mammalian cell cycle, the circadian clock, the p53/Mdm2 DNA-damage repair system, and the irinotecan metabolism. Irinotecan is an anti-carcinogenic inhibitor of topoisomerase-1 which started to be used in clinical treatments approximately twenty years ago. It shows significant efficacy against a variety of solid tumors, including lung, colorectal, and cervical cancers. Scientists are currently trying to optimize the irinotecan therapy in order to understand how to limit its toxicity on healthy cells and to increase its efficacy. In this context, it is crucial to comprehend how the administration of this medicament influences cellular proliferation. For this purpose, the observed effects of the circadian rhythm on the toxicity and efficacy of anti-tumor drugs should be taken into account. In fact, the effectiveness of anti-cancer drugs on a healthy as well as tumorous cells is dependent on the phase of the cell cycle in which those cell lie.

Under the hypothesis that the cell cycle in healthy tissues is mainly entrained by the circadian clock, it is possible to reduce the toxicity on healthy cells by injecting antitumor drugs in precise periods of the circadian clock. There are in the literature many models of the mammalian cell cycle and of the circadian biochemical clock, a few ones of the cell's DNA-damage repair network, and recently some preliminary models of irinotecan intracellular pharmacodynamics. I considered a detailed model of the mammalian cell cycle proposed by Novàk and Tyson in 2004 and extended by Zàmborszky et al.in 2007, a detailed model of the circadian clock introduced by Leloup and Goldbeter in 2003, a model of the p53/Mdm2 DNA-damage repair system proposed by Ciliberto et al. in 2005, and a pharmacokinetics/pharmacodinamics model of irinotecan developed by Ballesta in 2009. After encoding these models in the rule-based language of the biochemical abstract machine BIOCHAM, which is similar to (and compatible with) the Systems Biology Markup Language, I incorporated some experimental data to them. To assemble the four models together, I inserted some linking rules coming from literature and I exploited a parameter learning procedure to find parameter values for the new kinetic rules so that some expected properties are verified by the resulting model. It is the same technique used to incorporate experimental data to the models; it is an original technique based on temporal logic

constraints and non linear optimization and it is available in BIOCHAM. I took advantage of such a technique also to optimize parameters relative to irinotecan control laws, detecting in such a way optimal injection times and doses.
To further validate the coupled model, I studied the influence of some circadian clock genes knock outs on the phenotype of the cell cycle, obtaining results qualitatively in accordance with literature.

II- Publication(s) during the fellowship

E. De Maria, F. Fages, and S. Soliman.
On Coupling Models using Model-Checking: Effects of Irinotecan Injections on the Mammalian Cell Cycle.
In Proceedings of CMSB 2009: 6th International Conference on Computational Methods in Systems Biology, LNBI 5688, Springer-Verlag, Bologna, Italy, August-September 2009, pp. 142-157.

Abstract: In systems biology, the number of models of cellular processes increases rapidly, but re-using models in different contexts or for different questions remains a challenging issue. In this paper, we show how the validation of a coupled model and the optimization of its parameters with respect to biological properties formalized in temporal logics, can be done automatically by model-checking. More specifically, we illustrate this approach with the coupling of existing models of the mammalian cell cycle, the p53-based DNA-damage repair network, and irinotecan metabolism, with respect to the biological properties of this anticancer drug.

Furthermore, we have been invited to submit an extended version of the paper to the special issue of the Journal of Theoretical Computer Science C devoted to selected papers from CMSB 2009. We submitted the paper on November 23rd, 2009.

III -Attended Seminars, Workshops, and Conferences

August 31st -September 1st , 2009: "6th International Conference on Computational Methods in Systems Biology" (CMSB 2009), Bologna, Italy.

September 21st , 2009: Meeting of "National contract ANR BioSys Calamar", Paris, France.

November 19th –20th , 2009: Final meeting of "EU FP6 Strep Tempo", Paris, France.

IV – Research Exchange Programme (12 month scheme)

First Exchange institute: Centrum Wiskunde & Informatica (*CWI), Amsterdam, The Netherlands*
Exchange dates: June 7-14, 2009
Research contact: Joke Blom

During this week I was introduced to most of the members of the research group "Life Sciences", an interdisciplinary team of computer scientists, mathematicians and theoretical biologists developing algorithms, theory, and models, and performing simulations for a wide range of biological topics, with a strong focus on systems biology. In particular, I had the opportunity to have profitable talks with several researchers belonging to the subgroups "Scientific Computing for System Biology" and "Algorithmic Computational Biology". As for the first group, headed by Joke Blom (my scientific coordinator), it focuses on multiscale modelling, analytical and numerical topics (diffusion-reaction systems at the macroscopic and mesoscopic level, hybrid ODE/PDF systems), and parameter estimation (parameter identification, model discrimination and optimal experimental design). As for the second group, headed by Gunnar Klau, it addresses the problems of comparing and aligning proteins, RNA molecules, and biological networks as well as integrating high-throughput data and network topology in the context of cancer research. Several conversations with Ph.D. students, post Doc fellows and researchers allowed me not only to understand the issues they study, but also to have an insight on the methodologies they exploit to solve them. Furthermore, Joke Blom explained me how research is organized at CWI, what a good researcher is expected to do, etc.
At midweek I gave a one-hour-talk in the weekly seminar that the Life Sciences group at CWI organizes in cooperation with the Netherlands Institute of System Biology (NISB). The seminar is devoted to any aspects at the interface of mathematics or computer science and the life sciences. During my talk I described my past and present researches and I got from the audience many helpful suggestions concerning the development of my work and some contacts of renowned European research groups dealing with the same topics I do. The day after my talk I discussed with Jan van Schuppen, a CWI researcher who is currently involved in a European project that aims at analizing genetic regulatory networks through piecewise-affine hybrid systems. In order to detect several properties of these systems, such as the presence of steady states or cycles, model checking technicques are adopted.

Second Exchange institute: Fraunhofer Institute for Algorithms and Scientific Computing SCAI, Sankt Augustin, Germany
Exchange dates: September 13-19, 2009
Research contact: Martin Hofmann-Apitius

During my stay at SCAI I visited the Department of Bioinformatics headed by Martin Hofmann-Apitius. I had the oppotunity to have profitable discussions with Erfan Younesi, a PhD student who works on disease modelling approaches in the area of human neuro-dementia. We mutually benefited from our expertises (Erfan´s being more on the biology side; mines being more on the modelling side). On the one hand, I suggested him the use of some tools that allow to model a biological network in terms of a cellular automaton for subsequent applications of principles of Ising models; on the other hand, he transmitted to me some important knowledge relative to the relation among genes, mRNAs, and proteins.
At the end of the week I was invited to give a 25 minutes talk in the weekly seminar organized by the department of Bioinformatics. In this context I presented my researches relative to the influence of an anticancerogenic drug on the mammalian cell cycle, getting from some biologists some positive feedback about the usefulness of my approach in studying metabolic pathways.