Guest Editors’ Introduction to the Special Section on Computational Methods in Systems Biology

François Fages and Sylvain Soliman

This special section contains the extended versions of a selection of papers presented at the Ninth International Conference on Computational Methods in Systems Biology, CMSB 2011, held in cooperation with the ACM SIG Bioinformatics, at Institut Henri Poincaré, Paris, France, on 21-23 September 2011.

CMSB is an annual series of conferences, initiated in 2003, on the design of computational methods for modeling and analyzing biological systems, networks, data, and on their applications to study cases. The conference brings together computer scientists, biologists, mathematicians, engineers, and physicists interested in a system-level understanding of biological processes, their control by experimental or therapeutic means, or even their design or optimization by synthetic biology means.

This selection of CMSB 2011 is composed of eight papers that will be published in two parts in two TCBB issues. The first part, published in this issue, contains five papers.

One central challenge in systems biology is model calibration, i.e., the fitting of models to data and the inference of parameters that cannot be measured. “Evaluation of Design Strategies for Time Course Experiments in Genetic Networks: Case Study of the XlnR Regulon in Aspergillus niger” by Jimmy Omony, Astrid R. Mach-Aigner, Leo H. de Graaff, Gerrit van Straten, and Anton J.B. van Boxtel considers the design of experiments that maximize the information contained in mRNA time courses for the construction of genetic networks. This article presents, through a study of the XlnR regulon in Aspergillus niger, the use of parameter sensitivity analysis, Fisher Information Matrix, and the E-modified criterion to optimize experimental design. This study case shows that a second inducer impulse, instead of a single impulse, just before the disappearance of the first impulse, optimizes the estimation of the kinetic parameters. This paper received the best student paper award at CMSB 2011.

“The Phosphorylation of the Heat Shock Factor as a Modulator for the Heat Shock Response” by Eugen Czeizler, Vladimir Rogojin, and Ion Petre studies the phosphorylation-mediated transcription of heat-shock proteins, which are responsible for chaperoning protein refolding after a prolonged elevated heat in eukaryotes. This paper presents several mechanistic models obtained by refinement, all based on ordinary differential equations, and investigates three alternative phosphorylation mechanisms for the regulation of heat shock factors. Only the models based on the third mechanism, either detailed or reduced, could be fitted to experimental data, thereby providing novel insights on this well-studied biological pathway. This paper received the best paper award at CMSB 2011.

Parameterization is also crucial for logical models of gene regulatory networks. “Time Series Dependent Analysis of Unparametrized Thomas Networks” by Hannes Klärner, Heike Siebert, and Alexander Bockmayr presents a constraint-based method to compute parameter pools that reproduce time series in Thomas’s genetic regulatory networks. The presented method combines graph constraints, monotonicity constraints, and Computation Tree Logic model-checking to efficiently delineate the parameter sets that are consistent with experimental data. This approach is illustrated with time series from experimental data on the IRMA network inserted in yeast in several synthetic biology experiments.

“A Hybrid Factored Frontier Algorithm for Dynamic Bayesian Networks with a Biopathways Application” by Suchenendra K. Palaniappan, S. Akshay, Bing Liu, Blaise Genest, and P.S. Thiagarajan considers the modeling of biopathways with dynamic Bayesian networks, and presents an approximate algorithm, HFF, to compute the probability distribution of states at given time points by maintaining, and propagating, a few states in full dimension in addition to abstract states in reduced dimension. The paper provides theoretical results for bounding the error made and a practical evaluation on the EGF-NGF pathway comparing this new approach to the existing approximation algorithms, Factored Frontier, from which HFF is an evolution, and Boyen-Koller.

Another key challenge in systems biology is the handling of multiscale spatial models. “Multilevel Computational Modeling and Quantitative Analysis of Bone Remodeling” by Nicola Paolotti, Pietro Lio, Emanuela Merelli, and Marco Viceconti illustrates the use of a spatial process algebra and a stochastic agent-based simulator to investigate the effects of the Rank/Rankl/OPG signaling pathway at the molecular level in bone remodeling and osteoporosis at the tissue level. This model shows that small dynamic concentration defects in Rankl can result in large structural bone defects.

As guest editors of this special section, we would like to take the opportunity to thank the reviewers, who did a very good job in improving the quality of the papers by their constructive criticisms and kept publishing delays short. We would like also to thank the sponsors of CMSB 2011, who helped make this kind of event possible.

Francisco Fages
Sylvain Soliman

Guest Editors
François Fages received the PhD degree in computational logic in 1983 from the University Pierre and Marie Curie UPMC of Paris, and the habilitation degree in automated deduction from the University Denis Diderot of Paris in 1992. From 1983 to 1999, he held a research position at CNRS at the Ecole Normale Supérieure, ENS Paris, with a part-time associate professorship position at the Ecole Polytechnique from 1985 to 1996, and consultancy at Thomson CSF (now Thales) company from 1985 to 1998. Since 1999, he has been a senior research scientist at Inria Paris-Rocquencourt, where he leads the Contraintes group. His main activity is in the design and application of formal methods in systems biology and constraint-based methods in combinatorial optimization.

Sylvain Soliman received the PhD degree in computer science in 2001 from the University Paris Diderot after graduating from the Ecole Polytechnique in 1996. He worked for one and a half years for a DGA (French DoD) laboratory and was hired as a junior researcher at Inria in 2003, and promoted in 2005. He is responsible for the constraint programming course at Master Parisien de Recherche en Informatique, and is the former secretary of the ERCIM Working Group on Constraints. His research topics include bioinformatics, formal semantics of constraint programming languages, model-checking, and ODE-based biological modeling.

For more information on this or any other computing topic, please visit our Digital Library at www.computer.org/publications/dlib.