SAgE Singapore Scholarships

Newcastle University

Model-based design in synthetic biology, linking continuous differential equations with discrete logical network dynamics

Computing Science
School of Computing Science, Newcastle University
School of Computer Engineering, NTU, Singapore

Supervisory Team	• **Dr. Jason Steggles: http://tinyurl.com/hyu69u8 http://www.ncl.ac.uk/computing/people/profile/jason.steggles** • **Professor Anil Wipat: http://tinyurl.com/ppqsl35** • **Dr. Goksel Misirli: http://homepages.cs.ncl.ac.uk/goksel.misirli/** • **Assistant Professor Jie Zheng, School of Computer Engineering, NTU: http://www.ntu.edu.sg/home/zhengjie** • **Assistant Professor Chueh Loo Poh, School of Chemical and Biomedical Engineering, NTU:http://www3.ntu.edu.sg/home/clpoh/** • **The Lead Supervisor is Early Career or newly hired Staff** ☐
Key Words	**Mathematical modelling, synthetic biology, differential equations, logical modelling, network dynamics**

Overview

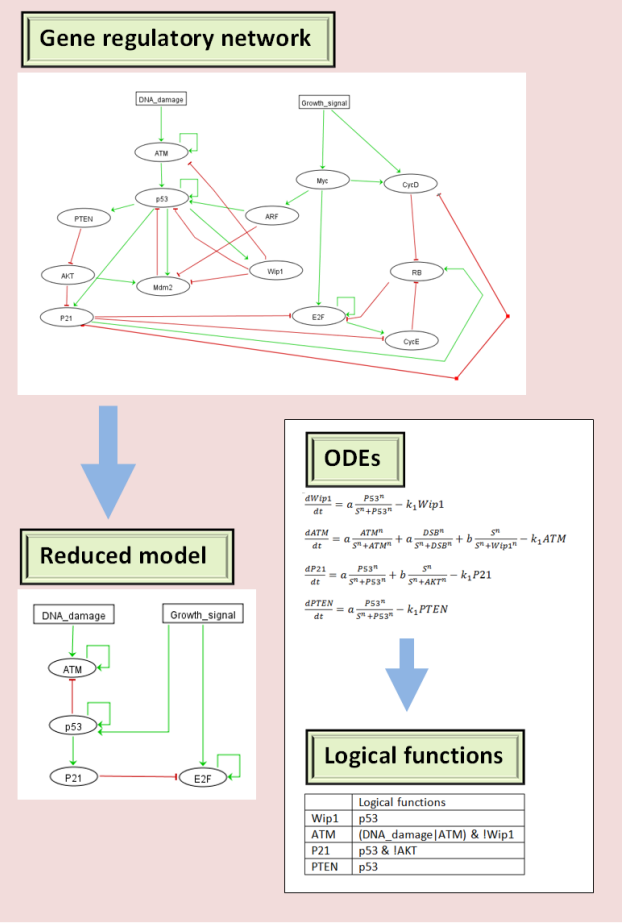
Computational cell modelling has been successfully used to study the complexity of biological networks that consist of multiple feedback regulations[1]. Particularly, the use of continuous differential equations as a well-established method to formulate the molecular interactions in biological networks is crucial for building quantitative models. However, the use of differential equations often involves many unknown biochemical mechanisms and parameters that have to be estimated, and is hard to scale to large networks. In order to overcome the issues of parameter values and lack of scalability, qualitative and logical modelling (such as Boolean networks) has been increasingly used to model large biological networks[2].

Both differential equations and logical modelling play important roles in understanding a cell's molecular systems[3]. A few studies have linked the continuous differential equations with discrete logical models[4,5]. Recently, logical modelling with model reduction has been shown to be a powerful technique for studying large networks[6]. This project aims to conduct a study to use logical (Boolean or multilevel) network or extended logical model (e.g. Fuzzy logic) to scale the dynamic modelling of ODEs to relatively large regulatory networks (say, of size > 100 genes). The aim of the project is to research less granular approaches to simulation and model-based design in synthetic biology[7] and will investigate the use of modular, composable, qualitative Boolean models. The system will be tested in the model-based design and construction of regulatory networks in *Escherichia coli* and *Bacillus subtilis*.

Methodology

Designing large/complex biological systems requires *in silico* modelling to guide more predictive design. Traditional dynamic modelling based on differential equations requires the details for the design specification and does not scale well for large systems. Hence, we need an intermediate form of modelling that is able to capture the required dynamic/functional behaviour but is more abstract and therefore more scalable. The methods used in this project will involve non-linear ordinary differential equations and logical (Boolean or multilevel) modelling. Existing computer software for ODE modelling (e.g. XPPAUT, CellDesigner) and logical modelling software (e.g.

GINsim) will be used. In qualitative Boolean models, molecular interactions (activation or inhibition) are represented as logical functions and implemented with two types of updating schemes: synchronous and asynchronous. The synchronous mode assumes that all processes happen at the same time and asynchronous update assumes that processes happen at different times. State transition graphs will be used to visualize the activities of gene expression and signaling pathways. The recent technique of model reduction[6,8] in asynchronous update will be used to map the large biological system to a reduced model that still contains the essential dynamics of the system such as stable states and conserved attractors. Furthermore, high-performance computing software (e.g. cloud computing, GPGPU) suitable for application to systems and synthetic biology, as well as biomedicine, will be developed. Synthetic biology



requires the design and composition of models from parts and so theories for composing logical models will be investigated and developed to provide a basis for model construction and analysis.

Timeline

1st Year: Literature review of mathematical modelling of cell and synthetic biology in continuous differential equations and discrete logical modelling methods. Technical background or knowledge in computational cell modelling and dynamical system theory. Project plan. 2nd Year: Construct the method/software for logical modelling in synthetic biology. Mathematical models developed. Model composition explored. Construct and test the synthetic regulatory networks 3rd Year: Documentation and testing of the method/software or models. Conference paper written. Model analysis and interpretation of the results. 4th Year: Thesis preparation and writing scientific publications. Journal paper produced.

Training & Skills

The student will receive training in computational and mathematical modelling, model analysis and interpretation in a biological context. Training in conceptual model construction or computational cell biology and molecular biology will also be provided. The Ph.D. project will primarily be based at School of Computing Science, Newcastle University where computational and experimental work will be carried out. The student will attend regular ICOS and ASL meetings. Research will be communicated in research seminars at the both Universities and at international conferences. Dr. Zheng and Dr. Poh (NTU) will provide additional complementary training in Boolean and advanced biological systems modelling. The student will be supported to travel to Singapore for about a year as part of the exchange program, and thereby gain international experience of learning and living. Through this project, the student will become an independent researcher in solving problems and perform interdisciplinary research.

References & Further Reading

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Further Information

Professor Anil Wipat: anil.wipat@ncl.ac.uk
Assistant Professor Jie Zheng: ZhengJie@ntu.edu.sg