Advance development of techniques for modelling, validation and analysis of biological systems in synthetic biology

1. Introduction

State of the art computational approaches in synthetic biology are based on the establishment of various computational and mathematical models that are able to mimic the behaviour of arbitrary biological systems in a specific environment. These models can be *reverse engineered* from existing biological systems using experimentally measured data, which is also called *network inference* (*top-down* approach), or they can be constructed using already known *biological modelling primitives* (*bottom-up* approach). Top-down modelling approaches are used to better understand underlying dynamics of biological systems and enable us to apply this newly obtained knowledge as potential modification to their behaviour. On the other hand, bottom-up approaches are used to model novel biological systems allowing us to optimize their *in-vivo* implementation and therefore significantly reducing costs and time of the experimental work. In this project we aim to develop new and improve existing techniques for modelling, parameter estimation, model validation and analysis of biological systems in synthetic biology.

2. Methods

- Modelling techniques:

  Established models serve as an insight into the behaviour of observed biological system. Based on the desired accuracy of behaviour description we can use different modelling techniques. These can be exploited to analyse and deduct behavioral properties which cannot be obtained experimentally. Moreover, we can use them to observe changes in behaviour when we apply modifications to the model of the original biological system. The aim of our work is to develop novel modelling approaches which will be able to overcome the problems of the existing methodologies. We intend to improve current methods by decreasing computational complexity with the aim of the *multi-scale* modelling and apply various *fuzzy logic* approaches as a possible solution to the problem of unknown parameter values. These enhanced

techniques will improve the usage of modelling biological systems for experimental validation.

- Parameter estimation

  Modelling accuracy is tightly related to accuracy of parameter values defining the dynamic and behavioural properties of observed biological system. While these parameters are often very hard or even impossible to determine accurately with laboratory experiments, several parameter estimation methods can be used. Additionally, some parameter estimation methods are used to build a model of a biological system, which exhibits a desired behaviour. Part of our work will focus on estimating parameter values from experimental data. In addition, we also intend to use the desired behaviour of a biological system as an input to the model, which will determine the needed parameters values in order to achieve that predefined behaviour.

- Metrics and compatibilities

  When comparing different modelling approaches or when validating simulation results with experimental data, certain *evaluation metrics* need to be established. We will use already established metrics as well as define new evaluation techniques, in order to prove reliability and satisfiability of the designed systems. By using our methods, we will be able to quantitatively compare modelling and experimental results. In addition, our methods will allow testing for compatibility among different biological primitives in order to improve *automatic construction* of more complex systems.

- Stability, robustness and sensitivity analysis

  In addition to biological systems' initial behavioural properties, we are usually interested in how much the environmental changes may affect the behavior of the system, specifically the response of slightly disturbs from its steady states or modifications of any parameter values which govern its dynamics. We use different *stability*, *robustness* and *sensitivity* analyses to test the model of observed biological system in order to obtain any quantitative data as a metric of reliability and robustness.

3. Relevance and benefits of the project results

- Standardization of modelling, validation and analysis methods as a service to synthetic biology

  We strive to combine existing and newly developed methods for modelling, validation and analysis into an *easy-to-use package*, which will be publicly available as computational service for the needs of life sciences. The first step towards building the concept of *Computational Biology as a Service (CBaaS)* is to connect different sciences to form a project group that will be able to establish state of the art computational approaches and tailor them to the needs of life sciences. CBaaS package could be used as a standard for developing new computational methods as well as a tool for life sciences that require computational support for smoother experimental work.

- Using computational techniques and analysis to decrease time and costs of experimental work

  The aim of proposed project is to enhance the development of novel computational methods in the field of synthetic biology with partners, which will be able to perform the verification of the proposed methods with their experimental work. Developed methods will on the other hand be applied to *in silico* design of novel biological system with the purpose of guiding their experimental work. As a result of the project, developed methods would be offered to other consortia members as a CBaaS to use them freely in their on-going projects. We expect to embed the developed methods in a freely available web-based computational tool which would be easy to use and designated for the ERASynBio projects as well as non-ERASynBio project once CBaaS will be established. As a result of this ERASynBio project, the field of synthetic biology would therefore have a standardized complete-computational platform for on-going and future projects.

Contact information:

Head of group: prof. Miha Mraz, miha.mraz@fri.uni-lj.si
Computational Biology Group
Faculty of Computer and Information Science
University of Ljubljana
http://lrss.fri.uni-lj.si/bio/index.html