Making Systems Biology Work: Roadmap to Multiscale Predictive Modeling

Thierry Mondeel[1] Hans V. Westerhoff[1,2,3] Matteo Barberis[1]

[1]Synthetic Systems Biology Group, The Swammerdam Institute for Life Sciences, University of Amsterdam, The Netherlands

[2]VU University Amsterdam, The Netherlands, [3]The University of Manchester, United Kingdom

Objectives

Making systems biology work through multiscale integration of regulatory layers

- Uncover design principles of the minimal regulatory network of the Budding yeast cell cycle
- Incorporate interacting modules of metabolism into the cell cycle model
- Link such models to metabolic maps and be able to deduce dynamic consequences of individual impairments
- Translate the design principles of yeast to the mammalian cell cycle

Introduction

A current challenge in systems biology is the need for multiscale models covering a broad range of biological functions and scales. This requires the integration of the hierarchical layers of regulation and control present in the cell.

This project aims to increase our understanding of bodily function in terms of *dynamically* interacting *modules* in space and time (see Figure 1).

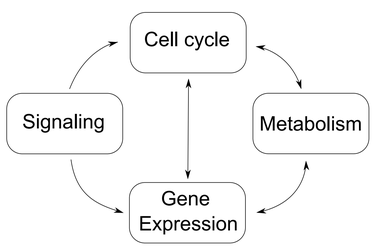

Figure 1: Schematic of interacting modules of metabolism, signal transduction, gene expression and the cell cycle.

Design Principles of the Cell Cycle Module

Our aim will be to increase our understanding of the *design principles* of the cell cycle regulatory network. We intend to

- Investigate activator-inhibitor interactions that generate cyclin wave patterns (see Figure 2)
- Uncover *minimal* networks that reproduce the essential properties of the cell cycle
- Generate *autonomous* cell cycle oscillations

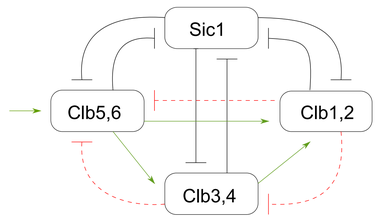

Figure 2: Feed-forward interactions between cyclins (green), inhibition between Sic1 and Cdk1-Clb cyclins (black), APC-mediated feedback inhibition (red). Black and green interactions appear sufficient for cyclin wave formation [2].

The Key Idea

A complete *systems* understanding of the cell requires integrated, multiscale modeling of the hierarchical layers of regulation and control. We aim to design such a multiscale model focused on the cell cycle. We especially intend to incorporate interacting modules of metabolism to be able to link metabolic impairments to dynamic consequences for the cell cycle.

From Metabolic Maps to Individualized Medicine

Using genome-wide metabolic maps [1] we are able to predict individual impairments in phenotype for metabolism of a single cell.

Multiscale integration of metabolism with other modules increases our understanding of the ripple effects that metabolic impairments may have. This paves the way for individualized medicine.

We will specifically focus on:

- The role of feedback between dynamic modules
- How to integrate different modules and modeling formalisms across scales
- The integration of metabolism with the cell cycle module

Overview

This project aims to improve the ways computational systems biology can integrate functions in different areas of biology.

On the one hand, it will connect dynamic modules of metabolic, cell cycle and epigenetic networks to metabolic maps.

On the other hand, it will take genome-wide maps starting from model organisms to individual humans, and calculate possible impairments of each individual. This should provide a basis for individualized medicine.

References

[1] Thiele, et al. "A Community-Driven Global Reconstruction of Human Metabolism" Nature Biotechnology 31, no. 5 (May 2013): 419-25.

[2] Barberis, et al. "Sic1 Plays a Role in Timing and Oscillatory Behaviour of B-Type Cyclins." Biotechnology Advances 30, no. 1 (February 2012): 108-30.

Contact Information

- Email: d.g.a.mondeel@uva.nl

Universiteit van Amsterdam

vrije Universiteit amsterdam

The University of Manchester