ERCIM "Alain Bensoussan"
Fellowship Scientific Report

Fellow:	Manuel Lopes
Visited Location:	VTT – Espoo, Finland
Duration of Visit:	6 months

I - Scientific activity
(1 page at maximum)

Introduction/Goals

Understand the function of coactivators in the regulation of metabolism.
Several techniques were studied to model this system:

Metabolic control analysis (MCA) is a computational method for analyzing variation in fluxes and intermediate concentrations in a metabolic pathway. It allows relating the effects of the different enzymes that constitute the pathway. Several insights into metabolism were possible due to MCA studies, e.g. the non-existence of rate-limiting enzymes, at least generally, the reduced effect of enzymes in near-equilibrium reactions or the control properties of specific types of network.

Metabolic engineering aims to optimize genetic and regulatory processes within cells to increase the production of a certain substance. The first step is to analyze the metabolic pathway to identify if the desired changes are possible or not, and then the second step is to determine how can those changes be accomplished.

Results

We have seen which changes should be made in a metabolic pathway to have a desired change in flux or concentration, while simultaneously maintaining other system state variables constant. With knowledge of the elasticities of the system the proposed method gives directly the solution for the problem. We also defined simple algebraic conditions that give information about the controllability properties of the system.
Although the simulations where done with reversible Michaelis-Menten equations, our method is not restricted to these specific reactions types making our method more general than others.
Our method, similarly to the ones proposed by others, needs information around a steady-state and the computed parameter are only valid for small changes. On the contrary, the controllability test is valid in a larger sub-space of the parameter space. It becomes invalid when there are changes in the degrees of freedom of the system, this can happen when enzymes saturate or a reaction reaches equilibrium.
The simulations were inspired from the effect PGC−1α and PGC − 1β have in the regulation of glucose and fatty-acids regulation. As no data was provided only simulations were made without biologically grounded value. We saw that they have an overlapping and multi-functional effect in all the regulation, as already discussed by several authors.

Some of the insight brought from the presented simulation can already be applied to this regulation mechanism. Although PGC − 1α also regulates fatty-acids oxidation, its effect is not as complete as PGC − 1β and so we have to expect side-effects in the metabolic pathway due to the substitution of PGC − 1β by PGC − 1α.

II- Publication(s) during your fellowship

Controllability of metabolic pathways – coactivators and MCA, Manuel Lopes, unsubmitted report.

III -Attended Seminars, Workshops, and Conferences

Conferences :

- 25th International Specialised Symposium on Yeasts, ISSY25, June 18-21, Espoo, Finland
- IEEE/RSJ International Conference on Intelligent Robots and Systems, Oct 9-15, Beijing, China

Seminars :

- A talk on bayesian approach to metabolomics data analysis, Aki Vehtari
- Systems Biology Approach to Multivariate Modeling of Biological Systems , Sampsa Hautaniemi
- Metabolic control theory, Marta Cascante
- Modeling and Simulation to support early clinical development design and decision making, Roland Fisch
- Phylogenetic Reconstruction from Non-Genomic Data, Gabriel Valiente