Identification of cell signaling pathways based on biochemical reaction kinetics repositories

Gustavo Estrela de Matos

Dissertation presented
to
Institute of Mathematics and Statistics
of the
University of São Paulo
For
The Degree Of Master Of Science

Field of knowledge: Computer Science

Advisor: Dr. Marcelo da Silva Reis

Center of Toxins, Immune-Response and Cell Signaling (CeTICS)

Special Laboratory of Cell Cycle, Butantan Institute

During the development of this work the author received financial support of FAPESP.

São Paulo, March 4, 2019

Abstract

Cell signaling pathways are composed of a set of biochemical reactions that are associated with signal transmission within the cell and its surroundings. Traditionally, these pathways are identified through statistical analyses on results from biological assays, in which involved chemical species are quantified. However, once generally it is measured only a few time points for a fraction of the chemical species, to effectively tackle this problem it is required to design and simulate functional dynamic models. Recently, it was introduced a method to design functional models, which is based on systematic modifications of an initial model through the inclusion of biochemical reactions, which in turn were obtained from the interactome repository KEGG. Nevertheless, this method presents some shortcomings that impair the estimated model; among them are the incompleteness of the information extracted from KEGG, the absence of rate constants, the usage of sub-optimal search algorithms and an unsatisfactory overfitting penalization. In this project, we propose a new methodology for identification of cell signaling pathways, which will make use of a myriad of public interactome and biochemical reaction kinetics repositories to deal with the incompleteness of a priori information. Moreover, we will use optimal algorithms for model selection, as well as more effective cost functions for overfitting penalization. The new methodology will be tested on artificial instances and also on cell signaling pathways identification in our case study, the Y1 mouse adrenocortical tumor cell line. (AU)

Contents

Chapter 1

Introduction

Cell Signaling pathways are cascades of chemical interactions that allow the communication between the cell environment and the cell itself. These pathways also are able to regulate many cell functions, including DNA replication, cell division and cell death. We can observe the functioning of signaling pathways as a mechanism that can conform the cell behaviour with signals that come from the environment conditions in which the cell is placed. The studies of cell signaling pathways can lead to determining how cells can respond to different stimulus; for instance, with the studies of signaling pathways activated by a chemical species, one could determine how an unhealthy cell would respond to a drug containing this species.

It's possible to construct mathematical models to represent a set of chemical reactions and consequently a signaling network. One approach on the modeling of those interactions is based on the law of mass action. This law proposes that the rate of a chemical reaction is proportional to the product of reactants concentrations, i.e we can calculate the concentration change rate of a species in an interaction by calculating the product of reactants concentrations up to a multiplying constant. If we consider the set of interactions of a signaling pathway, we can then come up with a system of ordinary differential equations (ODEs) that can model the dynamics of the concentration of each chemical species from the pathway. Generally, these systems are complex and cumbersome, if not impossible, to be solved analytically, therefore we resort on computational models that apply numerical methods to approximate solutions of these systems.

Chapter 2

Fundamental Concepts

Chapter 3

Conclusion

Bibliography

[Lic13] M. Lichman. *UCI Machine Learning Repository*. 2013. URL: `http://archive.ics.uci.edu/ml`.

[Rei12] M. S. Reis. "Minimization of decomposable in U-shaped curves functions defined on poset chains – algorithms and applications". PhD thesis. University of Sao Paulo, 2012.

[Wu15] Lulu Wu. "Um método para modificar vias de sinalização molecular por meio de análise de banco de dados de interatomas". MA thesis. University of Sao Paulo, 2015.