Identification of cell signaling pathways based on biochemical reaction kinetics repositories

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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)

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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 are also 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 behavior 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 stimuli; 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.

In this work, we are interested in computational models that can reproduce the behavior of signaling networks, comparing experimental measures—generally based on Western blot data—to simulated results. To create these computational models, two main tasks need to be accomplished.

The first task one must complete to create a model is to determine a set of interactions to consider in the ODE system. Looking for pathway maps on the Kyoto Encyclopedia of Genes and Genomes (KEGG) [KG00] is a good start. The KEGG PATHWAY Database provides manually drawn diagrams that represent signaling networks created with experimental evidences. However, it's possible that there's no pathway on KEGG that is able to correctly represent the biological experiment of interest; for those situations, it's necessary to modify the pathway by adding or even removing interactions. One might reason that we should use as many interactions as we can to get a better simulation, however, this usually implies in poor or computationally infeasible models because of two reasons: first, complex models will require more time in the numerical solution computation, which may be infeasible due to limited computational resources; and second, when considering many interactions, we are also placing many parameters (multiplying constants of the differential equations) on the model, and finding appropriate values for them becomes harder as we increase the number of parameters.

The second task to create a model is to find values for all the system parameters. There are two approaches for this task, you can either fetch values for these constants from the literature or you can find values that makes the model output approximate the experimental observations. For the first approach, repositories such as BioModels [**biomodelos**] can be used; for the second approach, statistical and optimization methods could be used. For optimization, it is necessary to define a metric that can evaluate how close the parameters brings the model output to the experimental observation so that you can search for the optimal parameter in the parameter space. Statistical inference, in the other hand, usually tries to maximize some likelihood function, which is defined to represent the probability of a model, with a set of parameter values, to reproduce the experimental observation.

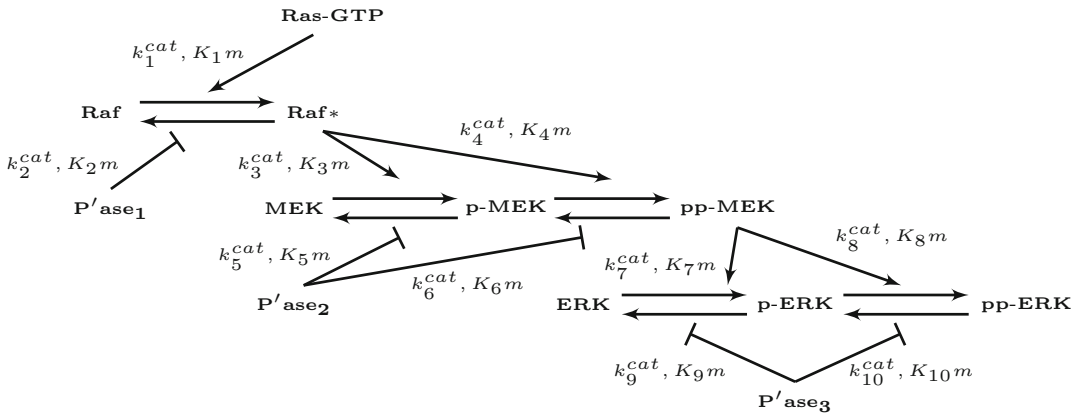

Figure 1.1: The above diagram show a hypothesis for a signaling pathway that flows through Raf-MEK-ERK cascade. Names in bold represent chemical species. Horizontal arrows represent phosphorilation when directed from left to right or dephosphorilation when directed in the opposite direction. Other arrows represent positive feedback if they are directed downwards or negative feedback otherwise. Names in italic represent parameters of the ordinary differential equation of each interaction.

Chapter 2

Fundamental Concepts

Chapter 3

Conclusion

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