Title :

Design and analysis of dynamical models of biochemical reaction networks

Authors :

Vincent Noel, Marcelo S. Reis, Matheus H.S. Dias, Layra L. Albuquerque, Ricardo Pariona-Llanos, Raphael S. Pavani, Ariel M. Silber, Maria Isabel N. Cano, Maria Carolina Elias, Fabio Nakano, Junior Barrera, and Hugo A. Armelin

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Abstract :

One of the current major challenges in Molecular Cell Biology is to properly analyze the big data yielded by modern high-throughput omics techniques (e.g. genomics, transcriptomics, proteomics). Classical biological intuition and qualitative, static interactome schemes are no longer sufficient to study underlying dynamical biological mechanisms from such huge amount of data. On the other hand, computational approaches are suitable to tackle this and other timely goals of nowadays biological research. Therefore, the objective of this work is the development of SigNetSim, an e-Science framework to assist mathematical modeling and computational analysis of biomolecular signaling network kinetics. This framework will allow the usage of big data and also the traditional low-throughput omics data (e.g. Western blot experiments) into modeling and validation processes.

As a case study, we used the framework to build a model of the competition between NAD+ and DNA's telomeres for binding to GAPDH in Trypanosoma cruzi. Using parameter sensitivity analysis, we showed the limitations of this model, and the need for more experiments to a full validation. We also modeled the Ras/MAPK signaling pathway in mouse Y1 adrenal tumor cell line and showed that [K-Ras-GTP] relatively high steady basal levels, a condition experimentally observed in Y1 cells, are achieved only with the inclusion in the model of SOS and also an additional guanine exchange factor (GEF). To experimentally validate this hypothesis, we probed Y1 cells for expression of additional GEFs by RT-PCR, confirming the expression of two additional GEFs.

The SigNetSim e-Science framework was successfully used to model two different sets of experiments. Presently, we are working on the design of a kinetic model that explains the crosstalk between the Ras/MAPK and

PI3K/Akt signaling pathways in the same cell line. In the mid-term, we intend to use high-throughput quantitative proteomic data in this modeling task, improve the framework to perform assessment of different hypotheses for the model structure, and add more analyses methods.