Modeling Cell Signaling through Concurrent Constraint Programming

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***Short Abstract* — To capture a detailed view of cell signaling, we used an approach based on Concurrent Constraint Programming that allows us to express partial information, concurrency, non-determinism and timed behavior, to model and simulate biochemical reactions networks at the level of transmembrane receptors by considering the interactions between the guanine nucleotide-binding proteins (G-proteins) and G-protein coupled receptors (GPCRs).**

***Keywords* — NTCC, GPCRs, G-proteins, cell signaling, computational and systems biology, formal modeling.**

I. Introduction

Many fundamental biological processes involve the flow of information. The potential for construct new biological knowledge arises from investigating the complex interactions of biological information at different levels of abstraction. In this order, the construction of executable models for describing biological systems as computer programs looks very promising for analyzing the processing of biological information, especially in the context of cell signaling networks. Cells receive external signals through sensing molecules or receptors embedded in the cell membrane. This information is transmitted sequentially throughout the cell via biochemical interactions. In this sense, a concurrent constraint approach for modeling cell signaling is suitable to face these distinctive characteristics of biochemical reactions networks: *(i)* they consist of the species and their interactions, *(ii)* several interactions can usually happen independently and in parallel, *(iii)* the timing behavior of the interactions is governed by stochastic laws, and *(iv)* partial information (incomplete information about the state of the system) arises naturally. We study in a compositional way a transmembrane cell signaling system mediated by the behavior of G-proteins [1-2].

II. Methodology

We represent and simulate a set of interactions between G-Proteins and GPCRs. In order to achieve this, we use the NTCC calculus [3] a non-deterministic temporal extension of Concurrent Constraint Programming (CCP) [4] a declarative model of concurrency closely related to logic for the specification of systems that continuously react with the environment. Following the operational rules of the NTCC calculus, we built an interpreter of NTCC processes on top of the Mozart programming language. In order to make available the tool on Internet, we embedded the NTCC interpreter into BioWays, a PHP based application freely available at [5].

III. Conclusion

Our model focuses on qualitative patterns (supported by quantitative information) of the time evolution of the key components. The integrated viewpoint of our method allows interesting interpretations of the system over three domains of interaction (extracellular, transmembrane and intracelullar) in a range of stimuli (varied simulation modes) that can be explored systematically at different levels of detail. These are governed by the rates of the reactions, a probabilistic execution of them, and the distinct states (and amount) of the molecules.

We have proposed a holistic and integrated view as a first step to capture the collective behavior of the interactions and to gain some insight into how this behavior generates a biological response. A salient feature of our framework for biologists is that they can observe the reaction of the system when parameters are adjusted. The modeler can start from an abstract model and build refinements by adding further details coming from different sources.

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