A MAS for the simulation and analysis of signaling pathways

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1 Introduction

A *signaling pathway* is any biological process that converts one kind of signal or stimulus into another; this convertion is also called *signal transduction*. In general, a signaling pathway results in a composition of biochemical reactions that are carried out by enzymes and linked through second messengers. Biological signal transduction allows a cell or organism to sense its environment and react accordingly. This is achieved through cascades of proteins that interact via activation and inhibition to convert an external signal into a physiological response. Tipically, a signalling pathway has one (or more) input, represented by an environmental stimuli, and one (or more) output, represented by an active protein.

A typical example of signaling pathway is the mitogen-activated protein kinase (MAPK) signaling cascade (Figure 1), which is is responsible for cell response to growth factors.

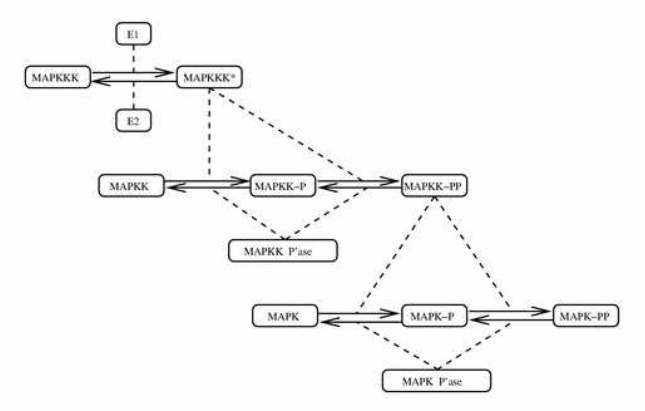

Figure 1: MAPK cascade.

Generally, biological signaling pathway networks are analysed using experimental and theoretical methods to describe specific protein components, interactions, and biochemical processes and to model network behaviour under various conditions (see for example [1, 2, 3, 4]).

2 Multi Agent Systems

Multiagent systems (MASs) have been recognised as a good approach for modelling and simulating complex systems. Recently, several MAS for the modeling, simulation and analysis of complex biological systems have been proposed (see for example [5, 6]). Here we propose a MAS for the simulation and analysis of signaling pathways.

Each entity or element present in a singaling pathway network can be represented and described using the notions of the A&A conceptual framework [8, 7]. In particular, a possible MAS for signaling pathways is the one presented in Tab.1.

proteins	→	agents
proteins domains	→	individual artifacts
protein-protein interactions	→	social artifact
environmental stimuli	→	environmental artifact

Table 1: The MAS.

2.1 Proteins as Agents and Artifacts

A protein is large organic compounds made of amino acids. By abstracting from its tridimensional structure, we can represent a protein as a biological entity composed by a set of *sensing domains* and a set of *effecting domains* (Figure 2). Sensing domains are the places where the protein receives signals, while the effecting domains are the places that a protein uses for propagating signals. Here we refer to protein domais with capital letters (A, B, C, A', A_0,...), but in general they can be represented with any kind of algebraic structure (eg. a string representing the chemical structure of the domain). Each domain can be present in two possible state: hide or unhide. The reception of a signal through a sensing domain can change the structure of a protein (eg. a domain can change its state).

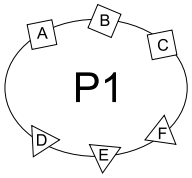

Figure 2: squares represent sensing domains, while triangles represent effecting domains. $P1$ represents the name of the protein species.

In order to represent a protein using the A&A conceptual framework, some general considerations are necessary. A protein can be viewed as a pro-active biological entity; the goal of a protein is to activate or inhibit its target protein(s) through its effecting domains. Moreover, the observable part of a protein is the surface and hence the set of unhide domains.

For these reasons we decided to represent a protein by using the concepts of agent and individual artifact.

The agent codifies for the mechanism that a protein uses for trasforming an input signal in a conformational change; this mechanism is not visible.

The individual artifact contains the observable part of the protein, which for us represent the status of the protein. Moreover, since we want to represent more than one protein for each protein species, the individual artifact contains the status of all the proteins belonging to the same species.

If the individual artifact is implemented using a *tuple centre*, we can imagine to represent the status of a protein with a string containing the list of the names of the unhide domains. For example, the tuple `A,B:E,F` indicates a status where the domains A, B, E and F are unhide. A and B are sensing domain, while E and F are effecting domains. In this case, the representation of a population of 5 proteins of the species $P1$ present in 3 different states is the one reported in Figure 3. The agent inserts and removes tuples in and from the tuple centre with the classical `in`, `out` and `read` operations [9].

An individual artifact is programmed to keep track of the agents requests and to generate the tuples that satisfy such requests. In particular, agents asks for input signals. The behaviour of individual artifacts can be implemented as a set of reactions in ReSpecT language [8].

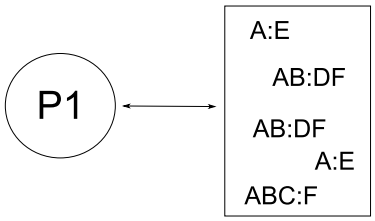

Figure 3: Example of protein represented using an agent and a individual artifact implemented as a tuple centre.

2.2 Protein-Protein interactions as Social Artifact

Social artifacts provide MASs with a service which is meant to achieve a social goal of the MAS, rather than an individual agent goal. Typically, in the domain of signaling pathway networks, the social goal is represented by the activation of one (or more) protein, which is the output of the pathway.

The individual artifacts of all the protein species are connected through a social artifact, which has the task to coordinate the interaction between the proteins. In particular, each individual artifact has to provide the social artifact with the information of the amount of available sensing and effecting domains. As an example, the individual artifact of Figure 3 has to provide to the social artifact the following informations: (a) 4 sensing domains of type A are available; (b) 3 sensing domains of type B are available; (c) 1 sensing domains of type C are available; (d) 2 effecting domains of type D are available; (e) 2 effecting domains of type E are available; (f) 2 effecting domains of type F are available; If we want to use a tuple centre for the implementation of the social artifact,

then we can imagine that this information is represented in the tuple centre with tuples. For example, the availability of 4 sensing domains of type A can be represented by the tuple:

```
P1@(A,<,4)
```

while availabily of 2 effecting domains of type B can be represented with the tuple:

```
P1@(B,>,2)
```

The symbol $<$ indicates that the domain is a sensing domain, while the symbol $>$ indicates that the domain is an effecting domain. Moreover, the substring `P1@` indicate the protein species. In Figure 4 an example that involves two protein species is depicted. In this scenario, we can intuitively imagine that each agent ask its individual artifact for an input signal. This request is reflected by the individual artifact to the social artifact. The individual artifact inserts and removes tuples in and from the social artifact tuple centre with the classical `in`, `out` and `read` operations.

The social artifact represent the cytosol and is programmed to accomplish the following two tasks: (1) it keeps track of the individual artifact requests and generates the tuples that satisfy such requests according to a selection algorithm that determines which protein-protein interactions happens; (2) it updates the protein domains availability.

Notice that several selection algorithms (eg. a stochastic selection algorithm) can be implemented and that different choiches determines different techniques for the coordination of protein interactions. Moreover, since protein interaction depends on the affinity of the domains, we can also think to add to our MAS a database environmental artifact (eg. BioGRID,DIP [1]) that provides the social artifact with the information of the affinity of protein domains; affinity is essential for calculating protein-protein interactions rates.

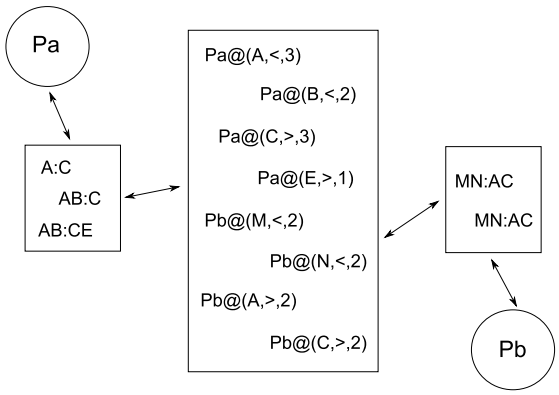

Figure 4: Example of a MAS with 2 protein species.

Also in this case the behaviour of the social artifact can be implemented as a set of reactions in ReSpecT language.

[1] http://www.thebiogrid.org/ - http://dip.doe-mbi.ucla.edu/

2.2.1 A simple example

We assume that the domain of type C is compatible with the domain of type M. Now, suppose that the protein $AB : C$, belonging to the species Pa, can interact with the protein $MN : AC$, belonging to the species Pb, and suppose that this result in a change of the status of $MN : AC$ in $MN : AD$.

The execution of such a reaction in our MAS results in chain of artifact and agents action and reaction that changes the system configuration in the one reported in Figure 5. Notice that in the individual artifact of the protein species Pb one of the tuple $MN : AC$ change in $MN : AD$ and that in the social artifact the tuple $Pb@(C, >, 2)$ change in $Pb@(C, >, 1)$ and the new tuple $Pb@(D, >, 1)$ is introduced.

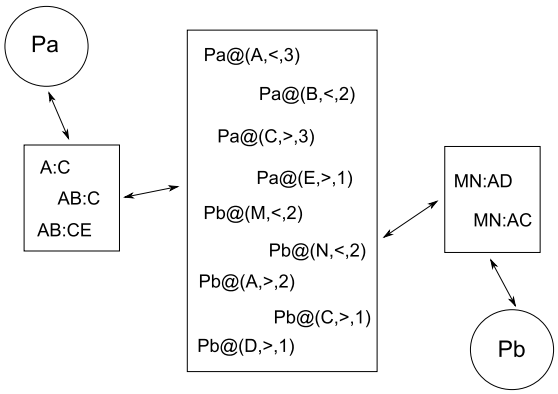

Figure 5: MAS configuration after a protein-protein interaction.

2.3 Environmental stimuli as Environmental artifact

Enviromental stimuli can be simply implmented with an artifact that is programmed for inserting in the system a certain amount of stimuli for protein sensing domains. In particular, the environmental artifact controls the presence of stimuli by inserting or deleting tuples in and from the social artifact. This tuples can have the same format of the other tuples:

```
Env@(A,>,n)
```

A represent the specificity of the stimuli, $>$ means that this is an output (and hence an input for the other proteins) and n represents the number of stimuli of this type. Moreover, the $Env@$ substring indicates that the tuple is related to the environmental artifact. Several different types of stimuli can be inserted and controlled.

The social artifact has to be programmed for managing in the proper way also environmental tuples.

3 Potential

This MAS system can be used for simulating the behaviour of signaling pathway networks. By observing the artifact content we are always able to establish

the current state of the system (eg. we can measure the time evolution of the cardinality of the protein output of the considered pathway). Moreover, the possibility to manipulate the MAS run time (activate and deactivate agents, activate and deactivate environmental stimuli, change the environmental stimuli, modify parameters, etc) could be really interesting in order to perturbate and analyze the behaviour of the signaling pathway networks.

References

[1] Bray, D., Bourret, R.B., et al.: *Computer simulation of the phosphorylation cascade controlling bacterial chemotaxis*. Mol. Biol. Cell 4 (5), 469482. 1993

[2] Morton-Firth, C.J., Bray, D.: *Predicting temporal fluctuations in an intracellular signalling pathway*. J. Theor. Biol. 192 (1), 117128. 1998.

[3] Bhalla, U.S., Iyengar, R.: *Emergent properties of networks of biological signaling pathways*. Science 283 (5400), 381387. 1999.

[4] Shimizu, T.S., Aksenov, S.V., et al.: *A spatially extended stochastic model of the bacterial chemotaxis signalling pathway*. J. Mol. Biol. 329 (2), 291309. 2003.

[5] Montagna, S., Ricci, A., Omicini, A.: *Agents & Artifacts for Systems Biology: Toward a Framework based on TuCSoN*. EUROSIS (The European Simulation Society) & ETI (The European Technology Institute). 2006.

[6] Salim, K., Ravi M., Foster, M., Keith, D., William G., Carl S.: *A multiagent system for the quantitative simulation of biological networks* AAMAS '03: Proceedings of the second international joint conference on Autonomous agents and multiagent systems. 2003.

[7] Omicini, A., and E. Denti. *From tuple spaces to tuple centres*. Science of Computer Programming 41 (3): 277294. 2001.

[8] Omicini, A., A. Ricci, and M. Viroli. *Agens Faber: Toward a theory of artefacts for MAS*. Electronic Notes in Theoretical Computer Sciences. 1st International Workshop Coordination and Organization (CoOrg 2005), COORDINATION 2005, Namur, Belgium, 22 April 2005. Post-proceedings. 2006.

[9] Gelernter, D.: *Generative communication in Linda.* ACM Transactions on Programming Languages and Systems, Vol 7 No 1, January 1985.