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# A multi-agent approach for biological models cooperation

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## Introduction

Several formalisms and approaches exist for mathematically modeling biological processes. The same process can be modelled using different formalisms. Each obtained model could be considered as a “point of view” of the biological model, or an “approach” for studying *in silico* the biological process. It is therefore interesting to be able to make cooperating different mathematical modeling of the same biological process, in order to display behaviors that could not be seen in single model. For this purpose, we propose a multi-agent approach for implementing this cooperation. We have experimented our approach on a well known biological example, the *bacteriophage lambda*. The *bacteriophage lambda* is a virus which infects *Escherichia Coli* bacteria. It is considered as a very simple organism and has been greatly studied. In this abstract, we show with a small example, how a deterministic model and a stochastic model of the *genetic switch of the phage*, cooperate in order to deal with rare chemical reactions and frequent ones according to their relevance.

## The multi-agent approach applications

A multi-agent system (m.a.s.) is a system composed of multiple interacting entities called agents. Each agent is able to: (i) deal with its local problems, (ii) answer other agents requests, or (iii) propose a help to another agent. It operates in a decentralized, autonomous and proactive way [Singh 94]. Such systems are useful for problems that are difficult or impossible to solve for an individual agent or a monolithic system. Interactions between agents are exhibited as communication with messages exchanges and/or perception of their environment. Multi-agent systems have been tested and used in different research domains, such as the allocation of resources in a distributed system or the modeling of social structures [Van der Hoek and al. 07]. Diagnosis of faults, requiring different kinds of heterogeneous expertises, is also addressed by m.a.s. in order to design applications able to deal with distributed expertise [Jennings and Sycara 98].

Of course, multi-agents systems are also used for biological simulation applications [Ballet and Redou 08], [Lepagnot and Hutzler 09]. However, our multi-agents approach differs from the existing systems by using m.a.s as means to integrate several formalisms for biological modeling rather than to modelise biological applications.

## Cooperation of bacteriophage lambda regulation models

### The bacteriophage lambda regulation

We are interested here by a specific aspect of regulation of the *bacteriophage lambda* (phage  $\lambda$ ), the “genetic switch”. The infection cycle of *phage lambda* can take two pathways: (i) lytic pathway where the virus uses the host machinery in order to create new viruses; the bacterium is then destroyed and the viruses are released in the external media; (ii) lysogenetic pathway where the virus integrates its genetic material in the host cell genome and duplicates when this genome duplicates. In some cases,

the virus can extract itself from the bacterial genome and enter a lytic phase. The choice between the two pathways is the result of a genetic mechanism, encoded by two proteins: CI protein, called lambda repressor, encoded by *cI* gene, which is expressed during lysogenic phase and which can activates other genes including itself, and represses other genes; CRO protein, encoded by *cro* gene expressed during lytic growth. Note that the competition between CI and CRO is also influenced by the number of phages entering in the host cell (called API for Average Phage Input) and by the host environment [Adam and al. 98]. There are several chemical reactions, involving the proteins CI and CRO and their respective dimmers (CI1 and CRO1), and the number of viruses in each step of the regulation.

### **Cooperative multi-agent approach for modeling the bacteriophage lambda**

We have developed a multi-agent system where each agent represents a particular way of modeling the *bacteriophage lambda*. On the basis of their own local views, the goal of the agents is to choose, at each step, the “right” action which leads the whole system exhibiting a coherent modelling of the bacteriophage lambda. The architecture of the agents differentiates between (i) the basic behaviour (engine) of the agent and (ii) the (biological) domain knowledge and ((iii) the cooperation knowledge necessary for cooperative reasoning between the agents. The cooperation knowledge is a kind of meta-level knowledge that describes characteristics of the biological models without describing in detail how the models work. For example, knowing that a model has a specific temporal scale allows the agent to choose an appropriate period for communicating relevant information.

In a first step of our study, we choose the deterministic and stochastic modelling approaches. The first approach is suitable for rapid and frequent reactions since it allows modelling in a continuous scale time, whereas the second one is suitable for slow and rare reactions, since it considers discrete scale time. These two points of views are chosen to be integrated and made cooperating in a m.a.s.

Our m.a.s. is illustrated here with a small scenario of cooperation between a deterministic and a stochastic modelling of the *bacteriophage lambda*. The system is composed of two principal agents, one representing the deterministic model and the other the stochastic model. The classification of the reactions according to their type (rare/slow or frequent/rapid) is done in a dynamic way since it depends on the rate of the molecules (CRO et CI) quantities contained in the blood volume. Each agent determines the relevance of the use of the local model before its use. When it detects that information deduced on a local level is appropriate to the other agent, it sends it to him (by messages) and when it detects that its methods are restricted, it asks the other agent to provide him help. This metaphor is summarized below by the behavior of both StochasticAgent and DeterministicAgent agents.

Behaviour of StochasticAgent:

1. Perceive the quantities (number) of molecules
2. Identify the type of appropriate reaction
3. Calculate the time of the next reaction
4. Send this delay to the agent DeterministicAgent
5. Receive and take into account the values of DeterministicAgent

Behaviour of DeterministicAgent:

1. Perceive the quantities (concentrations) of molecules
2. Take into account the date sent by StochasticAgent
3. Make evolving its (rapid) reactions during the received time
4. Send the quantity of molecules to the agent StochasticAgent

The interest of our approach is that the classification of reactions in rare and slow or frequent and rapid is determined by the system in an absolutely dynamic and automatic manner. In fact, it depends in most cases on the evolution of the rates of the concentrations exchanged between agents.

## Conclusion

We have presented here an exploration of using the multi-agent approach for biological models cooperation. We considered in a first step a simple and well-know biological example, the genetic switch of bacteriophage lambda. We focused on two modeling approaches or formalisms, the deterministic modelling and the stochastic modelling. The obtained results are conclusive. We show the possibility and the pertinence of making cooperating different biological models as heterogeneous point of view of the same biological problem. Besides, with a multi-agents approach, we obtain a system able of being enriched with new models without taking a new look at what is already conceived. The perspectives to this work are numerous: addition of other models of bacteriophage lambda, application to other biological examples, realization and experimentation of different strategies of cooperation. In more long-term, we envisage the development of a generic platform offering (via an appropriate interface) a library of biological models on one hand and a group of strategies of collaboration on the other hand. The user would have to choose group of models with the cooperation strategies he would like to use for cooperating the chosen models.

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