Multi-Agent Model for Simulation at the Subcellular Level

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Abstract. From the beginning of biological modeling, simulations were an efficient way to understand local mechanisms linked to whole system behaviors. Cellular automata and more recently Multi-Agent Systems (MAS) are currently used to model ecological systems. Virus dissemination through population or insect collaborations are well known examples of how simple interactions between entities (agents) are able to build a complex situation at the level of the whole population. But use of MAS to design biological system at the cellular or subcellular level, mainly for enzymatic reactions, is a relatively new application of the agent paradigm. In fact, agents used for ecology simulations are ‘non-physical’ agents, i.e. in general they do not have any explicit representation of their geometry, their space bulk or the articulated movements of their body parts. These characteristics are essential in enzymatic behaviors. The three dimension structure and movements of this structure condition the realisation of the reaction that can be stopped or conversely favored by specific conformations. In order to simulate subcellular biological processes, we defined agents capable of simulating molecular conformational changes. These agents integrate molecular modeling data, for conformational change methods, and biological ontology data, for conformational change conditions. As some biological entities are motor of the enzymatic reactions while others are simple partners, we defined two agent subtypes, active and passive agents. As a proof of concept, we applied our model to the simulation of enzymatic oxydo-reduction reactions.

Introduction

Metabolic processes are mainly biochemical processes. They work at the subcellular level. In general, for one species they implicate a few hundreds of molecule types. The complexity of such processes is not due to the complexity of each mechanism of metabolic reactions but more to the multiplicity of used molecules and competitiveness between reactions to capture and to transform molecules. The whole set of reactions implicated in a specific metabolism is a network which can be described as an interaction graph where the nodes are metabolites and the edges are enzymes which catalyze reactions. Understanding how the modification of one reaction process influences other ones through the network is a key point
in system biology research. The chains of metabolic reactions have been currently modelled by reaction-diffusion equations \cite{1} and simulated by differential equations in general \cite{2}. But these models ignore a part of metabolic processes characteristics like those linked to the spatial molecule structures. They do not also take into account information about the molecule location. These information can be very important if there is a kind of competition between processes to use some molecules.

Multi-agent systems are well known to simulate simple local behavior of entities which generate complex behavior at the system scale\cite{3}. Many examples exist where agent modelling has been able to provide realistic explanations of what happens in “real life”. Most famous ones are the way to find the shortest path to food by ants or the capability for some birds to keep a specific organisation during their flight \cite{4}. In these models the agents are described as reactive agents. Complex agent models have been made to mimic the behavior of human societies or to test hypotheses in economy or in artificial intelligence. These models most often use cognitive agents, i.e. agents able to plan their action, to build strategy and to take decisions. At the cellular or subcellular level it is not appropriated to talk of molecule intentions, so if molecules are agents it is a kind of evidence that they are reactive agents. One can note that most often all these models do not ever propose to represent explicitly the geometry or the physical structures of agents. In our project BASiL to model metabolism of species with a multi-agent system, we have defined an extended reactive agent model able to take into account physical properties of implicated molecules, their internal movements and their interaction at different levels. After a presentation of the type of processes we need to model, we will explain the BASiL agent model and we will finish with a concrete example of the modelling of the electron transfer chain into the mitochondrial respiratory chain.

1 Biological Processes at the Subcellular Level

Metabolic processes imply proteins or enzymatic complexes, and metabolites which interact at the intra or inter molecular levels. Most often, metabolites are small molecules and enzymes macromolecules. Enzymes exhibit capabilities to capture molecules through binding sites and each reaction they catalyse is characterized by a reaction velocity. Enzymatic reactions can be influenced by several elements: presence or absence of inhibitors/activators, environment parameters like temperature and so on. All these elements affect both external and internal macromolecular motion. For example temperature augmentation increase the velocity of the enzyme in a medium (for example, a cytoplasm). We should also note that enzymes are composed of a huge number of atoms and that temperature can also affect the relative spatial arrangement of their atoms (as studied in stereochemistry). This means that a macromolecule can assume different shapes. It is well known in biology that the probability of an enzymatic reaction to occur is controlled by the macromolecule current shape \cite{5}\cite{6}.