



CNR - Short term mobility program 2008: final report

**“A formal approach to the simulation of
biochemical reactions in the cell membrane.”**

The contemporary paradigm of modular biology suggests an integrative approach, where different kinds of knowledge cooperate to build a unique representation of biological systems. In particular, systems biology is dealing with the challenge of describing, representing and simulating biological processes, from metabolic networks to social activities. In doing this, several basic problems arise like that of simulating biochemical reactions at microscopic scale. Chemical theory of reactions, in fact, is focused on bulk reactions, where molecules concentrations are large and the reaction time is intended as the average time computed on a large number of molecules.

At a microscopic scale, things change very deeply: the reaction between two single molecules has to be represented in terms closer to statistical physics, than to standard chemistry. Based on this point of view, Dan Gillespie has performed a fundamental work, where he proposed a stochastic method (SSA, stochastic simulation algorithm) which describes the reaction between two molecules in such a way that the limit for large number of molecules in (relatively) long times is exactly the chemical master equation of the macroscopic chemistry. In other words, it is an exact algorithm that simulates the matches between two molecules in such a way that gives exactly the results known from standard chemistry if used repeatedly on large populations of molecules.

Gillespie's algorithm is considered at the foundation of systems biology, since most of the biochemical reactions that take place in a cell concern very small amount of molecules and their behavior can vary stochastically and be very far from that of standard chemical systems.

Despite the high consistency of this approach, this algorithm suffers of two main problems: a) from a computational point of view, it is too expensive (Gillespie himself has proposed different approximate, computationally less expensive, versions of it); b) from a biological point of view, it is designed to simulate non-enzymatic reactions.

Since almost all the reactions that take place in a cell are enzyme driven, this is a hard problem for systems biology. To bypass it, an enzymatic reaction can be represented, in a combinatorial way, as the sum of several standard reactions, each of which has its own kinetic constants. This solution has, of course, a high computational cost.

There is, moreover, another problem of great importance in using Gillespie's algorithm to represent



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membrane reactions: all the proposed algorithms, in fact, assume a “well-stirred” molecular system, since any alternative hypothesis causes a relevant increment on the information required to describe the system. Unfortunately, membrane processes cannot be represented as well-stirred systems.

Intrinsic membrane proteins, in fact, are often linked to the membrane, where motile membrane proteins are not diffusing freely. Diffusion on the membrane, in fact, is very complex, as indicated by a very low diffusion speed with respect to artificial membranes like liposomes. This evidence has been tentatively represented in several ways, but the most reliable model is to imagine the cell membrane divided into compartments, within which the diffusion is normal, but very limited between compartments (hop-diffusion). Starting from this point of view, the research activity carried out during the period spent at Harvard University was aimed at building up a stochastic algorithm to simulate early stages in signalling pathways, in particular those of signal transduction chains.

We started our research program from a simple model of membrane receptor-transducer complexes, in the presence of several possible competitors for the same receptor. We firstly described this interaction in terms of the standard Gillespie's algorithm and computed the rate and kinetic parameters for the different biochemical processes. Subsequently, we added several constraints taking into account the hop-diffusion, building twodifferent heuristic models of membrane processes. Finally, we compared experimental data obtained in the host laboratory at Harvard, and other data from the literature, with the results of the different implemented models.

We were able to prove that the Gillespie's algorithm is unsuitable to describe membrane processes and we could estimate the relative error introduced by it in simulating these processes. We could, moreover, show that the heuristic models developed during this research program give results compatible with the experimental data. On the basis of these results we are now developing alternative algorithms able to deal with receptor/ligands interactions. We are, in particular, applying them to describe the photoperception system in *H. salinarium*.

The obtained results will be presented, in a preliminary form, in a poster communication presented at ECCB2008; further results will be published in papers, where the CNR contribution will be properly acknowledged.

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