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2009 : July 2009 - Fast Moving Fronts : Santiago Schnell

## FAST MOVING FRONTS - 2009

July 2009



**Santiago Schnell talks with ScienceWatch.com and answers a few questions about this month's Fast Moving Front in the field of Computer Science.**



**Article: Stochastic approaches for modelling in vivo reactions**

Authors: Turner, TE; Schnell, S; Burrage, K

Journal: COMPUT BIOL CHEM, 28 (3): 165-178 JUL 2004

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### SW: Why do you think your paper is highly cited?

In our paper we unravel a new debate in the field of systems biology: What is the appropriate modeling formulation to investigate reactions inside cells? The biological revolution unleashed by systems biology is taking an unfashionable stand against reductionism. Systems biologists are developing sophisticated computational models of protein-protein interaction networks, which require understanding the kinetic of enzyme catalyzed reactions.

The traditional approach in modeling enzyme kinetics, which encompasses the law of mass action, has been the basis for kinetic modeling for over a century. However, the adequacy of this approach has been questioned for describing reactions inside the cells. The problem is aggravated further in the literature, because there are numerous approaches for modeling reactions inside cells. However, it is not entirely clear which approaches are best suited for a particular set of reaction conditions inside cells.

### SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

Our article provides a state-of-the-art synthesis of stochastic approaches available for modeling reactions inside the cells. We critically investigated the current approaches available to model reaction stochastically. When these models are applied to investigate reactions inside cells, it is assumed that the random fluctuations in the reactions are a consequence of the small number of reactant molecules inside cells.

Although these models have been used successfully to describe certain cellular physiological processes, they can lead to qualitatively different physiological predictions. This is because they do not take into account the compartmented and highly heterogeneous environment inside the cell.

We describe our recent efforts through Monte Carlo simulations to include the

fluctuations in reaction rates caused by the structural organization of cells and limited diffusion of reacting molecules, due to large molecular solvents inside cells. So, in our article, we emphasize the likely contribution of non-reacting collisions with macromolecular solvents and limited diffusion in the fluctuations of reactions inside cells.

*"If we could miniaturize ourselves and travel inside a cell, we would discover that reactions occur randomly"*

**SW: Would you summarize the significance of your paper in layman's terms?**

The cell can be considered the unit of life, because the microscopic interactions inside cells underlie the cause and order of the complex processes occurring in an organism. This is only possible because the cell is a dynamical entity, continuously changing. Almost everything that happens inside the cell boils down to reactions between molecules. Cells are able to process the input and output of reactions into hundreds of specific cellular functions, such as secretion of molecules, cell movement, or differentiation, into other cell types.

If we could miniaturize ourselves and travel inside a cell, we would discover that reactions occur randomly. We would also find that the interior of a cell is a very crowded jungle of molecules. Random fluctuations in reaction rates are inevitable, because molecules occur in low numbers inside the cell. Interactions occur because molecules are constantly diffusing and colliding with the surrounding jungle of other molecules.

Traditionally, researchers considered observed fluctuations in the reaction rates to be experimental noise, which could be ignored. However, we recently discovered that the intrinsic noise has important information vital to understanding the association, location, and function of molecules inside the cells.

In our paper, we have brought the current controversies about the appropriate mathematical formulations for investigating the dynamical behavior of reactions inside cells to the attention of other scientists. While there is some arbitrariness about the choice of mathematical framework in any scientific enterprise, different mathematical formulations are better able to capture one or more particular features of the data, and represent the underlying hypotheses of a theory more or less faithfully.

We critically review the state-of-the-art approaches for describing the fluctuations in chemical reactions inside the cells. We show that these approaches are effective for modeling reactions exhibiting fluctuations due to the small number of molecules inside the cells. However, we also show that they fail to describe the fluctuations in reaction rates which result from the random collisions with the jungle of solvent molecules. We conclude our paper by presenting an alternative approach, which we developed, to model reactions more realistically inside cells.

**SW: How did you become involved in this research and were any particular problems encountered along the way?**

Since I was an undergraduate student in the biomedical sciences, I have been investigating the mathematical and computational approaches to understanding the dynamical behavior of reactions under cellular physiological conditions. At the time, biomedical scientists were not paying enough attention to these problems. The main focus of attention was uncovering the interaction map of genes and proteins.

I found myself rather isolated, and decided to move out of my research home in a traditional biomedical department into the physical and mathematical sciences. While the biomedical scientists were making spectacular advances in the interaction maps, I focused my research attention on one key aspect of biology that an interaction map cannot get us close to: the dynamical behavior of biochemical reactions and physiological processes.

The transition from experimental to theoretical biology was very difficult, because I had to learn advanced mathematical techniques and sophisticated physical concepts to be successful in my research. However, it was worth the effort! After revisiting the traditional approaches for modeling reactions, I discovered that most of the mathematical approximations for investigating reactions under physiological conditions are not valid. This has been one of the focuses of my research for more than 10 years.

**SW: Where do you see your research leading in the future?**

I will continue investigating the dynamical behavior of complex biological processes. My main research interest is investigating cellular physiology systems comprising many interacting components, where modeling and theory may aid in the identification of the key mechanisms underlying the behavior of the system as a whole. In my lab, we are currently focused on investigating the dynamics and regulation

mechanisms of the protein synthesis and aggregation inside our cells. By using our new mathematical and computational approaches to model reactions inside the cells, we expect to construct more realistic models, which will help us to predict, prevent, or remedy potential health problems caused by failure to produce functional proteins.

**SW: Do you foresee any social or political implications for your research?**

Not directly. However, the determination of the reaction dynamics inside our cells will be invaluable for understanding how the interactions between different biological molecules make a cell function. If we do not understand the appropriate physicochemical laws describing the reaction behavior inside cells, our understanding of life will be very limited.

Consolidating the detailed information we have gained from the gene and protein interaction maps with dynamical models of cellular reactions and physiological processes will propel us towards a true mechanistic understanding of life. The practical impact will be considerable in understanding disease and developing new drugs.

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