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Review of the PhD thesis "Organization and fluctuations in living systems " by Gabriel Morgado

The scientific project elaborated by Gabriel Morgado as a partial fulfillment of requirements for granting the PhD degree is rooted in statistical mechanics of nonequilibrium systems. Author's aim was to analyze optimal approaches to model spatio-temporal structures in chemical and biological systems.

The mesoscopic scale of these approaches renders biochemical reaction networks driven by fluctuations and therefore - stochastic in nature. Mr. Morgado presents results of his studies in the form of a series of five published articles accompanied with an introductory discussion of analytical and numerical methods adapted for the purpose of studies.

After short recollection of basic theory of chemical kinetics, linearisation technique and stability analysis, Chapter I of the thesis introduces the concepts of stochastic description in terms of Langevin and Master equations, followed by the introduction to essentials of chemical Monte Carlo methods and steady state approximation (Chapter II). Author focuses on the Gillespie's stochastic simulation algorithm (known also as kinetic Monte Carlo) which so far has been widely used to simulate biochemical and autocatalytic reactions, although mainly, in the homogeneous regime. In an elegant work on the subject (the article *Elimination of fast variables in stochastic nonlinear kinetics*, coauthored with B. Nowakowski and A. Lemarchand and published in PCCP), the algorithm is used to test reduced dynamics of three-variable kinetic models on the slow manifold defined by relaxation of one variable to its stationary concentration. Such reduction scheme may lead to non-trivial nonlinearities of two-variable systems, and in effect, bring about results which significantly differ from the conclusions drawn from a complete kinetic scheme. By designing two various three-species models of chemical kinetics which are contracted to the same form

of the reduced system, this paper demonstrates that the variances and covariances of fluctuations of slow ingredients derived from Master equation and linearised form of the associated Langevin equation do not coincide with results derived for the three variable models. The discrepancies are more pronounced for systems consisting of small number of reactants. Author speculates that conclusions indicating deficiencies of a reduced chemical scheme in analysis of experiments on small samples may be essential for interpretation of the results from the fluorescence correlation spectroscopy (FCS).

Chapter III disputes an important class of pattern forming systems, i.e. inhomogeneous reaction-diffusion models which describe the reaction dynamics of diffusing species. Inspired by emergence of periodic spatial patterns in systems of that type Author addresses the problem of possible termination of the periodic (infinite) Turing spatial structure, i.e. analyzes conditions for the development of a finite-size structure whose growth stops by loss of stability and decrease of the wavelength of the periodic structure. By use of the Monte Carlo method adapted to the simulations of concentrated solutions, Gabriel Morgado has performed numerical analysis of sub-micrometric Turing pattern and shown the effect of solvent in controlling wavelength of the structure. Results of the analysis and conjecture on possible application of the phenomenon in morphogenesis have been published in two articles attached (*Scaling of submicrometric Turing patterns in concentrated growing systems* and *Termination of Turing mechanism*).

In Chapter IV Author discusses effects of concentration-induced perturbation of diffusion on the pulled FKPP (Fisher-Kolmogorov-Petrovsky-Piskunov) wave front. In the article published with B. Nowakowski and A. Lemarchand in Physical Review E, Authors study a reaction-diffusion wave front of the FKPP type propagating in a confined, concentrated system. For such a system Authors derive a generalized form of the Fick diffusion leading to diffusion flux depending on concentration gradients of all substituents. In the next step they analyze effects of the diffusion on the wave front profile width and difference in concentrations of reacting species. It is shown that the sensitivity of the front to small perturbations can be used to decipher deviation from dilution limit.

The thesis ends up with Conclusion section and Bibliography.

A few critical comments: Although Author has paid attention to proper structuring of the thesis and its logical content, there are several points which I would like to bring about. Some definitions or short-cut terms are misleading, eg. in Preamble Author writes "the crudest stochastic method used to describe reaction-diffusion system consists in adding a Langevin force to the deterministic equations..." What is Langevin force (interpretation) ? On page 5, the sentence "in small systems close to situations where dynamics is sensitive to small perturbations, such as bifurcations, a deterministic analysis may be insufficient" ... What is a statistical argument behind that statement ? On page 107 - a comment on Ilya Prigogine's group and its impact on analysis of "temporal organization in homogeneous chemical systems, from periodic oscillations to chaos" - interpreted in the context of dynamical systems theory: In fact, the major achievement of the "Brussel's School" was systematic analysis of the

effect of fluctuations on self-organization phenomena in complex systems and introduction of stochastic methods into the field of thermodynamics.

Altogether, the thesis presents many new results and although it does not solve a well posed biological problem, it clearly indicates benefits of mesoscopic, stochastic approach in solving such problems. Author made a fair effort to present analytical methods involved and performed elaborated numerical simulations to control used approximation schemes. Despite the enormous success of the Gillespie algorithm and several subsequent modifications that are computationally more efficient, the issues of how to treat spatial inhomogeneity and take into account diffusion of molecules remain an ongoing research effort. Gabriel Morgado contributed to this intriguing field by adaptation of the known algorithms to new problems of pattern organization and control in reaction-diffusion systems. Results of his PhD thesis are original and valuable. Their merits are interesting to a broader class of researchers working in biological and soft-matter physics, what has been well evidenced by very good publications in high impact journals.

The dissertation has been prepared as a part of the EU Horizon 2020 research project concerted by the Sorbonne Université and Institute of Physical Chemistry Polish Academy of Sciences indicating a successful collaboration of the parties. The thesis meets all criteria and standards of the dissertation assessment process and substantiates my recommendation to award Mr. Morgado with the PhD degree.



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