A 24 months post-doc position in systems biology, financed by the Labex EpigenMed, is offered jointly by the "Biological Physics and Systems Biology team" of DIMNP (UMR 5235) and CBS (Centre de Biochimie Structurale) in Montpellier.
We are seeking highly motivated candidates with a phD in mathematics, or physics, or computer science, or systems biology.

The successful applicant will be involved in a project aiming to relate, by mathematical and physical modeling, the characteristics of gene regulatory mechanisms to properties of the measured expression fluctuations in the gene network controlling the central carbon metabolism (CCM) of B.subtilis. Building on cutting-edge single molecule spectroscopy data produced at CBS Montpellier, the post-doc will develop mathematical methods and computer software for modeling stochastic expression of gene regulatory networks. He/she will contribute to the analysis of data resulting from microscopy experiments and will adapt the physical and mathematical modeling of fluorescence fluctuation-based spectroscopy and microscopy data to the particular case of protein expression in small prokaryotic cells.

Keywords: systems biology, stochastic modeling, machine learning, fluorescence fluctuation-based spectroscopy.

Applications, including a CV, a cover letter and the contact information of at least two referees, should be send by email to Ovidiu Radulescu (ovidiu.radulescu@univ-montp2.fr) with the subject “Epigenmed postdoc application’’.

About the project.

FLUCTUOME : **Quantitative study and models of stochastic fluctuations in the gene network controlling the central carbon metabolism of Bacillus subtilis**

Participants and their roles.

Nathalie Declerck (Centre de Biochimie Structurale, Montpellier): production of fluorescence Number & Brightness data.

Andrea Parmeggiani (Biological Physics and Systems Biology team, DIMNP, and the Institute of Physics Montpellier): biological physics, modelling finite resource, transport and crowding aspects.

Ovidiu Radulescu (Biological Physics and Systems Biology team, DIMNP): gene network modelling, continuous time discrete and hybrid Markov processes, model reduction, machine learning.

Summary of the project.

Recent advances in real-time single cell imaging, micro-fluidic manipulation and synthetic biology have shown that at the molecular level, functioning of cellular processes is stochastic. In particular, gene expression is produced by the accumulation of multiple random events, whose types and rates define the characteristics of the gene regulatory mechanisms.

The outcome of this process, namely the gene expression level, can be more or less noisy, depending on the details of the regulation mechanisms. In isogenic population of bacteria, noisy gene expression leads to random cell-to-cell variations of the concentrations of proteins and even to random transitions to different cell fates. The probabilities of these transitions are regulated and submitted to evolutionary forces. Bacteria can modulate the amplitudes of gene expression fluctuations in their adaptation strategies to environmental changes. The study of stochastic gene expression is thus undeniably needed for understanding bacterial behavior, and has potential applications to fighting against infectious diseases.

Using cutting-edge single molecule spectroscopy, the distribution of copy numbers of proteins expressed by a bacterium can be quantitatively characterized and one finds out that it satisfies precise mathematical laws. It turns out that measuring not only the average copy numbers, but also their cell-to-cell variability, represents a rich source of information that can be exploited for the identification of the gene expression regulatory mechanisms. Thus, quantification of stochastic gene expression can be used as a new tool for probing molecular interactions in gene networks.

The aim of the project is to relate, by mathematical and physical modeling, the characteristics of gene regulatory mechanisms to properties of the measured expression fluctuations in the gene network controlling the central carbon metabolism (CCM) of B.subtilis. Models and experimental data will be used to generate and check hypotheses about the origin and role of noise in cellular processes. We will develop exact and approximate methods allowing prediction of the probability distributions of protein copy numbers for stochastic gene network models. By machine learning methods and parsimony principles, we will associate to differences in noise patterns, differences in critical features of the molecular mechanisms controlling the CCM gene promoters. Well stirred chemical reaction approaches will be combined with more realistic biological physics models for evaluating extrinsic effects such as crowding that may account for observed discrepancies between *in vivo* and *in vitro* studies. The combination of mathematical and physical biology approaches is an important component of our proposal, and also a substantial challenge of multiscale modeling of biological cells.

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