**Offre n°2023-07021**

**PhD Position F/M Spatial statistics and machine learning for molecular dynamics analysis in 2D/3D microscopy**

Le descriptif de l’offre ci-dessous est en Anglais

**Type de contrat :** CDD  
**Niveau de diplôme exigé :** Bac + 5 ou équivalent  
**Fonction :** Doctorant

**Contexte et atouts du poste**

Le thesis will take place in the SAIRPICO project-team, which is specialized in the development of innovative methods for image restoration/reconstruction, motion analysis and computation of molecule trajectories in live cell imaging, and biophysical parameter estimation. The thesis we propose is at the frontier of applied mathematics, image processing/analysis, machine learning, and computer science. The goal is to develop statistical and machine learning methods and algorithms for analyzing intracellular motion and molecular dynamics observed in vector-valued microscopy images.

**Mission confiée**

During the past two decades, many ground-breaking technologies emerged and allowed the visualization of tissues, cells, organelles, proteins, and viruses at all levels of spatial resolution (from 10 nm to 150 nm). The development of novel fluorescent labeling probes and recent advances in optics and digital sensors (PALM, STED, SIM) have been key developments which have served to overcome the theoretical optical diffraction barrier (Abbe’s law). Because of these technological breakthroughs and their impacts in life sciences, fluorescence microscopy has become the **figurehead** of modern biology and is also proving to be of immense clinical relevance, especially for the study of cancer and viral infections.

In a conventional fluorescence microscopy photons are collected at a given pixel/voxel and the registered scalar value (fluorescence intensity) is proportional to the density of tagged-molecules within the pixel/voxel (size about 80-100 nm). Unlike popular scalar-valued fluorescence microscopy, polarized microscopy has the potential to probe the dipole orientation of fluorophores rigidly attached to a biomolecule or an organelle of interest, at any spatial position [1, 2]. Consequently, polarized microscopy is the next generation technology able to better reveal the function of biomolecules in cells, and to decipher complex biological mechanisms. Nevertheless, as the corresponding data are potentially multi-channel 3D+Time vector-valued signals, the analysis of images represents a new challenge in signal-image processing and analysis, and one for which several scientific barriers must be overcome. In this thesis, we will focus on the interpretation of dynamical and structural information content of vector-valued images, as well as the possibility of producing 3D super-resolved maps of molecular motions from polarized microscopy images.

Our case-studies in cell biology will be related to the analysis of intracellular trafficking and molecule transport pathways, as they represent a major contributory factor to a number of diseases such as cancer, and viral infection. The resulting algorithms will serve to characterize the dynamics of biomolecules and to decipher the molecular transport pathways, which are of considerable of interest in fundamental cell biology and for future precision medicine.


**Principales activités**

The thesis will be articulated around 2 axes:

1/ **Development of methods to estimate spatial high-resolution maps of biomolecule mobility from dipole orientation and fluorescence intensity** – We will investigate the computation of dense spatial high-resolution diffusion maps from orientation and intensity measurements provided by conventional polarized microscopy instruments. Initially, we assume that the motion of molecules is driven by the following stochastic differential equation [1, 2]: \[ dX_t = b(X)dt + (2D(X))^{1/2}dW_t \] where \( X_t \) denotes the 3D
Informations générales

We are looking for a candidate with an engineer or master’s degree with a background in statistics and therapy. To precise intracellular locations within specialized cells for immunotherapy, or to tumors for targeted innovative vaccine strategies and therapies by cellular entry mechanisms, we expect that our results will be helpful to the development of a series of pathogens as well as many physiological and cellular biological molecules are concerned expected to affect membrane organization [9, 10, 11]. Since a broad spectrum of motility mechanisms exists in cancer cells, which all depend on the reorganization of the actin cytoskeleton and endocytic trafficking. The algorithms will serve to determine the actin filament organization in cells, and to link this structural information to different stages of the biogenesis of tubular endocytic pits, under variable conditions of reduced cholesterol levels in membranes, and upon perturbation of the actin cytoskeleton which is expected to affect membrane organization [9, 10, 11].

Since a series of pathogens as well as many physiological and cellular biological molecules are concerned by cellular entry mechanisms, we expect that our results will be helpful to the development of innovative vaccine strategies and therapies, in particular the design of therapeutic compounds delivered to precise intracellular locations within specialized cells for immunotherapy, or to tumors for targeted therapy.

2/ Computational spatial statistics and co-orientation field estimation – We will fully exploit the intensity and orientation measurements embedded in spatial statistics-based schemes to detect and quantify interactions between several molecular species. Given two orientation fields associated with two different molecular species (two-channel polarized images), our goal is to translate the conventional co-localization problem into a contemporary co-orientation problem [7]. To that end, we will investigate non-parametric testing procedures and random set framework [8]. An additional outcome will be to estimate dense interaction maps from sparse co-orientation estimators.

3/ Application to cell imaging

Our aim is to associate the resulting algorithms to decipher intracellular mechanisms and elucidate the key role of molecules in transport pathways. We will first adapt the algorithms to two different polarized microscopy instruments with increasing grades of sophistications: confocal, multiform, TIRF-3D, STORM. Second, the methods and algorithms will be used to study endocytosis and actin cytoskeleton organization during cell migration. A broad spectrum of motility mechanisms exists in cancer cells, which all depend on the reorganization of the actin cytoskeleton and endocytic trafficking. The algorithms will serve to determine the actin filament organization in cells, and to link this structural information to different stages of the biogenesis of tubular endocytic pits, under variable conditions of reduced cholesterol levels in membranes, and upon perturbation of the actin cytoskeleton which is expected to affect membrane organization [9, 10, 11].

Since a series of pathogens as well as many physiological and cellular biological molecules are concerned by cellular entry mechanisms, we expect that our results will be helpful to the development of innovative vaccine strategies and therapies, in particular the design of therapeutic compounds delivered to precise intracellular locations within specialized cells for immunotherapy, or to tumors for targeted therapy.


Compétences

We are looking for a candidate with an engineer or master’s degree with a background in statistics and high skills in machine learning and programming (python, C++)

Informations générales

- Thème/Domaine : Approches stochastiques
- Biologie et santé, Sciences de la vie et de la terre (BAP A)
- Ville : Rennes
- Centre Inria : Centre Inria de l’Université de Rennes
Date de prise de fonction souhaitée : 2024-02-01
Durée de contrat : 3 ans
Date limite pour postuler : 2024-01-31

Contacts
- Équipe Inria : SAIRPICO
- Directeur de thèse :
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