
Contract type: Public service fixed-term contract
Level of qualifications required: PhD or equivalent
Function: Post-Doctoral Research Visit

Context

Team

Contacts
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Assignment

Context
Cryo-electron microscopy (cryo-EM) is an imaging technique in which a beam of electrons is projected through a thin film of multiple copies of a biomolecular sample suspended at low temperature in a vitreous ice matrix. Consequently, the first step in the analysis of the sample is the reconstruction of the 3D images of the sample molecule. A three-dimensional (3D) density map of a single particle may be reconstructed from the 2D images using computational tomography techniques. If the density map is of sufficient resolution, an atomistic model of the sample biomolecule may then be built. Historically, the resolution of density maps obtained by cryo-EM was very low. However, thanks to the development of modern complementary metal oxide semiconductor (CMOS) direct detection devices and recent improvements in high-throuput sample handling techniques, the resolution of cryo-EM density maps has drastically improved [1]. Thus it is now technically possible to obtain density maps at near atomic resolution. In such cases, an atomistic model can potentially be derived directly from the density map. However, while modern CMOS detectors can allow very high resolution density maps to be calculated in favourable conditions, in practice many cryo-EM density maps can only be calculated at low resolution. Indeed, according to recent statistics from the public “EMDB” repository, the average resolution of the deposited cryo-EM maps is actually falling, having gone from around 16 Å in 2012 to around 20 Å RMSD in 2015 (http://www.ebi.ac.uk/pdbe/emdb/statistics/sp_res.html). Furthermore, it remains very challenging to build atomistic models from low resolution 3D density maps, especially if the target 3D structure is flexible or if it contains multiple protein components. Often, previously solved high resolution structures of the protein components (e.g. from X-ray crystallography) are fitted into a density map in order to build the final atomistic model. However, if the map contains one or more flexible protein components, this is an extremely difficult problem due to the very high dimensionality of the search space. A standard fitting method will involve a six-dimensional (6D) rigid-body search of each component and then flexibly relaxing its conformation from the initial 3D density maps. This could start from a NMA analysis of a contoured surface which was developed previously for the protein docking problem [3]. This method performs the rigid search in a five-dimensional (5D) spherical space and uses the properties of the spherical harmonics to quickly sample the rotations of the atomistic model. Because molecular density fitting is primarily a rotational search problem, as opposed to a translational search, working in spherical coordinates seems to betruly more natural choice of coordinate system than classical coordinates, however, to our knowledge, this possibility has not been explored previously in the cryo-EM literature. Conventional approaches to treat macromolecular flexibility typically require an atomistic model from which MD trajectories or NMA principal components may be calculated. However, in the context of flexible cryo-EM fitting, accurate atomistic models are usually not available. Therefore, approaches based on MD or on NMA of structural homologues are at risk of missing relevant conformational poses. Thus, the second aim of this project is to develop a flexible fitting approach that can work directly from the initial 3D density maps. This could start from a NMA analysis of a contoured surface representation of the density, for example. Projecting such a flexible representation into the SPF basis would then offer the possibility of performing both the rigid-body search and flexible refinement entirely in the 5D SPF basis. The ideal candidate for this project will have a good knowledge of mathematical techniques for 3D image processing, as demonstrated by previous publications in a relevant field. A strong interest in structural biology and/or cryo-EM would be particularly welcome, as would strong experience of scientific programming in C or C++.

Main activities

Project Description
The overall aim of this project is to develop novel computational techniques to improve both the rigid body FFT search and the flexible refinement stages of the above modeling problem. Traditionally, FFT-based density fitting is done using conventional 3D Cartesian grids. In this project, the first aim is to apply and extend the spherical polar Fourier (SPF) correlation technique which was developed previously for the protein docking problem [3]. This method performs the rigid search in a five-dimensional (5D) spherical space and uses the properties of the spherical harmonics to quickly sample the rotations of the atomistic model. Because molecular density fitting is primarily a rotational search problem, as opposed to a translational search, working in spherical coordinates seems to be a much more natural choice of coordinate system than Cartesian coordinates. However, to our knowledge, this possibility has not been explored previously in the cryo-EM literature. Conventional approaches to treat macromolecular flexibility typically require an atomistic model from which MD trajectories or NMA principal components may be calculated. However, in the context of flexible cryo-EM fitting, accurate atomistic models are usually not available. Therefore, approaches based on MD or on NMA of structural homologues are at risk of missing relevant conformational poses. Thus, the second aim of this project is to develop a flexible fitting approach that can work directly from the initial 3D density maps. This could start from a NMA analysis of a contoured surface representation of the density, for example. Projecting such a flexible representation into the SPF basis would then offer the possibility of performing both the rigid-body search and flexible refinement entirely in the 5D SPF basis.

Skills

Required Qualifications
PhD in Computing or one of the Mathematical/Physical Sciences

Language
French or English

General Information

- Theme/Domain: Computational Biology
- Scientific computing (BAP E)
- Town/city: Villers-lès-Nancy
- Inria Center: CRI Nancy – Grand Est
- Starting date: 2018-10-01
- Duration of contract: 1 year, 4 months
- Deadline to apply: 2018-06-06

Contacts
Inria Team: CAPSID (DDG-5)
Recruiter: Ritchie David / dave.ritchie@inria.fr

About Inria
Inria, the French National Institute for computer science and applied mathematics, promotes “scientific excellence for technology transfer and society”. Graduates from the world’s top universities, Inria’s 2700 employees rise to the challenges of digital sciences. With its open, agile model, Inria is able to explore original approaches with its partners in industry and academia and provide an efficient response to the multidisciplinary and application challenges of the digital transformation. Inria is the source of many innovations that add value and create jobs.

The keys to success

Application Deadline
June 6th, 2018 (Midnight Paris time)

How to Apply
Upload your file on jobs.inria.fr in a single pdf or zip file, and send it as well by email to dave.ritchie@inria.fr.

Your file should contain the following documents:
- CV including a description of your research activities (2 pages max) and a short description of what you consider to be your best contributions and why (1 page max and 3 contributions max); the contributions could be theoretical or practical. Web links to the contributions should be provided. Include also a brief description of your scientific and career projects, and your scientific positioning regarding the proposed subject.
- The report(s) from your PhD
Benefits package
- Subsidised catering service
- Partially-reimbursed public transport
- Social security
- Paid leave
- French courses

Remuneration
Salary: 2653€ gross/month

In addition, at least one recommendation letter from your PhD advisor should be sent directly by their author(s) to dave.ritchie@inria.fr.

Applications are to be sent as soon as possible.

Conditions for application

Defence Security:
This position is likely to be situated in a restricted area (ZRR), as defined in Decree No. 2011-1425 relating to the protection of national scientific and technical potential (PPST). Authorization to enter an area is granted by the director of the unit, following a favourable Ministerial decision, as defined in the decree of 3 July 2012 relating to the PPST. An unfavourable Ministerial decision in respect of a position situated in a ZRR would result in the cancellation of the appointment.

Recruitment Policy:
As part of its diversity policy, all Inria positions are accessible to people with disabilities.

Warning: you must enter your e-mail address in order to save your application to Inria. Applications must be submitted online on the Inria website. Processing of applications sent from other channels is not guaranteed.