PhD Position
Computational developments for integrative structural biology: small-angle scattering using polynomial expansions

SECTOR: Higher Education Institution

LOCATION: France, Grenoble

RESEARCHER PROFILE:
□ First stage researcher,

INSTITUTION: Univ. Grenoble Alpes, University of Innovation

One of the major research-intensive French universities, Univ. Grenoble Alpes enjoys an international reputation in many scientific fields, as confirmed by international rankings. It benefits from the implementation of major European instruments (ESRF, ILL, EMBL, IRAM, EMFL*). The dynamic ecosystem, grounded on a close interaction between research, education and companies, has earned Grenoble to be ranked as the 5th most innovative city in the world. Surrounded by mountains, the campus benefits from a natural environment and a high quality of life and work environment. With 7000 foreign students and the annual visit of more than 8000 researchers from all over the world, Univ. Grenoble Alps is an internationally engaged university.

A personalized Welcome Center for international students, PhDs and researchers facilitates your arrival and installation.

In 2016, Univ. Grenoble Alpes was labeled «Initiative of Excellence ». This label aims at the emergence of around ten French world class research universities. By joining Univ. Grenoble Alpes, you have the opportunity to conduct world-class research, and to contribute to the social and economic challenges of the 21st century ("sustainable planet and society", "health, well-being and technology", "understanding and supporting innovation: culture, technology, organizations" "Digital technology").

* ESRF (European Synchrotron Radiation Facility), ILL (Institut Laue-Langevin), IRAM (International Institute for Radio Astronomy), EMBL (European Molecular Biology Laboratory), EMFL (European Magnetic Field Laboratory)

Key figures:

- + 50,000 students including 7,000 international students
- 3,700 PhD students, 45% international
- 5,500 faculty members
- 180 different nationalities
- 1st city in France where it feels good to study and 5th city where it feels good to work
- ISSO: International Students & Scholars Office affiliated to EURAXESS
SUBJECT DESCRIPTION:

While crystallography has been providing atomic-resolution structures of biomolecules for over half a century, the real challenge of today’s biophysicists is to correlate molecules’ structure and dynamics in solution with their function. Small-angle scattering (SAS) is the fundamental techniques for structural studies of biological systems in solution. Thanks to advances in instrumentation and data analysis software, Small-angle X-ray scattering (SAXS), complemented by other methods, is becoming very popular in structural biology. Over the years, a number of computational tools have been developed for the analysis of SAXS curves, calculation of theoretical profiles and low-resolution reconstruction of model shapes. Many efforts have been spent to reduce the running time of these tools without degrading the quality of their approximations, most prominently the ATSAS package developed at EMBL Hamburg. Particularly, the Crysol program calculates a model SAXS profile to test a structural hypothesis of a SAXS experiment. The number of Bio-SAXS publications exploded as a result of this effort. Comparatively, the lack of user-friendly analysis tools has hindered the development of Small Angle Neutron Scattering (SANS), more complex but providing more information.

Very recently, we developed a computational tool called Pepsi-SAXS that outperforms all the competitors for atomistic modelling in both speed (5 – 50 times faster on average) and accuracy. However, Pepsi-SAXS developments were very much restricted by the lack of human resources and, more importantly, by the lack of support and expertise from experimental teams. Also, SANS experiments are somehow more complex and bring different information than SAXS experiments because they offer the possibility to tune the scattering of the solvent to match the scattering of some compounds included in a particle to determine the structure of the compounds that remain visible. The current project is devoted to the novel computational developments for SAXS and SANS with applications to integrative structural biology.

Challenges and tasks:

The overall research topic of the current project is to extend the state-of-the-art computational methods for small-angle (both SAXS and SANS) scattering experiments and to provide the algorithmic foundation to the upcoming single-molecule experimental techniques. In particular, the practical aim of the project is the development of software tools with intuitive user-interaction feedback.

Mathematically, the project will rely on the very efficient representation of the scattering profiles based on polynomial expansions of the scattering amplitudes using spherical harmonics. Structural optimization will be performed using the fast Fourier transform–accelerated techniques and the polynomial translation theorems and large collective structural motions using Normal Mode Analysis.

Three main axes of the proposed project are: (i) Molecular flexibility and the ways of modelling it; (ii) Algorithmic developments for new experimental setups, particularly combining SAXS and SANS data, and
2D scattering; (iii) Practical software development with intuitive user interfaces. Below we detail the main research axes of the project.

More precisely, the planned developments include the following:

• Modelling thermal fluctuations (see review by Hub, 2018) using an analytical model of the scattering profile resulting from thermal molecular vibrations. This will be possible thanks to the (i) expression of normal modes in spherical coordinates expanded in the Spherical Harmonics basis, and (ii) computing molecular fluctuations in this basis analytically using the algebra for triple and quadruple overlap integrals of spherical harmonics.

• Flexible fitting of atomistic structures into small-angle scattering profiles. This includes combination the Pepsi-SAXS / Pepsi-SANS engines with the NOLB NMA method for the large-scale flexible structure optimization along the lowest-frequency normal modes. A working prototype exists, however, a proper analytical optimization technique with respect to the goodness of fit should be added. Also, the method needs to be extended to SANS data. Finally, the method needs to be made more robust and user-friendly, possibly, with a GUI inside the SAMSON modelling platform.

• Application of motion planning to adapt the sampling techniques for flexible unstructured regions of the molecules.

• In some cases it is impossible to represent the molecular structural heterogeneity continuously. This situation will require fitting the experimental SAS curves with an ensemble of structures. Therefore, we plan to extend the Pepsi-SAXS / Pepsi-SANS methods for the cases of multiple models, whose contributions will be adjusted with stochastic optimization techniques.

• We will consider the case when the molecular system can be represented with a set of rigid domains. Here we can compute scattering profiles for supra-molecular assemblies based on the precomputed scattering amplitudes of individual rigid bodies with subsequent rigid-body transforms applied to the amplitudes in the Fourier space.

• Fitting of atomic-resolution structures into multiple profiles obtained in different experimental configurations from the same sample. Indeed, the current modelling pipelines merge different experimental measurements into a single scattering profile. This approach has a significant drawback since the scaling factors for individual scattering components are generally unknown and can be erroneously guessed upon merging. A much more general, and also more computationally elegant approach would be to adjust the scaling factors of individual scattering profiles upon fitting atomistic models into multiple scattering curves. This approach would also have an obvious advantage of mixing different experimental information, e.g. SAXS and SANS experiments.

• Novel developments for 2D scattering based on the spherical harmonics and cylindrical harmonics representation. Many elongated or polymeric molecules can be aligned in space along the magnetic field. Thanks to this spatial alignment, their scattering profiles wouldn’t be axially symmetric any longer and will contain much more information compared to profiles from spherically averaged particles. We plan to extend the current method for analytical cylindrical averaging of spherical harmonics with multiple advantages over the standard approaches.

ELIGIBILITY CRITERIA

Applicants must hold a Master’s degree (or be about to earn one) or have a university degree equivalent to a European Master’s (5-year duration).

Applicants will have to send an application letter in English and attach:
- Their last diploma
- Their CV
- A short presentation of their scientific project (2 to 3 pages max)
- Letters of recommendation are welcome.

Address to send their application: sergei.grudinin@inria.fr
SELECTION PROCESS
Application deadline: **30 June 2018** at 17:00 (CET)
Applications will be evaluated through a three-step process:

1. Eligibility check of applications in July 2018
2. 1st round of selection: the applications will be evaluated by a Review Board in July 2018.
3. 2nd round of selection: shortlisted candidates will be invited for an interview session in Grenoble. (if necessary)

**TYPE of CONTRACT:** temporary-3 years of doctoral contract
**JOB STATUS:** Full time
**HOURS PER WEEK:** 35
**OFFER STARTING DATE:** October 2018
**APPLICATION DEADLINE:** 30 June 2018
**Salary:** between 1768.55 € and 2100 € brut per month (depending on complementary activity or not)