Experimental and theoretical characterization of macromolecular assemblies at low resolution

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Organizer1
Chantal Prévost
UPR 9080 – Institut de Biologie Physico-Chimique
chantal.prevost@ibpc.fr

Organizer2
Tâp Ha-Duong
UMR 8076 - Université Paris Sud
tap.ha-duong@u-psud.fr

Organizer3
Mounir Tarek
UMR 7565 – Université de Lorraine
mounir.tarek@univ-lorraine.fr

1. Proposal

1.1 Introduction and motivation

It is now well-known that cellular functions are achieved through various molecular machineries composed of several biomolecules. To gain a better insight into their mechanism, it is important to characterize the structure of these macromolecular assemblies. However, given their large size, it is still quite difficult to study these molecular complexes using the standard structural approaches such as crystallography or NMR. From the molecular modelling point of view, the classical techniques such as all-atom molecular dynamics simulations are also limited to provide unbiased informations on these macromolecular complexes, despite the parallel computing advances.

In this context, useful data on the structure of these biomolecular assemblies can be obtained experimentally using Small Angle X-ray Scattering (SAXS), neutron diffraction techniques or Cryo-Electronic Microscopy (Cryo-EM), or theoretically using Coarse-Grained (CG) molecular modelling. We believe that combining these low resolution approaches can significantly help the determination of molecular machineries structure and mechanism.

1.2 State of the art

During the last decade, theoretician groups have developed coarse grain representations of biological macromolecules in order to fill the gap between atomic representation and the mesoscopic level. These models conserve the granular aspect of atomic representation, but each grain groups several atoms or residues. Notably, the models with medium granularity, where a grain typically represents about 4 to 5 heavy atoms, allow conservation of properties of the atomic representation that are important for macromolecular assembly, such as surface characteristics (concavity, convexity), electrostatic properties, or hydrogen bond donor/acceptor character. This level of granularity can also handle flexibility, therefore enabling large amplitude explorations of the conformational space.

Beyond their variety and the different objectives that have prompted their developments, coarse grain models are now sufficiently mature to be confronted with two essential questions. The first one concerns their validation, and the set up of optimization steps like those which accompanied the validation of atomic model representations, starting from quantum mechanics. The second concerns the predictive potential of these coarse grain models directly at the low resolution level and their limit of validity: for example, to which point a coarse grain model can discriminate a correct geometry of association from an incorrect one. Establishing these points raises very interesting perspectives for modelers who would be able to concentrate their algorithmic and computational efforts on intensifying the exploration of large amplitude internal macromolecular movements or constructing large macromolecular assemblies.

We believe that this also raises perspective for experimental researchers who determine the structure of complex macromolecular systems at low resolution, using methods such as neutron diffraction, SAXS or Cryo-EM, which can provide information on their size, shape, characteristic distances and even structural data on the nanometer scale. It can be expected that existence of modeling tools that may be directly used at low resolution will boost the development of both experimental and theoretical fields, in the same kind of synergy that has accompanied the development of atomic resolution modelling methods in conjunction with experimental structure determination at the atomic level (X-ray crystallography, NMR).

1.3 Objectives

The aim of this meeting is, for modellers, to explore the possibility of confronting CG models of biomolecular assemblies directly with structural data, experimentally obtained at comparable levels of resolution. For experimentalists, the objective is to prompt the development of robust methods to assist structural determination at low resolution, which would respond to their specific needs. From the meeting between experimentalists and modellers, we also expect some future collaborative works that could significantly improve the structural characterization of theses cellular machineries.

1.4 Participant List

Chantal PREVOST (chantal.prevost@ibpc.fr) (Modelling)
Tâp HA DUONG (tap.ha-duong@u-psud.fr) (Modelling)
Mounir TAREK (mounir.tarek@univ-lorraine.fr) (Modelling)
Marc BAADEN (marc.baaden@ibpc.fr) (Modelling)
Coralie BOMPARD (coralie.bompard@iri.univ-lille1.fr) (Experiment)
Denis CHRETIEN (denis.chretien@univ-rennes1.fr) (Experiment)
Olivier DELALANDE (olivier.delalande@univ-rennes1.fr) (Modelling)
Philippe DERREUMAUX (philippe.derreumaux@ibpc.fr) (Modelling)
Sébastien FIORUCCI (sebastien.fiorucci@unice.fr) (Modelling)
Emmanuel GIUDICE (emmanuel.giudice@univ-rennes1.fr) (Mod+Exp)
Gerald KNELLER (gerald.kneller@cnrs-orleans.fr) (Modelling)
Luca MONTICELLI (luca.monticelli@inserm.fr) (Modelling)
Samuela PASQUALI (samuela.pasquali@ibpc.fr) (Modelling)
Javier PEREZ (javier.perez@synchrotron-soleil.fr) (Experiment)
Sophie SACQUIN-MORA (sophie.sacquin-mora@ibpc.fr) (Modelling)
Giuseppe ZACCAI (zaccai@ill.fr) (Experiment)
Nathalie BASDEVANT (nbasdeva@univ-evry.fr) (Modelling)

Possible additional participants (contacted):
Françoise LIVOLANT (livolant@lps.u-psud.fr) (Experiment)
Sergio MARCO (sergio.marco@curie.fr) (Experiment)
Daniel BORGIS (daniel.borgis@ens.fr) (Modelling)

2. *Financial Support*

The meeting will be held on one and a half days which are scheduled on March 2013. The exact dates will be fixed later according to the participants availability. Most of the expected participants come from the region Ile-de-France, but we wish to invite also two or three experts from the provinces (Nancy, Grenoble, Rennes). Therefore, we request the CFCAM to fund the meeting with a grant of about 4000 euros in order to pay the participants coffee breaks and lunches, as well as the train tickets for the guests from outside of Paris area.