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Short Talk 2, Sergei Grudinin - Novel algorithms for integrative structural biology.

Wednesday, 9 October 2019 14:15 (20)

In my talk I will present our approach for modeling macromolecular flexibility of large molecular assemblies and how it can be combined with sparse experimental data obtained with small-angle and cross-linking experiments.
Large macromolecular machines, such as proteins and their complexes, are typically very flexible at physiological conditions, and this flexibility is important for their structure and function. Computationally, it can be often approximated with just a few collective coordinates, which can be computed e.g. using the Normal Mode Analysis (NMA). NMA determines low-frequency motions at a very low computational cost and these are particularly interesting to the structural biology community because they are commonly assumed to give insight into protein function and dynamics [1].
One of the challenges in the community is the explanation of solution smallangle scattering profiles. Very recently, we designed a computational scheme that uses the nonlinear normal modes [2] as a low-dimensional representation of the protein motion subspace and optimizes protein structures guided by the SAXS and SANS profiles [3,4]. For example, in the CASP12 and CASP13 exercises, this scheme obtained best models for some (3 out of 9 in CASP12) SAXS-assisted targets [5,6]. Overall, the flexible fitting scheme typically allows a significant improvement of the goodness of fit to experimental profiles in a very reasonable computational time. The NMA analysis also allows to automatically split macromolecules into rigid domains, or to be used together with the cross-linking data, as we demonstrated in the recent CASP13 challenge [7].

References:
[1] Grudinin, S., Laine, E., & Hoffmann, A. (2019). Predicting protein functional motions: an old recipe with a new twist. bioRxiv, 703652.
[2] Hoffmann, A. & Grudinin, S. (2017). J. Chem. Theory Comput. 13, 2123 – 2134. For more information https://team.inria.fr/nano-d/software/nolbnormal-modes/
[3] Grudinin, S. et al. (2017). Acta Cryst. D, D73, 449 – 464. For more information https://team.inria.fr/nano-d/software/pepsi-saxs/
[4] https://team.inria.fr/nano-d/software/pepsi-sans/
[5] http://predictioncenter.org/casp13/zscores_final_assisted.cgi?target_flag=S
[6] Tamò, G. E., Abriata, L. A., Fonti, G., & Dal Peraro, M. (2018). Proteins: Structure, Function, and Bioinformatics, 86, 215-227.
[7] http://predictioncenter.org/casp13/zscores_final_assisted.cgi?target_flag=X

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