eSSENCE international workshop on macromolecular structure and dynamics

3-5 June 2013, Uppsala University
BMC, Room B42

Free attendance! (registration requested)
http://xray.bmc.uu.se/flores/eSSENCE-Workshop-2013.html

A 3-day workshop: 2 full days of conferences and poster sessions followed by a full day hands-on session (optional).

Key topics: Computational modeling of and simulation of biomolecules, including: Membrane proteins, Drug design and Chemometrics, Nucleic Acids and Protein-protein interactions.

Who: This workshop is mainly addressed to all researchers, from graduate students to staff scientists, either computational or experimental, working in the areas of molecular biology, biochemistry, biophysics or chemical biology.

Invited Speakers

Mark Bathe, Massachusetts Institute of Technology, USA

Andreas Bender, Cambridge University (UK)

Paolo Carloni, Institute for Advanced Simulation (IAS), Jülich (Germany)

Jens Carlsson, Stockholm University, (Sweden)

Thomas Caulfield, Mayo Clinic, Florida (USA)

Juan Fernandez Recio, Barcelona Supercomputing Center (Spain)

Mikael Lund, University of Lund (Sweden)

Lennart Nilsson, Karolinska Institute, (Sweden)

Joost Schymkowitz, Leuven University (Belgium)

Magnus Ullner, University of Lund (Sweden)

Jordi Villà-Freixa, University of Vic (Spain)

Eric Westhof, Université de Strasbourg & CNRS (France)

Hands-on sessions

GPCR-ModSim (Hugo Gutiérrez-de-Terán, Uppsala University)

MMB (Samuel Flores, Uppsala University)

THE e-SCIENCE COLLABORATION

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Oleksandr Savytskyi (Institute of Molecular Biology and Genetics, NASU, Kyiv, Ukraine) "*Domain binding interfaces in human tyrosyl-trna synthetase studied by the Hierot technique and molecular dynamics simulations"*

Tyrosyl-tRNA synthetase (TyrRS) is the key enzyme of protein biosynthesis, which catalyzes the aminoacylation of tRNATyr. The full-length TyrRS does not have cytokine activity, but its proteolytic cleavage reveals IL8-like activity of the N-terminal catalytic module and EMAP II-like activity of non-catalytic C-terminal domain. Earlier, it was found that the ELR-motif (E91, L92, R93) in TyrRS is responsible for IL8-like cytokine activity (Wakasugi and Schimmel, 1999), but the 3D structure of the full-length human TyrRS (HsTyrRS) is still unknown.

In this work we modelled the full-length HsTyrRS and studied its putative compactization by the coarse-grained Hierarchical Rotations Technique (HIEROT) and molecular dynamics simulations (MD). All computations were performed using grid-services of the MolDynGrid virtual laboratory (http://moldyngrid.org). The model of 3D structure of HsTyrRS was constructed in Modeller 9.7 using templates (PDB codes: 1N3L, 1NTG and 1OPL for interdomain linker). The best 10 structures were selected and 20 independent HIEROT simulations were performed for each of them. Six independent 100 ns MD trajectories of HsTyrRS were computed using GROMACS 4.0.5 software and G43a1 force field. The Contacts Analyzer Script (CAS) was used to characterize domains in human TyrRS. The tRMSF tool of the Pteros molecular modeling library was used to calculate fluctuations in different time intervals. The Distributed Analyzer Script (DAS) was used for analytical tools automation.
The domain binding interfaces obtained by MD and HIEROT methods were compared. The main "binding hot spot" on the N-terminal module contains the residues: E25-K26, E29-R34, G46-K47, Y79-L89, R93, R135, V139, K154, E157-H158, E175-D180, F192-V208, E227-K231, L235-C250, K243, F328-P342 which correspond "binding hot spot" regions obtained by HIEROT: Y79–L89, P200–Y204, K335, S338, A339.

The strongest binding energy of ~1000 kJ/mol is observed for the second C-module in simulation 1 and for the first C-module in simulation 6. In trajectories 1 and 6, only one of the C-modules binds strongly, whereas in trajectory 4, both C-modules exhibit almost identical binding energies of ~400–500 kJ/mol. In contrast, the binding energies in simulations 2, 3, and 5 are much smaller (300–400 kJ/mol).

Our data suggest that HsTyrRS molecules in solution coexist in a number of compact asymmetric conformations, which differ significantly by their general rigidity, mobility of C-modules, and the strength of their binding to the dimer of N-modules. The orientation of bound C-modules is rather unspecific while there is a pronounced set of binding hot spots on the surface of N-modules.

We observed the hydrogen bonding between the residue R93 of the ELR motif and the residues A340 and E479 in C-module in our MD simulations. This supports the idea that the full-length TyrRS lacks its cytokine activity because of the interactions between N-terminal and the C-terminal modules, which protect the ELR cytokine motif.