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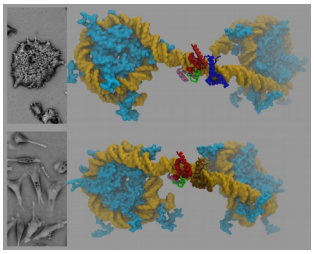

2 M.Sc. Projects in Computational Stem Cell Biology

Two projects suitable for Master theses are available in the Computational Structural Biology Laboratory within the Department of Cell and Developmental Biology at the Max Planck Institute for Molecular Biomedicine.

We are interested in the mechanisms by which transcription factors induce cell fate transitions. Transcription factors are proteins that bind to DNA regulatory regions to trigger gene regulation programs. They bind to specific DNA sequences alone or in cooperation with other transcription factors. In particular, we are interested in how cellular pluripotency is maintained and induced by transcription factors. Pluripotency refers to the capacity of stem cells to differentiate in cell types of all three germ layers (endoderm, mesoderm, and ectoderm). Pluripotent stem cells are key to future regenerative medicine approaches and therefore understanding the mechanisms by which they are regulated is highly important. Pluripotency is regulated by a core transcriptional circuitry established by a set of transcription factors. Remarkably, some of these are also capable of inducing pluripotency in somatic cells. We use molecular modeling and simulations to decipher how the above mentioned transcription factors recognize DNA in different genomic and cellular contexts. Our work is aimed both at understanding the basic principles of transcription factor-mediated regulation of pluripotency and at designing means to manipulate transcriptional circuitries for regenerative medicine approaches.

The first project involves setting up and performing simulations or protein-DNA unbinding and calculating unbinding free energy profiles. Predicting DNA-binding affinities of transcription factors based on atomistic molecular dynamics simulations is of particular challenge due to the long time scale and the complexity of protein-DNA binding and unbinding processes. We recently showed that one-dimensional free energy profiles tend of overestimate DNA-binding affinities possibly due to the poor sampling of the unbound state. The project is aimed at identifying the best combination of order

parameters to characterize the unbinding process, the setup of simulations to reconstruct free energy profiles along the chosen order parameters, and the application of different simulation methods (e.g. umbrella sampling, metadynamics, adaptive biasing force etc.). The final goal is to design a protocol that would minimize the overestimation of protein-DNA binding affinities and can be further used for simulations of protein-DNA unbinding to reveal both accurate binding affinities and realistic dynamics of the binding-unbinding process.

The second project involves modeling of the binding of pioneer transcription factors to nucleosomes. Pioneer transcription factors have the exceptional ability to bind DNA wrapped in nucleosomes in closed chromatin states and trigger opening of chromatin. Many of them have highly important biological functions such as cellular identity induction and determination. However, the mechanism by which they recognize wrapped DNA and promote opening of chromatin is unknown. In particular, the master regulators of pluripotency OCT4 and SOX2 were recently shown to be pioneer transcription factors. The project is aimed at identifying possible binding modes of OCT4 and SOX2 to nucleosomes. The expected deliverables are: (i) an automated procedure to build models of OCT4 and SOX2 bound to different nucleosome sequences in different configurations; (ii) energetic evaluation of the models, and (iii) prediction of favorable and unfavorable binding modes.

Both projects will be performed in close collaboration with experimenters such as that predictions can be directly tested in different types of experimental assays.

For both projects, we are seeking students highly motivated to work in an exceptionally inter-disciplinary environment and aiming to obtain a Master of Science degree in natural sciences. Knowledge of chemistry and physics concepts related to molecules and molecular interactions as well as computer skills such as operating in Unix/Linux are required. Previous acquaintance with molecular dynamics simulations and/or with advanced programming languages may be an advantage. The students will benefit from working in a team with a very strong expertise in stem cell biology and in biomolecular modeling and simulations. Students will gain not only the technical skills and knowledge related to the methods used and biological processes investigated but also other skills such as developing a research project, working in a team, presenting their work, and writing scientific documents for large audiences.

If interested in any of these projects, please send a short curriculum vitae including the contact details of two potential referees as soon as possible to vlad.cojocaru@mpi-muenster.mpg.de