Structure/function relationships of the GLIC channel investigated by multiscale simulation

Project description

A joint PhD position is immediately available in the groups of Dr. Paolo Carloni and Dr. Marc Baaden. The teams are located at Forschungszentrum Jülich/RWTH-Aachen University, Germany and in the Institut de Biologie Physico-Chimique (CNRS), Paris, France. The two labs have solid and internationally recognized expertise in computational modeling of membrane proteins, and in particular ion channels. This project will combine methodological expertise from Jülich, in particular the use of a High-Performance Computing (HPC) based-QM/MM approach, with biological applications to the pentameric ligand-gated ion channel family, and in particular the experimentally very well characterized GLIC channel. The student will spend roughly half time in Paris and half in Jülich.

The Student will finally defend her/his PhD at RWTH-Aachen University. The latter is currently one of the ten German Universities currently part of the so-called “Excellent Initiative” across all of Germany’s Institutions.

In Jülich, the student will calculate the pKa of a specific histidine (His235) by QM/MM methods. The protonation state of this residue, currently controversial, is key for the study of this important channel: some groups even indicate that this is the only group governing pH-induced gating (the channel is open at pH 4.6; closed at pH7).

In Paris, the student will confront the QM/MM results with a large series of existing molecular dynamics (MD) trajectories of roughly microsecond length and with variations on the protonation state. Complementary MD simulations based on the most likely protonation state (as determined in Jülich) and the (a)symmetry of protonation among the five subunits will be carried out and analyzed for at least four combinations: most likely protonation states at pH 4.6 and pH 7 simulated for both open and closed channel forms. In addition, the energy cost of changing protonation state will be quantified by a perturbation approach. These calculations may answer the questions how the protonation state alters the conformation and dynamics of the channel and how the protonation change modulates the energy landscape of the channel.

The PhD candidate will be trained to perform and analyze atomistic and advanced, highly parallel QM/MM molecular dynamics simulations, in particular learning how to exploit multi-scale approaches for representing complex biological models.

The successful candidate for this PhD position is a creative, highly motivated student. (S)he has a solid background in physics/chemistry, along with excellent computational skills and knowledge of the English language. Preferably, she/he has some knowledge of biophysics.

About the host institutes

The "Institut de Biologie Physico-Chimique" was created in 1930 by the Foundation Edmond de Rothschild. It is associated with the CNRS (Centre National de la Recherche Scientifique), a leading international scientific institution offering an exceptional environment to scientists early in their carreer, with a dynamic international exposure animated by regular seminars and meetings. The Laboratoire de Biochimie Théorique is an internation-

ally recognized laboratory with the mission of developing and applying computational methodologies to solve biological relevant problems. The members are active in the fields of docking, atomistic and coarse-grained simulations tackling problems as protein/protein and protein/DNA interactions, dynamics and function of membrane proteins, protein folding and aggregation.

Forschungszentrum Jülich (FZJ), member of the Helmholtz Association, is one of the largest interdisciplinary research centers in Europe. It manages one of the most important supercomputing centers in the world. Here, the Institute "Computational Biomedicine" makes advances in molecular biology by performing HPC-based molecular simulations, structural bioinformatics and ligand design.

Closing date: December 31 2016

Interested candidates should send a detailed CV and a statement of research interests as PDF documents, and have three reference letters sent to baaden@ibpc.fr.

Executive summary:

When? 36 months starting ASAP

Where?	Laboratoire de Biochimie Théorique, Paris, France and Forschungszentrum Jülich, Germany, with frequent moves from Paris to Jülich supported by the contract.
Salary:	ca. 2300 €/month (before tax)
Team Leaders:	Paolo Carloni / Marc Baaden
Collaborators:	Jérôme Hénin / Antoine Taly

Websites:

http://www.grs-sim.de/research/computational-biophysics/

http://www.baaden.ibpc.fr