



ISTITUTO ITALIANO
DI TECNOLOGIA

PHD Neurosciences, curriculum "Neurosciences and Neurotechnologies, XXXVII cycle

Project title:

Multi-scale computational study of PRRT2-NaV interactions

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The Proline-rich transmembrane protein 2 (PRRT2) is a recently discovered protein that has been linked to several juvenile paroxysmal disorders, and whose atomic structure is still unknown from experiments. We have proposed a refined, full-atom structural model of PRRT2 transmembrane domain, whose topology is consistent with experimental observations. Recent work conducted at NSYN has demonstrated that the PRRT2 protein exerts a fundamental role in controlling neuronal excitability via interactions with voltage-dependent sodium channels NaV1.2 and NaV1.6, while it does not interact with Nav1.1. The aim of the present project is to investigate PRRT2-NaV association computationally, by studying the differential binding between the transmembrane segment of PRRT2 and NaV1.1, Nav1.2 and Nav1.6 channels. The project will be tackled at a multi-scale level. Molecular docking will be performed to find the preferred interacting surface between NaV channels and PRRT2, using different conformations extracted from extended, all-atom Molecular Dynamics simulations of the individual proteins in a membrane environment. At the same time, coarse-grained simulations will be exploited to investigate the spontaneous association of the proteins over time scales that are not accessible to all-atom models. Results from multiple-conformations docking and coarse-grained simulations will provide the most probable protein-protein binding surface. Comparing the outcomes for Nav1.1 and Nav1.2/6 will elucidate the molecular basis of the differential interaction. The project is part of a collaboration with experimental molecular biology and electrophysiology groups that will perform direct testing of the modeling hypothesis by mutating selected amino acids in the predicted protein-protein interaction surface. For further information, please contact dr. Luca Maragliano (luca.maragliano@iit.it), and dr. Fabio Benfenati (fabio.benfenati@iit.it).