51. Molecular Modelling and Dynamics of Membrane Proteins

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Using computational methods, we generate structures of membrane proteins and use a range of motion analysis approaches to study their motions in order to understand their mechanism of function. These methods range from molecular dynamics simulations (GROMACS) which allow analysis on the atomic level, to coarse-grain methods such as the Gaussian Network Models (GNM) and CONCOORD.

Using computational methods, we generate the structure of membrane proteins and study the structural variability and relevant motions of the nicotinic acetylcholine receptor (nAChR) and related proteins in the Ligand Gated Ion Channel (LGIC) family with a variety of computational dynamics methods to gain understanding of their function from various angles.

Our method constructs models of proteins where only partial crystallographic, electro-microscopic, or NMR structures are available. Using the partial structures, the full protein is constructed by a series steps involving homology modelling, combining the separate domains, analysis of possible models and finally selection of the optimal model which is then used for structural studies.

A range of motion analysis approaches are employed to study the relevant motions of proteins in order to understand their mechanism of function. These methods range from molecular dynamics simulations (GROMACS) which allow analysis on the atomic level, to coarse-grain methods such as the Gaussian Network Models (GNM) and CONCOORD. Large-scale motions of the proteins are explored through the coarse-grain methods as atomics simulations cannot explore the time-scale required to study functionally relevant motions, such as the gating of ion channels. Further coarse-grain methods and other molecular modelling techniques are being developed to study the structure, dynamics, and plausible functions of these large proteins. The various methods of motion analysis provide us with ways of studying the dynamics involved in the function of the receptors at different time-scales.

Molecular dynamics simulations of the ligand binding domain of the nAChR using nicotine, carbamylcholine, and HEPES as ligands has been carried out to study the motions of this receptor at the atomic level. Principle Component Analysis (PCA) and other tools are being used to study the relevant motions of subunits upon ligand binding to help understand how the binding of a ligand results in conformational changes which ultimately open the channel pore and allow for the passage of ions. Further dynamics studies of the role of water in the binding pocket are investigated in conjunction with docking studies of the various ligands to gain a better understanding of the different modes and conditions of binding.

The computational methods used to study the conformational dynamics of ion channels on various levels (atomistic and coarse-grained), provides an avenue for exploring the motions and actions of the ligands of proteins on a range of time-scales. These methods complement experimental methods and could suggest new avenues of research and understanding of protein function.