Project Proposal for Join A*STAR Graduate Scholarship (Overseas) with the University of Oxford:

"Development of Long-Time Scale Simulation Methods to Neuroreceptors."

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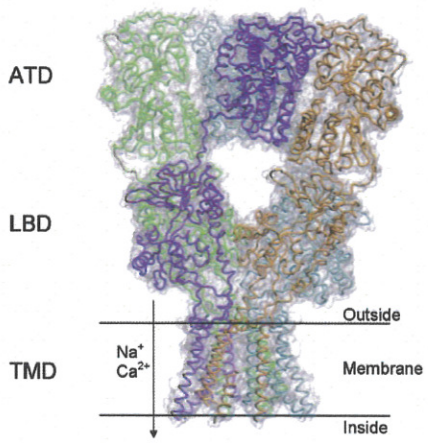
Background and Current Situation

The ionotropic glutamate receptors mediate most of the fast neurotransmission in the brain and have been associated with memory and learning. Defects in iGluRs has been linked to many different neurological disease states including Alzheimer's, Huntingdon's, epilepsy and the effects of stroke. They are therefore of major pharmaceutical interest. Upon binding neurotransmitter (glutamate in this case), they open a transmembrane pore, which allows the flux of ions into or out of the cell – this is the basis of neurotransmission. Despite much work, the exact nature of the conformational changes that these receptors undergo is not well-understood.[1] Thus there is considerable interest in developing computational methods that can allow us to explore these changes in more detail. The structure of a complete iGluR is shown below and the central unresolved question is how does binding to the ligand-binding domain (LBD) lead to the opening of the transmembrane domain (TMD) pore?

Objective and Approach

From a studentship point of view, these receptors are an ideal target on which to work, as certain parts of the molecule (the LBD region) are well characterized and have been extensively studied. Their movement between pairs of ligand-domains is less well understood and the large conformational change that allows ligand-binding to actually open the channel is extremely poorly understood. A better understanding of the nature of these conformational changes could lead to better prospects for selective therapeutic intervention.



We will develop and apply computational methods to examine conformational changes associated with ligand-binding. We will make use of molecular dynamics (MD) simulations, which can provide a route to characterize the conformational plasticity of proteins in atomic detail.[2,3] However, understanding iGluR mechanism using standard simulation approaches alone is challenging, due to the large system sizes and correspondingly large numbers of degrees of freedom, combined with the fact that ligand binding and conformational changes in the receptor may occur over significantly different timescales. This project will therefore be focused on overcoming this challenge, by making use of multi-scale modelling approaches.[4] We will utilize all-atom simulations to characterize the free-energy landscape underlying different receptor states, and use this to build multi-state, Go-like and lipid-partitioning-based coarse-grained models. We will design and test the models using the ligand-binding domain as our initial test case. There is a wealth of crystallographic, SAXS and computational data for this system so it will be easy to validate the methodology. Once the method has been developed we can move on to applying it to the more complex desensitization process[2] and ultimately the movement of the whole receptor. The project will combine the multi-component complex modelling[3] and coarse-grained/multiscale simulation capability[4] of the Bond laboratory at BII A*STAR with the iGluR and free energy calculation expertize of the Biggin laboratory in Oxford.[2] Successful completion of the project will improve our fundamental understanding of the molecular basis for ionotropic glutamate receptor signalling associated with neurotransmission, and provide a structural basis for potential pharmaceutical exploitation.

References

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(3) Paramo T., Piggot, T. J., Bryant, C. E., and Bond, P. J. (2013) The structural basis for endotoxin-induced allosteric regulation of the Toll-like receptor 4 (TLR4) innate immune receptor. *J. Biol. Chem.* 288, 36215-36225.

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