Project Proposal for Join A*STAR Graduate Scholarship (Overseas) with the Imperial College London:

Integrated Multiscale Approaches of Theory and Experiments to Characterise Amyloid Formation at Membrane Surfaces.

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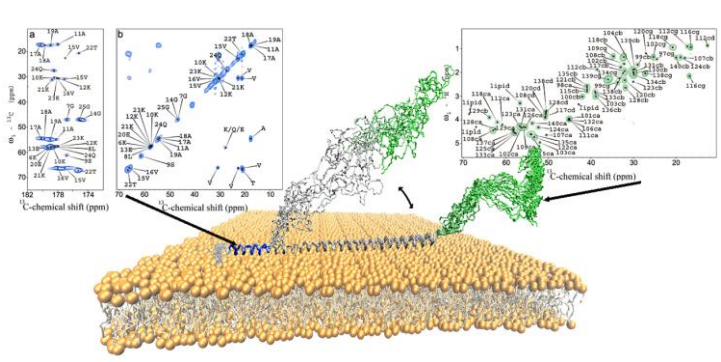
Background.
Cellular membranes host fundamental biomolecular interactions of key relevance for functional and pathological processes. Most of these interactions involve transient and dynamical states, which are hardly characterised by current analytical techniques. This methodological gap poses a tremendous scientific challenge of strategic relevance for both academia and industry. There is indeed a demand for innovative and interdisciplinary methods that could address the nature of heterogeneous processes such as cellular signalling, endocytosis and protein assembly at the surface of lipid membranes. The latter case is particularly relevant in the context of the molecular bases of neurodegenerative disorders such as Parkinson's and Alzheimer's. To provide a step forward in our understanding of the molecular origins of these diseases, we would ultimately need to account for molecular dynamics extending across a large range of timescales and involving protein-protein and protein-lipid interactions.

Objectives.
We will merge our complementary skills across A*STAR and Imperial College to define a new team that integrates fine grained (De Simone/Bond) and coarse grained simulations (Bond) with biomolecular NMR experiments (De Simone) to characterise heterogeneous processes of protein assembly at the surface of membrane proteins. In particular, we will develop and apply experimentally restrained multiscale simulations to account for transient interactions between multiple molecules. Full atom simulations will accurately describe the system at a fine grained level by incorporating solid state nuclear magnetic resonance (ssNMR) data, such as chemical shift (isotropic and anisotropic), dipolar couplings and distance restraints. Besides generating an accurate representation of the structure and dynamics of proteins and lipids, fine grained simulations will be used to parameterise coarse grained simulations (CG), which will account for the collective behaviour of multimolecular systems. We will focus on the key topic of alpha-synuclein (Asyn) aggregation at the cellular membrane. In doing so, our method development will be associated with a key challenge in Parkinson's research. The multiscale approach will characterise the entire process of Asyn assembly, i.e. from its monomeric, disordered form to the membrane-associated and amyloid states. The De Simone lab has recently been able to obtain breakthrough ssNMR measurements of Asyn at the surface of synaptic-like lipid vesicles (Figure and **[1]**). The lab has also advanced the use of ssNMR restraints in full atom simulations of membrane proteins **[2]**. The combination of the expertise in NMR and atomistic simulations of membrane proteins (De Simone) and the world-class expertise in protein-lipid interactions **[3]** and multiscale simulations of membrane proteins **[4]** (Bond) represents the perfect interdisciplinary setting to provide a breakthrough step forward in this field. The methodology developed will have a general applicability and should be effectively applied to a variety of topics including biomaterial assembly, hydrogels, molecular vesicles for drug delivery etc.



References

[1] Fusco et al, Nature Communications (2014) 5:3827.
[2] De Simone et al, Biophys J (2014) 106:1771-9.
[3] Khalid & Bond, Methods Mol Biol (2013) 924:635-57.
[4] Paramo et al, J Biol Chem (2013) 288:36215-25.