Membrane proteins present both experimentalists and computational scientists with special challenges. For the biochemist, they are often difficult to overexpress, purify and study in isolation. As a result, only a few percent of all known crystal structures representing membrane proteins. Yet, for the computational biologist the field of membrane protein structure/function prediction is fertile ground, partly because the experimental studies are so difficult, partly because the structural characteristics of membrane proteins are in some respects simpler than those of soluble proteins.

From the computational point of view, one main area of study is topology prediction. Up until recently, almost all topology-prediction methods have been based on statistical analysis of known structures and more or less sophisticated machine-learning approaches. We have taken a different approach, trying to derive basic free energies of membrane insertion for the different amino acids from in vivo studies of membrane insertion of transmembrane α-helices. Using this kind of experimental data, we have been able to develop a very simple topology prediction scheme that performs on par with the best HMM-based methods. Our results further show that the 'hydrophobicity threshold' required for efficient membrane insertion of TM helices in multi-spanning membrane proteins can be considerably higher than that seen for single-spanning membrane proteins, strongly suggesting that tertiary interactions between TM helices can be important for membrane insertion.