Structural modeling of membrane proteins from viruses.

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Abstract

Computational methods comprise a valuable tool to close the sequence – structure gap, especially for membrane proteins. At this stage secondary structure prediction programs are available to identify putative stretches of helical transmembrane domains (TMDs) while a few programs are developed to predict a beta sheet fold as the membrane spanning motif. With the knowledge about the putative TMDs, here adopting a helical motif, at hand these TMDs can be assembled into a tertiary structure, and finally into putative quaternary structures using docking approaches

As a test case, viral channel forming proteins (VCPs), sometimes also called viroporins, are used to develop strategies to generate plausible structures [1]. VCPs are about five time smaller than human ion channels and therefore used as a miniaturized system to investigate how ion channels are formed. Using E5 protein of human papilloma virus type 16 (HPV-16) the assembly of a poytopic membrane protein with three TMDs is presented in its hexameric form [2]. Using a docking approach, the monomeric form is generated first before assembling into the hexamer. The quality of the model is assessed using potential of mean force calculations (PMF) identifying weak ion selectivity. Principle component analysis (PCA) of the data from a classical molecular dynamics simulations reveal asymmetric dynamics of the monomers. These dynamics are compared with those derived for other VCPs such as polytopic p7 of hepatitis C virus (HCV) with two TMDs [3] and bitopic M2 of influenza A [4]. Finally, coarse grained simulations are applied to probe the formation of the quaternary structure of e.g. Vpu of HIV-1 [5].

Recent Publications

1. J. Krüger, W. B. Fischer; Assembly of viral membrane proteins. *J. Chem. Theory Comput. (2009) 5, 2503-2513*
2. Mahato DR, Fischer WB (2016) Weak selectivity predicted for modeled bundles of the viral channel forming protein E5 of human papillomavirus-16. J. Phys. Chem. B 120:13076-13085.
3. M. M. Kalita, W. B. Fischer; Asymmetric dynamics of ion channel forming proteins - hepatitis C virus (HCV) p7 bundles. *Biochim. Biophys. Acta (2016) 1858, 1462-1470*
4. M. M. Kalita, W. B. Fischer; Decoupled side chain and backbone dynamics for proton translocation - M2 of influenza A. *J. Mol. Mod. (2017) 23, 212*
5. C.-P. Chen, M.-H. Lin, Y.-T. Chan, L.-C. Chen, C. Ma, W. B. Fischer; Membrane protein assembly: two cytoplasmic phosphorylated serine-sites of Vpu from HIV-1 affect oligomerization. *Sci. Rep. (2016) 6, 28866*

Biography

Dr. Wolfgang Fischer is Professor at the Institute of Biophotonics, School of Biomedical Science and Engineering, National Yang-Ming University, Taipei, Taiwan (www.ym.edu.tw/~wfischer/). He has obtained his PhD in Chemistry at Heidelberg University, Germany, working in the field of vibrational spectroscopy in 1991. After years in the US (Boston University, postdoctoral fellow working on bacteriorhodopsin using vibrational spectroscopy), Germany (TU-Dresden, Analytical Chemistry, working on ion channels as potential biosensors), UK (Oxford University as EU Marie Curie Research Fellow and later as Lecturer working on viral ion channels using bilayer recordings and molecular dynamics simulations) he moved to Taiwan. The field of research is on biophysical aspects describing dynamics and energetic of protein-protein interactions (PPIs) of membrane proteins. The focus is on the development of computational platform technologies to support structural modeling for drug discovery and design as well as for materials sciences.

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Notes/Comments