New Tools for Membrane Peptide Simulation using Angular Dynamics

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In 1988, the first tilted peptide was highlighted in the protein responsible for the fusion in the New Castle virus (*Brasseur R., Lorge,P., Espion,D., Goormaghtigh,E., Burny,A. and Ruysschaert,J.M. Virus Genes 1 (1988) 325-332 "The Mode of insertion of the paramyxovirus F1 N-terminus into lipid matrix, an initial step in host cell-virus fusion"*). Afterwards, it was shown that this kind of peptide exists not only in the proteins implicated in viral fusion, but also in lipases, in signal sequences, in some apolipoproteins and in other proteins involved in interactions with the membrane leading to fusions, crossings or substrates (*Brasseur R. Molecular Membrane Biology, 17 (2000) 31-40 "Tilted peptides: a motif for membrane destabilisation (Hypothesis)"*).
These peptides are short and are constituted of between 10 to 20 residues. They can be found both at the N- and at the C-terminal of the protein. For instance, in the case of viruses, fusion peptides, which are tilted peptides, are located at the N-terminal while in some neurodegeneratives disease, such as Alzheimer's. This tilted peptide is found at the C-terminal of the βA4 protein. This kind of peptide can also be located in the middle of the protein sequence; this is the case of lipases. In fact, these peptides present an inversed hydrophobic and hydrophilic gradient; which means that from one extremity to another, their hydrophobicity increases, and hydrophilicity decreases. Because of this asymmetry of hydrophobicity, the peptide tries to place itself at an angle in relation to the hydrophobic-hydrophilic interface, made up of a biological membrane. It orientates the axis of the helix at around 45° from the membrane surface. It is for this reason that such peptides are called tilted.
Recent neutron diffraction measures carried out by Dr Bradshaw in partnership with Dr Epand (*Bradshaw J.P., Darkes M.J.M, Harroun T.A., Katsaras J. and Epand R.M. Biochemistry 39 (2000) 6581-6585 "Oblique membrane-insertion of viral fusion peptide probed by neutron diffraction"*), have shown a placement and orientation compatibles with what was theoretically predicted for these tilted peptides. The group led by Tamm (*X. Han, J.H. Bushweller, D. S. Cafiso and L. K. Tamm. Nature Structural Biology 8n°8 (2001) 715-720 "Membrane structure and fusion triggering conformational change of the fusion domain from influenza hemagglutinin"*.) has shown using NMR that the HA2 fusion peptide is tilted in the membrane. They observed a tilted orientation in relation to the interface, which is pH dependent. This means that at pH 7.4 the tilt is slight, around 21°, whereas at pH 5 it increases to around 37°. These peptides were first discovered using molecular modelisation technology, by constructing peptides in a helical structure and studying the way they interact with membrane. Recently, it has been shown that studying the dynamics, as well as the orientation in the membrane is very important. Unfortunately, this type of simulation is extremely time-consuming and limits considerably the field of study that can be carried out using the tilted peptides currently known to exist.
In the 90s, we developed a procedure for studying protein folding, which included a technique called angular dynamics. (*Benhabiles N., Gallet X., Thomas-Soumarmon A. and Brasseur R. J. Computational Biology. 5:2 (1998) 351-366 "A descriptive analysis of populations of three-dimensional structures calculated from primary sequences of proteins by OSIRIS"*). Angular dynamics involves distributing the system's energy to each of the freedom degrees in the system, the torsion angles, and applying Verlet's equations as they are used in molecular dynamics on freedom degrees. We intend to show that this type of method is useful for studying the way in which peptides insert into the membrane, and opens up a simulation zone with reasonable calculation times, for understanding certain membrane mechanisms.