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Determining the Structures of Peptides in Membranes Using Diffraction and MD Simulations.

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Quantitative structural images of peptides in oriented arrays of fluid lipid bilayers are necessary for interpreting thermodynamic measurements of peptide-bilayer energetics in molecular terms. Lamellar x-ray and neutron diffraction provide a starting point for obtaining structural images. But the high thermal motion of fluid bilayers limits "structures" to so-called bilayer profiles, representing a time-averaged projection of the unit-cell contents onto an axis normal to the bilayer plane. Specific deuteration of lipid structural groups combined with neutron diffraction difference methods allow these profiles to be decomposed into a collection of groups (phosphates, carbonyls, etc.) representing transbilayer probability distribution functions. The power of this method has been extended through the inclusion of x-ray data and a joint-refinement protocol. We have developed an x-ray method, referred to as absolute-scale refinement, that permits the determination of the disposition of peptides in fluid bilayers. These various approaches can be used in concert as a powerful tool for gaining structural information. But that information is still only one-dimensional. We are now developing methods for obtaining experimentally validated three-dimensional structures by combining the diffraction methods with molecular dynamics simulations. In essence, our goal is to convert 1-D experimental data into 3-D images. Importantly, these images will be dynamic, which will permit the ensembles of peptide-lipid structures to be explored in detail. An essential issue, however, is the validation of MD simulations using diffraction data. A method of accomplishing this objective will be described.

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