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Pulse Dipolar ESR and Protein Superstructures and Function

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Pulse dipolar electron-spin resonance (PDS-ESR) has emerged as a powerful methodology for the study of protein structure and function. This technology, in the form of double quantum coherence (DQC) – ESR and double-electron-electron resonance (DEER) in conjunction with site-directed spin-labeling will be described. It enables the measurement of distances and their distributions in the range of 1-9 nm between pairs of spins labeled at two sites in the protein. Many biological objects can be studied: soluble and membrane proteins, protein complexes, etc. Many sample morphologies are possible: uniform, heterogeneous, etc. thereby permitting a variety of sample types: solutions, liposomes, micelles, bicelles. Concentrations from micromolar to tens of millimolar are amenable, requiring only small amounts of biomolecules. The distances are quite accurate, so a relatively small number of them are sufficient to reveal structures and functional details. Several examples will be shown. The first is defining the protein complexes that mediate bacterial chemotaxis, which is the process whereby cells modulate their flagella-driven motility in response to environmental cues. It relies on a complex sensory apparatus composed of transmembrane receptors, histidine kinases, and coupling proteins. PDS-based models have captured key architectural features of the receptor kinase arrays and the flagellar motor, and their changes in conformation and dynamics that accompany kinase activation and motor switching. Another example will be determining the conformational states and cycling of a membrane transporter, GltPh, which is a homotrimer, in its apo, substrate-bound, and inhibitor-bound, states in membrane vesicles providing insight into its energetics. In a third example the structureless (in solution) proteins alpha-synuclein and tau, which are important in Parkinson's disease and in neurodegeneration will be described and the structures they take on in contact with membranes will be described. Another important development is that of extending ESR to much higher frequencies (ca. 250 GHz), which has enabled a multi-frequency ESR approach to the study of protein dynamics that enables the separation of their complex modes of motion in terms of their different time scales.