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Life of Molecules in Space and Time

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Abstract:

Structural transitions and configurational energy landscapes are fundamental to the description of physical, chemical, and biological change, and even for the cosmological (inflation) events following the Big Bang. Over the past two decades, it has become possible to observe atomic motions with femtosecond resolution (*femtochemistry*) during the course of the change and for different systems. However, when chemical and especially biological changes involve complex transient structures with hundreds of atoms and many possible conformations, one must address the nature of the three-dimensional (3D) molecular structures, but at different times during the change. Such direct determination of *molecular structures in space and time* requires the resolution of the fourth dimension, defining 4D diffraction, crystallography, and microscopy.

At the turn of the twentieth century, beginning with x-rays, diffraction techniques have allowed determination of *equilibrium* (time-averaged) 3D structures with atomic-scale resolution in systems ranging from diatoms (NaCl) to DNA, proteins, and complex assemblies such as viruses. Electron diffraction has also made major strides in the determination of structures, and in fact the first membrane protein (water insoluble) structure of bacteriorhodopsin was determined using electron diffraction/microscopy. Such a membrane crystal is only *ca.* 10 nm thick, which is far too thin for x-ray diffraction studies. Later, determination of the structure of the photosynthetic reaction center, a membrane

protein by x-ray diffraction techniques was achieved, and more recently the structure of ion channels was successfully completed. However, mechanisms of function have not yet been fully elucidated as the understanding of the function requires knowledge of the dynamics.

In this talk, we will highlight recent developments of 4D ultrafast electron diffraction (UED), crystallography (UEC), and microscopy (UEM) at Caltech. With joint spatial (picometer) and temporal (picosecond to femtosecond) resolutions, it is now possible to determine complex molecular structures and observe their evolution during the change. We will discuss applications in different areas, including studies of interfaces, self-organization, bilayers, and nanocrystals. We conclude by reporting the progress made in the direct imaging of nano-to-micro structures and cells in space and time, and the potential for exploration in areas of physics, chemistry, and biology.

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