Macromolecular Complexes: The Frontier with Cell Biology: Chairman's Introductory Remarks

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Order in nature appeals to the orderly mind of the protein crystallographer. Many cellular processes are not the result of random collisions between freely diffusing molecules but the result of protein molecules acting in concert in macromolecular assemblies to produce a coordinated response. There is the expectation that once structures of these complexes are known, deeper insights into specificity and mechanisms may be obtained, similar to those that have been achieved for individual enzymes and recognition proteins. Already there have been spectacular examples such as the structure of the *S. cerevisiae* 20S proteasome (28 subunits), the mitochondrial F1 ATPase ($\alpha_3\beta_3\gamma\delta\varepsilon$ molecular weight 372 kDa) and both eukaryotic and prokaryotic cytochrome C oxidases, the protein complex located in the inner membrane of mitochondria and many bacteria. Principles of protein-protein recognition and how such interactions can modulate biological activity have been obtained from complexes such as: spherical viruses with their beautiful icosahedral symmetry; multi domain structures (e.g., as src kinase); and multi-component complexes (e.g., heterotrimeric G proteins and the complex of G$s\alpha$ with adenylcyclase, or the HIV gp120 envelope protein in complex with CD4 receptor and a neutralising antibody, or the GroEL/GroES/ADP chaperone complex). The structure of the Bluetongue virus (BTV) has demonstrated power to elucidate not only the topology of the structural protein subunits and their principles of self-assembly based on the quasi-equivalence principle and variations of this principle but also to reveal the packaging of the genomic dsRNA and the multi-enzyme transcriptase complexes, in a model of a transcriptionally active compartment.

What remains to be done? Undoubtedly there are a number of complexes where structural studies are demanded in order to illuminate biology, especially in the areas of DNA replication and transcription, in control of cell cycle processes, in motility, and in membrane transport. Securing sufficient soluble material for crystallisation trials is a major problem. How can we use heterogeneous recombinant DNA expression systems for the assembly of particles that may contain more than a dozen proteins? Advances in single particle imaging in the electron microscope give rise to the expectation that low-resolution images can be achieved with relatively little material and without the need for crystals and provide an image that can be the starting point for a high resolution interpretation, as for example in the structural studies on the topology of the core protein of the hepatitis B virus (a complex that did reassemble from proteins expressed in bacteria). Structural studies on the ribosome, both the individual proteins and the whole complex, are moving forward rapidly with high-resolution images from electron microscopy and promising diffraction quality crystals. In general, crystals of macromolecular complexes are likely to be small and weakly diffracting. The recent structure determination of bacteriorhodopsin from micro-crystals grown in lipidic cubic phases using the microfocus beam line at ESRF has shown that data can be obtained with crystals as small as 30µ x 30µ x 5µ. The introductory remarks will review some of the achievements to date and lead into the papers in the session that will address some of the problems for the future.