density map using the MDFF method (Molecular Dynamics Flexible Fitting). The structure allowed for the identification of ribosome–lipid interactions. The rRNA helix 59 (H59) directly contacts the lipid surface and appears to modulate the membrane in immediate vicinity to the proposed lateral gate of the PCC. Based on our map and molecular dynamics simulations we present a model of a signal anchor–gated PCC in the membrane.

Keywords: cryo-EM, SecYEG, MDFF,

MS.02.2

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Dynamics and stability in virus maturation: mechanisms of a molecular machine

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Assembly of quasi-equivalent virus capsids engages molecular switches to create different interface contacts between the same gene products. The particle often assembles as a fragile, spherical shell in which the subunits are properly positioned on the appropriate surface lattice and then quasi-equivalent subunit contacts differentiate during maturation, creating a robust, faceted particle. Folding of the switch regions of the subunit depends on assembly and maturation that are affected by biochemical cues. NwV is a quasi-equivalent virus, with a *T*=4 surface lattice, where this process is dramatic (a change in particle size of 100Å during maturation) and can be investigated *in vitro*. Here we use biochemistry [1], Small Angle X-ray Scattering [2] and electron cryo-microscopy and image reconstruction (CryoEM) [3] to characterize maturation intermediates and an associated auto-catalytic cleavage, the kinetics of morphological change and to demonstrate that regions of NwV subunit folding are maturation-dependent and occur at rates determined by their quasi-equivalent position in the capsid.

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Keywords: virus, dynamics, maturation

MS.02.3

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Lessons learned from the cryoEM and x-ray structures of the human adenovirus

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Structural information of macromolecular complexes in the form of atomic coordinates is essential to uncovering the mechanisms of action of biological functions and to designing compounds for therapeutic interventions of human diseases. X-ray diffraction and Nuclear magnetic resonance spectroscopy (NMR) have been very successful in solving atomic structures of biomedical importance and are the primary contributors of atomic structures determined to date. The emerging technology of single-particle cryo electron microscopy (cryoEM) has less stringent requirement for sample purity and quantity than x-ray crystallography and NMR but resolution achieved by cryoEM is often limited to nanometer or molecular resolutions, thus severely limited its value and application in biomedical research.

Recently, several cryoEM structures have crossed the resolution barrier of 4 Å. This progress in cryoEM was made possible by a number of advancements, such as atomic-resolution image acquisition and efficient molecular model building. Of special note, the structure of the human adenovirus has been determined by both methods of cryo-EM and x-ray crystallography, independently by two groups. Here we provide the first direct comparisons (Figure 1) of these cryoEM [1] and x-ray structures [2], at resolutions of 3.6 Å and 3.5 Å, respectively. This comparison shows an excellent match between the structures of the "major" proteins, revealed by the cryoEM and x-ray structures of the human adenovirus. It also highlights significantly richer information content in the cryoEM structures of the three "minor" proteins IIIa, VIII and IX, which play essential role in adenovirus assembly and genome packaging. In particular, extended regions in these proteins that are involved in molecular interactions are resolved in the cryoEM structure, but not in the x-ray structure. These results support our argument that cryoEM offers advantages over x-ray crystallography in studying the structure of large macromolecular complexes with flexible and transiently stable structural elements [3].

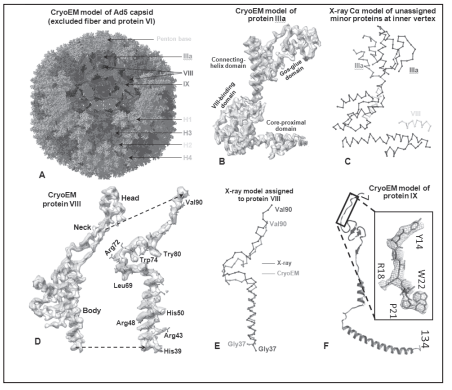

Figure 1. Comparison of cryoEM and XDR structure of the human adenovirus. (A) CryoEM atomic model. (B-C) Minor protein IIIa. (D-E) Minor protein VIII. (F) CryoEM model of protein IX.

[1] H. Liu, L. Jin, S.B. Koh, I. Atanasov, S. Schein, L. Wu, Z.H. Zhou. *Science* **2010,** *329,* 1038-1043. [2] V.S. Reddy, S.K. Natchiar, P.L. Stewart, G.R. Nemerow, *Science* **2010,** *329,* 1071-1075. [3] Supported in part by NIH grants GM071940 and AI069015.

Keywords: adenovirus, cryoEM, x-ray crystallography

MS.02.4

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Crystal structure of the open conformation of the mammalian chaperonin CCT in complex with tubulin

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Protein folding is assisted by molecular chaperones. CCT

(chaperonin containing TCP-1, or TRiC) is a 1-MDa oligomer that is built by two rings comprising eight different 60-kDa subunits. This chaperonin regulates the folding of important proteins including actin, α-tubulin and β-tubulin. We used an electron density map at 5.5 Å resolution to reconstruct CCT, which showed a substrate in the inner cavities of both rings. Here we present the crystal structure of the open conformation of this nanomachine in complex with tubulin, providing information about the mechanism by which it aids tubulin folding. The structure showed that the substrate interacts with loops in the apical and equatorial domains of CCT. The organization of the ATP-binding pockets suggests that the substrate is stretched inside the cavity. Our data provide the basis for understanding the function of this chaperonin.

I.G. Muñoz, H. Yébenes, M. Zhou, P. Mesa, M. Serna, A.Y. Park, E. Bragado-Nilsson, A. Beloso, G. de Cárcer, M. Malumbres, C.V. Robinson, J.M. Valpuesta, and G. Montoya. *Nature Structural & Molecular Biology* **2011**, *18*, 14-9.

Keywords: macromolecular complex, chaperonin, tubulin

MS.02.5

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Pattern recognition for modeling in very low resolution density maps

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We present a novel method for the interpretation of low-resolution maps, which does not rely on any map segmentation or knowledge about the position of the individual structural fragments. The structures of the fragments should be known in advance.

3D structural studies of macromolecular complexes often yield data to only very low resolution (cryo EM/X-ray Crystallography). The interpretation of such data usually starts with the segmentation of the map (e.g., with Watershed algorithm), which does not always give satisfactory results (over-segmentation/incorrect structural borders). Overall, docking of known structures currently requires a lot of human expert knowledge and interaction so that an automated procedure is a highly desirable.

We use 3rd order moment invariants, chirality, skewness and kurtosis of the density to identify regions in density maps of macromolecular complexes that match the corresponding regions in the known structures of the constituting fragments. Finally the structures of the fragments are placed into the map. The used features give a concise but comprehensive description of 3D objects in only a few numerical values, providing convenient means for fast search through a large amount of 3D data. The method has been tested on calculated structure factors for large macromolecular complexes (genotoxin and GroEL) with 10 or 15 Å high-resolution limit. The individual subunits were fitted in the low-resolution density maps with an average r.m.s.d. on C α atoms of 2 Å. New results obtained for interpretation of EM data will also be presented.

Since the last decade there have been many attempts to develop reliable 3D map segmentation algorithms with varying success, in order to reduce the complexity of the challenging task of low-resolution density map interpretation. The method presented here does not require a map segmentation step and provides accurate results without human interaction in reasonable time, due to the use of sophisticated pattern recognition algorithms. Implementation of real-space refinement procedures is expected to improve the results even further.

Keywords: low_resolution, macromolecular_modelling, novel_ algorithms

MS.03.1

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Structure and self-assembly of amyloid peptide-based hydrogelators

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There has been great interest recently in the fibrillisation of peptides, especially the amyloid beta (A β) peptide which is involved in diseases such as Alzheimer's [1]. We have recently commenced a study of the self-assembly of peptides and peptide copolymers based on a fragment KLVFF, corresponding to the core region of A β (16-20). A β self-assembly is driven by inter-molecular β -sheet self-assembly into fibrils. A primary objective of our work is to identify fragments that bind to amyloid fibrils and disrupt fibrillisation (aggregation inhibitors based on self-recognition elements [2]). We are also interested in peptides and peptide/polymer conjugates as hydro- and organo-gelators. I will present results on the self-assembly of peptides such as AAKLVFF [3], [4] and PEGylated diblock copolymers of these peptides [5], [6]. Self-assembly, using techniques including SAXS, SANS and fibre diffraction, is studied in water for hydrophilic peptides and peptide copolymers and in organic solvents for hydrophobic peptides. Gelation at higher concentration is also discussed. Peptide AAKLVFF is the subject of detailed studies (FTIR, CD, NMR, molecular dynamics simulations) of its self-assembly into nanotubes in methanol and twisted fibrils in water [4], [7]. Very recently we have discovered a novel twisted ribbon fibril structure by adding β_2-amino acids to the N terminus of KLVFF to give β A β AKLVFF [8], and the fascinating structural properties of this will be discussed. We have recently examined the binding of this peptide to the amyloid β peptide A β (1-42), as part of a project to develop aggregation inhibitors, which may be useful in the treatment of amyloid disease [9]. In addition, we have found that a PEGylated version of this peptide forms spherical micelles in aqueous solution, pointing to the ability to modulate the self-assembled structure by introduction of amphiphilicity [10]. The enzymatic cleavage (using α-chymotrypsin) of the peptide from the PEG3000 chain (between phenylalanine residues) leads to release of unassociated peptide monomers [10]. This nanocontainer delivery and release system could be useful in therapeutic applications. As another example, we have investigated the self-assembly of a novel peptide amphiphile (PA) Matrixyl, with collagen-stimulating properties [11]. It forms self-assembled tape-like structures in aqueous solution. These can be dispersed into amyloid-like fibrils by use of the anionic surfactant SDS.

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Keywords: peptide, gel, SAXS

MS.03.2

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Crystalline vs Amorphous molecular gels: two distinct classes of self-assembled structures with unique biological connections

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