1113-Pos Salt Dependence Of RNA Loop Stability And Hairpin Folding Free Energy

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Board B89

Single-stranded nucleic acid loops are important structural and functional segments. Due to the polyanionic nature of nucleic acids, metal ions in solutions are crucial to the loop folding thermodynamics. Here, we use the previously developed tightly bound ion theory [1,2] to quantify the contributions of Na^+ and Mg^{2+} to the loop thermodynamics, where the loop conformational ensembles are produced based on the virtual-bond model [3]. The predicted loop thermodynamics are strongly dependent on loop length, end-to-end distance, and Na^+/Mg^{2+} concentrations. Based on the calculations, we derive the empirical formulas for the loop thermodynamic parameters as functions of chain length, end-to-end distance, and Na^+/Mg^{2+} concentrations. For the three specific loops, namely, hairpin, bulge, and internal loops, the predicted entropies agree with the experimental data at standard salt (1M Na^+). Furthermore, we apply the calculated loop free energy to predict RNA hairpin stability in Na^+/Mg^{2+} solutions. The results show good agreement with available experimental data. We find that both helix and loop can cause significant salt-dependence for the hairpin stability.

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Virus Structure & Assembly

1114-Pos Tobacco Mosaic Virus Assembly of Fibrous and Macroscopic Bundled Arrays Mediated by Surface Aniline Polymerization

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One-dimensional (1D) polyaniline/tobacco mosaic virus (TMV) composite nanofibers were synthesized by the self-assembly of rod like TMV particles assisted by the polymerization of aniline on its surface. At near-neutral reaction pH (6.0 – 8.0), branched polyaniline formed on the surface of TMV prevented lateral association and therefore long 1D nanofibers were observed with high aspect ratios and excellent processibility. At a lower pH (4.0–5.0), transmission electron microscopy (TEM) analysis revealed that initially long nanofibers were formed and upon long reaction time resulted in bundled structures. This association of single nanofibers to form bundled structures is presumably mediated by the hydrophobic interaction of polyaniline on the surface of these composite nanofibers. In-situ time-resolved small-angle X-ray scattering study on the formation of polyaniline/TMV composite nanofibers at two different reaction pH conditions (5.1 and 6.5) supported our mechanism. The polyaniline layer formed on the external surface of TMV is thicker for reaction at pH 5.1 than for reaction at pH 6.5. This novel strategy to assemble TMV into well-organized composites could be utilized in the fabrication of advanced materials for potential applications including electronics, optics, sensing, and biomedical engineering.

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1115-Pos Plastic deformation of viral capsids

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From theoretical considerations on the response of viral capsids to deformation one expects that next to

(i) complete elastic deformation and
(ii) capsid failure upon deformation, there is a third possibility:
(iii) plastic deformation.

Whereas the first two regimes have already experimentally been observed (1, 2), the plastic deformation regime has not. Here we report on experiments in this intermediate response regime. The studies were performed with nanoindentation techniques using an Atomic Force Microscope (AFM), an approach which is becoming a standard method to measure the mechanical properties of viral particles (1, 2). Capsids of the Hepatitis B Virus (HBV) were used as a model system. This virus was chosen because its capsid is made up out of many copies of a single protein and it can form in either a T=3 or a T=4 morphology. After a certain indentation both capsid types show permanent plastic deformations in their structures and the mechanics of this deformation can be described by the Föppl-von Kármán (FvK) number. It is shown that the experimental observations match the expected behaviour as deduced from simulations (3). Overall the two morphologies possess the same mechanical characteristics, but a slight difference in deformation characteristics is predicted by theoretical considerations on the difference in FvK number. We are able to observe this difference experimentally, which illustrates the resolution of our approach.

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1116-Pos Molecular Dynamics Study of DNA Translocation in Phi 29

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Board B92

Phi 29 bacteriophage infects the bacterium B. subtilis. During infection Phi 29 packs its newly produced DNA into an empty capsid, against a very high pressure of ca. 50 atm. For this purpose, a packaging machine containing five ATPase units, six pRNAs and a head-tail connector translocates the DNA into the capsid. The ATPase units provide energy for the translocation, the connector has a portal to the capsid and the pRNAs connect the ATPs with the connector. For the role of the connector during packaging three mechanisms have been proposed so far. One suggests a nut-bolt like packaging of the DNA. In the second one, the connector acts as a torrsion spring driving the DNA in a ratchet like fashion. According to the third proposed mechanism, the connector is a valve preventing the packed DNA from leaving, without any active parts at all. Using molecular dynamics simulations of the connector in complex with DNA, and aiming at distinguishing between these three models, we calculated mechanical properties of this system. First we calculated a spring constant and potential for the torsion around the connector axis. Comparing the potential energy of the torsion with ATP hydrolysis energy help to decide whether the connector is too rigid for the torrsion spring mechanism or not. Second we have pulled the DNA through the connector's portal to decide whether the connector has an active part in DNA translocation.

1117-Pos Cryoem Reconstructions Of Bacteriophage Lambda Offer Insights Into Phage Organization And Evolution

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The bacteriophage lambda is composed of an icosahedral capsid, into which a 48.5 kbp double-stranded DNA genome is packaged, and a long non-contractile tail consisting of 34 disk-like structures. While models describing the organization of these isolated structures have been proposed, there is a lack of complementary structural evidence in the literature. Through cryo-EM analysis of this phage, we are gaining a better understanding of its assembly and organization. There is a prominent surface feature present at the quasi 3-fold axes corresponding to the cementing protein gpD that is positioned directly over the covalent cross-linking portion of the docked HK97 crystal structure, suggesting an evolutionary replacement of this gene product by a chemical autocatalytic cross-link in HK97. Asymmetric reconstructions of both the empty and fully packaged lambda phage have provided three-dimensional views of the phage interior in the presence and absence of packaged DNA, as well as how the tail assembly is attached to the capsid. A comparison between central slices of the asymmetric wild type and empty particles show clear density depicting the dsDNA and portal proteins, along with evidence that upon completion of packaging, a plug-like gene product or conformational change of the portal closes the portal opening.

1118-Pos Fusion vs. Endocytosis: The stochastic entry of viruses

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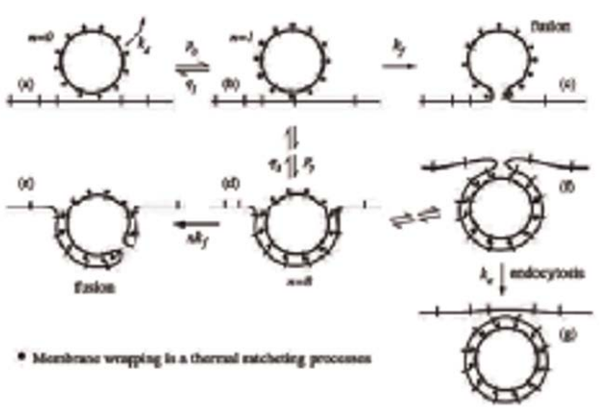
Board B94

Infection by membrane-enveloped viruses requires the binding of receptors on the target cell membrane to glycoproteins, or ''spikes,'' on the viral membrane. The initial entry is usually classified as fusogenic or endocytotic. However binding of viral spikes to cell surface receptors not only initiates the viral adhesion and the wrapping process necessary for internalization, but can simultaneously initiate direct fusion with the cell membrane. Both fusion and internalization have been observed to be viable pathways for many viruses. We develop a stochastic model for viral entry that incorporates a competition between receptor mediated fusion and endocytosis. The relative probabilities of fusion and endocytosis of a virus particle initially nonspecifically adsorbed on the host cell membrane are computed as functions of receptor concentration, binding strength, and number of spikes. We find different parameter regimes where the entry pathway probabilities can be analytically expressed. Experimental tests of our mechanistic hypotheses are proposed and discussed.



1119-Pos Conformational Changes Of Gag HIV-1 On A Tethered Bilayer Measured By Neutron Reflectivity Provides Insights Into Viral Particle Assembly

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Board B95

Formation of the HIV-1 is mediated by the Gag polyprotein at the cytoplasmic membrane surface of the infected host cell. Individual Gag molecules contain several domains connected by flexible linkers. Early cryo-EM data showed Gag in the immature virus as elongated rods radial from the membrane with one termini tightly bound to the viral genome [Current Biology, 1997 (*7*) p.729]. However, in vitro assembly with purified Gag incubated with nucleic acids, forms virus particles significantly smaller in radius than the natural virion [J. Virology, 1999 (*73*) p.2270]. Furthermore, solution measurements using SANS and other techniques suggest a compact structure for Gag [J. Mol. Biol. 2007 (*365*) p. 812]. These studies indicate large conformational changes in the Gag protein must occur concomitant with virus assembly. The dimension of Gag bound to the bilayer interface was determined at high resolution by neutron reflectometry. The bio-mimetic environment for observing Gag association consisted of a supported membrane attached to a gold surface via a PEO tether. The membrane was a ternary composition of DMPS:DMPC:Cholesterol lipids capturing key characteristics of the viral lipodome. The Gag protein bound to the lipid membrane was shown to adopt a folded conformation of ∼75Å. Upon addition of a 14 base pair DNA oligo (TGx7), a significantly thicker protein layer of ∼200Å was observed. A high salt buffer rinse reversed the conformational change. These results suggest a mechanism by which Gag extension is possible only once bound to the plasma membrane and in the presence of the viral genome. This provides a picture consistent with earlier in vivo and solution studies. A detailed understanding of the viral particle assembly process may elucidate susceptible points providing opportunities to inhibit proper virus formation.

1120-Pos Structural Proteomics Of The Sars Coronavirus: Structure, Function And Interaction Of The Replicase Proteins

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Board B96

The 2003 outbreak of severe acute respiratory syndrome (SARS), caused by a previously unknown coronavirus called SARS-CoV, had profound social and economic impacts worldwide. Since then, structure-function studies of SARS-CoV proteins have provided a wealth of information that increases our understanding of the underlying mechanisms of SARS.

We have adopted a structural proteomics approach targeting the 16 SARS-CoV non-structural proteins that assemble to form a sophisticated machinery required for viral replication/transcription. We have determined 14 protein and complex structures from SARS-CoV and other coronaviruses to date, including: the first structure of the SARS-CoV Mpro and its complex with an inhibitor; broad-spectrum inhibitor design targeting coronavirus Mpro; the SARS-CoV nsp7-nsp8 super-complex; SARS-CoV nsp10, a novel zinc-finger protein; and MHV nsp15, an endoribonuclease. The structure of another replicase protein was recently determined by our group. Furthermore, we have been working towards understanding the molecular interactions between the various non-structural protein components of the replicase machinery.

No effective therapy against SARS is currently available, and considerable efforts have been made by our group towards preventing SARS-CoV infection. We have used a structure-guided drug discovery approach to design potent inhibitors of the coronavirus Mpro, and have also developed a novel method for structure-based drug design using a library of natural mixtures.

1121-Pos Ordering Of DNA Confined Inside Bacteriophages Of Various Shapes Described By Computer Simulations

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Board B97

Packaging of the genetic material inside bacteriophages is aided by ATP-driven motors and leads to the arrangement of DNA into highly-packed and ordered structures. Using a coarse-grained model for DNA and capsid we performed simulations of DNA packaging inside bacteriophages of different shape and size. We found that the final DNA conformations depend on the size and shape of the capsid, as well as the size of the protein portal, if any. In particular, isometric capsids with small or absent portals tend to form concentric spools, whereas the presence of a large portal favors coaxial spooling; slightly and highly elongated capsids result in folded and twisted toroidal conformations, respectively. By introducing several order parameters and analyzing the conformations of linear polymers confined inside irregular closed cavities over a wide range of packing densities we found that the ordering of DNA to its fully packed structure occurs through two transitions: The first transition is associated with the formation of the global patterns. The second transition corresponds to the loss of mobility and disappearance of the undulations of DNA strands.

1122-Pos CryoEM Structure of the Vesicular Stomatitis Virus Revealed More Than Virulence

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Board B98

Helical symmetry is an architectural schema that is widely imitated in the world. A helical structural is particularly suitable for electron cryo-microscopy study in that it displays a multitude of copies of its constituent asymmetric unit in diversified views. Here we report the structural determination by helical reconstruction of a biological structure that was previously considered not suitable for this approach.

Vesicular stomatitis virus is a negative strand RNA virus that has long served as a model system for influenza viruses. The system has not previously been subjected to helical cryoEM reconstruction due to several concerns. First, there is insufficient confidence that this macromolecular assembly has a unique helicity and diameter among individual particles. Second, the axial rise per subunit for this helix is particularly small, whilst having a large diameter. Moreover, the naturally occurring structure is short in its length, not even twice its diameter. These properties have obstructed previous attempts for helical reconstruction. However, using an integrative approach with techniques from single particle reconstruction and helical reconstruction, we have pursued to outwit these technical barriers.

The resulting structure is a helix of an unbelievably exact repeat number, 37.50 units per turn. In this structure, the viral RNA genome is encapsidated by N nucleoproteins which in turn align in a left handed helical cylinder. This core is further reinforced by M matrix proteins interleaved into a chain-mail mash. On the opposite side, M proteins introduce the nucleocapsid to the envelope. In contrast with the nucleocapsid of other negative-strand RNA viruses, only one form of helix was captured with 3D helical reconstruction among the working population of virions, suggestive of internal measures to control particle modality.

From the density map, some interesting features of the viruses have been discussed.

1123-Pos Techniques For Coarse-Grained Modeling and Mechanics of Viral Capsids

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Board B99

As revealed by techniques of structural biology and single-molecule experimentation, the capsids of viruses are some of nature's best examples of highly symmetric multiscale self-assembled structures with impressive mechanical properties of strength and elasticity. We present a novel method for creating three-dimensional finite element meshes of viral capsids from both atomic data from PDB files and electron density data from EM files. The meshes capture heterogeneous geometric features and are used in conjunction with three-dimensional continuum elasticity to simulate nanoindentation experiments as performed using atomic force microscopy. The method is extremely flexible; able to produce meshes with varying levels of coarseness, in addition to being able to capture varying levels of detail in the three-dimensional structure. Meshes and nanoindentation simulations are presented for several viruses: Hepatitis B, CCMV, HK97, and Phi 29. In addition to purely continuum elastic models, for those viruses with atomic coordinate information available, a multiscale technique is developed that combines the coarseness of the three-dimensional meshes with the atomic level forces calculated from an atomic force-field, using a mathematical mapping scheme. In this way, large-scale deformations such as nanoindentation are simulated without the cumbersome nature of other all-atom simulations, such as molecular dynamics. Simulations of these capsid deformation experiments provide a testing ground for the techniques, as well as insight into the strength-determining mechanisms of capsid deformation. These methods can be extended as a framework for modeling other proteins and macromolecular structures in cell biology.

1124-Pos Electron Cryo-Tomography of Viral Infection and Assembly Within a Host Cell

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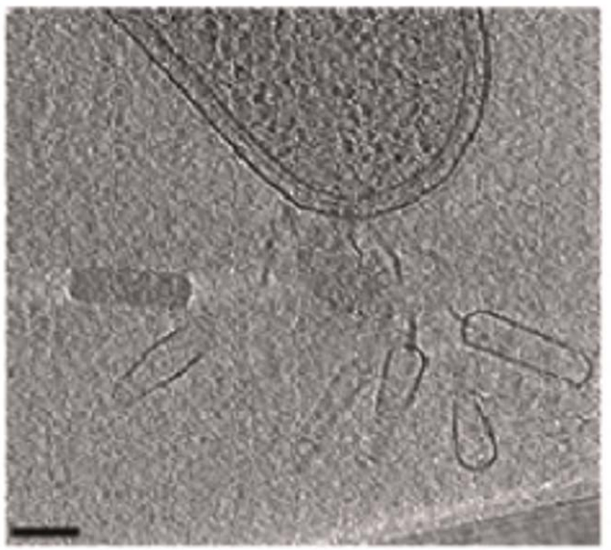
Board B100

A major challenge in examining the structural aspects of viral assembly is it has been mostly unexplored within the context of the host. Much of what we understand today has been generated from computational models and *in vitro* crystallographic and electron microscopy analyses. The advent of electron cryo-tomography has now made it possible to obtain full three-dimensional reconstructions of unique, asymmetric objects such as whole cells and viruses (Lucic et al., 2005; Jensen & Briegel, 2007). Here, we report on the three-dimensional reconstructions of intact *Caulobacter* phage ϕCb13 infecting and assembling inside whole *Caulobacter crescentus* cells. Through this analysis we have been able to examine individual phage ultrastrucutre, phage attachment to the host cells, and phage DNA packing within the cellular context.

Figure 1. A 12 nm slice through a tomogram of a ϕCb 13 infected *Caulobacter crescentus* cell that was frozen in vitreous ice. Scale bar 50 nm.



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1125-Pos Methods for Multiscale Stochastic Simulation of Molecular Self-Assembly

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Board B101

Macromolecular self-assembly is a crucial component of nearly every major cellular process. Simulation methods provide a valuable adjunct to experimental work in understanding self-assembly by allowing us to perform model-assisted interpretation of assembly systems too complex for detailed experimental dissection and to extrapolate results from in vitro experimental systems to the cellular environment. Unfortunately, it remains computationally intractable to simulate detailed self-assembly dynamics within several biologically important parameter domains, including long time scales needed to understand some in vitro assembly models and dense crowding conditions relevant to in vivo assembly. We have developed simulation methods based on stochastic models of reaction chemistry aimed at extending feasible parameter domains in these biologically important directions. We have applied several heuristics based on Markov model and spectral graph theory to accelerate the Stochastic Simulation Algorithm for some hard conditions that arise at extremes of in vitro assembly conditions. We have also developed simulations based on Green's Function Reaction Dynamics models of spatially heterogeneous environments to better capture some difficult high-concentration domains. We demonstrate these methods using coarse-grained models of the assembly of icosahedral virus capsids as well as several simpler models of generic assembly chemistry.

1126-Pos Menagerie of Viruses: Diverse Chemical Sequences or Simple Electrostatics?

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Board B101.01

The genome packing in hundreds of viruses is investigated by analyzing the chemical sequences of the genomes and the corresponding capsid proteins, in combination with experimental facts on the structures of the packaged genomes. Based on statistical mechanics arguments and computer simulations, we have derived a universal model, based simply on non-specific electrostatic interactions. Our model is able to predict the essential aspects of genome packing in diversely different viruses, such as the genome size and its density distribution. Our result is in contrast to the long-held view that specific interactions between the sequenced amino acid residues and the nucleotides of the genome control the genome packing. Implications of this finding in the evolution and biotechnology will be discussed.

1127-Pos Triatoma Virus (TrV) self-aggregation at low PH: A possible electrostatic explanation

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Board B102

Triatoma virus (TrV) is a +ssRNA, non-enveloped virus of the insect virus family Dicistroviridae. TrV capsid has icosahedral T=1 pseudo T=3 symmetry, and is composed of three proteins named VP1, VP2 and VP3, which MW are 39, 37 and 33 kDa respectively. We report that the TrV capsid remains assembled at very acidic pH

values, while at pH's lower than 4.0 the virus particles reversibly aggregate without any noticeable structural change, as analyzed under Transmission Electron Microscopy, Static and Dynamic Light Scattering and Fluorescence Spectroscopy. In this study, we also compute at different pH values TrV surface electrostatic potential and we postulate that the virus aggregation is due to electrostatic effects.

1128-Pos Rigidity of the Influenza Virus During its Infectious Cycle

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Board B102.01

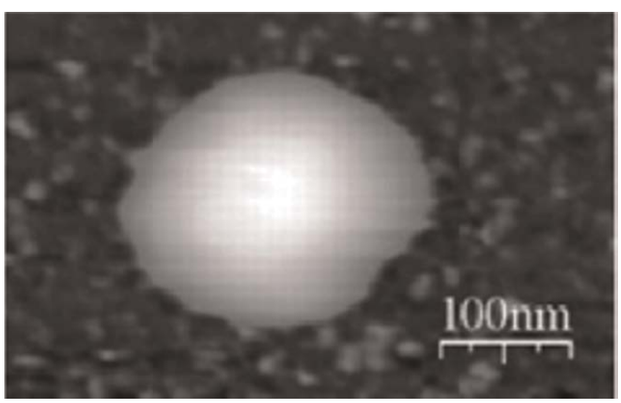
The influenza virus is an enveloped virus from the Orthomyxovirus family. The protein rich lipid membrane of the virus particle needs to persist in the often hostile extra-cellular environment when the virus transmits from host to host organism, but it also needs to permit membrane fusion with the target cell to allow infection.

We set out to investigate how this virus negotiates these apparently conflicting demands on its membrane rigidity during its life-cycle. We have developed methods to image this relatively large (diameter ~100 nm) virus and to measure its mechanical properties using an Atomic Force Microscope (AFM).

We have measured the stiffness of the viral membrane under conditions mimicking the different stages of the viral life-cycle including different pH levels. We have further compared the complex response of the viral membrane with the behavior of simplified model systems to understand the role of the various part of the viral structure for its mechanical properties.

(supported by MRC; I.A.T.S. is supported by the European Community through a Marie Curie Fellowship)

Figure, AFM scan of an influenza virus attached to a substrate



Membrane Fusion

1129-Pos Energetics And Dynamics Of SNAREpin Folding Across Lipid Bilayers

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Board B103

Membrane fusion occurs when SNAREpins fold up between lipid bilayers. How much energy is generated during SNAREpin folding and how this energy is coupled to the fusion of apposing membranes is still a mystery. We have utilized the Surface Forces Apparatus to determine the energetics and dynamics of SNAREpins formation and characterize the different intermediate structures sampled by cognate SNAREs in the course of their assembly. The force versus distance profiles of assembling SNAREpins reveal that SNARE motifs begin to interact when the membranes are 8 nm apart. Even after very close approach of the bilayers ($\sim$ 2–4 nm), the SNAREpins remain partly unstructured in their membrane-proximal region. The energy stabilizing a single SNAREpin in this configuration (35 kBT) corresponds closely with the energy needed to fuse outer but not inner leaflets (hemifusion) of pure lipid bilayers (40–50 kBT). The cooperative effect of a few SNAREpins at the site of exocytosis would thus be sufficient to overcome the high energetic barriers of membrane fusion.

1130-Pos SNAREs Drum Up In Silico: Molecular Dynamics Simulations Of The Synaptic Fusion Complex

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IBPC, CNRS UPR9080, Paris, France.

Board B104

The SNARE protein complex is central to membrane fusion, a ubiquitous process in biology. Modeling this system in order to better understand its guiding principles is a challenging task. This is mainly due to the complexity of the environment: two adjacent membranes and a central bundle of four helices made up by vesicular and plasma membrane proteins as shown in the Figure below.

We have modeled this system at several levels of detail, reaching from coarse grained representations of the Synaptobrevin transmembrane helix in a single lipid bilayer up to an atomistic model of the full membrane-embedded synaptic fusion complex shown above. Molecular dynamics simulations of these models were carried out to characterize the conformational dynamics and key interactions in these systems. No evidence for directionality in the