the mechanism underlying AMPs' ability to disrupt cell membrane defense are not completely understood. We present computational and experimental evidence showing that the β-hairpin PG-1 aggregates and forms ion channels in target cell membranes. We used complementary approaches, including Molecular Dynamics (MD) simulations, Atomic Force Microscopy (AFM) imaging, Planar Lipid Bilayer (PLB) reconstitution and cellular toxicity measurements. MD simulations indicate that PG-1 does not form fibrillar structures on the surface of DOPS/POPE bilayers. However, PG-1 aggregates into channel-like structures with loosely attached subunits when inserted into anionic lipid bilayers. AFM images show no PG-1 fibril formations on the lipid bilayers. However, on a negative non permeable surface, PG-1 formed fibrils that bear some resemblance to amyloids fibers. On the other hand, AFM images show channel-like structures formed by PG-1 when reconstituted in DOPS/POPE bilayers. In PLB electrical conductance measurements, we observed multiple single channel conductances consistent with the heterogeneous oligomeric channel structures seen in AFM images. In addition, PG-1 channel formation seems to be lipid-dependent: PG-1 does not form channels in PC membranes, but forms channels in membranes rich in PE, PG or PS. Unlike amyloid channels, Zn^{2+} does not inhibit PG-1 channel conductance. Microbial cells treated with PG-1 showed antimicrobial activity consistent with ion leakage. The combined results support a model where the β-hairpin PG-1 antibiotic permeates membranes by forming ion conductive channel-like structures and cause cell injury.
Supported by NIH (NIA) and NCI Contract HHSN261200800001E.

52-Plat
S-Layer Self-Assembly on Supported Lipid-Bilayers: The Importance of Amorphous Precursors and Folding Transitions
Sungwook Chung, Seong-Ho Shin, Stephen Whitelam, Carolyn Bertozzi, Jim De Yoreo.
Lawrence Berkeley National Laboratory, Berkeley, CA, USA.
The outermost membranes of many archaea and bacteria are comprised of highly-ordered 2D arrays of surface layer (S-layer) proteins. Their functions include selective transport, structural scaffolding, mineral templating and propagation of or protection from pathogenesis. Although the primary and secondary structures of the isolated proteins determine their governing interactions, their functions emerge from the tertiary and quaternary architecture that stems from S-layer self-assembly, a process that is poorly understood. Here we report results using *in situ* AFM to follow 2D self-assembly of monomeric SbpA of *Lysinibacillus sphaericus* on supported lipid bi-layers (SLBs) at the molecular-scale. We show that the assembly process begins with adsorption of unstructured monomers, which form a mobile phase on the SLBs. These then condense into amorphous clusters, which undergo a phase transition to ordered 2D clusters of 2 to 15 folded tetramers. The ordered clusters then enter a growth phase in which new tetramers form from unstructured monomers exclusively at unoccupied lattice sites along the cluster edges, implying that new tetramer formation is auto-catalytic. We show that the analysis of growth dynamics leads to a quantitative model in which the main rate limiting parameter is the probability of tetramer creation. The estimated energy barrier of 51 kJ/mole for this process is much less than expected form scaling laws for folding of isolated proteins. Finally we present preliminary results from dynamic Monte Carlo simulations that show how the combination of non-specific interactions and directional bonds characteristic of many proteins lead to non-classical assembly pathways, such as the one observed here involving formation of amorphous clusters followed by relaxation to the ordered state.

53-Plat
A Predictive Theoretical Model For Clathrin Self-Assembly
Shafigh Mehraeen, Nick Cordella, Andrew J. Spakowitz.
Stanford University, Stanford, CA, USA.
Clathrin is a protein that plays a major role in the creation of membrane-bound transport vesicles in cells. Clathrin forms soccer-ball-shaped lattices that coat a new vesicle as it forms. The clathrin molecule is known to take the shape of a triskelion, a figure with three bent legs. In vitro assembly of clathrin within a solution results in closed, nanoscale assemblies with various shapes and sizes. To understand how clathrin functions, particularly how it forms the lattice, we develop a theoretical model for the thermodynamics and kinetics of clathrin assembly in order to guide experiments toward the design of targeted nanoscale structures. Our model addresses the behavior in 2 and 3 dimensions, relevant to membrane/surface and bulk assembly, respectively. The clathrin triskelions are modeled as effective flexible pinwheels that form leg-leg associations and resist elastic bending and stretching deformations. Thus, the pinwheels are capable of forming a range of ring structures including 5-, 6-, and 7-member rings that are observed experimentally. Our theoretical model employs Brownian dynamics to track the motion of clathrin pinwheels at sufficiently long time scales to achieve complete assembly. With this theoretical model, we predict the phase diagram for clathrin assembly incorporating binding interactions, elastic deformation, and phonon modes. To verify the phase diagram, we perform dynamic simulations for a range of quenches into the phase diagram and compare phase separation across the binodal curve. We show that resulting Brownian dynamics simulations exhibit the hallmark behavior of spinodal decomposition with subsequent coarsening of ordered domains. These simulations demonstrate the effect of quench rate and leg elasticity on the final configurations of the lattice network and cluster-size distribution. We then proceed to discuss the assembly of specific nanoscale structures.

Platform E: Computational Methods

54-Plat
Molecular Dynamics Simulation of Phospholipid Bilayers and Monolayers Using a Polarizable Force Field
Edward Harder[1], Benoit Roux[1], Alex D. MacKerell Jr.[2].
[1]University of Chicago, Chicago, IL, USA, [2]University of Maryland, Baltimore, MD, USA.
The assumptions that underlie empirical force field models based on fixed molecular charge densities become questionable in the strongly heterogeneous electrostatic environment of bilayer membranes. Membranes contain regions that are polar (bulk water) highly charged (zwitterionic lipid head groups) and decidedly non-polar (hydrocarbon core). Using a recently developed polarizable Drude oscillator force field for lipids and water we present a study that illustrates the significant role played by electronic polarization effects in the electrostatic modeling of a phospholipid membrane. Specifically, we show that the inclusion of such many-body polarization effects can bring macroscopic electrostatic properties into quantitative precision with experimental observation.

55-Plat
The Small Angle Scattering Toolbox
Haiguang Liu, Peter H. Zwart.
Lawrence Berkeley National Lab, Berkeley, CA, USA.
Small Angle Scattering (SAS) is a technique used to investigate structure and dynamics of macromolecules in solution. Proteins in buffer conditions close to their physiological environment, are subject to Xray or Neutron scattering experiments. The resulting one-dimensional scattering curves are directly related to their three-dimensional structure. The SAS technique is routinely used to determining the low resolution shape of protein and map specific large scale conformation changes in protein structures.
We present a recently developed computational platform for SAS data analysis and model construction/refinement.The Small Angle Scattering Toolbox (SASTBX) has tools four major modules: (1) Raw data reduction; (2) theoretical scattering profile calculation based on PDB structures; (3) Pair distance distribution function (PDDF) estimation; and (4) 3D model construction and structure refinement.
The toolbox can be utilized to read raw scattering images obtained from the detector to generate an intensity profile. The basic analyses, such as Guiner and Kratky plots can be carried out in real time to assess the sample and data quality while collecting data. The PDDF estimation is a fully automated procedure, linked with a database a known PDDF's allowing for a rough initial classification of the shape of the protein. Model data can be calculated on the basis of a spherical harmonics expansions. Initial structures can be further refined with normal mode movements or rigid-body motions.
The sastbx is built on the open source Computational Crystallography Toolbox (CCTBX). The toolbox is implemented by using Python/C++ hybrid approach: the computing intensive jobs are handled in C++, and the python allows easy integration between other components. The source code will be distributed as open source project.

56-Plat
Large-Scale Simulations of Fluctuating Biological Membranes
Lutz Maibaum[1,2], Andrea Pasqua[1], George Oster[1], Daniel A. Fletcher[1,2], Phillip L. Geissler[1,2].
[1]University of California, Berkeley, CA, USA, [2]Lawrence Berkeley National Laboratory, Berkeley, CA, USA.
We present a new computational model for lipid bilayers that allows the simulation of membrane systems on the micrometer scale. In our model, each ~25 nm^2 patch of bilayer is represented by a spherical particle. Mimicking the forces of hydrophobic association, many-body interactions suppress the exposure of each sphere's equator to the implicit solvent. This driving force towards high equatorial density stabilizes two-dimensional aggregates without necessitating crystalline order. This allows us to match both the surface