Of domains and boundaries: lipid bilayer membranes with phase coexistence

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Lipid bilayer membranes of biological cells are likely to be non-random mixtures of membrane components. Lateral membrane domain formation is thought to be involved in essential functions of the membrane, including signaling, sorting, and trafficking. In order to elucidate the physical, mechanical, and physico-chemical basis and consequences of membrane heterogeneity, model systems have been developed. These typically consist of ternary lipid mixtures that under suitable conditions segregate into two fluid phases, a liquid ordered, and a liquid disordered phase. Of particular interest to us are the boundaries of domains in membranes with phase coexistence due to interfacial tension (line tension) at fluid phase boundaries. We find that this line tension couples to three dimensional membrane shape, modulating biologically relevant phenomena, including vesicle budding and fission. Line tension is also a control parameter regulating domain size and growth kinetics. We are therefore developing methods to precisely measure line tension as a function of membrane composition, using micropipette aspiration of giant vesicles, as well as capillary wave spectroscopy of thermal boundary fluctuations. We demonstrate that these two complementary techniques probe different line tension regimes. Furthermore, we are developing experimental methods to investigate the partitioning of both lipids and proteins among curvature gradients. We find that lipids are not detectably sorted among membrane with steep curvature difference, whereas peripherally membrane binding proteins are efficiently sorted. We discuss the biological relevance of our findings.

A boundary layer analysis for two-phase lipid bilayer vesicle and vesicle adhesion

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Lipid bilayer vesicles with two coexisting phases are promising model systems for cell membranes and promote the understanding of mechanical and physico-chemical aspects of biological membrane functions. They consist of many of the same phospholipids that, in association with cholesterol, form cell membranes. They are fluid-like, spontaneously form in aqueous solution, resist bending, and have a large variety of shapes. The shapes are characterized locally by their mean and Gaussian curvatures.

We present approximate solutions to the equations that govern the shape of two-phase lipid bilayer vesicles obtained via a boundary layer analysis. The equations involve a dimensionless small parameter related to the resistance to changes in mean curvature. We determine a relationship between the tangent angle at the interface and the difference in the Gaussian curvature stiffnesses of the co-existing phases. This relationship demonstrates that a difference in the Gaussian curvature stiffnesses moves the phase boundary, as determined in previous numerical studies. The analytical expression for the tangent angle obtained can be used to determine elastic parameters for the membranes from experimental data. We also describe a boundary layer analysis for the vesicle or cell adhesion which is a key mechanism for the survival of cells.

Derivation of a new free energy for biological membranes

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A new free energy for thin biomembranes depending on chemical composition, degree of order and membranal-bending deformations is derived in this paper. This is a result of constitutive and geometric
assumptions at the three dimensional level. The enforcement of a new symmetry group introduced in a work in progress by Deseri, Paroni and Healey, the assumption of bulk incompressibility and a $3D-2D$ dimension reduction procedure are among the ingredients of our methodology. Finally, the identification of the lower order term of the energy (i.e. the membranal contribution) on the basis of a bottom-up approach is performed; this relies upon standard statistical mechanics calculations. The main result is an expression of the biomembrane free energy density, whose local and non-local counterparts are weighted by different powers of the bilayer thickness. The result exhibits three striking aspects: (i) the local (purely membranal) energy counterpart turns out to be completely determined through the bottom-up approach mentioned above, which is based on experimentally available information on the nature of the constituents; (ii) the non-local energy terms, that spontaneously arise from the $3D-2D$ dimension reduction procedure, account for both bending and non-local membranal effects; (iii) the non-local energy contributions turn out to be uniquely determined by the knowledge of the membranal energy term, which in essence represents the only needed constitutive information of the model. It worth noting that no heuristic coupling among the variables appearing in the energy is forced.

Detection and Prediction of Nanodomains in Lipid Bilayer Model Membranes

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We are studying nanodomains in spherical membrane-enclosed "giant" unilamellar vesicles (GUVs), diameter $>10\mu m$. Phase domains in GUVs can be specifically labeled with fluorescent probes. To measure nanodomains below the optical resolution limit we use methods based on fluorescence fluctuations. As fluorescent molecules diffuse through a small illuminated spot (300nm radius), the fluorescence fluctuates correspondingly. Autocorrelation of the fluctuations yields diffusion coefficients of the fluorescent nanodomains; statistical analysis of the fluctuation amplitudes yields information about their size distribution.

Although the sizes of membrane domains are controlled by the balance between surface energy and cohesive interactions among the molecules in a domain, phase separation, is also linked to membrane mechanical properties including membrane curvature. We are using a chemomechanical model to examine this linkage. The energy of the membrane is estimated as the sum of a chemical and a curvature-dependent mechanical contribution. This yields the relative chemical potentials of the species and ultimately an evolution equation for the local densities of the two components over time. Our long range goal is to discover the factors that control the distributions of sizes, stabilities and evolution rates of nanodomains in GUVs of defined compositions.

Stresses in Fluid Membranes

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The physics of a fluid membrane is very well described on mesoscopic scales by a Hamiltonian quadratic in curvature. A remarkable consequence is that the state of stress in the membrane is determined completely by the geometry. In this talk, various features of this direct connection between stress and geometry will be described. In particular, it will be shown how membrane mediated interactions are captured by the geometry. The extension of this framework to accommodate additional structure (tilt or composition, for example) or local constraints on the geometry (inextensibility, for example) will be discussed.

A New Model for Nucleation in Two-Phase Lipid Bi-layer Membrane Vesicles

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In this talk we present and analyze a new model for two-phase lipid bi-layer membranes. The work is motivated by the recent experiments of Baungart, et. al. [1], on liposome vesicles [1]? in this case, giant unilamellar vesicles (GUVs) - demonstrating remarkable two-phase patterns under the variation
of osmotic pressure and/or temperature. The two phases observed in [1] are each fluid-like - an ordered phase and a disordered phase. In particular, the membrane is observed to be slightly thicker in the ordered phase.

Heretofore in the biophysics literature, a Ginzburg-Landau type model has been considered for such phenomena, the former possessing an ad-hoc term in the energy that engenders intrinsic curvature when the phase field variable is non-zero. Here we propose a rational model for pressure-induced phase transitions, incorporating the associated change in thickness within the bending potential energy. Our proposed model incorporates no intrinsic curvature in either phase.

We derive the equilibrium equations and consider a nominally spherical vesicle under inflationary pressure $p > 0$ (so that we do not confuse things with standard shell buckling under compression). We then linearize the equations about the spherically symmetrical state, looking for the existence of non-spherical states. We perform a rigorous nonlinear bifurcation analysis, using well-known group-theoretic strategies, showing the existence of symmetry-broken bifurcated equilibria. The latter, representing phase-nucleated states from the homogeneous vesicle, bear striking similarity to many of the non-spherical states observed in the experiments of [1].


AFEM for Parametric Surface Flows: Applications to Biomembranes

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When lipid molecules are immersed in aqueous environment they aggregate spontaneously into 2 mono-molecular layers or (bio)membranes that form an encapsulating bag called vesicle. This happens because lipids consist of a hydrophilic head group and a hydrophobic tail, which isolate itself in the interior of the membrane.

As a first approach, we have studied a model based on geometry assuming that the equilibrium shapes are the minimizers of the Willmore energy under area and volume constraints. In this context, the membrane is the preponderant factor influencing the shape of the vesicle. A gradient flow is established to reach these equilibrium shapes. Then, the effect of the inside (bulk) fluid is taken into account leading to more physical dynamics. The boundary conditions couple Stokes equations to the constrained Willmore force.

A parametric approach is employed, which leads to forth order highly nonlinear PDEs on surfaces and involves large domain deformations. An adaptive finite element method (AFEM), with either piecewise linear or quadratic polynomials, is used for both the geometric and coupled problems.

Theory and analysis of coexistent phases in biomembranes

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The foundation of the theory of biomembranes with curvature elasticity in the context of the theory of elastic surfaces is discussed. Convexity conditions and Weirstrass-Erdmann conditions for energy minimizers are presented. These are applied to the description of coexistent phases by adapting classical ideas in the theory of phase transitions based on non-convex energy densities. Some simple solutions relevant to budding vesicles are given and further applications of the general theory are developed.