A theoretical model of a two-component fluid membrane containing lipids and two-state active inclusions is presented. Under strong inclusion activities the membrane can be unstable due to pump-driven undulation or aggregation of high curvature excited inclusions. Depending on the structural details of the inclusions, the active conformation change of the inclusions can also induce finite size domains on the membrane. At long wavelengths a stable membrane has a height fluctuation spectrum similar to previous studies which neglected the inclusion internal states. For a tensionless membrane, \( \langle |h(q_\perp,t)h(-q_\perp,t)| \rangle \sim T_{eff} q_\perp^4 \), where \( T_{eff} \) is an effective temperature which depends on the details of inclusion activities.

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A biological membranes is a multi-component mixture of lipids, proteins, carbohydrates, and other materials. Since the active inclusions (e.g., proteins) in the membranes participate in physiological processes such as ion transport, signal transduction, and cell locomotion, recent theoretical and experimental studies have focused on the collective effect of these active inclusions on the membranes. An important conclusion of these studies is that, unlike equilibrium membranes, the height fluctuation of a tensionless active membrane in the long wavelength regime depends on the inclusion activities. Activity-induced instabilities are also predicted in previous theoretical models. On the other hand, the fact that these active inclusions have more than one internal conformation state has been discussed for a single transmembrane protein and for a single ion pump. Although the elastic interaction between lipids and an active inclusion have significant effect on the behaviors of a single inclusion, the equally important question of how this interaction affects the collective behavior of the lipid-inclusion system is seldom addressed in previous studies of active membranes.

In this Letter, I discuss the dynamics of a fluid membrane containing lipids and identical two-state active inclusions. As shown in Figure 1, inclusions in different conformation states have different couplings to the local mean curvature of the membrane. Recent experiments on the structures of potassium channels and K⁺ channels have provided structural evidences of such inclusion conformation changes. A conformation change of an inclusion can be induced by external stimuli (active transition) or by the lateral pressure exerted by the surrounding medium (passive transition). During a conformation change, an inclusion also exerts forces to the lipids and the solvent. By taking these effects into account, the main predictions of the model are: (i) The height variance of a stable tensionless membrane in the long wavelength limit is \( \langle |h(q_\perp,t)|^2 \rangle \sim T_{eff} q_\perp^4 \), where \( T_{eff} \) is an effective temperature which depends on the inclusion activities. For a stable tense membrane, surface tension dominates the long wavelength membrane height variance, therefore \( \langle |h(q_\perp,t)|^2 \rangle \sim T_{eff} q_\perp^4 \), the same as that of an equilibrium tense membrane. (ii) The system has two types of long wavelength instabilities. They are pump-driven undulation instability due to the pumping-induced attraction between the inclusions, and the excitation-driven undulation instability due to excitation-induced aggregation of the excited inclusions in the case when the excited inclusions have sufficiently higher curvature than the ground state inclusions. (iii) Depending on the structural details of the inclusions, the system can have a finite wavelength instability which leads to domains with a characteristic length depending on the active transition rates. At high active transition rates, the activities can even drive the system to a homogeneous state. Therefore it is possible to control the membrane morphology in experiments by tuning the activities of the inclusions.

In the Monge representation the shape of the membrane is described by \( h(x,y) \). The number density of inclusions in state \( \alpha \) \( (\alpha = 1 \text{ or } 2) \) is \( \Phi_\alpha(r_\perp,t) \) where \( r_\perp = (x,y) \). It is useful to introduce \( \Phi_\pm = (\Phi_1 + \Phi_2)/2 \) and \( \Phi_\pm^{(0)} = \int d^2 r_\perp \Phi_\pm/\int d^2 r \). The coarse grained Hamiltonian of the system \( H = H_m + H_i + H_c \) includes the elastic energy of the membrane, the direct interaction energy of the inclusions, and the membrane-inclusion coupling. To lowest order \( H_m \) has the form

\[
H_m = \frac{1}{2} \int d^2 r_\perp (\kappa (\nabla_\perp^2 h)^2 + \gamma (\nabla_\perp h)^2),
\]

where \( \kappa \) is the bending rigidity, \( \gamma \) is the surface tension of the membrane. In this Letter I consider the regime where the system is close to a phase separation in \( \Phi_- \), and \( \Phi_+ \) is non-critical. Therefore the interaction energy
of the inclusions in the harmonic theory is \[ H_i = \int d^2r_\perp \left\{ \frac{1}{2} (\epsilon^2 (\nabla_\perp \Phi_-)^2 + r_2 \Phi_-^2) + \frac{m}{2} (\Phi_+ - \Phi_+^{(0)})^2 - \Delta \epsilon \Phi_- \right\}, \] 

where \( r_2 > 0 \) is small and \( m \gg r_2 \). \( \Delta \epsilon > 0 \) is the excitation energy for an inclusion to change its conformation from state 1 to state 2. Thus “state 1 (2)” is the “ground (excited) state” of an inclusion. The couplings between the inclusion densities and the membrane curvature depend on the shapes of the inclusions, it can be expressed by

\[
H_e = \int d^2r_\perp \kappa (c_1 \Phi_1 + c_2 \Phi_2) \nabla_\perp^2 h
= \int d^2r_\perp \kappa (c_+ \Phi_+ + c_- \Phi_-) \nabla_\perp^2 h,
\]

where \( c_{\pm} = c_1 \pm c_2 \). The equilibrium properties of this model Hamiltonian is briefly summarized in the following. The stability criterion of the membrane is

\[
\phi(t) = \Omega(t) + \delta h(t) \hat{\mathbf{z}}.
\]

where the vector thermal noise \( \zeta_\perp \) has zero mean and variance \( \langle \nabla_\perp \cdot \zeta_\perp(r, t) \nabla_\perp \cdot \zeta_\perp(r', t') \rangle = 2k_B T \lambda_\perp \nabla^2 \delta^3(\mathbf{r} - \mathbf{r}') \delta(t - t'). \) In general, \( \phi \) satisfies an equation of the following form,

\[
\frac{\partial \phi_-}{\partial t} = (-\lambda_0 + \lambda_2 \nabla^2 \phi_-) \cdot \phi_- + k_- \phi_+ - k_0 \phi_- + \zeta_-.
\]

The passive conformation change of the inclusions is taken into account by \( \lambda_0 \) term, \( \lambda_2 \) term represents the mutual diffusion of the inclusions, the conformation changes due to external stimulations (active transitions) are taken into account by \( -k_+ \phi_+ - k_- \phi_- \) \( \zeta_- \), the thermal noise \( \zeta_- \) has zero mean and variance \( 2k_B T (\lambda_0 + \lambda_2 \nabla^2 \phi_-) \). The hydrodynamic flow, the permeation of solvent through the membrane, and the force exerted on the membrane by the inclusions during active transitions all contribute to the dynamics of the membrane, thus

\[
\frac{\partial h}{\partial t} = v_z - \lambda_p \left( \frac{\partial h}{\partial \lambda} + P^a_k e\phi_1 + P^a_k r \phi_2 \right) + \zeta_h.
\]

Here \( \zeta_h \) is the momentum transferred from an inclusion during an active excitation (relaxation) process. The thermal noise \( \zeta_h \) has zero mean and variance \( 2k_B T \lambda_p \). The solvent which embeds the membrane satisfies the modified Stokes equation

\[
0 = -\nabla p(r, t) - \lambda_0 \frac{\partial h}{\partial \lambda} (r, t) \delta(z) \hat{\mathbf{z}} + P^a_k \delta(z - w_1^d) k_e \phi_1 \hat{\mathbf{z}} + P^a_k \delta(z - w_2^d) k_r \phi_2 \hat{\mathbf{z}} + \eta \nabla^2 \mathbf{v} + \mathbf{f}_0.
\]

To discuss the dynamics, I introduce suitable variables \( \phi_{\pm} \). When \( c_2(q_{\perp}) > 0 \), \( \phi_{\pm} \) are chosen to be the deviation from the equilibrium solution, i.e., \( \phi_+ = \Phi_+ - \Phi_+^{(0)} \) and \( \phi_- = \Phi_- - \Phi_-^{(0)} \), where \( \Phi_+^{(0)} \) is the equilibrium value of \( \Phi_+ \). When \( c_2(q_{\perp}) < 0 \), \( \phi_{\pm} \) are chosen to be \( \phi_+ = \Phi_+ - \Phi_+^{(0)} \) and \( \phi_- = \Phi_- \) such that the effect of non-equilibrium activities on the stability of the membrane can be discussed conveniently. On most experimental time scales the membrane does not exchange inclusions with the solvent, therefore \( \phi_+ \) obeys the conserved dynamics

\[
\frac{\partial \phi_+}{\partial t} = \lambda_+ \nabla^2 \frac{\partial h}{\partial \phi_+} + \nabla_\perp \cdot \zeta_+.
\]
where

\[
D_h(q_\perp) = -\frac{1}{4\eta q_\perp} \left( \left( \kappa - \frac{\kappa^2 c_+ c_-^a}{m} \right) q_\perp^4 + \gamma q_\perp^2 \right),
\]
\[
D_\phi(q_\perp) = -(\lambda_0 + \lambda_2 q_\perp^2)(\epsilon^2 q_\perp^4 + r_2) - k_-, \quad D_{\phi h}(q_\perp) = \frac{1}{4\eta q_\perp} \kappa c_-^a q_\perp^3,
\]
and

\[
D_{\phi h}(q_\perp) = (\lambda_0 + \lambda_2 q_\perp^2)\kappa_{c_-}^a q_\perp^2 - k_+ \frac{\kappa c_+}{m} q_\perp^2, \quad (11)
\]

\[\kappa c_+^a \equiv \kappa c_+ + v_+^2, \quad \text{and} \quad v_\pm \equiv P_\pm k_\epsilon (-w_1^2)^2 + (w_1^2)^2)/2 \pm P_\epsilon k_\epsilon (-w_1^2)^2 + (w_1^2)^2)/2. \]

It is convenient to think \( c_\pm^a \) as the “renormalized” inclusion-membrane coupling in the presence of non-equilibrium activities. Magnitudes of \( v_\pm \) depend on structural details and active transition rates of the inclusions. Dimensional analysis in previous studies \[3, 4\] show that \( v_\pm \sim f^{1/2} \), where \( f \sim 5n \) is a typical length associated with an inclusion, and \( f \) has the dimension of a force. At high activities \( f \sim 10^{-12} N \) \[3, 4\], together with \( \kappa c_\pm \sim f k_B T \) gives \( v_\pm /\kappa c_\pm \lesssim O(1) \). Therefore \( \kappa c_+^a \) and \( \kappa c_-^a \) are of the same order of magnitude, and usually have the same sign. The noises \( f_h(q_\perp, t) \) and \( f_\phi(q_\perp, t) \) have zero mean and variances \( \langle f_h(q_\perp, t) f_h(q_\perp^l, t^l) \rangle = 2k_B T q_\perp^2 (1 + v_-^4 q_\perp^4 /4\eta \kappa c_+^a) \delta(t-t^l) \delta(q_\perp - q_\perp^l), \quad \langle f_\phi(q_\perp, t) f_\phi(q_\perp^l, t^l) \rangle = 2k_B T (\lambda_0 + \lambda_2 q_\perp^2 + \kappa^2 c_+^a / \eta \kappa c_-^a) \delta(t-t^l) \delta(q_\perp - q_\perp^l). \]

Notice that there are contributions from the activities of the inclusions. They are no longer equilibrium thermal noises.

The stability of the system is determined by the eigenvalues of the \( 2 \times 2 \) matrix in Eq. \( 10 \). When both \( D_h \) and \( D_\phi \) are positive, the stability condition for a tensionless membrane is

\[
A_{\phi f} = \left( \frac{\lambda_0}{\kappa^2 c_+^a} q_\perp^4 \right. + \left. \left( \frac{\lambda_0}{\kappa^2 c_-^a} \kappa_{c_-}^a + \lambda_2 \kappa_{c_-}^a \right) \frac{r_2}{m} \right) q_\perp^2 > 0, \quad \text{or} \quad T_{\text{eff}} = \frac{T \kappa_{c_-}^a}{\kappa - \kappa^2 c_+ c_-^a / m} - \frac{\kappa^2 c_+ c_-^a / \lambda_0 m}{r_2 - k_- f_0}. \quad (14)
\]

If the passive conformations changes of the inclusions are extremely rare such that \( \lambda_0 \ll \lambda_2 q_\perp^2 \) in all experimental length scales, \( T_{\text{eff}} \) has the following form,

\[
T_{\text{eff}} = \frac{T \kappa_{c_-}^a}{\kappa - \kappa^2 c_+ c_-^a / m} - \frac{\kappa^2 c_+ c_-^a / \lambda_0 m}{r_2 - k_- f_0}. \quad (15)
\]

The resulting steady state has an average domain size \( R \) which can be estimated by the following scaling analysis. \[18 \[19 \] When there is no budding, the growth of intramembrane domains in the absence of inclusion activities corresponds to a two-dimensional phase separation dynamics, i.e., \( R(t) \sim t^\alpha, \quad \alpha \approx 1/3 \) \[20 \]. This growth eventually saturates due to the active transitions. Since the time scales associated with active transitions are \( k_\pm \), the steady state domain size \( R \) should obey \( R \sim k_\pm^{-\alpha} \), where \( k_\pm = (k_\pm(-) \pm k_\pm(+) \kappa^2 c_+ c_-^a / m \) is larger (smaller) than \( k_- \), \( k_+ \). Notice that this instability is suppressed at large \( k_- = k_r + k_\pm \). This is because when the inclusions change their conformations at extremely high rates, the membrane feels the time-averaged inclusion conformation, therefore there is no finite size domains in the steady state. When \( \kappa^2 c_+ c_-^a > 0 \), an excited state inclusion has smaller curvature than a ground state inclusion, sufficiently large \( k_- \) stabilizes the membrane because strong active transitions excite the inclusions to the smaller curvature excited state.

When the membrane is stable, its height fluctuations in the long wavelength limit is expressed by \( B_{\phi f} / q_\perp^4 \), where

\[
T_{\text{eff}} = \frac{T \kappa_{c_-}^a}{\kappa - \kappa^2 c_+ c_-^a / m} - \frac{\kappa^2 c_+ c_-^a / \lambda_0 m}{r_2 - k_- f_0}. \quad (14)
\]

Eqs. \[14 \[15 \] are similar to previous studies on the active membranes which neglected the internal states of the inclusions. \[4 \] For a membrane under tension the \( B_{\phi f} / \kappa_{c_-}^a \) behavior is cut off at long wavelengths. The membrane height fluctuation at large lengths in this case is simply \( k_B T / \gamma q_\perp^4 \) where \( T \) is the temperature of the solvent.

In summary, a theory of active membranes with two-state active inclusions is discussed. Although current analysis is restricted to a relatively small region of the parameter space, the rich dynamical behaviors shown in the analysis are believed to exist in more general situations. These include instability induced by active pumping, instability induced by inclusion-excitation, finite size
domains controlled by activities, and activity-restored homogeneous morphology. In the stable case, the membrane height fluctuation is similar to several previous theoretical and experimental studies. The analysis of this model in a broader parameter range and the effects of nonlinearity will be included in a future work. It is my hope that this model might be of relevance to active conformational transitions in biological membranes, and experimental work on artificial membranes might be designed to confirm the main ideas of this model.

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**Figures**

![FIG. 1: Schematics of an inclusion in different conformation states](image1.png)

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![FIG. 2: Large negative $k_{eff}$ instability: pumping-induced attraction between inclusions induces inclusion aggregation.](image2.png)

**FIG. 2:** Large negative $k_{eff}$ instability: pumping-induced attraction between inclusions induces inclusion aggregation.

![FIG. 3: The presence of many high-curvature excited state inclusions induces a long wavelength instability.](image3.png)

**FIG. 3:** The presence of many high-curvature excited state inclusions induces a long wavelength instability.