

Indissoluble biomolecular condensates via elasticity

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While biomolecular condensates are often liquidlike, many experiments found that condensates also exhibit solidlike behaviors, making them indissoluble in conditions liquid condensates dissolve. Despite the biological significance of indissoluble condensates to cellular fitness, the mechanisms underlying the indissolubility of solidlike condensates are still unclear. In this work, we study the effects of elasticity on the dissolution of biomolecular condensates. We demonstrate that the bulk stress inside condensates may prevent the condensates from dissolution and obtain a mechanical equilibrium condition of elastic condensates. Moreover, we predict a phase diagram of indissolubility for biomolecular condensates and identify a minimum bulk modulus for the condensates to be indissoluble. To verify our theories, we simulate the two-fluid model in which the slow component corresponding to biomolecules generates elastic stress. Our theoretical predictions are nicely confirmed and independent of microscopic details. Our works show that elasticity makes biomolecular condensates less prone to dissolution.

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Biomolecular condensates are ubiquitous in various organisms, usually composed of proteins and RNAs [1–9]. They often have crucial biological functions [8,10–16], such as adaptive responses to stresses, accelerating biochemical reactions, and sequestering molecules from reactions. Therefore, the accurate regulation of biomolecular condensates' formation and dissolution is critical. Meanwhile, experiments have also found that biomolecular condensates are viscoelastic [17]: they are solidlike on a short timescale and liquidlike on a long timescale. Interestingly, they often exhibit aging behaviors, and the viscoelastic relaxation time, which separates solid and liquid behaviors, increases over time [18]. Indeed, aged condensates may become indissoluble or infusible in conditions where newly formed condensates can easily dissolve or fuse [3,4,9,10,14,19–21]. The resistance to dissolution of solidlike condensates is particularly significant when the condensates are induced by deep supersaturation [7]. Dissolution of solidlike condensates may need assistance by energy-consuming enzymes [20,22–24], therefore, reducing cellular fitness. Moreover, failure to dissolve condensates during mitosis leads to aberrant condensates that cause cell-cycle arrest and ultimately cell death [25].

Despite the importance of solidlike nature on the dissolution of condensates [15,18], theoretical studies on the formation and dissolution of biomolecular condensates have so far been limited to fluid models, in which the elastic nature of condensates is neglected [26]. Among the most common theoretical models, the hydrodynamic model involving

diffusion and advection, often called Model H [26,27], can successfully incorporate the physics needed to describe the dynamics of phase separation and droplet growth. However, it does not include the elastic nature of condensates. Therefore, it cannot explain the indissolubility of solidlike condensates in conditions where liquid condensates dissolve.

In this work, we investigate the effects of elasticity on the dissolubility of biomolecular condensates, combining both theories and numerical simulations. In the following, we first introduce our theoretical frameworks, focusing on elastic condensates subject to an abrupt control parameter change that reduces the attractive strength between biomolecules. Biologically, one of the most relevant perturbations is the post-translational modification such as phosphorylation, which introduces Coulomb repulsive interaction between biomolecular monomers and reduces the attractive interaction [5,13,28]. Other perturbations that can lead to similar effects include changing temperature, pH, and salt concentrations. Without elasticity, biomolecular condensates are supposed to dissolve. However, for elastic condensates, the bulk stress generated by elasticity may prevent the dissolution and render the condensates indissoluble, with a new mechanical equilibrium condition involving the bulk stress. To test our theoretical predictions, we simulate the two-fluid model [29,30] beyond the traditional Model H, in which the biomolecule velocity field and the elastic stress are dynamically coupled. Numerical simulations of the two-fluid model nicely confirm our theories. Our theories' validity is independent of the microscopic details, such as the free energy forms of the biomolecule density field, as we confirm numerically.

Furthermore, we theoretically predict a phase diagram of indissolubility as a function of effective temperature and the condensate's bulk modulus. We demonstrate a minimum bulk modulus for the condensate to be indissoluble. Numerical simulations nicely confirm our predictions regarding the

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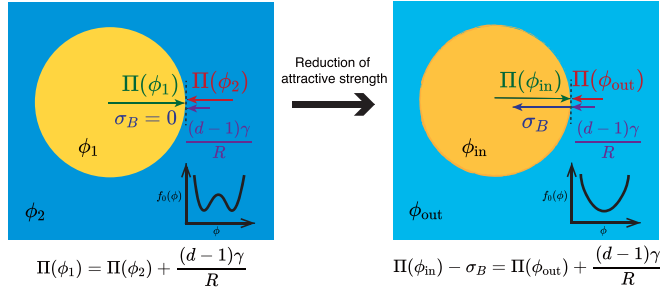


FIG. 1. Mechanical equilibrium conditions of elastic condensates. In this schematic, a condensate is initially in equilibrium with its surroundings. An abrupt change in the attractive strength between biomolecules is introduced, corresponding to a change in the shape of the biomolecule free energy $f_0(\phi)$ from two minimums to a single minimum. Here ϕ is the biomolecule density. As a result, the condensate expands to reach a new equilibrium with the biomolecules escaping from the condensate simultaneously. The elasticity of the condensate generates a bulk stress σ_B , which is involved in the new equilibrium condition.

boundary between the dissoluble and indissoluble phases. Our results suggest that the dissolution of elastic condensates can be facilitated by decreasing the biomolecules' attractive strength and lowering the condensates' bulk moduli. Finally, we discuss the biological implications of our work and propose potential experiments to test our predictions.

Equilibrium conditions of elastic condensates. Biomolecular condensates usually have well-defined viscoelastic relaxation times, below which the condensates behave as elastic materials [17,18]. In this work, we simplify the problem by considering aged condensates with their viscoelastic relaxation times much longer than the timescales of biological interests, e.g., the duration of cell-cycle phases. Therefore, the viscoelastic relaxation time can be taken as infinite, which is the main focus of this work.

We consider an elastic condensate that is initially in equilibrium with its surroundings and then introduce an abrupt reduction to the attractive strength between the biomolecules, e.g., through phosphorylation. The free energy as a function of the biomolecule density changes from a function with two minimums to a function with only one minimum (Fig. 1). Therefore, the condensate will expand and eventually completely dissolve in the absence of elasticity. However, in the presence of elasticity, the condensate may expand to reach a new equilibrium, with the biomolecules escaping from the condensate during the expansion. During this process, the density inside the condensate decreases, and the bulk stress inside the condensate increases, similar to the equilibrium swelling of a polymer network [31]. When the bulk stress balances the osmotic pressure difference inside and outside the condensate, also minus the surface tension stress, the new equilibrium is established:

$$\sigma_B = \Pi_{\text{in}} - \Pi_{\text{out}} - \frac{(d-1)\gamma}{R}. \quad (1)$$

Here, σ_B is the bulk stress generated by elasticity and $\Pi_{\text{in(out)}}$ is the osmotic pressure inside (outside) the condensate. d is the spatial dimension, γ is the surface tension constant, and

R is the condensate radius. For liquid condensates without elasticity, $\sigma_B = 0$ in Eq. (1) [32,33]. The establishment of the equilibrium in our case is similar to the equilibrium swelling of a polymer network in which it is also the elastic stress that balances the osmotic pressure, which we will discuss in more detail in the Discussion section.

To find the expression of σ_B , we use the constitutive equation of the bulk stress and the continuity equation of biomolecule density (ϕ),

$$\frac{\partial \sigma_B}{\partial t} = G_B \nabla \cdot \mathbf{v}_p, \quad (2)$$

$$\frac{\partial \phi}{\partial t} = -\phi \nabla \cdot \mathbf{v}_p. \quad (3)$$

Here $\mathbf{v}_p$ is the velocity field of the biomolecules, which is responsible for the bulk stress. G_B is the bulk modulus. In writing the above two equations, we assume that ϕ and σ_B are uniform inside the condensate, which we confirm numerically later. Combining Eqs. (2) and (3), we obtain

$$\sigma_B = G_B \ln \left(\frac{\phi_1}{\phi_{\text{in}}} \right), \quad (4)$$

where ϕ_1 and ϕ_{in} are the biomolecule densities inside condensates before and after the reduction of attractive strength between the biomolecules. The equilibrium condition must be satisfied for all condensates in a system of multiple condensates with the bulk stress determined by Eq. (4), and Π_{in} and Π_{out} determined by ϕ_{in} and ϕ_{out} , respectively. Each condensate can have different ϕ_{in} 's although they share the same biomolecule density ϕ_{out} outside them. Given the radii R 's and the densities ϕ_{in} 's of each condensate, ϕ_{out} can be calculated using the conservation of total molecular number: $V\phi_0 = \sum_i V_i \phi_{\text{in},i} + (V - \sum_i V_i) \phi_{\text{out}}$. Here, V is the total volume, V_i is the volume of condensate i assuming a spherical shape, and the summation is over all condensates. ϕ_0 is the average density over the total volume.

To uniquely determine the densities inside condensates, we still need one more equation. For liquid condensates, it is a uniform chemical potential. However, in our case, the condensate is solid, so the exchange of molecules is suppressed as soon as the mechanical equilibrium is established [3,8,15]. Instead, we propose that condensate size does not change upon the weakening of attractive interaction between biomolecules, namely, $R = R_0$, where R and R_0 are the radii of an elastic condensate before and after the condition changes. We confirm this assumption numerically later. Note that the condensate size does not have to increase since the biomolecules escape the condensate simultaneously as the condensate expands. The condensate's constant radius and decreased density do not conflict with the suppressed exchange of molecules since the density change happens when the system is initially out of equilibrium after the attractive strength suddenly decreases. Finally, we remark that in our case, the bulk stress inside the condensate stabilizes the condensate, in contrast to the bulk stress outside a condensate, e.g., due to the surrounding polymer network that suppresses the formation of condensates [34–41].

Simulations of the two-fluid model. To mimic the aged condensates, we numerically simulate the two-fluid model in two dimensions [29,30] with two components: the slow

component corresponding to the biomolecules and the fast component corresponding to the solvent. It is the biomolecule component that generates the elastic stress. The average velocity field $\mathbf{v} = \phi \mathbf{v}_p + (1 - \phi) \mathbf{v}_s$ where $\mathbf{v}_p$ and $\mathbf{v}_s$ are, respectively, the biomolecule and solvent velocity field. In the two-fluid model, the biomolecule density field ϕ is spatially dependent with its value between 0 and 1. The dynamics of the biomolecule density and velocity field follows (see details in the Supplemental Material [42]):

$$\frac{\partial \phi}{\partial t} = -\nabla \cdot (\phi \mathbf{v}) + \nabla \cdot \left(\frac{\phi(1-\phi)^2}{\zeta} (\nabla \cdot \mathbf{\Pi} - \nabla \cdot \sigma) \right), \quad (5)$$

$$-\nabla \cdot \mathbf{\Pi} + \nabla \cdot \sigma - \nabla p + \eta \nabla^2 \mathbf{v} = 0. \quad (6)$$

Here, ζ is the friction constant between biomolecules and solvent, and η is the viscosity. The pressure p is determined by the incompressible condition: $\nabla \cdot \mathbf{v} = 0$. The stress tensor $\sigma = \sigma_s + \sigma_B \mathbf{I}$ where σ_B is the bulk stress and σ_s is the shear stress tensor. They follow the Maxwellian dynamics such that (Supplemental Material [42])

$$\frac{\partial \sigma_B}{\partial t} = -(\mathbf{v}_p \cdot \nabla) \sigma_B - \frac{1}{\tau_B(\phi)} \sigma_B + G_B(\phi) \nabla \cdot \mathbf{v}_p, \quad (7)$$

where $G_B(\phi)$ is the bulk modulus. To simulate elastic condensates, we take the relaxation time of bulk stress to be diverging at a critical density ϕ_c such that $\tau_B^{-1}(\phi) = (\phi_c - \phi) \Theta(\phi_c - \phi)$, where $\Theta(x)$ is the Heaviside function. We remark that if we take the stress tensor to be zero in Eqs. (5) and (6), they are reduced to the classical Model H [27]. The osmotic stress tensor is determined by the biomolecule free energy $f(\phi)$, $\nabla \cdot \mathbf{\Pi} = \phi \nabla f'(\phi)$ where $f(\phi) = f_0(\phi) + \frac{C}{2} (\nabla \phi)^2$ and C is a constant. If not mentioned explicitly, we use the Flory-Huggins free energy density: $f_0(\phi) = \epsilon_0 [\phi \ln(\phi) + (1 - \phi) \ln(1 - \phi) + \chi \phi(1 - \phi)]$. Here $\epsilon_0 = k_B T / V_0$ where k_B is the Boltzmann constant, T is the temperature, and V_0 is the biomolecular monomer volume. We note that the condition of stable liquid condensate for the Flory-Huggins model is that the parameter $\chi > 2$. We use the osmotic pressure Π to represent the scalar osmotic stress computed from $f_0(\phi)$, $\Pi = \phi f'_0(\phi) - f_0(\phi)$. By nondimensionalizing Eqs. (5) and (6), we choose the unit of elastic modulus as ϵ_0 , the time unit $t_0 = \eta / \epsilon_0$, and the length unit $l_0 = \sqrt{\eta / \zeta}$ (see estimations in the Supplemental Material [42]).

We note that the osmotic stress and the elastic stress are fundamentally different as the osmotic stress is a function of the instantaneous density field while the elastic stress depends on the accumulated change of the density field. One may attempt to compute an effective elastic free energy that is a function of ϕ so that the elastic bulk stress is included in the osmotic pressure as $\phi f'_{\text{el}}(\phi) - f_{\text{el}}(\phi) = -\sigma_B$. However, the resulting effective chemical potential $\mu_{\text{eff}} = f'(\phi) + f'_{\text{el}}(\phi)$ is not uniform across the system, which suggests that the elastic stress cannot be included in the free energy as a function of the density field (Supplemental Material Fig. S1). We also calculate a correction to the chemical potential due to the bulk stress using the Gibbs-Duhem relation $d\mu = \sigma_B / \phi$, but the overall chemical potential is still not uniform in the system (Fig. S2).

Tests of theoretical predictions. We simulate multiple co-existing condensates, first generated by the two-fluid model

without elasticity from a uniform density ϕ_0 as the initial condition (see details in the Supplemental Material [42]). The average density is therefore set by the initial condition. The initial Flory-Huggins parameter $\chi_i = 3$. We add elasticity to the condensates after the formation of multiple spherical condensates to mimic the aging process. After a short time, we change χ to $\chi_f = 1.5$ so that the free energy $f_0(\phi)$ changes from a form with two minimums to a form with only one minimum (Fig. 1).

After the reduction of χ , we find that these condensates are indissoluble under the parameters we take. The density field inside condensates is indeed uniform as assumed [Fig. 2(a)]. We also confirm our assumptions of uniform bulk stress [Fig. 2(c)] and constant radii (Fig. S3). An example of the simulations is shown in Supplemental Material Movie S1. The osmotic pressure is significantly different across the boundaries of condensates [Fig. 2(b)]. For liquid condensates, they will quickly dissolve due to the large pressure difference. In contrast, the bulk stress balances the osmotic pressure difference for elastic condensates. Indeed, we find that the difference between the osmotic pressure and bulk stress ($\Pi - \sigma_B$) is uniform across the boundaries [Fig. 2(d)]. We note that the uniform $\Pi - \sigma_B$ is not valid near the condensate boundaries due to the surface tension. Using the variable sizes of condensates, we compute the radius dependence of surface tension constant γ , and find that γ converges to a constant value in the large radius limit [Fig. 3(a)], suggesting that it is well defined in the thermodynamic limit.

To compute the predicted densities inside and outside multiple condensates, we numerically solve n equations of Eq. (1) with n unknown ϕ_{in} 's, where n is the number of condensates. The bulk stress σ_B is related to ϕ_{in} through Eq. (4). The osmotic pressures Π_{in} and Π_{out} are, respectively, functions of the densities ϕ_{in} and ϕ_{out} inside and outside the condensate. Note that ϕ_{out} is not an independent variable, and it is determined from ϕ_{in} 's by the conservation of total biomolecules. The radii of condensates used in theoretical predictions are calculated from the simulation before changing χ .

We remark that if we neglect the contribution of surface tension in Eq. (1), we can combine all condensates together to find the common ϕ_{in} that works for all condensates. We find that the surface tension constant is relatively small in our simulations, so our predictions of the densities ϕ_{in} and ϕ_{out} with $\gamma = 0$ [Fig. 3(b)] are very close to the predictions with a finite γ (Fig. S4). Therefore, we neglect the surface tension in the following theoretical calculations.

To test the generality of our theories, we also use the Landau-Ginzburg free energy and find that our theories are equally applicable [Figs. 3(c) and 3(d)]. In both cases, the condensates can be indissoluble after changing the forms of free energies from two minimums to a shape with only one minimum. We find that the numerical densities ϕ as a function of the distance from the condensate center precisely match the theoretical predictions. We also test our theories using the asymmetric Flory-Huggins model and again obtain satisfying agreements between simulations and theoretical predictions [Fig. S5(a)].

To test the effects of the shear modulus, we repeat the above simulations with the Flory-Huggins free energy and

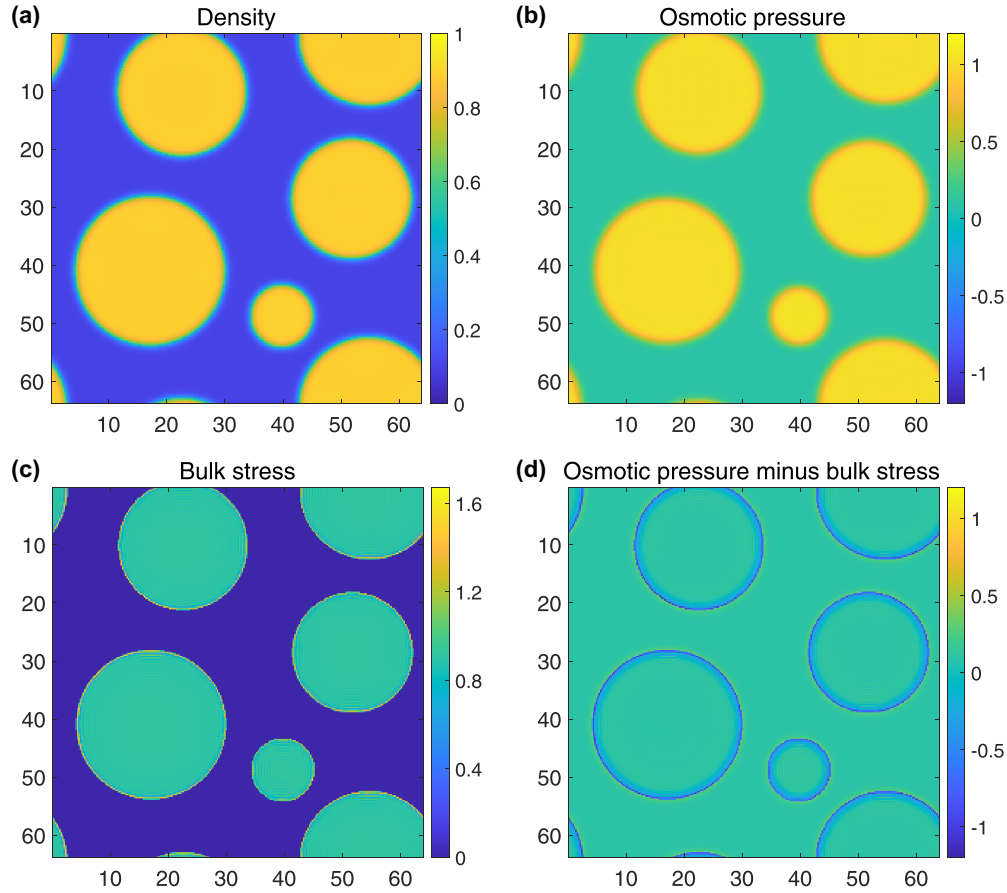


FIG. 2. Simulations of multiple coexisting elastic condensates. (a) The density field ϕ after decreasing the χ parameter in the Flory-Huggins free energy from 3.0 to 1.5. For liquid condensates, they will simply dissolve. In contrast, the elastic condensates can be indissoluble. (b) The osmotic pressure Π from the same simulation of (a). (c) The bulk stress σ_B from the same simulation of (a). (d) $\Pi - \sigma_B$ from the same simulation of (a). In this figure, we take $\phi_0 = 0.45$, $G_B = 20$, $G_S = 20$, and $\phi_c = 0.5$.

change the shear modulus with the same bulk modulus. We find that the density distributions are insensitive to the values of shear moduli (Fig. S6), corroborating the major role of bulk stress in the mechanical equilibrium conditions. Finally, we also test the effects of the critical density and find that our results are valid independent of ϕ_c [Figs. S5(b) and S7–S9].

Phase diagram of indissolubility. In the following, we systematically investigate the indissoluble conditions of elastic condensates. We compute the theoretically predicted ϕ_{in} after χ is lowered from $\chi_i = 3$ to χ_f as a function of G_B using Eq. (1). We find that ϕ_{in} decreases as G_B decreases [Fig. S10(a)]. From this calculation, we predict the critical bulk modulus $G_{B,c}$ for the condensate to be indissoluble given χ_f , based on the condition $\phi_{in} > \phi_c$ where ϕ_c is the critical density above which the condensates become elastic. Because both χ and G_B appear linearly in Eq. (1), the phase boundary separating the dissoluble and indissoluble phase must be linear in the χ_f - G_B parameter space.

To test our predictions, we simulate a single condensate with two control parameters χ_f and G_B and monitor its dissolution dynamics after χ is reduced from $\chi_i = 3$ to χ_f . We label the condensate as dissoluble or indissoluble depending on if the system becomes uniform or not after a long waiting time $t = 10^4$ [see examples in Figs. S10(b) and 10(c) and Supplemental Material Movie S2]. As expected, when $G_B = 0$, the

condensate is stable only if $\chi_f > 2$. For $\chi_f < 2$, the condensate becomes indissoluble if the bulk modulus is larger than a critical value. The numerically simulated phase diagram nicely matches the predicted phase diagram [Fig. 4(a)]. Our results are not sensitive to the values of ϕ_c as we get similar results using different ϕ_c (Fig. S11). We also simulate a modified model in which the relaxation time of bulk stress increases with density continuously without a critical density. Our main conclusions, including the phase diagram of indissolubility, are still valid with an effective critical density (Fig. S12).

We find that to match the predicted phase boundary to the simulations accurately, we need to solve the equation $\phi_{in} = \theta \phi_c$ with $\theta = 1.1$ to find the critical bulk modulus [Figs. 4(a) and S10(a)]. To understand why θ is close but slightly larger than 1, we remark that for the elastic condensate to be stable, ϕ_{in} must be larger than ϕ_c to ensure force balance across the condensate boundary. The biomolecules are subject to two types of force: the force from the gradient of the osmotic tensor ($-\nabla \cdot \Pi$) and the force from the gradient of the elastic stress ($\nabla \cdot \sigma$). We can further decompose the former force into two parts: one is from the free energy $f_0(\phi)$, which we call the osmotic force, and the other is from the $\frac{c}{2}(\nabla \phi)^2$ term in the free energy, which we call the surface tension force. For a liquid condensate, the osmotic force always balances the surface tension force across the condensate boundary. Because the

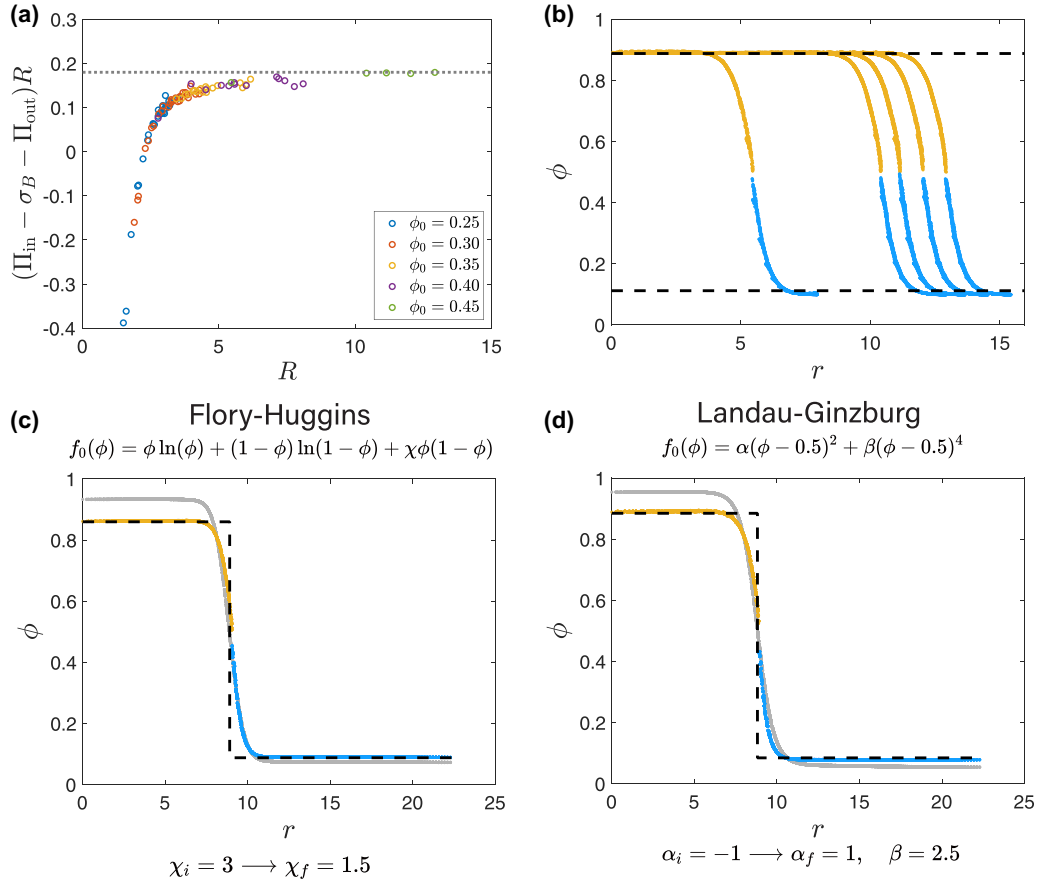


FIG. 3. Computations of the surface tension constant γ and predictions of the density field using different types of free energy. (a) The inferred surface tension constant $\gamma = (\Pi_{\text{in}} - \sigma_B - \Pi_{\text{out}})R$ approaches an asymptotic value in the large radius limit. (b) A comparison of the theoretical predictions of ϕ_{in} and ϕ_{out} (black dashed lines) and the simulations (yellow dots above ϕ_c and blue dots below ϕ_c) [same as Fig. 2(a)]. Each yellow and blue curve represents one condensate and r is the distance from the condensate center. (c) For the Flory-Huggins free energy, the initial density field (gray dots) cannot be maintained after χ decreases and the final density field is established. (d) For the Landau-Ginzburg free energy, the equilibrium density field can also be predicted by our theories after the control parameter α increases from -1 to 1 . In (a) and (b), $G_B = 20$, $\chi_i = 3.0$, $\chi_f = 1.5$, $\phi_0 = 0.45$ in (b). In (c) and (d), we simulate a single condensate (see details in the Supplemental Material [42]) with $R_0 = 9$. $G_B = 10$ in (c) and $G_B = 20$ in (d). In all figures, $G_S = 20$ and $\phi_c = 0.5$.

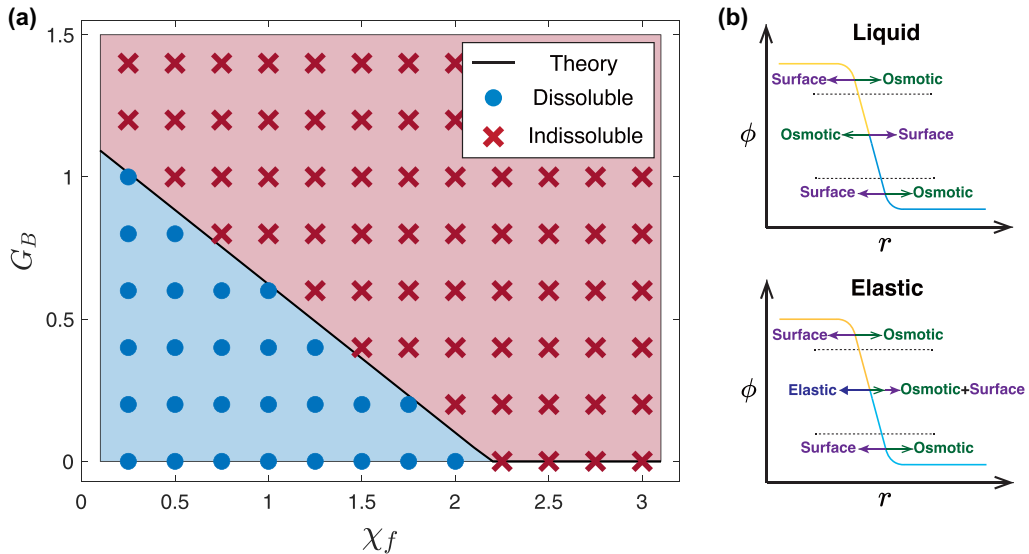


FIG. 4. A critical bulk modulus $G_{B,c}$ above which condensates are indissoluble. (a) Phase diagram of condensate indissolubility with control parameters χ_f and G_B . The theoretical predicted $G_{B,c}$ is the black line and the simulation results are the blue dots and red crosses. (b) Schematics for the force balance in the crossover regime of condensates.

osmotic pressure is a nonmonotonic function of density, in this case, the crossover regime can be separated into three parts in which both the surface tension force and the osmotic force change their signs [see the schematic in Fig. 4(b) and numerical simulations in Fig. S13(a)]. For an elastic condensate, the osmotic force always points outwards from the condensates since the osmotic pressure is now a monotonically increasing function of ϕ , while the surface tension force still changes its sign. Therefore, in this case, an inward elastic force must exist to balance the sum of surface tension force and osmotic force in the crossover regime [Figs 4(b) and S13(b)]. In conclusion, ϕ_{in} should be larger than ϕ_c to ensure a finite elastic force in the crossover regime; therefore, $\theta \gtrsim 1$.

Discussion. Our work provides a mechanistic understanding of the indissolubility of solidlike biomolecular condensates. We show that the bulk stress can balance the osmotic pressure difference inside and outside the condensates, therefore preventing the dissolution. Numerical simulations of the two-fluid model nicely confirm our theoretical predictions of the mechanical equilibrium condition. Moreover, we theoretically and numerically obtain a phase diagram of indissolubility for elastic condensates and obtain a minimum bulk modulus for condensates to be indissoluble.

There remain some open questions, including the effects of shear modulus. While we numerically find that our simulations are mostly independent of the values of shear moduli, a small but finite shear modulus is nevertheless necessary to maintain the spherical shapes of condensates. When the shear modulus is zero, the spherical condensate becomes distorted and unstable. It dissolves even when the bulk modulus is above the critical bulk modulus (Supplemental Material Movie S3), which may be similar to the instability of stressed rocks in geoscience [43]. We remark that the simulations of the two-fluid model are crucial to confirm the major role of bulk stress in mechanical equilibrium and the constant radius before and after the control parameter changes.

We expect a more realistic description of dissolution to include bond breaking between monomers via molecular dy-

namical simulations so that they can detach and dissolve into the surroundings. While our continuous model cannot capture such microscopic details, we simulate an alternative model in which the elastic stress vanishes if the chemical potential difference inside and outside the condensate is above some critical value to mimic such a scenario. Our conclusions regarding a critical bulk modulus for the condensate to be indissoluble are still valid (Fig. S14).

Our results share some similarities with the equilibrium swelling of a polymer network, e.g., the Flory-Rehner theory since both models include the equilibrium between the osmotic pressure and the elastic stress [31,44]. We remark that the biomolecules in our system can move from the condensates to the surrounding environment before the equilibrium is established. Meanwhile, in the case of polymer network swelling, the network materials are conserved so that the polymer network always swells.

Finally, our results demonstrate that the bulk modulus is the primary material property determining condensates' indissolubility. The phase diagram of indissolubility (Fig. 4) can be experimentally tested, e.g., by measuring the critical pH or salt concentrations (corresponding to the χ parameter in the Flory-Huggins free energy) to dissolve the condensates and in the meantime, measuring the bulk modulus separately. We note that the shear modulus of gel is usually the order of $nk_B T$ where n is the cross-linker density, and meanwhile, the bulk modulus is typically hundreds of shear modulus [32]. Note that the unit of the bulk modulus is $k_B T/V_0$ in the two-fluid model, which suggests that the critical bulk moduli that are of order 1 in the phase diagram [Fig. 4(a)] may be biologically relevant. Our results may have implications for developing condensate-targeting drugs to change condensate properties inside cells, e.g., lowering the bulk moduli to dissolve irreversible condensates.

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