

Surface phase separation in a confined space

Daoning Wu¹ and Jie Lin^{2,3,*}

¹*Yuanpei College, Peking University, Beijing, China*

²*Center for Quantitative Biology, Peking University, Beijing, China*

³*Peking-Tsinghua Center for Life Sciences, Peking University, Beijing, China*



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Biomolecular condensates frequently form near surfaces, including lipid membranes. However, the effect of a surface on phase separation within a cell, a confined system, remains elusive. In this work, we study surface phase separation under the constraint of a finite number of molecules in a confined space and identify three wetting states: thin, intermediate, and thick. Notably, the intermediate state, which is unstable in a fixed-chemical-potential system, can be stabilized in confinement below a critical width. Intriguingly, in wider systems, the intermediate solution becomes unstable due to a negative relationship between the chemical potential and particle number, leading to partial-wetting or prewetting droplets. Importantly, as the particle volume fraction increases from a lower value starting from a homogeneous surface, droplets form when the average volume fraction reaches the threshold of the intermediate state, which can be much lower than the threshold of bulk spinodal decomposition. Our theory elucidates the kinetic pathways of droplet formation in a confined system, providing crucial insights into how biomolecular condensates near surfaces respond to cellular events, such as the synthesis of biomolecules.

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I. INTRODUCTION

Numerous experiments have shown that liquid-liquid phase separation (LLPS) drives the formation of biomolecular condensates that are essential for various cellular functions [1–10]. To date, theoretical studies of LLPS have primarily focused on bulk systems, where surface effects are not considered. However, cells are full of surfaces: plasma membranes, organelle membranes, nuclear membranes, etc. [11–13]. Many experiments have reported critical interactions between surfaces and biomolecular condensates, e.g., regulation of membraneless organelles by endoplasmic reticulum [14,15], formation of autophagosomes at the surface of condensates [16], scission of endosome membranes by biomolecular condensates [17], the formation of transcriptional condensates on the surface of DNA [18], and the alignment of meiotic chromosomes through the synaptonemal complex by wetting [19].

Simulations and theories have suggested that these surfaces constrain molecular mobility and amplify local concentrations through surface phase separation [20–23]. In a binary solution where a dense and a dilute phase coexist, a surface that has a high affinity with the solute molecules exhibits a wetting transition at the wetting-transition temperature T_w [24–27].

Typically, the wetting transition is a first-order transition between a partial-wetting state (a thin layer covering the surface, potentially with wetting droplets) and a complete wetting state (a thick layer covering the entire surface).

The classical theory of surface phase separation developed by Cahn considered a semi-infinite system with a fixed chemical potential [24]. In this framework, the grand potential is minimized at thermal equilibrium and the number of molecules is not conserved. However, cell compartments such as the cytoplasm and the nucleus are confined spaces. We expect that thermodynamic equilibrium can be established below the timescale when molecule synthesis and degradation are significant, supported by the observations that P granule assembly and disassembly are governed by phase separation based on local thermal equilibrium [6]. Indeed, for bulk phase separation, most theoretical studies and even textbooks have focused on systems with a fixed number of molecules [4,28–31]. A biologically relevant theory of surface phase separation should also study a confined system with a fixed number of molecules. Are the classical theories still valid, and are there any unexpected but biologically/physically critical effects in a confined system? To our knowledge, these questions are still elusive.

Here, we address these questions by studying a binary solution in a confined space that interacts with an attractive surface. First, we investigate the stability and configuration of homogeneous wetting, where the volume fraction of solute molecules depends only on the distance z from the surface. We reveal three homogeneous wetting solutions: thin, intermediate, and thick. Remarkably, in the intermediate state, an increase in the number of molecules leads to a decrease in chemical potential, indicating that it is thermodynamically

*Contact author: linjie@pku.edu.cn

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unstable [32]; however, it can remain stable in a confined system with a fixed number of molecules. Surprisingly, we unveil a new critical temperature T_{sc} , distinct from the prewetting temperature T_{pw} and the wetting temperature T_w of the classical theory of wetting transition [24,26]. Above T_{sc} , the system exhibits a continuous change of the surface wetting profile as one changes the total number of solute molecules. In contrast, below T_{sc} , the system exhibits a discontinuous transition between two states with different thicknesses.

We next allow the volume fraction profile to be inhomogeneous in the x direction parallel to the surface. Using linear stability analysis, we demonstrate that there exists a threshold system width d_c , above which the intermediate state is unstable against small perturbations. In particular, $d_c \propto 1/\sqrt{-\partial\mu/\partial\bar{\phi}}$, where μ is the chemical potential and $\bar{\phi}$ is the average volume fraction. Below the wetting temperature, the intermediate state evolves into a partial-wetting state, characterized by droplets with a finite contact angle. Above the wetting temperature, the intermediate state evolves into a prewetting state characterized by pancakelike droplets of finite thickness. Remarkably, the instability of the intermediate state itself is independent of whether the temperature T is below or above the wetting temperature T_w . We confirm all of our predictions by simulating a two-dimensional continuum system.

Our theory sheds light on how biomolecular condensates near surfaces transition between different wetting configurations in response to cellular triggers, such as the synthesis or degradation of molecules, and to changes in physiological parameters, including temperature, pH, and molecular crowding. In recent experiments by Morin *et al.* [18], the authors observed a transition from a thin absorbed layer of transcription factors to a partial-wetting state in which multiple droplets wet the DNA as the total number of transcription factors increased. We remark that this partial-wetting state is likely triggered by the transition between the thin and intermediate solutions, as a consequence of increasing $\bar{\phi}$ in our phase diagram below T_w [Fig. 3(a)]. To confirm this, we also simulate a quasistatic increase or decrease of $\bar{\phi}$ in a two-dimensional system. Indeed, when $\bar{\phi}$ increases to the intermediate region, droplets start to form on the surface, and the system state is history dependent because both the homogeneous states and partial-wetting/prewetting states can be locally stable.

II. THE MODEL

We study a binary solution in a confined space where the system length in the z direction is L . To simplify the problem, we let the volume fraction of the solute molecule ϕ be homogeneous in the xy plane and only depend on z . Later, we will extend our model to allow the volume fraction to vary along the x direction. The system's Helmholtz free energy per unit area is

$$F = \int_0^L \left[f_0[\phi(z)] + \frac{1}{2}\kappa \left(\frac{d\phi(z)}{dz} \right)^2 \right] dz + J(\phi_s). \quad (1)$$

Here, $f_0[\phi(z)]$ is the free energy density, $\frac{1}{2}\kappa(d\phi(z)/dz)^2$ is the energy cost due to the gradient of $\phi(z)$ [33], and $J(\phi_s)$ is the interaction energy between the surface at $z = 0$ and the solute

molecule where $\phi_s \equiv \phi(z = 0)$. For simplicity, we use the free energy of a regular solution [29]:

$$\tilde{f}_0(\phi) = \phi \ln(\phi) + (1 - \phi) \ln(1 - \phi) + \chi \phi(1 - \phi). \quad (2)$$

Here, $\tilde{f}_0(\phi) = f_0(\phi)/(k_B T/V_0)$, where f_0 is the Helmholtz free energy density, k_B is the Boltzmann constant, T is the temperature, and V_0 is the molecule volume. The bulk interaction strength $\chi = 2T_c/T$, where T_c is the bulk critical temperature. When $T < T_c$, the system exhibits phase separation in bulk with a dense phase and a dilute phase. We set the interaction energy between the surface and the solute molecules as $J(\phi_s) = -a\phi_s$, where $a > 0$. In the following, we use the nondimensionalized version of the model unless otherwise specified: the energy density unit is $\epsilon_0 = k_B T/V_0$ and the length unit is $l_0 = \sqrt{\kappa V_0/k_B T}$.

For a system with a fixed number of molecules, $\int_0^L \phi(z) dz = L\bar{\phi}$ is constant and the Helmholtz free energy is minimized in equilibrium. In contrast, for a system with a fixed chemical potential, the grand potential

$$\Omega = F - \mu \int_0^L \phi(z) dz \quad (3)$$

is minimized in equilibrium. To study the volume fraction profile for a system of a fixed number of molecules at thermal equilibrium, a trick is to compute the equilibrium profile and the resulting $\bar{\phi}$ given a fixed chemical potential μ and then find the appropriate μ that gives the target $\bar{\phi}$. As we show later, this method enables us to find all possible equilibrium states that minimize the Helmholtz free energy.

Minimization of the grand potential leads to the equilibrium condition as $d^2\phi(z)/dz^2 = f'_0(\phi(z)) - \mu$ for $0 < z < L$ with the boundary condition $\phi'(z) = -a$ at $z = 0$ and $\phi'(z) = 0$ at $z = L$. The boundary condition at $z = L$ results from the absence of interaction between the surface at $z = L$ and the solute molecules. The equilibrium condition leads to the conservation equation $\phi'(z)^2/2 = W(\phi(z))$, where we introduce the W function $W = f_0(\phi) - \mu\phi - f_0(\phi_L) + \mu\phi_L$. The constant terms in W allow the boundary condition $\phi'(z = L) = 0$ to be satisfied. In this work, we mostly study an attractive surface, and the volume fraction monotonically decreases from the surface at $z = 0$, which means that

$$\frac{d\phi}{dz} = -\sqrt{2W(\phi(z))}. \quad (4)$$

We treat the chemical potential in $W(\phi)$ as a changing parameter, and the intersection of the line $-J'(\phi)$ and $\sqrt{2W(\phi)}$ determines the equilibrium surface volume fraction ϕ_s [Figs. 1(a)–1(c)]. Given a fixed chemical potential, there are three possible solutions of ϕ_s at most. The solution below ϕ_L is not considered because the volume fraction near an attractive surface must be higher than ϕ_L . We denote the three solutions from low to high value of ϕ_s as thin, intermediate, and thick [Figs. 1(d)–1(f)]. As we show later, the intermediate solution can be stable for a confined system; in contrast, it must be unstable for a system with a fixed chemical potential [26]. We remark that the chemical potential can be lower [Figs. 1(a) and 1(b)] or higher [Fig. 1(c)] than the equilibrium value μ_c at which bulk phase separation occurs (for the regular-solution model, $\mu_c = 0$). The thick solution for

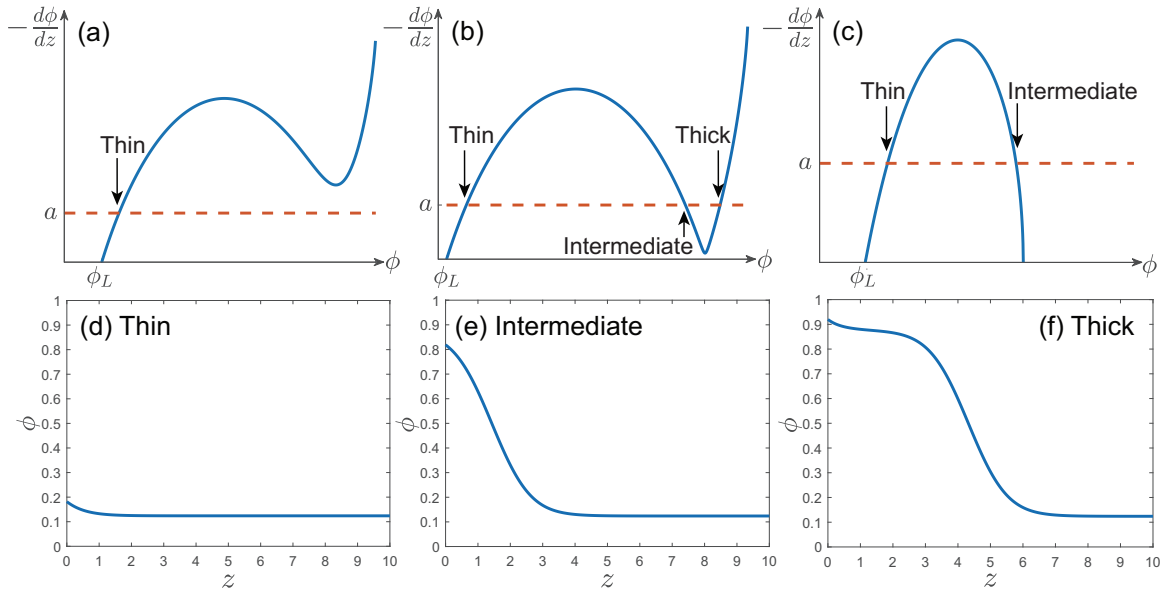


FIG. 1. (a)–(c) The intersections between $-J'(\phi)$ (the red dashed line) and $\sqrt{2W(\phi)}$ (the blue solid line) determine the volume fraction at the surface, ϕ_s . Here, we show three different chemical potentials with one [panel (a)], three [panel (b)], and two [panel (c)] solutions. (d)–(f) The equilibrium volume-fraction profiles for the thin [panel (d)], intermediate [panel (e)], and thick [panel (f)] solutions. In this work, we set $a = 0.1$ and $L = 10$ unless otherwise mentioned.

$\mu > \mu_c$ is unphysical and excluded because $\phi'(z)$ is imaginary when $W < 0$ [Fig. 1(c)].

Given the chemical potential, we compute the average volume fraction $L\bar{\phi} = L\phi_L + \int_0^L (\phi(z) - \phi_L) dz$, which we rewrite as

$$\bar{\phi} = \frac{1}{L} \int_{\phi_L}^{\phi_s} \frac{\phi - \phi_L}{\sqrt{2W(\phi)}} d\phi + \phi_L. \quad (5)$$

The chemical potential is related to ϕ_L by $\mu = f'_0(\phi_L)$ since near $z = L$, $\phi(z)$ is virtually a constant, which we confirm numerically later. We prove that there is always a one-to-one correspondence between μ and ϕ_L (Appendix A).

III. HOMOGENEOUS EQUILIBRIUM PROFILES

We compute the phase diagram of wetting transition in a confined space as a function of the average volume fraction of solute molecules and temperature [Fig. 3(a)]. We remark that for a system with a fixed molecule number, the emergence of three homogeneous solutions occurs at the prewetting critical temperature T_{pw} [24,26]. Above T_{pw} [the orange dashed line in Fig. 3(a)], the intermediate solution does not exist. The thin and thick solutions are indistinguishable from each other. We also highlight the wetting temperature T_w [the green dashed line in Fig. 3(a)] at which point the thick and thin solutions have the same grand potential if the system's chemical potential is fixed at the bulk-phase-separation value μ_c [24]: below T_w at μ_c , droplets, if formed, must have finite contact angles; above T_w at μ_c , droplets with finite contact angles cannot form.

Surprisingly, we unveil a previously unknown critical temperature at T_{sc} [the purple dashed line in Fig. 3(a)] that is unique for systems with a fixed molecule number below which a bistable region emerges [Fig. 3(a)]. For $T > T_{sc}$, as one

continuously changes $\bar{\phi}$, a unique solution exists (Figs. 2(a) and 2(b)). The transition between the thin and intermediate solutions occurs at $\bar{\phi}_{right}$, where $-J'(\phi)$ is tangent to $\sqrt{2W(\phi)}$ at its local maximum [Fig. 2(a), inset]. The transition point between the intermediate and thick solutions occurs at $\bar{\phi}_{left}$, where $-J'(\phi)$ is tangent to $\sqrt{2W(\phi)}$ at its local minimum [Fig. 2(a), inset]. As $\bar{\phi}$ quasistatically decreases from high to low, the volume fraction profile transitions through thick, intermediate, and thin solutions sequentially, with a smooth transition in between. We verify our predictions numerically by directly minimizing the Helmholtz free energy with a conserved number of molecules with a homogeneous volume-fraction profile $\phi(z)$. We confirm that the equilibrium profiles are at the minimum point of the Helmholtz free energy [Fig. 2(b), inset]. We note that the chemical potential at $\bar{\phi}_{right}$ is higher than μ_c in Fig. 2. Nevertheless, if the temperature is close enough to the bulk critical value, the chemical potential at $\bar{\phi}_{right}$ can still be lower than μ_c (Fig. S1 in the Supplemental Material [34]).

Intriguingly, as $\bar{\phi}$ decreases from high to low, the chemical potential exhibits a nonmonotonic behavior, which increases during the intermediate state [Fig. 2(a)]. Remarkably, the intermediate solution is stable even if $\partial\bar{\phi}/\partial\mu < 0$. For bulk systems, a necessary condition for a stable state is $\partial\bar{\phi}/\partial\mu > 0$; otherwise, the system is unstable against random fluxes of molecules [32]. In our case, an attractive surface in a confined space breaks down the stability condition of bulk systems. Later, we show that the intermediate solution indeed becomes unstable when the system width in the x direction exceeds a threshold.

In contrast, for $T < T_{sc}$, a first-order transition occurs: as $\bar{\phi}$ decreases from high to low and reaches $\bar{\phi}_{low}$, the intermediate solution disappears. The system abruptly jumps to a thin solution [Fig. 2(c)]. In contrast, as $\bar{\phi}$ increases from low to

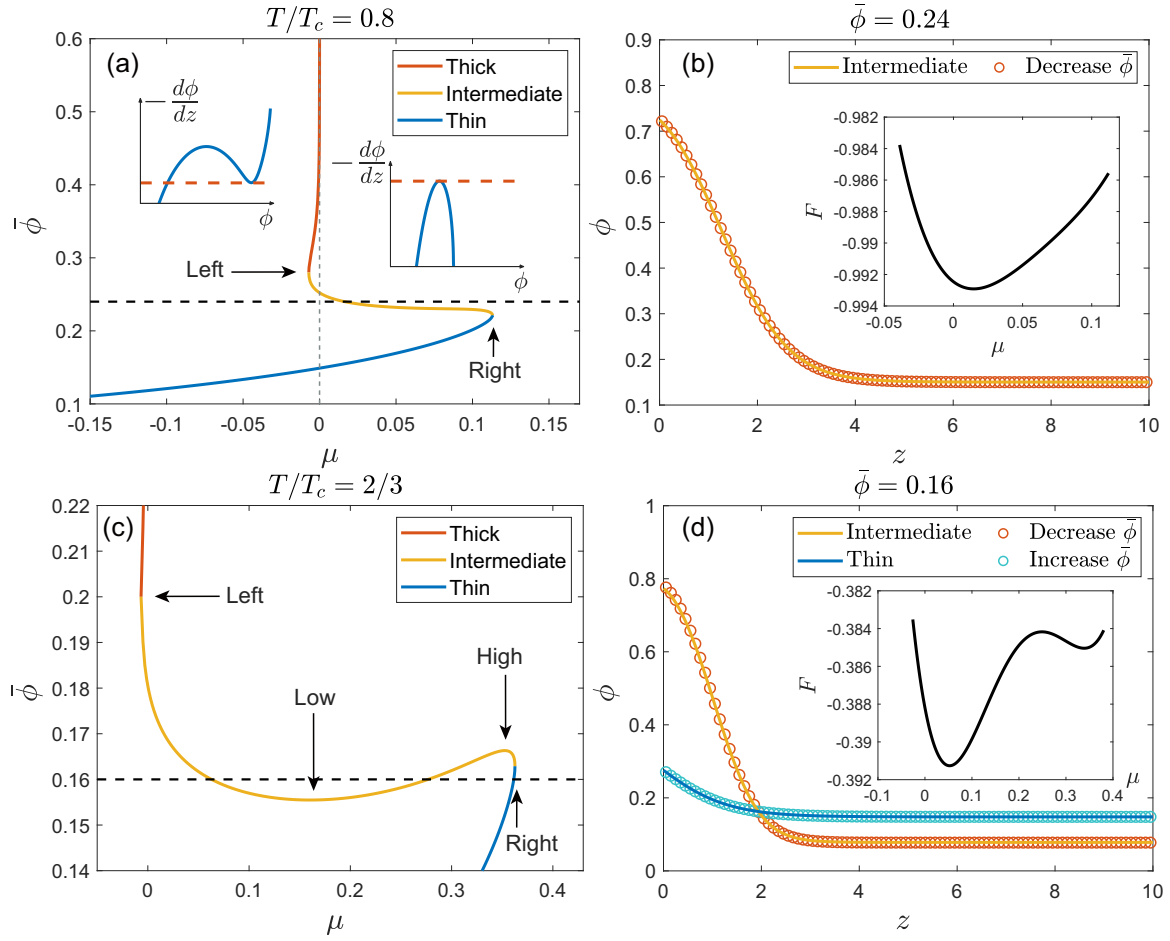


FIG. 2. (a) $\bar{\phi}$ vs μ for $T > T_{sc}$. The insets show $-J'(\phi)$ (the red dashed line) and $\sqrt{2W(\phi)}$ (the blue solid line) at $\bar{\phi}_{\text{left}}$ and $\bar{\phi}_{\text{right}}$. (b) The theoretical (solid line) and numerical (circles) volume-fraction profiles at $\bar{\phi} = 0.24$ [the horizontal dashed line in panel (a)] for an intermediate solution. The inset shows the Helmholtz free energy F as a function of μ . (c) $\bar{\phi}$ vs μ for $T < T_{sc}$. The bistable region is for $\bar{\phi}$ between $\bar{\phi}_{\text{low}}$ and $\bar{\phi}_{\text{high}}$. (d) The theoretical and numerical volume-fraction profiles at $\bar{\phi} = 0.16$ [the horizontal dashed line in panel (c)], where the volume-fraction profile is history dependent. If $\bar{\phi}$ decreases from 0.17 to 0.16, the profile takes the intermediate solution; in contrast, if $\bar{\phi}$ increases from 0.15 to 0.16, the profile takes the thin solution. The inset shows the Helmholtz free energy F as a function of μ with two minima.

high and reaches $\bar{\phi}_{\text{high}}$, the system abruptly jumps from one intermediate solution to another with lower μ [Fig. 2(c)]. We verify the existence of hysteresis numerically by implementing a quasistatic decrease or increase of $\bar{\phi}$. As predicted, the equilibrium profile depends on the history of parameter changes [Fig. 2(d)], and the Helmholtz free energy also exhibits two minima in the bistable region [Fig. 2(d), inset].

We remark that as L approaches infinity, the first term on the right-hand side of Eq. (5) can be neglected for the intermediate solutions. Therefore, we must have $\bar{\phi}_{\text{left}} = \bar{\phi}_{L,\text{left}}$ and $\bar{\phi}_{\text{right}} = \bar{\phi}_{L,\text{right}}$, which means that $\bar{\phi}_{\text{left}}$ approaches the bulk saturation concentration in the $L \rightarrow \infty$ limit at low temperature (Figs. S2 and S3 in the Supplemental Material [34]).

IV. INHOMOGENEOUS PROFILES

We next allow the volume-fraction profile to be inhomogeneous in the x direction. We find that for the intermediate state where the chemical potential decreases with $\bar{\phi}$ (Fig. 2), interfacial instability occurs when the system width d is above

d_c (Appendix C), which satisfies

$$d_c \sim \left(-\frac{\partial \mu}{\partial \bar{\phi}} \right)^{-1/2}. \quad (6)$$

We numerically simulate a two-dimensional system in which the molecular flux is proportional to the gradient of the chemical potential (see simulation details in Appendix B). Starting from an intermediate homogeneous state, we add a small perturbation to the profile and observe the resulting interfacial shape. We confirm the existence of a minimum system width to generate the interfacial instability and its relation to the derivative between μ and $\bar{\phi}$ [Fig. 3(b)]. As we predict, the thick and thin states are always stable (Fig. S4 in the Supplemental Material [34]).

What might be the final states after the initial instability of the intermediate solution? Intriguingly, the unstable intermediate state evolves to a partial-wetting state with droplets of a finite contact angle where the chemical potential approximately equals the bulk-phase-separation value μ_c for $T < T_w$ [Fig. 3(c)]. Meanwhile, for $T > T_w$, the droplets in

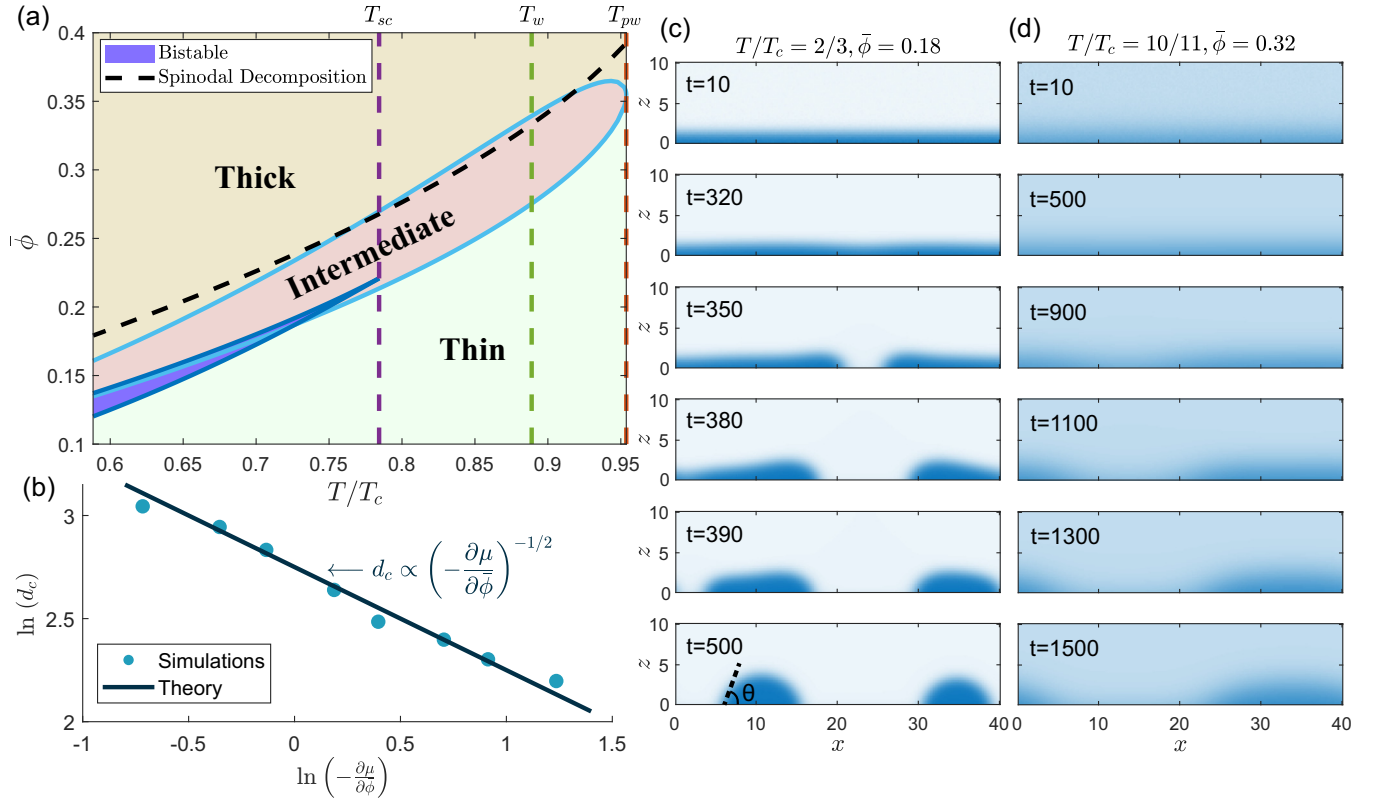


FIG. 3. (a) The phase diagram of surface phase separation in a confined system with a fixed number of molecules. The bistable region can be divided into an upper region with two coexisting intermediate solutions and a lower region with an intermediate solution and a thin solution that coexist. The black dashed line shows the saturation concentration for bulk spinodal decomposition. (b) Log-log plot of the minimum width to generate instability d_c vs $-\partial\mu/\partial\bar{\phi}$. The simulation results for $T/T_c = 2/3$ fall approximately on a line of slope $-1/2$, verifying our prediction. (c) Simulations of the two-dimensional system below the wetting temperature T_w at different times. Periodic boundary conditions are applied in the x direction with $d = 40$. At $t = 0$, a small perturbation is added to a homogeneous intermediate profile. The measured contact angle $\theta \approx 70^\circ$, close to $\theta_{\text{theory}} = 72.7^\circ$ predicted by Young's formula (Appendix D). (d) The same as panel (c) but for $T > T_w$.

the final state have blurred boundaries and pancakelike shapes [Fig. 3(d)], corresponding to the prewetting state where the thin and thick states coexist. Indeed, the volume-fraction profiles of the droplet region and the nondroplet region, as a function of z , are close to the predicted profiles of the thick solution and the thin solution, respectively (Fig. S5 in the Supplemental Material [34]), given that the chemical potential is fixed at the simulated value. We note that the intermediate and thin states can be bistable for $T < T_{sc}$ in a homogeneous system. In this case, we find that the initial intermediate state also evolves into a partial-wetting state, rather than the thin state (Fig. S6 in the Supplemental Material [34]).

To investigate how the synthesis or degradation of molecules affects wetting configuration, we simulate a quasistatic increase of $\bar{\phi}$ from a low value (Figs. 4(a) and 4(c), and Movies S1 and S2 in the Supplemental Material [34]). When $\bar{\phi}$ reaches the threshold of the intermediate state, which is still much lower than the threshold value corresponding to spinodal decomposition in bulk [Fig. 3(a), even in the $L \rightarrow \infty$ limit; see the $\bar{\phi}_{\text{right}}$ curve in Fig. S3 in the Supplemental Material [34]], partial-wetting or prewetting droplets form quickly on the surface as long as the instability condition is satisfied. As $\bar{\phi}$ keeps increasing, droplets grow in size until they fully occupy the system, which then transitions to the homogeneous thick state [not shown in Fig. 4(a)].

When decreasing $\bar{\phi}$ from a high value, the initial homogeneous layer can be maintained until the system reaches the intermediate region [Figs. 4(b) and 4(d), and Movies S3 and S4 in the Supplemental Material [34]]. Again, the partial-wetting/prewetting state is locally stable and can be maintained even in the thin region. We notice that when $\bar{\phi}$ exceeds the critical value for spinodal decomposition, droplets can form in the bulk. However, this state is unstable since the molecules will be absorbed by the surface (Movie S5 in the Supplemental Material [34]).

V. DISCUSSION

In this work, we study the wetting transition in a confined space with a fixed number of molecules. Compared with the traditional Cahn model, where the chemical potential is fixed, our model is more relevant to surface separation phenomena in biological systems. To our surprise, the intermediate solution, which is deemed unstable in the fixed-chemical-potential scenario, can be stable in our case as long as the system width is below a threshold. Furthermore, we identify a new critical temperature T_{sc} , below which the transition of volume-fraction profiles is discontinuous. We note that $\bar{\phi}_{\text{high}} - \bar{\phi}_{\text{low}}$ increases continuously as T decreases from T_{sc} . Meanwhile, we also find that T_{sc} increases as L increases (Fig. S7 in the

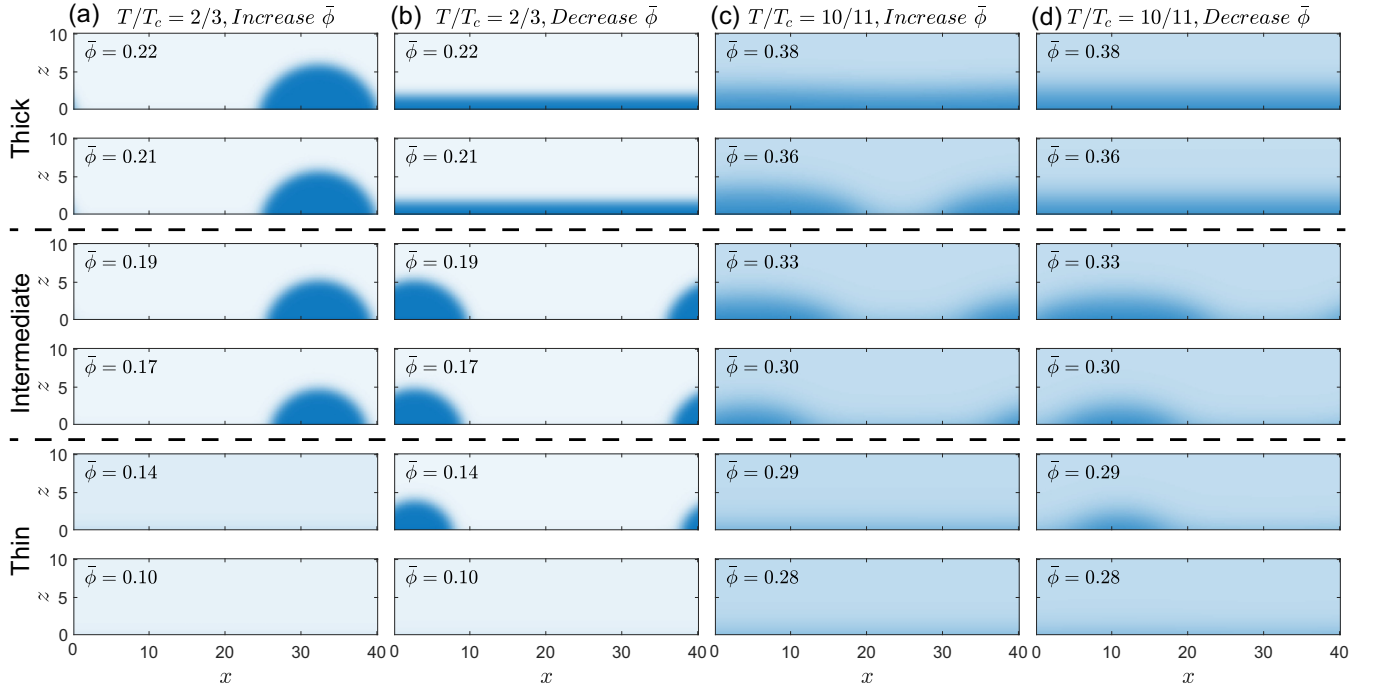


FIG. 4. Simulated volume fraction distributions when $\bar{\phi}$ increases [panels (a) and (c)] or decreases [panels (b) and (d)] quasistatically, below [panels (a) and (b)] or above [panels (c) and (d)] the wetting temperature. We highlight the entrance and departure of the intermediate state by the dashed lines.

Supplemental Material [34]) and approaches T_{pw} as L goes to infinity (Appendix E).

While previous work mainly focuses on confinement in the direction perpendicular to the surface [35], our work demonstrates that confinement in the direction parallel to the surface can also significantly influence the stability of the interface and the formation of droplets. When the system width is above the threshold value d_c , the intermediate solution is unstable against infinitesimal perturbations. It tends to evolve into a partial-wetting ($T < T_w$) or prewetting ($T > T_w$) state, depending on the temperature. Importantly, as one quasistatically increases the average volume fraction $\bar{\phi}$ from a low value, the homogeneous state becomes unstable only when $\bar{\phi}$ reaches the threshold of the intermediate state, which can be much lower than the threshold volume fraction for spinodal decomposition. Interestingly, the partial-wetting/prewetting states are locally stable, and the system's actual state, whether homogeneous in the x direction or not, depends on its history.

The interfacial instability we find in this work results from a negative correlation between chemical potential and particle number, which is different from other instability mechanisms. For example, Rayleigh-Taylor instability is generated due to competition between gravity and surface tension; spinodal dewetting is triggered by attractive long-range forces [25]. In Plateau-Rayleigh instability, the surface tension is the driving force of interfacial instability, which has been identified in two-phase systems confined in cylindrical pores [36–38]. We note that the length of the capsules or plugs resulting from interfacial instability in cylindrical pores is history dependent, and that coarsening is extremely slow after their formation due to the absence of a curvature difference between them. This metastability depends on the one-dimensional geometry of the pore and is not relevant in our system.

In the previous work [39], the authors investigated droplet formation in a confined system. They obtained a phase diagram showing an unstable regime between the stable thin- and thick-layer regimes, similar to ours. In contrast to our work, in which the phase diagram is obtained from first principles by directly minimizing the grand potential, they used an effective interface potential containing phenomenological parameters. The bistable regime we identify is also unknown in previous work. Interestingly, using Monte Carlo simulations of a finite number of molecules, the authors found that above the wetting temperature, “flat” droplets can form, which are similar to the pancakelike droplets we observe.

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DATA AVAILABILITY

The data that support the findings of this article are openly available [40].

APPENDIX A: PROOF OF THE ONE-TO-ONE CORRESPONDENCE BETWEEN μ AND ϕ_L

In the main text, we introduce the W function $W(\phi) = f_0(\phi) - \mu\phi - f_0(\phi_L) + \mu\phi_L$. Because $W(\phi_L) = 0$

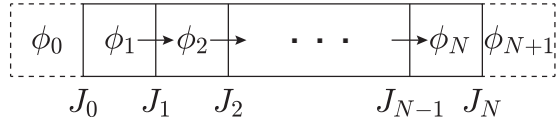


FIG. 5. A schematic of the numerical simulations in one dimension.

and $W'(\phi_L) = 0$, we find that

$$\begin{aligned} W(\phi_L + \delta\phi) &= \frac{1}{2}W''(\phi_L)(\delta\phi)^2 + O((\delta\phi)^3) \\ &= \frac{1}{2}f_0''(\phi_L)(\delta\phi)^2 + O((\delta\phi)^3), \end{aligned} \quad (\text{A1})$$

where $0 < \delta\phi \ll 1$. Whenever there is a solution for the equilibrium volume-fraction profile, $W(\phi_L + \delta\phi)$ should be positive; otherwise, $\phi'(z) = -\sqrt{2W(\phi(z))}$ is imaginary. Thus, we conclude that $f_0''(\phi_L) > 0$; in other words, $\mu = f_0'(\phi_L)$ increases monotonically with ϕ_L .

APPENDIX B: DETAILS OF NUMERICAL SIMULATIONS

In simulations of homogeneous profiles, the system is one dimensional in the z direction. We divide the system into N cells along the z direction, each with a uniform width of $\Delta z = L/N$, where L is the system length in the z direction. The volume fraction in the i th cell is ϕ_i ($i = 1, 2, \dots, N$). Considering that $\mu = f_0'(\phi) - d^2\phi/dz^2$, the chemical potential of the cells are

$$\mu_i = f_0'(\phi_i) - \frac{\phi_{i+1} + \phi_{i-1} - 2\phi_i}{(\Delta z)^2}, \quad i = 1, 2, \dots, N. \quad (\text{B1})$$

ϕ_0 and ϕ_{N+1} are the volume fractions in the auxiliary cells (the cells with dashed borders in Fig. 5). To enforce the boundary condition $\phi'(z) = -a$ at $z = 0$ and $\phi'(z) = 0$ at $z = L$, we let $\phi_0 = \phi_1 + a\Delta z$ and $\phi_{N+1} = \phi_N$ after each time step.

Let J_i be the flux of solute molecule from the i th cell to the $(i+1)$ th cell. As the system is bounded at $z = 0$ and $z = L$, we have $J_0 = J_N = 0$. The remaining fluxes can be calculated by

$$J_i = \frac{\mu_i - \mu_{i+1}}{\Delta z}, \quad i = 1, 2, \dots, N-1. \quad (\text{B2})$$

For each time step Δt , we update the volume fractions with

$$\Delta\phi_i = (J_{i-1} - J_i)\Delta t, \quad i = 1, 2, \dots, N. \quad (\text{B3})$$

In simulations of two-dimensional inhomogeneous profiles, the system is divided into cells with width $\Delta z = L/N$ in both the x and z directions. The approach to the boundary condition in the z direction is the same as the homogeneous case. For the x direction, a periodic boundary condition is applied with auxiliary cells.

In this work, a small perturbation is added by superimposing a random number matrix with a sum of zero onto the volume fraction distribution, where the random numbers are uniformly distributed between -0.01 and 0.01 .

APPENDIX C: DERIVATION OF THE INTERFACE INSTABILITY CONDITION

Imagine introducing a small perturbation $\delta h(x, t)$ to a flat interface whose initial height is h_0 . The surface tension tends

to restore the interface to flatness. Meanwhile, we can imagine cutting the system into many small compartments, each with a small width. A local increase in the interface height in one compartment increases its local $\bar{\phi}$, which leads to a decrease in its local chemical potential if $\partial\mu/\partial\bar{\phi} < 0$, inducing a molecule flux into the compartment and further amplifying the height increment. Combining the two competing factors, we propose the following dynamics of $\delta h(x, t)$ in the linear order:

$$\frac{\partial\delta h(x, t)}{\partial t} \propto \gamma_1 \frac{\partial^2\delta h}{\partial x^2} - A \frac{\partial\mu}{\partial\bar{\phi}} \delta h. \quad (\text{C1})$$

Here, γ_1 is the surface tension constant and A is a constant depending on the diffusion constant of the solute molecules. By introducing a periodic perturbation to the interface, $\delta h(x, t) = h_1 \cos(qx)$, which satisfies $\dot{h}_1 \sim -[\gamma_1 q^2 + A(\partial\mu/\partial\bar{\phi})]h_1$, we identify the critical wavelength $q_c \sim (-\partial\mu/\partial\bar{\phi})^{1/2}$ below which the system is unstable against perturbation. Therefore, we obtain the critical system width in the main text.

APPENDIX D: ESTIMATION OF CONTACT ANGLE WITH YOUNG'S FORMULA

We approximate Young's formula as $\gamma \cos(\theta) = a\phi_b - a\phi_a$ [22], where θ is the predicted contact angle, γ is the surface tension between the dense and dilute phases, and ϕ_a and ϕ_b are the volume fractions of the dense phase and the dilute phase, respectively. We use the volume fractions of the dense phase and the dilute phase to approximately compute the solid-dilute-phase surface tension $a\phi_a$ and the solid-dense-phase surface tension $a\phi_b$, respectively. To compute the surface tension between the dilute and dense phases, we consider an infinite system in which the volume fraction only depends on the coordinate z and satisfies $\phi(z = \infty) = \phi_a$ and $\phi(z = -\infty) = \phi_b$. The system's chemical potential is fixed at the bulk-phase-separation value, and its grand potential per unit area is

$$\Omega = \int_{-\infty}^{\infty} \left[f_0(\phi) + \frac{1}{2} \left(\frac{d\phi}{dz} \right)^2 - \mu_c \phi - f_0(\phi_a) + \mu_c \phi_a \right] dz. \quad (\text{D1})$$

Minimizing the grand potential leads to the equilibrium condition $d^2\phi(z)/dz^2 = f_0'(\phi(z)) - \mu_c$. The equilibrium condition leads to the conservation equation

$$\frac{1}{2} \left(\frac{d\phi(z)}{dz} \right)^2 = W(\phi), \quad (\text{D2})$$

where the W function is $W(\phi) = f_0(\phi) - \mu_c \phi - f_0(\phi_a) + \mu_c \phi_a$. Since the volume fraction must decrease from $z = -\infty$ to $z = \infty$, we obtain

$$\frac{d\phi}{dz} = -\sqrt{2W(\phi)}. \quad (\text{D3})$$

Finally, we obtain the expression of the surface tension constant, which is simply the grand potential per unit area as

$$\gamma = \int_{-\infty}^{\infty} \left[\frac{1}{2} \left(\frac{d\phi(z)}{dz} \right)^2 + W(\phi) \right] dz = \int_{-\infty}^{\infty} \left(\frac{d\phi(z)}{dz} \right)^2 dz$$

$$= \int_{-\infty}^{\infty} \frac{d\phi(z)}{dz} d\phi = \int_{\phi_a}^{\phi_b} \sqrt{2W(\phi)} d\phi. \quad (\text{D4})$$

For $T/T_c = 2/3$, $\phi_a = 0.0707$, $\phi_b = 0.9293$, from which we can calculate that $\gamma = 0.2883$. Thus, the contact angle predicted by the Young's formula is $\theta_{\text{theory}} = 72.7^\circ$.

APPENDIX E: DERIVATION OF THE SCALING RELATION BETWEEN ΔT AND L

We introduce T_{lr} as the temperature at which $\bar{\phi}_{\text{left}} = \bar{\phi}_{\text{right}}$. For a certain L , as the $\bar{\phi}$ versus μ diagram of the intermediate solution at T_{lr} must include a segment with a positive slope, we must have $T_{\text{lr}} < T_{\text{sc}}$. On the other hand, T_{sc} must be below T_{pw} for the intermediate solution to occur in the first place [Fig. 3(a)]. Therefore, we obtain $T_{\text{lr}} < T_{\text{sc}} < T_{\text{pw}}$ (Fig. S7 in the Supplemental Material [34]). Let $\Delta T = T_{\text{pw}} - T_{\text{lr}}$. In this Appendix, we prove that $\Delta T \sim L^{-1}$ as $L \rightarrow \infty$. Therefore, we conclude that both T_{lr} and T_{sc} approach T_{pw} as L goes to infinity.

We denote $\int_{\phi_L}^{\phi_s} (\phi - \phi_L)/\sqrt{2W(\phi)} d\phi$ as n_b ; thus, $\bar{\phi} = \frac{1}{L}n_b + \phi_L$. Let $\Delta\phi_L = \phi_{L,\text{right}} - \phi_{L,\text{left}}$, $\Delta n_b = n_{b,\text{left}} - n_{b,\text{right}}$, and $\Delta\phi_s = \phi_{s,\text{left}} - \phi_{s,\text{right}}$. When $\bar{\phi}_{\text{left}} = \bar{\phi}_{\text{right}}$, we have $\frac{1}{L}\Delta n_b = \Delta\phi_L$.

When $T = T_{\text{pw}}$, there exists a special ϕ_L , which we denote as ϕ_{L0} , at which $\sqrt{2W(\phi)}$ is tangent to a at $(\phi_0, \sqrt{2W(\phi_0)})$, where the first and second derivatives of $\sqrt{2W(\phi)}$ are both zero. Let $x = \phi - \phi_0$, $y = \sqrt{2W(\phi)} - \sqrt{2W(\phi_0)}$, then for small x and y , $y \sim x^3$. When $T = T_{\text{pw}} - \Delta T$ and $\phi_L = \phi_{L0}$, one can approximate y as $y \sim x^3 - \Delta T \times x$ where coefficients

are neglected for simplicity. Denoting the two extremum points of this function as $(-x_c, y_c)$ and $(x_c, -y_c)$, where $x_c > 0$ and $y_c > 0$, we must have $\Delta\phi_s \sim x_c \sim \Delta T^{\frac{1}{2}}$ and $\Delta\phi_L \sim y_c \sim \Delta T^{\frac{3}{2}}$.

With a change of variables, we can obtain that

$$\begin{aligned} n_{b,\text{left}} &= \int_{\phi_{L,\text{left}}}^{\phi_{s,\text{left}}} \frac{\phi - \phi_{L,\text{left}}}{\sqrt{2W(\phi)}} d\phi \\ &= \int_0^{\phi_{s,\text{left}} - \phi_{L,\text{left}}} \frac{\delta\phi}{\sqrt{2W(\delta\phi + \phi_{L,\text{left}})}} d\delta\phi. \end{aligned} \quad (\text{E1})$$

Similarly,

$$n_{b,\text{right}} = \int_0^{\phi_{s,\text{right}} - \phi_{L,\text{right}}} \frac{\delta\phi}{\sqrt{2W(\delta\phi + \phi_{L,\text{right}})}} d\delta\phi. \quad (\text{E2})$$

Omitting terms of order $\Delta T^{\frac{3}{2}}$ and above, we obtain that $\Delta n_b \sim \Delta\phi_s \sim \Delta T^{\frac{1}{2}}$.

From the analysis above, we obtain $\Delta\phi_L \sim \Delta T^{\frac{3}{2}}$ and $\Delta n_b \sim \Delta T^{\frac{1}{2}}$. When $\bar{\phi}_{\text{left}} = \bar{\phi}_{\text{right}}$, we have $\frac{1}{L}\Delta n_b = \Delta\phi_L$ and

$$\frac{\Delta T^{1/2}}{L} \sim \Delta T^{3/2}. \quad (\text{E3})$$

Thus,

$$\Delta T \sim \frac{1}{L}. \quad (\text{E4})$$

We verify our predictions numerically (Figs. S8 and S9 in the Supplemental Material [34]).

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