

Scaling laws for phase coexistence in multicomponent mixtures

Yicheng Qiang¹, Chengjie Luo¹, and David Zwicker^{1*}*Max Planck Institute for Dynamics and Self-Organization, Am Faßberg 17, 37077 Göttingen, Germany*

(Received 2 May 2024; accepted 8 September 2025; published 1 October 2025)

Liquid mixtures of many interacting components often exhibit numerous coexisting types of droplets. An exciting example is the cytosol of biological cells, where diverse droplets, known as condensates, enable cellular functions. However, how much their formation is constrained by thermodynamics is currently unclear because we lack predictions for generic multicomponent fluids. Linear stability analysis suggests that homogeneous mixtures become more robust to fluctuations as the number of components increases, so droplets might not form easily in multicomponent mixtures. In contrast, we show through numerical simulations and analytical scaling laws that the number of coexisting phases typically increases with the number of components in equilibrium. The combination of both results suggests that generic multicomponent mixtures can maintain many metastable states with various droplets, generalizing the nucleation-and-growth regime of binary mixtures. Our scaling laws also indicate why cells exhibit much fewer condensates than components and how they could exploit multistability to form various condensates independently.

DOI: [10.1103/zcvb-9t4b](https://doi.org/10.1103/zcvb-9t4b)

I. INTRODUCTION

Mixtures with many components are ubiquitous in nature. One interesting case is the cytosol of biological cells, which contains millions of different molecules [1]. Despite this complexity, cells fulfill their function flexibly and robustly. In part, this is because they leverage the physics of phase coexistence to form various biomolecular condensates [2–7]. How do cells ensure that the right condensates form? Can most of this be attributed to equilibrium thermodynamics or are many condensates maintained by active processes? These questions are currently difficult to answer because we lack an understanding of the basic equilibrium behavior of multicomponent mixtures.

Multicomponent mixtures have been analyzed in the limit of small compositional variations. In particular, such stability analysis revealed that homogeneous states become more robust to fluctuations with larger component counts [8–11], suggesting that mixtures of many components should stay homogeneous [12]. However, stability analysis cannot assess consequences of large fluctuations, which could lead to the formation of various droplets. Such behavior is familiar from simple binary mixtures in the nucleation-and-growth regime (Fig. 1), which explains many aspects of the formation of individual in cells [2,13]. One example is P granules, which form and dissolve in response to temperature changes [14]. However, P granules, and other condensate [15], contain

many different components, warranting a multicomponent description. Moreover, cells contain many different condensates simultaneously; their number is estimated to be between tens and thousands [16]. Is the formation of these different condensates coupled or do they form independently? In other words, can we generalize the nucleation-and-growth regime to multicomponent mixtures? How many phases do we expect in equilibrium? To answer these questions, we need to understand the high-dimensional phase diagrams of multicomponent mixtures (Fig. 1).

We study the generic behavior of multicomponent mixtures and investigate their phase coexistence in a simple model system. In particular, we tackle the challenge of computing high-dimensional phase diagrams [17–19] by combining a numerical method detecting phase-separated equilibrium states with analytically derived scaling laws for the number of coexisting phases. Our analysis shows that the number of coexisting phases typically increases with component count, while the homogeneous state remains metastable, indicating that the nucleation-and-growth region expands with component count. Taken together, our analysis paints a comprehensive picture of the generic behavior of multicomponent mixtures, which we then use to discuss the phase behavior of cytosol.

II. EQUILIBRIUM MODEL OF GENERIC MULTICOMPONENT MIXTURES

To study the generic phase behavior, we consider a closed system (canonical ensemble) filled with a mixture of N_c different components. Since we want to understand how such mixtures segregate into many coexisting phases, we investigate a thermodynamically large system, where interfaces do not influence the bulk properties of the phases. Each phase α is homogeneous and characterized by a relative volume J_α and the volume fractions $\phi_i^{(\alpha)}$ of all components $i = 1, \dots, N_c$.

*Contact author: david.zwicker@ds.mpg.de

Published by the American Physical Society under the terms of the [Creative Commons Attribution 4.0 International](https://creativecommons.org/licenses/by/4.0/) license. Further distribution of this work must maintain attribution to the author(s) and the published article's title, journal citation, and DOI. Open access publication funded by Max Planck Society.

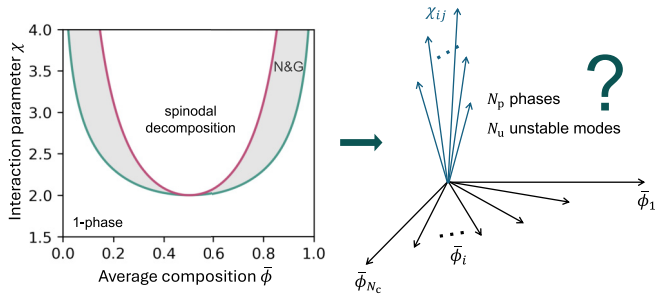


FIG. 1. Phase diagrams of multicomponent mixtures are complex. Phase diagrams distinguish parameter regions leading to distinct states, which might differ in the number of equilibrium phases, N_p , and number of unstable modes, N_u . Binary mixtures have a simple phase diagram (left) with only three regions: the one-phase region ($N_p = 1$, $N_u = 0$), a nucleation-and-growth region (N&G, $N_p = 2$, $N_u = 0$), and the spinodal decomposition region ($N_p = 2$, $N_u = 1$), separated by the binodal line (green) and the spinodal line (red). This paper presents scaling laws for the expected values of N_p and N_u for high-dimensional phase diagrams of generic mixtures of many components (right).

Together, the phases fill the entire system, implying the constraint $\sum_{\alpha=1}^{N_p} J_{\alpha} = 1$, and mass conservation additionally fixes the average volume fraction $\bar{\phi}_i = \sum_{\alpha=1}^{N_p} J_{\alpha} \phi_i^{(\alpha)}$ of each component i . The system's behavior is governed by the average free energy

$$\bar{f}(N_p, \{J_{\alpha}\}, \{\phi_i^{(\alpha)}\}) = \sum_{\alpha=1}^{N_p} J_{\alpha} f(\{\phi_i^{(\alpha)}\}), \quad (1)$$

where f captures the free energy density of phase α with composition $\{\phi_i^{(\alpha)}\}$. To derive generic results, we consider a free energy that combines translational entropies with pairwise interactions between components,

$$f(\{\phi_i\}) = \sum_{i=1}^{N_c} \phi_i \ln \phi_i + \frac{1}{2} \sum_{i,j=1}^{N_c} \chi_{ij} \phi_i \phi_j. \quad (2)$$

Note that f only has $N_c - 1$ independent variables since the mixture fills space, $\sum_{i=1}^{N_c} \phi_i = 1$, which also allow us to choose $\chi_{ii} = 0$ [17]. The symmetric interaction parameters $\chi_{ij} = \chi_{ji}$ can be interpreted as second virial coefficients or as Flory parameters that quantify the interaction energy between species i and j in units of the thermal energy $k_B T$ per unit volume [20,21]. Higher-order interactions could also be included in f [22], but we here focus on the pairwise interactions since they are sufficient for phase coexistence.

The thermodynamics of the multicomponent mixture are fully determined by the interaction matrix χ_{ij} and the average composition $\bar{\phi}_i$. For instance, we can in principle minimize $\bar{f}$ to obtain the equilibrium phase count N_p together with the fractions of volume J_{α} and compositions $\phi_i^{(\alpha)}$ of all phases. However, this task is complex since generic multicomponent mixtures vary in the number of components (N_c), their average composition ($\bar{\phi}_i$), and the pairwise interactions (χ_{ij}). We thus approach this problem by increasing complexity step by step: We first study a very symmetric system and then relax the associated constraint on $\bar{\phi}_i$ and χ_{ij} successively.

III. STABILITY OF HOMOGENEOUS STATE DOES NOT PREDICT EQUILIBRIUM STATE IN SYMMETRIC MIXTURES

To build intuition for the behavior of multicomponent mixtures, we start by analyzing the special case of identical interactions ($\chi_{i \neq j} = \bar{\chi}$) and symmetric compositions ($\bar{\phi}_i = 1/N_c$), so we only vary the interaction strength $\bar{\chi}$ and the component count N_c .

We first investigate homogeneous states and ask when they become unstable, so phase separation is inevitable. This is the case when the Hessian matrix $\mathbf{H} = \{H_{ij}\}_{i,j=2}^{N_c}$ with $H_{ij} = \partial^2 f / \partial \bar{\phi}_i \partial \bar{\phi}_j$ is no longer positive definite, i.e., when at least one eigenvalue is negative. For $\chi_{i \neq j} = \bar{\chi}$ and $\bar{\phi}_i = 1/N_c$, the Hessian matrix simplifies to $H_{ij} = (\delta_{ij} + 1)(N_c - \bar{\chi})$. The associated eigenvalues, $N_c - \bar{\chi}$ and $N_c(N_c - \bar{\chi})$, are negative when

$$\bar{\chi} > N_c. \quad (3)$$

If this condition is fulfilled, the homogeneous state is unstable and phase separation must occur. Conversely, the homogeneous state is robust to small fluctuations for $\bar{\chi} < N_c$. However, large fluctuations could drive the system to a completely different state. In particular, phase separation could still happen if there exists another state with multiple phases that has lower free energy than the homogeneous state [23,24]. In this case, the homogeneous state would only be metastable, even if $\bar{\chi} < N_c$.

To determine when phase separation happens, we next discuss equilibrium states, which correspond to global minima of the free energy density $\bar{f}$ given by Eq. (1). In the symmetric case considered in this section, the only possible phase-separated state in equilibrium is the one where the number of coexisting phases equals the number of components N_c , with each phase concentrating one component to a high fraction ϕ^+ while diluting the others to $\phi^- = (1 - \phi^+) / (N_c - 1)$. Consequently, the minimal interaction strength to have phase coexistence in equilibrium can be determined numerically by comparing the free energy of this phase-separated state with the homogeneous state. To get an estimate for the minimal interaction strength, we use a variational principle: We identify a suboptimal phase-separated state and require it to have lower energy than the homogeneous state. Since the state where each of the N_c phases enriches exactly one component ($\phi^+ = 1$, $\phi^- = 0$) has $\bar{f} = 0$, the equilibrium state must be a phase-separated state when the homogeneous state has $\bar{f} > 0$, implying the sufficient condition

$$\bar{\chi} > \frac{2N_c}{N_c - 1} \ln N_c. \quad (4)$$

Figure S1 of the Supplemental Material [25] shows that Eq. (4) provides a good approximation for the numerically determined critical value of $\bar{\chi}$, especially for large N_c . A more detailed analysis presented in the Supplemental Material [25] shows that the diluted components have the fraction

$$\phi^-(N_c) \approx -\frac{W_0[-e^{-\bar{\chi}}(N_c(\bar{\chi} - 1) + 1)]}{N_c(\bar{\chi} - 1) + 1} \stackrel{\bar{\chi} \gg 1}{\approx} e^{-\bar{\chi}}, \quad (5)$$

where $W_0(r)$ is the principal branch of the Lambert W function satisfying $W_0(r)e^{W_0(r)} = r$. The limit for large $\bar{\chi}$ shows that dilute fractions are suppressed exponentially.

These results confirm the expectation that stronger repulsion (i.e., larger $\bar{\chi}$) destabilizes the homogeneous state [Eq. (3)], induces phase separation [Eq. (4)], and enhances the compositional differences between phases [Eq. (5)]. However, comparing Eqs. (3) and (4) reveals a huge discrepancy between the stability analysis and equilibrium: While the typical interaction $\bar{\chi}$ needs to scale with the component count N_c to destabilize the homogeneous state, phase coexistence is already possible when $\bar{\chi}$ scales only logarithmically with N_c . These scaling laws already suggest that the parameter region where the homogeneous state is metastable but the equilibrium state exhibits phase separation (corresponding to the nucleation-and-growth regime; see Fig. 1) expands with larger component count N_c .

IV. SCALING LAWS FOR ENSEMBLE AVERAGES OVER COMPOSITIONAL VARIATIONS

Phase coexistence of multicomponent mixtures depends not only on interactions but also on composition [11]. We thus next test how compositional variations affect homogeneous states and equilibria. To capture compositional variations in an unbiased way, we average over all permissible volume fractions ($\bar{\phi}_i \geq 0$, $\sum_{i=1}^{N_c} \bar{\phi}_i = 1$), maintaining identical interactions for now ($\chi_{i \neq j} = \bar{\chi}$). Since this system is more variable than the one discussed above, we can distinguish various degrees of instability of the homogenous state by counting the number of negative eigenvalues of the Hessian $\mathbf{H}$, denoted as the number of unstable modes, N_u . If the homogeneous state is the equilibrium state, we necessarily have $N_u = 0$ and $N_p = 1$. In contrast, for very strong phase separation, the homogeneous state will be maximally unstable, $N_u = N_c - 1$, and the phase count assumes the maximal value $N_p = N_c$ allowed by Gibbs phase rule [26]. In both extremes we have $N_p = N_u + 1$, but these two values might deviate from each other substantially in intermediate parameter regions. To quantify this behavior, we next study the mean values $\bar{N}_p$ and $\bar{N}_u + 1$ averaged over all permissible compositions.

A. Average number of unstable modes

To determine the average number of unstable modes, $\bar{N}_u$, we diagonalized the Hessian matrix $\mathbf{H}$ numerically for many different uniformly sampled compositions [27]. Figure 2(a) shows that $\bar{N}_u$ increases with the mean interaction strength $\bar{\chi}$, as expected. An analytical estimate for $\bar{N}_u$ follows from Cauchy's interlacing theorem [28]: The number N_u of negative eigenvalues of $\mathbf{H}$ equals the number of sign changes in the sequence $\{\det \mathbf{H}_0, \det \mathbf{H}_1, \dots, \det \mathbf{H}_{N_c-1}\}$, where $\det \mathbf{H}_n$ is the determinant of the rank- n leading minor of $\mathbf{H}$. For identical interactions ($\chi_{i \neq j} = \bar{\chi}$), we obtain $\det \mathbf{H}_n = (\prod_{i=1}^{n+1} q_i)(\sum_{i=1}^{n+1} q_i^{-1})$ with $q_i = \bar{\phi}_i^{-1} - \bar{\chi}$. The number of sign changes in the sequence is thus either N_- or $N_- - 1$, where N_- is the number of negative q_i , since each negative q_i contributes one sign change in the product $\prod_{i=1}^{n+1} q_i$ when varying n , while a potential sign change of the second factor, $\sum_{i=1}^{n+1} q_i^{-1}$, cancels at most one sign change; see the Supplemental Material

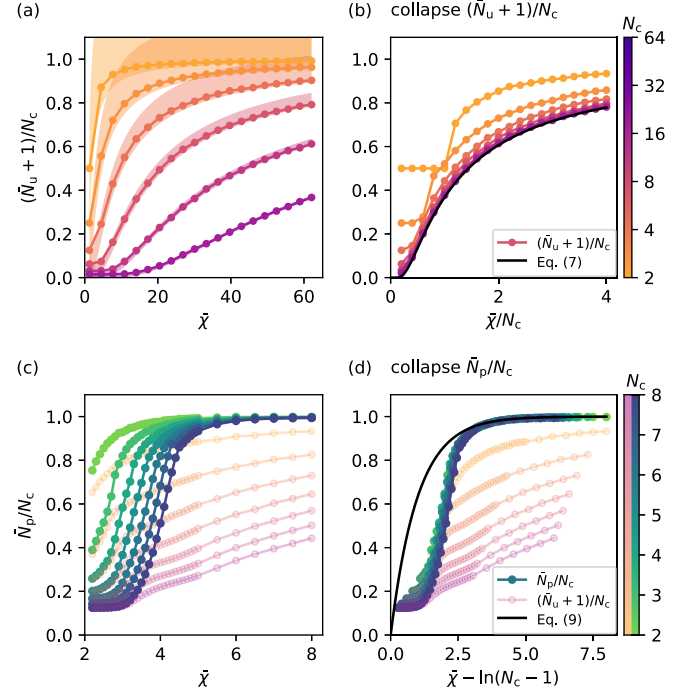


FIG. 2. Average number of phases exceeds number of unstable modes for identical interactions. Normalized average number of unstable modes, $(\bar{N}_u + 1)/N_c$, as a function of the mean interaction strength $\bar{\chi}$ in panel (a) and the scaled interaction $\bar{\chi}/N_c$ in panel (b) for various component counts N_c . The shaded area in panel (a) indicates the bounds given by Eq. (6), and the black line in panel (b) marks the asymptotic expression (7). Normalized average number of coexisting phases, $\bar{N}_p/N_c$, (green-blue) and $(\bar{N}_u + 1)/N_c$ (orange-purple) as a function of $\bar{\chi}$ in panel (c) and $\bar{\chi} - \ln(N_c - 1)$ in panel (d). The black line in panel (d) marks the asymptotic expression (9). (a)–(d) Each dot results from an average over 500–20 000 uniformly sampled compositions $\bar{\phi}_i$.

[25] for a detailed derivation. Since N_- simply counts how many $\bar{\phi}_i$ are larger than $\bar{\chi}^{-1}$, $\bar{N}_u$ is bounded by $E_{N_c}[\bar{\phi}_i > \bar{\chi}^{-1}] \leq \bar{N}_u + 1 \leq E_{N_c}[\bar{\phi}_i > \bar{\chi}^{-1}] + 1$, where $E_{N_c}[\bar{\phi}_i > h] = N_c(1 - h)^{N_c-1}$ denotes the expected number of $\bar{\phi}_i$ larger than h when $\bar{\phi}_i$ is drawn randomly on the phase diagram. Taken together, the normalized average number of unstable modes, $(\bar{N}_u + 1)/N_c$, is bounded by

$$\left(1 - \frac{1}{\bar{\chi}}\right)^{N_c-1} \leq \frac{\bar{N}_u + 1}{N_c} \leq \left(1 - \frac{1}{\bar{\chi}}\right)^{N_c-1} + \frac{1}{N_c}, \quad (6)$$

consistent with numerical data [Fig. 2(a)]. The two bounds in Eq. (6) converge for large N_c , implying

$$\frac{\bar{N}_u + 1}{N_c} \stackrel{N_c \gg 1}{\approx} \left(1 - \frac{1}{\bar{\chi}}\right)^{N_c-1} \stackrel{\bar{\chi} \gg 1}{\approx} e^{-N_c/\bar{\chi}}. \quad (7)$$

The limit on the right suggests that the normalized number of unstable modes averaged over the phase diagram, $(\bar{N}_u + 1)/N_c$, only depends on the single scaled interaction parameter $\bar{\chi}/N_c$. The data collapse shown in Fig. 2(b) indeed confirms this scaling for $N_c \gtrsim 16$.

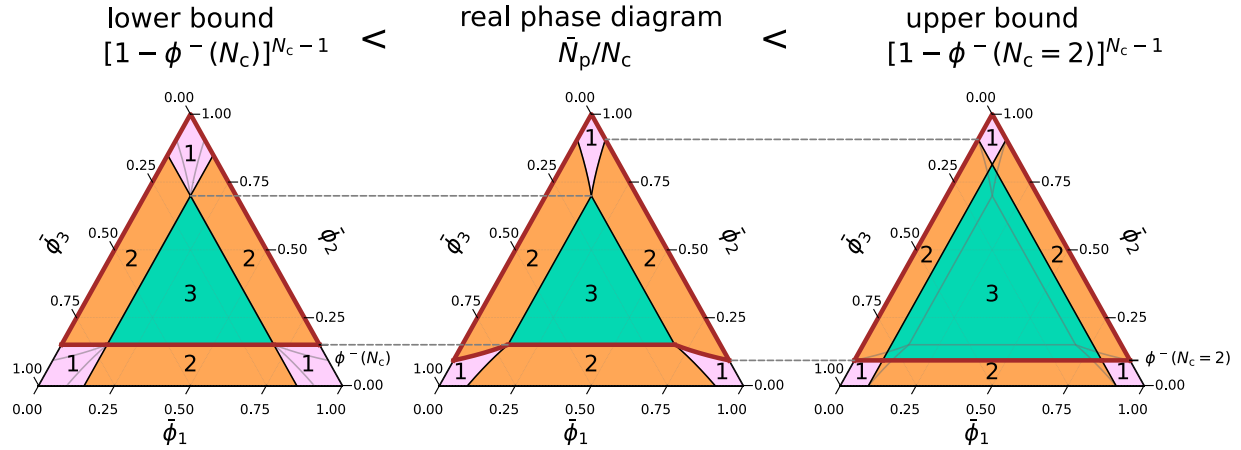


FIG. 3. Illustration of phase count bounds. The central panel shows the phase diagram as a function of the volume fractions ϕ_i of $N_c = 3$ components for $\chi_{i \neq j} = 2.8$. The colored regions indicate the number of coexisting phases, $N_p = 1, 2, 3$. The adjacent panels approximate the phase diagram using boundaries parallel to the axes, obtained by expanding the $N_p = 1$ region (left) and the central region with $N_p = N_c$ (right). They, respectively, provide lower and upper bounds to the average phase count $\bar{N}_p$, which can be obtained from the fraction covered by an area associated with each component (thick red lines). The average phase count $\bar{N}_p$ for the three panels is 2.17, 2.22, and 2.47 (from left to right).

B. Average number of coexisting phases

To test how well the average number $\bar{N}_u$ of unstable modes predicts the average phase count $\bar{N}_p$, we next investigate equilibrium states by numerically minimizing the mean free energy $\bar{f}$ given by Eq. (1). We designed an efficient algorithm to determine coexisting phases for arbitrary interactions and mean compositions [29], which is similar to the Gibbs ensemble method [30–33]. The method represents the system's state by many candidate phases called compartments. It then minimizes $\bar{f}$ by redistributing components and volumes between compartments while obeying volume and material conservation. To ensure that we detect the global minimum of $\bar{f}$, we use many more compartments than the maximal phase count $N_p^{\max} = N_c$ imposed by Gibbs phase law. Consequently, many compartments will attain very similar compositions at equilibrium, and we combine them to detect the number N_p of distinct phases; see the Supplemental Material [25] for numerical details. In a key improvement over our earlier implementation [19,27], we now initialize compartments with controlled average fractions $\bar{\phi}_i$. This allows us to sample phase counts N_p uniformly over the entire phase diagram to estimate the average number of coexisting phases, $\bar{N}_p$, in equilibrium.

The numerical results shown in Fig. 2(c) indicate that $\bar{N}_p$ increases much more quickly as a function of the interaction strength $\bar{\chi}$ than the mode count $\bar{N}_u$. Moreover, the scaled interaction strength $\bar{\chi}/N_c$, derived for $\bar{N}_u$ from Eq. (7), cannot collapse these data. To derive an alternative scaling law, we focus on strong interactions, where Eq. (4) is satisfied, so we have the maximal number of phases ($N_p = N_c$) for equal composition at the center of the phase diagram ($\bar{\phi}_i = 1/N_c$). The region where the N_c -phase state is stable forms an $(N_c - 1)$ -dimensional simplex (green region in Fig. 3), which covers a larger area for higher $\bar{\chi}$. While fewer phases are observed outside this region, the symmetric structure of the phase diagram still allows us to determine the average phase count $\bar{N}_p$. In essence, the phase diagram has a threefold rotational symmetry in the example of Fig. 3, so we can focus on one

primitive region (highlighted by the red outlines). Since the phase count at each point in the phase diagram equals the number of (symmetric) primitive regions covering that point, $\bar{N}_p/N_c$ is simply given by the fraction of the phase diagram covered by a single primitive region. We next derive lower and upper bounds by approximating the primitive region by inscribed and circumscribed simplexes. For the example shown in the central panel of Fig. 3, we thus replace the lower boundary of the primitive region by a straight line coinciding with the boundary of the central three-phase region (left panel in Fig. 3). The composition of the three-phase region is $\phi^-(N_c)$ given by Eq. (5), so the relative area of the simplex is given by $[1 - \phi^-(N_c)]^{N_c-1}$. In contrast, for the upper bound we replace the boundary by a straight line anchored at the corner points of the primitive region (right panel in Fig. 3). The corresponding fraction is $\phi^-(N_c = 2)$ since the edge of the phase diagram corresponds to a binary system. These arguments generalize to higher dimensions, so the normalized average phase count $\bar{N}_p/N_c$ is generally bounded by

$$[1 - \phi^-(N_c)]^{N_c-1} \leq \frac{\bar{N}_p}{N_c} \leq [1 - \phi^-(N_c = 2)]^{N_c-1}. \quad (8)$$

The fraction $\phi^-(N_c)$ given by Eq. (5) converges to $e^{-\bar{\chi}}$ for all N_c if $\bar{\chi} \gg 1$, so

$$\frac{\bar{N}_p}{N_c} \stackrel{\bar{\chi} \gg 1}{\approx} (1 - e^{-\bar{\chi}})^{N_c-1} \approx 1 - (N_c - 1)e^{-\bar{\chi}}. \quad (9)$$

This approximation reveals that $\bar{N}_p$ is asymptotically given by $E_{N_c}[\bar{\phi}_i > e^{-\bar{\chi}}]$, i.e., the expected number of $\bar{\phi}_i$ larger than $e^{-\bar{\chi}}$. This result is similar to that for $\bar{N}_u$ following from Eq. (7), except the threshold is now $1/e^{\bar{\chi}}$ instead of $1/\bar{\chi}$, implying an exponential scaling when switching from stability analysis to equilibrium. Transforming Eq. (9), we obtain that $\bar{N}_p/N_c$ is governed by the single shifted interaction parameter $\bar{\chi} - \ln(N_c - 1)$. Indeed, Fig. 2(d) shows that this scaling collapses the data in a surprisingly large parameter range, even when the limits used to derive Eq. (9) are violated. The data collapse

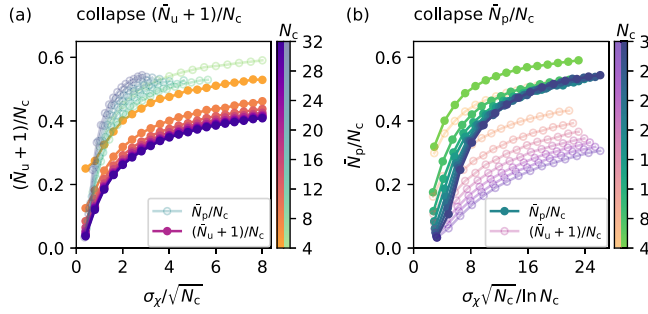


FIG. 4. More variable interactions elicit more phases. Normalized average number of unstable modes, $(\bar{N}_u + 1)/N_c$ (orange-purple), and normalized average number of coexisting phases, $\bar{N}_p/N_c$ (green-blue), as a function of two different scalings of the standard deviation σ_χ of the interactions for various component counts N_c and $\bar{\chi} = 0$. Each dot results from an average over 10^3 – 10^4 randomly chosen pairs of interaction matrices χ_{ij} and compositions $\bar{\phi}_i$.

that we identify in Fig. 2(d) indicates that the interaction parameter $\chi_{i \neq j} = \bar{\chi}$ needs to exceed roughly $3 + \ln(N_c - 1)$ to have many phases ($\bar{N}_p \approx N_c$). In contrast, the stability analysis predicted a linear scaling of $\bar{\chi}$ with N_c , so that the discrepancy between the phase count and the number of unstable modes increases with larger component count N_c .

V. SCALING LAWS INVOLVING RANDOM INTERACTIONS

Beside compositional variations, realistic mixtures exhibit large variations in the strength of the pairwise interaction between components. To test how variable interactions affect the scaling laws for homogeneous states and equilibria, we next consider random interaction matrices χ_{ij} . To focus on general features, we draw the entries χ_{ij} for $i < j$ independently from the normal distribution $\mathcal{N}(\bar{\chi}, \sigma_\chi)$, which allows us to vary the typical interaction strength $\bar{\chi}$ and the associated standard deviation σ_χ . In particular, this choice allows direct comparison with previous results on the stability of homogeneous states [8–11].

A. Vanishing mean interaction

For simplicity, we first vary only the standard deviation σ_χ of the normal distribution governing the symmetric interaction matrix χ_{ij} while keeping a vanishing mean interaction ($\bar{\chi} = 0$). For symmetric compositions ($\bar{\phi}_i = 1/N_c$), $\bar{N}_u$ can be obtained by treating the Hessian $\mathbf{H}$ as a random matrix. In particular, $\mathbf{H}$ consists of an enthalpic part given by the random χ_{ij} matrix and an entropic part given by a diagonal matrix with $\bar{\phi}_i^{-1}$ on the diagonal. The corresponding eigenvalues read $\lambda_i + \bar{\phi}_i^{-1}$, where the distribution of eigenvalues λ_j of χ_{ij} forms a semicircle of radius of $2\sigma_\chi\sqrt{N_c}$ centered at the origin [8]. In particular, the average number of negative eigenvalues is then $\bar{N}_u = E_{N_c}[\lambda_j > \bar{\phi}_i^{-1}]$. Geometrically, the fraction of the average number of unstable modes, $\bar{N}_u/N_c$, thus equals the fraction of the semicircle right of $\bar{\phi}_i^{-1}$, which is a function of the single parameter $\sigma_\chi\sqrt{N_c}/\bar{\phi}_i^{-1} = \sigma_\chi N_c^{-1/2}$. This scaling even persists for random compositions $\bar{\phi}_i$ [11], where the above analysis does not hold. Figure 4(a) confirms that this

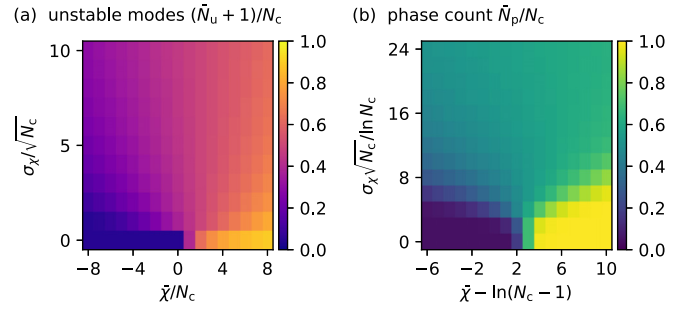


FIG. 5. Scaling functions for mixtures with random interactions. (a) Normalized average number of unstable modes, $(\bar{N}_u + 1)/N_c$, as a function of scaled mean interaction $\bar{\chi}$ and standard deviation σ_χ . (b) Normalized average number of coexisting phases, $\bar{N}_p/N_c$, as a function of scaled $\bar{\chi}$ and σ_χ . (a), (b) The shown master functions were obtained by averaging 300 samples of random interaction matrices and compositions for each value of $\bar{\chi}$ and σ_χ for component counts $N_c = 16, 20, 24, 28, 32$.

scaling collapses data for $\bar{N}_u$, whereas it fails for the phase counts $\bar{N}_p$ that we determined using our numerical algorithm.

To also obtain a scaling relation for the phase count $\bar{N}_p$, we exploit an analogy between $\bar{N}_u$ and $\bar{N}_p$ that we derived above for identical interactions ($\chi_{i \neq j} = \bar{\chi}$): We found $\bar{N}_u \sim E_{N_c}[\bar{\chi} > \bar{\phi}_i^{-1}]$ and $\bar{N}_p \sim E_{N_c}[e^{\bar{\chi}} > \bar{\phi}_i^{-1}]$, indicating that the two quantities only differ in the dependence on $\bar{\chi}$ in the argument. For random interactions, we thus speculate that the scaling of $\bar{N}_p$ can be inferred from the result for $\bar{N}_u$ by substituting e^{λ_i} for the eigenvalues λ_i . This procedure suggests that $\bar{N}_p/N_c$ can be expressed as a function of the scaling parameter $\sigma_\chi\sqrt{N_c}/\ln N_c$ for sufficiently large N_c , which is confirmed by the data collapse shown in Fig. 4(b). Thus, larger variations σ_χ of the interactions generally lead to more phases, and $\bar{N}_p/N_c$ even grows with N_c when σ_χ is fixed. In contrast, the stability analysis suggests that σ_χ needs to grow with $\sqrt{N_c}$ to have the same fraction of unstable modes, so $\bar{N}_u$ severely underestimates the phase count $\bar{N}_p$, particularly for large N_c .

B. Finite mean interaction

We next study the impact of nonzero mean interactions $\bar{\chi}$: Combining the scalings for identical interactions [$\sigma_\chi = 0$; see Eqs. (7) and (9)] and vanishing mean interactions ($\bar{\chi} = 0$; see the previous section), we postulate that the average number of unstable modes and phase count, respectively, scale as

$$\frac{\bar{N}_u + 1}{N_c} \approx g_u\left(\frac{\bar{\chi}}{N_c}, \frac{\sigma_\chi}{\sqrt{N_c}}\right) \quad \text{and} \quad (10a)$$

$$\frac{\bar{N}_p}{N_c} \approx g_p\left(\bar{\chi} - \ln(N_c - 1), \frac{\sigma_\chi\sqrt{N_c}}{\ln N_c}\right), \quad (10b)$$

where g_u and g_p are the associated master functions, which we determine numerically by averaging over random interaction matrices and compositions (Fig. 5). The deviation of the actually measured data to this prediction is generally low (see Fig. S2 of the Supplemental Material [25]), implying that the proposed scaling captures the dominant behavior. The two master functions shown in Fig. 5 are qualitatively similar: For strongly attractive interactions (large negative $\bar{\chi}$ and small

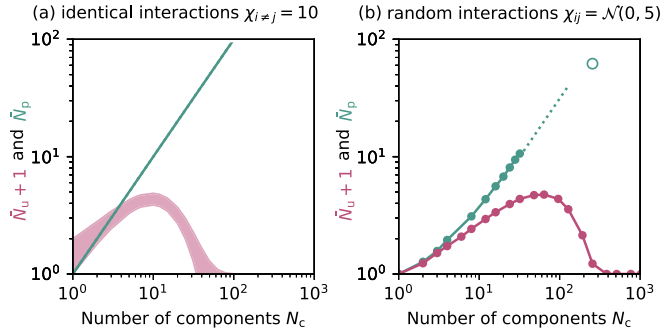


FIG. 6. Mixtures with metastable homogeneous states can have many coexisting phases in equilibrium. (a) Analytical estimates of average number of coexisting phases $\bar{N}_p$ [green line, Eq. (8)] and average number of unstable modes $\bar{N}_u$ [red region, Eq. (6)] as a function of component count N_c for mixtures with identical interactions ($\chi_{i \neq j} = 10$). (b) Numerically determined $\bar{N}_p$ (green dots) and $\bar{N}_u$ (red dots) as a function of N_c for random interactions ($\bar{\chi} = 0$, $\sigma_\chi = 5$) and compositions. The green dotted line shows a linear extrapolation toward the single data point at $N_c = 256$ (open circle).

σ_χ), they are close to 0, implying that only very few phases form. In contrast, when repulsive interactions dominate (large $\bar{\chi}$ and small σ_χ), the master functions converge to 1, implying N_c phases coexist. For strongly varying interactions (small $\bar{\chi}$ and large σ_χ), both master functions converge to $\frac{1}{2}$ and the respective influence of $\bar{\chi}$ can be approximated analytically (see the Supplemental Material [25]). While the master functions exhibit similarities, the axes are scaled very differently, implying different interpretations of what constitutes large interactions: For large N_c , the mean interactions $\bar{\chi}$ and the variance σ_χ^2 need to scale with N_c to obtain similar fractions $\bar{N}_u/N_c$ of unstable modes. In contrast, the predicted phase count $\bar{N}_p$ exhibits a much weaker dependence on N_c : For instance, the influence of N_c on the mean interaction is only logarithmically. Moreover, the predicted fraction $\bar{N}_p/N_c$ increases with N_c even if σ_χ is kept constant. These scaling laws also hold for different samplings of the compositions (see the Supplemental Material [25]) and are thus likely robust. In particular, we conclude that multicomponent mixtures typically have many more phases in equilibrium than the stability analysis of the homogeneous state predicts.

VI. MULTICOMPONENT MIXTURES EXHIBIT A LARGE NUCLEATION-AND-GROWTH REGIME

The scaling laws given by Eq. (10) allow us to speculate about the expected number N_u of unstable modes and the equilibrium phase count N_p in realistic systems. As an example, we focus on biological cells, where a typical interaction strength of molecules involved in phase separation is a few $k_B T$, but the actual component count N_c can vary over several orders of magnitude; there are an estimated number of 10^5 different proteins [1]. For this scenario, numerical data indicates that the homogeneous state becomes more robust ($\bar{N}_u$ approaches 0) [12], whereas the expected phase count in equilibrium increases linearly with N_c for identical interactions [Fig. 6(a)] and randomly distributed interactions [Fig. 6(b)].

This behavior can be understood based on the scaling laws given in Eq. (10): For large N_c at fixed $\bar{\chi}$ and σ_χ , the fraction of unstable modes approaches $g_u(0, 0) = 0$. In contrast, the governing parameters for N_p scale much slower, keeping the phase count fraction almost constant in a wide range of N_c . The number N_p of coexisting phases would only decrease at much larger values of N_c , implying a huge parameter range where the homogeneous state is metastable while the equilibrium state exhibits many phases.

The discrepancy between the number of unstable modes and the equilibrium phase count generalizes the familiar nucleation-and-growth regime in binary mixtures (Fig. 1). Even in binary mixtures, the fraction beyond which phase separation sets in (the binodal) is approximately given by $e^{-\chi}$, whereas the homogeneous state only becomes unstable for fractions larger than $\frac{1}{2}\chi^{-1}$ (the spinodal) [34,35]. These scalings are consistent with the respective exponential and linear scalings that we revealed above, but we additionally find a strong influence of the component count N_c . Since N_c sets the dimensionality of the phase diagram, we speculate that its influence is of geometric origin: The region where the homogeneous state is unstable typically occupies the central region of the phase diagram, so multistability might be more likely for parameters close to boundaries. The fraction of the phase diagram that is close to boundaries increases dramatically with dimension, suggesting that the behavior at boundaries dominates for large N_c .

VII. MULTICOMPONENT MIXTURES EXHIBIT MANY METASTABLE STATES

We showed that many multicomponent mixtures have a metastable homogeneous state, while their equilibrium state exhibits many coexisting phases. A system that starts in the homogeneous state thus needs to nucleate all these phases to reach equilibrium. We speculate that this nucleation happens consecutively, implying the existence of intermediate metastable states with fewer coexisting phases than the equilibrium state. To explore this exciting possibility, we use our numerical method [29] to discover such intermediate states. Briefly, we generate candidate states by either constraining the phase count or by removing phases from the equilibrium state. In all cases, we then minimize $\bar{f}$ to find the nearest local free energy minimum, corresponding to a (meta)stable state. Using this procedure, we find multiple metastable states between the homogeneous and the equilibrium state for a particular mixture with $N_c = 32$ components (Fig. 7). In this case, the metastable homogeneous state has the highest energy of all tested states. The energy tends to decrease with the phase count N_p , suggesting that phases can be nucleated successively to reach the equilibrium state with the lowest energy. This analysis demonstrates that multicomponent mixtures typically exhibit many metastable states.

VIII. SURFACE TENSION DOES NOT IMPAIR MULTISTABILITY

So far, we considered thermodynamically large systems, but biological cells are relatively small, so interfacial effects could matter. To check whether generic multicomponent

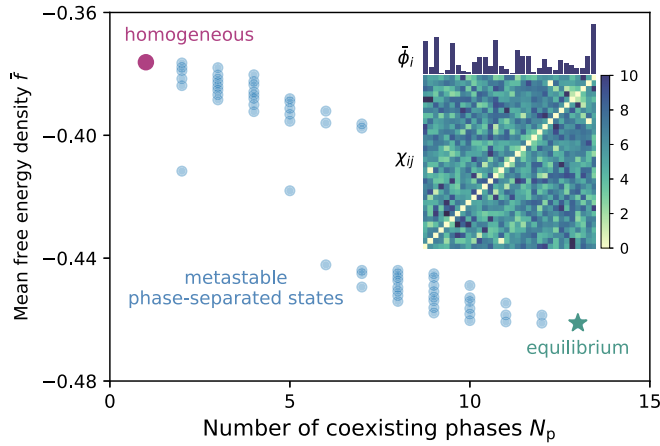


FIG. 7. Generic mixtures exhibit many metastable phase-separated states. Mean free energy density $\bar{f}$ for multiple (meta)stable states arranged by their phase count N_p . The metastable homogeneous state (purple disk) has the highest free energy, whereas the free energy minimum corresponds to the equilibrium state with 13 phases (green star). The inset shows the interaction matrix χ_{ij} and the average composition $\bar{\phi}_i$ of the investigated mixture with $N_c = 32$ components.

mixtures still exhibit multistability in this case, we next consider spatially extended volume fraction fields $\phi_i(\mathbf{r}, t)$ in a periodic system conserving the average fractions $\bar{\phi}_i = \langle \phi_i(\mathbf{r}, t) \rangle_r$. The corresponding gradient descent dynamics that minimize the overall free energy are given by the Cahn-Hilliard equation [34,36], $\partial_t \phi_i = \sum_j \nabla \cdot [\Lambda_{ij} \nabla (\partial f / \partial \phi_j - \ell^2 \nabla^2 \phi_j)]$ for $i = 2, \dots, N_c$, where the mobility matrix Λ_{ij} sets time scales and ℓ controls the width of interfaces and is related to surface tension [17]. Evolving these coupled equations numerically from various initial configurations, we find stationary configurations (Fig. 8). Similar to the example shown in Fig. 7, the spatially extended system exhibits a metastable homogeneous state and multiple other states with various droplets. This suggests that multistability remains in

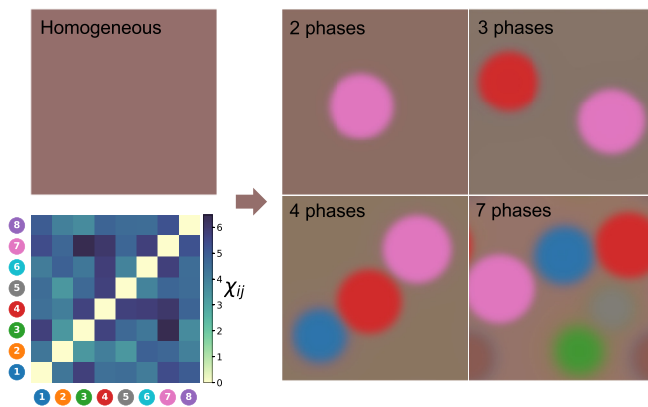


FIG. 8. Metastable states prevail in finite systems. Density plots of (meta)stable configurations of a mixture with $N_c = 8$ components with interaction matrix χ_{ij} (lower left) and symmetric composition ($\bar{\phi}_i = \frac{1}{8}$). Stationary configurations have been obtained by solving the Cahn-Hilliard equation (see the Supplemental Material [25]).

finite systems even when inevitable surface tension is present, and our scaling laws can be used to estimate the expected number of coexisting phases.

IX. DISCUSSION

We investigated the generic behavior of multicomponent mixtures by analyzing two extreme states, namely the homogeneous and the equilibrium state, in detail. The associated scaling laws given by Eq. (10) allow us to predict how these states behave as a function of interaction strengths and component count N_c . In particular, we find that homogeneous states tend to become more stable with increasing N_c , whereas equilibrium states gain more phases.

The fact that equilibrium states can exhibit many phases even when the homogeneous state is metastable further suggests that there are additional metastable states with fewer phases (Fig. 7). Since we only considered passive systems governed by equilibrium thermodynamics, these states must be separated by energy barriers, which could be overcome by nucleation. We thus expect that starting from the homogeneous state, several different types of droplets can be nucleated independently of each other, giving rise to a sequence of states with increasing droplet counts (Fig. 8). Experimentalists begin to analyze such behaviors [37], but there are many open questions, including the number of metastable states, the magnitude of energy barriers, and whether there is a hierarchy of nucleation.

Our theory predicts two fundamental aspects of phase coexistence inside biological cells. First, the fact that cells comprise millions of different components that phase separate due to weak interactions on the scale of the thermal energy $k_B T$ suggests that the equilibrium phase count is small compared to the component count [lower left corner of Fig. 5(b)], which is consistent with the observed 10^1 – 10^3 different condensates [16] that form from 10^5 – 10^7 different biomolecules [1]. Second, our theory implies multistability, which cells could exploit to create and remove different droplets independently of each other to fulfill separate functions robustly. Such multistability is a typical behavior, which does not require specifically designed interactions. However, there is also the exciting possibility that formation of different droplets is coupled, which might be functionally relevant, e.g., if two types of condensates must not coexist. In both cases, cells could fine-tune the interactions of molecules, e.g., through evolutionary adaptation of the respective genes [27], even though our theory suggests that such fine-tuning is not necessary to obtain many multistable droplets. Moreover, active processes would allow cells to exert finer control on when droplets form and how large they get [24,34,38–40]. Taken together, our theory paints a picture of a multistable cytosol where hundred types of condensates can coexist independently, and it is exciting to see that experimental methods for measuring such systems are being developed [41].

We validated our scaling laws against numerical data, although the computational complexity limits the maximal component count N_c we can handle. While most scaling laws were derived based on analytical estimates, the dependence of the phase count $\bar{N}_p$ on the interaction variance σ_χ^2 was only obtained by analogy and might thus break down beyond the

tested regime. We here also only focused on interactions that are randomly distributed with little structure, whereas realistic systems will likely have higher order [22] and structured interactions [42–44], e.g., arising from evolutionary optimization, which affects phase coexistence [45,46]. Moreover, the composition of various components is typically broadly distributed, which might affect accessible phases. We expect that such details affect the precise number of phases and their compositions, but our scaling should still be predicting the generic behavior. To address these aspects in detail, it would be helpful to understand the geometry of phase space, which certainly warrants further investigations and experimental validation. Our results on the generic behavior of multicomponent mixtures will guide future research in these directions.

ACKNOWLEDGMENTS

We thank Frank Jülicher, Eric Dufresne, Thomas Michaels, Filipe Thewes, and Peter Sollich for helpful discussions. We thank Filipe Thewes and Gerrit Wellecke for critical reading of the manuscript. We gratefully acknowledge funding from the Max Planck Society and the European Union (ERC, Emul-Sim, 101044662).

DATA AVAILABILITY

The data that support the findings of this article are openly available [29].

- [1] G. M. Cooper and K. W. Adams, *The Cell: A Molecular Approach* (Oxford University Press, New York, 2023).
- [2] A. A. Hyman, C. A. Weber, and F. Jülicher, Liquid-liquid phase separation in biology, *Annu. Rev. Cell Dev. Biol.* **30**, 39 (2014).
- [3] S. F. Banani, H. O. Lee, A. A. Hyman, and M. K. Rosen, Biomolecular condensates: Organizers of cellular biochemistry, *Nat. Rev. Mol. Cell Biol.* **18**, 285 (2017).
- [4] W. M. Jacobs and D. Frenkel, Phase transitions in biological systems with many components, *Biophys. J.* **112**, 683 (2017).
- [5] P. Sartori and S. Leibler, Lessons from equilibrium statistical physics regarding the assembly of protein complexes, *Proc. Natl. Acad. Sci. USA* **117**, 114 (2020).
- [6] D. L. J. Lafontaine, J. A. Riback, R. Bascetin, and C. P. Brangwynne, The nucleolus as a multiphase liquid condensate, *Nat. Rev. Mol. Cell Biol.* **22**, 165 (2021).
- [7] C. A. Azaldegui, A. G. Vecchiarelli, and J. S. Biteen, The emergence of phase separation as an organizing principle in bacteria, *Biophys. J.* **120**, 1123 (2021).
- [8] R. P. Sear and J. A. Cuesta, Instabilities in complex mixtures with a large number of components, *Phys. Rev. Lett.* **91**, 245701 (2003).
- [9] W. M. Jacobs and D. Frenkel, Predicting phase behavior in multicomponent mixtures, *J. Chem. Phys.* **139**, 024108 (2013).
- [10] K. Shrinivas and M. P. Brenner, Phase separation in fluids with many interacting components, *Proc. Natl. Acad. Sci. USA* **118**, e2108551118 (2021).
- [11] F. C. Thewes, M. Krüger, and P. Sollich, Composition dependent instabilities in mixtures with many components, *Phys. Rev. Lett.* **131**, 058401 (2023).
- [12] R. P. Sear, The cytoplasm of living cells: A functional mixture of thousands of components, *J. Phys.: Condens. Matter* **17**, S3587 (2005).
- [13] J. Berry, C. P. Brangwynne, and M. Haataja, Physical principles of intracellular organization via active and passive phase transitions, *Rep. Prog. Phys.* **81**, 046601 (2018).
- [14] A. W. Fritsch, A. F. Diaz-Delgadillo, O. Adame-Arana, C. Hoegge, M. Mittasch, M. Kreysing, M. Leaver, A. A. Hyman, F. Jülicher, and C. A. Weber, Local thermodynamics govern formation and dissolution of *Caenorhabditis elegans* P granule condensates, *Proc. Natl. Acad. Sci. USA* **118**, e2102772118 (2021).
- [15] J.-Y. Youn, B. J. Dyakov, J. Zhang, J. D. Knight, R. M. Vernon, J. D. Forman-Kay, and A.-C. Gingras, Properties of stress granule and p-body proteomes, *Mol. Cell* **76**, 286 (2019).
- [16] N. Rostam, S. Ghosh, C. F. W. Chow, A. Hadarovich, C. Landerer, R. Ghosh, H. Moon, L. Hersemann, D. M. Mitrea, I. A. Klein, A. A. Hyman, and A. Toth-Petroczy, CD-CODE: Crowdsourcing condensate database and encyclopedia, *Nat. Methods* **20**, 673 (2023).
- [17] S. Mao, D. Kuldinow, M. P. Haataja, and A. Košmrlj, Phase behavior and morphology of multicomponent liquid mixtures, *Soft Matter* **15**, 1297 (2019).
- [18] S. Mao, M. S. Chakraverti-Wuerthwein, H. Gaudio, and A. Košmrlj, Designing the morphology of separated phases in multicomponent liquid mixtures, *Phys. Rev. Lett.* **125**, 218003 (2020).
- [19] W. M. Jacobs, Theory and simulation of multiphase coexistence in biomolecular mixtures, *J. Chem. Theory Comput.* **19**, 3429 (2023).
- [20] P. J. Flory, Thermodynamics of high polymer solutions, *J. Chem. Phys.* **10**, 51 (1942).
- [21] M. L. Huggins, Solutions of long chain compounds, *J. Chem. Phys.* **9**, 440 (1941).
- [22] C. Luo, Y. Qiang, and D. Zwicker, Beyond pairwise: Higher-order physical interactions affect phase separation in multicomponent liquids, *Phys. Rev. Res.* **6**, 033002 (2024).
- [23] L. P. McMaster, Aspects of polymer-polymer thermodynamics, *Macromolecules* **6**, 760 (1973).
- [24] D. Zwicker, The intertwined physics of active chemical reactions and phase separation, *Curr. Opin. Colloid Interface Sci.* **61**, 101606 (2022).
- [25] See Supplemental Material at <http://link.aps.org/supplemental/10.1103/zcvb-9t4b> for details of theoretical derivations, numerical methods for free energy minimization, and additional figures.
- [26] J. W. Gibbs, On the equilibrium of heterogeneous substances, *Trans. Conn. Acad. Arts Sci* **3**, 108 (1876).
- [27] D. Zwicker and L. Laan, Evolved interactions stabilize many coexisting phases in multicomponent liquids, *Proc. Natl. Acad. Sci. USA* **119**, e2201250119 (2022).
- [28] R. Bellman, *Introduction to Matrix Analysis* (SIAM, Philadelphia, PA, 1997).

- [29] Y. Qiang and D. Zwicker, Flory: A Python package for finding coexisting phases in multicomponent mixtures, *J. Open Source Softw.* **10**, 7388 (2025).
- [30] Z. Mester, N. A. Lynd, and G. H. Fredrickson, Numerical self-consistent field theory of multicomponent polymer blends in the gibbs ensemble, *Soft Matter* **9**, 11288 (2013).
- [31] F. Schmid, Self-consistent-field theories for complex fluids, *J. Phys.: Condens. Matter* **10**, 8105 (1998).
- [32] A. Z. Panagiotopoulos, Gibbs ensemble techniques, in *Observation, Prediction and Simulation of Phase Transitions in Complex Fluids*, edited by M. Baus, L. F. Rull, and J.-P. Ryckaert (Springer Netherlands, Dordrecht, 1995), pp. 463–501.
- [33] B. Smit and D. Frenkel, Calculation of the chemical potential in the Gibbs ensemble, *Mol. Phys.* **68**, 951 (1989).
- [34] D. Zwicker, O. W. Paulin, and C. ter Burg, Physics of droplet regulation in biological cells, [arXiv:2501.13639](https://arxiv.org/abs/2501.13639).
- [35] D. Qian, T. C. T. Michaels, and T. P. J. Knowles, Analytical solution to the Flory–Huggins model, *J. Phys. Chem. Lett.* **13**, 7853 (2022).
- [36] J. W. Cahn and J. E. Hilliard, Free energy of a nonuniform system. I. Interfacial free energy, *J. Chem. Phys.* **28**, 258 (1958).
- [37] N. A. Erkamp, M. A. M. Verwiel, D. Qian, T. Sneideris, F. A. Spaepen, D. A. Weitz, J. C. M. van Hest, and T. P. J. Knowles, Biomolecular condensates with complex architectures via controlled nucleation, *Nat. Chem. Eng.* **1**, 430 (2024).
- [38] J. Kirschbaum and D. Zwicker, Controlling biomolecular condensates via chemical reactions, *J. R. Soc. Interface* **18**, 20210255 (2021).
- [39] J. Söding, D. Zwicker, S. Sohrabi-Jahromi, M. Boehning, and J. Kirschbaum, Mechanisms for active regulation of biomolecular condensates, *Trends Cell Biol.* **30**, 4 (2020).
- [40] C. A. Weber, D. Zwicker, F. Jülicher, and C. F. Lee, Physics of active emulsions, *Rep. Prog. Phys.* **82**, 064601 (2019).
- [41] S. Ye, N. B. Goldfajn, C. L. So, T. Inoue, and D. Cai, Rainbow nucleus charts dynamic interactome of membrane-less organelles, *bioRxiv* (2025), <https://doi.org/10.1101/2025.05.14.654140>.
- [42] F. Chen and W. M. Jacobs, Programmable phase behavior in fluids with designable interactions, *J. Chem. Phys.* **158**, 214118 (2023).
- [43] D. Qian, H. Ausserwoger, W. E. Arter, R. M. Scrutton, T. J. Welsh, T. Kartanas, N. Ermann, S. Qamar, C. Fischer, T. Sneideris, P. S. George-Hyslop, R. V. Pappu, and T. P. J. Knowles, Linking modulation of bio-molecular phase behaviour with collective interactions, *bioRxiv* (2024), <https://doi.org/10.1101/2023.11.02.565376>.
- [44] H. R. Kilgore, I. Chinn, P. G. Mikhael, I. Mitnikov, C. Van Dongen, G. Zylberberg, L. Afeyan, S. F. Banani, S. Wilson-Hawken, T. I. Lee, R. Barzilay, and R. A. Young, Protein codes promote selective subcellular compartmentalization, *Science* **387**, 1095 (2025).
- [45] I. R. Graf and B. B. Machta, Thermodynamic stability and critical points in multicomponent mixtures with structured interactions, *Phys. Rev. Res.* **4**, 033144 (2022).
- [46] R. Braz Teixeira, G. Carugno, I. Neri, and P. Sartori, Liquid Hopfield model: Retrieval and localization in multicomponent liquid mixtures, *Proc. Natl. Acad. Sci. USA* **121**, e2320504121 (2024).