

Born to Condense: Polysomes Drive Cotranslational Condensation of Biomolecular Condensate Proteins

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Biomolecular condensates formed by liquid-liquid phase separation organize many cellular processes, yet it remains unclear how condensate localization is coupled to protein synthesis. In particular, proteins are often translated on polysomes, where multiple ribosomes on a single mRNA generate a bottlebrush-like assembly of nascent chains, raising the possibility that translation itself could be spatially coupled to condensates. Here we develop a theoretical framework for CoTranslational Condensation (CTC), in which nascent chains on a polysome for condensate proteins interact with their condensate and thus localize translation there. Using coarse-grained simulations, we show that protein domain architecture dictates the thermodynamics of CTC, consistent with a Langmuir adsorption model. Proteins with high-affinity regions exposed early on nascent chains display much stronger condensate association than architectures in which these regions appear only late in translation. A bioinformatic analysis of 7667 condensate-associated proteins further shows that sequence architectures compatible with strong CTC are common. At the dynamical level, combining simulations with reaction-diffusion modeling reveals that CTC is kinetically feasible within typical polysome lifetimes, either through densely packed polysomes nucleating new condensates or via diffusion to preexisting condensates. As an illustrative consequence, we show that CTC can reduce the accumulation of unmodified protein intermediates by localizing their synthesis with condensates, where modification can occur promptly. Together, our results establish physical principles for how translation can couple to phase separation and identify protein architectures and cellular regimes that favor CTC.

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I. INTRODUCTION

Biomolecular condensates formed via liquid-liquid phase separation (LLPS) exemplify how fundamental principles of polymer physics and soft condensed matter physics structure and organize life processes. These dynamic membrane-less compartments contribute to key functions such as RNA metabolism, gene expression, and stress responses [1–6]. A fundamental question is how the localization of proteins into condensates is connected to its prerequisite—protein synthesis. It is known that translation can be localized to membrane-bound organelles [7], and here we explore how translation can be localized to membrane-less organelles.

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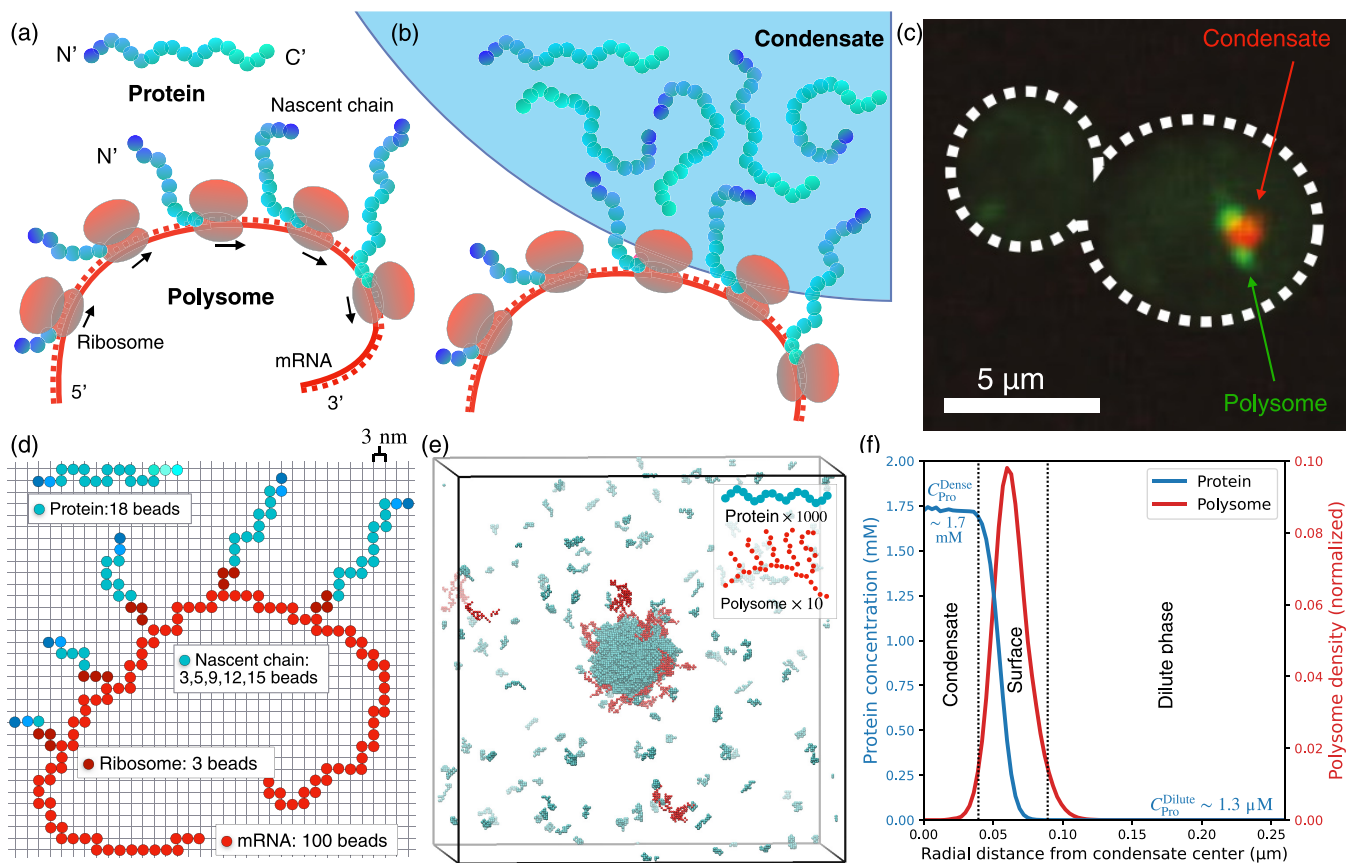


FIG. 1. CoTranslational Condensation (CTC): Polysomes and condensates of the encoded protein. (a) Cartoon of a polysome translating condensate-associated proteins and the corresponding protein. Nascent protein chains closer to the mRNA 3' end are longer. The N termini are located at the tips of the nascent chains. (b) Cartoon of a polysome's nascent proteins interacting with a condensate. (c) Experimental observation of CTC: polysomes (green) are colocalized with a condensate enriched in the encoded protein (red) in yeast; see Heidenreich *et al.* [11] for methodological details. (d) 3D lattice coarse-grained model of polysomes and proteins. Each lattice length measures 3 nm. Proteins are coarse grained to 18 beads, and polysomes are represented as Sparse (5 nascent chains with 160 beads), Medium (9 nascent chains with 208 beads), or Dense (15 nascent chains with 265 beads); see SM [24] for details. (e) Representative simulation snapshot of 1000 proteins (homopolymers) and 10 Sparse polysomes in a cubic box with length of 600 nm (200 lattice sites). Most polysomes localize to condensate surfaces; see Movie II for the full trajectory, see SM [24]. (f) Radial distribution of material from the condensate center, time-averaged after equilibration, quantifying polysome localization. c_{Pro} denotes protein concentration.

During translation, multiple ribosomes (typically ~ 10 per mRNA [8–10]) move along a single transcript to generate a bottlebrush-like structure, the polysome, where the nascent chains act as densely grafted side chains, as shown in Fig. 1(a). This creates a distinct physical possibility: if the translated protein is a condensate scaffold (drives condensate formation) or a client (partitions into preexisting condensates) [2], then the multiple nascent chains on the polysome should also interact with the corresponding condensate and thus localize synthesis with condensate. We term this process CoTranslational Condensation (CTC).

Limited but direct experimental evidence supports this concept. Heidenreich *et al.* engineered proteins that phase separate upon expression in yeast and showed that their translating polysomes colocalize with the condensate via protein-protein interactions, where no RNA-binding domains are present [11] [Fig. 1(c)]. More indirect support comes from studies of axonemal dynein heavy chains, where translating polysomes associate with condensates enriched in chaperones and assembly factors [12]. These observations indicate that

translation can be spatially coupled to condensates, but the physical basis, prevalence across biology, and key determinants of CTC remain unclear.

The central hypothesis of this work is that the interactions from the nascent chains of bottlebrush-like polysomes lead to cotranslational condensation. For this to follow, it must satisfy both thermodynamic and kinetic considerations. Using multiscale modeling, we establish a biophysical framework for CTC and predict that many condensate-associated proteins are likely to undergo this process. Coarse-grained simulations across diverse protein architectures show that proteins interacting through their N-terminal regions exhibit especially strong polysome-condensate association, although many other architectures also show appreciable association. Complementary bioinformatic analysis of annotated condensate-associated proteins further suggests that a majority possess architectures favorable for CTC. Building on these results, we parametrize a reaction-diffusion model at cellular length and time scales and show that polysomes persist long enough to colocalize with condensates before disassembly.

In addition, our coarse-grained simulations reveal that condensates can nucleate on polysomes, further promoting CTC. Finally, we provide a proof-of-principle example showing how CTC can functionally benefit cells by increasing the fidelity of protein modifications that occur in condensates.

II. METHODS: MULTISCALE MODELING

We performed 3D lattice-based Monte Carlo polymer simulations [13], coarse-graining proteins into bead-spring polymers with excluded volume at a lattice length of ~ 3 nm, corresponding to a folded domain or ~ 30 disordered residues [14]. This approach enables simulations of 10^4 polymers in $1 \mu\text{m}^3$ and has been successfully used to study multiple condensates [5,15–23]; see the Supplemental Material (SM) for details [24].

All proteins are represented as linear chains of 18 lattice beads [Fig. 1(d)]. Because translation elongation is slow (~ 5 amino acids/s) [25] compared to polymer dynamics [26], we model the polysome as a quasistatic bottlebrush structure, i.e., flexible polymers and no explicit translation. The main chain represents the mRNA, and each side chain represents a ribosome with its nascent protein chain [Fig. 1(d)]. The nascent chains have the same interaction parameters as the proteins for which the mRNA codes. Because translation is directional, the N terminus of each nascent chain is located at the side-chain tip.

Polysome-condensate association can be driven by interactions involving nascent chains, mRNA, and ribosomes. For a protein of interest, the condensation strength and protein architecture defines the strength of protein-nascent chain interactions. We choose to model the protein-mRNA and protein-ribosome interactions as excluded-volume interactions, which is expected to give the minimal driving force for polysome localization. This choice provides a conservative baseline for CTC: if nascent chain interactions alone are sufficient to localize polysomes to condensates, then additional mRNA- or ribosome-mediated attractions would only strengthen this association. We note a direct consequence of this minimal interaction limit is that associated polysomes preferentially localize at condensate interfaces, where nascent chains gain attractive contacts with the condensate while the mRNA-ribosome scaffold avoids the dense phase.

The minimal interaction limit is representative of biological systems where the condensate proteins do not contain motifs that interact with ribosomes nor mRNA noncoding regions (translating ribosomes locally occlude the mRNA coding region and can limit protein-mRNA contacts). Additional attractions (protein-mRNA or protein-ribosome) are expected to strengthen CTC and potentially shift the phenomenology from interfacial adsorption toward partitioning of polysomes into condensates. Alternatively, polysomes could cluster with additional mRNA-mRNA interactions or at subsaturated protein concentrations (no condensates). We discuss how the framework can be extended to include these cases in the SM [24].

We considered three polysomes representing different ribosome packing densities [8–10]: Sparse polysomes with 5 nascent chains (160 beads per polysome), Medium polysomes with 9 nascent chains (208 beads per polysome), and

Dense polysomes with 15 nascent chains (265 beads per polysome), see SM [24].

In cells, polysomes typically disassemble after translating proteins for minutes to tens of minutes [27]. These timescales, and the corresponding cellular length scales, exceed the reach of coarse-grained simulations. Therefore, we used simulations to parametrize reaction-diffusion models that capture the emergent behavior at cellular scales.

III. THERMODYNAMICS OF COTRANSLATIONAL CONDENSATION

We begin by examining homopolymer-like proteins (Homo), in which all coarse-grained beads are identical and interact via uniform medium-affinity interactions. The interaction strength was chosen such that the proteins phase separate at a saturation concentration of $\sim 1 \mu\text{M}$ (see the Supplemental Material and Movie I [24]), placing the system in a biologically relevant concentration regime. This model represents proteins with relatively uniform interaction propensities along their sequences [28] and serves as a baseline test of whether CTC is feasible. We use Sparse polysomes, the lowest-valency polysome construct considered here, and a condensate geometry in which the available surface area exceeds the area required to accommodate all ten polysomes, while the condensate volume remains small compared to the dilute-phase volume. Under these conditions, most polysomes localize to the condensate surface ($78.7\% \pm 0.5\%$; Figs. 1(e) and 1(f) and Movie II [24]), demonstrating substantial polysome-condensate association.

Polysomes translating proteins with stronger phase-separation propensity will exhibit stronger CTC as the nascent chains are more attractive, see SM [24]. Polysomes for client proteins associate with condensates similarly, as their nascent chains are also attractive to the scaffold condensate, see SM [24]. CTC increases with polysome ribosome packing density, reflecting the greater number of nascent chains available for condensate interactions, see SM [24]. Likewise, polysomes translating longer proteins exhibit stronger CTC due to both longer nascent chains and mRNAs that accommodate more ribosomes, see SM [24].

A. From homogeneous proteins to sequence architecture

The Homo model establishes polysome-condensate association and provides a baseline for understanding how architecture influences CTC. Real proteins, however, are not homogeneous: condensate-promoting interactions can be concentrated in specific parts of the sequence. Because translation progressively exposes different regions on the nascent chains of a polysome, we hypothesize that the large-scale arrangement of high-affinity regions should be the primary determinant of CTC.

To identify a minimal set of architectures relevant for CTC, we analyzed predicted LLPS-propensity profiles of condensate-associated proteins from the CD-CODE database [29] using catGRANULE 2.0 [30]. The resulting LLPS propensity profiles motivated us to model five distinct and biologically meaningful protein architectures to allow clear comparison based on the arrangement of high-affinity regions

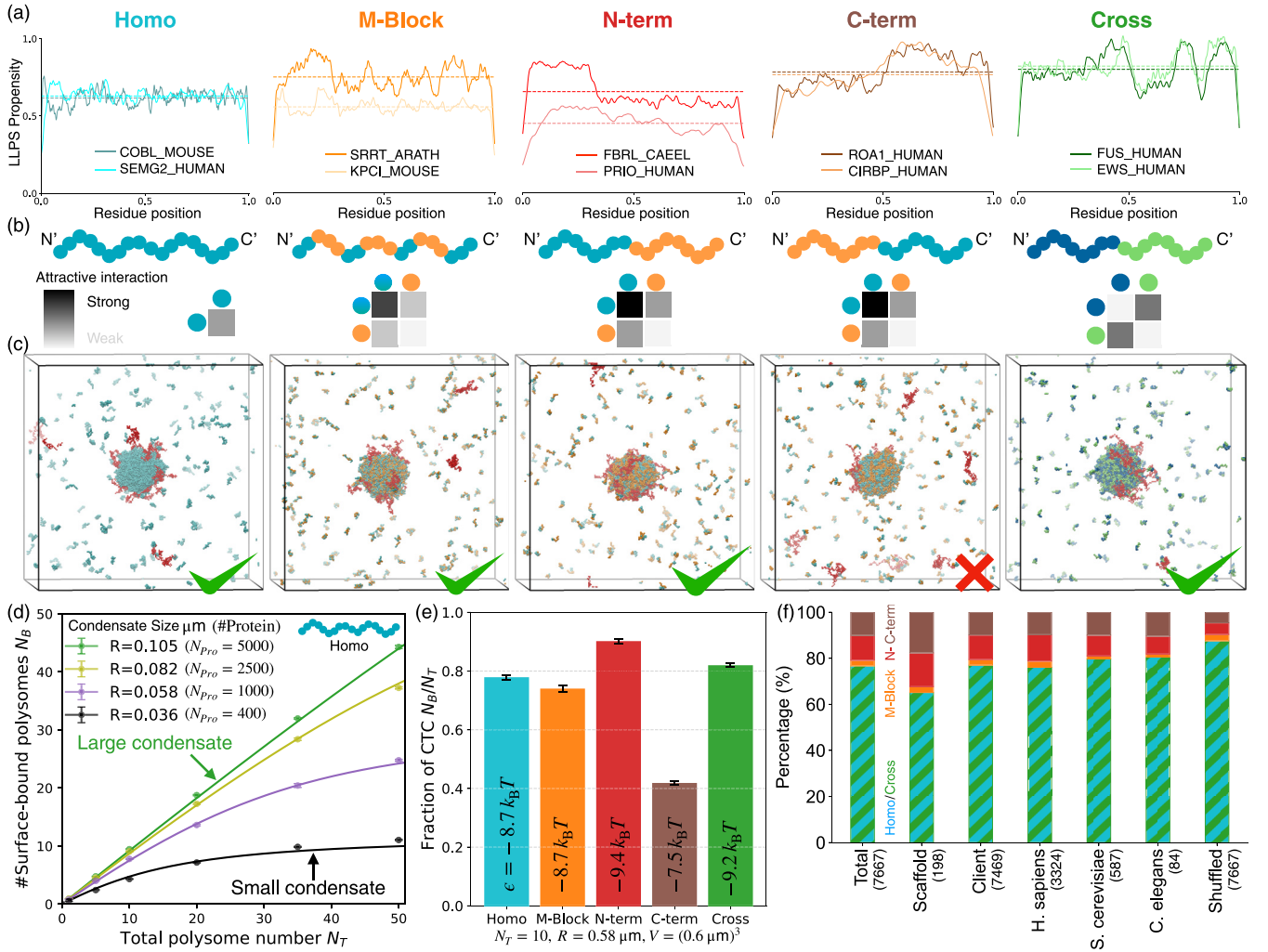


FIG. 2. Protein architecture influences the extent of cotranslational condensation. (a) Predicted LLPS propensity profiles along the sequence of representative proteins from five distinct architecture classes, see SM [24]. Regions exceeding the average LLPS propensity (dashed line) indicate high-affinity regions for that protein. We note that the Cross examples are annotated by experimental results [31] because based on LLPS propensity we cannot distinguish between Homo and Cross architectures. (b) Schematics for the architectures with interaction legends shown below; darker shading indicates higher-affinity interactions between regions. (c) Simulation snapshots showing the spatial distribution of polysomes and proteins for each architecture. All classes except C-term show substantial CTC. Simulation conditions are as in Fig. 1(d) and 1(e). See (d) and (e) and, see SM [24] for quantification and Movies II–VI for simulation trajectories shown in (c), see SM [24]. (d) Surface-bound polysome number N_B versus total polysome number N_T (Homo architecture; see SM [24] for others). Data points represent mean values from 10 independent simulations, where the error bars show the standard error. Different colored points show different condensate sizes (measured without polysomes). The curves show the global fit to a Langmuir adsorption model Eq. (2). N_B plateaus for smaller condensates because the surface becomes saturated. N_B increases linearly for larger condensates, reflecting an unsaturated surface. (e) Fraction of surface-bound polysome (fraction of CTC $f = N_B/N_T$) for different architectures with a medium-sized condensate ($R = 0.058 \mu m$). N-term and Cross architecture show strong CTC and C-term shows the weakest. The extracted binding energies for each architecture are printed on the bars. Data shown for (c)–(e) are results from Sparse polysomes; see SM [24] for all other setups. (f) Distribution of protein architectures in the CD-CODE database ($N = 7667$) [29]. Scaffold proteins exhibit a higher percentage of N-/C-term architectures. For details of the classification, additional analysis and comparison to random shuffled control dataset see SM [24].

(regions with above-average LLPS propensity); see SM [24] for architecture distributions. Representative LLPS profiles [5,31] for each architecture are shown in Fig. 2(a):

- (1) *Homo*: Interaction regions are evenly distributed along the sequence.
- (2) *M-Block*: Multiple high-affinity blocks alternate with low-affinity ones.
- (3) *N-term*: High-affinity regions are concentrated near the N terminus.

- (4) *C-term*: High-affinity regions are concentrated near the C terminus.

- (5) *Cross*: The highest-affinity interactions occur between N-terminal:C-terminal regions.

B. Protein architecture dictates cotranslational condensation

To compare their CTC behavior, we constructed coarse-grained bead-spring models for each architecture [Fig. 2(b)].

Interaction strengths were calibrated to yield approximately equal saturation concentrations ($\sim 1 \mu\text{M}$) across all architectures, ensuring that observed differences in CTC stem from architecture rather than phase-separation driving forces, see SM [24]. Notably, N-term and C-term are mirror images; while indistinguishable for phase separation, they differ in which part of the protein is displayed in the nascent chains of their polysome.

Figure 2(c) shows that different architectures lead to different degrees of CTC. We quantified this by fitting the number of colocalized (surface-bound) Sparse polysomes N_B to a Langmuir adsorption model on a spherical surface with a finite reservoir and an ideal-chain unbound state, see SM [24]. The corresponding free energy in units of $k_B T$ is

$$F = (\epsilon + 1)N_B + N_B \ln \frac{N_B}{N_S} + (N_S - N_B) \ln \left(1 - \frac{N_B}{N_S}\right) + N_U \ln \frac{v N_U}{V}, \quad (1)$$

where N_B is the number of bound polysomes, ϵ is the corresponding binding energy, N_S is the maximum number of polysomes that can fit on a condensate surface ($N_S = 4\pi R^2/\sigma$ with condensate radius R , and σ is the polysome binding area), N_U is the number of unbound polysomes in the dilute phase, v is the volume of a polysome, and V is the dilute phase volume (finite reservoir). Note $N_T = N_B + N_U = \text{const.}$ At equilibrium, minimizing the free energy with respect to N_B yields

$$N_B = \frac{1}{2} \left(N_T + \frac{4\pi R^2}{\sigma} + \frac{V}{v} e^\epsilon - \sqrt{\left(N_T + \frac{4\pi R^2}{\sigma} + \frac{V}{v} e^\epsilon \right)^2 - 4N_T \frac{4\pi R^2}{\sigma}} \right). \quad (2)$$

For each protein architecture, we globally fit N_B from simulations across different N_T and R to extract ϵ and σ as phenomenological adsorption parameters, with the aims of comparing architectures in a system-size independent manner and parametrizing our multiscale model. The adsorption model agrees well with simulations across different condensate sizes (shows little curvature dependence, see SM [24]) for each architecture [Fig. 2(d) and, see SM [24]]. The model also clarifies how condensate size affect CTC: For smaller condensates, N_B plateaus at moderate N_T , indicating surface saturation. In contrast, larger condensates provide more available binding sites and therefore favor CTC. Larger condensates are also more representative of the cellular environment, where we expect the surface is far from saturation.

The σ values are similar across the architectures thus the ϵ values are the primary drivers of differences in CTC ability. Therefore, we report the fraction of CTC for each architecture with ϵ indicated in Fig. 2(e). Among the five architectures, N-term and Cross exhibits the strongest CTC, as all the high-affinity regions are fully exposed at tips of the polysome branches. In contrast, C-term shows weak CTC because the high-affinity regions are only exhibited by a few nearly completed nascent chains.

Finally, Fig. 2(f) shows the architecture distributions for the condensate-associated proteins, additionally with this broken down into scaffold and client as well as multiple common species. Most condensate-associated proteins exhibit Homo, M-Block, N-term, or Cross architectures, indicating that architectures favorable for CTC are common. The last bar in Fig. 2(f) shows that shuffling the proteins in the CD-CODE database, see SM [24] rarely yields proteins that are classified as N- or C-term architectures, highlighting a potential selective bias for N- and C-term architectures. This bias could be more pronounced for scaffold proteins. Protein classifications for the full dataset are provided in tables of SM [24].

C. Dense polysomes stabilize small condensate

Polysomes have more protein interaction regions through their multiple nascent chains than a single protein, giving them a disproportionate influence on the phase diagram. This effect is amplified in Dense polysomes with more nascent chains. However, the fraction of proteins present as nascent chains in polysomes is less than 0.1% of the total protein pool [27]. We therefore asked whether this disproportionate influence can overcome their marginal concentration.

The impact of polysomes on the phase diagram is quantified by the change of c^{Dilute} , the concentration of the protein in the bulk phase outside the condensate, with increasing polysome number. As shown in Figs. 3(a) and 3(b), Sparse polysomes do not alter c^{Dilute} for condensates of any size. In contrast, Dense polysomes promote phase separation (lowering c^{Dilute}) for small condensates. Large condensates are unaffected. We note that c^{Dilute} is condensate-size dependent due to surface tension [32], distinguishing it from the binodal of an infinite system. All architectures behave similarly; see SM [24] for further discussion. Since biologically relevant condensates are typically larger than 100 nm, our results indicate that binodals measured experimentally reflect the underlying protein phase behavior and can safely be interpreted without considering polysomes.

IV. KINETICS OF COTRANSLATIONAL CONDENSATION

Polysomes have finite lifetimes, raising the question of whether CTC, even if thermodynamically favored, can occur quickly enough. We examine if this can happen through two routes: either condensates nucleate directly on polysomes, or polysomes diffuse to existing condensates.

A. Dense polysomes nucleate new condensates

To investigate nucleation on polysomes, we simulated condensate formation with one polysome, see SM [24]. Figures 3(c) and 3(d) shows the size of the largest cluster as a function of time for 100 independent simulations. Random fluctuations lead to the formation of a small cluster which grows into an equilibrated condensate ($\sim 60\%$ of the total proteins). The polysome may (red) or may not (blue) be colocalized with the nucleation and growth of condensates. Sparse polysomes are scarcely colocalized with a growing condensate; see Fig. 3(c). Dense polysomes display a strong correlation with nucleation of condensates.

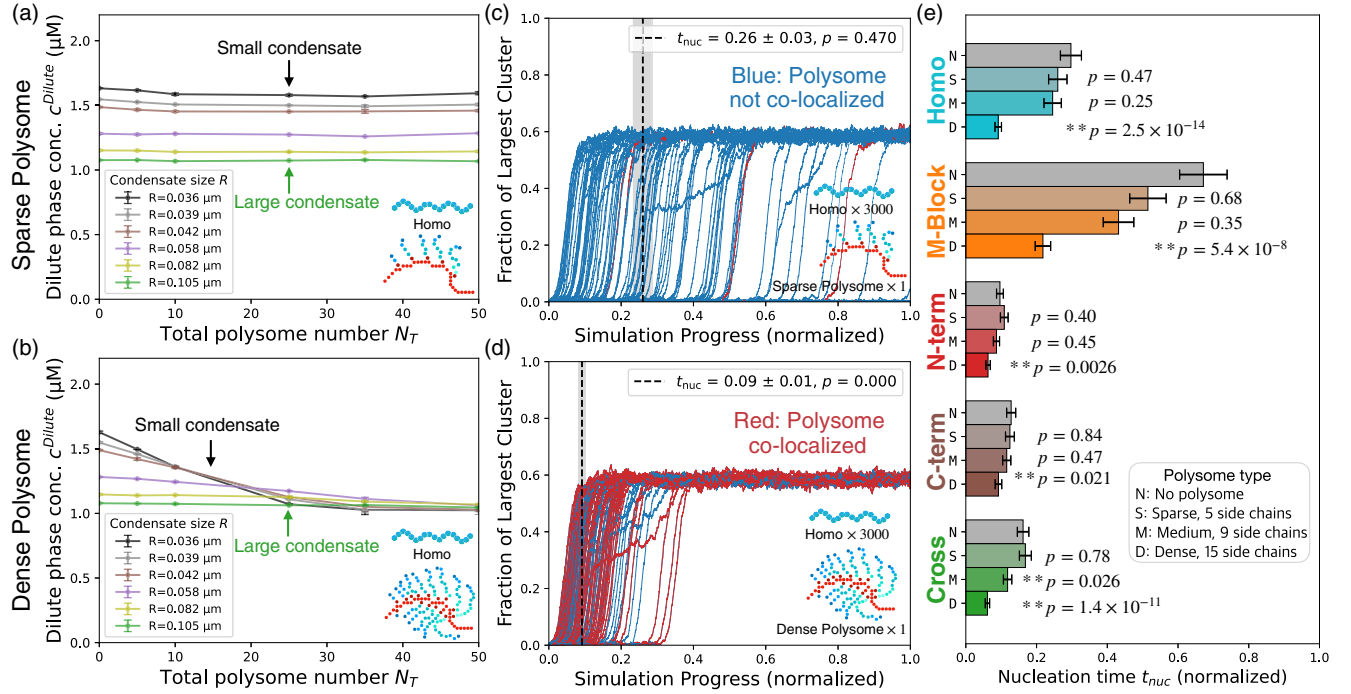


FIG. 3. Dense polysomes impact phase behavior and serve as nucleation centers. (a) and (b) Dilute phase concentration c^{Dilute} versus numbers of polysomes N_T for different condensate sizes R (measured without polysomes). The size dependence of dilute concentration is consistent with surface tension effects (Kelvin equation), see SM [24]. Error bars denote standard errors. Data shown are for Homo; see SM [24] for other architectures and polysome sizes. (a) Sparse polysomes have negligible impact on condensate thermodynamics, seen as no slope with respect to polysome number. (b) Dense polysomes perturb the thermodynamics of small condensates (black) significantly, with this perturbation decreasing rapidly with condensate size (yellow and green). (c) and (d) Fraction of proteins in the largest cluster (condensate) with 3000 proteins and one polysome. Each curve corresponds to an independent simulation (100 replicas). (c) Sparse polysome; (d) Dense polysome. The nucleation time is defined as the last point before the largest cluster reaches 5% of total proteins, and the plateau at $\sim 60\%$ corresponds to the equilibrium condensate. Red and blue indicate colocalization and delocalization with the cluster (shown for Homo; see SM [24] for simulations without polysomes and with other architectures). Dashed lines mark the mean nucleation time, with standard error in gray. These results show that Dense polysomes accelerate condensate nucleation by serving as nucleation centers. See SM [24] for nucleation simulation trajectories. (e) Summary of the nucleation time for different protein architectures with error bars indicating standard errors. The statistical significance p values of different polysome sizes by comparing to no polysome case are labeled, $p < 0.05$ means the two cases are statistically significantly different. See SM [24] for detailed method and analysis.

We define the nucleation time (t_{nuc}) as the average of the times when individual simulations reach a cluster size threshold (5%), see SM [24]. We quantify the impact from polysomes by changes in $\langle t_{\text{nuc}} \rangle$, see SM [24]. For comparison, simulations without a polysome have $\langle t_{\text{nuc}} \rangle = 0.30 \pm 0.03$.

A Dense polysome reduces $\langle t_{\text{nuc}} \rangle$ by a factor of three (0.09 ± 0.01 , $p = 2.5 \times 10^{-14}$). In contrast, the effect of a Sparse polysome on $\langle t_{\text{nuc}} \rangle$ is not statistically significant (0.26 ± 0.03 , $p = 0.470$). This is consistent with our observation that Dense polysomes colocalize with nucleation events, whereas Sparse polysomes do not. Moreover, the formation of new condensates is limited by the stability of small clusters. As shown in Figs. 3(a) and 3(b), Dense polysomes stabilize condensates in a size-dependent manner, with the effect strongest for the smallest condensates, whereas Sparse polysomes show no measurable stabilization.

Figure 3(e) shows the impact of the protein architectures on nucleation from the static structure of a polysome. For the conditions we studied, we observed enhanced nucleation from Dense polysomes of Homo, M-Block, and Cross architectures but not for N-term or C-term. The many nascent chains of

Dense polysomes lower the nucleation barrier and accelerate condensate formation by stabilizing otherwise unstable small condensates.

In addition to this static multivalency effect, active translation could further promote nucleation through a kinetic local-source mechanism. A translating polysome continuously releases newly synthesized proteins into its immediate surroundings, creating a locally elevated concentration near the polysome even when the bulk concentration remains below the level required for rapid nucleation. This local concentration can increase the probability that a condensate nucleates on or near the polysome.

B. Polysomes diffuse to existing condensates

For Short or Sparse polysomes (weaker nucleators, faster diffusion), we anticipate CTC will primarily occur through polysomes diffusing to existing condensates. This is limited by two factors: (1) CTC thermodynamics—polysome-condensate association versus translational entropy—and (2) CTC kinetics—polysome diffusion length scale versus the

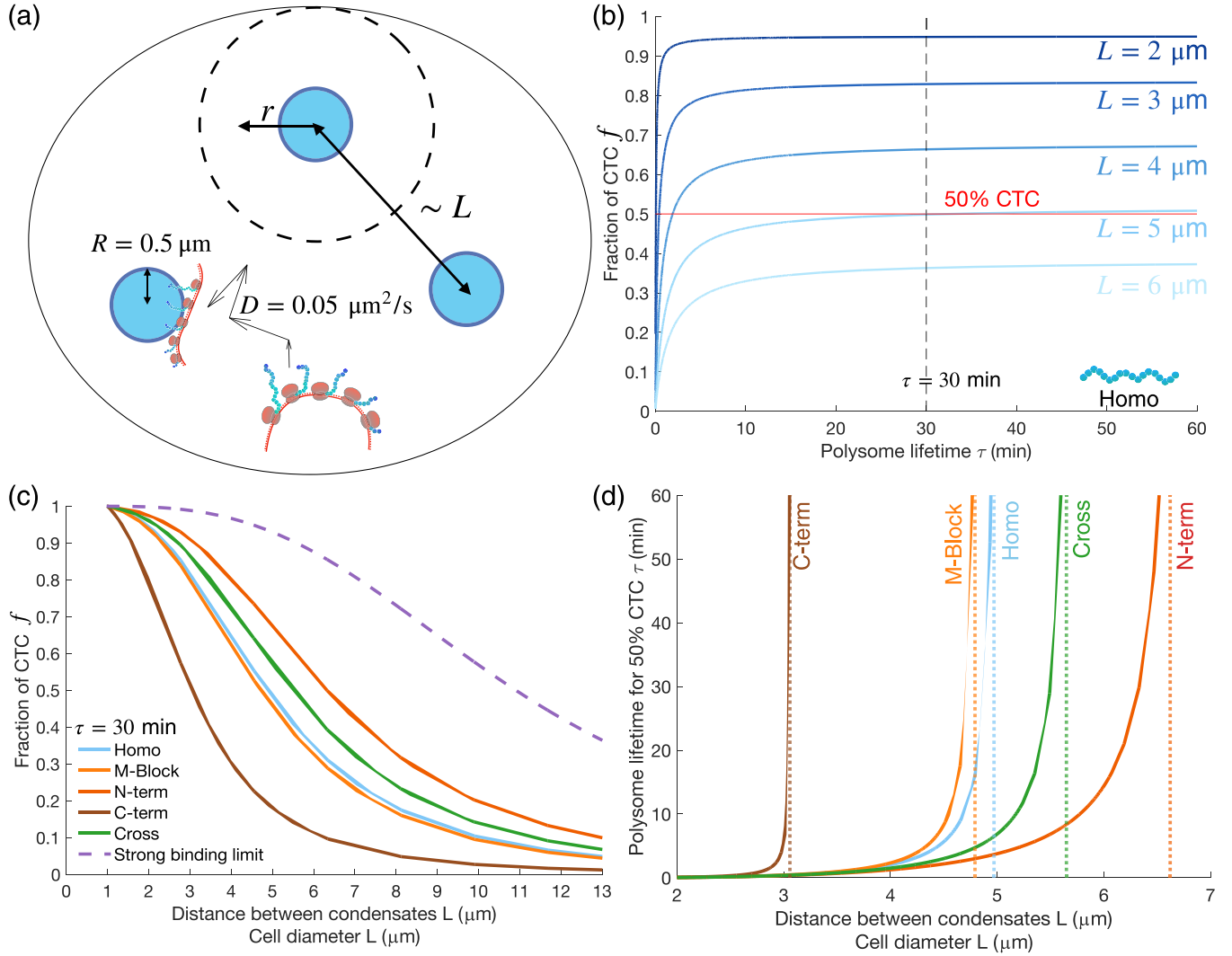


FIG. 4. Combined dynamics and thermodynamics of cotranslational condensation. (a) Cartoon of reaction-diffusion model. Typically, a cell contains multiple condensates of the same kind, where L describes the average distance between condensates. This reduces the diffusion length scale so we model from a condensate to the midpoint between neighboring condensates with a spherical symmetry. The thermodynamics of binding at the condensate surface are chosen to match the Langmuir model Eq. (4) and see SM [24] for details. (b) Fraction of CTC f versus polysome lifetime τ for Sparse polysome with Homo architecture. Different lines denote different distances between condensates L . This suggests that for a moderate spacing ($L \sim 5 \mu\text{m}$), a medium-lifetime polysome ($\tau \sim 30 \text{ min}$) can reach $\sim 50\%$ CTC. (c) Fraction of CTC f versus distance L for $\tau = 30 \text{ min}$ for all architectures (different colors). For small L , most polysomes are bound to the surface. For medium L , f is limited by the thermodynamics of the architecture. For large L , f is limited by the kinetics. Binding energies are extracted from the Sparse polysome setup. Purple dashed curve denotes the strong binding limit ($\epsilon \ll -1 k_B T$), indicating the extension of relevant CTC spacial range with stronger binding (e.g., larger polysomes); see SM [24] for details. (d) Polysome lifetime required for 50% CTC. There is a maximal value of L beyond which 50% CTC is no longer possible. This is set by the thermodynamics of binding, hence each architecture has its own maximal value of L^* (dotted lines, determined by $\tau = 120 \text{ min}$).

distance to a condensate. The characteristic length of the system, L , can be interpreted in two ways: if there is one condensate in a cell, then it is the size of the cell; if there are multiple condensates in a cell, it is the average distance between condensates; see Fig. 4(a). This highlights the benefits of having multiple condensates by decreasing the relevant length of the system [33].

Diffusion and disassembly of polysomes are modeled by a steady-state reaction-diffusion equation with spherical symmetry for the region outside the condensate of radius R :

$$\dot{c}(r) = k^+ - \tau^{-1}c + D\nabla^2 c(r) = 0, \quad (3)$$

where $c(r)$ is the polysome concentration at radius r , $k^+ = N_T V^{-1} \tau^{-1}$ is the polysome assembly rate yielding a fixed number of polysomes N_T , τ is the polysome's lifetime (short: $\tau = 5 \text{ min}$, long: $\tau = 30 \text{ min}$ [34]), and $D = 0.05 \mu\text{m}^2/\text{s}$ is the diffusion coefficient of the polysome [35–38].

We imposed an absorbing boundary condition at the condensate surface $r = R = 0.5 \mu\text{m}$ governed by the Langmuir adsorption model (see SM [24] for derivation),

$$c(R) = \frac{N_B}{N_S - N_B} \frac{e^\epsilon}{v}. \quad (4)$$

Here ϵ is the binding energy obtained from the coarse-grained simulations for each architecture with Sparse polysomes; see Eq. (1) and [24]. The polysomes bound to condensates, N_B , also have finite lifetimes τ , giving the additional condition,

$$\dot{N}_B = J - \tau^{-1}N_B = 0, \quad (5)$$

where $J = 4\pi R^2 D \frac{dc}{dr}|_{r=R}$ is the net flux.

We imposed a reflective boundary condition at half the characteristic length, $r = L/2$,

$$\left. \frac{dc}{dr} \right|_{r=L/2} = 0. \quad (6)$$

If only one condensate exists, this boundary represents the cell membrane. For multiple condensates, it represents the symmetric point between neighboring condensates where the net flux vanishes.

The resulting fraction of CTC is defined as the fraction of polysomes bound to the surface $f = N_B/N_T$, see SM [24]. In Fig. 4(b) we show how the fraction of CTC depends on τ and L . When lengths are small (small cell or closely spaced condensates), even short-lived polysomes achieve high CTC ($L = 3 \mu\text{m}$, $\tau = 5 \text{ min} \rightarrow f = 80\%$). At intermediate spacing, a longer lifetime is required to reach $f \simeq 50\%$ CTC ($L = 5 \mu\text{m}$, $\tau = 30 \text{ min}$). At large separations, binding of polysomes to condensates is unlikely such that there is no lifetime long enough to achieve a high fraction of CTC ($L = 6 \mu\text{m}$, $\tau = 60 \text{ min} \rightarrow f = 30\%$).

Due to differences in binding energies ϵ , different architectures yield varying levels of CTC at a fixed lifetime. Here we chose $\tau = 30 \text{ min}$ as a reference for a typical lifetime of mRNA in yeast [34,39]. Figure 4(c) shows how f depends on the separation between condensates for different architectures. As expected from the analysis of ϵ [Fig. 2(e)], N-term produce the strongest CTC even for moderate L , while C-term suppresses CTC for all but the shortest distances between condensates.

To quantify the max separation between condensates where CTC can occur, we define the critical characteristic length L^* beyond which 50% CTC is no longer achievable within a polysome lifetime of $\tau = 120 \text{ min}$. As shown in Fig. 4(d), each sequence has a distinct L^* , beyond which the required lifetime diverges. For example, N-term maintain efficient CTC up to $L^* \approx 6.5 \mu\text{m}$, whereas C-term loses CTC potential beyond $L^* \approx 3 \mu\text{m}$.

CTC can occur through diffusion of polysomes to condensate surfaces with moderate separation between condensates and average polysome lifetimes. The critical characteristic length L^* is comparable to the size of small organisms such as yeast [11,27] and condensate separations seen in many cells [1,40–43]. We note that smaller polysomes can diffuse faster to existing condensates than large polysomes, allowing CTC with shorter lifetime of polysomes. Additionally, stronger polysome associations (lower saturation concentration, denser polysomes, longer mRNA/protein, etc.) allow CTC at longer length scales. As shown in Fig. 4(c), the strong binding limit ($\epsilon \ll -1 k_B T$) yields a theoretical maximum of $L \sim 11 \mu\text{m}$, indicating the CTC spatial range could be extended beyond the size of most cells, see SM [24].

V. FUNCTIONAL IMPLICATIONS OF COTRANSLATIONAL CONDENSATION

CTC facilitates efficient posttranslational modifications

Biomolecular condensates can act as active reaction crucibles that spatially organize and regulate biochemical processes [2,44–48]. One possible functional consequence of CTC is that it localizes newly synthesized proteins to condensates where posttranslational modification (PTM) machinery is enriched and can thus promptly modify synthesized proteins.

To illustrate this idea, we consider a minimal model in which an immature protein species A is converted into its functional form, species B , by an enzymatic reaction localized inside the condensate [Fig. 5(a)]. This reaction may be viewed as a generic PTM process, such as phosphorylation or SUMOylation.

In the absence of CTC ($f = 0$), illustrated in the upper half of Fig. 5(a), protein A is synthesized and degraded throughout the cytoplasm (Phase II: $R < r < L/2$, where L is the characteristic length: cell diameter or distance between condensates) and converted into B only after diffusing into the condensate (Phase I: $0 < r < R$). With full CTC ($f = 1$), illustrated in the lower half of Fig. 5(a), polysomes are localized to the condensate surface, so protein A is synthesized directly at the interface and can be modified immediately. The steady-state reaction-diffusion equations are

Condensate ($0 < r < R$):

$$\dot{c}_A^I = D^I \nabla^2 c_A^I - k c_A^I = 0, \quad (7a)$$

$$\dot{c}_B^I = k c_A^I + D^I \nabla^2 c_B^I = 0, \quad (7b)$$

Cytoplasm ($R < r < L/2$):

$$\dot{c}_A^{II} = (1-f) \frac{\lambda N_T}{V^{II}} + D^{II} \nabla^2 c_A^{II} - \tau^{-1} c_A^{II} = 0, \quad (8a)$$

$$\dot{c}_B^{II} = D^{II} \nabla^2 c_B^{II} - \tau^{-1} c_B^{II} = 0. \quad (8b)$$

Here c is the radial protein concentration, with superscripts I and II denoting the dense and dilute phases and subscripts A and B denoting the unmodified and modified species; $D^I = 1 \mu\text{m}^2/\text{s}$ and $D^{II} = 10 \mu\text{m}^2/\text{s}$ are the diffusion coefficients [49,50], k is the PTM reaction rate [27,51], $\tau = 24 \text{ h}$ is the protein lifetime [27,52], f is the fraction of CTC, and λN_T is the total translation rate of protein A. All parameter choices are physiologically realistic and chosen to be representative or conservative rather than optimized to maximize the effect.

At the condensate interface, we impose a protein partition factor boundary condition

$$c^I(R) = P c^{II}(R), \quad (9)$$

where $P = 1300$ is extracted from our simulations and is consistent with experimental measurements [53], and a flux balance boundary condition

$$f \lambda N_T + J_{\text{out},A} + J_{\text{in},A} = 0, \quad (10a)$$

$$J_{\text{out},B} + J_{\text{in},B} = 0, \quad (10b)$$

where $f \lambda N_T$ is the synthesis of unmodified protein A at the surface, $J_{\text{out}} = -4\pi R^2 D^{II} \frac{dc^{II}}{dr}|_{r=R}$ is the outward flow just outside the condensate, and $J_{\text{in}} = 4\pi R^2 D^I \frac{dc^I}{dr}|_{r=R}$ is the inward

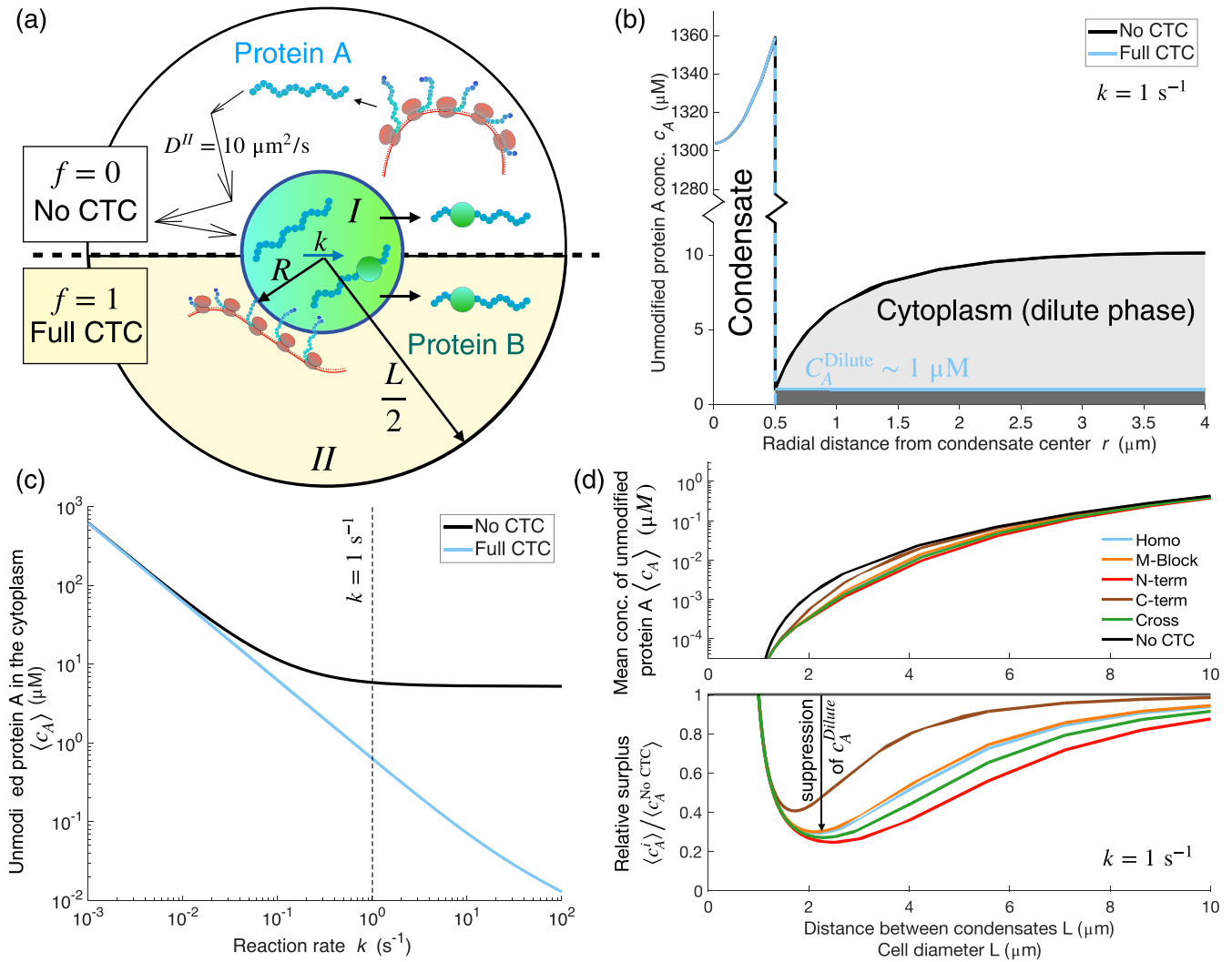


FIG. 5. CTC facilitates protein posttranslational modifications. (a) Model system of posttranslational protein modifications in condensates, $A \rightarrow B$. Top half $f = 0$. Translation occurs without CTC; the unmodified protein A has to diffuse in the cytoplasm to locate the condensate before it can be modified. Bottom half $f = 1$. Translation occurs with CTC; protein A is synthesized directly at the surface of the condensate and is immediately ready for modification. (b) Concentration profile of unmodified protein A for two cases. With no CTC $f = 0$ (black), the concentration profile shows a large accumulation of material that is diffusing to the condensate. We note the break in the y axis to accommodate the visualization of the condensate. With full CTC $f = 1$ (blue), the concentration profile outside the condensate is low and flat. Data shown for (b) and (c) correspond to condensates of size $R = 0.5 \mu\text{m}$ and distances between condensates of $L = 8 \mu\text{m}$. (c) The mean concentration of A in the cytoplasm $\langle c_A \rangle$ as a function of PTM reaction rate. When the reaction rate is higher, diffusion can be the limiting step for catalyzing PTMs. This is realized as a plateau in $\langle c_A \rangle$ without CTC where synthesized proteins must diffuse to condensates (black). With CTC $\langle c_A \rangle$ does not plateau because it does not need to diffuse to condensates (blue). Dashed line denotes $k = 1 \text{ s}^{-1}$, the parameter used for (b) and (d). (d) Unifying the PTM dynamics with the combined dynamics and thermodynamics of CTC. Top: Mean concentration of A, no CTC $f = 0$ (black) and all five architectures $0 < f^i(L) < 1$ (colored), where $f^i(L)$ is the emerging fraction of CTC for each architecture i and distance between condensates L [Fig. 4(c), Sparse polysomes]. Bottom: Degree of impact from CTC with different architectures. The relative surplus is defined as the mean concentration in the cytoplasm with different architectures compared to the null case of no CTC. The suppression of A is the distance from unity. Architectures with greater CTC propensity achieve stronger suppression and maintain this effect across a broader range of condensate spacings.

flow just inside the condensate. Additionally, we impose regular behavior at the center of the condensate $\frac{dc^d}{dr}|_{r=0} = 0$ and, as before, reflective boundary condition at the midpoint between condensates $\frac{dc^H}{dr}|_{r=L/2} = 0$.

To quantify the functional impact of CTC, we focus on the accumulation of the unmodified intermediate, pro-

tein A, as our primary metric. Excess A is inefficient from a resource-allocation perspective and may also be undesirable if A preforms an unneeded function or is aggregation prone. We first compare two limiting cases: no CTC ($f = 0$) and full CTC ($f = 1$). Figure 5(b) shows the corresponding concentration profiles. Without CTC, A accumulates in the cytoplasm before diffusing into the condensate for modification.

With CTC, much less unmodified A accumulates outside the condensate because synthesis occurs directly at the condensate surface. Figure 5(c) shows the mean concentration of A in the dilute phase as a function of the PTM reaction rate k . The reduction in unmodified A is most pronounced when modification is fast compared to diffusion ($k > D^H/(L/2)^2$). In this regime, protein A is synthesized at the condensate surface and can be modified promptly, enabling coupling between translation and PTM without requiring direct enzyme association with the polysome. This has an analogy to compartmentalizing multistep reactions to reduce intermediate accumulation [54,55].

We next considered the intermediate regime $0 < f < 1$, in which the fraction of CTC f is set by both the architecture-dependent adsorption and diffusion. Using the values of f obtained from the polysome diffusion model [Fig. 4(c)], we computed the mean dilute phase concentration $\langle c_A \rangle$. As shown in the top panel of Fig. 5(d), $\langle c_A \rangle$ increases with the characteristic length L because translation is less effectively localized to condensates when they are farther apart.

To isolate the impact of including CTC, we examine the relative surplus of unmodified protein, $\langle c_A \rangle / \langle c_A^{\text{No CTC}} \rangle$. The bottom panel of Fig. 5(d) shows that this quantity is minimized at intermediate condensate spacing. Architectures with stronger CTC maintain a lower dilute phase concentration of unmodified A over a broader range of condensate separations. Thus, protein architecture affects not only whether CTC occurs, but also how robustly it suppresses unmodified intermediates across cellular conditions.

VI. OUTLOOK: INTERPRETING PROTEIN ORGANIZATION AND EVOLUTION

Our study establishes CoTranslational Condensation (CTC) as a general mechanism that links translation to phase separation. The central feature is that polysomes, by virtue of their many nascent chains, can be localized with condensates. Our coarse-grained simulations are consistent with this idea in that polysome size, ribosome density, and proteins' propensity for phase separation all increase the strength of this adsorption. Importantly, we demonstrated that protein domain architecture has a large impact on CTC. Stronger affinity contrast will yield stronger CTC contrast between protein architectures, e.g., concentrating affinity towards the N or C terminal lead to stronger or weaker CTC.

Additionally, our bioinformatic analysis suggests that most condensate-associated proteins have architectures favorable for CTC; in fact, the most and least favorable architectures, N-term and C-term, are overrepresented relative to expectations from random-shuffled sequences. We include tables in Supplemental Material of the predicted architectures as a community resource for experimental validation, see SM [24].

Using multiscale modeling, we see that CTC occurs under realistic parameters. Coarse-grained simulations of polysomes for proteins that phase separate with biologically relevant energy scales (saturation concentration $\sim 1 \mu\text{M}$) strongly associate with their respective condensates ($\sim -8 k_B T$). Using these binding strengths in reaction-diffusion models, we extrapolate to systems with biologically relevant length scales

(condensates diameter $\sim 1 \mu\text{m}$, cell diameter $\sim 10 \mu\text{m}$) and timescales (polysome diffusion coefficient $\sim 0.05 \mu\text{m}^2/\text{s}$, lifetimes $\sim 30 \text{ min}$).

Our work shows that polysomes can associate with condensates either by diffusion or by acting as nucleation centers. In particular, Dense polysomes lower the nucleation barrier and can promote the formation of multiple condensates of the same type, a cellular feature that is consistent with this mechanism.

CTC could offer physiological advantages. Often enzymes modify proteins to provide them with the desired biological function after translation. We have demonstrated that CTC can accelerate such posttranslational modifications, thereby minimizing intermediates and enhancing signaling responsiveness. Additionally, CTC could lead to cotranslational modifications (modifications that occur during translation). CTC may be especially important in pathways requiring rapid feedback, such as immune response or stress dynamics.

Cotranslational folding could also be impacted by CTC for good or bad. Folded protein structures depend on the local chemical environment [56,57], the presence of chaperones [58], and translational pauses [59]. Cotranslational folding has been shown to assist all three of these [60]. CTC could influence each of these aspects as well by bringing translation to condensates that have distinct chemical environments [61,62], concentrate chaperones [63,64], and alter the local pool of tRNAs [65].

A previous study has focused on proteins that form homo-oligomers with themselves. They showed that the oligomerization regions of the proteins are preferentially located at the C terminal, presumably to avoid premature self-association and aberrant aggregation during translation [66]. Our bioinformatic analysis suggests that proteins that are associated with condensates shows the opposite trend where architectures favor cotranslational interactions. This suggests different evolutionary pressures between oligomerization proteins and condensate proteins [67]. Additionally, similar proteins can belong to different architecture classes. An example of this is the FET family of proteins, where the prion-like domains can be located at either terminus [31].

We propose that CTC represents a robust and versatile scenario along which protein function, folding fidelity, and spatial organization could be regulated. The architectural classes defined in this work offer a conceptual framework for predicting which proteins are good candidates for CTC. This framework may also prove useful for informing the rational design of synthetic systems, either to harness CTC for enhanced efficiency or to avoid it when premature interactions are detrimental.

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DATA AVAILABILITY

All raw and processed data necessary to reproduce the results of this study are available in a Zenodo data repository [68]. The source code for the polymer lattice simulations, together with documentation, is available in a GitHub repository [13] in the folder “Polymer lattice simulation” versions “G_6.11.f90” for all the non-nucleation simulations and “G_6.11_nuc.f90” for the nucleation simulations.

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- discussion that support the conclusions of the main text. Four types of Excel files are provided: (1) Best_CTC_Candidates.xlsx, listing predicted top CTC candidates; (2) All_proteins.xlsx, containing five sheets with protein architecture classifications; (3) All_proteins_shuffled.xlsx, contains shuffled sequences as control set; and (4) five species-specific Excel files, each containing architecture classifications for a single species. Ten movies (.mpg files) showing representative simulation trajectories of condensate formation, polysome-condensate association, polysome clustering, CTC with slab geometry, and condensate nucleation with and without CTC are included, which also includes Refs. [43,69,70].
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