

Entropic clustering of stickers induces aging in biocondensates

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Biomolecular condensates are cellular phase-separated droplets that usually exhibit a viscoelastic mechanical response, a behavior rationalized by modeling the complex molecules that make up a condensate as stickers and spacers, which assemble into a network-like structure. Condensates usually exhibit a solidification over a long period of time (days), a phenomenon described as aging. The emergence of such a long timescale of evolution from microscopic processes, as well as the associated microscopic reorganization leading to aging, remains mostly an open question. In this article, we explore the connection between the mechanical properties of the condensates and their microscopic structure. We propose a minimal model for the dynamics of stickers and spacers and show that entropy maximization of spacers leads to an attractive force between stickers. Our system displays a surprisingly slow relaxation toward equilibrium, reminiscent of glassy systems and consistent with the liquid-to-solid transition observed. To explain this behavior, we study the clustering dynamics of stickers and successfully explain the origin of glassy relaxation.

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I. INTRODUCTION

Liquid-liquid phase separation has emerged as a major organizing principle for the compartmentalization of cellular processes into membraneless organelles known as biomolecular condensates. Condensates are associated with various functions of the cell, although their precise role often remains elusive [1], to the point that it is not even clear whether some of them are functional, incidental, or pathological [2]. Similarly, little is known about the complete composition of condensates; however, one or several scaffolding components that drive the phase separation can usually be identified, including proteins, DNA [3,4], and RNA [5,6]. Despite their diversity, condensates also display common features. It is usually accepted that their formation requires weak multivalent interactions [7], mediated by disordered portions of proteins [8] or by RNA- or DNA-protein interactions [9]. Similarly, microrheology experiments suggest that biocondensates exhibit a general viscoelastic mechanical response [10,11]. This picture has been rationalized through the sticker and spacer model, which describes proteins as generic sequences of sticky (stickers) and nonsticky (spacers) regions [12]. The complex interactions that make up a condensate give rise to an emergent long-time transition to a solid-like state, usually described as aging [13,14]. This process has been associated with protein denaturation [15], amyloid formation [16], and, from a physiological perspective, neurodegenerative diseases

[17]. Current physical pictures of condensate aging either rely on the modeling of specific proteins' interaction, like β -sheet stacking [18], or do not model the microscopic dynamics of the components [19,20]. Yet aging seems to be a fairly general behavior, suggesting that its occurrence does not depend on specific compositional details. This aligns with experimental evidence of a disordered-to-order transition [21] or the formation of substructures [15,22], which collectively suggest that some of the features of this transition can be governed by a universal physical mechanism. A general microscopic picture explaining how large timescales (days or more) emerge from a collection of microscopic processes that typically occur on much shorter timescales (microseconds) is missing.

In this work, we use the sticker and spacer framework to model the microscopic structural rearrangement taking place in condensates and leading to aging. We do not investigate the phase separation process; instead, we consider the components of a droplet as a heterogeneous collection of localized, attractive regions (stickers) and longer, neutral regions (spacers). Stickers reversibly associate via noncovalent interactions, while spacers provide flexibility and connection between stickers, resulting in the formation of a percolating network. The ensuing mechanical behavior of this network is typical of an associative gel, characterized by a viscoelastic response to stress. At timescales much smaller than the sticker lifetime, the gel displays solid, elastic-like behavior due to the entropic elasticity of the spacers, resisting deformation. Conversely, over longer timescales, the reversible binding and unbinding dynamics of stickers enables the material to flow, displaying liquid-like characteristics. Homogeneous associative gels display a soft relaxation over a single characteristic timescale, directly related to the unbinding dynamics of the stickers [23]. In contrast, heterogeneous gels feature multiple coexisting timescales, each corresponding to a different sub-region within the system, and a complex relaxation behavior

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emerges from their superposition [24]. Strong heterogeneity results in a broad distribution of timescales, sometime heavy tailed. In these extreme cases, a portion of these timescales is arbitrarily large, and relaxation seemingly never ends, a phenomena typical of glasses and known as aging [25,26]. To investigate how aging can emerge from the collective rearrangement of the gel components, we model them as stickers and spacers, the former acting as diffusing particles that can bind to (and unbind from) the latter, which represent Gaussian polymers, possibly capturing intrinsically disordered regions of proteins or long RNA strands. Using a combination of analytical results and simulations, we show that an entropic Casimir-like force drives the clustering of stickers, reminiscent of substructures observed experimentally [3,15,27]. We find that collective rearrangement of the stickers induces a slowdown of the dynamics of the system. As a consequence, the relaxation toward equilibrium is surprisingly slow and reminiscent of the usual glass dynamics [28]. To explain our observations, we introduce a minimal model for the dynamics of clusters, which provide a scaling law for the dynamical slowing down. Finally, we compute the associated dynamic modulus of our system, which demonstrates the long-time solidification resulting from aging. Despite its simplicity, our model displays a rich phenomenology leading to glassy dynamics which includes the emergence of large timescales, ergodicity breaking, and aging. By using a minimal model for the emergence of soft glassy relaxation, we propose a fairly general driving mechanism for the aging of biocondensates.

II. RESULTS

A. Dynamics of stickers and spacers

We consider a situation in which the system is already demixed and focus on the dynamics of stickers and spacers. Spacers—corresponding to RNA or DNA strands or intrinsically disordered segments of proteins—are modeled here as linear Gaussian polymers. This description assumes a regime in which topological constraints and excluded volume interactions are negligible.

This minimal model ensures that the system remains analytically tractable and numerically accessible over long timescales, and it allows us to highlight the emergence of entropic attractive forces driving between stickers, even if their magnitude might be quantitatively modulated by steric repulsion in a more accurate description.

Stickers are modeled as diffusive particles that can transiently bind to spacers, forming reversible cross-links. Stickers may represent adhesive domains within a polymer or separate binding proteins. We model both cases similarly by simulating a single polymer while treating the surrounding environment, composed of other polymers and stickers, as an effective bath of mobile particles that diffuse freely when unbound but become immobilized when bound to the simulated polymer. Specifically, we focus on a single polymer chain interacting with multiple linkers. We define a “polymer strand” as any segment of the chain located between two consecutive binding sites. This dynamic for stickers reflects the formation

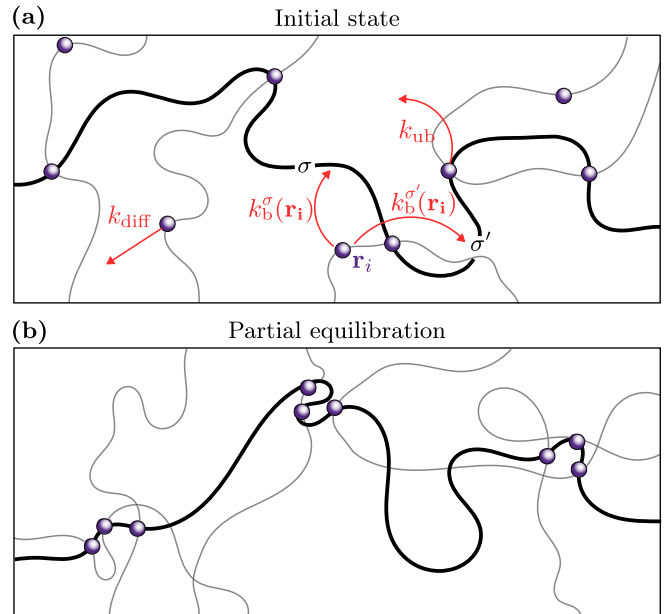


FIG. 1. Schematic representation of our sticker and spacer model. The disordered background potential is represented as a color coding, while stickers are represented as diffusing particles. We focus on the single polymer dynamics highlighted in black, while the other effective polymers are in gray. (a) represents the initial state in which stickers are homogeneously spread in space. The dynamics of stickers are also represented as small arrows: Stickers bound to one polymer can diffuse or bind to another, whereas those bound to two polymers create a cross-link and must unbind before diffusing further. (b) qualitatively represents a typical final state as predicted by our model.

of cross-links with other effective spacers that impair their diffusion and locally restrict polymer fluctuations, as shown in Fig. 1(a). Assuming that the dynamics of the one polymer simulated is representative of the others in the system, we are able to compute the viscoelastic response of such a polymer network.

While the diffusion dynamics of stickers may differ from that of free particles depending on their exact nature, we will show that the long-time evolution of the system is controlled by the binding and unbinding dynamics. As a result, we expect that variations in the diffusion properties will not significantly affect our results.

Here, we neglect the possibility that a sticker simultaneously interacts with other effective spacers. This may lead to a slight overestimation of the number of free diffusing stickers or an underestimation of their effective diffusion. The goal of this modeling is to describe the essential physical trade-off: Cross-linking lowers the system’s free energy but constrains its ability to rearrange.

To describe the dynamics of the stickers, we now consider the probability that the i th sticker is in position $\mathbf{r}_i$ at time t in the bound state with any polymer strand, denoted by $p_b(\mathbf{r}_i, t)$. Similarly, we write the probability that it is unbound as $p_{ub}(\mathbf{r}_i, t)$. Given the previously introduced dynamics, the time evolution of these two probability distributions is

governed by the two coupled master equations:

$$\begin{aligned}\partial_t p_b(\mathbf{r}_i, t) &= \sum_{\sigma} k_b^{\sigma}(\mathbf{r}_i) p_{ub}(\mathbf{r}_i, t) - k_{ub} p_b(\mathbf{r}_i, t), \\ \partial_t p_{ub}(\mathbf{r}_i, t) &= k_{ub} p_b(\mathbf{r}_i, t) - \sum_{\sigma} k_b^{\sigma}(\mathbf{r}_i, \ell) p_{ub}(\mathbf{r}_i, t) \\ &\quad + D \nabla^2 p_{ub}(\mathbf{r}_i, t),\end{aligned}\quad (1)$$

where $k_b^{\sigma}(\mathbf{r}_i)$ is the binding rate of the linker located in $\mathbf{r}_i$ with polymer strand σ . We first write the unbinding rate using a single energy scale under the Kramers approximation:

$$k_{ub} = \frac{1}{\tau_0} e^{-\beta E_b}, \quad (2)$$

where $\beta = 1/(k_B T)$ is the inverse temperature, E_b is the binding energy scale, and τ_0 is a timescale associated with the microscopic escape process. While the complexity of real proteins' interaction should lead to a distribution of binding energies, we show here that this assumption is not necessary for the system to display a glassy dynamics and address the effect of a more complex model in Sec. III.

Concerning the binding rate, we assume that polymers have time to equilibrate between two binding and unbinding events. As a consequence, we represent the polymers through their equilibrium spatial probability distribution. We show in Supplemental Material [29] that the probability for a given conformation of the polymer to meet a sticker located at $\mathbf{r}$ at a lineic position ℓ is given by

$$P_{\text{meet}}(\mathbf{r}) = \int d\ell e^{S_b(\mathbf{r}, \ell) - S_{ub}} b^2, \quad (3)$$

where S_b and S_{ub} correspond to the entropy of the polymer strand when bound and unbound to the sticker, respectively. b is the typical size of a sticker, taken to be equal to 1 in the rest of the paper. Our approximation of fast polymer conformational exploration means that the limiting timescale is the binding time. Thus, we write the binding rate of the sticker to the polymer as

$$k_b(\mathbf{r}) = 1/\tau_0 P_{\text{meet}}(\mathbf{r}). \quad (4)$$

Together with (2), this expression respects the detailed balance, thus guaranteeing that the evolution of the system is consistent with thermodynamic equilibrium. Note that $S_b(\mathbf{r}, \ell)$ introduces a coupling between the dynamics of the different stickers that ultimately depends on where all the other stickers are bound (see Supplemental Material [29] for the full expression). As a result, we cannot directly solve this system of equations without further approximation. In the next section, we use a Gillespie simulation to study the time evolution of Eq. (1), generating exact stochastic trajectories for the system without requiring further analytical approximations.

B. Early time behavior

We simulate a polymer of length L , which defines the system size, surrounded by N initially unbound stickers spread homogeneously in a three-dimensional space. Consistent with the transition rates defined in Eq. (1), each Gillespie step consists of a move chosen among sticker diffusion, binding to a polymer in the vicinity of the sticker, and unbinding if

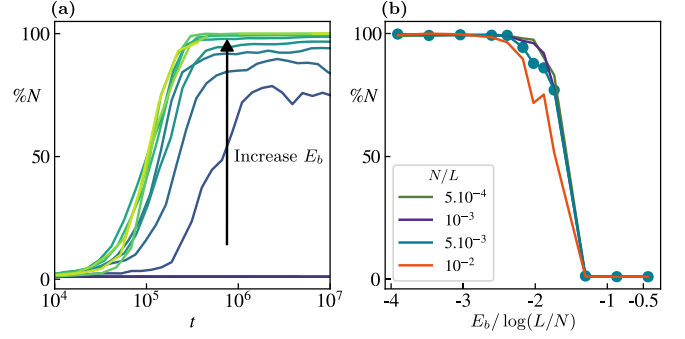


FIG. 2. (a) Early time evolution of the percentage of bound stickers in the system. Here, we use $L = 2.10^4$ and $N = 100$. (b) Plateau value of the percentage of bound stickers as a function of the binding energy, rescaled by the lineic density of stickers. The scattered points correspond to the measurements obtained from (b).

it was bound. All the rates are computed at the beginning of the step according to Eqs. (4) and (2) using Eq. (S5) in Supplemental Material [29], and a move is selected with a probability proportional to its rate. After a specific move is selected and applied, a time increment is drawn from an exponential distribution with a rate equal to the sum of the rates of all the possible moves of the system. After each move, the rates are locally updated to be consistent with the new configuration of the system.

Looking at the early time evolution of the system, we observe in Fig. 2(a) a rapid increase in the number of stickers bound to the polymer until a plateau is reached. We show in Fig. 2(b) how the height of the plateau depends on the binding energy, observing a sharp increase from 0% of the bound stickers to 100% at a critical value of the binding energy. This phenomenon is reminiscent of the phase transition observed in the Poland-Scheraga model of DNA denaturation [30]. In that model, two DNA strands can bind to one another through sticky base pairs that are regularly spaced along the strands. Similar to our model, the energetic binding energy must overcome the loss of entropy associated with the binding. As the linear density of stickers increases, it becomes increasingly favorable to bind them because the entropic cost for successive binding decreases. The Poland-Scheraga theory predicts a phase transition with a critical energy scaling, $E_c \propto \ln(L/N)$. We observe that our model consistently displays a similar scaling based on the collapsed curves in Fig. 2. As a consequence, for our system, low values of the binding energy (or high temperature) mean that stickers are mostly unbound, and the system mechanically responds like a liquid. If the value of the binding energy is higher than its critical value (or the temperature is lower than its critical value), stickers remain bound most of the time, leading to a viscoelastic mechanical response similar to that of an associative gel. This type of gel displays a solid-like mechanical response at timescales lower than the unbinding time and a liquid-like response at timescales much larger than the unbinding time. In this work, we focus on the viscoelastic aging regime; for this reason, we always consider a binding energy that is above its critical value. In this case, unbinding becomes the time-limiting process for the dynamics of the system. In the following, we

do not discuss the influence of the binding energy, which can be ruled out by rescaling times with respect to $1/k_{ub}$. In the high-energy regime, the phenomena discussed are insensitive to the value of the binding energy.

C. Glassy relaxation

Once all the stickers are bound, the system's energy essentially becomes fixed. However, the entropy of the polymer also depends on the positions of the stickers. We study the equilibration of the system through the diffusion of stickers. We first derive a mean-field model of the equilibrium pair probability distribution for two stickers. To obtain an analytical form, we employ the single-ended propagator approximation (see Supplemental Material [29]), which is justified here because the probability density is highly peaked near the tethering points ($r \approx R_l, R_r$) where this approximation holds. We find that for a system with a density of stickers L/N , the probability of finding two stickers at a distance $|r|$ from each other is given by

$$p(r) = \frac{3\text{erfc}\left(\sqrt{\frac{3}{2L/N}}|r|\right)}{2\pi L/N|r|}. \quad (5)$$

The simulated time evolution of the probability distribution toward the expected equilibrium analytic solution for smaller systems is depicted in Fig. 3(a). Contrastingly, Fig. 3(b) shows that larger systems, while converging similarly, do not reach our approximated equilibrium solution. The time evolution of the pair probability distribution reveals a contraction of the system. We compute the corresponding relative volume decay in Supplemental Material [29]. This phenomenon of aging-induced densification has been experimentally observed in protein condensates [31].

To determine whether the discrepancy arises from limitations in our mean field model or from the system's inability to further equilibrate, we plot in Fig. 3(c) the free energy per unit length difference between our system and the theoretical free energy of an unconstrained polymer, calculated as $f_{\text{free}} = F_{\text{free}}/L = NE_b/L - \log(4\pi)$ (where 4π is the solid angle between two monomers). We use a fixed lineic density of stickers ($N/L = 5 \cdot 10^{-2}$) and different system sizes, characterized by L . We observe a slow logarithmic decay of the free energy, followed by a plateau, where the total relaxation time depends on the system size. This type of logarithmic relaxation is usually associated with glassy systems [28], and in the next section we propose a model to better understand this unique behavior. Looking at the height of the plateau, we notice that it first increases with the system size before becoming independent of it. This is an unexpected behavior because the system is self-similar along the polymer and the equilibrium free energy per unit length is an intensive quantity with respect to L . Additionally, we show in Supplemental Material [29] that the height of the plateau also depends on the diffusion constant k_{diff} . These results suggest that systems above a certain size are unable to fully relax to equilibrium. Instead, they form substructures, each equilibrated, that we call clusters. We propose in Fig. 3(d) a one-dimensional schematic of this picture. Starting from a homogeneous distribution of stickers, they aggregate into equilibrated clusters. If the total

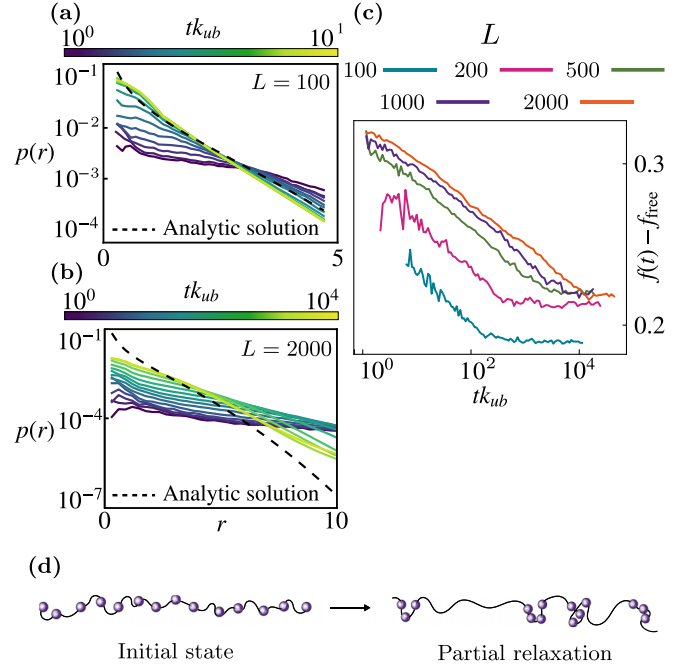


FIG. 3. (a) Sticker distance probability distribution at different time points. The color coding corresponds to the time, and the analytical solution is shown by the dotted line. We simulate systems with fixed lineic density: $N/L = 5 \cdot 10^{-2}$. Small systems of length $L = 100$ successfully converge toward the predicted equilibrium distribution. (b) Large systems, of length $L = 2000$, evolve toward the analytic solution without reaching it. (c) We follow the equilibration process by looking at the decay of the free energy per unit length over time; the initial binding regime has been removed for improved visibility. Using a fixed lineic density of stickers, we expect all curves to converge to the same relative value. However, large systems are stuck at a higher value of the free energy, stressing its inability to reach equilibrium. (d) Schematic representation of the partial equilibration of the system into subclusters.

system size is similar to the typical cluster size, the plateau free energy is the equilibrium one. For a system much larger than the cluster size, the plateau free energy is higher on average and intensive again.

To further examine the formation of equilibrated subsystems, we employ a hierarchical clustering algorithm to group stickers into clusters. This algorithm uses a single maximum length to define connectivity; here, we use the characteristic length scale in Eq. (5) to match the definition of clusters as equilibrated subsystems. Figure 4(a) illustrates the time evolution of the relative cluster size, showing that smaller systems tend to converge into a single cluster, while larger systems form clusters of fixed size, effectively showing a decay in the relative size. We show illustrative snapshots of these systems in Supplemental Material [29].

D. Origin of the glassy relaxation

We now investigate the origin of the slow logarithmic relaxation dynamics of the free energy. Logarithmic decay typically implies a continuous slowing down of the dynamics during relaxation. To confirm this, we examine the

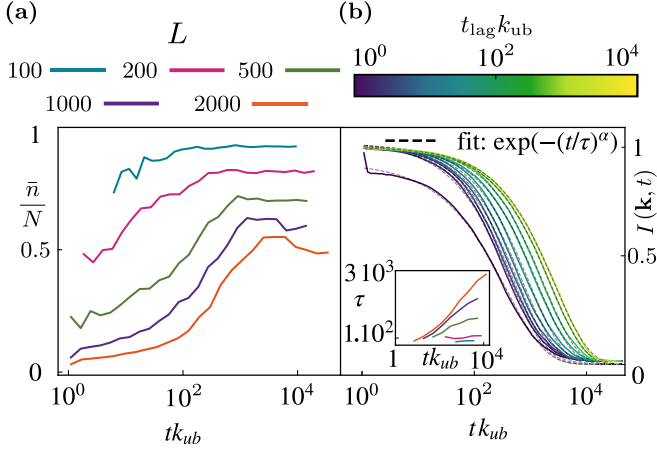


FIG. 4. (a) Average cluster size evolution; clusters are built using a hierarchical algorithm that uses a minimum distance linkage criteria. The distance used is the average sticker distance computed using the pair correlation function in Eq. (5), in our case $\bar{d} = 3.6$. (b) Real part of the intermediate scattering function for $|k| = 1/\bar{r} = 0.37$, where $\bar{r}$ is the average distance between stickers. The stretched exponential fits are in good agreement, and the corresponding τ values obtained are plotted in the inset. The value of α does not evolve significantly over time and remains ≈ 0.7 . Note the abrupt decay for small t_{lag} that corresponds to the initial binding regime.

intermediate scattering function (ISF), defined as

$$I(\mathbf{k}, t, t_{lag}) = \frac{1}{N} \sum_{i=0}^N \langle e^{i\mathbf{k}[\mathbf{r}_i(t) - \mathbf{r}_i(t_{lag})]} \rangle. \quad (6)$$

In an isotropic system, the imaginary part vanishes, and the real part of the ISF characterizes the spatial and temporal dependence of the relaxation dynamics. It is commonly used to study glassy relaxations [32]. Here, we focus on the wave vector associated with the intersticker distance, $k = 1/\langle r \rangle$, where $\langle r \rangle$ is the average sticker distance computed from Eq. (5). In Fig. 4(b), we plot the decay of the ISF over time, quantifying the decorrelation of the stickers' positions after a lag time denoted t_{lag} along the relaxation. Unlike an exponential decay consistent with a normal random walk, we observe a stretched exponential relaxation defined by $\exp[-(t/\tau)^\alpha]$, with $\alpha \approx 0.7$. This stretched exponential decay is characteristic of the α relaxation in glassy liquids [33,34] and indicates a relaxation slower than exponential, usually associated with subdiffusive microscopic processes [35] and a heavy tail of the displacement probability distribution. By fitting the measured ISF with a stretched exponential, we extract the characteristic relaxation time of the system. The inset of Fig. 4(b) shows the increase of the characteristic relaxation time τ as a function of the simulation time, confirming our intuition of a dynamical slowdown.

We now propose a model for the origin of this dynamical slowdown. In the previous section, we showed that equilibration can be interpreted as the growth of clusters. Individual exchanges of stickers between clusters do not modify the average size; to increase the average cluster size, it is necessary to dissolve another cluster. To compute the dissolution time of a cluster, we consider a system with N stickers spread

inside different clusters. The average number of stickers in a cluster is denoted $\bar{n}$. We model the exchange of stickers as a two-step process: unbinding from one cluster and then rebinding in a random cluster, selected uniformly and with equal probability from all clusters. Each exchange occurs according to a Poisson process with a constant rate $1/\tau_{exch}$, which effectively encapsulates a complex process of diffusion coupled to the binding-unbinding dynamics, which we do not investigate here. For a given cluster, between two dissolution events, the probability $P(n, t)$ to contain n stickers at time t evolves as

$$\frac{dP(n, t)}{dt} = 1/\tau_{exch} [P(n+1, t)(n+1) + P(n-1, t)\bar{n} - P(n, t)(n+\bar{n})], \quad (7)$$

derived from the master equation, where a cluster with n stickers loses one at a rate $1/\tau_{exch}n$ and gains one from any of the $N/\bar{n}$ clusters at a rate $N/(N/\bar{n})/\tau_{exch} = \bar{n}/\tau_{exch}$. Whenever a cluster's size reaches $n = 0$, it is dissolved, and $\bar{n}$ needs to be updated. Therefore, we set $n = 0$ as an absorbing boundary condition:

$$\begin{aligned} \frac{dP(0, t)}{dt} &= 1/\tau_{exch} P(1), \\ \frac{dP(1, t)}{dt} &= 1/\tau_{exch} [2P(2, t) - P(1, t)(1+\bar{n})]. \end{aligned} \quad (8)$$

This dynamics maps onto an $M/M/\infty$ queueing system. An exact solution for the mean escape time (corresponding to the mean busy period in queueing theory) is provided in [36]. Adapting their result [their Eq. (2.8)] to our problem yields the following asymptotic behavior:

$$\tau(\bar{n}) \approx \tau_{exch} \frac{e^{\bar{n}}}{\bar{n}}, \quad (9)$$

which shows a rapid, exponential growth of the dissolution time with the average cluster size that grows over time.

To model the long-time collective growth of clusters resulting from the dissolution of other clusters, we assume that a cluster dissolves at a rate $1/\tau(\bar{n})$ and its stickers are redistributed among the $N/\bar{n} - 1$ other clusters. We describe the dissolution events as continuous in time and write a differential equation for the time evolution of the average cluster size:

$$\frac{d\bar{n}}{dt} = 1/\tau_{exch} e^{-\bar{n}} \frac{\bar{n}}{N/\bar{n} - 1}. \quad (10)$$

This nonlinear differential equation cannot be solved analytically; however, we show in Supplemental Material [29] that for large systems ($1 \ll \bar{n} \ll N$), it indicates the cluster dissolution time grows over time as $\tau(t) \sim t \log(t)$. This corresponds to an essentially linear aging regime with a logarithmic correction, usually called “super-aging.” Figure 4(b) successfully captures the linear part of this scaling, confirming the relation between the macroscopic relaxation of the ISF and the microscopic dissolution of growing clusters. Our focus here is on these dominant scaling factors, neglecting secondary processes, as we believe this qualitative linear aging behavior is the most robust feature of the entropic clustering mechanism.

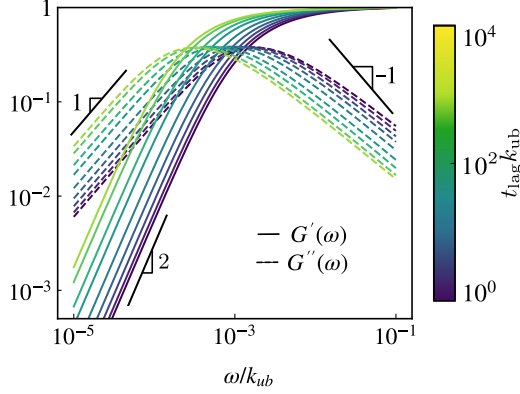


FIG. 5. Estimated storage (G') and loss (G'') moduli, obtained from Eq. (11), using ISF measured after different lag times. Slopes characteristics of Maxwell viscoelastic gel are displayed for reference.

E. Viscoelastic response

We now use our measurements of the ISF to estimate the long-time evolution of the dynamic relaxation modulus of our system. The mechanical relaxation of a chemically cross-linked polymer gel occurs through the unbinding of stickers. When a loaded bond breaks, the stress stored in that cross-link is relieved. If the unbound sticker has sufficient mobility, future rebinding occurs without reintroducing stress into the network. In our model, bound stickers remain fixed, while unbound stickers diffuse. Consistent with our previous assumptions, we assume that unbound stickers diffuse rapidly compared to the relaxation dynamics of the polymer network.

Based on these principles, in Supplemental Material [29] we derive a relation connecting the ISF to the dynamic modulus for wave vector $k = 1/\langle r \rangle$:

$$G(\omega; t_{\text{lag}}) = j\omega \int_0^{+\infty} e^{-j\omega t} I(t, t_{\text{lag}}) dt, \quad (11)$$

where $\text{Re}[G(\omega; t_{\text{lag}})] = G'(\omega; t_{\text{lag}})$ is the storage modulus and $\text{Im}[G(\omega; t_{\text{lag}})] = G''(\omega; t_{\text{lag}})$ is the loss modulus at angular frequency ω .

The results are shown in Fig. 5 and are consistent with previous experimental [13] and simulation results [37]. As expected from the growing relaxation timescales of the ISF, the crossover frequency, where the storage modulus exceeds the loss modulus, marking the transition from liquid-like to solid-like behavior, shifts to lower values as the lag time increases. This confirms that the material becomes progressively more solid-like at long times.

To aid interpretation, we also provide reference scaling laws characteristic of Maxwell viscoelastic behavior. Although the measured curves resemble those of a Maxwell material, the scalings differ slightly. This deviation arises because the ISF follows a stretched exponential form rather than a single exponential. However, the stretching exponent α remains close to 1, leading to a viscoelastic response that closely approximates Maxwellian behavior.

III. DISCUSSION

We have introduced a minimal model to describe the dynamics of protein or RNA- or DNA-protein condensates. By utilizing the general sticker and spacer framework, we examined the long-time structural evolution of these systems. Our investigation primarily focused on two general effects: the entropic cost associated with binding and the increasing difficulty for the system to rearrange upon equilibration. Our model reveals two distinct mechanisms: the emergence of a Casimir attractive force between stickers mediated by spacers and the clustering of stickers leading to glassy relaxation. The first mechanism is reminiscent of bridging-induced phase separation, where RNA or DNA-protein binding is driven by a similar entropic force, triggering condensation [3,9]. Here, the entropy is that of Gaussian polymers. This is an overestimation of the reality wherein the excluded volume reduces the loss of entropy due to binding. In our framework, this entropic attractive force appears for high binding energy, as the simultaneous unbinding of multiple stickers would disrupt the attractive interaction. This approximation might not be universally valid for all biological systems. In fact, we anticipate that in many cases, the Casimir force will not be the primary driver of structural reorganization. Nonetheless, in our model, this attractive force is only useful to drive sticker clustering, which is ultimately responsible for glassy relaxation. This clustering can also be driven by system-specific mechanisms, such as three-body stabilizing interactions and multiple- β -sheet stacking, and has been observed in experimental systems [15,22,27]. In fact, such clustering is also a general behavior of random walkers in disordered media, commonly known as localization in this context [38]. For these reasons, we are confident that the clustering of stickers described here is a fairly universal feature, from which we have highlighted only the entropic minimization effect.

Finally, our model offers several concrete predictions that can be directly tested in experiments. First, regarding the role of temperature, our framework distinguishes between thermodynamic and kinetic effects. Thermodynamically, a phase transition occurs at a critical temperature $T_c = E_c/k_B$ (Fig. 2). Above this threshold, entropy dominates, preventing stable cross-links and aging. Below T_c , the system enters the aging regime where kinetics dominate: The global reorganization timescale $k_{\text{ub}}^{-1} \propto e^{E_b/k_B T}$. Consequently, we predict that lowering the temperature (while staying below T_c) will exponentially slow down the aging process. This relationship between interaction strength and relaxation dynamics is a hallmark of glassy dynamics [39] and was substantiated in recent protein condensate experiments [21]. Second, our model reconciles the seemingly contradictory aging behaviors of stiffness versus viscosity reported in [13]. Using rubber elasticity theory to estimate the elastic modulus, we find $G_0 = 3k_B T v_s$, where v_s is the density of elastically active polymer strands. Up to a change in the volume of the condensate v_s and thus G_0 both remain constant through aging. On the other hand, the viscosity $\eta \approx \tau G_0$ increases with relaxation time of the growing clusters, as shown in the inset of Fig. 4(b). Third, regarding microrheology, the stretched exponential decay observed in the ISF (Fig. 4) implies a deviation of the particle displacement probability distribution

from simple Brownian motion. Consequently, we predict that this distribution will be non-Gaussian with heavy tails, exhibiting exponential rather than Gaussian decay. Fourth, at the macroscopic level, our model predicts a gradual densification of the condensate driven by the reduction of the average intersticker distance (Fig. 3). We estimate the resulting relative volume contraction in Supplemental Material [29] (Fig. S1). This aging-induced shrinkage agrees with recent experimental measurements [31].

Our model has phenomenological similarities to previously studied random trap models [40,41], which reproduce key features such as glass transition, subdiffusion, and localization. However, these models typically rely on an *a priori* broad (e.g., exponential) distribution of binding energies, where aging arises from the progressive exploration of ever-deeper traps. While real proteins do exhibit sequence-specific heterogeneity [42], the fundamental noncovalent interactions (electrostatic, hydrophobic, hydrogen bonding) generally fall within a restricted energy range ($\approx 5\text{--}15k_B T$). Consequently, the intrinsic energetic diversity of individual bonds is likely too narrow to justify *a priori* the existence of the extremely deep traps required for long-time aging. Our model offers a microscopic rationale for the emergence of such a broad

distribution of relaxation times from a single energy scale, as proposed phenomenologically in previous studies [19,39]. By focusing on the exponential scaling of the dissolution time in Eq. (9), we identify that a cluster of size $\bar{n}$ behaves effectively as a trap of depth $\bar{n}$ times the single-bond energy. This renormalization of the trap depth explains how entropic clustering can amplify small energetic heterogeneities, leading to complex viscoelastic relaxation [43].

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DATA AVAILABILITY

All the data presented in this article come from C++ and PYTHON simulations. The source codes are available from Refs. [44,45].

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