

Mesoscopic viscous-to-elastic transition as a signature of aging of biomolecular condensates

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Aging of biomolecular condensates, which progressively leads to solidlike states, is closely linked to biological functions and diseases. However, a unified physical picture that captures the aging dynamics remains elusive. Here, we introduce a viscoelastic model in which a condensate is a composite of viscous and elastic elements with coexisting serial and parallel connections. The model naturally yields a complex modulus with two relaxation times, unifying the Maxwell and Jeffreys models as special limits. When applied to aging PGL-3 condensates, our model reveals that an important driving force of aging is the conversion of viscous elements into elastic ones. In contrast, the mesoscopic structure topology of the condensates remains approximately invariant. Our stochastic aging model predicts that the condensate viscosity increases either exponentially or as a power-law function of the waiting time, in agreement with experiments.

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Introduction. Biomolecular condensates formed through liquid-liquid phase separation are essential for cellular organizations and functions [1–11]. Theoretical and experimental studies have provided profound insights into the molecular interactions governing the formation of condensates [12–18]. Meanwhile, biomolecular condensates often undergo aging [19–28], progressively hardening into solidlike states [25,29], or even pathological aggregates associated with neurodegenerative diseases [30–33]. Therefore, understanding the physical principles governing the transition in rheological properties during the aging of biomolecular condensates is extremely important. Recent experiments have characterized biomolecular condensates as viscoelastic materials, fitting the dynamic modulus data using the Maxwell model [34] or the Jeffreys model [35]. Nevertheless, it is still unclear whether a theoretical framework can unify these experimental observations and quantify the mechanical states of biomolecular condensates during aging.

Previous studies have proposed various microscopic mechanisms for the aging of biomolecular condensates from different perspectives. For instance, molecular dynamics simulations employing all-atom or coarse-grained approaches have been used to compute intermolecular interactions and extract aging dynamics [14,15,36–40]. However, a unified physical picture of condensate aging remains lacking. On the other hand, phenomenological theories have been proposed in which the condensate is composed of mesoscopic elements, and aging is attributed to the change in the energy barrier (i.e., yield energy or binding energy) distribution of the traps these

elements inhabit. These theories predict temporal scaling for the viscosity, $\eta \sim t^{1-\alpha}$, where $\alpha = 0$ [41] or $0 < \alpha < 1$ [42] and t is the waiting time since droplet formation. However, experiments showed that viscosity increases approximately exponentially with the waiting time [34]. Furthermore, these theories predict a single relaxation time for the viscoelastic response of biomolecular condensates [41,42]. However, experimental data of dynamic moduli appear to be better described by more complex models with two relaxation times [34,43].

In this work, we introduce a viscoelastic model of biomolecular condensates. Our model conceptualizes a condensate as a composite material composed of viscous and elastic elements. Importantly, we assume that a finite fraction of these elements are connected in parallel, while the rest are connected in serial, which reflects the mesoscopic structure topology of the condensate. Intriguingly, our model naturally predicts a relaxation modulus with two relaxation times. Our theory reconciles the previous Maxwell and Jeffreys descriptions as limiting cases of our model [34,35], and also fit the experimental data reasonably well. We also provide a kinetic model to describe the time dependence of the fraction of viscous elements (P). Motivated by experiments and simulations that show the aging of protein condensates is driven by the slow accumulation of strong interactions, notably the formation of β -sheets [15,25,26,28,37,40], we introduce a deep energy barrier representing these stable structures alongside a population of exponentially distributed barriers representing transient weak interactions. Notably, this minimal model successfully explains the exponential increase in viscosity over time.

In the following, we first introduce the viscoelastic model and show that it predicts an effective Maxwell model with two relaxation times that depend on the fractions of viscous and serial elements. We then apply our model to data of aging PGL-3 condensates [34]. Remarkably, we find that the aging of PGL-3 condensate is not driven by a change in the

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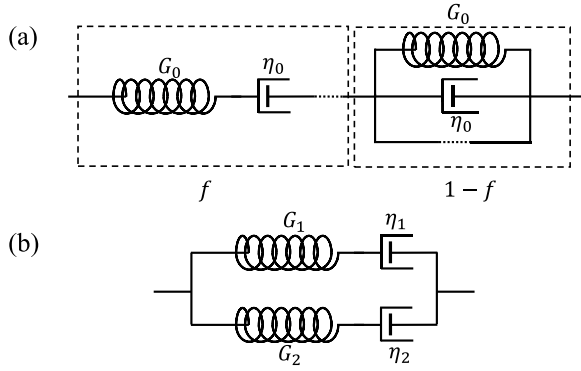


FIG. 1. A phenomenological viscoelastic model of biomolecular condensates. (a) The model consists of elastic and viscous elements, represented here by springs and dashpots connected in series or in parallel. We use the ellipses to indicate unshown elements. A fraction P of the elements are viscous elements, and a fraction f of the elements are in the serial section. (b) The viscoelastic response of the model in panel (a) is equivalent to two Maxwell fluids with different shear moduli and viscosities connected in parallel.

mesoscopic structure topology (the fraction of serial connections, f , remains approximately constant), but rather by the progressive conversion of viscous elements into elastic ones (the fraction of viscous elements, P , decays approximately exponentially). This conversion elucidates the mesoscopic origin of the exponential increase in viscosity, as our model predicts a simple relationship, $\eta \propto 1/(fP)$.

We then introduce the stochastic aging model to explain the dynamics of the fraction of viscous elements. The theory predicts two distinct aging modes: The viscosity may increase exponentially with time or grow as a power-law function of time $\eta \sim t^{1+\alpha}$, with $0 < \alpha < 1$ in the long-time limit. Importantly, the transition in the viscosity scaling law can be triggered by varying temperature. Our framework thus provides a bridge from mesoscopic state transitions to the macroscopic material fate of biomolecular condensates, offering insights into the physical principles underlying their aging.

Viscoelastic model. We divide a biomolecular condensate into mesoscopic elements, whose sizes are sufficiently small that a condensate is composed of numerous elements, yet large enough that their mechanical response can be quantified by strain and stress. We consider two types of elements: For elastic elements, they have locally percolated structures and can bear shear stress, while viscous elements have locally unpercolated structures. For simplicity, we model them as simple elastic solids with constant shear modulus G_0 and viscous fluids with constant viscosity η_0 , respectively, similar to previous work [42]. The fraction of viscous elements is P . In the soft glassy rheology model [44,45], multiple Maxwell-fluid elements are connected in parallel, sharing the same strain and contributing together to the stress. In the model by Takaki *et al.* [42], elements are connected in series, sharing the same stress and contributing together to the strain.

Here, we introduce a viscoelastic model in which serial and parallel connections coexist, with the fraction of elements in the serial section denoted by f (Fig. 1). As the condensate ages, the fraction of viscous elements P and the fraction of elements in the serial section f may change. The serial and

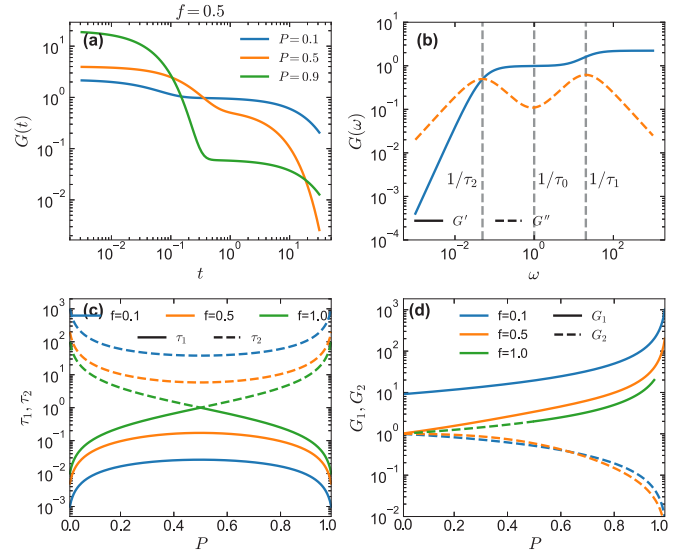


FIG. 2. Predictions of the viscoelastic model. (a) The relaxation modulus $G(t)$ vs time t for different values of the viscous fraction P at a fixed serial fraction $f = 0.5$. (b) The storage (G' , solid lines) and loss (G'' , dashed lines) moduli vs frequency ω for $f = 0.5$, $P = 0.1$. We highlight the frequencies corresponding to the slow mode $1/\tau_2$, the fast mode $1/\tau_1$, and the mesoscopic timescale $1/\tau_0$. In the limit $\omega \rightarrow 0$, $G' \propto \omega^2$ and $G'' \propto \omega$. In the limit $\omega \rightarrow \infty$, $G' \rightarrow 1/[f(1-P)]$ and $G'' \propto \omega^{-1}$. (c) The relaxation times τ_1 and τ_2 as functions of P for different values of f . For $f = 1$, the curves of τ_1 and τ_2 intersect at $P = 0.5$. (d) The amplitudes G_1 and G_2 as functions of P for different f . In this figure, the modulus unit is G_0 and the time unit is η_0/G_0 .

parallel sections satisfy the following constitutive relationship:

$$\dot{\gamma}_s = \frac{P}{\eta_0} \sigma + \frac{1-P}{G_0} \dot{\sigma}, \quad (1a)$$

$$\sigma = P\eta_0\dot{\gamma}_p + (1-P)G_0\gamma_p. \quad (1b)$$

Here, σ is the stress, and γ_s and γ_p are the strains of the serial and parallel sections, respectively. The total strain of the whole condensate is $\gamma = f\gamma_s + (1-f)\gamma_p$. Note that the system size should not appear in Eqs. (1a) and (1b) since strain and stress are intensive variables.

The relaxation modulus of the above viscoelastic model (i.e., the stress relaxation given a step unit strain) is precisely a double-exponential decay function with a short relaxation time τ_1 and a long relaxation time τ_2 [Fig. 2(a); see detailed derivation in Appendix A of the Supplemental Material [46]]:

$$G(t) = G_1 e^{-t/\tau_1} + G_2 e^{-t/\tau_2}. \quad (2)$$

Here, the two relaxation times and their corresponding amplitudes are given by

$$\tau_{1,2} = \frac{1 - 2\phi \mp \sqrt{1 - 4\phi}}{2\phi} \tau_0, \quad (3a)$$

$$G_{1,2} = \mp \frac{G_0}{\sqrt{1 - 4\phi}} \left[(1-P) + P \frac{2\phi - 1 \mp \sqrt{1 - 4\phi}}{2\phi} \right], \quad (3b)$$

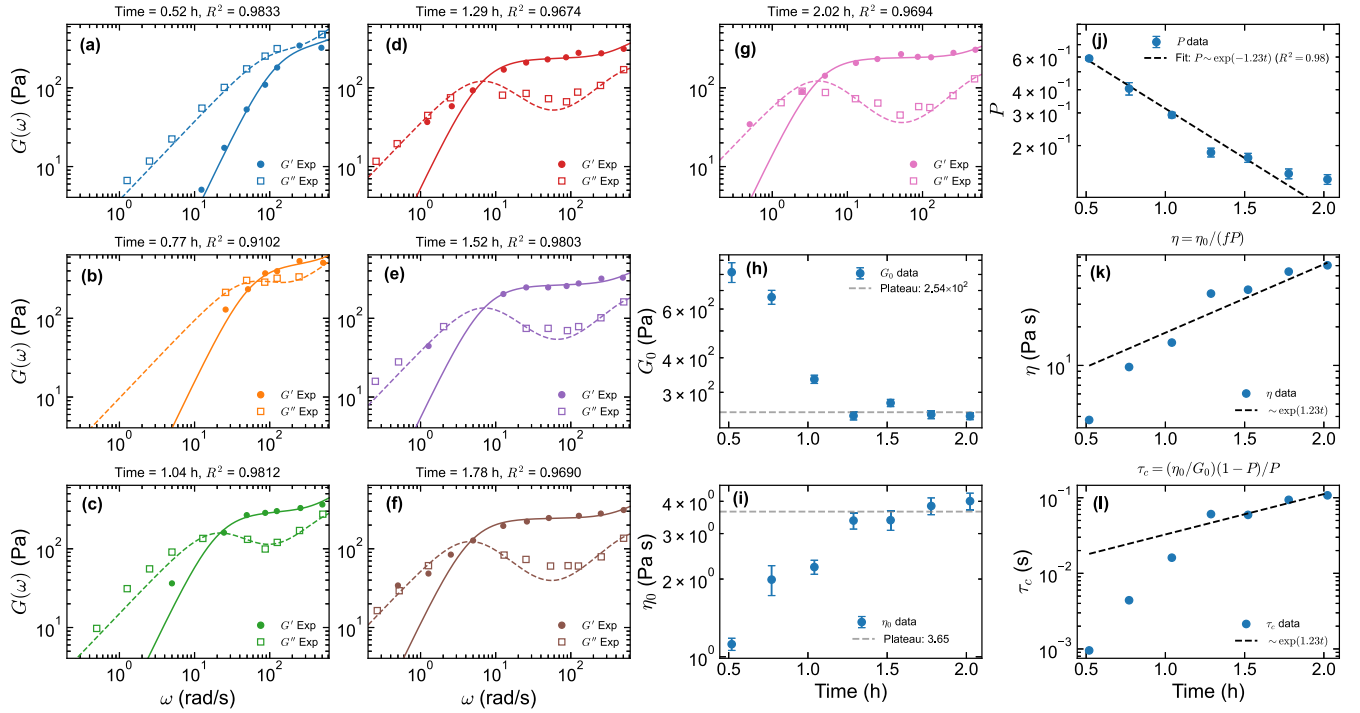


FIG. 3. Fitting of active microrheology data for PGL-3 condensates. (a)–(g) We fit the experimental data of $G'(\omega)$ (solid lines) and $G''(\omega)$ (dashed lines) at different waiting times to the viscoelastic model [Eq. (5)]. (h)–(j) The fitting parameters G_0 , η_0 , and P at different waiting times. We note that G_0 and η_0 reach a plateau for $t \geq 1.29$ h (gray dashed lines). P vs t can be well fitted by an exponential function (dashed line). (k), (l) The time dependence of η and τ_c calculated from the parameters in panels (h)–(j). The viscosity and average relaxation time increase approximately exponentially at long waiting times. In this figure, f is fixed at 0.505. The experimental data in this figure are from active microrheology measurements of aging PGL-3 condensates performed at 25°C and 100 mM KCl in Ref. [34].

where $\tau_0 = \eta_0/G_0$ and $\phi = fP(1 - P)$ [Figs. 2(c) and 2(d)]. Notably, the relaxation times exhibit the symmetry $\tau_1 \tau_2 = \tau_0^2$ [Fig. 2(b)]. In particular, $\tau_1 \propto fP$ and $\tau_2 \propto 1/(fP)$ as $P \rightarrow 0$. Given the relaxation modulus, it is straightforward to compute the zero-shear viscosity and the instantaneous modulus:

$$\eta = \int_0^\infty G(t)dt = \frac{\eta_0}{fP}, \quad (4a)$$

$$G(t=0) = \frac{G_0}{f(1-P)}. \quad (4b)$$

The condensate becomes a solid when $f = 0$, that is, all elements are connected in parallel; in this case, the plateau modulus $G_\infty = (1 - P)G_0$. In the following, we apply our theory to fit the dynamic moduli of protein condensates at different waiting times after condensate formation.

Analysis of experimental data. Our viscoelastic model predicts that the complex modulus of the condensate is equivalent to two Maxwell fluids connected in parallel:

$$G^*(\omega) = G_1 \frac{i\omega\tau_1}{1 + i\omega\tau_1} + G_2 \frac{i\omega\tau_2}{1 + i\omega\tau_2}. \quad (5)$$

Previous works have suggested that the dynamics moduli of biomolecular condensates can be described by the Maxwell model [34] and the Jeffreys model [35]. Our model unifies the two different hypotheses. There are two possible scenarios that Eq. (5) reduces to a Maxwell model: (1) $\tau_1 \approx \tau_2$, i.e., the two relaxation times are close; and (2) the loss modulus $G''(\omega)$ is still decreasing due to the slow mode even at the largest frequency $\omega_{\max}$ the experiment can probe,

i.e., $G_2/(\omega_{\max}\tau_2) > G_1\omega_{\max}\tau_1$, which means that $\omega_{\max} < \sqrt{G_2/(G_1\tau_1\tau_2)}$. For Eq. (5) to resemble Jeffreys model, we require that $G''(\omega)$ starts to increase due to the fast mode at high frequencies but does not reach the second peak yet, i.e., $\sqrt{G_2/(G_1\tau_1\tau_2)} < \omega_{\max} < 1/\tau_1$ [Fig. 2(b)].

We use Eq. (5), together with Eqs. (3a) and (3b), to fit the dynamic moduli data of PGL-3 protein measured by active microrheology [34]. We initially use four fitting parameters, P , f , G_0 , and η_0 (Fig. S2 of the Supplemental Material [46]). Interestingly, we observe a relatively constant fraction of serial elements, $f(t)$, suggesting that the condensate's mesoscopic structure topology does not change significantly during aging. We then fix $f = 0.505$, which is its average fitted value at the long waiting times (Fig. S2 of the Supplemental Material [46]). Using this method, we achieve a much more accurate estimate of the fitting parameters G_0 , η_0 , and P than the initial method in which the parameter f is fitted separately for each waiting time (Fig. 3). We consistently observe an approximately exponential decay of the fraction of viscous elements $P(t)$ in both fitting methods, in agreement with the prediction of the stochastic aging model as we show later [Fig. 3(j) and Fig. S2 of the Supplemental Material [46]]. Details of data fitting are included in Appendix C of the Supplemental Material [46].

We calculate the viscosity η of the condensate by Eq. (4a) and the average relaxation time as $\tau_c = \eta/G(t=0)$, which is a weighted average of τ_1 and τ_2 (see Appendix A of the Supplemental Material [46]; Figs. 3(k) and 3(l)). We note that both G_0 and η_0 undergo a fast change in the early stage and

reach a plateau in the later stage [Figs. 3(h) and 3(i)]. Thus, the behaviors of the inferred viscosity and average relaxation time at long waiting times approximately match that of $P(t)$ [Figs. 3(k) and 3(l)]. Our analysis suggests that aging of PGL-3 condensates stems from changes in G_0 , η_0 , and P . In the following, we explain the mechanism of the exponential decay of $P(t)$.

Aging dynamics of condensates. We introduce a stochastic aging model to describe the time dependence of $P(t)$. Our approach builds upon the general framework of trap models [44,47], which has recently been adapted to biomolecular condensates by one of us [41] and by Takaki *et al.* [42]. In Ref. [42], elements transition between a viscous (unbound) state and an elastic (bound) state for which the energy barriers are drawn from an exponential distribution. Here, we extend this framework to capture richer aging dynamics, particularly the exponential decay of $P(t)$ and the exponential increase in viscosity over time, which have been observed experimentally [Figs. 3(j) and 3(k)] [34].

We consider the transition between elastic and viscous elements, e.g., from a percolated to an unpercolated one due to the unbinding of cross-links, which is governed by the energy barriers between local structures in our stochastic aging model. We introduce $p_e(E, t)$ for the distribution of elastic elements as a function of their energy barriers, which satisfies $P(t) + \int_0^\infty p_e(E, t) dE = 1$. The change of the state of each element is stochastic, governed by the following master processes:

$$\begin{aligned} \frac{\partial p_e(E, t)}{\partial t} = & -p_e(E, t)\Gamma_0 e^{-\beta E} \\ & + P(t)\Gamma_0\beta_0 e^{-\beta_0 E} + P(t)\Gamma_1\delta(E - E^*), \end{aligned} \quad (6)$$

where $\beta \equiv k_B T$, with k_B the Boltzmann constant and T the temperature. Here, the elastic state is further divided into two substates. The weak elastic substate, characterized by an exponential distribution of energy barriers $P(E) = \beta_0 e^{-\beta_0 E}$, represents transient and weak interactions. In contrast, the strong elastic substate, described by a delta function $P(E) = \delta(E - E^*)$ with $E^* \gg k_B T$, represents the deep energy trap associated with stable structures, such as β -sheets, which drive the liquid-to-solid transition [15,25,26,28,37,40]. The transitions from the viscous state to the weak and strong elastic substates are characterized by rate constants, Γ_0 and Γ_1 , respectively. For both substates, the transition rate from them to the viscous state follows the Arrhenius law, $\Gamma = \Gamma_0 e^{-\beta E}$. We introduce the parameter $\alpha \equiv \beta_0/\beta$ and summarize the temporal scaling behavior of the viscous fraction in the following (see detailed derivation in Appendix B of the Supplemental Material [46]).

For $\alpha > 1$, starting from the initial condition $P(t) = 1$, i.e., a fresh condensate, $P(t)$ first enters a plateau regime $P(t) = (\alpha - 1)/(2\alpha - 1)$ and then decays exponentially as

$$P(t) \sim e^{-\frac{\alpha-1}{2\alpha-1}\Gamma_1 t}, \quad (7)$$

in agreement with experimental data [Fig. 3(j)]. Note that the viscosity and average relaxation time are related to $P(t)$ via $\eta \sim 1/P(t)$ and $\tau_c \sim (1 - P(t))/P(t)$, respectively; therefore, their asymptotic scalings are simply the inverse of $P(t)$ (Fig. S1 of the Supplemental Material [46]).

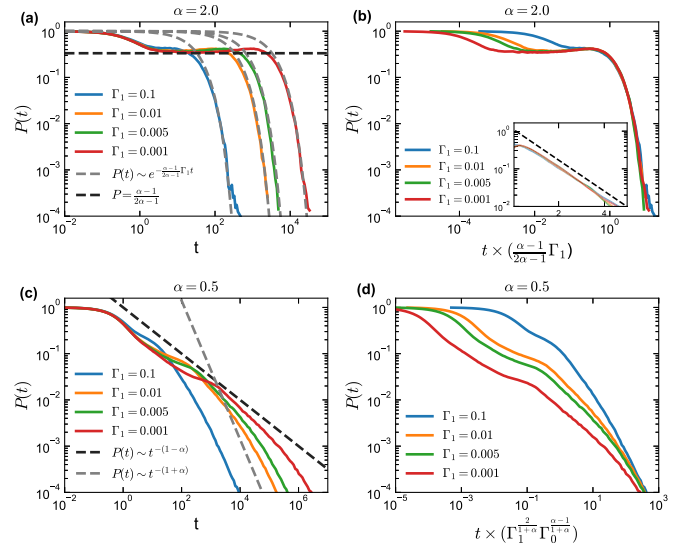


FIG. 4. Aging dynamics of the fraction of viscous elements. (a) We compare the simulation results (solid lines) with the theoretical predictions (dashed lines). $P(t)$ first reaches a plateau and then decays exponentially for $\alpha = 2$. (b) The long-time behaviors of the $P(t)$ vs t curves collapse on a master curve after rescaling the time as $t \frac{\alpha-1}{2\alpha-1} \Gamma_1$. (c) The same as panel (a) but for $\alpha = 0.5$ in which $P(t)$ transitions between two power-law decay regimes. (d) The same as panel (c) but with a rescaling factor. In this figure, we simulate $N = 10\,000$ elements with $E^* = 30$, the energy unit as $k_B T$, and the time unit as $1/\Gamma_0$.

The transition between the plateau and the exponential decay occurs at $t_c \sim 1/\Gamma_1$ [Figs. 4(a) and 4(b)]. For $\alpha < 1$, $P(t)$ decays as a two-stage power law

$$\begin{aligned} P(t) & \sim \frac{1}{\Gamma_0^{1-\alpha} t^{1-\alpha}}, \quad t < t_c, \\ P(t) & \sim \frac{1}{\Gamma_0^{\alpha-1} \Gamma_1^2} \frac{1}{t^{1+\alpha}}, \quad t > t_c. \end{aligned} \quad (8)$$

Here, the crossover between the two power-law regimes occurs at $t_c \sim \Gamma_1^{-\frac{1}{\alpha}} \Gamma_0^{\frac{1-\alpha}{\alpha}}$ [Figs. 4(c) and 4(d)]. To confirm our predictions, we simulate the stochastic model using the Gillespie algorithm and find perfect agreement (Fig. 4). We note that a power-law function can also fit the experimental data of $P(t)$ and the stochastic aging model predicts that the exponent must be between -2 and -1 in the long-time limit, in agreement with the fitting (Fig. S4 of the Supplemental Material [46]).

Discussion. We notice that the agreement between the fit and the data is not perfect (Fig. 3). We highlight that the low-frequency deviation between the storage modulus and the Maxwell scaling ($G'(\omega) \sim \omega^2$) may be generated by the polymer nature of the condensate-forming biomolecules [48,49]. We highlight that our model should be considered a minimal model that captures the existence of double relaxation times in the complex modulus, which extends beyond the Maxwell model.

In the stochastic aging model, each element alternates between viscous and elastic states. For elastic elements, the

energy barriers for them to switch to a viscous element are also random. Thus, over a given time window, elements in deep traps spend a significantly larger fraction of their time in the elastic state than those in shallow traps. Therefore, the time-averaged mechanical response remains highly heterogeneous across elements despite the fact that they share the same viscosity or shear modulus.

Our viscoelastic model operates within the linear viscoelastic regime, where shear is a nondestructive probe. The internal state variables in our stochastic aging model evolve spontaneously due to thermodynamic and kinetic processes. Our model setup differs from structural kinetic models of thixotropy, where the state variables are explicitly driven by applied shear [50–52]. Our model also allows both parallel and serial connections between elements, yielding an effective Maxwell model with two relaxation times. In contrast, previous trap-based models of aging materials assumed either all-parallel or all-serial connections among elements [41,42,44,45], which cannot capture the complex behaviors of dynamic moduli observed in experiments.

Our model includes two subtypes of elastic elements. The energy barriers of the weak elastic substates follow an exponential distribution, consistent with previous work [42,44,45], whereas the energy barrier of the strong elastic substate is much higher than the thermal energy. Based on the assumption of two elastic substates, our model predicts that the fraction of viscous elements $P(t)$ decays either exponentially or as

a power-law function of time with an exponent between -2 and -1 asymptotically. Meanwhile, the model in Ref. [42] with only weak elastic elements predicts that $P(t)$ decreases as a power-law function of time with an exponent between -1 and 0 . Interestingly, a power-law function can also fit the experimental data of $P(t)$; however, even in this case, the fitted exponent is about -1.14 (Fig. S4 of the Supplemental Material [46]), which is consistent with our model predictions.

Our model is a scalar model, which should be a good approximation for mechanical perturbations with simple geometry in the linear viscoelastic regime. Nevertheless, many biologically relevant flows of biomolecular condensates involve tensorial stresses, requiring an extension of our scalar model to tensorial descriptions that can be nontrivial. Developing three-dimensional rheological models is a promising direction for future investigation.

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Data availability. The data that support the findings of this article are openly available [53].

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