

Modeling the aging of protein condensates

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Protein condensates formed by liquid-liquid phase separation exhibit aging rheological properties and are considered under biological regulation and related to multiple diseases. In this work we provide a mesoscopic framework to describe the rheology of protein condensates. A phase transition from a nonaging phase to an aging phase occurs when the temperature is below a critical value. In the aging phase, we find that protein condensates behave as Maxwell fluids at all ages in the linear viscoelastic regime and the viscosities increase linearly over time. We also show that protein condensates are non-Newtonian fluids under a constant shear rate and the stress-strain curve exhibits a power-law scaling at large strain. Our theories are consistent with experimental observations and also make general predictions that are experimentally testable.

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Introduction. Aging phenomena are widely observed in various soft-matter systems, including polymers [1], soft glasses [2,3], and disordered mechanical systems [4]. Recently, many experiments have found that protein condensates formed by liquid-liquid phase separation [5–7] also exhibit aging behavior: Their dynamics slow over time and become more solidlike [8–15], which is considered to be related to multiple neurodegenerative diseases [16]. More quantitatively, Jawerth *et al.* [17] studied the aging of protein condensates by investigating their rheological properties in the linear viscoelasticity regime using laser tweezers [18]. The authors found that the complex moduli of protein condensates are self-similar at all ages: They exhibit the same viscoelastic behavior of Maxwell fluids with the relaxation times increasing as the materials age. This aging behavior appears generic because it is observed in various protein condensates, including PGL-3 and FUS proteins. However, a theoretical understanding of this aging behavior is lacking despite its universality and fundamental importance to cell biology and disease [16,17].

Previous theoretical works studying the aging rheology of disordered materials mostly discussed yield stress materials [19–25] such that a finite stress is needed to shear the material in the zero shear rate limit. For example, the soft glassy rheological model [19–21] shows that a glassy material behaves like a Maxwell fluid at high temperature but without aging; aging occurs at low temperature, but the material also becomes solid. According to previous theories, aging appears to be irrelevant for fluids, contradicting experimental observations of protein condensates [17]. In this work we

propose a mesoscopic framework of protein condensates in which the condensate is in a fluid state and simultaneously exhibits aging phenomena. In this framework, a condensate consists of many mesoscopic parts, which can transit between different metastable configurations. Previous works [19,20] usually assumed a mean-field model such that these metastable configurations were uncorrelated, but here we relax this assumption and consider the scenario of correlated metastable configurations.

In the linear viscoelasticity regime, we predict a phase transition from a nonaging phase to an aging phase when the temperature is below a critical value. We demonstrate that in the aging phase, a protein condensate behaves like an aging Maxwell fluid with a relaxation time increasing linearly as a function of the condensate's age. We also study nonlinear rheology and show that for aging Maxwell fluids, the shear stress σ increases with strain γ under constant shear rate with a power-law scaling $\sigma \sim \gamma^\alpha$. The exponent α can be 1/3 or 1/5, depending on the underlying parameters. Our work predicts that protein condensates are rheopectic fluids. These theoretical predictions are verified using numerical simulations. We conclude by discussing the relation between our theory and experimental observations.

Aging maxwell fluid model. A protein condensate, which can be formed by liquid-liquid phase separation, is conceptually subdivided into mesoscopic parts, called elements in the following. Their sizes are small enough so that a macroscopic droplet contains a large number of them. Meanwhile their sizes are large enough so that their deformations can be described by an elastic strain variable. For simplicity, we ignore tensorial aspects, restricting our analysis to simple shear strains. Because condensate-forming proteins have large regions of disorder, they can have a large number of molecular configurations [12]. As the system is sheared, each element will first deform elastically with a local strain l from a local equilibrium configuration and then transit to a different configuration [26] with a yielding rate $R(E, l) = \Gamma_0 \exp[-\beta$

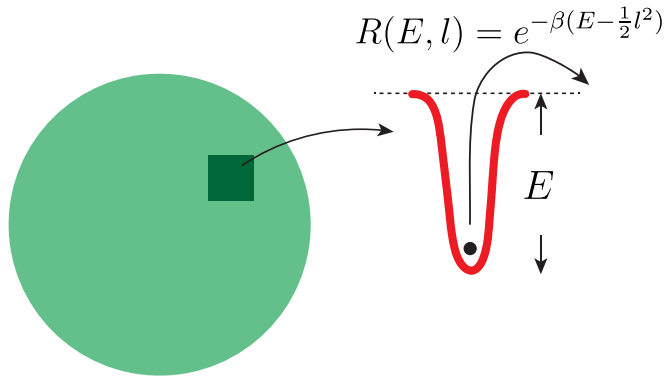


FIG. 1. A protein condensate is conceptually subdivided into mesoscopic elements. Each element is in a metastable state with yield energy E and local strain l , and the yielding rate to escape the metastable configuration is $R(E) = e^{-\beta(E - \frac{1}{2}l^2)}$. The macroscopic stress is an average over all the mesoscopic elements.

$(E - \frac{1}{2}kl^2)$. Here E is the yield energy of the initial configuration, k is the elastic constant, and Γ_0 is the attempt frequency for yield $\beta = 1/T$, where T is the temperature and the Boltzmann constant is set as 1.

Between successive local yield events, changes in local strain follow those of the macroscopic shear such that $\dot{l} = \dot{\gamma}$. We assume that the local strain is reset to 0 right after the yielding of an element [20]. The state of the condensate is characterized by the probability distribution $P(E, l, t)$, which satisfies

$$\begin{aligned} \frac{\partial P}{\partial t} = & -\dot{\gamma} \frac{\partial}{\partial l} P(E, l, t) - e^{-\beta(E - kl^2/2)} P(E, l, t) \\ & + \delta(l) \int H(E|E') P(E', l', t) e^{-\beta(E' - kl'^2/2)} dE' dl'. \end{aligned} \quad (1)$$

Here $H(E|E')$ is the probability distribution of the yield energy of the new configuration given the previous configuration has a yield energy E' . In the soft glassy rheological model [19,27], $H(E|E')$ is assumed to be independent of E' . The macroscopic stress is defined as an average over all elements $\sigma(t) = k \int l P(E, l, t) dl dE$ [20,28]. In the following, we use nondimensional units for time and stress by setting $\Gamma_0 = 1$ and $k = 1$. The model is summarized in Fig. 1.

In the regime of linear viscoelasticity with an oscillatory strain $\gamma(t) = \gamma \cos(\omega t)$, the yielding of elements is completely due to thermal noise because the elastic energy $\frac{1}{2}l^2$ is much smaller than the yield energy. Therefore, the yielding rate can be approximated as $R(E) = e^{-\beta E}$. The average local stress of elements with yield energy E evolves as $d\sigma(E)/dt = \dot{\gamma} - \exp(-\beta E)\sigma(E)$. We note that the above evolution equation is a dynamic average over the stresses of all elements with their current yield energies equal to E , which do not contribute to the average if they reach a new configuration with different yield energy. The corresponding Fourier transformation of its stress in the frequency space follows $\sigma(E, \omega) = \frac{i\omega\tau(E)}{1+i\omega\tau(E)}\gamma(\omega)$, where $\tau(E) = \exp(\beta E)$. Because the macroscopic shear stress is the average over all elements, the whole

system's complex modulus becomes

$$G(\omega) = \left\langle \frac{i\omega\tau(E)}{1+i\omega\tau(E)} \right\rangle_E. \quad (2)$$

The average is over the yield energy distribution $P(E, t)$, which in the regime of linear viscoelasticity satisfies

$$\frac{\partial P(E, t)}{\partial t} = -P(E, t)e^{-\beta E} + \int H(E|E') P(E', t) e^{-\beta E'} dE'. \quad (3)$$

We note that, rigorously speaking, this equation requires that $P(E, t)$ changes little for the duration of the rheological measurement so that a quasiequilibrium yield energy distribution is a good approximation. We will show later that current experiments support that this quasiequilibrium condition is generally satisfied. Therefore, to find the complex modulus, we only need to find the yield energy distribution $P(E, t)$, which we discuss in the following.

Assuming a complete loss of memory of the previous metastable configuration is a theoretical simplification, making the model analytically solvable. In more realistic models, the correlation between the new metastable configuration and the previous one should be considered. To incorporate this correlation, we make a simple assumption that the transition kernel $H(E|E') = h(E' - E)$ and is also short ranged, so the new metastable configurations are close to the previous ones in the yield energy space. Therefore, we propose a simple form of Eq. (3) in the continuum limit as

$$\frac{\partial P(E, t)}{\partial t} = -v \frac{\partial [P(E, t)e^{-\beta E}]}{\partial E} + D \frac{\partial^2 [P(E, t)e^{-\beta E}]}{\partial E^2}. \quad (4)$$

Here $v = \int h(x)x dx$ is the drift and $D = \int h(x)x^2 dx/2$ is the diffusion constant. Note that a positive v means a drift towards positive E . Equation (4) resembles the standard diffusion equation, but exhibits a critical difference. For example, even if $P(E, t)$ is independent of E , the diffusion term has a flux towards the positive direction of E due to the $\exp(-\beta E)$ factor.

Intriguingly, we find that Eq. (4) has an analytical solution that has a traveling-wave form $P(E, t) = f(E - v_t t)$ with a time-dependent traveling speed $v_t = T \ln(t)/t$ (Fig. 2),

$$P(E, t) \sim \frac{e^{(\beta+v/D)E}}{t^{1+v/D\beta}} \exp\left(-\frac{e^{\beta E}}{D\beta^2 t}\right), \quad (5)$$

where we drop the normalization constant, which is straightforward to compute (see the Supplemental Material [29]). The traveling-wave solutions are confirmed numerically (see Fig. S1 in [29]).

The traveling-wave solution suggests aging phenomena. We find that the average yield energy increases logarithmically with time $\langle E \rangle = T[\ln(D\beta^2 t)] + \text{const}$ (see the expression of the constant term in [29]). Meanwhile, the average relaxation time $\tau_c = \int e^{\beta E} P(E, t) dE$ increases linearly with time:

$$\tau_c = \left(\frac{D}{T^2} + \frac{v}{T}\right)t. \quad (6)$$

The time t here can be considered as the waiting time t_w after the formation of protein condensates. Note that, according to

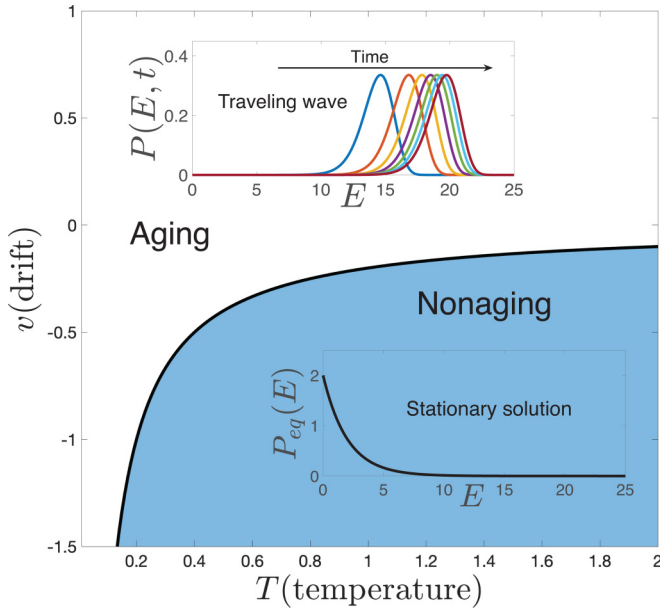


FIG. 2. Phase diagram of the aging Maxwell fluid model. In the aging phase in which $T < -D/v$, the yield energy distribution is a traveling wave with a time-dependent traveling speed. Therefore, the system's macroscopic viscosity gradually increases over time. In the nonaging phase, the system exhibits a stationary state with a constant viscosity.

Eq. (6), the average relaxation time $\tau_c(t=0) = 0$, which is a good approximation if $\tau_c(t=0)$ is negligible compared with the average relaxation time for large t . When this approximation is not valid, we find that the yield energy distribution can be well approximated by Eq. (5) with a constant shift in time (see [29]). We find a phase transition from the aging phase to a nonaging phase when $T > -D/v$ (Fig. 2). In the nonaging phase, the yield energy distribution becomes a stationary solution $P_{eq}(E) = -e^{(\beta+v/D)E}/(\beta + v/D)$, which can be derived directly from Eq. (4). Our model predicts that increasing the

temperature can slow down or even halt aging, consistent with experimental observations [17].

Self-similarity of the complex modulus. Imagine we prepare the material at time zero and implement the periodic shear experiment after a waiting time t_w . The complex shear modulus $G(\omega) = G'(\omega) + iG''(\omega)$ can be calculated using Eqs. (2) and (5) [Figure 3(a)]. We rescale the curves by the characteristic frequency ω_c at which $G'(\omega_c) = G''(\omega_c)$. The shear modulus curves can be nicely collapsed on a master curve, with the signature scaling of Maxwell fluids $G'(\omega) \sim \omega^2$ and $G''(\omega) \sim \omega$ at low frequency [Fig. 3(b)]. The self-similarity of the complex modulus is a direct consequence of the traveling-wave solution in the aging phase, and also robust, as we confirm using multiple sets of parameters, including positive and negative drifts (Fig. S2 in [29]). Furthermore, the characteristic timescale of the whole system, which is defined as $1/\omega_c$, can be well approximated by the average relaxation time τ_c (Fig. S3 in [29]). For a Maxwell fluid, $\omega_c = k/\eta$, where k is the elastic modulus and η is the macroscopic viscosity. Since the elastic constant is constant, our model predicts that the macroscopic viscosity increases linearly with the waiting time t_w .

We now discuss the validity of our quasiequilibrium assumption. Imagine one does a rheology experiment with time interval δt so that the change of τ_c in this interval is $\delta\tau_c = (D\beta^2 + v\beta)\delta t$. The condition of $\delta\tau_c \ll \tau_c$ becomes $\delta t \ll t_w$. To accurately measure the complex modulus at frequency ω , multiple periods of shear are necessary, $\delta t \gtrsim 1/\omega$. Therefore, the minimum frequency we can accurately measure should satisfy $\omega_{min} \gg 1/t_w$. To measure the complex modulus over a broad range of frequency, we require that $1/t_w \ll 1/\tau_c$, and according to Eq. (6) this means $D/T^2 + v/T \ll 1$. We note that experiments have indeed observed that the waiting times are much longer than the characteristic relaxation times ($t_w \gg \tau_c$) for various protein condensates [17].

Time-dependent viscosity under constant shear rate. We now discuss the case of constant shear rate $\dot{\gamma}$, which is one of the simplest probes of nonlinear rheology. We consider

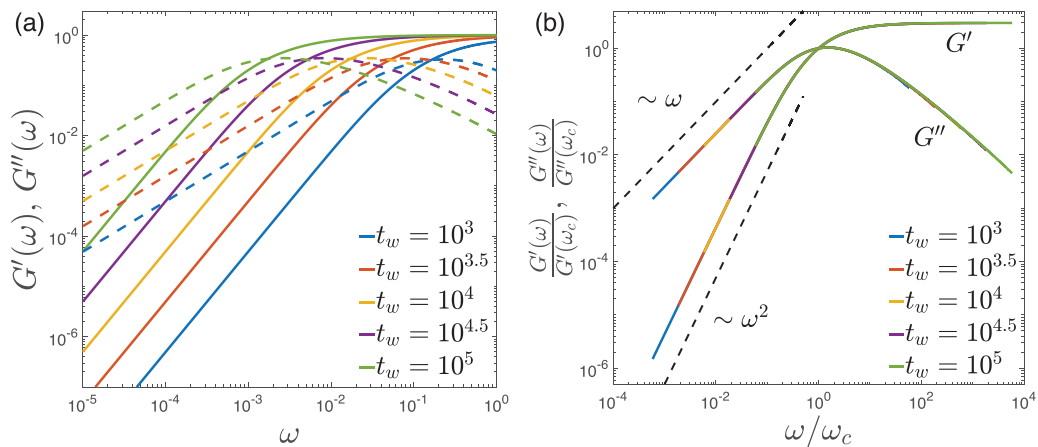


FIG. 3. Self-similarity of aging Maxwell fluids at different waiting times. In this figure, $D = 0.2$, $T = 2$, and $v = 0$. (a) Complex modulus as a function of frequency at different waiting times. Here G' is the real part (solid lines) and G'' is the imaginary part (dashed lines). (b) Rescaled plot of (a) where ω_c is the characteristic frequency at which $G'(\omega_c) = G''(\omega_c)$. The same plots with different parameters are shown in Fig. S2 in [29].

such an experiment in which we first let the system relax for a finite waiting time t_w and then implement a constant shear rate. For an idealized Maxwell fluid with a relaxation time τ_c , the stress-strain curve is universal, $\sigma = \dot{\gamma}\tau_c(1 - e^{-\gamma/\dot{\gamma}\tau_c})$, which means that for two different materials with different relaxation times, their stress-strain curves are identical if they have the same $\dot{\gamma}\tau_c$. However, for aging Maxwell fluids, the average relaxation time depends on the waiting time t_w .

We present a scaling analysis to derive the long-time behavior of the stress-strain response of an aging Maxwell fluid. Given a constant shear rate, the typical duration for an element to escape a metastable configuration with yield energy E becomes $\tau(E) \approx \sqrt{2E}/\dot{\gamma}$, namely, the duration after which the elastic energy is equal to the yield energy. Here we neglect the contribution of thermal noise since the average yield energy keeps increasing over time and eventually becomes larger than the thermal energy.

We consider that one element has a 1/2 probability to reach a new configuration with a yield energy $E + \Delta E_1$ and another 1/2 probability to reach a new configuration with a yield energy $E - \Delta E_2$, where E is the yield energy of the current state. We approximate the average yield energy increment due to one yielding out of a metastable configuration as an average over the two new configurations weighted by their lifetimes $\Delta\langle E \rangle = [\Delta E_1\sqrt{2(E + \Delta E_1)} - \Delta E_2\sqrt{2(E - \Delta E_2)}]/[\sqrt{2(E + \Delta E_1)} + \sqrt{2(E - \Delta E_2)}]$, which we expand to second order and obtain $\Delta\langle E \rangle = (\Delta E_1 - \Delta E_2)/2 + (\Delta E_1 + \Delta E_2)^2/8E \approx v + D/E$. Finally, we obtain the time derivative of the average yield energy as $d\langle E \rangle/dt \approx \Delta\langle E \rangle/\tau(\langle E \rangle) \sim \dot{\gamma}(v + D/\langle E \rangle)/\sqrt{\langle E \rangle}$. From the above equation and using $\sigma \sim \tau(\langle E \rangle)\dot{\gamma} \sim \sqrt{\langle E \rangle}$, we obtain three different scaling regimes of the stress response:

$$\begin{aligned} \sigma &\sim (v\dot{\gamma}t_s)^{1/3} & \text{for } v > 0, \\ \sigma &\sim (D\dot{\gamma}t_s)^{1/5} & \text{for } v = 0, \\ \sigma &\sim \sqrt{-D/v} & \text{for } v < 0. \end{aligned} \quad (7)$$

Here t_s is the duration of constant shear and the total strain $\gamma = \dot{\gamma}t_s$. Our model predicts that aging Maxwell fluids are rheopectic fluids; the shear stress increases with time under constant shear rate. We numerically test our predictions by directly simulating a condensate with $N = 10^4$ elements. The transition kernel $H(E|E') = \delta(E - E' - \Delta E_1)/2 + \delta(E - E' + \Delta E_2)/2$, where ΔE_1 and ΔE_2 are chosen such that v and D are equal to the values we set. Each element has a yielding rate $R(E, l) = e^{-\beta(E - l^2/2)}$ to escape its current configuration and reach a new configuration with a different yield energy. We first let the system relax for a finite time t_w without shear and after that we add a constant shear rate. After the yielding of an element, its local strain is reset to 0 (see simulation details in [29]). Our theoretical predictions are nicely confirmed (Fig. 4).

Equation (7) shows that the stress σ is only a function of the strain γ for large γ , while the stress-strain curve of a normal Maxwell fluid depends on the product of $\dot{\gamma}$ and its relaxation time. Therefore, we propose that the stress-strain curves of aging Maxwell fluids have universal functional forms $\sigma = F(\gamma, \dot{\gamma}\tau_c)$, where τ_c is the average relaxation time

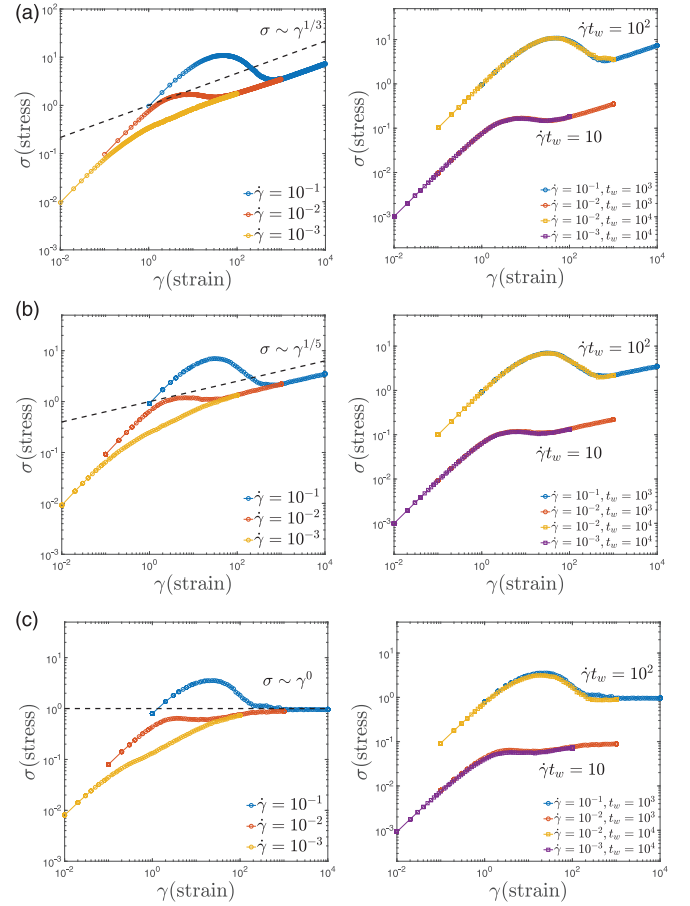


FIG. 4. Nonlinear rheology of aging Maxwell fluids under constant shear rate. (a) In the left panel, $D = 0.2$, $v = 0.1$, $T = 1$, and the waiting time $t_w = 10^3$ with three different shear rates. The dashed line represents the predicted scaling. In the right panel, the four curves have different $\dot{\gamma}$ and t_w as shown in the legend. Stress-strain curves with the same $\dot{\gamma}t_w$ collapse on the same curve. Note that the two curves with $\dot{\gamma}t_w = 10$ are rescaled by a factor of 0.1 on the y axis for better illustration. (b) Same analysis as in (a) for the same parameters but with $v = 0$. (c) Same analysis as in (a) for the same parameters but with $v = -0.1$.

right before the shear. Furthermore, since τ_c is proportional to the waiting time in our model, we propose a universal shape of the stress-strain curve as $\sigma = F(\gamma, \dot{\gamma}t_w)$. We confirm this functional form numerically and find that the stress-strain curves with equal $\dot{\gamma}t_w$ indeed collapse on the same curve (Fig. 4).

Conclusion. In this Letter we have proposed a mesoscopic framework to describe the aging properties of protein condensates in which a protein condensate is subdivided into multiple mesoscopic elements. Each element has a local yield energy which changes after the element escapes the current configuration and reaches a new metastable configuration. A key assumption of the model is to assume that the transition kernel in the yield energy space is short ranged so that the equation of motion of the yield energy distribution becomes continuous with a drift term and a diffusion term. Surprisingly, the equation has an analytical solution exhibiting a phase transition from the aging phase to the

nonaging phase. The order parameter is the aging rate, changing from zero to a finite value continuously as the temperature decreases.

In the linear viscoelasticity regime, we predict that the complex modulus is self-similar at all times after the formation of condensates. The material behaves as a Maxwell fluid with a characteristic relaxation time increasing linearly over time. The transition kernel of our model can be generalized to the long ranged case such that $H(E|E') \sim |E - E'|^{-\eta}$, where η is an exponent. The generalized model may lead to a new scaling relationship $\tau_c \sim t_w^\delta$ and $\sigma \sim \gamma^\alpha$, where $\delta = 1$ and $\alpha = 1/3$ or $1/5$ in our current model, which is left for future investigation. We note that the exponent δ is in the range from 2.1 to 6.4 in the experiments by Jawerth *et al.* [17]. *In vivo* experiments found that aging processes can be significantly slowed down inside living cells [16]. While the microscopic mechanisms of how biological activities affect the transition between metastable configurations are far from clear, our results suggest the effects of biological activities may be increasing the temperature to a higher effective value. Finally, our model can also be extended to include spatial structures by labeling elements with their spatial positions. A local yield event generates a long ranged stress

perturbation to other elements and may trigger more yield events [28].

We also discuss nonlinear rheology with a constant shear rate and find that protein condensates exhibit non-Newtonian rheological behavior with a viscosity increasing over time. This type of complex fluid, called rheopectic fluid, is relatively rare compared with thixotropic fluid, whose viscosity decreases over time under shear. If confirmed by experiments, our results suggest that protein condensates exhibit an uncommon rheological property, which may have special biological meaning and practical applications. We remark that while the power-law exponents may depend on the long ranged nature of the transition kernel, the rheopectic behavior of protein condensates should be robust. This is because as we shear the material and trigger the yielding of local elements, those elements with higher updated yield energies always have longer lifetimes before the next yielding. Therefore, the external shear always increases the average yield energy and therefore increases the average relaxation time of the system.

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